UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

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

For the Quarterly Period Ended March 31, 2006

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 ☒ No o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer or a non-accelerated filer (as defined in Rule 12b-2 of the Exchange Act): Large Accelerated Filer o Accelerated Filer ☒ Non-Accelerated Filer 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 ☒

The number of shares of voting common stock outstanding as of May 3, 2006 was 72,768,057.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.
Vitravene® is a registered trademark of Novartis AG.
Affinitak™ is a trademark of Eli Lilly and Company.

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

	March 31, 2006 (Unaudited)	December 31, 2005
ASSETS		
Current assets:		
Cash and cash equivalents	$ 1,711	$ 3,650
Short-term investments	76,850	90,739
Contracts receivable	3,503	3,918
Inventory	749	951
Other current assets	7,918	6,600
Total current assets	90,731	105,858
Property, plant and equipment, net	8,208	9,130
Licenses, net	23,186	23,770
Patents, net	18,875	18,773
Deposits and other assets	2,883	3,201
Long-term investments	6,754	5,641
Total assets	$ 150,637	$ 166,373
LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 2,483	$ 2,095
Accrued compensation	1,517	3,706
Accrued liabilities	7,871	8,643
Current portion of long-term obligations	7,863	7,835
Current portion of deferred contract revenue	1,111	1,514
Total current liabilities	20,845	23,793

5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	12,942	14,915
Stockholders' equity (deficit):		
Common stock, $0.001 par value; 100,000,000 shares authorized, 72,681,425 shares and 72,201,505 shares issued and outstanding at March 31, 2006 and December 31, 2005, respectively	73	72
Additional paid-in capital	774,366	770,263
Accumulated other comprehensive income	5,739	3,178
Accumulated deficit	(788,328)	(770,848)
Total stockholders' equity (deficit)	(8,150)	2,665
Total liabilities and stockholders' equity (deficit)	$ 150,637	$ 166,373

See accompanying notes

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

	Three Months Ended March 31,	
	2006	2005
Revenue:		
Research and development revenue under collaborative agreements	$ 4,468	$ 7,135
Licensing and royalty revenue	490	307
Total revenue	4,958	7,442
Operating expenses:		
Research and development (including non-cash compensation expense related to stock options of $1.2 million and $0 in 2006 and 2005, respectively)	18,372	22,361
General and administrative (including non-cash compensation expense related to stock options of $221,000 and $0 in 2006 and 2005, respectively)	2,566	2,137
Compensation benefit related to variable accounting of stock options	—	(633)
Restructuring activities	36	7,084
Total operating expenses	20,974	30,949
Loss from operations	(16,016)	(23,507)
Other income (expenses):		
Investment income	811	504
Interest expense	(2,275)	(6,655)
Net loss applicable to common stock	$ (17,480)	$ (29,658)
Basic and diluted net loss per share	$ (0.24)	$ (0.52)
Shares used in computing basic and diluted net loss per share	72,377	57,521

See accompanying notes

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

	Three Months Ended March 31,	
	2006	2005
Net cash used in operating activities	$ (16,063)	$ (22,032)
Investing activities:		
Purchase of short-term investments	(9,031)	(3,306)
Proceeds from the sale of short-term investments	23,000	8,985
Purchase of property, plant and equipment	(117)	(277)
Proceeds from the sale of property, plant and equipment	—	165
Other assets	(514)	(1,173)
Net cash provided by investing activities	13,338	4,394

Financing activities:		
Net proceeds from issuance of equity	2,731	353
Proceeds from long-term borrowings	—	5,000
Principal payments on debt and capital lease obligations	(1,945)	(2,959)
Net cash provided by financing activities	786	2,394
Net increase (decrease) in cash and cash equivalents	(1,939)	(15,244)
Cash and cash equivalents at beginning of period	3,650	27,250
Cash and cash equivalents at end of period	$ 1,711	$ 12,006
Supplemental disclosures of cash flow information:		
Interest paid	$ 409	$ 522

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2006
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three-month periods ended March 31, 2006 and 2005 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2005. The financial statements include all adjustments, which Isis considers 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, 2005 included in Isis' Annual Report on Form 10-K filed with the Securities and Exchange Commission.

The condensed consolidated financial statements include the accounts of Isis and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Ltd, Hepasense, Ltd., Orasense, Ltd and Ibis Biosciences, Inc. On July 25, 2005, Isis dissolved its Hepasense, Ltd. subsidiary.

2. Significant Accounting Policies

Revenue Recognition

Isis recognizes revenue when it has satisfied all contractual obligations and Isis is reasonably certain it can collect the receivable.

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as Isis satisfies its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with Emerging Issues Task Force Issue No. 00-21 ("EITF 00-21") *Accounting for Revenue Arrangements with Multiple Deliverables*. This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis records revenue from federal research grants during the period in which it incurs the related expenditures. Isis recognizes revenue from product sales as it ships the products.

Isis has implemented the provisions of Staff Accounting Bulletin No. 104 ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 in order to make this interpretive guidance consistent with current authoritative accounting guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured.

As part of Isis' Eli Lilly and Company ("Lilly") alliance, in 2001 Lilly provided Isis a $100.0 million interest-free loan to fund the companies' joint research collaboration. Isis discounted the loan amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to Isis to help fund the research collaboration. Isis accounted for this difference as deferred revenue and recognized it as revenue over the period of performance. In August 2005, in accordance with its terms, Isis converted this loan into 2.5 million shares of its common stock. Concurrent with the conversion, Isis extended the research collaboration.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, for arrangements in which Isis is not required to provide services in the future.

Concentration of Credit Risk

Financial instruments that potentially subject Isis to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. Isis places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. Isis invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. Isis and its audit committee established guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, Cash Equivalents and Short-Term Investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income. Isis determined that there were no other-than-temporary declines in value of its investments during the three months ended March 31, 2006 and 2005.

Valuation of Inventory

Isis includes in inventory raw material costs for drugs that Isis manufactures for its partners under contractual terms, and that it uses primarily in its clinical development activities and drug products. Isis expenses these costs when it delivers its drugs to partners, or as it uses these drugs in its own clinical trials. Isis reflects its inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. Isis reviews inventory periodically and reduces its carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. Isis considers several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for its drugs and clinical trial materials and historical write-offs. Total inventory, which consisted solely of raw materials, was $749,000 and $951,000 as of March 31, 2006 and December 31, 2005, respectively.

Licenses

Isis obtains licenses from third parties and capitalizes the cost related to exclusive licenses. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between 7 years and 15 years.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews its capitalized patent costs regularly to determine that they include costs for patent applications that have future value. Isis evaluates costs related to patents that it is not actively pursuing for impairment and writes off any of these costs, if appropriate. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued.

Fair Value of Financial Instruments

Isis has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. Isis reports its investment securities at their estimated fair value based on quoted market prices of comparable instruments.

Long-Lived Assets

Pursuant to the provisions of SFAS No. 144, *Accounting for the Impairment of Long-Lived Assets*, Isis evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. In the first quarter of 2006 and 2005, Isis incurred a charge related to restructuring activities of $25,000 and $1.6 million, respectively. The charge in 2005 was primarily related to the write-down of capitalized leasehold improvements in a building, which Isis vacated during March 2005.

Use of Estimates

The preparation of 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.

Consolidation of Variable Interest Entities

Isis has implemented the provisions of Financial Accounting Standards Board Interpretation ("FIN") No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, which addresses consolidation by business enterprises of 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 March 31, 2006, Isis had collaborative arrangements with four entities that it considers to be variable interest entities ("VIE") under FIN 46. Additionally, in April 2006, Isis entered into a collaboration with Symphony Capital Partners, L.P. and a group of co-investors to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. Symphony Capital has formed Symphony GenIsis, Inc, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis will treat Symphony GenIsis as a VIE for which Isis is the primary beneficiary. As a result, beginning in the second quarter of 2006, Isis will include the financial condition and results of operations of Symphony GenIsis in its condensed consolidated financial statements. For a further discussion see Note 7 – *Subsequent Events*.

As part of the collaboration between Isis and Ercole Biotech, Inc., during 2003 and early 2004, Isis paid Ercole $750,000 in exchange for a convertible promissory note. Isis expensed the payments when made. The promissory note will convert into securities that Ercole issues in a financing. Isis is not required to consolidate Ercole's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Sarissa Inc., during February 2005, Isis licensed an anti-cancer antisense drug to Sarissa in exchange for a $1.0 million convertible promissory note. The promissory note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1.0 million to offset the debt instrument, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and iCo Therapeutics, Inc., during August 2005, Isis licensed iCo 007, an antisense drug, to iCo in exchange for a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note. The note will convert into securities that iCo issues in a financing. Isis has recognized a valuation allowance of $250,000 to offset the note, as realization of this asset is uncertain. In December 2005, the Company entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note, which will convert into iCo stock upon iCo's completion of a financing. The remaining $175,000 will be paid upon shipment of the drug. Isis has recognized a valuation allowance of $350,000 to offset the note, as realization of this asset is uncertain. Isis is not required to consolidate iCo's results of operations under FIN No. 46 as Isis is not the primary beneficiary. In May 2006, Isis received 869,025 shares of iCo common stock for the conversion of both convertible notes.

As part of the collaboration between Isis and Achaogen, Inc., during January 2006, Isis licensed its proprietary aminoglycosides program in exchange for $1.5 million of Achaogen Series A Preferred stock. Isis has recognized a valuation allowance of $1.5 million to offset the equity instrument, as realization of this asset is uncertain. Isis is not required to consolidate Achaogen's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

Stock-Based Compensation

On January 1, 2006, Isis adopted SFAS No. 123 (revised 2004), *Share-Based Payment*, ("SFAS 123(R)") which requires the measurement and recognition of compensation expense for all stock based payment awards made to employees and directors including employee stock options and employee stock purchases related to the Company's Employee Stock Purchase Plan ("ESPP") based on estimated fair values. SFAS 123(R) supersedes Isis' previous accounting under Accounting Principles Board Opinion No. 25, *Accounting for Stock Issued to Employees* ("APB 25") and SFAS 123, *Accounting for Stock-Based Compensation* ("SFAS 123"), for the period beginning January 1, 2006. In March 2005, the Securities and Exchange Commission issued Staff Accounting Bulletin No. 107 ("SAB 107") relating to SFAS 123(R). Isis has applied the provisions of SAB 107 in its adoption of SFAS 123(R).

Isis adopted SFAS 123(R) using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of the Company's fiscal year 2006. Isis' Consolidated Statement of Operations as of and for the three months ended March 31, 2006 reflects the impact of SFAS 123(R). In accordance with the modified prospective

transition method, Isis' Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123(R).

SFAS 123(R) requires companies to estimate the fair value of share-based payment awards on the date of grant using an option-pricing model. The value of the portion of the award that is ultimately expected to vest is recognized as expense over the requisite service period as stock-based compensation expense in Isis' Consolidated Statement of Operations. For the three months ended March 31, 2006, Isis' Consolidated Statement of Operations included compensation expense for share-based payment awards granted prior to, but not yet vested as of December 31, 2005, based on the grant date fair value estimated in accordance with the pro forma provisions of SFAS 123 and compensation expense for the share-based payment awards granted subsequent to December 31, 2005 based on the grant date fair value estimated in accordance with the provisions of SFAS 123(R). Isis recognizes compensation expense for all share-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front loaded over the vesting period. As stock-based compensation expense recognized in the Consolidated Statement of Operations for the first three months of fiscal 2006 is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123(R) requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. In Isis' pro forma information required under SFAS 123 for the periods prior to fiscal 2006, Isis accounted for forfeitures as they occurred.

As permitted by SFAS 123(R), Isis utilizes the Black-Scholes option-pricing model ("Black-Scholes model") as its method of valuation for share-based awards granted. The Black-Scholes model was previously utilized for Isis' pro forma information required under SFAS 123. Isis' determination of the fair value of share-based payment awards on the date of grant using an option-pricing model is affected by Isis' stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, Isis' expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because Isis' employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of Isis' employee stock options. Although the fair value of employee stock options is determined in accordance with SFAS 123(R) using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

Prior to January 1, 2006, Isis had adopted the disclosure-only provision of SFAS 123. Accordingly, Isis had not previously recognized compensation expense for the Isis stock option plans and Isis' ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program. Non-cash stock-based compensation expense recognized under SFAS 123(R) for the three months ended March 31, 2006 was $1.4 million. Non-cash stock-based compensation benefit of $633,000 for the three months ended March 31, 2005 was related to the 2003 option exchange program.

In April 2003, Isis implemented an employee stock option exchange program that allowed employees during the offering period to surrender options granted prior to January 5, 2002. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having

an exercise price of $5.15. The new options, fully vested as of January 31, 2006, expire on December 31, 2008. Isis previously accounted for the affected options using variable accounting consistent with the provisions of APB 25 and FIN 44. As a result, Isis recorded non-cash compensation expense/(benefit) related to stock options on the Consolidated Statements of Operations.

See Note 6—*Stock-Based Compensation Plans* for additional information regarding Isis' share-based compensation plans and the impact of adopting SFAS 123(R).

Comprehensive Loss

SFAS No. 130, *Reporting Comprehensive Income*, requires Isis to report, in addition to net loss, comprehensive loss and its components. A summary follows (in thousands):

	Three Months Ended March 31,	
	2006	2005
Comprehensive loss:		
Change in unrealized gains (losses)	$ 2,561	$ (2,079)
Net loss applicable to common stock	(17,480)	(29,658)
Comprehensive loss	$ (14,919)	$ (31,737)

Impact of Recently Issued Accounting Standards

In February 2006, the Financial Accounting Standards Board issued SFAS No. 155, *Accounting for Certain Hybrid Financial Instruments*, which amends SFAS No. 133, *Accounting for Derivative Instruments and Hedging Activities* and SFAS No. 140, *Accounting for Transfers and Servicing of Financial Assets and Extinguishments of Liabilities.* This Statement is aimed at improving the financial reporting of certain hybrid financial instruments by requiring more consistent accounting that eliminates exemptions and provides a means to simplify the accounting for these instruments. This Statement is effective for all financial instruments acquired or issued after the beginning of an entity's first fiscal year that begins after September 15, 2006. Isis does not believe the adoption of SFAS 155 will have a material impact on its financial statements.

3. Strategic Alliances

Drug Discovery and Development

Rosetta Genomics, Inc.

In January 2006, Isis initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma. For each drug that meets specific success factors outlined in the collaboration, Isis and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

Achaogen, Inc.

In January 2006, Isis licensed its proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and are used to treat serious bacterial infections. The program Isis licensed to Achaogen resulted from research conducted in Isis' Ibis division to identify drugs to treat antibiotic-resistant infections.

In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to Isis $1.5 million of Achaogen Series A Preferred stock. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, Isis will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, Isis will receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

ImQuest Pharmaceuticals, Inc.

In April 2006, Isis granted an exclusive worldwide license to ImQuest for the development and commercialization of ISIS 5320, a compound that has been shown in vitro and in vivo to be a potent and specific inhibitor of HIV, the virus that causes AIDS. ImQuest plans to develop ISIS 5320 as a topical microbicide therapy to prevent the sexual transmission of HIV throughout the world, but especially in developing countries. In exchange for the exclusive worldwide license, Isis will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, Isis is entitled to a portion of the consideration received.

4. Segment Information and Concentration of Business Risk

Segment Information

The following is information for revenue and loss from operations by segment.

	Drug Discovery and Development	Ibis	Corporate	Total
Three Months Ended March 31, 2006				
Revenue:				
Research and development	$ 1,270	$ 3,198	$ —	$ 4,468
Licensing and royalty	490	—	—	490
Total segment revenue	$ 1,760	$ 3,198	$ —	$ 4,958
Loss from operations	$ (15,449)	$ (531)	$ (36)	$ (16,016)

Three Months Ended March 31, 2005				
Revenue:				
Research and development	$ 4,810	$ 2,325	$ —	$ 7,135
Licensing and royalty	307	—	—	307
Total segment revenue	$ 5,117	$ 2,325	$ —	$ 7,442
Loss from operations	$ (15,944)	$ (1,112)	$ (6,451)	$ (23,507)

Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

Concentrations of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	Three Months Ended March 31,	
	2006	2005
Partner A	29%	11%
Partner B	18%	12%
Partner C	15%	57%
Partner D	14%	7%

For the three months ended March 31, 2006 and 2005, Isis derived approximately 64% and 34%, respectively, of its revenue from agencies of the United States Government, including approximately 29% and 11% respectively, of revenue from one significant customer.

Contract receivables from four significant partners comprised approximately 43%, 22%, 18%, and 11% of contract receivables at March 31, 2006. Contract receivables from four significant partners comprised 39%, 13%, 12%, and 12% of contract receivables at December 31, 2005.

5. Restructuring Activities

In connection with the decision to reorganize and refocus the Company's resources, in January 2005, Isis commenced several cost containment measures, including a reduction in workforce of approximately 160 employees, the consolidation of its facilities in the United States, and the closure of the Company's research and development laboratory in Singapore.

Pursuant to SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities*, the following table sets forth the activity in the restructuring reserve, which is included in accrued liabilities at March 31, 2006 (in thousands).

	Facility Consolidation and Closure Related Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2005	$ 856	$ 765	$ 126	$ 1,747
Accrued and expensed	11	—	25	36
Charged against accrual	(143)	—	(32)	(175)
Balance at March 31, 2006	$ 724	$ 765	$ 119	$ 1,608

6. Stock-Based Compensation Plans

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

The 1989 Stock Option Plan (the "1989 Plan") provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to its employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year period. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. As of March 31, 2006, 2,631,145 shares were available for future grant.

2000 Broad Based Equity Incentive Plan

The 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, the Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange

program expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the option holder's employment or service as a consultant, employee or director. Options were fully vested on January 31, 2006. As of March 31, 2006, 2,097,978 shares were available for future grant.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis' Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to Isis' non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 Plan"), and it had an aggregate of 600,000 shares of common stock authorized for issuance. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. As of March 31, 2006, 131,000 shares were available for future grant. In May 2006, after receiving approval from its stockholders, Isis amended its 2002 Non-Employee Directors' Stock Option Plan to increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares.

Employee Stock Purchase Plan

Under the 2000 ESPP, Isis reserved 200,000 shares of common stock for issuance. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the ESPP, resulting in a total of 1.4 million shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offering period or the end of each six-month purchase period. At March 31, 2006, 200,056 shares were available for purchase under this plan.

Stock Option Activity and Share-Based Compensation Expense

The following table summarizes stock option activity for the three months ended March 31, 2006 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2005	7,979	$ 7.86		
Granted	1,710	$ 5.41		
Exercised	(450)	$ 8.07		
Cancelled/forfeited/expired	(341)	$ 8.55		
Outstanding at March 31, 2006	8,898	$ 7.46	5.52	$ 20,922
Exercisable at March 31, 2006	5,315	$ 8.66	4.73	$ 9,027

The following table summarizes information concerning outstanding and exercisable options as of March 31, 2006 (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$2.8600 - $5.24	1,180	4.90	$ 4.83	717	$ 5.00
$5.2500 - $5.25	1,441	6.76	$ 5.25	3	$ 5.25
$5.3500 - $6.59	1,644	6.10	$ 5.91	603	$ 6.00
$6.6000 - $6.81	1,487	5.78	$ 6.81	1,131	$ 6.81
$6.8125 - $9.63	1,767	5.48	$ 7.92	1,488	$ 7.96
$9.7500 - $22.83	1,379	3.83	$ 14.00	1,373	$ 14.01
	8,898	5.52	$ 7.46	5,315	$ 8.66

The weighted average fair values of options granted were $3.13 and $3.79 for the three months ended March 31, 2006 and 2005, respectively. The total intrinsic value of options exercised during the three months ended March 31, 2006 was $1.0 million, determined as of the date of exercise and the amount of cash received from the exercise of stock options was $2.7 million. As of March 31, 2006, there was $8.8 million of total unrecognized compensation cost related to non-vested share-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.5 years.

Share-based Valuation and Compensation Expense Information under SFAS 123(R)

Impact of the Adoption of SFAS 123(R)

The following table summarizes stock-based compensation expense related to employee stock options and employee stock purchases under SFAS 123(R) for the three months ended March 31, 2006 (in thousands, except per share data), which was allocated as follows:

	Three Months Ended March 31, 2006
Research and development	$ 1,153
General and administrative	$ 221
Non-cash compensation expense related to stock options included in operating expenses	$ 1,374
Basic and diluted net loss per share	$ 0.02

Prior to the adoption of SFAS 123(R), Isis had adopted the disclosure-only provision of SFAS 123. Accordingly, Isis had not previously recognized compensation expense for the Isis stock option plans and the ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program.

Prior to the adoption of SFAS 123(R), Isis presented deferred compensation as a separate component of stockholders' equity. In accordance with the provisions of SFAS 123(R), on January 1, 2006, Isis reclassified the balance in deferred compensation to additional paid-in capital on the balance sheet.

The table below reflects net loss along with basic and diluted net loss per share (in thousands, except per share amounts) assuming Isis determined compensation expense consistent with SFAS 123 for the three months ended March 31, 2005:

	Three Months Ended March 31, 2005
Net loss applicable to common stock—as reported	$ (29,658)
Net loss applicable to common stock—pro forma	$ (31,864)
Basic and diluted net loss per share—as reported	$ (0.52)
Basic and diluted net loss per share—pro forma	$ (0.55)

Determining Fair Value

Valuation. Isis utilizes the Black-Scholes model as its method of valuation for share-based awards granted. Isis recognizes the value of the portion of the award that is ultimately expected to vest as expense over the requisite service period as stock-based compensation expense in Isis' Consolidated Statements of Operations. Isis recognizes compensation expense for all share-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front loaded over the vesting period.

Isis estimated the fair value of each stock option grant and the ESPP purchase rights on the date of grant using the Black-Scholes model with the following weighted-average assumptions:

Options:

	March 31,	
	2006	2005
Risk-free interest rate	4.3%	4.2%
Dividend yield	0.0%	0.0%
Volatility	68.7%	82.7%
Expected Life	4.6 years	4.8 years

ESPP:

	March 31,	
	2006	2005
Risk-free interest rate	4.4%	2.63%
Dividend yield	0.0%	0.0%
Volatility	45.8%	56.6%
Expected Life	6 months	6 months

Risk-Free Interest Rate. The risk-free interest rate assumption is based upon observed interest rates appropriate for the term of Isis' employee stock options or ESPP.

Dividend Yield. The dividend yield assumption is based on Isis' history and expectation of dividend payouts. Isis has not paid dividends in the past and does not expect to in the future.

Volatility. Isis used a weighted average of the historical stock price volatility of Isis' stock for the Black-Scholes model consistent with SFAS 123(R). Prior to fiscal 2006, Isis also used its historical stock price volatility in accordance with SFAS 123 for purposes of its pro forma information.

Expected Life. The expected life of employee stock options represents the average of the life of the options and the average vesting period, and is a derived output of the simplified method, as allowed under SAB 107.

Forfeitures. As stock-based compensation expense recognized in the Consolidated Statement of Operations is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123(R) requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Forfeitures were estimated based on historical experience. In the Company's pro forma information required under SFAS 123 for the periods prior to fiscal 2006, the Company accounted for forfeitures as they occurred.

7. Subsequent Events

On April 7, 2006, Isis entered into a series of related agreements in connection with a transaction with Symphony Capital Partners, L.P. and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial

hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of the two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows Isis to continue to control and manage the development of these three drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. Isis has received an exclusive purchase option from Symphony GenIsis' investors that will allow Isis to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and Isis common stock (up to 33% of the purchase price), at Isis' discretion.

In exchange for the purchase option, Isis granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over Isis' prior 60 day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay certain of its expenses, Isis paid a structuring fee of $3.75 million.

In accordance with FIN 46, Isis has determined that Symphony GenIsis is a variable interest entity for which Isis is the primary beneficiary. As a result, beginning in the second quarter of 2006, Isis will include the financial condition and results of operations of Symphony GenIsis in its consolidated financial statements.

In May 2006, after receiving approval from its stockholders, Isis amended its 2002 Non-Employee Directors' Stock Option Plan to increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares and amended its Restated Certificate of Incorporation to increase the authorized number of shares of its common stock from 100,000,000 shares to 200,000,000 shares.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In addition to historical information contained in this Report on Form 10-Q, this Report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc. and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. 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, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. 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, 2005, which is on file with the U.S. Securities and Exchange Commission, and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 26 of this Report.

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense

drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and successfully turned our expertise into one marketed product and currently 15 antisense drugs, which we continue to advance in preclinical and clinical development either internally or with our partners. Most of these are in Phase 1 and Phase 2 human clinical trials. Our internal drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Our partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, such as oral and inhaled delivery, as well as infrequent dose administration. Our pipeline has matured to consist primarily of drugs based on our proprietary second generation chemistry. Our second generation antisense drugs offer a number of advantages over first generation drugs. Specifically, second generation drugs offer the potential for improved safety and increased potency. In addition, because second generation drugs have a longer half-life, they have the potential to produce long-duration of therapeutic response and to support more convenient, less frequent dosing.

During 2005 and to date in 2006, we and our partners have made important progress on all of our second generation drugs in development. In particular, we reported positive results from Phase 1, Phase 2 and animal studies of ISIS 301012, our apoB-100 inhibitor for the lowering of high cholesterol. In a Phase 1 study, ISIS 301012 produced rapid, dose-dependent and prolonged reductions in apoB-100, low-density lipoprotein cholesterol, or LDL, and very low-density lipoprotein, or VLDL, total cholesterol and triglycerides, and was well tolerated. These positive results supported the initiation of a Phase 2 development program for ISIS 301012. In a Phase 2 study of ISIS 301012 as a single-agent in patients with high cholesterol, ISIS 301012 continued to produce rapid, dose-dependent and prolonged reductions in apoB-100, LDL, VLDL, total cholesterol and triglycerides. At a dose of 200 mg/week for three months, ISIS 301012 achieved a median percent reduction from baseline of 47% in apoB-100, 42% in LDL, 34% in total cholesterol and 46% in triglycerides at day 99. ISIS 301012 was well tolerated in this study. We also recently announced that in a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. Additionally, we reported data from a Phase 2 study in diabetic patients in which ISIS 113715, our PTP-1b inhibitor for the treatment of type 2 diabetes, improved glucose control, did not cause hypoglycemia and was well tolerated. Our partnered drugs in development also met important milestones. For example, OncoGenex Technologies Inc. recently announced encouraging data from a Phase 1 study of OGX-011 in patients with non-small cell lung cancer, which supports their ongoing Phase 2 study. Phase 2 studies evaluating OGX-011 in prostrate and breast cancers are also ongoing. Eli Lilly and Company initiated Phase 1 studies of LY2275796, a cancer drug targeting eIF-4E and the second drug from our research collaboration.

We have a broad patent portfolio covering our technologies. We own or exclusively license approximately 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are

exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. As of March 31, 2006, we had generated more than $76 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

In our Ibis division, we have developed a revolutionary biosensor system, utilizing a U.S. government funded technology called T.I.G.E.R., or Triangulation Identification for Genetic Evaluation of Risk, that can, with a single test, simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample. During 2005 and the first quarter of 2006, our Ibis scientists advanced application development through contracts with our government partners in the areas of biowarfare defense, epidemiological surveillance, biological products screening and microbial forensics. This work has added value to us in that we can also apply much of this application development to non-government commercial opportunities. Further, this shift from basic instrument and system development to application development under our government contracts reflects the progression from technology development to commercial viability.

Through our Ibis division, we plan to commercialize the Ibis biosensor system and infectious organism ID kits to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control, and infectious disease diagnostics. We began executing our commercialization plans for the Ibis biosensor system in 2005 and to date have delivered three Ibis biosensor systems to our government partners, each for a different application. Our most recent delivery was to the Naval Health Research Center for use in epidemiological surveillance. Prior to that, we delivered Ibis biosensor systems to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics and the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense. We plan to deliver Ibis biosensor systems to additional government customers in 2006. We also plan to begin shipping infectious organism ID kits in 2006.

Much of the development of our Ibis biosensor system and related applications has been funded through government contracts and grants. As of March 31, 2006, we had earned $51.1 million in revenue from numerous government agencies. In addition we have an additional $5.6 million committed under our existing contracts and grants. These agencies include the Defense Advanced Research Projects Agency (DARPA), Department of Homeland Security (DHS), the Centers for Disease Control (CDC), the Federal Bureau of Investigation (FBI), the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), and the National Institute of Allergy and Infectious Diseases (the NIAID), a part of the National Institutes of Health (NIH).

We pursue early-stage antisense research programs, including RNA interference (RNAi), microRNA, and alternative splicing through research collaborations and partnerships, similar to our strategic alliances with Alnylam Pharmaceuticals, Inc. (Alnylam), Ercole and Rosetta.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. We continue to utilize our proprietary technology to discover and characterize novel antisense inhibitors through which our scientists modify the properties of our antisense drugs for optimal use with particular targets and thus, produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, our scientists have made significant advances in oligonucleotide chemistries, including what we call our second generation antisense drugs. Second generation, including generation 2.2, drugs provide increased potency, stability, oral bioavailability and an improved side effect profile. We and our partners are studying antisense drugs in intravenous, subcutaneous, intravitreal, enema, aerosol, intrathecal, oral and topical formulations.

Along with our partners we currently have 15 drugs in development, of which five are in Phase 2 clinical development, three are in Phase 1 clinical development and seven are in preclinical development. Our partners are licensed to develop, with our support, nine of these 15 drugs, which substantially reduces our development costs.

Ibis Division. Our Ibis division has developed a revolutionary biosensor system, utilizing a U.S. government funded technology called T.I.G.E.R., or Triangulation Identification for Genetic Evaluation of Risk, that can simultaneously identify thousands of infectious organisms in a sample, without needing to know beforehand what might be present in the sample. Ibis plans to commercialize the Ibis biosensor system to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control and infectious disease diagnostics.

Recent Events

Symphony GenIsis, Inc.

In April 2006, we entered into a series of related agreements in connection with a transaction with Symphony Capital Partners, L.P. and a group of co-investors to provide $75 million to fund the development of our cholesterol-lowering drug, ISIS 301012, and two novel drugs from our metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of the two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows us to continue to control and manage the development of these three drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, Inc., capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with us. We licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. We have received an exclusive purchase option from Symphony GenIsis' investors that will allow us to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and our common stock (up to 33% of the purchase price), at our discretion.

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over our prior 60 day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay certain of its expenses, we paid a structuring fee of $3.75 million.

In accordance with FIN 46, we have determined that Symphony GenIsis is a variable interest entity for which we are the primary beneficiary. As a result, beginning in the second quarter of 2006, we will include the financial condition and results of operations of Symphony GenIsis in our consolidated financial statements.

Critical Accounting Policies

We prepare our 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. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- 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 the appropriateness of the judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option and the expected stock price volatility over the term of the expected life.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions as set forth by current accounting rules, which primarily include SAB 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and EITF 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

We generally recognize revenue when we have satisfied all contractual obligations and we 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 billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the balance sheet.

We often enter into collaborations where we receive non-refundable up-front payments for prior or future expenditures. We recognize revenue related to up-front payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Lilly, OncoGenex, and Pfizer.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest-free loan to fund the companies' joint research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. In August 2005, in accordance with its terms, we converted this loan into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration. As part of the conversion and collaboration extension, Lilly has agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestones and royalties in the event of a stock price decline.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as

defined by the underlying agreements. We generally recognize revenue related to milestones upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated to future performance related to the achievement of the milestone. To date, we have earned milestone payments totaling $1.2 million under our Pfizer collaboration. Additionally, in January 2006, Lilly initiated clinical trials of LY2275796 for which we received a $750,000 milestone payment.

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

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 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.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* We carry these investments at fair market value based upon market prices quoted on the last day of the fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in marketable securities, we also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. In the first quarter of 2006 and 2005, we did not have any other-than temporary declines in value of any of our investments.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider the following, among other factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;
- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and
- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and the scope of our issued patents.

Pursuant to the provisions of SFAS No. 144, *Accounting for the Impairment of Long-Lived Assets*, we evaluate carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. In the first quarter of 2006 and 2005, we incurred a charge related to restructuring activities of $25,000 and $1.6 million, respectively. The charge in 2005 was primarily related to the write-down of capitalized leasehold improvements in a building, which we vacated during March 2005.

Valuation of Inventory

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 expense these costs when we deliver our drugs to partners, or as we use these drugs in 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 our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value of our inventory, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. Total inventory, which consisted solely of raw materials, was $749,000 and $951,000 as of March 31, 2006 and December 31, 2005, respectively.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs and analysis, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our consolidated financial statements.

Valuation Allowance for Net Deferred Tax Assets

We recorded a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future taxable income and record an appropriate reversal to the valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis division based on the segregation of revenue and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment.

Stock-Based Compensation

Prior to January 1, 2006, we adopted the disclosure-only provision of SFAS No. 123, *Accounting for Stock-Based Compensation*. Accordingly, we have not previously recognized compensation expense for our stock option plans and our ESPP, except for compensation expense primarily related to the variable accounting of options from the 2003 option exchange program.

Effective January 1, 2006, we adopted SFAS No. 123 (revised 2004), *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all share-based payment awards made to employees and directors including employee stock options and employee stock purchases related to our ESPP based on estimated fair values. We elected to use the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of our fiscal year 2006. Our Consolidated Statement of Operations as of and for the three months ended March 31, 2006 reflects the impact of SFAS 123(R). In accordance with the modified prospective transition method, our Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123(R). As of March 31, 2006, there was $8.8 million of total unrecognized compensation cost related to non-vested share-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.5 years.

We utilize the Black-Scholes model and assumptions discussed in Note 6 for estimating the fair value of the share-based awards we granted. Compensation expense for all share-based payment awards will continue to be recognized using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front loaded over the vesting period. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our

employee stock options and our ESPP. The dividend yield assumption is based on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123. The expected life of employee stock options represents the average of the life of the options and the average vesting period, and is a derived output of the simplified method, as allowed under SAB 107. We estimated forefeitures based on historical experience. For the periods prior to fiscal 2006, we accounted for forfeitures as they occurred in our pro forma information required under SFAS 123.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2006 was $5.0 million, compared to $7.4 million for the same period in 2005. Our revenue frequently fluctuates based on the timing of activities and achievements under contract. Our ability to maintain revenue at current levels will depend on new revenue sources and the expansion of existing revenue sources for the remainder of 2006.

The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended March 31,	
	2006	2005
Drug Discovery and Development:		
Research and development revenue	$ 1,270	$ 4,810
Licensing and royalty revenue	490	307
	$ 1,760	$ 5,117
Ibis Division:		
Research and development revenue	$ 3,198	$ 2,325
Licensing and royalty revenue	—	—
	$ 3,198	$ 2,325
Total revenue:		
Research and development revenue	$ 4,468	$ 7,135
Licensing and royalty revenue	490	307
	$ 4,958	$ 7,442

Drug Discovery and Development

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Research and development revenue under collaborative agreements for the three months ended March 31, 2006 was $1.3 million, compared to $4.8 million for the same period in 2005. The decrease was primarily related to a decrease in revenue associated with our collaboration with Lilly, which was extended in August 2005 to focus on a select number of targets. Our revenue from licensing activities and royalties for the three months ended March 31, 2006 was $490,000, compared to $307,000 for the same period in 2005.

Ibis Division

Our Ibis division generates research and development revenue from grants and contracts from United States government agencies, including DARPA, CDC, FBI, DHS, and NIAID, a part of the NIH. To date, Ibis has delivered its first three biosensor systems to its government partners for use in biowarfare defense, epidemiological surveillance and forensics. These deliveries represent Ibis' initial steps in commercializing its biosensor system and related applications-specific infectious organism ID kits. Our Ibis division generated revenue of $3.2 million for the quarter ended March 31, 2006 compared to revenue of $2.3 million for the same period in 2005. The increase in revenue primarily relates to an increase in the number and size of active government contracts that Ibis scientists were working on in the first quarter of 2006 compared to the same period in 2005. These new contracts contributed to an increase in the utilization of internal labor on government-funded contracts as opposed to internal research and development projects. Although Ibis' labor utilization has steadily increased over the past several quarters, Ibis' contribution margin decreased in the first quarter of 2006 compared to the previous two quarters. This decrease reflected a short-term shift of labor to lower margin contracts to support deployed Ibis biosensor systems. Isis expects contribution margins to return to 2005 levels in the second half of 2006.

We receive our DARPA funding through a subcontract with San Diego-based Science Applications International Corporation or SAIC. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This

collaboration accounted for approximately 29% and 11% of our total revenue in the first quarter of 2006 and 2005, respectively, which represents 44% and 34% of our first quarter 2006 and 2005 Ibis division revenue, respectively. During 2005, we entered into several new government contracts, expanding our reach to multiple government agencies. Our government-funded revenue may fluctuate, depending on the timing of when we enter into and commence work under various contracts with government agencies.

From inception through March 31, 2006, Ibis has earned $51.1 million in revenue from various government agencies to further the development of our Ibis biosensor system and application-specific infectious organism ID kits. An additional $5.6 million is committed under existing contracts and grants. We may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. In addition, these agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Operating Expenses

Total operating expenses for the three months ended March 31, 2006 were $21.0 million, compared to $30.9 million for the same period in 2005. We achieved a 32% decrease in our operating expenses in the first quarter of 2006 compared to the same period in 2005 principally through a reorganization in early 2005 that focused our resources on key programs. The cost savings we achieved through the reorganization led to a decrease in R&D and G&A expenses of $4.9 million, which excludes $1.4 million of non-cash compensation expense related to stock options. Also contributing to the decrease from the first quarter of 2005 to the same period in 2006 was a decrease in restructuring activities of $7.0 million.

Included in our operating results in the first quarter of 2006 is $1.4 million of non-cash compensation expense related to stock options as required by SFAS 123(R). Our operating expenses for the quarter ended March 31, 2005 included non-cash compensation benefit of $633,000 for the quarter ended March 31, 2005, as a result of variable accounting for stock options. 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 related to stock options and costs associated with restructuring activities. We believe the excluded items are not indicative of our operating results or cash flows from our operations. We internally evaluate the performance of our operations without the excluded items.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations, our Ibis division, and R&D support costs. The following table sets forth information on research and development costs (in thousands):

	Three Months Ended March 31,	
	2006	2005
Research and development expenses	$ 17,218	$ 22,361
Non-cash compensation expense related to stock options	1,154	—
Total research and development as reported	$ 18,372	$ 22,361

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

	Three Months Ended March 31,	
	2006	2005
Drug Discovery and Development	$ 15,092	$ 19,216
Ibis Division	3,280	3,145
Total research and development expenses	$ 18,372	$ 22,361

For the three months ended March 31, 2006, we incurred research and development expenses, excluding stock compensation, of $17.2 million, compared to $22.4 million for the same period in 2005. The $5.2 million decrease is attributed to cost savings achieved as a result of our restructuring activities, including significant reductions in personnel costs, as well as a reduction in third party clinical development costs attributed to our decision to focus our research and development resources on our most promising second-generation drugs and the resulting decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease.

Antisense Drug Discovery

Antisense drug discovery costs for the three months ended March 31, 2006 were $3.4 million, compared to $5.1 million for

the same period in 2005. The decrease of $1.7 million was principally the result of cost savings achieved as a result of our 2005 restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs. 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.

Antisense Drug Development

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

	Three Months Ended March 31,	
	2006	2005
Alicaforsen for Crohn's disease	$ 2	$ 246
Other antisense development products	4,454	5,811
Development overhead costs	1,128	1,620
Total antisense drug development	$ 5,584	$ 7,677

Antisense drug development expenditures were $5.6 million for the three months ended March 31, 2006, compared to $7.7 million for the same period in 2005. The decrease of $2.1 million was primarily due to cost savings achieved as a result of our decision to focus our research and development resources on our most promising second generation drugs, including ISIS 301012 and ISIS 113715, and the resulting decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for crohn's disease. In addition, the first quarter of 2005 included costs for toxicology studies of ISIS 113715, which we completed in the first quarter of 2005. Clinical trial costs for ISIS 113715 were essentially flat from the first quarter of 2005 to the same period in 2006. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. 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 really 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, nine of our 15 drug candidates, which substantially reduces our development costs.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense research and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements. These costs for the three months ended March 31, 2006 were $1.7 million and essentially flat as compared to $1.5 million in the same period in 2005.

Ibis Division

Our Ibis research and development expenses are primarily the result of our performance under our contracts with DARPA, CDC, FBI, DHS and NIAID, a part of the NIH, in support of our ongoing development of our Ibis biosensor system and application-specific infectious organism ID kits. We include in our Ibis division expenses all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title as well as costs required to advance towards commercialization. Research and development expenditures in our Ibis division include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of our Ibis biosensor program technology. In addition, we allocate a portion of R&D support costs and general and administrative costs to our Ibis division. Our Ibis division R&D expenses, excluding stock-based compensation expense, were essentially flat at $3.1 million for the three months

ended March 31, 2006 and 2005. Ibis has deployed its first three Ibis biosensor systems to its government partners for use in biowarfare defense, epidemiological surveillance and forensics, and plans to deploy additional systems to its government partners this year. We also plan to begin shipping application specific infectious organism ID kits in 2006. We expect our costs, including our selling, general and administrative costs, for our Ibis division to increase as we continue to expand this business.

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 March 31,	
	2006	2005
Personnel costs	$ 1,568	$ 1,502
Occupancy	1,527	2,076
Depreciation and amortization	1,244	1,293
Insurance	256	299
Other	498	431
Total R&D support costs	$ 5,093	$ 5,601

R&D support costs for the three months ended March 31, 2006 were $5.1 million, compared to $5.6 million for the same period in 2005. The decrease of $508,000 was primarily due to decreased personnel, facilities and equipment depreciation and patent amortization costs resulting from our restructuring activities, which included employee terminations, consolidation and closure of facilities, and the write-down of equipment and patent costs.

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

	Three Months Ended March 31,	
	2006	2005
Drug Discovery and Development	$ 4,411	$ 4,833
Ibis Division	682	768
Total R&D support costs	$ 5,093	$ 5,601

General and Administrative

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

	Three Months Ended March 31,	
	2006	2005
General and administrative expenses	$ 2,345	$ 2,137
Non-cash compensation expense related to stock options	221	—
Total general and administrative as reported	$ 2,566	$ 2,137

General and administrative expenses, excluding stock-based compensation expense, for the three months ended March 31, 2006 were $2.3 million and essentially flat compared to $2.1 million for the same period in 2005. As Ibis continues to execute its commercialization plan, we expect general and administrative expense for Ibis to increase.

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

	Three Months Ended March 31,	
	2006	2005
Drug Discovery and Development	$ 2,117	$ 1,845
Ibis Division	449	292
Total general and administrative expenses	$ 2,566	$ 2,137

Compensation Expense Related to the Variable Accounting of Stock Options

Compensation benefit related to the variable accounting of stock options for the three months ended March 31, 2005 was $633,000. Changes in compensation expense (benefit) were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with APB Opinion No. 25 and FIN 44.

Restructuring Activities

During the three months ended March 31, 2006 and 2005, we recorded charges of $36,000 and $7.1 million, respectively, for restructuring activities resulting from our decision to focus our resources on key programs. The 2005 charge for restructuring activities consists of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore.

Investment Income

Investment income for the three months ended March 31, 2006 totaled $811,000 compared to $504,000 for the same period in 2005. The increase in investment income for the first three months of 2006 over the same period in 2005 was primarily due to our higher average returns on our investments caused by higher interest rates for the first three months of 2006 compared to the first three months of 2005.

Interest Expense

Interest expense for the three months ended March 31, 2006 totaled $2.3 million, compared to $6.7 million for the same period in 2005. This decrease was due to the effect of a lower debt balance during 2006 than during 2005 primarily related to the conversion of our $100 million Lilly loan in the third quarter of 2005.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three months ended March 31, 2006 was $17.5 million, or $0.24 per share, compared with a net loss applicable to common stock of $29.7 million, or $0.52 per share, for the same period in 2005. In August 2005, we issued approximately 12 million shares of common stock in a private placement that raised net proceeds of $48 million. Also in August 2005, we issued 2.5 million shares to Lilly in connection with the conversion of our $100 million Lilly loan. These additional shares were the primary reason for the significant decrease in net loss per share from the first quarter of 2005 to the same period in 2006. The decrease in the net loss applicable to common stock was the result of a decrease in our loss from operations and a decrease in interest expense.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. 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 March 31, 2006, we have earned approximately $488.2 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $645.1 million from the sale of equity securities. We have borrowed approximately $386.7 million under long-term debt arrangements to finance a portion of our operations.

At March 31, 2006, we had cash, cash equivalents and short-term investments of $78.6 million, working capital of $69.9 million and a stockholders' deficit of $8.2 million. In comparison, we had cash, cash equivalents and short-term investments of $94.4 million, working capital of $82.1 million and a stockholders' equity of $2.7 million as of December 31, 2005. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations, pursue patents, and to pay our debt and capital lease obligations offset by cash received from contracts and cash received from stock option exercises.

As of March 31, 2006, our debt and other obligations totaled $145.8 million, compared to $147.8 million at December 31, 2005.

We will continue to use lease financing as long as the terms remain commercially attractive. Consistent with this, in July 2005, we entered into a $3.0 million equipment lease line with General Electric Capital Corporation. The lease line is effective for purchases through May 2006 and carries an interest rate of the three-year treasury rate plus 1.06% at the time of drawdown. This

lease line will be secured by any equipment purchased under the line. To date, we have not drawn any funds under this lease line.

Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. The following table summarizes our contractual obligations as of March 31, 2006. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided 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**
5 1/2% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ 125.0	$ —
Silicon Valley Bank Term Loan	18.6	6.3	12.3	—	—
Capital Lease and Other Obligations	2.2	1.5	0.7	—	—
Operating Leases	21.7	3.5	4.4	3.1	10.7

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a term loan from Silicon Valley Bank, capital leases and other obligations.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to Boehringer Ingelheim, and Elan Corporation. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 7.50% at March 31, 2006. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at March 31, 2006 was $18.6 million.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5.5%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At March 31, 2006, the principal outstanding on the notes was $125.0 million.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2006 for the purchase of services, equipment and materials as part of our normal course of business.

We plan to continue to enter into more collaborations with partners to provide for additional revenue and cash 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. In addition to the other information in this report on Form 10-Q, you should carefully consider the risks described below before purchasing our securities. 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.

Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of March 31, 2006, we had accumulated losses of approximately $788.3 million and stockholders' deficit of approximately $8.2 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 interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited

sales potential. 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.

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

All of our product candidates are undergoing clinical trials or are in the early stages of research and development. All of our products 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. Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. 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;
- success in developing and commercializing a business based on our Ibis biosensor system to identify infectious organisms; 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. In addition, if our stockholders do not approve an increase in our authorized capital stock, it may limit our ability to raise funds. 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, product candidates or products.

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, 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. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

We have entered into collaborative arrangements with third parties to develop many of our product candidates. We enter into these collaborations in order to:

- Fund our research and development activities;
- Access manufacturing by third parties;
- Seek and obtain regulatory approvals;
- Conduct clinical trials; and
- Successfully commercialize existing and future products.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. 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 outcome of both Phase 3 trials, Lilly discontinued its investment in Affinitak.

Other drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, Inc., OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-funded grants and contracts for our Ibis division and the

development of our Ibis biosensor system. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical companies or government partners stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

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 drug and, as a result, could delay or otherwise negatively affect the commercialization of our drug.

In addition, the disappointing results of the two Affinitak trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trial failures 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.

If we cannot protect our patents or our proprietary rights, others may compete more directly 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.

If a third party claims that our products or technology infringe their 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. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

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. 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. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2006, the market price of our common stock ranged from $2.76 to $9.34 per share. 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.

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

We are developing our Ibis biosensor system in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis biosensor system and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods and fires, 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% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% 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 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.

If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.

We have granted registration rights to Lilly and Symphony GenIsis Holdings LLC, which cover approximately 6.75 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities or are issuable upon the exercise of warrants we issued to Symphony GenIsis Holdings. We also registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of warrants, which we issued as part of our August 2005 private placement. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. The addition of these shares into the 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 Securities and Exchange Commission, the Public Company Accounting Oversight Board (PCAOB), or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drug candidates, 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 before a drug can be approved for sale. We must conduct these trials in compliance with United States Food and Drug Administration 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, 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. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product 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 will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

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

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease; the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings; the risk that a compound is not safe or effective for use in humans; and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. 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 non-small cell lung cancer 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 enough to support an NDA 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 trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

We have licensed the intellectual property, including commercialization rights, to our apoB-100, GCGR, and GCCR programs to Symphony GenIsis, Inc. and will not receive any future royalties or revenues with respect to the product in these programs, including ISIS 301012 and ISIS

325568 unless we exercise our option to acquire all of these product candidates in the future. We may not have the financial resources to exercise this option or sufficient clinical data in order to determine whether we should exercise this option.

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our apoB-100, GCGR, and GCCR Programs in exchange for Symphony GenIsis' investment of $75.0 million to advance the clinical development of these programs. In exchange for this investment and for five-year warrants to purchase shares of our common stock, we received an exclusive purchase option to acquire all of the equity of Symphony GenIsis, thereby allowing us to reacquire our apoB-100, GCGR and GCCR programs, which include ISIS 301012 and ISIS 325568. The purchase option exercise price reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. We may pay the option exercise price in cash or a combination of cash and our common stock, at our sole discretion, provided that the common stock portion may not exceed 33% of the purchase option exercise price.

If we elect to exercise the repurchase option, we will be required to make a substantial cash payment and/or issue a substantial number of shares of our common stock, or enter into a financing arrangement or license arrangement with one or more third parties, or some combination of the foregoing. A payment in cash would reduce our capital resources. A payment in shares of our common stock could result in dilution to our stockholders at that time. Other financing or licensing alternatives may be expensive or impossible to obtain. If we do not exercise the purchase options prior to their expiration, we will lose our rights in our apoB-100,

GCGR, and GCCR programs. We may not have the financial resources to exercise the repurchase option, which may result in our loss of these rights. Additionally, we may not have sufficient clinical data in order to determine whether we should exercise the options.

Disagreements between Symphony GenIsis and us regarding the development of our product candidates in our apoB-100, GCGR, and GCCR programs may cause significant delays and other impediments in the development of these product candidates, which could negatively affect the value of these product candidates.

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our product candidates in our apoB-100, GCGR, and GCCR programs in exchange for Symphony GenIsis' investment of $75.0 million to advance the clinical development of these programs. We are responsible for developing these product candidates in accordance with a specified development plan and related development budget. The Symphony GenIsis development committee supervises our development activities. The development committee is comprised of an equal number of representatives from Isis and Symphony GenIsis. If the development committee cannot resolve a particular development issue, the issue will be referred to the chief executive officers of Isis and Symphony GenIsis. Any disagreements between Symphony GenIsis and us regarding a development decision may cause significant delays in the development and commercialization of our product candidates within our apoB-100, GCGR, and GCCR programs.

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

Our success will depend upon the medical community, patients and third-party payers accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available drug product, Vitravene, a treatment for cytomegalovirus, or 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;
- 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 payers.

Based on the profile of our drugs, physicians, patients, patient advocates, payers 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 may be required to establish large-scale commercial manufacturing capabilities. 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 our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

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 or unique methods of identifying

infectious organisms. Our competitors may succeed in developing drugs or technologies

that are more effective than any drugs or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

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.

We depend on third parties in the conduct of our clinical trials for our product candidates 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 product candidates and expect to continue to do so in the future. 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 each of our clinical trials is conducted 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 could delay or prevent the development, approval and commercialization of our product candidates.

Risks Associated with our Ibis Division

We may not successfully develop or derive revenues from our business based on our Ibis biosensor system.

Our Ibis biosensor system is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our Ibis biosensor system due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our Ibis biosensor system business could fail to meet our business and financial objectives.

If we fail to secure commercial partners for our Ibis biosensor system, our commercialization efforts for our Ibis biosensor system may be harmed or delayed.

We expect to depend on third parties to commercialize our Ibis biosensor system, particularly in the areas of manufacturing, selling and servicing the instruments. In addition, we expect to depend on third parties to sell and distribute our infectious organism ID kits to non-government customers in the healthcare-associated infection control and infectious disease diagnostic markets. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for the Ibis biosensor system. We may not successfully establish a distribution, manufacturing, sale or service relationship or be able to make alternative arrangements. Moreover, these relationships may not succeed, may require us to give up a part of our ownership interest, or may diminish our profit margins on our Ibis instruments and ID kits.

We depend on government contracts for most of our revenues and the loss of government contracts or a decline in funding of existing or future government contracts could adversely affect our revenues and cash flows and our ability to fund our growth.

Virtually all of our Ibis business' revenue is from the sale of services and products to the United States government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, any of which could reduce our revenues and cash flows from U.S. government contracts. Our revenues and cash flow from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the three months ended March 31, 2006, Isis derived approximately 64% of its revenue from agencies of the United States government, including through our subcontract with SAIC. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our United States Government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons. If United States defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

We may be liable for penalties under a variety of procurement rules and regulations, and changes in government regulations could adversely impact our revenues, operating expenses and operating margins.

Under our agreements with the United States government, we must comply with and are affected by various government regulations that impact our operating costs, operating margins and our internal organization and operation of our businesses. These regulations affect how our customers and Isis do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of our Ibis business. With respect to U.S. government contracts, any failure to comply with applicable laws could result in contract termination, price or fee reductions or suspension or debarment from contracting with the U.S. government. Among the most significant regulations are the following:

- the U.S. Federal Acquisition Regulations, which comprehensively regulate the formation, administration and performance of government contracts;
- the U.S. Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with contract negotiations; and

- the U.S. Cost Accounting Standards, which impose accounting requirements that govern our right to reimbursement under certain cost-based government contracts.

If our Ibis biosensor system's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

Complex diagnostic instruments such as our Ibis biosensor system typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis biosensor system and its related applications we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

If we had to replace a supplier of one of the major hardware components of our Ibis biosensor system, it could delay our commercialization efforts and lengthen our sales cycle.

We have a single supplier for each major hardware component of our Ibis biosensor system. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle.

If our Ibis business fails to compete effectively, it may not succeed or contribute significant revenues.

Many of our competitors have, and in the future these and other competitors may have, significantly greater financial, marketing, sales, manufacturing, distribution and technological resources than us. Moreover, these companies may have substantially greater expertise in conducting clinical trials and research and development, greater ability to obtain necessary intellectual property licenses and greater brand recognition than we do. In addition, our competitors may be in a better position to respond quickly to new or emerging technologies, may be able to undertake more extensive marketing campaigns, may adopt more aggressive pricing policies and may be more successful in attracting potential customers, employees and strategic partners than we are.

The diagnostics industry is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. In order to achieve market acceptance of our Ibis biosensor system, we will be required to demonstrate that it provides accurate, cost-effective and/or time saving alternatives to tests performed by traditional laboratory procedures and products made by our competitors.

Improvements in preventing major diseases could reduce the need for our Ibis biosensor instruments and ID kits, which in turn could reduce our revenues.

We expect to derive a significant portion of our revenues from the sale of the infectious organism ID kits necessary to use our Ibis biosensor system. The need to quickly identify and contain major threats, such as the avian flu, could increase the demand for our infectious organism ID kits. Conversely, improvements in containing or treating a threat, such as vaccines, would significantly reduce the need to identify and contain the threat. Any reduction in the need to identify or contain a threat could diminish the need for our infectious organism ID kits, which could reduce our revenues.

If we cannot access or license rights to particular nucleic acid sequences for targeted diseases in the future, we may be limited in our ability to develop new products and access new markets.

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially reasonable terms, we may not be able to develop new diagnostic products or enter new markets.

The sales cycles for our Ibis biosensor systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis biosensor systems or services.

The sales cycles for Ibis biosensor systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

If we or our partners are required to obtain regulatory approval for our Ibis biosensor system applications, we may not successfully obtain approval.

Depending on their intended use, our Ibis biosensor systems may be regulated as a medical device by the FDA and comparable agencies of other countries and require either premarket approval (PMA) or 510(k) clearance from the FDA, prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of trials do not necessarily predict final results, and acceptable results in early trials may not be repeated in later trials. We or

our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review.

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.

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 March 31, 2006. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2006.

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

Ajinomoto Co., Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto, filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand relates to a February 17, 1994 license agreement between Ajinomoto and us, that purports to license certain intellectual property, including United States Patent No. 5,013,830, or the '830 patent, in exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleges that several products developed by us are covered by the '830 patent, and thus by the license. Ajinomoto seeks a determination of products covered by the license, along with an accounting of any sums due as a result. In October 2005, we filed our answering statement. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position. Ajinomoto and Isis agreed to a bifurcated arbitration process in which the arbitrator would first hear contract arguments and will then hear the patent arguments, if necessary, at a later date. The contract argument portion of the arbitration proceeding took place on February 22, 2006 resulting in an Arbitrator's Interim Award. This Interim award as anticipated is not determinative of all issues in dispute. As a result, Isis and Ajinomoto are proposing a mediation conference before proceeding with the second phase of the bifurcated arbitration process.

Isis estimates that the potential range of loss on this claim is zero to $2.1 million, and believes it is reasonably possible, not probable, that it will ultimately pay any amounts to Ajinomoto related to this claim. As such, Isis has not recorded a loss related to this claim as of March 31, 2006.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
3.1	Certificate of Amendment to Restated Certificate of Incorporation filed May 4, 2006.
3.2	Amended and Restated Certificate of Incorporation filed June 19, 1991(1)
10.2	Purchase Option Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).
10.3	Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted).
10.4	Novated and Restated Technology License Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).
10.5	Amended and Restated Research and Development Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).
10.6	Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC.
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.

(1) Filed as an exhibit to the Company's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.

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)	May 10, 2006
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 10, 2006

CERTIFICATE OF AMENDMENT TO THE RESTATED CERTIFICATE OF INCORPORATION

Isis Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: The name of the Corporation is Isis Pharmaceuticals, Inc. (the "Corporation").

SECOND: The date on which the Corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware is March 25, 1991.

THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on December 13, 2005 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

> The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 215,000,000 shares, consisting of 200,000,000 shares of Common Stock, each having a par value of $.001, and 15,000,000 shares of Preferred Stock, each having a par value of $.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

FOURTH: The foregoing amendment was submitted to the stockholders of the Corporation for their approval and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this 3rd day of May, 2006.

By: /s/ B. Lynne Parshall
B. Lynne Parshall
Executive Vice President

Exhibit 10.2

EXECUTION COPY

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

PURCHASE OPTION AGREEMENT

by and among

ISIS PHARMACEUTICALS, INC.,

SYMPHONY GENISIS HOLDINGS LLC

and

SYMPHONY GENISIS, INC.

Dated as of April 7, 2006

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PURCHASE OPTION AGREEMENT

This PURCHASE OPTION AGREEMENT (this "***Agreement***") is entered into as of April 7, 2006 (the "***Closing Date***") by and among ISIS PHARMACEUTICALS, INC., a Delaware corporation ("***Isis***"), SYMPHONY GENISIS HOLDINGS LLC, a Delaware limited liability company ("***Holdings***"), and SYMPHONY GENISIS, INC., a Delaware corporation ("***Symphony GenIsis***"). Capitalized terms used herein and not defined herein shall have the meanings assigned to such terms in Annex A attached hereto.

PRELIMINARY STATEMENT

WHEREAS, Isis and Holdings have entered into a Technology License Agreement pursuant to which Isis has granted Holdings an exclusive license (the "***License***") to the use of certain intellectual property related to the Programs owned or controlled by Isis;

WHEREAS, contemporaneously with the execution of this Agreement, Isis, Holdings and Symphony GenIsis are entering into a Novated and Restated Technology License Agreement, pursuant to which, among other things, Holdings will assign by way of novation the License to Symphony GenIsis;

WHEREAS, Isis and Holdings have entered into a Research and Development Agreement pursuant to which Isis has agreed, among other things, to perform, on behalf of Holdings, research and development of the Programs;

WHEREAS, contemporaneously with the execution of this Agreement, Isis, Holdings and Symphony GenIsis are entering into an Amended and Restated Research and Development Agreement, pursuant to which, among other things, Holdings will assign its rights and obligations under the Research and Development Agreement to Symphony GenIsis;

WHEREAS, contemporaneously with the execution of this Agreement, in order to fund such research and development, institutional investors are committing to invest $75,000,000 in Holdings (the "***Financing***") in exchange for membership interests in Holdings and for warrants (the "***Warrants***") to purchase up to a total of 4.25 million shares of Isis Common Stock, to be initially issued to Holdings, and Holdings will agree to contribute the net proceeds of the Financing to Symphony GenIsis;

WHEREAS, Holdings desires, in consideration for the Warrants, to grant Isis an option to purchase all of the Common Stock of Symphony GenIsis and any other Equity Securities issued by Symphony GenIsis (together, the "***Symphony GenIsis Equity Securities***") owned, or hereinafter acquired, by Holdings on the terms described in this Agreement; and

WHEREAS, Symphony GenIsis and Holdings have determined that it is in each of its best interest to perform and comply with certain agreements and covenants relating to each of its ongoing operations contained in this Agreement;

NOW, THEREFORE, in consideration of the foregoing and for other good and

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valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto (the "***Parties***") agree as follows:

Section 1. Grant of Purchase Option.

(a) Holdings hereby grants to Isis an exclusive option (the "***Purchase Option***") to purchase all, but not less than all, of the outstanding Symphony GenIsis Equity Securities owned or hereinafter acquired by Holdings, in accordance with the terms of this Agreement.

(b) Symphony GenIsis hereby covenants and agrees that all Symphony GenIsis Equity Securities issued by Symphony GenIsis at any time prior to the expiration of the Term (including to Holdings on, prior to, or after the date hereof or to any other Person at any time whatsoever, in all cases prior to the expiration of the Term) shall be subject to a purchase option on the same terms as the Purchase Option (except as provided by the immediately following sentence) and all of the other terms and conditions of this Agreement without any additional action on the part of Isis or Holdings. Further, to the extent Symphony GenIsis shall issue any Symphony GenIsis Equity Securities (including any issuance in respect of a transfer of Symphony GenIsis Equity Securities by any holder thereof, including Holdings) after the date hereof to any Person (including Holdings) (any issuance of such Symphony GenIsis Equity Securities being subject to the prior written consent of Isis as set forth in Sections 5(c) and 7(b) hereof, as applicable), Symphony GenIsis hereby covenants and agrees that it shall cause such Symphony GenIsis Equity Securities to be subject to the Purchase Option without the payment of, or any obligation to pay, any additional consideration in respect of such Symphony GenIsis Equity Securities by Isis, Symphony GenIsis or any Symphony GenIsis Subsidiary to the Person(s) acquiring such subsequently issued Symphony GenIsis Equity Securities, the Parties acknowledging and agreeing that the sole consideration payable by Isis pursuant to this Agreement for all of the outstanding Symphony GenIsis Equity Securities now or hereinafter owned by any Person shall be the Purchase Price.

(c) Isis' right to exercise the Purchase Option granted hereby is subject to the following conditions:

(i) The Purchase Option may only be exercised for the purchase of all, and not less than all, of Holdings' Symphony GenIsis Equity Securities;

(ii) The Purchase Option may only be exercised a single time;

(iii) Except as expressly provided in Sections 1(c)(iv) and (v), the Purchase Option may be exercised only during the period (the "***Purchase Option Period***") commencing on and including April 7, 2007 (the "***Purchase Option Commencement Date***") and ending on and including the earlier of (x) April 7, 2010 (the "***Final Termination Date***"), and (y) the 90th calendar day (such 90th calendar day, the "***Funds Termination Date***") immediately following the first date (each, a "***Balance Sheet Deficiency Date***") on which a notice of an impending Funds Termination Date (a "***Funds Termination Notice***") is delivered to Isis in accordance with Section 13 hereof, accompanied by an internally prepared, unaudited, balance sheet of Symphony GenIsis (prepared in accordance with GAAP) stating that the aggregate amount of cash and cash

equivalents held by Symphony GenIsis is less than [***] net of all accrued and unpaid amounts owing by Symphony GenIsis at such time;

(iv) In the event that Isis has agreed to share the costs of additional research pursuant to the Research Cost Sharing and Extension Agreement, the Purchase Option Period shall be determined in accordance with the Research Cost Sharing and Extension Agreement (for the avoidance of doubt, funds advanced by Isis pursuant to the Research Cost Sharing and Extension Agreement shall not be included in any calculation of the Purchase Price hereunder); and

(v) In the event that Holdings terminates the Amended and Restated Research and Development Agreement pursuant to Section 17.2 thereof, Isis shall have five (5) Business Days to notify Holdings of its exercise of the Purchase Option under the terms of this Agreement. Such exercise of the Purchase Option by Isis may occur prior to the Purchase Option Commencement Date (an "***Early Purchase Option Exercise***").

Section 2. Exercise of Purchase Option.

(a) Exercise Notice. Isis may exercise the Purchase Option only by delivery of a notice in the form attached hereto as Exhibit 1 (the "***Purchase Option Exercise Notice***") during the Purchase Option Period. The Purchase Option Exercise Notice shall be delivered on a Business Day to Holdings and Symphony GenIsis and shall be irrevocable once delivered. The date on which the Purchase Option Exercise Notice is first delivered to Holdings and Symphony GenIsis is referred to as the ***"Purchase Option Exercise Date."*** The Purchase Option Exercise Notice shall contain (1) an estimated date for the settlement of the Purchase Option (the "***Purchase Option Closing***"), which date shall be estimated in accordance with this Section 2(a), (2) the Purchase Price, determined in accordance with Section 2(b) hereof, and (3) if Isis intends to pay part of the Purchase Price in Isis Common Stock, notice of such intent, the number of shares to be transferred as such purchase price, the valuation thereof and the percentage such portion bears to (A) the Purchase Price, and (B) the total amount of Isis Common Stock then issued and outstanding (which shall be no greater percentages than are permitted under Section 2(c)). Such notice and election shall be irrevocable once given and made. If, during the period following the delivery of the Purchase Option Exercise Notice, the amount of cash and cash equivalents held by Symphony GenIsis is an amount less than or equal to [***], then Symphony GenIsis shall cease payment of any amounts owed to Isis in respect of its activities pursuant to the Amended and Restated Research and Development Agreement, but shall continue to pay amounts owed to all other Persons. The date of the Purchase Option Closing (the "***Purchase Option Closing Date***") shall be determined as follows:

(i) If Isis elects to pay the entire Purchase Price in cash, the Purchase Option Closing Date shall be the date that is the later of: (A) five (5) Business Days following the Purchase Option Exercise Date; and (B) five (5) Business Days following the date that Isis receives all necessary Government Approvals related to its HSR Filings; provided, however that unless Holdings receives from Isis an opinion from nationally recognized anti-trust counsel (which opinion is acceptable in form and substance to Holdings) to the effect that no HSR Filings are required, Isis and Holdings shall make all necessary HSR Filings within five (5) Business Days following the Purchase Option

Exercise Date and shall diligently pursue the related regulatory process; and provided, further that (1) if there is no second request from the Federal Trade Commission or the Department of Justice, as applicable, with respect to Isis' or Holdings' HSR Filings, then in no event shall the Purchase Option Closing Date be more than sixty (60) days following the Purchase Option Exercise Date, and (2) if there is a second request from the Federal Trade Commission or the Department of Justice, as applicable, with respect to Isis' or Holdings' HSR Filings, then in no event shall the Purchase Option Closing Date be more than one hundred and twenty (120) days following the Purchase Option Exercise Date. If Isis shall fail to make such cash payment within such sixty (60) day period or one hundred and twenty (120) day period, as applicable, then in addition to any other rights that Holdings shall have hereunder, this Agreement shall terminate and Isis shall relinquish all rights hereunder to purchase the Symphony GenIsis Equity Securities; or

(ii) If Isis elects to pay a portion of the Purchase Price in Isis Common Stock (subject to the limitations set forth herein and in the Registration Rights Agreement), the Purchase Option Closing Date shall be the date that is the later of:

(A) five (5) Business Days following the Effective Registration Date of such Isis Common Stock; provided, that Isis shall file the Registration Statement contemplated by Section 3(b)(i) within (x) [***] Business Days after the Purchase Option Exercise Date if Isis is eligible to use Form S-3 under the Securities Act (or any successor form), or (y) [***] Business Days after the Purchase Option Exercise Date if Isis is not eligible to use Form S-3 under the Securities Act (or any successor form); and

(B) five (5) Business Days following the date that Isis receives the necessary Government Approvals related to its HSR Filings (if any); provided, however, that Isis and Holdings shall make all necessary HSR Filings within five (5) Business Days following the Purchase Option Exercise Date and shall diligently pursue the related regulatory process;

provided, further, that Isis shall use commercially reasonable efforts to have such Registration Statement declared effective by the United States Securities and Exchange Commission as promptly as possible. In the event that such Registration Statement is not declared effective within [***] days of the Purchase Option Exercise Date, Isis shall pay the full Purchase Price in cash within two (2) Business Days thereafter (in which event the Purchase Option Closing Date shall be the date upon which such cash payment is made by Isis). If Isis shall fail to make such cash payment within such two (2) Business Day period, then in addition to any other rights or remedies that Holdings shall have arising from such breach, this Agreement shall terminate and Isis shall relinquish all rights hereunder to purchase the Symphony GenIsis Equity Securities.

(b) Purchase Price Upon Option Exercise. Upon exercise of the Purchase Option and as complete and full consideration for the sale to Isis by Holdings of its Symphony GenIsis Equity Securities (and for the Symphony GenIsis Equity Securities of any other Person), Isis shall pay to Holdings (i) the "Quarterly Price" set forth on Schedule I hereto for the applicable quarter following the Closing Date in which the Purchase Option Closing Date actually occurs,

minus (ii) the aggregate amount of all Discontinuation Prices and other amounts paid directly to Holdings or to Symphony GenIsis pursuant to Section 11.1 of the Amended and Restated Research and Development Agreement and subsequently dividended or otherwise distributed to Holdings (if any) (the "***Purchase Price***"). In the event of the Early Purchase Option Exercise, pursuant to Section 1(c)(v) hereof, the "Purchase Price" shall be an amount equal to (x) the amount set forth on Schedule I applicable to the Quarterly Price for the 5th Quarter, *minus* (y) the aggregate amount of all Discontinuation Prices and other amounts paid directly to Holdings or to Symphony GenIsis pursuant to Section 11.1 of the Amended and Restated Research and Development Agreement and subsequently dividended or otherwise distributed to Holdings (if any).

(c) Form of Payment. Subject to Sections 2(a) and 2(e), the Purchase Price may be paid in cash or in a combination of cash and Isis Common Stock, at the sole discretion of Isis; provided, that in no event may the value of Isis Common Stock (determined in accordance with Section 2(e) hereof) delivered in connection with the exercise of the Purchase Option constitute more than either (x) 33% of the total consideration to be tendered for payment of the Purchase Option Exercise Price, calculated using the Isis Common Stock Valuation (as defined herein) procedure, or (y) 10% of all the Isis Common Stock then issued and outstanding.

(d) Surrender of Symphony GenIsis Equity Securities. Subject to the terms and conditions of this Agreement, on or prior to the Purchase Option Closing Date, Holdings shall surrender to Isis its certificates representing its Symphony GenIsis Equity Securities, and shall convey good title to such Symphony GenIsis Equity Securities, free from any Encumbrances and from any and all restrictions that any sale, assignment or other transfer of such Symphony GenIsis Equity Securities be consented to or approved by any Person. On or prior to the Purchase Option Closing Date, Holdings shall remove all directors serving on the Symphony GenIsis Board, other than the Isis Director (as defined in Section 4(b)(iv) hereof) from the Symphony GenIsis Board as of the Purchase Option Closing Date. Furthermore, Holdings shall use commercially reasonable efforts to deliver to Isis, promptly after the Purchase Option Closing Date, any certificates representing Symphony GenIsis Equity Securities which were not surrendered to Isis on the Purchase Option Closing Date.

(e) Valuation of Isis Stock. In the event that Isis elects to pay part of the Purchase Price through the delivery to Holdings of Isis Common Stock, the value per share thereof (the "***Isis Common Stock Valuation***") shall equal the average closing price of Isis Common Stock, as reported by the NASDAQ National Market, or other national exchange that is the primary exchange on which Isis Common Stock is listed, for the sixty (60) trading days immediately preceding (but not including) the second trading day prior to the Purchase Option Exercise Date. If Isis Common Stock is not traded on a national exchange or the NASDAQ National Market, then Isis shall be obligated to pay the Purchase Price solely in cash on the Purchase Option Closing Date. Isis shall calculate the Isis Common Stock Valuation in accordance with this Section 2(e), subject to review and confirmation by Holdings.

(f) Government Approvals. On or prior to the Purchase Option Closing Date, each of Isis, Symphony GenIsis and Holdings shall have taken all necessary action to cause all Governmental Approvals with respect to such Party (including, without limitation, the preparing and filing of any pre-merger notification and report forms required under the Hart-Scott-Rodino

Antitrust Improvements Act of 1976, as amended ("***HSR Filings***")) required to be in effect in connection with the transactions contemplated by this Agreement to be in effect; provided, however, that with respect to Government Approvals required by a Governmental Authority other than the United States federal government and its various branches and agencies, the Parties' obligations under this Section 2(f) shall be limited to causing to be in effect only those Government Approvals, the failure of which to be in effect would, either individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on any of the Parties. Each of Symphony GenIsis and Isis shall pay its own costs associated with taking such action. Symphony GenIsis shall pay any costs of Holdings associated with obtaining Government Approvals required in connection with the exercise of the Purchase Option. All other costs and expenses of Holdings shall be paid by Holdings pursuant to Section 8(b) hereof, including any costs arising from any error in Holdings' initial valuation of its investment in Symphony GenIsis.

(g) Transfer of Title. Transfer of title to Isis of all of the Symphony GenIsis Equity Securities shall be deemed to occur automatically on the Purchase Option Closing Date, subject to the payment by Isis on such date of the Purchase Price and its performance of its other obligations herein required to be performed under Sections 2(e) and (f), and under the Registration Rights Agreement, as applicable, on or prior to the Purchase Option Closing Date to the reasonable satisfaction of Holdings, and thereafter Symphony GenIsis shall treat Isis as the sole holder of all Symphony GenIsis Equity Securities, notwithstanding the failure of Holdings to tender certificates representing such shares to Isis in accordance with Section 2(d) hereof. After the Purchase Option Closing Date, Holdings shall have no rights in connection with such Symphony GenIsis Equity Securities other than the right to receive the Purchase Price; provided, however, that nothing in this Section 2(g) shall affect the survivability of any indemnification provision in this Agreement upon termination of this Agreement.

(h) Consents and Authorizations. On or prior to the Purchase Option Closing Date, Isis shall have obtained all consents and authorizations necessary from stockholders and/or its board of directors for the consummation of the exercise and closing of the Purchase Option, as may be required under the organizational documents of Isis, any prior stockholders or board resolution, any stock exchange or similar rules or any applicable law; provided, however, that with respect to consents or authorizations required by a Governmental Authority other than the United States federal government and its various

branches and agencies, the Parties' obligations under this Section 2(h) shall be limited to obtaining only those consents and authorizations, the failure of which to be obtained would, either individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on any of the Parties.

Section 2A. Put Option.

(a) Holdings has an exclusive put option (the "***Put Option***") for 100% of the Symphony GenIsis Equity Securities which may be exercised if, following a Change of Control with respect to Isis, the successor entity breaches a material term of any Operative Document and such breach continues unremedied for a period of thirty (30) days after Holdings has delivered written notice thereof to such successor entity.

(b) Holdings may exercise the Put Option only by delivery of written notice (the "***Put Option Exercise Notice***") during the Purchase Option Period. The Put Option Exercise

Notice shall be delivered on a Business Day to the successor entity to Isis and Symphony GenIsis, and shall thereafter be deemed for all purposes under the terms of this Agreement to be a Purchase Option Exercise Notice by Isis (in accordance with the provisions of Section 2 hereof) as of the date such notice is delivered (such date to be deemed for all purposes under the terms of this Agreement as the Purchase Option Exercise Date). The Purchase Price with respect to such an exercise of the Put Option shall be the Purchase Price otherwise applicable (under Section 2(b) hereof) to the Purchase Option Closing Date selected by Isis following Isis' receipt of the Put Option Exercise Notice.

Section 3. Isis Representations, Warranties and Covenants.

(a) As of the date hereof, Isis hereby represents and warrants, and, except to the extent that any of the following representations and warranties is limited to the date of this Agreement or otherwise limited, on the Purchase Option Closing Date, shall be deemed to have represented and warranted, to Holdings and Symphony GenIsis that:

(i) Organization. Isis is a corporation, duly organized, validly existing and in good standing under the laws of the State of Delaware.

(ii) Authority and Validity. Isis has all requisite corporate power and authority to execute, deliver and perform its obligations under this Agreement and to consummate the transactions contemplated hereby. The execution, delivery and performance by Isis of this Agreement and the consummation of the transactions contemplated hereby have been duly and validly authorized by all necessary action required on the part of Isis, and no other proceedings on the part of Isis are necessary to authorize this Agreement or for Isis to perform its obligations under this Agreement. This Agreement constitutes the lawful, valid and legally binding obligation of Isis, enforceable in accordance with its terms, except as the same may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the enforcement of creditors' rights generally and general equitable principles regardless of whether such enforceability is considered in a proceeding at law or in equity.

(iii) No Violation or Conflict. The execution, delivery and performance of this Agreement and the transactions contemplated hereby do not (A) violate, conflict with or result in the breach of any provision of the Organizational Documents of Isis, (B) as of the date of this Agreement, and as of the Purchase Option Closing Date if Isis elects to pay part of the Purchase Price through the delivery of Isis Common Stock (a "***Partial Stock Payment***"), conflict with or violate any law or Governmental Order applicable to Isis or any of its assets, properties or businesses, or (C) conflict with, result in any breach of, constitute a default (or event that with the giving of notice or lapse of time, or both, would become a default) under, require any consent under, or give to others any rights of termination, amendment, acceleration, suspension, revocation or cancellation of, or result in the creation of any Encumbrance on any of the assets or properties of Isis, pursuant to, any note, bond, mortgage or indenture, contract, agreement, lease, sublease, license, permit, franchise or other instrument or arrangement to which Isis is a party except, in the case of clauses (B) and (C), to the extent that such conflicts, breaches, defaults or other

matters would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis.

(iv) Governmental Consents and Approvals. Other than any HSR Filings which, if the Purchase Option is exercised by Isis and if such HSR Filings are required pursuant to Section 2(a)(i) hereof, will be obtained on or prior to the Purchase Option Closing Date, the execution, delivery and performance of this Agreement by Isis do not, and the consummation of the transactions contemplated hereby do not and will not, require any Governmental Approval which has not already been obtained, effected or provided, except with respect to which the failure to so obtain, effect or provide would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis.

(v) Litigation. As of (A) the date of this Agreement, except as disclosed on the Isis 2005 10-K, and (B) the Purchase Option Closing Date if Isis elects to make a Partial Stock Payment, there are no actions by or against Isis pending before any Governmental Authority or, to the knowledge of Isis, threatened to be brought by or before any Governmental Authority, that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis. There are no pending or, to the knowledge of Isis, threatened actions, to which Isis is a party (or is threatened to be named as a party) to set aside, restrain, enjoin or prevent the execution, delivery or performance of this Agreement or the Operative Documents or the consummation of the transactions contemplated hereby or thereby by any party hereto or thereto. As of the date of this Agreement, and as of the Purchase Option Closing Date if Isis elects to make a Partial Stock Payment, Isis is not subject to any Governmental Order (nor, to the knowledge of Isis, is there any such Governmental Order threatened to be imposed by any Governmental Authority) that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis.

(b) Isis hereby covenants and agrees with Holdings as follows:

(i) Immediately prior to the Purchase Option Closing Date, Isis shall have sufficient amounts of cash and/or firm commitments for such cash from third parties with the wherewithal to pay, and which third parties are reasonably acceptable to Holdings and, if applicable, sufficient authorized but unissued, freely transferable and nonassessable Isis Common Stock available to satisfy the portion of the Purchase Price to be paid in cash or Isis Common Stock pursuant to Sections 2(b) and 2(c). In the event that Isis elects to satisfy any portion of the Purchase Price in Isis

Common Stock (A) Isis shall have not later than the Purchase Option Closing Date, a Registration Statement declared effective by the Securities and Exchange Commission for the resale of any such shares of Isis Common Stock to be delivered in partial satisfaction of the Purchase Price, accompanied by evidence reasonably acceptable to Holdings that such Isis Common Stock has been approved for listing on the NASDAQ national market or such other national market on which the Isis Common Stock is then listed, and (B) Isis shall deliver to Holdings on or before the Purchase Option Closing Date, a legal opinion from Isis' General Counsel, or such other counsel as Isis and Holdings shall mutually agree, which opinion shall be, in form and substance, reasonably acceptable to Holdings and shall

contain, with respect to the Isis Common Stock to be used as partial payment of the Purchase Price, substantially the same opinions rendered by Isis' General Counsel in paragraphs 4, 5 and 8 of the opinion delivered to Holdings on the Closing Date, along with customary assumptions and limitations.

(ii) If Isis elects to satisfy any portion of the Purchase Price in Isis Common Stock, Isis shall convey good and marketable title to such Isis Common Stock, free from any Encumbrances and any and all other restrictions that any issuance, sale, assignment or other transfer of such Isis Common Stock be consented to or approved by any Person.

(iii) Upon the expiration of the Purchase Option or the termination of this Agreement pursuant to Section 9 hereof, or as soon thereafter as is practical, Isis shall (A) in accordance with and pursuant to Sections 2.7 and 2.8 of the Novated and Restated Technology License Agreement, deliver to Symphony GenIsis all Regulatory Files and Tangible Materials, and (B) in accordance with and pursuant to Section 2.11 of the Novated and Restated Technology License Agreement, negotiate in good faith, and on commercially reasonable terms and conditions, a supply agreement relating to materials, including compounds and Products, required by Symphony GenIsis or its partners or transferees for the continued development (including clinical development), manufacture and commercialization of Products.

(iv) In the event that Isis exercises the Purchase Option, then Isis shall maintain the separate corporate existence of Symphony GenIsis for a minimum of two (2) years following such exercise, unless such maintenance would have a Material Adverse Effect on Isis or any of its Affiliates.

Section 4. Holdings Representations, Warranties and Covenants.

(a) As of the date hereof, Holdings hereby represents and warrants, and, except to the extent that any of the following representations and warranties is limited to the date of this Agreement or otherwise limited, on the Purchase Option Closing Date, shall be deemed to have represented and warranted, to Isis and Symphony GenIsis that:

(i) Organization. Holdings is a limited liability company, duly formed, validly existing and in good standing under the laws of the State of Delaware.

(ii) Authority and Validity. Holdings has all requisite limited liability company power and authority to execute, deliver and perform its obligations under this Agreement and to consummate the transactions contemplated hereby. The execution, delivery and performance by Holdings of this Agreement and the consummation of the transactions contemplated hereby have been duly and validly authorized by all necessary action required on the part of Holdings, and no other proceedings on the part of Holdings are necessary to authorize this Agreement or for Holdings to perform its obligations under this Agreement. This Agreement constitutes the lawful, valid and legally binding obligation of Holdings, enforceable in accordance with its terms, except as the same may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the enforcement of creditors' rights generally and general equitable

principles regardless of whether such enforceability is considered in a proceeding at law or in equity.

(iii) No Violation or Conflict. The execution, delivery and performance of this Agreement and the transactions contemplated hereby do not (A) violate, conflict with or result in the breach of any provision of the Organizational Documents of Holdings, (B) as of the date of this Agreement, conflict with or violate any law or Governmental Order applicable to Holdings or any of its assets, properties or businesses, or (C) as of the date of this Agreement, conflict with, result in any breach of, constitute a default (or event that with the giving of notice or lapse of time, or both, would become a default) under, require any consent under, or give to others any rights of termination, amendment, acceleration, suspension, revocation or cancellation of, or result in the creation of any Encumbrance on any of the assets or properties of Holdings, pursuant to, any note, bond, mortgage or indenture, contract, agreement, lease, sublease, license, permit, franchise or other instrument or arrangement to which Holdings is a party except, in the case of clauses (B) and (C), to the extent that such conflicts, breaches, defaults or other matters would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Holdings.

(iv) Governmental Consents and Approvals. The execution, delivery and performance of this Agreement by Holdings do not, and the consummation of the transactions contemplated hereby do not and will not, require any Governmental Approval which has not already been obtained, effected or provided, except with respect to which the failure to so obtain, effect or provide would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Holdings.

(v) Litigation. As of the date of this Agreement, there are no actions by or against Holdings pending before any Governmental Authority or, to the knowledge of Holdings, threatened to be brought by or before any Governmental Authority, that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Holdings. There are no pending or, to the knowledge of Holdings, threatened actions to which Holdings is a party (or is threatened to be named as a party) to set aside, restrain, enjoin or prevent the execution, delivery or performance of this Agreement or the Operative Documents or the consummation of the transactions contemplated hereby or thereby by any party hereto or thereto. As of the date of this Agreement, Holdings is not subject to any Governmental Order (nor, to the knowledge of Holdings, is there any such Governmental Order threatened to be imposed by any Governmental Authority) that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Holdings.

(vi) Stock Ownership. All of Symphony GenIsis' issued and outstanding Symphony GenIsis Equity Securities are owned beneficially and of record by Holdings, free and clear of any and all encumbrances.

(vii) Interim Operations. Holdings was formed solely for the purpose of engaging in the transactions contemplated by the Operative Documents, has engaged in

no other business activities and has conducted its operations only as contemplated by the Operative Documents.

(viii) Accredited Investor.

(A) Holdings is and will remain at all relevant times an Accredited Investor.

(B) Holdings has relied completely on the advice of, or has consulted with or has had the opportunity to consult with, its own personal tax, investment, legal or other advisors and has not relied on Isis or any of its Affiliates for advice related to any offer and sale of Isis Common Stock in connection with the Purchase Option. Holdings has reviewed the Investment Overview and is aware of the risks disclosed therein. Holdings acknowledges that it has had a reasonable opportunity to conduct its own due diligence with respect to the Products, the Programs, Symphony GenIsis, Isis and the transactions contemplated by the Operative Documents.

(C) Holdings is able to bear the economic risk of such investment for an indefinite period and to afford a complete loss thereof

(D) Holdings agrees that the Isis Common Stock may not be resold (A) without registration thereof under the Securities Act (unless an exemption from such registration is available), or (B) in violation of any law.

(E) No person or entity acting on behalf of, or under the authority of, Holdings is or will be entitled to any broker's, finder's, or similar fees or commission payable by Isis or any of its Affiliates.

(b) Holdings hereby covenants and agrees with Isis as follows:

(i) Contribution to Symphony GenIsis. On or prior to the Stock Payment Date, Holdings shall, pursuant to the Subscription Agreement, contribute proceeds from the Financing of $75,000,000 to Symphony GenIsis, Inc.

(ii) Encumbrance. Holdings will not, and will not permit any of its Subsidiaries to, create, assume or suffer to exist any Encumbrance on any of its Symphony GenIsis Equity Securities except with the prior written consent of Isis.

(iii) Transfer and Amendment. Commencing upon the date hereof and ending upon the earlier to occur of (x) the Purchase Option Closing Date, (y) the unexercised expiration of the Purchase Option Period, and (z) the termination of this Agreement pursuant to Section 9 (such period, the "***Term***"), the manager of Holdings shall not (A) transfer, or permit the transfer of, any Membership Interest without the prior written consent of Isis or (B) amend, or permit the amendment of, any provisions relating to the transfer of Membership Interests, as set forth in Section 7.02 of the Holdings LLC Agreement, to the extent such amendment would adversely affect Isis' right of consent set forth in Sections 7.02(b)(i) and 7.02(c) of the Holdings LLC Agreement.

(iv) Symphony GenIsis Directors. During the Term, Holdings agrees to vote all of its Symphony GenIsis Equity Securities (or to exercise its right with respect to such Symphony GenIsis Equity Securities to consent to action in writing without a meeting) in favor of, as applicable, the election, removal and replacement of one director of the Symphony GenIsis Board, and any successor thereto, designated by Isis (the "***Isis Director***") as directed by Isis. In furtherance and not in limitation of the foregoing, Holdings hereby grants to Isis an irrevocable proxy, with respect to all Symphony GenIsis Equity Securities now owned or hereafter acquired by Holdings, to vote such Symphony GenIsis Equity Securities or to exercise the right to consent to action in writing without a meeting with respect to such Symphony GenIsis Equity Securities, such irrevocable proxy to be exercised solely for the limited purpose of electing, removing and replacing the Isis Director in the event of the failure or refusal of Holdings to elect, remove or replace such Isis Director, as directed by Isis. Additionally, Holdings agrees, during the Term, to elect [***] independent directors (of the [***] directors of Symphony GenIsis not chosen by Holdings at the direction of Isis), and any successors thereto, as shall be selected by mutual agreement of Isis and Holdings.

(v) Symphony GenIsis Board. During the Term, Holdings shall not vote any of its Symphony GenIsis Equity Securities (or exercise its rights with respect to such Symphony GenIsis Equity Securities by written consent without a meeting) to increase the size of the Symphony GenIsis Board to more than five (5) members without the prior written consent of Isis.

(vi) Symphony GenIsis Charter. During the Term, Holdings shall not approve or permit any amendment to Article IV, Paragraphs (1) and (3); Article VI; Article VII; Article X; Article XI or Article XIII of the Symphony GenIsis Charter without the prior written consent of Isis.

Section 5. Symphony GenIsis Representations, Warranties and Covenants.

(a) As of the date hereof, Symphony GenIsis hereby represents and warrants, and, except to the extent that any of the following representations and warranties is limited to the date of this Agreement or otherwise limited, on the Purchase Option Closing Date, shall be deemed to have represented and warranted, to Isis and Holdings that:

(i) Organization. Symphony GenIsis is a corporation, duly organized, validly existing and in good standing under the laws of the State of Delaware.

(ii) Authority and Validity. Symphony GenIsis has all requisite corporate power and authority to execute, deliver and perform its obligations under this Agreement and to consummate the transactions contemplated hereby. The execution, delivery and performance by Symphony GenIsis of this Agreement and the consummation of the transactions contemplated hereby have been duly and validly authorized by all necessary action required on the part of Symphony GenIsis, and no other proceedings on the part of Symphony GenIsis are necessary to authorize this Agreement or for Symphony GenIsis to perform its obligations under this Agreement. This Agreement constitutes the lawful, valid and legally binding obligation of Symphony GenIsis, enforceable in accordance

with its terms, except as the same may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the enforcement of creditors' rights generally and general equitable principles regardless of whether such enforceability is considered in a proceeding at law or in equity.

(iii) No Violation or Conflict. The execution, delivery and performance of this Agreement and the transactions contemplated hereby do not (A) violate, conflict with or result in the breach of any provision of the Organizational Documents of Symphony GenIsis, (B) conflict with or violate any law or Governmental Order applicable to Symphony GenIsis or any of its assets, properties or businesses, or (C) conflict with, result in any breach of, constitute a default (or event that with the giving of notice or lapse of time, or both, would become a default) under, require any consent under, or give to others any rights of termination, amendment, acceleration, suspension, revocation or cancellation of, or result in the creation of any Encumbrance on any of the assets or properties of Symphony GenIsis, pursuant to, any note, bond, mortgage or indenture, contract, agreement, lease, sublease, license, permit, franchise or other instrument or arrangement to which Symphony GenIsis is a party except, in the case of clauses (B) and (C), to the extent that such conflicts, breaches, defaults or other matters would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(iv) Governmental Consents and Approvals. The execution, delivery and performance of this Agreement by Symphony GenIsis do not, and the consummation of the transactions contemplated hereby do not and will not, require any Governmental Approval which has not already been obtained, effected or provided, except with respect to which the failure to so obtain, effect or provide would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(v) Litigation. There are no actions by or against Symphony GenIsis pending before any Governmental Authority or, to the knowledge of Symphony GenIsis, threatened to be brought by or before any Governmental Authority that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis. There are no pending or, to the knowledge of Symphony GenIsis, threatened actions to which Symphony GenIsis is a party (or is threatened to be named as a party) to set aside, restrain, enjoin or prevent the execution, delivery or performance of this Agreement or the Operative Documents or the consummation of the transactions contemplated hereby or thereby by any party hereto or thereto. Symphony GenIsis is not subject to any Governmental Order (nor, to the knowledge of Symphony GenIsis, is there any such Governmental Order threatened to be imposed by any Governmental Authority) that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(vi) Capitalization. Holdings is the beneficial and record owner of all issued and outstanding Symphony GenIsis Equity Securities. No shares of Symphony GenIsis capital stock are held in treasury by Symphony GenIsis or any Symphony GenIsis Subsidiary. All of the issued and outstanding Symphony GenIsis Equity Securities (A)

have been duly authorized and validly issued and are fully paid and nonassessable, (B) were issued in compliance with all applicable state and federal securities laws, and (C) were not issued in violation of any preemptive rights or rights of first refusal. No preemptive rights or rights of first refusal exist with respect to any Symphony GenIsis Equity Securities and no such rights will arise by virtue of or in connection with the transactions contemplated hereby (other than for the Purchase Option). Other than the Purchase Option, there are no outstanding options, warrants, call rights, commitments or agreements of any character to acquire any Symphony GenIsis Equity Securities. There are no outstanding stock appreciation, phantom stock, profit participation or other similar rights with respect to Symphony GenIsis. Symphony GenIsis is not obligated to redeem or otherwise acquire any of its outstanding Symphony GenIsis Equity Securities.

(vii) Interim Operations. Symphony GenIsis was formed solely for the purpose of engaging in the transactions contemplated by the Operative Documents, has engaged in no other business activities and has conducted its operations only as contemplated by the Operative Documents.

(viii) Investment Company. Symphony GenIsis is not, and after giving effect to the transactions contemplated by the Operative Documents will not be, required to register as an "investment company" as such term is defined in the Investment Company Act of 1940, as amended.

(b) Symphony GenIsis covenants and agrees that:

(i) Symphony GenIsis will comply with all laws, ordinances or governmental rules or regulations to which it is subject and will obtain and maintain in effect all licenses, certificates, permits, franchises and other Governmental Approvals necessary to the ownership of its properties or to the conduct of its business, in each case to the extent necessary to ensure that non-compliance with such laws, ordinances or governmental rules or regulations or failures to obtain or maintain in effect such licenses, certificates, permits, franchises and other Governmental Approvals would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(ii) Symphony GenIsis will file (or cause to be filed) all material tax returns required to be filed by it and pay all taxes shown to be due and payable on such returns and all other taxes imposed on it or its assets to the extent such taxes have become due and payable and before they

have become delinquent and shall pay all claims for which sums have become due and payable that have or might become attached to the assets of Symphony GenIsis; provided, that Symphony GenIsis need not file any such tax returns or pay any such tax or claims if (A) the amount, applicability or validity thereof is contested by Symphony GenIsis on a timely basis in good faith and in appropriate proceedings, and Symphony GenIsis has established adequate reserves therefor in accordance with GAAP on the books of Symphony GenIsis or (B) the failure to file such tax returns or the nonpayment of such taxes and assessments, individually or in the aggregate, could not reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(iii) Symphony GenIsis will at all times preserve and keep in full force and effect its corporate existence.

(iv) Symphony GenIsis will keep complete, proper and separate books of record and account, including a record of all costs and expenses incurred, all charges made, all credits made and received, and all income derived in connection with the operation of the business of Symphony GenIsis, all in accordance with GAAP (which GAAP shall be conformed to those used by Isis to the extent practicable), in each case to the extent necessary to enable Symphony GenIsis to comply with the periodic reporting requirements of this Agreement, and will promptly notify Isis if it adopts or changes any accounting principle pursuant to a change in GAAP or applicable Law.

(v) Symphony GenIsis will perform and observe in all material respects all of the terms and provisions of each Operative Document to be performed or observed by it, maintain each such Operative Document to which it is a party, promptly enforce in all material respects each such Operative Document in accordance with its terms, take all such action to such end as may be from time to time reasonably requested by Holdings or Isis and make to each other party to each such Operative Document such demands and requests for information and reports or for action as Symphony GenIsis is entitled to make under such Operative Document.

(vi) Symphony GenIsis shall permit the representatives of Holdings (including Holdings' members and their respective representatives), each Symphony Fund and Isis, at each of their own expense and upon reasonable prior notice to Symphony GenIsis, to visit the principal executive office of Symphony GenIsis, to discuss the affairs, finances and accounts of Symphony GenIsis with Symphony GenIsis' officers and (with the consent of Symphony GenIsis, which consent will not be unreasonably withheld) its Auditors, all at such reasonable times and as often as may be reasonably requested in writing.

(vii) Symphony GenIsis shall permit each Symphony Fund, at its own expense and upon reasonable prior notice to Symphony GenIsis, to inspect and copy Symphony GenIsis' books and records and inspect Symphony GenIsis' properties at reasonable times.

(viii) Symphony GenIsis shall allow Isis or its designated representatives to have reasonable visitation and inspection rights with regard to the Programs and materials, documents and other information relating thereto.

(ix) Symphony GenIsis shall permit each Symphony Fund to consult with and advise the management of Symphony GenIsis on matters relating to the research and development of the Programs in order to develop the Product.

(x) On the Purchase Option Closing Date, or as soon thereafter as is practical, Symphony GenIsis shall deliver to Isis all materials, documents, files and other information relating to the Programs (or, where necessary, copies thereof).

(xi) During the Term, Isis shall have the right to consent to any increase in the size of the Symphony GenIsis Board to more than five (5) directors.

(xii) During the Term, Isis shall have the right to designate, remove and replace [***] director of the Symphony GenIsis Board, including any successor thereto.

(xiii) Symphony GenIsis shall indemnify the directors and officers of Symphony GenIsis against liability incurred by reason of the fact that such Person is or was a director or officer of Symphony GenIsis, as permitted by Article VII of the Symphony GenIsis Charter and Section 9.01 of the Symphony GenIsis By-laws, as set forth in, and on the terms of, the Indemnification Agreement and the RRD Services Agreement, respectively.

(xiv) During the Term, Symphony GenIsis shall comply with, and cause any Persons acting for it to comply with, the terms of the Investment Policy with respect to the investment of any funds held by it.

(c) Symphony GenIsis covenants and agrees that, until the expiration of the Term, it shall not, and shall cause its Subsidiaries (if any) not to, without Isis' prior written consent (such consent, in the case of clause (x) below, not to be unreasonably withheld):

(i) issue any Symphony GenIsis Equity Securities or any Equity Securities of any Subsidiary thereof (other than any issuances of Equity Securities by Symphony GenIsis made in accordance with Section 1(b) hereof to Holdings so long as Symphony GenIsis is a wholly owned subsidiary of Holdings, or by a Subsidiary of Symphony GenIsis to Symphony GenIsis or to another wholly owned Subsidiary of Symphony GenIsis); provided, however, that in any event any such Symphony GenIsis Equity Securities shall be issued subject to the Purchase Option;

(ii) redeem, repurchase or otherwise acquire, directly or indirectly, any Symphony GenIsis Equity Securities or the Equity Securities of any Subsidiary of Symphony GenIsis;

(iii) create, incur, assume or permit to exist (A) any Encumbrance over or on any of its assets, other than (x) statutory liens or (y) liens created in the ordinary course of Symphony GenIsis' business securing obligations valued at less than [***] (unless the Development Committee shall authorize the existence of ordinary course liens securing obligations valued at greater than [***]), or (B) Debt other than any Debt incurred pursuant to the Operative Documents and the Development Budget (including payables incurred in the ordinary course of business) ("***Excepted***

Debt"); provided, however, that the aggregate outstanding principal amount of all such Excepted Debt for borrowed money shall not exceed [***] at any time;

(iv) declare or pay dividends or other distributions on any Symphony GenIsis Equity Securities other than any dividend declared from the proceeds of (x) the exercise of a Discontinuation Option, or (y) a sale or license of a discontinued Program to a third party, in each case in respect of which Symphony GenIsis shall be entitled to pay (subject to the existence of lawfully available funds) a dividend equal to the net amount (such net

amount calculated as the gross proceeds received less amounts required to be paid in respect of any and all corporate taxes owed by Symphony GenIsis as a result of the receipt of such gross amounts) of such Discontinuation Price or the amounts received from such third party, as the case may be;

(v) enter into any transaction of merger or consolidation, or liquidate, wind up or dissolve itself, or convey, transfer, license, lease or otherwise dispose of all, or a material portion of, its properties, assets or business;

(vi) other than in respect of the Programs, engage in the development of products for any other company or engage or participate in the development of products or engage in any other material line of business;

(vii) other than entering into, and performing its obligations under, the Operative Documents and participating in the Programs, engage in any action that negates or is inconsistent with any rights of Isis set forth herein;

(viii) (A) other than as contemplated by the RRD Services Agreement and Section 6.2 of the Amended and Restated Research and Development Agreement, hire, retain or contract for the services of, any employees until the termination of such agreements, or (B) appoint, dismiss or change any RRD Investment Personnel;

(ix) incur any financial commitments in respect of the development of the Programs other than those set forth in the Development Plan and the Development Budget, or those approved by the Development Committee and, if so required by the terms of Paragraph 11 of the Development Committee Charter, the Symphony GenIsis Board in accordance with the Operative Documents;

(x) other than any transaction contemplated by the Operative Documents, enter into or engage in any Conflict Transactions without the prior approval of a majority of the Disinterested Directors of the Symphony GenIsis Board; or

(xi) waive, alter, modify, amend or supplement in any manner whatsoever any material terms and conditions of the RRD Services Agreement, the Subscription Agreement, the Research Cost Sharing and Extension Agreement, or Articles 4 and 6 of the Amended and Restated Research and Development Agreement, except in compliance with the terms of the Operative Documents.

(d) Symphony GenIsis covenants and agrees to deliver, cause to be delivered, and provide access thereto, to each other Party, each Symphony Fund, and such Auditors as Isis may designate, so long as such Auditors shall (x) be subject to confidentiality requirements at least as stringent as the Confidentiality Agreement or (y) be an Isis Accounting Advisor retained pursuant to an agreement which incorporates confidentiality provisions substantially the same as the ones incorporated in the agreements in effect between Isis and such Accounting Advisors as of the Closing Date:

(i) upon request, copies of the then current Development Plan for each quarter, on or before March 31, June 30, September 30, and December 31 of each year;

(ii) upon request, copies of the then current Development Budget for each quarter, including a report setting forth in reasonable detail the projected expenditures by Symphony GenIsis pursuant to the Development Budget, on or before March 31, June 30, September 30, and December 31 of each year;

(iii) prior to the close of each fiscal year, Symphony GenIsis shall cause the Manager to seek to obtain from the Symphony GenIsis Auditors schedules of certain financial information to be provided to Isis' Auditors in connection with the Symphony GenIsis Auditors' audit of Symphony GenIsis. Within [***] Business Days after the close of each fiscal year, Symphony GenIsis (or the Manager acting on its behalf) will provide Isis' Auditors with the required Client Schedules. If the Symphony GenIsis Auditors deliver the Client Schedules after the end of the fiscal year, Symphony GenIsis (or the Manager acting on its behalf) will provide the completed Client Schedules to Isis' Auditors within [***] Business Days of such receipt;

(iv) prior to the close of each fiscal year, Isis' Vice President of Finance, the Symphony GenIsis Auditors, Isis' Auditors and Symphony GenIsis (or the Manager acting on its behalf) shall agree to a completion schedule that will include (A) the provision by Symphony GenIsis to Isis of the financial information reasonably necessary for Isis to consolidate the financial results of Symphony GenIsis and (B) the following financial statements, including the related notes thereto, audited and certified by the Symphony GenIsis Auditors: (1) a balance sheet of Symphony GenIsis as of the close of such fiscal year, (2) a statement of net income for such fiscal year, and (3) a statement of cash flows for such fiscal year. Such audited annual financial statements shall set forth in comparative form the figures for the previous fiscal year, all in reasonable detail, prepared in accordance with GAAP, and Symphony GenIsis (or the Manager acting on its behalf) shall, to the extent that Symphony GenIsis (or the Manager acting on its behalf), using commercially reasonable means, can procure such an opinion, be accompanied by an opinion thereon of the Symphony GenIsis Auditors to the effect that such financial statements present fairly, in all material respects, the financial position of Symphony GenIsis and its results of operations and cash flows and have been prepared in conformity with GAAP, and that the examination of such accountants in connection with such financial statements has been made in accordance with generally accepted auditing standards, and that such audit provides a reasonable basis for such opinion in the circumstances;

(v) within [***] Business Days following each calendar month and upon receipt from Isis of its monthly invoice to Symphony GenIsis, current accrued monthly vendor expenses and prepaid expenses, Symphony GenIsis (or the Manager acting on its behalf) will provide to Isis: (A) the unaudited balance sheet of Symphony GenIsis for the previous calendar month; (B) the unaudited statement of net income for such previous calendar month; (C) the unaudited statement of cash flows for such previous calendar month; (D) the trial balance schedule for such previous calendar month; and (E) related account reconciliations for such previous calendar month (collectively, "***Unaudited Financial Information***");

(vi) within [***] Business Days following its receipt thereof from Symphony GenIsis' tax return preparer, a copy of each income tax return filed by Symphony GenIsis with any foreign, federal, state or local taxing authority (including all supporting schedules thereto);

(vii) any other documents, materials or other information pertaining to the Programs or Symphony GenIsis as Isis may reasonably request, including preliminary financial information;

(viii) promptly, and in any event within [***] days of receipt thereof, copies of any notice to Symphony GenIsis from any federal or state Governmental Authority relating to any order, ruling, statute or other law or regulation that would reasonably be expected to have a Material Adverse Effect on Symphony GenIsis;

(ix) promptly upon receipt thereof, notice of all actions, suits, investigations, litigation and proceedings before any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, affecting Symphony GenIsis;

(x) promptly upon receipt thereof, copies of any other notices, requests, reports, financial statements and other information and documents received by Symphony GenIsis under or pursuant to any other Operative Document, including, without limitation, any notices of breach or termination of any subcontracts or licenses entered into or permitted pursuant to the Operative Documents; and

(xi) with reasonable promptness, such other data and information relating to the business, operations, affairs, financial condition, assets or properties of Symphony GenIsis or relating to the ability of Symphony GenIsis to perform its obligations hereunder and under the Operative Documents as from time to time may be reasonably requested by Isis and/or Holdings;

provided, that neither Symphony GenIsis, nor the Manager acting on behalf of Symphony GenIsis, shall have any liability to Isis for the failure to deliver financial documents or other materials hereunder, if such failure was caused by a failure of Isis to provide, in a timely manner, data required to prepare such financial documents or other materials to Symphony Isis in a timely manner.

(e) Symphony GenIsis will use commercially reasonable efforts, at its own expense (as set forth in the Management Budget), to cooperate with Isis in meeting Isis' government compliance, disclosure, and financial reporting obligations, including without limitation under the Sarbanes-Oxley Act of 2002 and any rules and regulations promulgated thereunder, and under FASB Interpretation No. 46. Without limiting the foregoing, Symphony GenIsis further covenants, until the completion of all the reporting, accounting and other obligations set forth therein with respect to the fiscal year in which this Agreement shall terminate, expire and end, that (w) the principal executive officer and the principal financial officer of Symphony GenIsis, or persons performing similar functions, shall provide certifications to Isis corresponding to those required with respect to public companies for which

a class of securities is registered under the Securities Exchange Act ("***Public Companies***") under Sections 302 and 906 of the Sarbanes-Oxley Act of 2002; (x) Symphony GenIsis shall maintain a system of disclosure controls and internal controls (as defined under the Exchange Act) and conduct quarterly and annual evaluations of the effectiveness of such controls as required under the Exchange Act for Public Companies; (y) Symphony GenIsis shall provide to Isis an attestation report of its Auditors with respect to Symphony GenIsis management's assessment of Symphony GenIsis' internal controls as required under the Exchange Act for Public Companies; and (z) Symphony GenIsis will maintain, or cause to have maintained, such sufficient evidentiary support for management's assessment of the effectiveness of Symphony GenIsis' internal controls as required under the Exchange Act for Public Companies.

Section 6. Notice of Material Event . Each Party agrees that, upon it receiving knowledge of a material event or development with respect to any of the transactions contemplated hereby that, to the knowledge of its executive officers, is not known to the other Parties, such Party shall notify the other Parties in writing within [***] Business Days of the receipt of such knowledge by any executive officer of such Party; provided, that the failure to provide such notice shall not impair or otherwise be deemed a waiver of any rights any Party may have arising from such material event or development and that notice under this Section 6 shall not in itself constitute notice of any breach of any of the Operative Documents.

Section 7. Assignment; Transfers; Legend.

(a) Assignment by Isis and Symphony GenIsis. Neither Isis nor Symphony GenIsis may assign, delegate, transfer, sell or otherwise dispose of (collectively, "***Transfer***"), in whole or in part, any or all of their rights or obligations hereunder to any Person (a "***Transferee***") without the prior written approval of each of the other Parties; provided, however, that Isis, without the prior approval of each of the other Parties, acting in accordance with Article 14 of the Amended and Restated Research and Development Agreement, may make such Transfer to any Person which acquires all or substantially all of Isis' assets or business (or assets or business related to the Programs) or which is the surviving or resulting Person in a merger or consolidation with Isis; provided, further, that in the event of any Transfer, Isis or Symphony GenIsis, as applicable, shall provide written notice to the other Parties of any such Transfer not later than thirty (30) days after such Transfer setting forth the identity and address of the Transferee and summarizing the terms of the Transfer. In no event shall such assignment alter the definition of "Isis Common Stock" except as a result of the surviving or resulting "parent" entity in a merger being other than Isis, in which case any reference to Isis Common Stock shall be deemed to instead reference the common stock, if any, of the surviving or resulting entity.

(b) Assignment and Transfers by Holdings. Prior to the expiration of the Purchase Option, Holdings may not Transfer, in whole or in part, any or all of its Symphony GenIsis Equity Securities or any or all of its rights or obligations hereunder to any Person (other than Isis) without the prior written consent of Isis. In addition, any Transfer of Symphony GenIsis Equity Securities by Holdings or any other Person to any Person other than Isis shall be

conditioned upon, and no effect shall be given to any such Transfer unless such transferee shall agree in writing in form and substance satisfactory to Isis to be bound by all of the terms and conditions hereunder, including the Purchase Option, as if such transferee were originally designated as "Holdings" hereunder.

(c) Legend. Any certificates evidencing Symphony GenIsis Equity Securities shall bear a legend in substantially the following form:

THE SECURITIES OF SYMPHONY GENISIS, INC., EVIDENCED HEREBY ARE SUBJECT TO AN OPTION, HELD BY ISIS, AS DESCRIBED IN A PURCHASE OPTION AGREEMENT (THE "PURCHASE OPTION AGREEMENT") DATED AS OF APRIL 7, 2006, BY AND AMONG ISIS PHARMACEUTICALS, INC., AND THE OTHER PARTIES THERETO, TO PURCHASE SUCH SECURITIES AT A PURCHASE PRICE DETERMINED PURSUANT TO SECTION 2 OF THE PURCHASE OPTION AGREEMENT, EXERCISABLE BY WRITTEN NOTICE AT ANY TIME DURING THE PERIOD SET FORTH THEREIN. COPIES OF THE PURCHASE OPTION AGREEMENT ARE AVAILABLE AT THE PRINCIPAL PLACE OF BUSINESS OF SYMPHONY GENISIS, INC. AT 7361 CALHOUN PLACE, SUITE 325, ROCKVILLE, MARYLAND 20855, AND WILL BE FURNISHED TO THE HOLDER HEREOF UPON WRITTEN REQUEST WITHOUT COST.

Section 8. Costs and Expenses; Payments.

(a) Symphony GenIsis Costs and Expenses. Symphony GenIsis shall pay any of its ongoing legal expenses with respect to the transactions described in the Operative Documents from the funds allocated for such purpose in the Management Budget.

(b) Costs and Expenses of the Purchase Option. Except as otherwise specified in Section 2(f) hereof, each Party shall pay its own costs and expenses incurred in connection with the exercise of the Purchase Option.

(c) Payments to Holdings. Payment of the Purchase Price, plus any costs and expenses payable by Symphony GenIsis under Section 2(f) hereof, shall be made to the account of Holdings contemporaneously with or prior to the payout of the Purchase Price on the Purchase Option Closing Date no later than 1:00 pm (New York time).

Section 9. Expiration; Termination of Agreement

(a) Termination.

(i) This Agreement shall terminate upon the mutual written consent of all of the Parties.

(ii) Subject to Section 1(c)(v) hereof, each of Holdings and Symphony GenIsis may terminate this Agreement in the event that Symphony GenIsis terminates the Amended and Restated Research and Development Agreement in accordance with its terms.

Section 10. Survival; Indemnification.

(a) Survival of Representations and Warranties; Expiration of Certain Covenants.

(i) The representations and warranties of the Parties contained in this Agreement shall survive for a period of one year from the making of such representations. The liability of the Parties related to their respective representations and warranties hereunder shall not be reduced by any investigation made at any time by or on behalf of Holdings, Symphony GenIsis or Isis, as applicable.

(ii) For the avoidance of doubt, the covenants and agreements set forth in Sections 4(b), 5(b)(i), 5(b)(v), 5(b)(vii)-(ix), 5(b)(xi)-(xiv), 5(c), 5(d)(i), 5(d)(ii) and 5(d)(viii)-(xi) shall, upon the expiration of the Term, expire and end without any further obligation by Symphony GenIsis or Holdings thereunder.

(iii) For the avoidance of doubt, the covenants and agreements set forth in Sections 5(b)(ii)-(iv), 5(b)(vi), 5(b)(x), 5(d)(iii)-(vii) and 5(e) shall, upon the completion of all the reporting, accounting and other obligations set forth therein with respect to the fiscal year in which this Agreement shall terminate, expire and end without any further obligation by Symphony GenIsis or Holdings thereunder.

(b) Indemnification. To the greatest extent permitted by applicable law, Isis shall indemnify and hold harmless Holdings and Symphony GenIsis and Holdings shall indemnify and hold harmless Isis, and each of their respective Affiliates, officers, directors, employees, agents, partners, members, successors, assigns, representatives of, and each Person, if any (including any officers, directors, employees, agents, partners, members of such Person) who controls Holdings, Symphony GenIsis and Isis, as applicable, within the meaning of the Securities Act or the Exchange Act, (each, an ***"Indemnified Party"***), from and against any and all actions, causes of action, suits, claims, losses, costs, interest, fees, liabilities and damages, and expenses with an aggregate value of at least $25,000 (as determined by the applicable Indemnified Party acting in good faith), in connection therewith (irrespective of whether any such Indemnified Party is a party to the action for which indemnification hereunder is sought), and including reasonable attorneys' fees and disbursements (hereinafter, a "***Loss***"), incurred by any Indemnified Party to the extent resulting from, arising out of, or relating to: (i) in the case of Isis being the Indemnifying Party, (A) any breach of any representation or warranty made by Isis herein or in any other Operative Document, or (B) any breach of any covenant, agreement or obligation of Isis contained herein or in any other Operative Document, and (ii) in the case of Holdings being the Indemnifying Party, (A) any breach of any representation or warranty made by Holdings or Symphony GenIsis or in any other Operative Document, or (B) any breach of any covenant, agreement or obligation of Holdings or Symphony GenIsis contained herein or in any other Operative Document. To the extent that the foregoing undertaking by Isis or Holdings may be unenforceable for any reason, such Party shall make the maximum contribution to the payment and satisfaction of any Loss that is permissible under applicable law.

(c) Notice of Claims. Any Indemnified Party that proposes to assert a right to be indemnified under this Section 10 shall notify Isis or Holdings, as applicable (the "***Indemnifying Party***"), promptly after receipt of notice of commencement of any action, suit or proceeding against such Indemnified Party (an "***Indemnified Proceeding***") in respect of which a claim is to be made under this Section 10, or the incurrence or realization of any Loss in respect of which a claim is to be made under this Section 10, of the commencement of such Indemnified Proceeding or of such incurrence or realization, enclosing a copy of all relevant documents, including all

papers served and claims made, but the omission to so notify the applicable Indemnifying Party promptly of any such Indemnified Proceeding or incurrence or realization shall not relieve (x) such Indemnifying Party from any liability that it may have to such Indemnified Party under this Section 10 or otherwise, except, as to such Indemnifying Party's liability under this Section 10, to the extent, but only to the extent, that such Indemnifying Party shall have been prejudiced by such omission, or (y) any other indemnitor from liability that it may have to any Indemnified Party under the Operative Documents.

(d) Defense of Proceedings. In case any Indemnified Proceeding shall be brought against any Indemnified Party, it shall notify the applicable Indemnifying Party of the commencement thereof as provided in Section 10(c), and such Indemnifying Party shall be entitled to participate in, and provided such Indemnified Proceeding involves a claim solely for money damages and does not seek an injunction or other equitable relief against the Indemnified Party and is not a criminal or regulatory action, to assume the defense of, such Indemnified Proceeding with counsel reasonably satisfactory to such Indemnified Party. After notice from such Indemnifying Party to such Indemnified Party of such Indemnifying Party's election so to assume the defense thereof and the failure by such Indemnified Party to object to such counsel within ten (10) Business Days following its receipt of such notice, such Indemnifying Party shall not be liable to such Indemnified Party for legal or other expenses related to such Indemnified Proceedings incurred after such notice of election to assume such defense except as provided below and except for the reasonable costs of investigating, monitoring or cooperating in such defense subsequently incurred by such Indemnified Party reasonably necessary in connection with the defense thereof. Such Indemnified Party shall have the right to employ its counsel in any such Indemnified Proceeding, but the fees and expenses of such counsel shall be at the expense of such Indemnified Party unless:

(i) the employment of counsel by such Indemnified Party at the expense of the applicable Indemnifying Party has been authorized in writing by such Indemnifying Party;

(ii) such Indemnified Party shall have reasonably concluded in its good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between the applicable Indemnifying Party and such Indemnified Party in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes of action available to such Indemnified Party (it being agreed that in any case referred to in this clause (ii) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

(iii) the applicable Indemnifying Party shall not have employed counsel reasonably acceptable to the Indemnified Party, to assume the defense of such Indemnified Proceeding within a reasonable time after notice of the commencement thereof; provided, however, that (A) this clause (iii) shall not be deemed to constitute a waiver of any conflict of interest that may arise with respect to any such counsel, and (B) an Indemnified Party may not invoke this clause (iii) if such Indemnified Party failed to timely object to such counsel pursuant to the first paragraph of this Section 10(d) above

(it being agreed that in any case referred to in this clause (iii) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party); or

(iv) any counsel employed by the applicable Indemnifying Party shall fail to timely commence or reasonably conduct the defense of such Indemnified Proceeding and such failure has prejudiced (or is in immediate danger of prejudicing) the outcome of such Indemnified Proceeding (it being agreed that in any case referred to in this clause (iv) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

in each of which cases the fees and expenses of counsel for such Indemnified Party shall be at the expense of such Indemnifying Party. Only one counsel shall be retained by all Indemnified Parties with respect to any Indemnified Proceeding, unless counsel for any Indemnified Party reasonably concludes in good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between such Indemnified Party and one or more other Indemnified Parties in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes or action available to such Indemnified Party.

(e) Settlement. Without the prior written consent of such Indemnified Party, such Indemnifying Party shall not settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding, unless such settlement, compromise, consent or related judgment (i) includes an unconditional release of such Indemnified Party from all liability for Losses arising out of such claim, action, investigation, suit or other legal proceeding, (ii) provides for the payment of money damages as the sole relief for the claimant (whether at law or in equity), (iii) involves no finding or admission of any violation of law or the rights of any Person by the Indemnified Party, and (iv) is not in the nature of a criminal or regulatory action. No Indemnified Party shall settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding (A) in respect of which any payment would result hereunder or under any other Operative Document, (B) which includes an injunction that will adversely affect any Indemnifying Party, (C) which involves a finding or admission of any violation of law or the rights of any Indemnifying Party, or (D) which is in the nature of a criminal or regulatory action, without the prior written consent of the Indemnifying Party, such consent not to be unreasonably conditioned, withheld or delayed.

Section 11. No Petition . Each of Isis and Holdings covenants and agrees that, prior to the date which is one year and one day after the expiration of the Purchase Option Period, it will not institute or join in the institution of any bankruptcy, insolvency, reorganization or similar proceeding against Symphony GenIsis. The provisions of this Section 11 shall survive the termination of this Agreement.

Section 12. Third-Party Beneficiary . Each of the Parties agrees that each Symphony Fund shall be a third-party beneficiary of this Agreement.

Section 13. Notices. Any notice, request, demand, waiver, consent, approval or other communication which is required or permitted to be given to any Party shall be in writing and shall be deemed given only if delivered to the Party personally or sent to the Party by facsimile transmission (promptly followed by a hard-copy delivered in accordance with this Section 13), by next Business Day delivery by a nationally recognized courier service, or by registered or certified mail (return receipt requested), with postage and registration or certification fees thereon prepaid, addressed to the Party at its address set forth below:

Isis:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: B. Lynne Parshall
Facsimile: (760) 603-4652

with a copy to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: General Counsel
Facsimile: (760) 268-4922

Symphony GenIsis:

Symphony GenIsis, Inc.
7361 Calhoun Place, Suite 325
Rockville, MD 20850
Attn: Charles W. Finn, Ph.D.
Facsimile: (301) 762-6154

Holdings:

Symphony GenIsis Holdings LLC
7361 Calhoun Place, Suite 325
Rockville, MD 20850
Attn: Joseph P. Clancy
Facsimile: (301) 762-6154

with copies to:

Symphony Capital Partners, L.P.
875 Third Avenue
18th Floor
New York, NY 10022
Attn: Mark Kessel
Facsimile: (212) 632-5401

and

Symphony Strategic Partners, LLC
875 Third Avenue
18th Floor
New York, NY 10022
Attn: Mark Kessel
Facsimile: (212) 632-5401

or to such other address as such Party may from time to time specify by notice given in the manner provided herein to each other Party entitled to receive notice hereunder.

Section 14. Governing Law; Consent to Jurisdiction and Service of Process.

(a) This Agreement shall be governed by, and construed in accordance with, the laws of the State of New York; except to the extent that this Agreement pertains to the internal governance of Symphony GenIsis or Holdings, and to such extent this Agreement shall be governed and construed in accordance with the laws of the State of Delaware.

(b) Each of the Parties hereby irrevocably and unconditionally submits, for itself and its property, to the nonexclusive jurisdiction of any New York State court and Delaware State court or federal court of the United States of America sitting in The City of New York, Borough of Manhattan or Wilmington, Delaware, and any appellate court from any jurisdiction thereof, in any action or proceeding arising out of or relating to this Agreement, or for recognition or enforcement of any judgment, and each of the Parties hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in any such New York State court, any such Delaware State court or, to the fullest extent permitted by law, in such federal court. Each of the Parties agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. Nothing in this Agreement shall affect any right that any Party may otherwise have to bring any action or proceeding relating to this Agreement.

(c) Each of the Parties irrevocably and unconditionally waives, to the fullest extent it may legally and effectively do so, any objection that it may now or hereafter have to the laying of venue of any suit, action or proceeding arising out of or relating to this Agreement in any New York State or federal court, or any Delaware State or federal court. Each of the Parties hereby irrevocably waives, to the fullest extent permitted by law, the defense of an inconvenient

forum to the maintenance of such action or proceeding in any such court. Each of the parties hereby consents to service of process by mail.

Section 15. WAIVER OF JURY TRIAL. EACH OF THE PARTIES HERETO IRREVOCABLY WAIVES ALL RIGHT TO TRIAL BY JURY IN ANY ACTION, PROCEEDING OR COUNTERCLAIM (WHETHER BASED ON CONTRACT, TORT OR OTHERWISE) ARISING OUT OF OR RELATING TO THIS AGREEMENT.

Section 16. Entire Agreement. This Agreement (including any Annexes, Schedules, Exhibits or other attachments hereto) constitutes the entire agreement between the Parties with respect to the matters covered hereby and supersedes all prior agreements and understanding with respect to such matters between the Parties.

Section 17. Amendment; Successors; Counterparts.

(a) The terms of this Agreement shall not be altered, modified, amended, waived or supplemented in any manner whatsoever except by a written instrument signed by each of the Parties.

(b) Except as set forth in Section 12, nothing expressed or implied herein is intended or shall be construed to confer upon or to give to any Person, other than the Parties, any right, remedy or claim under or by reason of this Agreement or of any term, covenant or condition hereof, and all the terms, covenants, conditions, promises and agreements contained herein shall be for the sole and exclusive benefit of the Parties and their successors and permitted assigns.

(c) This Agreement may be executed in one or more counterparts, each of which, when executed, shall be deemed an original but all of which, taken together, shall constitute one and the same Agreement.

Section 18. Specific Performance. The Parties acknowledge that irreparable damage would result if this Agreement were not specifically enforced, and they therefore agree that the rights and obligations of the Parties under this Agreement may be enforced by a decree of specific performance issued by a court of competent jurisdiction. Such a remedy shall, however, not be exclusive, and shall be in addition to any other remedies which any Party may have under this Agreement or otherwise. The Parties further acknowledge and agree that a decree of specific performance may not be an available remedy in all circumstances.

Section 19. Severability. If any term or other provision of this Agreement is invalid, illegal or incapable of being enforced by any rule of law or public policy, all other conditions and provisions of this Agreement shall nevertheless remain in full force and effect so long as the economic or legal substance of the transactions contemplated hereby is not affected in a manner materially adverse to either party. Upon such determination that any term or other provision is invalid, illegal or incapable of being enforced, the parties hereto shall negotiate in good faith to modify this Agreement so as to effect the original intent of the parties as closely as possible in an acceptable manner to the end that the transactions contemplated hereby are fulfilled to the extent possible.

Section 20. Tax Reporting. The Parties acknowledge and agree that, for all federal and state income tax purposes:

(a) (i) Holdings shall be treated as the owner of all the Equity Securities of Symphony GenIsis; (ii) the Purchase Option shall be treated as an option to acquire all the Equity Securities of Symphony GenIsis; (iii) the Warrants shall be treated as option premium payable in respect of the grant of the Purchase Option; and (iv) Symphony GenIsis shall be treated as the owner of all the Licensed Intellectual Property and shall be entitled to all deductions claimed under Section 174 of the Code in respect of the Licensed Intellectual Property to the extent of the amounts funded by Symphony GenIsis (which, for the avoidance of doubt, shall not preclude Isis from claiming deductions under Section 174 of the Code to which Isis is otherwise entitled); and

(b) no Party shall take any tax position inconsistent with any position described in Section 20(a) above, except (i) in the event of a "determination" (as defined in Section 1313 of the Code) to the contrary, or (ii) in the event either of the Parties receives an opinion of counsel to the effect that there is no reasonable basis in law for such a position or that a tax return cannot be prepared based on such a position without being subject to substantial understatement penalties; provided, however, that in the case of Isis, such counsel shall be reasonably satisfactory to Holdings.

[SIGNATURES FOLLOW ON NEXT PAGE]

IN WITNESS WHEREOF, the parties hereto have signed this Agreement as of the day and year first above written.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall, J.D.
Name: B. Lynne Parshall, J.D.
Title: Executive Vice President, Chief Financial Officer and Secretary

SYMPHONY GENISIS HOLDINGS LLC

By: Symphony Capital Partners, L.P.,
its Manager

By: Symphony Capital GP, L.P.,
its general partner

By: Symphony GP, LLC,
its general partner

By: /s/ Mark Kessel
Name: Mark Kessel
Title: Managing Member

SYMPHONY GENISIS, INC.

By: /s/ Neil J. Sandler
Name: Neil J. Sandler
Title: Chairman of the Board

SCHEDULE I

PURCHASE PRICE TABLE

Quarter Following the Closing Date	First Date of Quarter	Last Date of Quarter	Quarterly Price (in millions)
5th Quarter	April 1, 2007	June 30, 2007	$ 112.5
6th Quarter	July 1, 2007	September 30, 2007	$ 120.0
7th Quarter	October 1, 2007	December 31, 2007	$ 127.5
8th Quarter	January 1, 2008	March 31, 2008	$ 135.0
9th Quarter	April 1, 2008	June 30, 2008	$ 142.5
10th Quarter	July 1, 2008	September 30, 2008	$ 150.0
11th Quarter	October 1, 2008	December 31, 2008	$ 157.5
12th Quarter	January 1, 2009	March 31, 2009	$ 165.0
13th Quarter	April 1, 2009	June 30, 2009	$ 172.5
14th Quarter	July 1, 2009	September 30, 2009	$ 180.0
15th Quarter	October 1, 2009	December 31, 2009	$ 187.5
16th Quarter	January 1, 2010	March 31, 2010	$ 195.0

ANNEX A

CERTAIN DEFINITIONS

CERTAIN DEFINITIONS

"***$***" means United States dollars.

"***Accredited Investor***" has the meaning set forth in Rule 501(a) of Regulation D promulgated under the Securities Act of 1933, as amended.

"***Act***" means the Delaware Limited Liability Company Act, 6 Del. C. § 18-101 et seq.

"***Ad Hoc Meeting***" has the meaning set forth in Paragraph 6 of Annex B of the Amended and Restated Research and Development Agreement.

"***Additional Party***" has the meaning set forth in Section 13 of the Confidentiality Agreement.

"***Additional Regulatory Filings***" means such Governmental Approvals as required to be made under any law applicable to the purchase of the Symphony GenIsis Equity Securities under the Purchase Option Agreement.

"***Adjusted Capital Account Deficit***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Affected Member***" has the meaning set forth in Section 27 of the Investors LLC Agreement.

"***Affiliate***" means, with respect to any Person (i) any Person directly or indirectly controlling, controlled by or under common control with such Person, (ii) any officer, director, general partner, member or trustee of such Person, or (iii) any Person who is an officer, director, general partner, member or trustee of any Person described in clauses (i) or (ii) of this sentence. For purposes of this definition, the terms "controlling," "controlled by" or "under common control with" shall mean the possession, direct or indirect, of the power to direct or cause the direction of the management and policies of a Person or entity, whether through the ownership of voting securities, by contract or otherwise, or the power to elect at least 50% of the directors, managers, general partners, or persons exercising similar authority with respect to such Person or entities.

"***Amended and Restated Research and Development Agreement***" means the Amended and Restated Research and Development Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis.

"***ApoB***" means apolipoprotein B.

"***ApoB Product***" means a pharmaceutical composition comprising an ASO that targets ApoB.

"***ApoB Program***" means the identification, development, manufacture and/or use of any ApoB Product in accordance with the Development Plan.

"***ASO***" means an oligonucleotide or analog, mimic or mimetic thereof having a sequence that selectively modulates protein synthesis via the binding, partially or wholly, of such oligomeric compound to a complementary nucleic acid sequence encoding, directly or indirectly, said protein.

"***Asset Value***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Auditors***" means an independent certified public accounting firm of recognized national standing.

"***Balance Sheet Deficiency Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Bankruptcy Code***" means the United States Bankruptcy Code.

"***Business Day***" means any day other than Saturday, Sunday or any other day on which commercial banks in The City of New York or the City of San Francisco are authorized or required by law to remain closed.

"***Capital Contributions***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Capitalized Leases***" means all leases that have been or should be, in accordance with GAAP, recorded as capitalized leases.

"***Cash Available for Distribution***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Chair***" has the meaning set forth in Paragraph 4 of Annex B to the Amended and Restated Research and Development Agreement.

"***Change of Control***" means and includes the occurrence of any of the following events, but specifically excludes (i) acquisitions of capital stock directly from Isis for cash, whether in a public or private offering, (ii) sales of capital stock by stockholders of Isis, and (iii) acquisitions of capital stock by or from any employee benefit plan or related trust:

(a) the merger, reorganization or consolidation of Isis into or with another corporation or legal entity in which Isis' stockholders holding the right to vote with respect to matters generally immediately preceding such merger, reorganization or consolidation, own less than fifty percent (50%) of the voting securities of the surviving entity; or

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(b) the sale of all or substantially all of Isis' assets or business.

"***Class A Member***" means a holder of a Class A Membership Interest.

"***Class A Membership Interest***" means a Class A Membership Interest in Holdings.

"***Class B Member***" means a holder of a Class B Membership Interest.

"***Class B Membership Interest***" means a Class B Membership Interest in Holdings.

"***Class C Member***" means a holder of a Class C Membership Interest.

"***Class C Membership Interest***" means a Class C Membership Interest in Holdings.

"***Client Schedules***" has the meaning set forth in Section 5(b) of the RRD Services Agreement.

"***Clinical Budget Component***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Closing Date***" means April 7, 2006.

"***CMC***" means the chemistry, manufacturing and controls documentation as required for filings with Regulatory Authority relating to the manufacturing, production and testing of drug products.

"***Code***" means the Internal Revenue Code of 1986, as amended from time to time.

"***Committed Capital***" means $75,000,000.00.

"***Common Stock***" means the common stock, par value $0.01 per share, of Symphony GenIsis.

"***Company Expenses***" has the meaning set forth in Section 5.09 of the Holdings LLC Agreement.

"***Company Property***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Confidential Information***" has the meaning set forth in Section 2 of the Confidentiality Agreement.

"***Confidentiality Agreement***" means the Confidentiality Agreement, dated as of the Closing Date, among Symphony GenIsis, Holdings, Isis, SCP, SSP, Investors, Symphony Capital and RRD, as such agreement may be amended or amended and restated from time to time.

"***Conflict Transaction***" has the meaning set forth in Article X of the Symphony GenIsis Charter.

"***Control***" means, with respect to any material, information or intellectual property right, that a Party owns or has a license to such item or right, and has the ability to grant the other Party access, a license or a sublicense (as applicable) in or to such item or right as provided in the Operative Documents without violating the terms of any agreement or other arrangement with any third party.

"***Debt***" of any Person means, without duplication:

(a) all indebtedness of such Person for borrowed money,

(b) all obligations of such Person for the deferred purchase price of property or services (other than any portion of any trade payable obligation that shall not have remained unpaid for 91 days or more from the later of (A) the original due date of such portion and (B) the customary payment date in the industry and relevant market for such portion),

(c) all obligations of such Person evidenced by bonds, notes, debentures or other similar instruments,

(d) all obligations of such Person created or arising under any conditional sale or other title retention agreement with respect to property acquired by such Person (whether or not the rights and remedies of the seller or lender under such agreement in an event of default are limited to repossession or sale of such property),

(e) all Capitalized Leases to which such Person is a party,

(f) all obligations, contingent or otherwise, of such Person under acceptance, letter of credit or similar facilities,

(g) all obligations of such Person to purchase, redeem, retire, defease or otherwise acquire for value any Equity Securities of such Person,

(h) the net amount of all financial obligations of such Person in respect of Hedge Agreements,

(i) the net amount of all other financial obligations of such Person under any contract or other agreement to which such Person is a party,

(j) all Debt of other Persons of the type described in clauses (a) through (i) above guaranteed, directly or indirectly, in any manner by such Person, or in effect guaranteed, directly or indirectly, by such Person through an agreement (A) to pay or purchase such Debt or to advance or supply funds for the payment or purchase of such Debt, (B) to purchase, sell or lease (as lessee or lessor) property, or to purchase or sell services, primarily for the purpose of enabling the debtor to make payment of such Debt or to assure the holder of such Debt against loss, (C) to supply funds to or in any other

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manner invest in the debtor (including any agreement to pay for property or services irrespective of whether such property is received or such services are rendered) or (D) otherwise to assure a creditor against loss, and

(k) all Debt of the type described in clauses (a) through (i) above secured by (or for which the holder of such Debt has an existing right, contingent or otherwise, to be secured by) any Encumbrance on property (including accounts and contract rights) owned or held or used under lease or license by such Person, even though such Person has not assumed or become liable for payment of such Debt.

"***Development Budget***" means the budget (comprised of the Management Budget Component and the Clinical Budget Component) for the implementation of the Development Plan (the initial form of which was agreed upon by Isis and Symphony GenIsis as of the Closing Date and attached to the Amended and Restated Research and Development Agreement as Annex D thereto), as may be further developed and revised from time to time in accordance with the Development Committee Charter and the Amended and Restated Research and Development Agreement.

"***Development Committee***" has the meaning set forth in Article 3 of the Amended and Restated Research and Development Agreement.

"***Development Committee Charter***" has the meaning set forth in Article 3 of the Amended and Restated Research and Development Agreement.

"***Development Committee Member***" has the meaning set forth in Paragraph 1 of Annex B to the Amended and Restated Research and Development Agreement.

"***Development Plan***" means the development plan covering all the Programs (the initial form of which was agreed upon by Isis and Symphony GenIsis as of the Closing Date and attached to the Amended and Restated Research and Development Agreement as Annex C thereto), as may be further developed and revised from time to time in accordance with the Development Committee Charter and the Amended and Restated Research and Development Agreement.

"***Development Services***" has the meaning set forth in Section 1(b) of the RRD Services Agreement.

"***Director(s)***" means the Persons identified as such in the Preliminary Statement of the Indemnification Agreement (including such Persons as may become parties thereto after the date hereof).

"***Disclosing Party***" has the meaning set forth in Section 3 of the Confidentiality Agreement.

"***Discontinuation Closing Date***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinuation Date***" means any date designated by Symphony GenIsis which shall occur on or after the 90th day following the receipt by Isis of notice from Symphony GenIsis of Symphony GenIsis' intent to discontinue a Program in accordance with the terms of the Amended and Restated Research and Development Agreement.

"***Discontinuation Option***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinuation Price***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinued Program***" has the meaning set forth in Section 2.12 of the Novated and Restated Technology License Agreement.

"***Disinterested Directors***" has the meaning set forth in Article IX of the Symphony GenIsis Charter.

"***Distribution***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Early Purchase Option Exercise***" has the meaning set forth in Section 1(c)(iv) of the Purchase Option Agreement.

"***Effective Registration Date***" has the meaning set forth in Section 1(b) of the Registration Rights Agreement

"***Encumbrance***" means (i) any security interest, pledge, mortgage, lien (statutory or other), charge or option to purchase, lease or otherwise acquire any interest, (ii) any adverse claim, restriction, covenant, title defect, hypothecation, assignment, deposit arrangement, license or other encumbrance of any kind, preference or priority, or (iii) any other security agreement or preferential arrangement of any kind or nature whatsoever (including, without limitation, any conditional sale or other title retention agreement).

"***Enhancements***" means findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Intellectual Property and/or Regulatory Files, in each case whether or not patentable.

"***Equity Securities***" means, with respect to any Person, shares of capital stock of (or other ownership or profit interests in) such Person, warrants, options or other rights for the purchase or other acquisition from such Person of shares of capital stock of (or other ownership or profit interests in) such Person, securities convertible into or exchangeable for shares of capital stock of (or other ownership or profit interests in) such Person or warrants, rights or options for the purchase or other acquisition from such Person of such shares (or such other interests), and other ownership or profit interests in such Person (including, without limitation, partnership, member or trust interests therein), whether voting or nonvoting, and whether or not such shares, warrants, options, rights or other interests are authorized or otherwise existing on any date of determination.

"***ERISA***" means the United States Employee Retirement Income Security Act of 1974, as amended.

"***Excepted Debt***" has the meaning set forth in Section 5(c)(iii) of the Purchase Option Agreement.

"***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

"***Exclusive Field***" means human therapeutics, but does not include the Nonexclusive Field.

"***Existing NDA***" has the meaning set forth in Section 2 of the Confidentiality Agreement.

"***Expert***" has the meaning set forth in Section 11.1(c) of the Amended and Restated Research and Development Agreement.

"***External Directors***" means, at any time, up to two (2) Persons elected to the Symphony GenIsis Board after the Closing Date (who shall be neither employees of the Symphony Capital nor of Isis) in accordance with the Symphony GenIsis Charter, the Symphony GenIsis By-laws and Section 4(b)(iv) of the Purchase Option Agreement.

"***FDA***" means the United States Food and Drug Administration or its successor agency in the United States.

"***FDA Sponsor***" has the meaning set forth in Section 5.1 of the Amended and Restated Research and Development Agreement.

"***Final Termination Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Financial Audits***" has the meaning set forth in Section 6.6 of the Amended and Restated Research and Development Agreement.

"***Financing***" has the meaning set forth in the Preliminary Statement of the Purchase Option Agreement.

"***Fiscal Year***" has the meaning set forth in each Operative Document in which it appears.

"***Form S-3***" means the Registration Statement on Form S-3 as defined under the Securities Act.

"***FTE***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Funds Termination Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Funds Termination Notice***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***GAAP***" means generally accepted accounting principles in effect in the United States of America from time to time.

"***GCCR***" means a glucocorticoid receptor.

"***GCCR Product***" means a pharmaceutical composition comprising an ASO that targets GCCR.

"***GCCR Program***" means the identification, development, manufacture and/or use of any GCCR Product in accordance with the Development Plan.

"***GCGR***" means a glucagon receptor.

"***GCGR Product***" means a pharmaceutical composition comprising an ASO that targets GCGR.

"***GCGR Program***" means the identification, development, manufacture and/or use of any GCGR Product in accordance with the Development Plan.

"***GenIsis Relevant Action***" means an action against others in the courts, administrative agencies or otherwise to prevent or terminate infringement, misappropriation, illegal use or misuse of the Licensed Patent Rights or other Licensed Intellectual Property due to the manufacture, use, sale or importation of an ASO that targets ApoB, GCCR or GCGR, as applicable, in the Exclusive Field.

"***Governmental Approvals***" means authorizations, consents, orders, declarations or approvals of, or filings with, or terminations or expirations of waiting periods imposed by any Governmental Authority.

"***Governmental Authority***" means any United States or non-United States federal, national, supranational, state, provincial, local, or similar government, governmental, regulatory or administrative authority, agency or commission or any court, tribunal, or judicial or arbitral body.

"***Governmental Order***" means any order, writ, judgment, injunction, decree, stipulation, determination or award entered by or with any Governmental Authority.

"***Hedge Agreement***" means any interest rate swap, cap or collar agreement, interest rate future or option contract, currency swap agreement, currency future or option contract or other similar hedging agreement.

"***Holdings***" means Symphony GenIsis Holdings LLC, a Delaware limited liability company.

"***Holdings Claims***" has the meaning set forth in Section 5.01 of the Warrant Purchase Agreement.

"***Holdings LLC Agreement***" means the Amended and Restated Limited Liability Company Agreement of Holdings dated as of the Closing Date.

"***HSR Filings***" means the pre-merger notification and report forms required under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended.

"***IND***" means an Investigational New Drug Application, as described in 21 U.S.C. § 355(i)(1) and 21 C.F.R. § 312 in the regulations promulgated by the United States Food and Drug Administration, or any foreign equivalent thereof.

"***Indemnification Agreement***" means the Indemnification Agreement among Symphony GenIsis and the Directors named therein, dated as of the Closing Date, as such agreement may be amended or amended and restated from time to time.

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

"***Indemnified Party***" has the meaning set forth in each Operative Document in which it appears.

"***Indemnified Proceeding***" has the meaning set forth in each Operative Document in which it appears.

"***Indemnifying Party***" has the meaning set forth in each Operative Document in which it appears.

"***Initial Development Budget***" means the initial development budget prepared by representatives of Symphony GenIsis and Isis prior to the Closing Date, and attached to the Amended and Restated Research and Development Agreement as Exhibit D thereto.

"***Initial Development Plan***" means the initial development plan prepared by representatives of Symphony GenIsis and Isis prior to the Closing Date, and attached to the Amended and Restated Research and Development Agreement as Exhibit C thereto.

"***Initial Holdings LLC Agreement***" means the Agreement of Limited Liability Company of Holdings, dated March 8, 2006.

"***Initial Investors LLC Agreement***" means the Agreement of Limited Liability Company of Investors, dated March 8, 2006.

"***Initial LLC Member***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Interest Certificate***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Investment Company Act***" means the Investment Company Act of 1940, as amended.

"***Investment Overview***" means the investment overview describing the transactions entered into pursuant to the Operative Documents.

"***Investment Policy***" has the meaning set forth in Section 1(a)(vi) of the RRD Services Agreement.

"***Investors***" means Symphony GenIsis Investors LLC.

"***Investors LLC Agreement***" means the Amended and Restated Agreement of Limited Liability Company of Investors dated as of the Closing Date

"***IRS***" means the U.S. Internal Revenue Service.

"***Isis***" means Isis Pharmaceuticals, Inc., a Delaware corporation.

"***Isis 2005 10-K***" means the annual report for fiscal year 2005 filed by Isis on Form 10-K on March 16, 2006, pursuant to the Exchange Act.

"***Isis Accounting Advisor***" means Ernst & Young LLP or Deloitte & Touche USA LLP.

"***Isis Common Stock***" means the common stock, par value $0.001 per share, of Isis.

"***Isis Commitment Amount***" has the meaning set forth in Paragraph 14 of Annex B to the Amended and Restated Research and Development Agreement.

"***Isis Common Stock Valuation***" has the meaning set forth in Section 2(e) of the Purchase Option Agreement.

"***Isis Funding Notice***" has the meaning set forth in Section 2 of the Research Cost Sharing and Extension Agreement.

"***Isis Obligations***" has the meaning set forth in Section 6.1 of the Amended and Restated Research and Development Agreement.

"***Isis Personnel***" has the meaning set forth in Section 8.4 of the Amended and Restated Research and Development Agreement.

"***Isis Subcontractor***" has the meaning set forth in Section 6.2 of the Amended and Restated Research and Development Agreement.

"***Key Personnel***" means those Isis Personnel listed on Schedule 6.4 to the Amended and Restated Research and Development Agreement, as such schedule may be updated from time to time by mutual agreement of the parties to the Amended and Restated Research and Development Agreement.

"***Knowledge***" means the actual (and not imputed) knowledge of the executive officers of Isis, without the duty of inquiry or investigation.

"***Law***" means any law, statute, treaty, constitution, regulation, rule, ordinance, order or Governmental Approval, or other governmental restriction, requirement or determination, of or by any Governmental Authority.

"***License***" has the meaning set forth in the Preliminary Statement of the Purchase Option Agreement.

"***Licensed Intellectual Property***" means the Licensed Patent Rights, Symphony GenIsis Enhancements, Licensor Enhancements and the Licensed Know-How.

"***Licensed Know-How***" means any and all proprietary technology that is Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option that relates to, or is exploitable in connection with, the Licensed Patent Rights, Regulatory Files, Products or the Programs, including without limitation, manufacturing processes or protocols, know-how, writings, documentation, data, technical information, techniques, results of experimentation and testing, diagnostic and prognostic assays, specifications, databases, any and all laboratory, research, pharmacological, toxicological, analytical, quality control pre-clinical and clinical data, and other information and materials, whether or not patentable.

"***Licensed Patent Rights***" means:

(a) any and all patents, patent applications and invention disclosures Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option and relating to, or exploitable in connection with, any Product and/or any Program;

(b) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) filed prior to the unexercised expiration or termination of the Purchase Option; and

(c) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) or (b) filed after the unexercised expiration or termination of the Purchase Option but solely to the extent the subject matter in any such continuation-in-part embodies Licensed Know-How or has been disclosed in the patents or patent applications described in (a) or (b).

Licensed Patent Rights include any and all patents and patent applications that claim Licensor Enhancements or Symphony GenIsis Enhancements and Program-Specific Patents.

"***Licensor***" means Isis.

"***Licensor Enhancements***" means all findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Know-How, Regulatory Files, Products or the Programs, in each case, developed by Licensor during the Term (in each case whether or not patentable), to the extent such items do not otherwise qualify as Symphony GenIsis Enhancements hereunder, regardless of whether such work is funded by Symphony GenIsis or Isis.

"***Lien***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Liquidating Event***" has the meaning set forth in Section 8.01 of the Holdings LLC Agreement.

"***LLC Agreements***" means the Initial Holdings LLC Agreement, the Holdings LLC Agreement, the Initial Investors LLC Agreement and the Investors LLC Agreement.

"***Loss***" has the meaning set forth in each Operative Document in which it appears.

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

"***Management Budget Component***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Management Fee***" has the meaning set forth in Section 6(a) of the RRD Services Agreement.

"***Manager***" means (i) for each LLC Agreement in which it appears, the meaning set forth in such LLC Agreement, and (ii) for each other Operative Document in which it appears, RRD in its capacity as manager of Symphony GenIsis.

"***Management Services***" has the meaning set forth in Section 1(a) of the RRD Services Agreement.

"***Manager Event***" has the meaning set forth in Section 3.01(g) of the Holdings LLC Agreement.

"***Material Adverse Effect***" means, with respect to any Person, a material adverse effect on (i) the business, assets, property or condition (financial or otherwise) of such Person or, (ii) its ability to comply with and satisfy its respective agreements and obligations under the Operative Documents or, (iii) the enforceability of the obligations of such Person of any of the Operative Documents to which it is a party.

"***Material Subsidiary***" means, at any time, a Subsidiary of Isis having assets in an amount equal to at least 5% of the amount of total consolidated assets of Isis and its Subsidiaries (determined as of the last day of the most recent reported fiscal quarter of Isis) or revenues or net

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income in an amount equal to at least 5% of the amount of total consolidated revenues or net income of Isis and its Subsidiaries for the 12-month period ending on the last day of the most recent reported fiscal quarter of Isis.

"***Medical Discontinuation Event***" means (a) as specified in each Protocol, those data that, if collected in such Protocol, demonstrate that such Protocol should not be continued or (b) a series of adverse events, side effects or other undesirable outcomes that, when collected in a Protocol, would cause a reasonable FDA Sponsor to discontinue such Protocol.

"***Membership Interest***" means (i) for each LLC Agreement in which it appears, the meaning set forth in such LLC Agreement, and (ii) for each other Operative Document in which it appears, the meaning set forth in the Holdings LLC Agreement.

"***MOE Gapmer***" means a single stranded antisense oligonucleotide of less than [***] nucleotides (i) wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (phosphorothioate) and (ii) comprising a region of at least [***] unsubstituted 2′-deoxy nucleotides with the remaining nucleotides contain a 2′-O-(methoxyethyl) substitution at the 2′ position.

"***NASDAQ***" means the National Association of Securities Dealers Automated Quotation System.

"***NDA***" means a New Drug Application, as defined in the regulations promulgated by the United States Food and Drug Administration, or any foreign equivalent thereof.

"***Nonexclusive Field***" means (i) manufacturing (including analytical methods) ASOs, (ii) formulating ASOs, (iii) conducting Research on ASOs and/or (iv) supplying ASOs solely to conduct Research.

"***Non-Isis Capital Transaction***" means any (i) sale or other disposition of all or part of the Symphony GenIsis Shares or all or substantially all of the operating assets of Symphony GenIsis, to a Person other than Isis or an Affiliate of Isis or (ii) distribution in kind of the Symphony GenIsis Shares following the expiration of the Purchase Option.

"***Novated and Restated Technology License Agreement***" means the Novated and Restated Technology License Agreement, dated as of the Closing Date, among Isis, Symphony GenIsis and Holdings.

"***Operative Documents***" means, collectively, the Indemnification Agreement, the Holdings LLC Agreement, the Purchase Option Agreement, the Warrant Purchase Agreement, the Registration Rights Agreement, the Subscription Agreement, the Technology License Agreement, the Novated and Restated Technology License Agreement, the RRD Services Agreement, the Research and Development Agreement, the Research Cost Sharing and Extension Agreement, the Amended and Restated Research and Development Agreement, the Confidentiality Agreement, and each other certificate and agreement executed in connection with any of the foregoing documents.

"***Organizational Documents***" means any certificates or articles of incorporation or formation, partnership agreements, trust instruments, bylaws or other governing documents.

"***Partial Stock Payment***" has the meaning set forth in Section 3(a)(iii) of the Purchase Option Agreement.

"***Party(ies)***" means, for each Operative Document or other agreement in which it appears, the parties to such Operative Document or other agreement, as set forth therein. With respect to any agreement in which a provision is included therein by reference to a provision in another agreement, the term "Party" shall be read to refer to the parties to the document at hand, not the agreement that is referenced.

"***Payment Terms***" has the meaning set forth in Section 8.2 of the Amended and Restated Research and Development Agreement.

"***Percentage***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Permitted Investments***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Permitted Lien***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Person***" means any individual, partnership (whether general or limited), limited liability company, corporation, trust, estate, association, nominee or other entity.

"***Personnel***" of a Party means such Party, its employees, subcontractors, consultants, representatives and agents.

"***Prime Rate***" means the quoted "Prime Rate" at JPMorgan Chase Bank or, if such bank ceases to exist or is not quoting a base rate, prime rate reference rate or similar rate for United States dollar loans, such other major money center commercial bank in New York City selected by the Manager.

"***Products***" means an ApoB Product, a GCCR Product and/or a GCGR Product.

"***Profit***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Programs***" means the ApoB Program, the GCCR Program and/or the GCGR Program.

"***Program-Specific Patents***" means

(a) any and all patents, patent applications and invention disclosures Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option that claim any composition of matter comprising, or method of using, an ASO targeting any of ApoB, GCCR or GCGR, including but not limited to, the patents and patent applications listed on Annex C to the Novated and Restated Technology License Agreement;

(b) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) filed prior to the unexercised expiration or termination of the Purchase Option; and

(c) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) or (b) filed after the unexercised expiration or termination of the Purchase Option but solely to the extent the subject matter in such any continuation-in-part embodyies Licensed Know-How or has been disclosed in the patents or patent applications described in (a) or (b).

"***Protocol***" means a written protocol that meets the substantive requirements of Section 6 of the ICH Guideline for Good Clinical Practice as adopted by the FDA, effective May 9, 1997 and is included within the Development Plan or later modified or added to the Development Plan pursuant to the Amended and Restated Research and Development Agreement.

"***Public Companies***" has the meaning set forth in Section 5(e) of the Purchase Option Agreement.

"***Purchase Option***" has the meaning set forth in Section 1(a) of the Purchase Option Agreement.

"***Purchase Option Agreement***" means this Purchase Option Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis.

"***Purchase Option Closing***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Closing Date***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Commencement Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Purchase Option Exercise Date***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Exercise Notice***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Interim Date***" has the meaning set forth in Section 2(b)(i) of the Purchase Option Agreement.

"***Purchase Option Period***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Purchase Price***" has the meaning set forth in Section 2(b) of the Purchase Option Agreement.

"***Put Option***" has the meaning set forth in Section 2A of the Purchase Option Agreement.

"***Put Option Exercise Notice***" has the meaning set forth in Section 2A of the Purchase Option Agreement.

"***QA Audits***" has the meaning set forth in Section 6.5 of the Amended and Restated Research and Development Agreement.

"***Quarterly Price***" has the meaning set forth in Section 2(b)(i) of the Purchase Option Agreement.

"***Registration Rights Agreement***" means the Registration Rights Agreement dated as of the Closing Date, between Isis and Holdings.

"***Registration Statement***" has the meaning set forth in Section 1(b) of the Registration Rights Agreement.

"***Regulatory Authority***" means the United States Food and Drug Administration, or any successor agency in the United States, or any health regulatory authority(ies) in any other country that is a counterpart to the FDA and has responsibility for granting registrations or other regulatory approval for the marketing, manufacture, storage, sale or use of drugs in such other country.

"***Regulatory Allocation***" has the meaning set forth in Section 3.06 of the Holdings LLC Agreement.

"***Regulatory Files***" means any IND, NDA or any other filings filed with any Regulatory Authority with respect to the Programs.

"***Representative***" of any Person means such Person's shareholders, principals, directors, officers, employees, members, managers and/or partners.

"***Research***" means research, including gene function, gene expression and target validation research, which may include small pilot toxicology studies but excludes IND-Enabling Studies or dosing humans. Research does not include commercialization.

"***Research Cost Sharing and Extension Agreement***" means the Research Cost Sharing and Extension Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis, Inc..

"***Research and Development Agreement***" means the Research and Development Agreement dated as of the Closing Date, between Isis and Holdings.

"***RRD***" means RRD International, LLC, a Delaware limited liability company.

"***RRD FTE Budget***" means the budget attached to the RRD Services Agreement as Exhibit 3 thereto.

"***RRD Indemnified Party***" has the meaning set forth in Section 10(a) of the RRD Services Agreement.

"***RRD Investment Personnel***" has the meaning set forth in Section 1(a)(v) of the RRD Services Agreement.

"***RRD Loss***" has the meaning set forth in Section 10(a) of the RRD Services Agreement.

"***RRD Personnel***" has the meaning set forth in Section 1(a)(ii) of the RRD Services Agreement.

"***RRD Services Agreement***" means the RRD Services Agreement between Symphony GenIsis and RRD, dated as the Closing Date, 2006.

"***Schedule K-1***" has the meaning set forth in Section 9.02(a) of the Holdings LLC Agreement.

"***Scheduled Meeting***" has the meaning set forth in Paragraph 6 of Annex B of the Amended and Restated Research and Development Agreement.

"***Scientific Discontinuation Event***" has the meaning set forth in Section 4.2(c) of the Amended and Restated Research and Development Agreement.

"***SCP***" means Symphony Capital Partners, L.P., a Delaware limited partnership.

"***SEC***" means the United States Securities and Exchange Commission.

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

"***Selling Stockholder Questionnaire***" has the meaning set forth in Section 4(a) of the Registration Rights Agreement.

"***Shareholder***" means any Person who owns any Symphony GenIsis Shares.

"***Solvent***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***SSP***" means Symphony Strategic Partners, LLC, a Delaware limited liability company.

"***Stock Payment Date***" has the meaning set forth in Section 2 of the Subscription Agreement.

"***Stock Purchase Price***" has the meaning set forth in Section 2 of the Subscription Agreement.

"***Subcontracting Agreement***" has the meaning set forth in Section 6.2 of the Amended and Restated Research and Development Agreement.

"***Sublicensed Intellectual Property***" has the meaning set forth in Section 3.2 of the Novated and Restated Technology License Agreement.

"***Sublicense Obligations***" has the meaning set forth in Section 3.2 of the Novated and Restated Technology License Agreement.

"***Subscription Agreement***" means the Subscription Agreement between Symphony GenIsis and Holdings, dated as the Closing Date.

"***Subsidiary***" of any Person means any corporation, partnership, joint venture, limited liability company, trust or estate of which (or in which) more than 50% of (a) the issued and outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether at the time capital stock of any other class or classes of such corporation shall or might have voting power upon the occurrence of any contingency); (b) the interest in the capital or profits of such partnership, joint venture or limited liability company; or (c) the beneficial interest in such trust or estate is at the time directly or indirectly owned or controlled by such Person, by such Person and one or more of its other Subsidiaries or by one or more of such Person's other Subsidiaries.

"***Surviving Entity***" means the surviving legal entity which is surviving entity to Isis after giving effect to a Change of Control.

"***Symphony Capital***" means Symphony Capital LLC, a Delaware limited liability company.

"***Symphony Fund(s)***" means Symphony Capital Partners, L.P., a Delaware limited partnership, and Symphony Strategic Partners, LLC, a Delaware limited liability company.

"***Symphony GenIsis***" means Symphony GenIsis, Inc., a Delaware corporation.

"***Symphony GenIsis Auditors***" has the meaning set forth in Section 5(b) of the RRD Services Agreement.

"***Symphony GenIsis Board***" means the board of directors of Symphony GenIsis.

"***Symphony GenIsis By-laws***" means the By-laws of Symphony GenIsis, as adopted by resolution of the Symphony GenIsis Board on the Closing Date.

"***Symphony GenIsis Charter***" means the Amended and Restated Certificate of Incorporation of Symphony GenIsis, dated as of the Closing Date.

"***Symphony GenIsis Director Event***" has the meaning set forth in Section 3.01(h)(i) of the Holdings LLC Agreement.

"***Symphony GenIsis Enhancements***" means findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Know-How, Regulatory Files, Products or the Programs, made by or on behalf of Symphony GenIsis during the Term, in each case whether or not patentable, including any such findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes related to data and information generated or derived by RRD and assigned to Symphony GenIsis pursuant to Section 12 of the RRD Services Agreement.

"***Symphony GenIsis Equity Securities***" means the Common Stock and any other stock or shares issued by Symphony GenIsis.

"***Symphony GenIsis Loss***" has the meaning set forth in Section 10(b) of the RRD Services Agreement.

"***Symphony GenIsis Shares***" has the meaning set forth in Section 2.02 of the Holdings LLC Agreement.

"***Tangible Materials***" means any tangible documentation, whether written or electronic, existing as of the Closing Date or during the Term, that is Controlled by the Licensor, embodying or relating to the Licensed Intellectual Property, Regulatory Files, Products or the Programs, including, but not limited to, safety, efficacy or other data related to the Products or Programs, documentation, patent applications and invention disclosures.

"***Tax Amount***" has the meaning set forth in Section 4.02 of the Holdings LLC Agreement.

"***Technology License Agreement***" means the Technology License Agreement, dated as of the Closing Date, between Isis and Holdings.

"***Term***" has the meaning set forth in Section 4(b)(iii) of the Purchase Option Agreement, unless otherwise stated in any Operative Document.

"***Territory***" means the world.

"***Third Party IP***" has the meaning set forth in Section 2.9 of the Novated and Restated Technology License Agreement.

"***Third Party Licensor***" means a third party from which Isis has received a license or sublicense to Licensed Intellectual Property.

"***Transfer***" has for each Operative Document in which it appears the meaning set forth in such Operative Document.

"***Transferee***" has, for each Operative Document in which it appears, the meaning set forth in such Operative Document.

"***Voluntary Bankruptcy***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Warrant Closing***" has the meaning set forth in Section 2.03 of the Warrant Purchase Agreement.

"***Warrant Date***" has the meaning set forth in Section 2.02 of the Warrant Purchase Agreement.

"***Warrant Purchase Agreement***" means the Warrant Purchase Agreement, dated as of the Closing Date, between Isis and Holdings.

"***Warrant Shares***" has the meaning set forth in Section 2.01 of the Warrant Purchase Agreement.

"***Warrant Surrender Price***" has the meaning set forth in Section 7.08 of the Warrant Purchase Agreement.

"***Warrants***" has the meaning set forth in Section 2.01 of the Warrant Purchase Agreement.

EXHIBIT 1

PURCHASE EXERCISE NOTICE

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Attention:

Ladies and Gentlemen:

Reference is hereby made to that certain Purchase Option Agreement dated as of April 7, 2006 (the "***Purchase Option Agreement***") by and among Isis Pharmaceuticals, Inc., a Delaware corporation ("***Isis***"), Symphony GenIsis Holdings LLC, a Delaware limited liability company, and Symphony GenIsis, Inc., a Delaware corporation. Capitalized terms used herein and not otherwise defined herein shall have the meanings assigned thereto in the Purchase Option Agreement.

Pursuant to Section 2(a) of the Purchase Option Agreement, Isis hereby irrevocably notifies you that it hereby exercises the Purchase Option.

Subject to the terms set forth therein, Isis hereby affirms the representations and warranties set forth in Section 3(a) of the Purchase Option Agreement, as of the date hereof.

Isis estimates that the Purchase Option Closing Date will be .

The Purchase Price will be $.

[Isis intends to pay % of the Purchase Price in Isis Common Stock.]

Very truly yours,

ISIS PHARMACEUTICALS, INC.

By: _____

Name: [B. Lynne Parshall, J.D].
Title: [Executive Vice President, Chief Financial Officer and Secretary]

EXHIBIT 2

[FORM OF OPINION OF ISIS' GENERAL COUNSEL]

[***]

Exhibit 10.3

EXECUTION COPY

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

REGISTRATION RIGHTS AGREEMENT

between

ISIS PHARMACEUTICALS, INC.

and

SYMPHONY GENISIS HOLDINGS LLC

Dated as of April 7, 2006

Table of Contents

REGISTRATION RIGHTS AGREEMENT

REGISTRATION RIGHTS AGREEMENT (this "***Agreement***"), dated as of April 7, 2006, by and between ISIS PHARMACEUTICALS, INC., a Delaware corporation ("***Isis***"), and SYMPHONY GENISIS HOLDINGS LLC, a Delaware limited liability company (together with its permitted successors, assigns and transferees, "***Holdings***").

RECITALS:

WHEREAS, in connection with the exercise by Isis of the Purchase Option under the Purchase Option Agreement, by and among Isis, Holdings and Symphony GenIsis, Inc., a Delaware corporation ("***Symphony GenIsis***"), of even date herewith (the "***Purchase Option Agreement***"), Isis may elect to issue

shares of Isis' common stock, par value $0.001 per share ("***Isis Common Stock***") (such shares of Isis Common Stock when and if issued, the "***Purchase Option Shares***") to Holdings in partial payment of the Purchase Price in accordance with the terms of the Purchase Option Agreement;

WHEREAS, in connection with the Warrant Purchase Agreement by and between the parties hereto of even date herewith (the "***Warrant Purchase Agreement***"), Isis has agreed, upon the terms and subject to the conditions of the Warrant Purchase Agreement, to issue and sell on the date hereof to Holdings certain warrants (the "***Warrants***") which will be exercisable to purchase shares of Isis Common Stock (such shares of Isis Common Stock as exercised, the "***Warrant Shares***") in accordance with the terms of the Warrants; and

WHEREAS, to induce Holdings to execute and deliver the Purchase Option Agreement and the Warrant Purchase Agreement, Isis has agreed to provide certain registration rights under the Securities Act of 1933, as amended (the "***Securities Act***"), and applicable state securities laws with respect to the Purchase Option Shares;

NOW, THEREFORE, in consideration of the premises and the mutual covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Isis and Holdings (the "***Parties***") hereby agree as follows:

Section 1. Definitions.

(a) Capitalized terms used but not defined herein are used as defined in the Purchase Option Agreement (including Annex A thereto).

(b) As used in this Agreement, the following terms shall have the following meanings:

(i) "***Effective Registration Date***" means the date that the Registration Statement (as defined below) is first declared effective by the SEC.

(ii) "***Investor(s)***" means Holdings, any transferee or assignee thereof to whom Holdings assigns its rights under this Agreement and who agrees to become bound by the provisions of this Agreement in accordance with Section 9 and any transferee or assignee

thereof to whom a transferee or assignee assigns its rights under this Agreement and who agrees to become bound by the provisions of this Agreement in accordance with Section 9.

(iii) "***Purchase Option Related Registrable Securities***" means (i) the Purchase Option Shares, and (ii) any Isis Common Stock issued with respect to the Purchase Option Shares as a result of any stock split, stock dividend, recapitalization, exchange or similar event or otherwise.

(iv) "***register***," "***registered***," and "***registration***" refer to a registration effected by preparing and filing one or more Registration Statements in compliance with the Securities Act and pursuant to Rule 415, and the declaration or ordering of effectiveness of such Registration Statement(s) by the SEC.

(v) "***Registrable Securities***" means, collectively, the Warrant Related Registrable Securities and the Purchase Option Related Registrable Securities; provided, however, that such securities will cease to be Registrable Securities on the earlier of (A) the date as of which the Investor(s) may sell such securities without restriction pursuant to Rule 144(k) (or successor thereto) promulgated under the Securities Act, or (B) the date on which the Investor(s) shall have sold all such securities.

(vi) "***Registration Statement***" means a registration statement or registration statements of Isis filed under the Securities Act covering the Registrable Securities.

(vii) "***Rule 144***" has the meaning set forth in Section 8 of this Agreement.

(viii) "***Rule 415***" means Rule 415 under the Securities Act or any successor rule providing for offering securities on a continuous or delayed basis.

(ix) "***Warrant Related Registrable Securities***" means (i) the Warrant Shares issued or issuable upon exercise of the Warrants; and (ii) any shares of capital stock issued or issuable with respect to the Warrant Shares or the Warrants as a result of any stock split, stock dividend, recapitalization, exchange or similar event or otherwise, and in the case of the Warrants, without regard to any limitations on exercise.

Section 2. Registration.

(a) Right to Registration.

(i) Purchase Option Related Registration. In the event Isis elects to exercise the Purchase Option as set forth in the Purchase Option Agreement, and in so doing elects to issue Purchase Option Related Registrable Securities, Isis shall prepare and, in accordance with Section 2(a)(ii)(A) of the Purchase Option Agreement, file with the SEC a Registration Statement on Form S-3 covering the resale of the Purchase Option Related Registrable Securities. The Registration Statement prepared pursuant hereto shall register for resale that number of shares of Isis Common Stock equal to the number of Purchase Option Related Registrable Securities as would be issued pursuant to the terms of the Purchase Option Agreement. Isis shall use commercially reasonable efforts to

have the Registration Statement declared effective by the SEC as soon as practicable following the Purchase Option Exercise Date.

(ii) Warrant Related Registration. Isis shall prepare, and, as soon as practicable but in no event later than [***] days after the Closing Date, file with the SEC a Registration Statement on Form S-3 covering the resale of all of the Warrant Related Registrable Securities. The Registration Statement prepared pursuant hereto shall register for resale at least that number of shares of Isis Common Stock equal to the number of Warrant Related Registrable Securities as of the trading day immediately preceding the date the Registration Statement is initially filed with the SEC, subject to adjustment as provided in Section 2(c). Isis shall use commercially reasonable efforts to have the Registration Statement declared effective by the SEC as soon as practicable following the Closing Date.

(b) Ineligibility for Form S-3. In the event that Form S-3 is not available for the registration of the resale of Registrable Securities hereunder, Isis shall (i) register the resale of the Registrable Securities on another appropriate form reasonably acceptable to Holdings (which acceptable forms shall include Form S-1) (in the case of the resale of Purchase Option Related Registrable Securities, in accordance with Section 2(a)(ii)(A) of the Purchase Option Agreement); and (ii) undertake to register the Registrable Securities on Form S-3 as soon as such form is available; provided that Isis shall maintain the effectiveness of the Registration Statement then in effect until such time as a Registration Statement on Form S-3 covering the Registrable Securities has been declared effective by the SEC.

(c) Sufficient Number of Shares Registered. In the event the number of shares available under a Registration Statement filed pursuant to Section 2(a) is insufficient to cover all of the Registrable Securities required to be covered by such Registration Statement, Isis shall amend the applicable Registration Statement, or file a new Registration Statement (on the short form available therefor, if applicable), or both, so as to cover at least 100% of the number of such Registrable Securities as of the trading day immediately preceding the date of the filing of such amendment or new Registration Statement, in each case, as soon as practicable, but in any event not later than fifteen (15) days after Isis becomes aware of the necessity therefor. Isis shall use commercially reasonable efforts to cause such amendment and/or new Registration Statement to become effective as soon as practicable following the filing thereof. For purposes of the foregoing provision, the number of shares available under a Registration Statement shall be deemed "insufficient to cover all of the Registrable Securities" if at any time the number of shares of Isis Common Stock available for resale under such Registration Statement is less than the number of Registrable Securities. The calculation set forth in the foregoing sentence shall be made without regard to any limitations on the exercise of the Warrants and such calculation shall assume that the Warrants are then exercisable into shares of Isis Common Stock.

Section 3. Related Obligations. At such time as Isis is obligated to file a Registration Statement with the SEC pursuant to Section 2(a), 2(b) or 2(c), Isis will use commercially reasonable efforts to effect the registration of the Registrable Securities in accordance with the intended method of disposition thereof and, pursuant thereto (except at such times as Isis may be required to suspend the use of a prospectus forming a part of the Registration Statement pursuant to Section 3(l), at which time Isis' obligations under Sections 3(a), (b), (c), (d), (i) and (k) may also be suspended, as required), Isis shall have the following

obligations:

(a) Isis shall keep each Registration Statement effective pursuant to Rule 415 at all times until the earlier of (i) the date as of which the Investor(s) may sell all of the Registrable Securities covered by such Registration Statement without restriction pursuant to Rule 144(k) (or successor thereto) promulgated under the Securities Act, or (ii) the date on which the Investor(s) shall have sold all the Registrable Securities covered by such Registration Statement (the "***Registration Period***").

(b) Isis shall prepare and file with the SEC such amendments (including post-effective amendments) and supplements to a Registration Statement and the prospectus used in connection with such Registration Statement as may be necessary to keep such Registration Statement effective at all times during the Registration Period, and, during such period, comply with the provisions of the Securities Act with respect to the disposition of all Registrable Securities of Isis covered by such Registration Statement until such time as all of such Registrable Securities shall have been disposed of in accordance with the intended methods of disposition by the seller or sellers thereof as set forth in such Registration Statement. In the case of amendments and supplements to a Registration Statement which are required to be filed pursuant to this Agreement (including pursuant to this Section 3(b)) by reason of Isis filing a report on Form 10-K, Form 10-Q or Form 8-K or any analogous report under the Exchange Act, Isis shall have incorporated such report by reference into such Registration Statement, if applicable, or shall file such amendments or supplements with the SEC on the same day on which the Exchange Act report is filed which created the requirement for Isis to amend or supplement such Registration Statement.

(c) Isis shall furnish to each Investor whose Registrable Securities are included in any Registration Statement, without charge, (i) promptly after the same is prepared and filed with the SEC, at least one copy of such Registration Statement and any amendment(s) thereto, including financial statements and schedules, and each preliminary prospectus; (ii) upon the effectiveness of any Registration Statement, ten (10) copies of the prospectus included in such Registration Statement and all amendments and supplements thereto (or such other number of copies as such Investor may reasonably request); and (iii) such other documents, including copies of any preliminary or final prospectus, as such Investor may reasonably request from time to time in order to facilitate the disposition of the Registrable Securities owned by such Investor.

(d) Isis shall use commercially reasonable efforts to (i) register and qualify, unless an exemption from registration and qualification applies, the resale by Investor(s) of the Registrable Securities covered by a Registration Statement under such other securities or "blue sky" laws of such jurisdictions in the United States as Investor(s) reasonably request; (ii) prepare and file in those jurisdictions such amendments (including post-effective amendments) and supplements to such registrations and qualifications as may be necessary to maintain the effectiveness thereof during the Registration Period; and (iii) take such other actions as may be necessary to maintain such registrations and qualifications in effect at all times during the Registration Period; provided, however, that Isis shall not be required in connection therewith or as a condition thereto to (x) qualify to do business in any jurisdiction where it would not otherwise be required to qualify but for this Section 3(d), (y) subject itself to general taxation in any such jurisdiction, or (z) file a general consent to service of process in any such jurisdiction. Isis shall promptly notify each Investor who holds Registrable Securities of the receipt by Isis of

any notification with respect to the suspension of the registration or qualification of any of the Registrable Securities for sale under the securities or "blue sky" laws of any jurisdiction in the United States or its receipt of actual notice of the initiation or threatening of any proceeding for such purpose.

(e) Isis shall notify each Investor in writing of the happening of any event, as promptly as practicable after becoming aware of such event, as a result of which the prospectus included in a Registration Statement, as then in effect, includes an untrue statement of a material fact or omission to state a material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading, and, subject to Section 3(l) hereof, promptly prepare a supplement or amendment to such Registration Statement to correct such untrue statement or omission. Isis shall also promptly notify each Investor in writing when a prospectus or any prospectus supplement or post-effective amendment has been filed, and when a Registration Statement or any post-effective amendment has become effective.

(f) Isis shall use commercially reasonable efforts to prevent the issuance of any stop order or other suspension of effectiveness of a Registration Statement, or the suspension of the qualification of any of the Registrable Securities for sale in any jurisdiction and, if such an order or suspension is issued, to obtain the withdrawal of such order or suspension at the earliest possible moment.

(g) In the event that any Investor is deemed to be an "underwriter" with respect to the Registrable Securities, upon the written request of such Investor in connection with such Investor's due diligence requirements, if any, Isis shall make available for inspection by (i) such Investor, and (ii) any legal counsel, accountants or other agents retained by the Investor (collectively, "***Inspectors***"), all pertinent financial and other records, and pertinent corporate documents and properties of Isis (collectively, "***Records***"), as shall be reasonably deemed necessary by each Inspector, and cause Isis' officers, directors and employees to supply all information which any Inspector may reasonably request; provided, however, that each Inspector and such Investor shall agree in writing to hold in strict confidence and shall not make any disclosure (except with respect to an Inspector, to the relevant Investor) or use of any Record or other information which Isis determines in good faith to be confidential, and of which determination the Inspectors are so notified, unless the release of such Records is ordered pursuant to a final, non-appealable subpoena or order from a court or government body of competent jurisdiction. Each Investor agrees that it shall, upon learning that disclosure of such Records is required or is sought in or by a court or governmental body of competent jurisdiction or through other means, give prompt notice to Isis and allow Isis, at its expense, to undertake appropriate action to prevent disclosure of, or to obtain a protective order for, the Records deemed confidential. Nothing herein (or in any other confidentiality agreement between Isis and any Investor) shall be deemed to limit the Investor(s)' ability to sell Registrable Securities in a manner which is otherwise consistent with applicable laws and regulations.

(h) Isis shall hold in confidence and not make any disclosure of information concerning an Investor provided to Isis unless (i) disclosure of such information is necessary to comply with federal or state securities laws or the rules of any securities exchange or trading market on which the Isis Common Stock is listed or traded, (ii) the disclosure of such information is necessary to avoid or correct a misstatement or omission in any Registration

Statement, or (iii) the release of such information is ordered pursuant to a subpoena or other final, non-appealable order from a court or governmental body of competent jurisdiction. Isis agrees that it shall, upon learning that disclosure of such information concerning an Investor is sought in or by a court or governmental body of competent jurisdiction or through other means, give prompt written notice to such Investor and allow such Investor, at the Investor's expense, to undertake appropriate action to prevent disclosure of, or to obtain a protective order for, such information.

(i) Isis shall use commercially reasonable efforts either to (i) cause all the Registrable Securities covered by a Registration Statement to be listed on each securities exchange on which securities of the same class or series issued by Isis are then listed, if any, if the listing of such Registrable Securities is then permitted under the rules of such exchange, or (ii) secure designation and quotation of all the Registrable Securities covered by a Registration Statement on the NASDAQ National Market. Isis shall pay all fees and expenses in connection with satisfying its obligation under this Section 3(i).

(j) Isis shall cooperate with the Investor(s) who hold Registrable Securities being offered and, to the extent applicable, facilitate the timely preparation and delivery of certificates representing the Registrable Securities to be offered pursuant to a Registration Statement and enable such certificates to be in such denominations or amounts, as the case may be, as the Investor(s) may reasonably request and registered in such names as the Investor(s) may request.

(k) If requested by an Investor, Isis shall (i) as soon as practicable incorporate in a prospectus supplement or post-effective amendment such information as an Investor reasonably requests to be included therein relating to the sale and distribution of Registrable Securities, including, without limitation, information with respect to the number of Registrable Securities being offered or sold, the purchase price being paid therefor and any other terms of the offering of the Registrable Securities to be sold in such offering and (ii) as soon as practicable make all required filings of such prospectus supplement or post-effective amendment after being notified of the matters to be incorporated in such prospectus supplement or post-effective amendment.

(l) Notwithstanding anything to the contrary herein, at any time after the Registration Statement has been declared effective by the SEC, Isis may delay the disclosure of material, non-public information concerning Isis the disclosure of which at the time is not, in the good faith opinion of Isis, in the best interest of Isis (a "***Grace Period***"); provided, that Isis shall promptly notify the Investor(s) in writing of the existence of a Grace Period in conformity with the provisions of this Section 3(l) and the date on which the Grace Period will begin (such notice, a "***Commencement Notice***"); and, provided further, that no Grace Period shall exceed [***] days during any [***] day period and during any [***] day period such Grace Periods shall not exceed an aggregate of [***] days. For purposes of determining the length of a Grace Period above, the Grace Period shall begin on and include the date specified by Isis in the Commencement Notice and shall end on and include the date the Investor(s) receive written notice of the termination of the Grace Period by Isis (which notice may be contained in the Commencement Notice). The provisions of Section 3(f) hereof shall not be applicable during any Grace Period. Upon expiration of the Grace Period, Isis shall again be bound by the first sentence of Section 3(e) with respect to the information giving rise thereto unless such material,

non-public information is no longer applicable. Notwithstanding anything to the contrary, Isis shall cause its transfer agent to deliver unlegended shares of Isis Common Stock to a transferee of an Investor in accordance with the terms of the Warrant Purchase Agreement in connection with any sale of Registrable Securities with respect to which an Investor has entered into a contract for sale, and delivered a copy of the prospectus included as part of the applicable Registration Statement, prior to the Investor's receipt of the notice of a Grace Period and for which the Investor has not yet settled.

Section 4. Obligations of the Investor(s).

(a) At least [***] Business Days prior to the first anticipated filing date of a Registration Statement, Isis shall notify each Investor in writing of the information Isis requires from each such Investor if such Investor elects to have any of such Investor's Registrable Securities included in such Registration Statement and provide each such Investor with a copy of Isis' then-current selling stockholder questionnaire (a copy of which is attached hereto as Exhibit A hereto, a "***Selling Stockholder Questionnaire***"). It shall be a condition precedent to the obligations of Isis to complete the registration pursuant to this Agreement with respect to the Registrable Securities of a particular Investor that such Investor shall furnish to Isis a completed Selling Stockholder Questionnaire, along with such other information regarding itself, the Registrable Securities held by it and the intended method of disposition of the Registrable Securities held by it as may reasonably be required to effect the effectiveness of the registration of such Registrable Securities, and shall execute other such documents in connection with such registration as Isis may reasonably request.

(b) Each Investor, by such Investor's acceptance of the Registrable Securities, agrees to cooperate with Isis as reasonably requested by Isis in connection with the preparation and filing of any Registration Statement hereunder, unless such Investor has notified Isis in writing of such Investor's election to exclude all of such Investor's Registrable Securities from such Registration Statement.

(c) Each Investor agrees that, upon receipt of any notice from Isis of the happening of any event of the kind described in Section 3(f) or the first sentence of Section 3(e), such Investor will immediately discontinue disposition of Registrable Securities pursuant to any Registration Statement(s) covering such Registrable Securities until such Investor's receipt of the copies of the supplemented or amended prospectus contemplated by the second sentence of Section 3(e) or receipt of notice that no supplement or amendment is required.

(d) Each Investor covenants and agrees that it will comply with any applicable prospectus delivery requirements of the Securities Act as applicable to it in connection with sales of Registrable Securities pursuant to a Registration Statement.

Section 5. Expenses of Registration. All reasonable expenses, other than underwriting discounts and commissions, incurred in connection with registrations, filings or qualifications pursuant to Sections 2 and 3 hereof, including, without limitation, all registration, listing and qualifications fees, printers and accounting fees, and fees and disbursements of counsel for Isis shall be paid by Isis. All underwriting discounts and selling commissions applicable to the sale of the Registrable Securities shall be paid by the Investor(s), provided, however, that Isis shall reimburse the Investor(s) for the reasonable actual fees and

disbursements of one legal counsel designated by the holders of at least a majority of the Registrable Securities in connection with registration, filing or qualification pursuant to Sections 2 and 3 of this Agreement, which amount shall be limited to [***] in total over the term of this Agreement.

Section 6. Indemnification. In the event any Registrable Securities are included in a Registration Statement under this Agreement:

(a) To the fullest extent permitted by law, Isis will, and hereby does, indemnify and hold harmless each Investor, the directors, officers, partners, members, employees, agents, representatives of, and each Person, if any, who controls any Investor within the meaning of the Securities Act or the Exchange Act (each, an "***Investor Indemnified Person***"), against any losses, claims, damages, liabilities, judgments, fines, penalties, charges, costs, reasonable attorneys' fees, amounts paid in settlement or expenses, joint or several with an aggregate value of at least [***] (as determined by the applicable Indemnified Parties acting in good faith), (collectively, "***Claims***"), incurred in investigating, preparing or defending any action, claim, suit, inquiry, proceeding, investigation or appeal taken from the foregoing by or before any court or governmental, administrative or other regulatory agency, body or the SEC, whether pending or threatened, whether or not an Indemnified Person is or may be a party thereto ("***Indemnified Damages***"), to which any of them may become subject to the extent that such Claims (or actions or proceedings, whether commenced or threatened, in respect thereof) arise out of or are based upon: (i) any untrue statement or alleged untrue statement of a material fact in a Registration Statement or any post-effective amendment thereto or in any filing made in connection with the qualification of the offering under the securities or other "blue sky" laws of any jurisdiction in which Registrable Securities are offered ("***Blue Sky Filing***"), or the omission or alleged omission to state a material fact required to be stated therein or necessary to make the statements therein not misleading; (ii) any untrue statement or alleged untrue statement of a material fact contained in any preliminary prospectus if used prior to the Effective Registration Date of such Registration Statement, or contained in the final prospectus (as amended or supplemented, if Isis files any amendment thereof or supplement thereto with the SEC) or the omission or alleged omission to state therein any material fact necessary to make the statements made therein, in the light of the circumstances under which the statements therein were made, not misleading; (iii) any violation or alleged violation by Isis of any federal, state or common law, rule or regulation applicable to Isis in connection with any Registration Statement, prospectus or any preliminary prospectus, any amendment or supplement thereto, or the issuance of any Registrable Securities to Holdings; or (iv) any material violation of this Agreement (the matters in the foregoing clauses (i) through (iv) being, collectively, "***Violations***"). Subject to Section 6(c), Isis shall reimburse the Investor Indemnified Persons, promptly as such expenses are incurred and are due and payable, for any legal fees or other reasonable expenses incurred by them in connection with investigating or defending any such Claim. Notwithstanding anything to the contrary contained herein, the indemnification agreement contained in this Section 6(a): (A) shall not apply to a Claim by an Investor Indemnified Person arising out of or based upon a Violation that occurs in reliance upon and in conformity with information furnished in writing to Isis by or on behalf of any such Investor Indemnified Person expressly for use in connection with the preparation of the Registration Statement or any such amendment thereof or supplement thereto if such information was timely made available by Isis pursuant to Section 3(c); (B) with respect to any preliminary prospectus, shall not inure to the benefit of any such Person from whom the Person asserting any such Claim purchased the Registrable Securities that are the

subject thereof (or to the benefit of any Person controlling such Person) if the untrue statement or omission of material fact contained in the preliminary prospectus was corrected in the prospectus, as then amended or supplemented, if such prospectus was timely made available by Isis pursuant to Section 3(d), and the Investor Indemnified Person was promptly advised in writing not to use the incorrect prospectus prior to the use giving rise to a violation and such Investor Indemnified Person, notwithstanding such advice, used it or failed to deliver the correct prospectus as required by the Securities Act and such correct prospectus was timely made available pursuant to Section 3(d); (C) shall not be available to the extent such Claim is based on a failure of the Investor Indemnified Person to deliver or to cause to be delivered the prospectus made available by Isis, including a corrected prospectus, if such prospectus or corrected prospectus was timely made available by Isis pursuant to Section 3(d); and (D) shall not apply to amounts paid in settlement of any Claim if such settlement is effected without the prior written consent of Isis, which consent shall not be unreasonably withheld or delayed. Such indemnity shall remain full

force and effect regardless of any investigation made by or on behalf of the Investor Indemnified Person and shall survive the transfer of the Registrable Securities by the Investor(s) pursuant to Section 9.

(b) In connection with any Registration Statement in which an Investor is participating, each such Investor agrees to severally and not jointly indemnify, and hold harmless, to the same extent and in the same manner as is set forth in Section 6(a), Isis, each of its directors, each of its officers who signs the Registration Statement, each Person, if any, who controls Isis within the meaning of the Securities Act or the Exchange Act, and Isis' general counsel to the extent that such counsel delivers one or more legal opinions in conjunction with the preparation and filing of the Registration Statement (each, a "***Company Indemnified Person***"), against any Claim or Indemnified Damages to which any of them may become subject, under the Securities Act, the Exchange Act or otherwise, insofar as such Claim or Indemnified Damages arise out of or are based upon any Violation, in each case to the extent, and only to the extent, that such Violation occurs in reliance upon and in conformity with written information furnished to Isis by such Investor expressly for use in connection with such Registration Statement; and, subject to Section 6(d), such Investor will reimburse, promptly as such expenses are incurred and are due and payable, any legal or other expenses reasonably incurred by a Company Indemnified Person in connection with investigating or defending any such Claim; provided, however, that the indemnity agreement contained in this Section 6(b) and the agreement with respect to contribution contained in Section 7 shall not apply to amounts paid in settlement of any Claim if such settlement is effected without the prior written consent of such Investor, which consent shall not be unreasonably withheld or delayed; provided, further, however, that an Investor shall be liable under this Section 6(b) for only that amount of a Claim or Indemnified Damages as does not exceed the net proceeds to such Investor as a result of the sale of Registrable Securities pursuant to such Registration Statement. Such indemnity shall remain in full force and effect regardless of any investigation made by or on behalf of such Company Indemnified Person and shall survive the transfer of the Registrable Securities by the Investor(s) pursuant to Section 9. Notwithstanding anything to the contrary contained herein, the indemnification agreement contained in this Section 6(b) with respect to any preliminary prospectus shall not inure to the benefit of any Company Indemnified Person if the untrue statement or omission of material fact contained in the preliminary prospectus was corrected on a timely basis in the prospectus, as then amended or supplemented.

(c) If either an Investor Indemnified Person or a Company Indemnified

Person (an "***Indemnified Person***") proposes to assert a right to be indemnified under this Section 6, such Indemnified Person shall notify either Isis or the relevant Investor(s), as applicable (the "***Indemnifying Person***"), promptly after receipt of notice of commencement of any action, suit or proceeding against such Indemnified Person (an "***Indemnified Proceeding***") in respect of which a Claim is to be made under this Section 6, or the incurrence or realization of any Indemnified Damages in respect of which a Claim is to be made under this Section 6, of the commencement of such Indemnified Proceeding or of such incurrence or realization, enclosing a copy of all relevant documents, including all papers served and claims made, but the omission to so notify the applicable Indemnifying Person promptly of any such Indemnified Proceeding or incurrence or realization shall not relieve (x) such Indemnifying Person from any liability that it may have to such Indemnified Person under this Section 6 or otherwise, except, as to such Indemnifying Person's liability under this Section 6, to the extent, but only to the extent, that such Indemnifying Person shall have been prejudiced by such omission, or (y) any other Indemnifying Person from liability that it may have to any Indemnified Person under the Operative Documents.

(d) In case any Indemnified Proceeding shall be brought against any Indemnified Person and it shall notify the applicable Indemnifying Person of the commencement thereof as provided by Section 6(c) and such Indemnifying Person shall be entitled to participate in, and provided such Indemnified Proceeding involves a claim solely for money damages and does not seek an injunction or other equitable relief against the Indemnified Person and is not a criminal or regulatory action, to assume the defense of, such Indemnified Proceeding with counsel reasonably satisfactory to such Indemnified Person, and after notice from such Indemnifying Person to such Indemnified Person of such Indemnifying Person's election so to assume the defense thereof and the failure by such Indemnified Person to object to such counsel within ten (10) Business Days following its receipt of such notice, such Indemnifying Person shall not be liable to such Indemnified Person for legal or other expenses related to such Indemnified Proceedings incurred after such notice of election to assume such defense except as provided below and except for the reasonable costs of investigating, monitoring or cooperating in such defense subsequently incurred by such Indemnified Person reasonably necessary in connection with the defense thereof. Such Indemnified Person shall have the right to employ its counsel in any such Indemnified Proceeding, but the fees and expenses of such counsel shall be at the expense of such Indemnified Person unless:

(i) the employment of counsel by such Indemnified Person at the expense of the applicable Indemnifying Person has been authorized in writing by such Indemnifying Person;

(ii) such Indemnified Person shall have reasonably concluded in its good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between the applicable Indemnifying Person and such Indemnified Person in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes of action available to such Indemnified Person (it being agreed that in any case referred to in this clause (ii) such Indemnifying Person shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Person);

(iii) the applicable Indemnifying Person shall not have employed counsel reasonably acceptable to the Indemnified Person, to assume the defense of such Indemnified Proceeding within a reasonable time after notice of the commencement thereof; provided, however, that (A) this clause (iii) shall not be deemed to constitute a waiver of any conflict of interest that may arise with respect to any such counsel, and (B) an Indemnified Person may not invoke this clause (iii) if such Indemnified Person failed to timely object to such counsel pursuant to the first paragraph of this Section 6(d) above (it being agreed that in any case referred to in this clause (iii) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party); or

(iv) any counsel employed by the applicable Indemnifying Person shall fail to timely commence or reasonably conduct the defense of such Indemnified Proceeding, and such failure has prejudiced (or is in immediate danger of prejudicing) the outcome of such Indemnified Proceeding (it being agreed that in any case referred to in this clause (iv) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

in each of which cases the fees and expenses of counsel for such Indemnified Person shall be at the expense of such Indemnifying Person. Only one counsel shall be retained by all Indemnified Persons with respect to any Indemnified Proceeding, unless counsel for any Indemnified Person reasonably concludes in good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between such Indemnified Person and one or more other Indemnified Persons in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes or action available to such Indemnified Person.

(e) Without the prior written consent of such Indemnified Person, such Indemnifying Person shall not settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding, unless such settlement, compromise, consent or related judgment (i) includes an unconditional release of such Indemnified Person from all liability for Losses arising out of such claim, action, investigation, suit or other legal proceeding, (ii) provides for the payment of money damages as the sole relief for the claimant (whether at law or in equity), (iii) involves no finding or admission of any violation of law or the rights of any Person by the Indemnified Person, and (iv) is not in the nature of a criminal or regulatory action. No Indemnified Person shall or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding (A) in respect of which any payment would result hereunder or under any other Operative Document, (B) which includes an injunction that will adversely affect any Indemnifying Person, (C) which involves a finding or admission of any violation of law or the rights of any Indemnifying Person, or (D) which is in the nature of a criminal or regulatory action, without the prior written consent of the Indemnifying Person, such consent not to be unreasonably conditioned, withheld or delayed.

(f) The indemnification required by this Section 6 shall be made by periodic payments of the amount of Claims during the course of the investigation or defense, as and when Indemnified Damages are incurred.

Section 7. Contribution. To the extent any indemnification by an Indemnifying Person is prohibited or limited by law, such Indemnifying Person agrees to make the maximum contribution with respect to any amounts for which it would otherwise be liable under Section 6 to the fullest extent permitted by law; provided, however, that: (i) no Person involved in the sale of Registrable Securities which Person is guilty of fraudulent misrepresentation (within the meaning Section 11(f) of the Securities Act) in connection with such sale shall be entitled to contribution from any Person involved in such sale of Registrable Securities who was not guilty of fraudulent misrepresentation; and (ii) contribution by any seller of Registrable Securities shall be limited in amount to the net amount of proceeds received by such seller from the sale of such Registrable Securities pursuant to such Registration Statement.

Section 8. Reports Under The Exchange Act. With a view to making available to the Investor(s) the benefits of Rule 144 promulgated under the Securities Act or any other similar rule or regulation of the SEC that may at any time permit the Investor(s) to sell securities of Isis to the public without registration ("***Rule 144***"), Isis agrees to use commercially reasonable efforts to:

(a) make and keep public information available, as those terms are understood and defined in Rule 144;

(b) file with the SEC in a timely manner all reports and other documents required of Isis under the Securities Act and the Exchange Act so long as Isis remains subject to such requirements and the filing of such reports and other documents is required for the applicable provisions of Rule 144; and

(c) furnish to each Investor so long as such Investor owns Registrable Securities, promptly upon request, (i) a written statement by Isis, if true, that it has complied with the reporting requirements of Rule 144, the Securities Act and the Exchange Act, (ii) a copy of the most recent annual or quarterly report of Isis and such other reports and documents so filed by Isis, and (iii) such other information as may be reasonably requested to permit the Investor(s) to sell such securities pursuant to Rule 144 without registration.

Section 9. Assignment of Registration Rights. The rights under this Agreement with respect to the Warrant Related Registrable Securities shall be automatically assignable by the Investor(s) to any transferee of all or at least [***] shares of such Investor's Registrable Securities (or if an Investor shall hold less than [***] such shares, then a transfer of all such shares) if: (i) the Investor agrees in writing with the transferee or assignee to assign such rights, and a copy of such agreement is furnished to Isis within a reasonable time after such assignment; (ii) Isis is, within a reasonable time after such transfer or assignment, furnished with written notice of (A) the name and address of such transferee or assignee, and (B) the securities with respect to which such registration rights are being transferred or assigned; (iii) immediately following such transfer or assignment the further disposition of such securities by the transferee or assignee is restricted under the Securities Act and applicable state securities laws; (iv) at or before the time Isis receives the written notice contemplated by clause (ii) of this sentence the transferee or assignee agrees in writing with Isis to be bound by all of the provisions contained herein and has provided Isis with a completed Selling Stockholder Questionnaire; and (v) such transfer shall have been made in accordance with the applicable transfer requirements set forth in Article VI of the Warrant Purchase Agreement.

Section 10. Amendment.

(a) The terms of this Agreement shall not be altered, modified, amended, waived or supplemented in any manner whatsoever except by a written instrument signed by each of (i) Isis and (ii) Investor(s) holding a majority of the Registrable Securities (other than in the case of any alteration, modification, amendment, waiver or supplement which affects any individual Investor in a manner that is less favorable or more detrimental to such Investor than to the other Investor(s) solely based on the face of such alteration, modification, amendment, waiver or supplement and without regard to the number of Registrable Securities held by such Investor, in which case, such alteration, modification, amendment, waiver or supplement must also be approved by such less favorably or more detrimentally treated Investor).

(b) Notwithstanding Section 10(a), any party hereto may waive, solely with respect to itself, any one or more of its rights hereunder without the consent of any other party hereto; provided that no such waiver shall be effective unless set forth in a written instrument executed by the party against whom such waiver is to be effective.

Section 11. Miscellaneous.

(a) A Person is deemed to be a holder of Registrable Securities whenever such Person owns or is deemed to own of record such Registrable Securities. If Isis receives conflicting instructions, notices or elections from two or more Persons with respect to the same Registrable Securities, Isis shall act upon the basis of instructions, notice or election received from the such record owner of such Registrable Securities.

(b) Any notice, request, demand, waiver, consent, approval or other communication which is required or permitted to be given to any party hereto shall be in writing and shall be deemed given only if delivered to the party personally or sent to the party by facsimile transmission (promptly followed by a hard-copy delivered in accordance with this Section 11(b)), by next Business Day delivery by a nationally recognized courier service, or by registered or certified mail (return receipt requested), with postage and registration or certification fees thereon prepaid, addressed to the party at its address set forth below:

If to Isis:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: B. Lynne Parshall
Fax: (760) 603-4652

with a copy to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: General Counsel
Fax: (760) 268-4922

If to Holdings:

Symphony GenIsis Holdings LLC
7361 Calhoun Place, Suite 325
Rockville, MD 20850
Attn: Joseph P. Clancy
Facsimile: (301) 762-6154

with a copy to:

Symphony Capital Partners, L.P.
875 Third Avenue, 18th Floor
New York, NY 10022
Facsimile: (212) 632-5401

and

Symphony Strategic Partners, LLC
875 Third Avenue, 18th Floor
New York, NY 10022
Facsimile: (212) 632-5401

or to such other address as such party may from time to time specify by notice given in the manner provided herein to each other party entitled to receive notice hereunder.

(c) This Agreement shall be governed by, and construed in accordance with, the laws of the State of New York; except to the extent that this Agreement pertains to the internal governance of Holdings, and to such extent this Agreement shall be governed and construed in accordance with the laws of the State of Delaware.

(d) Each of the parties hereto hereby irrevocably and unconditionally submits, for itself and its property, to the nonexclusive jurisdiction of any New York State court, any Delaware State court or federal court of the United States of America sitting in The City of New York, Borough of Manhattan or Wilmington, Delaware, and any appellate court from any jurisdiction thereof, in any action or proceeding arising out of or relating to this Agreement, or for recognition or enforcement of any judgment, and each of the parties hereto hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in any such New York State court, any such Delaware State court or, to the fullest extent permitted by law, in such federal court. Each of the parties hereto agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. Nothing in this Agreement shall affect any right that any party hereto may otherwise have to bring any action or proceeding relating to this Agreement.

(e) Each of the parties hereto irrevocably and unconditionally waives, to the fullest extent it may legally and effectively do so, any objection that it may now or hereafter have to the laying of venue of any suit, action or proceeding arising out of or relating to this Agreement in any New York State or federal court, or any Delaware State or Federal court.

Each of the parties hereto hereby irrevocably waives, to the fullest extent permitted by law, the defense of an inconvenient forum to the maintenance of such action or proceeding in any such court. Each of the parties hereby consent to service of process by mail.

(f) WAIVER OF JURY TRIAL. EACH OF THE PARTIES HERETO IRREVOCABLY WAIVES ALL RIGHT TO TRIAL BY JURY IN ANY ACTION, PROCEEDING OR COUNTERCLAIM (WHETHER BASED ON CONTRACT, TORT OR OTHERWISE) ARISING OUT OF OR RELATING TO THIS AGREEMENT.

(g) Entire Agreement. This Agreement (including any Annexes, Schedules, Exhibits or other attachments hereto) constitutes the entire agreement between the parties hereto with respect to the matters covered hereby and supersedes all prior agreements and understandings with respect to such matters between the parties hereto.

(h) Successors; Assignment; Counterparts.

(i) Nothing expressed or implied herein is intended or shall be construed to confer upon or to give to any Person, other than the parties hereto, any right, remedy or claim under or by reason of this Agreement or of any term, covenant or condition hereof, and all the terms, covenants, conditions, promises and agreements contained herein shall be for the sole and exclusive benefit of the parties hereto and their successors and permitted assigns provided, however, that, subject to the requirements of Section 9, this Agreement shall inure to the benefit of and be binding upon the permitted successors and assigns of each of the parties hereto.

(ii) This Agreement may be executed in one or more counterparts, each of which, when executed, shall be deemed an original but all of which taken together shall constitute one and the same Agreement.

(i) Each party shall do and perform, or cause to be done and performed, all such further acts and things, and shall execute and deliver all such other agreements, certificates, instruments and documents, as any other party may reasonably request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

(j) All consents and other determinations required to be made by the Investor(s) pursuant to this Agreement shall be made, unless otherwise specified in this Agreement, by Investor(s) holding at least a majority of the Registrable Securities.

[SIGNATURES FOLLOW ON NEXT PAGE]

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their respective officers or other representatives thereunto duly authorized, as of the date first above written.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall, J.D.

Name: B. Lynne Parshall, J.D.

Title: Executive Vice President, Chief Financial Officer and Secretary

SYMPHONY GENISIS HOLDINGS LLC

By: Symphony Capital Partners, L.P., its Manager

By: Symphony Capital GP, L.P., its general partner

By: Symphony GP, LLC, its general partner

By: /s/ Mark Kessel

Name: Mark Kessel

Title: Managing Member

FORM OF SELLING STOCKHOLDER QUESTIONNAIRE

NOTICE

The undersigned beneficial owner (the "***Selling Securityholder***") of Registrable Securities hereby gives notice to Isis Pharmaceuticals, Inc. (the "***Company***") of its intention to sell or otherwise dispose of Registrable Securities beneficially owned by it and listed below in Item 3 (unless otherwise specified under such Item 3) pursuant to the Registration Statement, pursuant to the terms of the Registration Rights Agreement (the "***Registration Rights Agreement***") dated as of April 7, 2006, by and between Isis and Symphony GenIsis Holdings LLC ("***Holdings***"). Capitalized terms used but not defined herein are used as defined in Registration Rights Agreement.

The undersigned hereby gives notice to the Company of its intention to sell the Registrable Securities listed in Item 3 below, pursuant to the Registration Statement and, provides the following information to the Company and represents and warrants that such information is accurate and complete:

QUESTIONNAIRE

1. (a) Full legal name of Selling Securityholder:

   (b) Full legal name of registered holder of the Registrable Securities (if not the same as (a) above) through which Registrable Securities listed in Item 3 below are held:

   (c) Full legal name of DTC participant (if applicable and if not the same as (b) above) through which Registrable Securities listed in Item 3 below are held:

   (d) Status (yes/no) of Selling Securityholder as a registered broker-dealer or an affiliate of a registered broker-dealer (please describe to the extent applicable):

2. Address for notices to Selling Securityholder:

   Telephone:

   Fax:

   Contact Person:

3. Beneficial Ownership of Registrable Securities:

   (a) Type and number of Registrable Securities beneficially owned:

   (b) CUSIP No(s). of such Registrable Securities beneficially owned:

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4. Beneficial ownership of other securities of the Company owned by the Selling Securityholder.

Except as set forth below in this Item 4, the undersigned is not the beneficial or registered owner of any securities of the Company other than the Registrable Securities listed above in Item 3.

   (a) Type and amount of other securities beneficially owned by the Selling Securityholder:

   (b) CUSIP No(s). of such other securities beneficially owned:

5. Relationships with the Company:

Except as set forth below, neither the undersigned nor any of its affiliates, officers, directors or principal equity holders (owners of 5% or more of the equity securities of the undersigned) has held any position or office or has had any other material relationship with the Company (or its predecessors or affiliates) during the past three years.

State any exceptions here:

6. Plan of Distribution:

Except as set forth below, the undersigned (including its donees, distributees or pledgees) intends to distribute the Registrable Securities listed above in Item 3 pursuant to the Registration Statement only as follows (if at all). Such Registrable Securities may be sold from time to time directly by the undersigned or, alternatively, through underwriters, broker-dealers or agents. If the Registrable Securities are sold through underwriters, broker-dealers or agents, the Selling Securityholder will be responsible for any related underwriting discounts or commissions or agents' commissions. Such Registrable Securities may be sold in one or more transactions at fixed prices, at prevailing market prices at the time of sale, at varying prices determined at the time of sale or at negotiated prices. The selling stockholders may sell their shares by one or more of, or a combination of, the following methods: (i) purchases by a broker-dealer as principal and resale by such broker-dealer for its own account pursuant to this prospectus; (ii) ordinary brokerage transactions and transactions in which the broker solicits purchasers; (iii) block trades in which the broker-dealer so engaged will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction; (iv) an over-the-counter distribution in accordance with the rules of the Nasdaq National Market; (v) in privately negotiated transactions; and (vi) in options transactions. The undersigned may also sell Registrable Securities

short and deliver Registrable Securities to close out short positions, or loan or pledge Registrable Securities to broker-dealers that in turn may sell such securities.

State any exceptions here:

Note: In no event will such method(s) of distribution take the form of an underwritten offering of the Registrable Securities without the prior agreement of the Company.

The undersigned acknowledges its obligation to comply with the provisions of the Exchange Act and the rules thereunder relating to stock manipulation, particularly Regulation M thereunder (or any successor rules or regulations), in connection with any offering of Registrable Securities pursuant to the Registration Rights Agreement. The undersigned agrees that neither it nor any person acting on its behalf will engage in any transaction in violation of such provisions.

In the event that the Selling Securityholder transfers all or a portion of the Registrable Securities listed in Item 3 above after the date on which such information is provided to the Company, the Selling Securityholder agrees to notify the transferee(s) at the time of the transfer of its rights and obligations under this Questionnaire and the Registration Rights Agreement.

The Selling Securityholder hereby acknowledges its obligations under the Registration Rights Agreement to indemnify and hold harmless certain persons as set forth therein.

Pursuant to the Registration Rights Agreement, the Company has agreed under certain circumstances to indemnify the Selling Securityholder against certain liabilities.

In accordance with the undersigned's obligation under the Registration Rights Agreement to provide such information as may be required by law for inclusion in the Registration Statement, the undersigned agrees to promptly notify the Company of any inaccuracies or changes in the information provided herein that may occur subsequent to the date hereof at any time while the Registration Statement remains effective, including, without limitation, any change in the undersigned's beneficial ownership of Registrable Securities.

All notices hereunder and pursuant to the Registration Rights Agreement shall be made in writing to the Selling Securityholder at the address set forth in Section 2 above, and to the Company at the address set forth below.

By signing below, the undersigned consents to the disclosure of the information contained herein in its answers to Items 1 through 6 above and the inclusion of such information in the Registration Statement and the related prospectus. The undersigned understands that such information will be relied upon by the Company in connection with the preparation or amendment of the Registration Statement and the related prospectus.

Once this Questionnaire is executed by the Selling Securityholder and delivered to the Company, the terms of this Questionnaire, and the representations and warranties contained

herein, shall be binding on, shall inure to the benefit of and shall be enforceable by the respective successors, heirs, personal representatives and assigns of the Company and the Selling Securityholder (with respect to the Registrable Securities beneficially owned by such Selling Securityholder and listed in Item 3 above). This Agreement shall be governed in all respects by the laws of the State of New York.

IN WITNESS WHEREOF the undersigned, by authority duly given, has caused this Questionnaire to be executed and delivered either in person or by its duly authorized agent.

Dated: _____

Beneficial Owner: _____

By: _____

Name: _____

Title: _____

PLEASE RETURN THE COMPLETED AND EXECUTED QUESTIONNAIRE TO ISIS PHARMACEUTICALS, INC. AT:

1896 Faraday Avenue
Carlsbad, California 92008
Attn: General Counsel

WITH A COPY TO:

1896 Faraday Avenue
Carlsbad, California 92008
Attn: Chief Financial Officer

Exhibit 10.4

EXECUTION COPY

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

NOVATED AND RESTATED

TECHNOLOGY LICENSE AGREEMENT

dated as of April 7, 2006

among

ISIS PHARMACEUTICALS, INC.,

SYMPHONY GENISIS, INC.

and

SYMPHONY GENISIS HOLDINGS LLC

Table of Contents

NOVATED AND RESTATED
TECHNOLOGY LICENSE AGREEMENT

This NOVATED AND RESTATED TECHNOLOGY LICENSE AGREEMENT (this "***Agreement***") is made and effective as of April 7, 2006 by and among, Isis Pharmaceuticals, Inc., a Delaware corporation (the "***Licensor***"), Symphony GenIsis, Inc., a Delaware corporation ("***Symphony GenIsis***") (each of Licensor and Symphony GenIsis being a "***Party***," and collectively, the "***Parties***"), and Symphony GenIsis Holdings LLC, a Delaware limited liability company ("***Holdings***").

WHEREAS, Licensor and Holdings have entered into that certain Technology License Agreement, dated April 7, 2006 (the "***Original Agreement***");

WHEREAS, Holdings desires to assign its right, title and interest in, and delegate and novate its obligations under the Original Agreement to Symphony GenIsis, and Licensor and Symphony GenIsis desire to novate and restate the terms and conditions of the Original Agreement to effect such novation;

WHEREAS, Licensor owns or has rights in certain technology, know-how, patents and other intellectual property rights related to the design, development, manufacture and/or use of the Products;

WHEREAS, Licensor desires to grant to Symphony GenIsis, and Symphony GenIsis desires to acquire, the exclusive (or nonexclusive, as the case may be) right to use such technology, know-how, patents and other intellectual property rights to develop and commercialize Products on the terms and conditions of this Agreement; and

WHEREAS, Licensor desires to receive, and Symphony GenIsis desires to grant to Licensor, the exclusive right to use such technology, know-how, patents and other intellectual property rights to develop Products on behalf of Symphony GenIsis on the terms and conditions of this Agreement.

NOW THEREFORE, in consideration of the mutual promises and agreements set forth herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

ARTICLE 1
DEFINITIONS

Capitalized terms used herein and not defined shall have the meanings assigned to such terms in Annex A attached hereto.

ARTICLE 2
GRANT OF RIGHTS

2.1. Assignment. Holdings hereby assigns to Symphony GenIsis all of its right, title and interest in and to the Original Agreement. The Parties agree that from and after the Closing Date, all of the right, title, interest and obligations of Holdings under the Original

Agreement will be assigned, novated and transferred to, and assumed by, Symphony GenIsis, as amended and restated by this Agreement.

2.2. License Grant.

(a) Subject to Sections 2.3, 2.4, 2.5 and 2.6 below, the limitations and restrictions set forth on Schedule 2.2, and the terms and conditions of this Agreement, Licensor hereby grants to Symphony GenIsis a fully paid, worldwide, exclusive license under the Licensed Intellectual Property, solely to develop, make, have made, use, offer for sale, sell, and import Products in the Exclusive Field; and

(b) Subject to Sections 2.3, 2.4, 2.5 and 2.6 below, the limitations and restrictions set forth on Schedule 2.2, and the terms and conditions of this Agreement, Licensor hereby grants to Symphony GenIsis a fully paid, worldwide, nonexclusive license under the Licensed Intellectual Property, solely to develop, make, have made, use, offer for sale, sell, and import Products in the Nonexclusive Field.

2.3. Sublicense to Licensor. Symphony GenIsis hereby grants to Licensor a fully paid, worldwide, exclusive (even as to Symphony GenIsis) sublicense under the Licensed Intellectual Property, with the right to grant further sublicense(s), to develop, make, have made, use and import Products, or otherwise as necessary or useful to carry out Licensor's obligations or exercise Licensor's rights under the Operative Documents. Notwithstanding the foregoing, Licensor shall only exercise its sublicense rights in connection with and for the purpose of carrying out Licensor's obligations or exercising Licensor's rights under the Operative Documents. In the event of the expiration of a Discontinuation Option without exercise by Licensor, the sublicense set forth in this Section 2.3 shall expire with respect to the Products relating to the Program to which such Discontinuation Option pertained. Upon the unexercised expiration or termination of the Purchase Option without Licensor's exercise of the Purchase Option, the sublicense set forth in this Section 2.3 shall expire with respect to all Products relating to the Program(s) for which Licensor has not exercised the Discontinuation Option.

2.4. Right to Sublicense. Subject to the limitations and restrictions set forth on Schedule 2.2, the license granted hereunder includes the right of Symphony GenIsis to grant sublicenses under the Licensed Intellectual Property, provided, that,

(a) subject to Sections 2.3 and 2.4(b), Symphony GenIsis shall not sublicense any of the rights granted pursuant to Section 2.2 to any third party (including without limitation any Affiliates) during the Term;

(b) notwithstanding (a), in the event of the expiration of a Discontinuation Option without exercise by Licensor, Symphony GenIsis may grant sublicense(s) to third parties (including without limitation Affiliates) of the rights granted pursuant to Section 2.2 with respect to the Products relating to the Program to which such Discontinuation Option pertained;

(c) each sublicense granted is (i) pursuant to a written contract, (ii) consistent with the terms of this Agreement, (iii) does not grant any rights beyond the scope of the license rights granted herein, and (iv) is as protective of Licensor's rights as set forth in this Agreement; and

(d) upon Licensor's written request, Symphony GenIsis shall provide to Licensor copies of any sublicense agreements, provided that (i) Symphony GenIsis may redact any financial or other proprietary information contained therein which does not affect Licensor's rights and (ii) Licensor shall treat its copy of the sublicense agreements as Confidential Information of Symphony GenIsis.

2.5. Partial Reversion of License upon Licensor's Exercise of Discontinuation Option. Licensor and Symphony GenIsis acknowledge that Licensor may exercise its Discontinuation Option pursuant to Section 11.1 of the Amended and Restated Research and Development Agreement. Upon the Discontinuation Option Closing Date, as applicable, (i) the license set forth in Section 2.2 (and the corresponding sublicense under Section 2.3) shall expire with respect to the Products relating to the Program for which Licensor exercised its Discontinuation Option, as applicable, (ii) those patents, know-how and enhancements that were previously part of the Licensed Intellectual Property and relate exclusively to such Program (including its Products) but not to the other Programs, shall be deleted from the relevant intellectual property definitions, and accordingly, Symphony GenIsis shall no longer be responsible for any obligations or costs (including royalties or fees to third parties, prosecution costs, maintenance costs and enforcement costs) accruing after such Discontinuation Option Closing Date with respect to such patents, know-how and enhancements; and (iii) Symphony GenIsis shall (a) at Licensor's request and option, promptly return to Licensor or destroy all Tangible Materials relating solely to such Program; and (b) upon Licensor's request, provide Licensor a copy of any Tangible Materials which relate to such Program (but not solely to such Program). The Parties shall, as necessary, promptly amend this Agreement, in connection with the exercise and consummation of the Discontinuation Option pursuant to Section 11.1 of the Amended and Restated Research and Development Agreement, to give Licensor all rights it needs to pursue the Program for which such option was exercised without any obligation to or dependency on Symphony GenIsis and to limit this Agreement to the other Programs.

2.6. Reservation of Rights. All rights not expressly granted to a Party hereunder shall remain the exclusive property of the other Party. Symphony GenIsis covenants and agrees not to use or exploit the Licensed Intellectual Property outside of the scope of the licenses granted herein.

Licensor covenants and agrees not to use or exploit the Licensed Intellectual Property in connection with the development, manufacture, use, sale, or importation of Products in the Exclusive Field after the expiration of all sublicenses granted pursuant to Section 2.3; provided, however, that such covenant by Licensor shall not apply to any Program for which Licensor exercises a Discontinuation Option or to any Products relating to such Program. For the avoidance of doubt, Isis shall not be restricted from using or otherwise exploiting any intellectual property relating to drug discovery platforms outside the fields of the Products and/or the Programs.

2.7. Regulatory Files After Expiration or Termination of Term or Discontinuation Option.

(a) As soon as reasonably practical after the expiration or termination of the Purchase Option without exercise by Licensor and as of a date to be agreed upon by Licensor and Symphony GenIsis, Licensor and Symphony GenIsis shall, at Symphony GenIsis' expense, take all actions necessary to effect the assignment to Symphony GenIsis or its designee of the

sponsorship to the Regulatory Files with respect to the Programs for which Licensor has not exercised its Discontinuation Option. After such Regulatory Files are assigned to Symphony GenIsis, Licensor shall have no further rights therein or obligations thereunder; provided, however, that during the one hundred eighty (180) days following such assignment of Regulatory Files, at Symphony GenIsis' reasonable request and expense, Licensor shall use commercially reasonable efforts to provide Symphony GenIsis or its designee with assistance in respect of such Regulatory Files. Licensor shall, at the reasonable request of Symphony GenIsis and at Symphony GenIsis' expense, perform any acts that Symphony GenIsis may reasonably deem necessary or desirable to evidence or confirm Symphony GenIsis' ownership interest in such Regulatory Files, including, but not limited to, making further written assignments in a form determined by Symphony GenIsis. Without limiting the license rights granted under this ARTICLE 2, the Parties understand and agree that the assignment of such Regulatory Files does not include an assignment of any Licensed Intellectual Property.

(b) As soon as reasonably practical after the expiration of a Discontinuation Option without exercise by Licensor and as of a date to be agreed upon by Licensor and Symphony GenIsis, Licensor and Symphony GenIsis shall, at Symphony GenIsis' expense, take all actions necessary to effect the assignment to Symphony GenIsis or its designee of the sponsorship to the Regulatory Files with respect to the Programs for which Licensor has not exercised its Discontinuation Option. After such Regulatory Files are assigned to Symphony GenIsis, Licensor shall have no further rights therein or obligations thereunder; provided, however, that during the one hundred eighty (180) days following such assignment of Regulatory Files, at Symphony GenIsis' reasonable request and expense, Licensor shall use commercially reasonable efforts to provide Symphony GenIsis or its designee with assistance in respect of such Regulatory Files. Licensor shall, at the reasonable request of Symphony GenIsis and at Symphony GenIsis' expense, perform any acts that Symphony GenIsis may reasonably deem necessary or desirable to evidence or confirm Symphony GenIsis' ownership interest in such Regulatory Files, including, but not limited to, making further written assignments in a form determined by Symphony GenIsis. Without limiting the license rights granted under this ARTICLE 2, the Parties understand and agree that the assignment of such Regulatory Files does not include an assignment of any Licensed Intellectual Property.

2.8. Delivery of Materials After Expiration or Termination of Term.

(a) Upon the unexercised expiration or termination of the Purchase Option without exercise by Licensor, Licensor shall, at Symphony GenIsis' expense, promptly deliver to Symphony GenIsis all copies of Tangible Materials existing as of the date of such unexercised expiration or termination that relate to the Programs for which Licensor has not exercised its Discontinuation Option; provided, however that Licensor may also retain copies of (and the right to use) those Tangible Materials that are required to be delivered to Symphony GenIsis hereunder but which also relate to (i) any Program for which Licensor has exercised its Discontinuation Option or (ii) any other product of Licensor.

(b) In the event of the expiration of a Discontinuation Option without exercise by Licensor, Licensor shall, at Symphony GenIsis' expense, promptly deliver to Symphony GenIsis all copies of Tangible Materials existing as of the date of such expiration that relate to the Program to which the Discontinuation Option pertained; provided, however that Licensor may

also retain copies of (and the right to use) those Tangible Materials that are required to be delivered to Symphony GenIsis hereunder but which also relate to any other Program or any other product of Licensor.

(c) Subsequent to any such unexercised expiration or termination of the Purchase Option without exercise by Licensor or expiration of a Discontinuation Option without exercise by Licensor, (i) Licensor shall promptly notify Symphony GenIsis (and any subsequent partners or transferees of Symphony GenIsis' rights hereunder) regarding any safety or other related issues that Licensor identifies in its safety database that may be relevant to a Product being developed by Symphony GenIsis (or any such partner or transferee) hereunder, and if requested, provide the data supporting Licensor's conclusions regarding such issues, and (ii) Symphony GenIsis shall use commercially reasonable, good faith efforts, to negotiate with any of its subsequent partners or transferees of Symphony GenIsis' rights hereunder to ensure, Isis' continued access to safety data and other related information acquired by Symphony GenIsis or any subsequent partners or transferees of Symphony GenIsis' rights hereunder [***].

2.9. License Opportunities. In the event that, during the Term, Licensor reasonably determines that it is necessary to license from any third party any intellectual property relating to the composition of matter, use, manufacture, formulation or exploitation of the Products ("***Third Party IP***") and Licensor desires to license such Third Party IP during the Term, then (i) if Licensor desires Symphony GenIsis to pay any or all of the financial obligations under such license, Licensor shall obtain Symphony GenIsis' written consent, which shall not be unreasonably withheld or delayed before acquiring such license; and (ii) if Symphony GenIsis provides such consent, then unless otherwise agreed to by the Parties in writing, Licensor shall use commercially reasonable efforts to obtain, at the time such license is granted, the right to sublicense such Third Party IP to Symphony GenIsis consistent with the terms of this Agreement as if such Third Party IP were Licensed Intellectual Property. Unless otherwise agreed to by the Parties in writing, the financial obligations under any licenses to Third Party IP obtained by Licensor with Symphony GenIsis' consent shall (1) be borne fully by Symphony GenIsis if such Third Party IP relates solely to the composition of matter, use, manufacture, formulation or exploitation of the Products and, at the time of entering into such third party license, Licensor has not exercised its Discontinuation Option with respect to the Program to which such Third Party IP relates; or (2) be shared by the Parties in amounts and/or percentages to be agreed upon by the Parties prior to Licensor entering into such third party license, if such Third Party IP relates (but does not relate solely) to the composition of matter, use, manufacture, formulation or exploitation of Products within Program(s) for which

Licensor has not exercised its Discontinuation Option and also relates to either (x) the composition of matter, use, manufacture, formulation or exploitation of Products within Program(s) for which Licensor has exercised its Discontinuation Option or (y) the composition of matter, use, manufacture, formulation or exploitation of other products of Licensor; or (3) be borne fully by Licensor if such Third Party IP relates solely to the composition of matter, use, manufacture, formulation or exploitation of Product(s) within a Program(s) for which Licensor has exercised its Discontinuation Option. Notwithstanding the foregoing, Licensor shall have no obligation to obtain any such third party licenses under this Agreement or, in the event that Symphony GenIsis does not give such consent, to grant any sublicenses to Symphony GenIsis. Upon obtaining a license to such Third Party IP and the right to sublicense to Symphony GenIsis, the Parties will, as necessary, promptly amend this Agreement to include such sublicensed intellectual property within the

license granted hereunder, incorporate any other limitations, royalties or other provisions required by such third party with respect to such sublicense, and address Symphony GenIsis' rights (if any) with respect to patent prosecution, maintenance and enforcement of patents and patent applications within such Third Party IP.

2.10. Separate Third Party License for Discontinued Program. In the event of the expiration of a Discontinuation Option without exercise by Licensor, Symphony GenIsis has the right to transfer to a third party Symphony GenIsis' rights to the Products relating to the Program to which such Discontinuation Option pertained (the "***Discontinued Program***"). If Symphony GenIsis identifies a third party that wishes to obtain such rights, then upon Symphony GenIsis' request, (i) Licensor and Symphony GenIsis shall amend this Agreement to terminate all of Symphony GenIsis' rights and obligations to the extent applicable to the Discontinued Program and (ii) Licensor shall enter into a separate license agreement with such third party in which all of such terminated rights and obligations shall be conferred upon and undertaken by such third party. The terms and conditions of such license agreement shall be identical to those contained herein, to the extent that such terms are applicable to the Discontinued Program and not dependent on any Operative Document other than this Agreement. Such terms shall include but not be limited to (1) provisions allowing for termination of such license agreement upon a material, uncured breach of such license agreement by the third party on similar terms as provided herein with respect to Symphony GenIsis and (2) a confidentiality provision that is not dependent on any of the Operative Documents. Termination of this Agreement shall not effect such license agreement and Licensor's obligation to enter into such a license agreement shall survive termination of this Agreement.

2.11. Supply of Materials After Expiration or Termination of Term. In the event of an unexercised expiration or termination of the Purchase Option, Licensor agrees to negotiate in good faith, and on commercially reasonable terms and conditions, a supply agreement relating to materials, including compounds and Products, required by Symphony GenIsis (or its partners or transferees hereunder) for the continued development (including clinical development), manufacture and commercialization of Products.

ARTICLE 3
SUBLICENSE TO CERTAIN THIRD PARTY INTELLECTUAL PROPERTY

3.1. Third Party Sublicense Payments. Unless otherwise agreed to by the Parties in writing, to the extent that (a) any Licensed Patent Rights are licensed to Licensor by a third party and sublicensed to Symphony GenIsis by Licensor hereunder or (b) a third party has previously collaborated with Isis with respect to GCCR or GCGR, and the development, manufacture, use, sale or other commercialization of any Product by Symphony GenIsis shall require the Licensor to make a royalty payment, milestone or any other payment obligation to the third party licensor of such Licensed Intellectual Property or previous collaborator, (i) Symphony GenIsis shall be responsible for the satisfaction of such royalty payment, milestone or any other obligation to such licensor if such payment is triggered by the development, manufacture, use, sale or other commercialization of any Product by Symphony GenIsis; or (ii) such royalty payment shall be shared by the Parties in amounts and/or percentages to be agreed upon by the Parties if such payment relates (but does not relate solely) to the manufacture, use, sale or other commercialization of any Product by Symphony GenIsis. Notwithstanding the foregoing, with

respect to agreements between Isis and any third party existing as of the Closing Date, Symphony GenIsis' obligations under this Section 3.1 for Products [***].

3.2. Sublicensed Intellectual Property. Symphony GenIsis acknowledges (i) that certain Licensed Intellectual Property is licensed to Licensor by third parties and will be sublicensed to Symphony GenIsis hereunder (the "***Sublicensed Intellectual Property***") and (ii) that such sublicense is subject to certain restrictions and obligations set forth in the applicable written agreements between Licensor and such third parties (the "***Sublicense Obligations***"), including but not limited to those restrictions and obligations set forth on Schedule 2.2. Symphony GenIsis agrees to either be bound by the Sublicense Obligations or forfeit the applicable sublicense of such Intellectual Property under Section 2.2 subject to the applicable Sublicense Obligation and sublicensed hereunder; provided, however, that Symphony GenIsis cannot use this Section to avoid any Sublicense Obligation that has accrued prior to the date Symphony GenIsis elects to forfeit the applicable sublicense.

ARTICLE 4
INTELLECTUAL PROPERTY

4.1. Ownership. The Parties acknowledge and agree that, as between Licensor and Symphony GenIsis, and subject to Schedule 2.2, Licensor or its licensors are the owners of all right, title and interest in and to the Licensed Intellectual Property, including without limitation Symphony GenIsis Enhancements. Symphony GenIsis hereby assigns to Licensor all of Symphony GenIsis' rights and interests in any Symphony GenIsis Enhancements, including any rights in inventions made jointly by Licensor and Symphony GenIsis. Symphony GenIsis shall promptly disclose any Symphony GenIsis Enhancement to Licensor, and shall use reasonable efforts, at Licensor's request and at no cost to Licensor, to cooperate fully with Licensor to transfer such Symphony GenIsis Enhancements to Licensor.

4.2. Marking. Symphony GenIsis shall mark, and shall cause all of its sublicensees to mark, all Products, or the packaging thereof or materials related thereto, with the number of the applicable patents licensed hereunder in accordance with applicable U.S. patent law.

4.3. Prosecution and Maintenance.

(a) Unless otherwise set forth in this Section 4.3, (i) Licensor shall prepare, file, prosecute and maintain those patents and patent applications in Licensed Patent Rights for which Licensor has patent prosecution and maintenance rights; and (ii) Licensor shall provide Symphony GenIsis with (1) quarterly reports regarding the status of the prosecution and maintenance of Program-Specific Patents, (2) copies of and/or access to any patent documents related to the Licensed Patent Rights as reasonably requested by Symphony GenIsis, (3) copies of patent applications and other substantive patent prosecution documents pertaining to the Program-Specific Patents prior to filing in the United States so as to afford Symphony GenIsis and its patent counsel, at Symphony GenIsis' expense, a reasonable opportunity to review and comment on such documents and (4) timely answers to Symphony GenIsis' questions regarding the status of patents and patent applications in Licensed Patent Rights.

(b) Licensor will use commercially reasonable efforts to seek the allowance of broad generic claims, consistent with Licensor's determination of enforceability, business considerations and other factors.

(c) Subject to any such costs paid by Third Party Licensors and a reasonable allocation of costs, to the extent that the Program-Specific Patents relate to Licensor's business other than the Programs, the cost of the prosecution and maintenance of Program-Specific Patents shall be paid by Symphony GenIsis. Upon the scope of any Licensed Patent Rights being amended so that the patent or patent application's claims no longer relate to, or are exploitable in connection with, any Product and/or any Program, for which Licensor has not exercised a Discontinuation Option, such patent or patent application shall cease to be a Licensed Patent Right and all rights and obligations with respect to such patent or patent application (including costs, fees, prosecution, maintenance and enforcement) shall revert to Licensor.

(d) Symphony GenIsis shall not be responsible for the costs of any opposition, interference or reexamination initiated by Licensor with respect to the Program Specific Patents (except to the extent allocated in the Development Budget), unless the Parties mutually agree in writing (i) that it is reasonably necessary or useful to file and prosecute such opposition, interference or re-examination in connection with such Program Specific Patents to protect their interests in such Program Specific Patents and (ii) to a reasonable allocation of costs to the extent that the Program Specific Patents relate to Licensor's business other than the Programs, which agreement will not be unreasonably withheld or delayed. In the event, however, that (i) Symphony GenIsis does not agree to pay such costs (or its share of costs as reasonably allocated as set forth above) of such opposition, interference or reexamination and (ii) Licensor successfully files and prosecutes or settles such opposition, interference or reexamination at its sole cost, then the licenses granted by Licensor to Symphony GenIsis in Section 2.2 herein shall immediately terminate with respect to specific Program Specific Patent subject to such opposition, interference or reexamination.

(e) Each Party shall provide the prosecuting Party with reasonable cooperation under this Section 4.3.

4.4. Abandonment. Subject to the limitations and restrictions set forth on Schedule 2.2, the Parties acknowledge that in the event Licensor desires to abandon any patent or patent application covering Program-Specific Patents within the Major Market during the Term or in any jurisdiction after the Term), Licensor shall provide prompt, timely, prior written notice of at least [***] days prior to abandonment thereof to Symphony GenIsis before any such abandonment. If Symphony GenIsis informs Licensor in writing at least [***] days before the relevant abandonment deadline that Symphony GenIsis desires to avoid such abandonment or lapse, then Licensor shall continue to prosecute or maintain such patent or patent application at Symphony GenIsis' request and sole expense.

4.5. Infringement. Each Party agrees to immediately notify the other Party upon becoming aware of any infringement, misappropriation, illegal use or misuse of the Licensed Intellectual Property in connection with Products in the Exclusive Field and provide to the other Party all available evidence of such infringement.

4.6. Enforcement Right During Term.

(a) Except as provided in Section 4.6(b), during the Term, Licensor has the first right, but not the obligation, to take action against others in the courts, administrative agencies or otherwise to prevent or terminate infringement, misappropriation, illegal use or misuse of the Licensed Patent Rights or other Licensed Intellectual Property.

(b) During the Term, Licensor has the first right, but not the obligation, to take action against others to terminate or prevent a GenIsis Relevant Action. The costs and expenses of any such action shall be borne by Symphony GenIsis to the extent the action relates to a GenIsis Relevant Action; provided, that Symphony GenIsis' prior, written consent was obtained prior to the initiation of such action, such consent not to be unreasonable withheld or delayed. Symphony GenIsis shall, at its expense, cooperate with and reasonably assist Licensor in any such action if so requested by Licensor, and, upon Licensor's request, execute, file and deliver all documents and proof necessary for such purpose, including being named as a party to such litigation if requested by Licensor or if required by Law. Symphony GenIsis shall have the right to participate and be represented by its own counsel at its own expense in any such action, suit or proceeding with respect to Licensed Patent Rights solely relating to Products for which Licensor has not exercised the relevant Discontinuation Option provided that Symphony GenIsis shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Licensor, which consent shall not be unreasonably withheld or delayed. Licensor shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior, written consent of Symphony GenIsis, which consent shall not be unreasonably withheld or delayed.

(c) Subject to the limitations and restrictions set forth on Schedule 2.2, if, (1) during the Term, Symphony GenIsis requests Licensor to take action pursuant to Section 4.6(b) with respect to a GenIsis Relevant Action that either (i) solely involves the enforcement of a Program Specific Patent or (ii) involves the enforcement of other Licensed Intellectual Property and there is not a claim of an issued Program Specific Patent that covers the infringing ASO, and (2) Licensor does not take such action within [***] days of Symphony GenIsis' written request that Licensor take such action, then Symphony GenIsis shall have the option to commence any such action under its own direction and control, and at Symphony GenIsis' cost and expense. Licensor shall, at Symphony GenIsis' expense, cooperate with and reasonably assist Symphony GenIsis in any such action if so requested by Symphony GenIsis, and, upon Symphony GenIsis' request, execute, file and deliver all documents and proof necessary for such purpose, including being named as a party to such litigation if requested by Symphony GenIsis or if required by Law. Licensor shall have the right to participate and be represented by its own counsel at its own expense

in any such action, suit or proceeding with respect to Licensed Patent Rights provided that Licensor shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Symphony GenIsis, which consent shall not be unreasonably withheld or delayed. Symphony GenIsis shall not enter into any settlement or compromise of such action, suit or proceeding that

affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior, written consent of Licensor, which consent shall not be unreasonably withheld or delayed.

4.7. Post-Term Enforcement.

(a) Program Specific Patents. Following the unexercised expiration or termination of the Purchase Option without Licensor's exercise of the Purchase Option, as between the Parties, and solely with respect to Program Specific Patents, Symphony GenIsis shall have the first right, but not the obligation, to take action against others to prevent or terminate GenIsis Relevant Actions. Licensor shall, at Symphony GenIsis' expense, cooperate and reasonably assist Symphony GenIsis in such action if so requested, and upon Symphony GenIsis' request, execute, file and deliver all documents and proof necessary for such purpose, including being named as a party to such litigation if requested by Symphony GenIsis or if required by Law. Licensor shall have the right to participate and be represented in any such action, suit or proceeding by its own counsel at its own expense provided that Licensor shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Symphony GenIsis, which consent shall not be unreasonably withheld or delayed. Symphony GenIsis shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Licensor, which consent shall not be unreasonably withheld or delayed.

(b) Following the unexercised expiration or termination of the Purchase Option without Licensor's exercise of the Purchase Option, if Symphony GenIsis does not take action under Section 4.7(a) within [***] days of Licensor's written request that Symphony GenIsis take such action, then Licensor shall have the option to commence any such action under its own direction and control, and at Licensor's cost and expense. Symphony GenIsis shall, at Licensor's expense, cooperate and reasonably assist Licensor in such action if so requested, and upon Licensor's request, execute, file and deliver all documents and proof necessary for such purpose, including being named as a party to such litigation if requested by Licensor or if required by Law. Symphony GenIsis shall have the right to participate and be represented in any such action, suit or proceeding by its own counsel at its own expense provided that Symphony GenIsis shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Licensor, which consent shall not be unreasonably withheld or delayed. Licensor shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Symphony GenIsis, which consent shall not be unreasonably withheld or delayed.

(c) Licensed Intellectual Property. Except as set forth in Section 4.7(a) and 4.7(b) above, following the unexercised expiration or termination of the Purchase Option without Licensor's exercise of the Purchase Option, as between the Parties, Licensor shall have the first

right, but not the obligation, to take action against others in the courts, administrative agencies or otherwise, under Licensor's direction and control and at Licensor's cost and expense, to prevent or terminate infringement, misappropriation, illegal use or misuse of any Licensed Intellectual Property, including but not limited to a GenIsis Relevant Action. Symphony GenIsis shall, at Licensor's expense, cooperate and reasonably assist Licensor in such action if so requested, and upon Licensor's request, execute, file and deliver all documents and proof necessary for such purpose, including being named as a party to such litigation if requested by Licensor or if required by Law. Symphony GenIsis shall have the right to participate and be represented in any such action, suit or proceeding by its own counsel at its own expense provided that Symphony GenIsis shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Licensor, which consent shall not be unreasonably withheld or delayed. Licensor shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Symphony GenIsis, which consent shall not be unreasonably withheld or delayed.

(d) Except as set forth in Section 4.7(a) and 4.7(b) above and subject to the limitations and restrictions set forth on Schedule 2.2, following the unexercised expiration or termination of the Purchase Option without Licensor's exercise of the Purchase Option, if Licensor does not take action under Section 4.7(c) with respect to a GenIsis Relevant Action within [***] days of Symphony GenIsis' written request that Licensor take such action, then Symphony GenIsis shall have the option to commence any such action under its own direction and control, and at Symphony GenIsis' cost and expense. Licensor shall, at Symphony GenIsis' expense, cooperate and reasonably assist Symphony GenIsis in such action if so requested, and upon Symphony GenIsis' request, execute, file and deliver all documents and proof necessary for such purpose, including being named as a party to such litigation if requested by Symphony GenIsis or if required by Law. Licensor shall have the right to participate and be represented in any such action, suit or proceeding by its own counsel at its own expense provided that Licensor shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Symphony GenIsis, which consent shall not be unreasonably withheld or delayed. Symphony GenIsis shall not enter into any settlement or compromise of such action, suit or proceeding that affects or concerns the validity, enforceability, or ownership of any Licensed Patent Rights or other Licensed Intellectual Property without the prior written consent of Licensor, which consent shall not be unreasonably withheld or delayed.

4.8. Withdrawal of Enforcement. If either Party brings an action under this ARTICLE 4 with respect to a GenIsis Relevant Action and subsequently ceases to pursue or withdraws from such action without resolution (which resolution may include the granting of a license by Isis to such third party that does not violate Section 2.2 or Section 2.6 of this Agreement), it shall promptly notify the other Party and the other Party may, to the extent permitted by Law, substitute itself for the withdrawing party under the terms of this ARTICLE 4.

4.9. Recoveries. All damages or other compensation of any kind recovered in such action, suit, or proceeding or from any settlement or compromise brought under this ARTICLE 4 shall first be used to reimburse each Party for its expenses in connection with such action, suit or proceeding, (in proportion to the expenses of each Party if recovery is insufficient to cover all such expenses) and the remainder of such recovery, shall be allocated [***] to the Party hereto taking the lead in the action, suit or proceeding.

ARTICLE 5
REPRESENTATIONS AND WARRANTIES

5.1. Representations and Warranties of Licensor. Licensor hereby represents and warrants to Symphony GenIsis, that, as of the Closing Date:

(a) Subject to Section 3.2 and Schedule 2.2, Licensor is the exclusive owner of all right, title, and interest in and to (i) all Licensed Patent Rights and not identified as jointly owned or licensed from a third party and (ii) the Regulatory Files;

(b) Licensor has sufficient rights to grant the licenses granted hereunder and the grant of such licenses does not and will not conflict with any agreement to which Licensor is a party or otherwise governing the Licensed Intellectual Property and Licensor further represents and warrants that, on an ongoing basis throughout the Term, Licensor shall not enter into any agreement that will conflict with the rights and licenses granted to Symphony GenIsis hereunder;

(c) To the Knowledge of Licensor, no third party is engaging in any activity that infringes or misappropriates the Program-Specific Patents or related know-how or trade secrets;

(d) No element of the Licensed Intellectual Property has been adjudged invalid or unenforceable in whole or part, and to the Knowledge of Licensor, the issued patents within the Licensed Intellectual Property are valid and enforceable;

(e) To the Knowledge of Licensor, no actions or claims have been asserted, are pending or have been threatened, against Licensor in writing alleging that the manufacture, use or sale of any Product misappropriates or infringes the intellectual property rights of any third party;

(f) Except as set forth on Annex D, Licensor and/or Symphony GenIsis shall not be liable or otherwise obligated to pay royalties, milestone payments or other consideration pursuant to any agreement Licensor may have with a third party existing on the Closing Date in connection with Symphony GenIsis' exploitation of the Licensed Intellectual Property (including Sublicensed Intellectual Property) in connection with the development, manufacture, use, sale, or importation of Products [***] hereunder; and

(g) To the Knowledge of Licensor, the manufacture, use or sale of any Product [***] by Symphony GenIsis (or its sublicensees) in strict accordance with the licenses herein and other terms of this Agreement will not misappropriate or infringe the intellectual property rights of any third party.

5.2. Disclaimer and Acknowledgement. EXCEPT AS EXPRESSLY SET FORTH IN THIS ARTICLE 5, THE LICENSED INTELLECTUAL PROPERTY, PRODUCTS, TANGIBLE MATERIALS AND REGULATORY FILES ARE PROVIDED "AS IS" WITH NO REPRESENTATIONS OR WARRANTIES OF ANY KIND, AND LICENSOR EXPRESSLY DISCLAIMS ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO ANY WARRANTIES OF MERCHANTABILITY, FITNESS FOR PARTICULAR PURPOSE, OR NON-INFRINGEMENT. LICENSOR DOES NOT WARRANT THE PERFORMANCE OF ANY PRODUCT, INCLUDING THEIR SAFETY, EFFECTIVENESS OR COMMERCIAL VIABILITY. ANY SYMPHONY GENISIS ENHANCEMENTS PROVIDED TO LICENSOR HEREUNDER ARE PROVIDED "AS IS" WITH NO REPRESENTATIONS OR WARRANTIES OF ANY KIND AND SYMPHONY GENISIS EXPRESSLY DISCLAIMS ALL WARRANTIES, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO ANY WARRANTIES OF MERCHANTABILITY, FITNESS FOR PARTICULAR PURPOSE, OR NON-INFRINGEMENT.

ARTICLE 6
INDEMNIFICATION AND LIMITATION OF LIABILITY

6.1. Indemnity. To the greatest extent permitted by applicable Law, Licensor shall indemnify and hold harmless Symphony GenIsis, its Affiliates, and each of their respective officers, directors, employees, agents, members, managers, successors and assigns (each, a "***Symphony GenIsis Indemnified Party***") and Symphony GenIsis shall indemnify and hold harmless Licensor, its Affiliates and each of their respective officers, directors, employees, agents, members, successors and assigns (each, a "***Licensor Indemnified Party***" and together with Symphony GenIsis Indemnified Party, the "***Indemnified Parties***"), from and against any and all claims, losses, costs, interest, awards, judgments, fees (including reasonable fees for attorneys and other professionals), court costs, liabilities, damages and expenses with an aggregate value of at least [***] (as determined by the applicable Indemnified Parties acting in good faith), incurred by any Symphony GenIsis Indemnified Party or Licensor Indemnified Party (irrespective of whether any such Symphony GenIsis Indemnified Party or Licensor Indemnified Party, as applicable, is a party to the action for which indemnification hereunder is sought), (collectively, a "***Loss***") to the extent resulting from, arising out of, or relating to any and all third party suits, claims, actions, proceedings, investigations, litigation or demands based upon:

(i) in the case of Licensor being the Indemnifying Party, (A) any breach of any representation or warranty made by Licensor herein or in any other Operative Document, (B) any breach of any covenant, agreement or obligation of Licensor contained herein, or in any other Operative Document, (C) any act of gross negligence or willful misconduct by Licensor in performing its obligations under this Agreement, or (D) the development, manufacture, use, handling, storage, sale or other disposition of any Product arising from a Program for which Licensor exercised a Discontinuation Option; in each case, except (1) with respect to Losses for which Licensor is entitled to indemnification under this ARTICLE 6 or (2) to the extent such Loss arises from the gross negligence or willful misconduct of a Symphony GenIsis Indemnified Party, and

(ii) in the case of Symphony GenIsis being the Indemnifying Party, (A) any breach of any representation or warranty made by Symphony GenIsis herein or in any

other Operative Document, (B) any breach of any covenant, agreement or obligation of Symphony GenIsis contained herein, or in any other Operative Document, (C) any act of gross negligence or willful misconduct by Symphony GenIsis in performing its obligations under this Agreement, or (D) the development, manufacture, use, handling, storage, sale or other disposition of Products (other than those Products arising from a Program for which Licensor exercised a Discontinuation Option) after the end of the Term or the unexercised expiration of the Discontinuation Option to which such Product related; in each case, except (1) with respect to Losses for which Symphony GenIsis is entitled to indemnification under this ARTICLE 6 or (2) to the extent such Loss arises from the gross negligence or willful misconduct of an Licensor Indemnified Party.

To the extent that the foregoing undertakings by Licensor and/or Symphony GenIsis may be unenforceable for any reason, such Party shall make the maximum contribution to the payment and satisfaction of any Loss that is permissible under applicable Law.

6.2. Notice of Claims. Any Indemnified Party that proposes to assert a right to be indemnified under this ARTICLE 6 shall notify Licensor or Symphony GenIsis, as applicable (the "***Indemnifying Party***"), promptly after receipt of notice of commencement of any action, suit or proceeding against such Indemnified Party (an "***Indemnified Proceeding***") in respect of which a claim is to be made under this ARTICLE 6, or the incurrence or realization of any Loss in respect of which a claim is to be made under this ARTICLE 6, of the commencement of such Indemnified Proceeding or of such incurrence or realization, enclosing a copy of all relevant documents, including all papers served and claims made, but the omission so to notify the applicable Indemnifying Party promptly of any such Indemnified Proceeding or incurrence or realization shall not relieve (a) such Indemnifying Party from any liability that it may have to such Indemnified Party under this ARTICLE 6 or otherwise, except, as to such Indemnifying Party's liability under this ARTICLE 6, to the extent, but only to the extent, that such Indemnifying Party shall have been prejudiced by such omission, or (b) any other indemnitor from liability that it may have to any Indemnified Party under the Operative Documents.

6.3. Defense of Proceedings. In case any Indemnified Proceeding shall be brought against any Indemnified Party, it shall notify the applicable Indemnifying Party of the commencement thereof and such Indemnifying Party shall be entitled to participate in, and provided such Indemnified Proceeding involves a claim solely for money damages and does not seek an injunction or other equitable relief against the Indemnified Party and is not a criminal or regulatory action, to assume the defense of, such Indemnified Proceeding with counsel reasonably satisfactory to such Indemnified Party, and after notice from such Indemnifying Party to such Indemnified Party of such Indemnifying Party's election so to assume the defense thereof and the failure by such Indemnified Party to object to such counsel within ten (10) Business Days following its receipt of such notice, such Indemnifying Party shall not be liable to such Indemnified Party for legal or other expenses related to such Indemnified Proceedings incurred after such notice of election to assume such defense except as provided below and except for the reasonable costs of investigating, monitoring or cooperating in such defense subsequently incurred by such Indemnified Party reasonably necessary in connection with the defense thereof. Such Indemnified Party shall have the right to employ its counsel in any such Indemnified Proceeding, but the fees and expenses of such counsel shall be at the expense of such Indemnified Party unless:

(a) the employment of counsel by such Indemnified Party at the expense of the applicable Indemnifying Party has been authorized in writing by such Indemnifying Party;

(b) such Indemnified Party shall have reasonably concluded in its good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between the applicable Indemnifying Party and such Indemnified Party in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes of action available to such Indemnified Party (it being agreed that in any case referred to in this clause (b) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

(c) the applicable Indemnifying Party shall not have employed counsel reasonably acceptable to the Indemnified Party, to assume the defense of such Indemnified Proceeding within a reasonable time after notice of the commencement thereof; provided, however, that (i) this clause shall not be deemed to constitute a waiver of any conflict of interest that may arise with respect to any such counsel, and (ii) an Indemnified Party may not invoke this clause (c) if such Indemnified Party failed to timely object to such counsel pursuant to the first paragraph of this Section 6.3 (it being agreed that in any case referred to in this clause (c) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party); or

(d) any counsel employed by the applicable Indemnifying Party shall fail to timely commence or reasonably conduct the defense of such Indemnified Proceeding, and such failure has prejudiced (or is in immediate danger of prejudicing) the outcome of such Indemnified Proceeding (it being agreed that in any case referred to in this clause (d) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

in each of which cases the fees and expenses of counsel for such Indemnified Party shall be at the expense of such Indemnifying Party. Only one counsel shall be retained by all Indemnified Parties with respect to any Indemnified Proceeding, unless counsel for any Indemnified Party reasonably concludes in good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between such Indemnified Party and one or more other Indemnified Parties in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes of action available to such Indemnified Party.

6.4. Settlement. Without the prior written consent of such Indemnified Party, such Indemnifying Party shall not settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding, unless such settlement, compromise, consent or related judgment (i) includes an unconditional release of such Indemnified Party from all liability for Losses arising out of such claim, action, investigation, suit or other legal proceeding, (ii) provides for the payment of money damages as the sole relief for the claimant (whether at law or in equity), (iii) involves no finding or admission of any violation of Law or the rights of any Person by the Indemnified Party, and (iv) is not in the nature of a criminal or

regulatory action. No Indemnified Party shall settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding (A) in respect of which any payment would result hereunder or under any other Operative Document, (B) which includes an injunction that will adversely affect any Indemnifying Person, (C) which involves a finding or admission of any violation of Law or the rights of any Indemnifying Person, (D) which is in the nature of a criminal or regulatory action, or (E) which admits the invalidity, misuse or unenforceability of a Licensed Patent Right, without the prior written consent of the Indemnifying Party, such consent not to be unreasonably conditioned, withheld or delayed.

6.5. Limitation of Liability. TO THE GREATEST EXTENT PERMITTED BY APPLICABLE LAW, NEITHER PARTY NOR ANY OF THEIR RESPECTIVE DIRECTORS, OFFICERS, MEMBERS, MANAGERS, EMPLOYEES, INDEPENDENT CONTRACTORS OR AGENTS SHALL HAVE ANY LIABILITY OF ANY TYPE (INCLUDING, BUT NOT LIMITED TO, CLAIMS IN CONTRACT, NEGLIGENCE AND TORT LIABILITY) FOR ANY SPECIAL, INCIDENTAL, INDIRECT, PUNITIVE OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, THE LOSS OF OPPORTUNITY, LOSS OF USE OR LOSS OF REVENUE OR PROFIT IN CONNECTION WITH OR ARISING OUT OF THIS AGREEMENT OR THE SERVICES PERFORMED HEREUNDER, EVEN IF SUCH DAMAGES MAY HAVE BEEN FORESEEABLE. THE FOREGOING SHALL NOT LIMIT EITHER PARTY'S INDEMNIFICATION OBLIGATIONS PURSUANT TO SECTION 6.1.

6.6. Insurance. The Parties shall maintain insurance as set forth in Section 6.7 of the Amended and Restated Research and Development Agreement.

ARTICLE 7
TERM AND TERMINATION

7.1. Term. This Agreement shall commence on the Closing Date and shall remain in force until terminated as provided herein.

7.2. Termination.

(a) Either Party may terminate this Agreement at any time if the other Party is in material default or breach of this Agreement that has resulted in, or would reasonably be expected to result in, a material adverse effect on the Programs or the non-breaching Party's rights under the Operative Documents, and such material default or breach continues unremedied for a period of sixty (60) days after written notice thereof is delivered to the defaulting or breaching Party.

(b) Licensor may terminate this Agreement at any time upon written notice to Symphony GenIsis if (i) Investors materially breaches Sections 2 or 3 of the Funding Agreement, (ii) Holdings breaches Section 2 of the Subscription Agreement or (iii) Holdings or Symphony GenIsis is in material default or breach the Purchase Option Agreement that has resulted in, or would reasonably be expected to result in, a material adverse effect on the Licensor's rights under the Purchase Option Agreement and such default or breach is not cured within thirty (30)

days after written notice of such default or breach under the Purchase Option Agreement is delivered to the defaulting or breaching Party.

(c) Licensor may terminate Symphony GenIsis' sublicense to a specific element of Sublicensed Intellectual Property if Symphony GenIsis is in material default or breach of a Sublicense Obligation relating to such Sublicensed Intellectual Property and such material default or breach continues unremedied for a period of sixty (60) days (or such shorter cure period as may be stipulated in the applicable Sublicense Obligation) after written notice thereof is delivered to Symphony GenIsis.

(d) Upon any termination of this Agreement, all license rights granted herein (except for those rights granted in or pursuant to Section 2.5) shall immediately terminate.

7.3. Survival. The following Sections and Articles shall survive any expiration or termination of this Agreement: Sections 2.11, 4.1, 5.2 and 7.3, and Articles 6 and 8.

7.4. Bankruptcy. All rights and licenses granted under this Agreement are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the United States Bankruptcy Code (the "***Code***"), licenses to "Intellectual Property" as defined in the Code. The Parties agree that each Party shall retain and may fully exercise all of its rights and elections under the Code.

ARTICLE 8
MISCELLANEOUS

8.1. Notices. Any notice, request, demand, waiver, consent, approval or other communication which is required or permitted to be given to any Party shall be in writing and shall be deemed given only if delivered to the Party personally or sent to the Party by facsimile transmission (promptly followed by a hard-copy delivered in accordance with this Section 8.1), by next Business Day delivery by a nationally recognized courier service, or by registered or certified mail (return receipt requested), with postage and registration or certification fees thereon prepaid, addressed to the Party at its address set forth below:

Licensor:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: B. Lynne Parshall

Facsimile: (760) 603-4652

with a copy to;

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: General Counsel
Facsimile: (760) 268-4922

Symphony GenIsis:

Symphony GenIsis, Inc.
7361 Calhoun Place, Suite 325
Rockville, MD 20855
Attn: Charles W. Finn, Ph.D.
Facsimile: (301) 762-6154

with a copy to;

Symphony Capital Partners, L.P.
875 Third Avenue
18th Floor
New York, NY 10022
Facsimile: (212) 632-5401

and

Symphony Strategic Partners, LLC
875 Third Avenue
18th Floor
New York, NY 10022
Facsimile: (212) 632-5401

or to such other address as such Party may from time to time specify by notice given in the manner provided herein to each other Party entitled to receive notice hereunder.

8.2. Entire Agreement. This Agreement (including any Annexes, Schedules, Exhibits or other attachments hereto) and the agreements referred to herein (including the Operative Documents) constitute the entire agreement between the Parties with respect to the subject matter hereof, and no oral or written statement may be used to interpret or vary the

meaning of the terms and conditions hereof. This Agreement supersedes any prior or contemporaneous agreements and understandings, whether written or oral, between the Parties with respect to the subject matter hereof, including the Original Agreement but excluding the Operative Documents.

8.3. Assignment. Neither Party may assign or otherwise transfer this Agreement without the prior written consent of the other Party; provided, however, that (i) Licensor may assign this Agreement or any of its rights and obligations hereunder without the consent of Symphony GenIsis (A) to an Affiliate or in connection with a merger or the sale of all or substantially all of the assets of the Licensor to which this Agreement relates, or (B) to the Surviving Entity in the event Licensor undergoes a Change of Control in compliance with Article 14 of the Amended and Restated Research and Development Agreement, provided, however, the Licensed Patent Rights and Licensed Know-How shall not be construed, as a result of such assignment, to include any patent rights, know-how, trade secret, and other intellectual property that, prior to such Change of Control, were owned or Controlled by the Person (other than Licensor) involved in such Change of Control; and (ii) after expiration of the Term without Licensor's exercise of the Purchase Option, Symphony GenIsis may assign this Agreement to any Person without the prior, written consent of Licensor. Assignment of this Agreement by either Party shall not relieve the assignor of its obligations hereunder. This Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns.

8.4. Headings. The descriptive headings contained in this Agreement are for convenience of reference only and shall not affect in any way the meaning or interpretation of the Agreement.

8.5. Independent Contractor. Each Party shall be acting as an independent contractor in performing under this Agreement and shall not be considered or deemed to be an agent, employee, joint venturer or partner of the other Party.

8.6. Severability. If any term or other provision of this Agreement is invalid, illegal or incapable of being enforced by any Law or public policy, all other terms and provisions of this Agreement shall nevertheless remain in full force and effect so long as the economic or legal substance of the transactions contemplated hereby is not affected in any manner materially adverse to any Party.

8.7. No Third-Party Beneficiaries. Except with respect to certain indemnification obligations and liability limitations pursuant to ARTICLE 6, nothing in this Agreement, either express or implied, is intended to or shall confer upon any third party any legal or equitable right, benefit or remedy of any nature whatsoever under or by reason of this Agreement.

8.8. Compliance with Laws. In performing under this Agreement, each Party shall comply with all applicable Laws rules and regulations, including without limitation, the United States Food and Drug Administration and the United States Export Administration Regulations.

8.9. Amendment. This Agreement may not be amended or modified except by an instrument in writing signed by authorized representatives of Licensor and Symphony GenIsis.

8.10. Governing Law; Consent to Jurisdiction and Service of Process.

(a) This Agreement shall be governed by, and construed in accordance with, the Laws of the State of New York.

(b) Each of the Parties hereby irrevocably and unconditionally submits, for itself and its property, to the nonexclusive jurisdiction of any New York State court or federal court of the United States of America sitting in The City of New York, Borough of Manhattan, and any appellate court from any jurisdiction thereof, in any action or proceeding arising out of or relating to this Agreement, or for recognition or enforcement of any judgment, and each of the Parties hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in any such New York State court or, to the fullest extent permitted by Law, in such federal court. Each of the Parties agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by Law. Nothing in this Agreement shall affect any right that any Party may otherwise have to bring any action or proceeding relating to this Agreement.

(c) Each of the Parties irrevocably and unconditionally waives, to the fullest extent it may legally and effectively do so, any objection that it may now or hereafter have to the laying of venue of any suit, action or proceeding arising out of or relating to this Agreement in any New York State or federal court. Each of the Parties hereby irrevocably waives, to the fullest extent permitted by Law, the defense of an inconvenient forum to the maintenance of such action or proceeding in any such court.

8.11. WAIVER OF JURY TRIAL. EACH OF THE PARTIES HERETO IRREVOCABLY WAIVES ALL RIGHT TO TRIAL BY JURY IN ANY ACTION, PROCEEDING OR COUNTERCLAIM (WHETHER BASED ON CONTRACT, TORT OR OTHERWISE) ARISING OUT OF OR RELATING TO THIS AGREEMENT.

8.12. Counterparts. This Agreement may be executed in one or more counterparts, and by the respective Parties in separate counterparts, each of which when executed shall be deemed to be an original but all of which taken together shall constitute one and the same Agreement.

8.13. No Waiver. The failure of either Party to enforce at any time for any period the provisions of or any rights deriving from this Agreement shall not be construed to be a waiver of such provisions or rights or the right of such Party thereafter to enforce such provisions.

SIGNATURES FOLLOW ON NEXT PAGE

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

SYMPHONY GENISIS, INC.

By: /s/ Neil J. Sandler
Name: Neil J. Sandler
Title: Chairman of the Board

SYMPHONY GENISIS HOLDINGS LLC

By: Symphony Capital Partners, L.P.,
its Manager

By: Symphony Capital GP, L.P.,
its general partner

By: Symphony GP, LLC,
its general partner

By: /s/ Mark Kessel
Name: Mark Kessel
Title: Managing Member

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall, J.D.
Name: B. Lynne Parshall, J.D.
Title: Executive Vice President, Chief Financial Officer and Secretary

ANNEX A

DEFINITIONS

CERTAIN DEFINITIONS

"***$***" means United States dollars.

"***Accredited Investor***" has the meaning set forth in Rule 501(a) of Regulation D promulgated under the Securities Act of 1933, as amended.

"***Act***" means the Delaware Limited Liability Company Act, 6 Del. C. § 18-101 et seq.

"***Ad Hoc Meeting***" has the meaning set forth in Paragraph 6 of Annex B of the Amended and Restated Research and Development Agreement.

"***Additional Party***" has the meaning set forth in Section 13 of the Confidentiality Agreement.

"***Additional Regulatory Filings***" means such Governmental Approvals as required to be made under any law applicable to the purchase of the Symphony GenIsis Equity Securities under the Purchase Option Agreement.

"***Adjusted Capital Account Deficit***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Affected Member***" has the meaning set forth in Section 27 of the Investors LLC Agreement.

"***Affiliate***" means, with respect to any Person (i) any Person directly or indirectly controlling, controlled by or under common control with such Person, (ii) any officer, director, general partner, member or trustee of such Person, or (iii) any Person who is an officer, director, general partner, member or trustee of any Person described in clauses (i) or (ii) of this sentence. For purposes of this definition, the terms "controlling," "controlled by" or "under common control with" shall mean the possession, direct or indirect, of the power to direct or cause the direction of the management and policies of a Person or entity, whether through the ownership of voting securities, by contract or otherwise, or the power to elect at least 50% of the directors, managers, general partners, or persons exercising similar authority with respect to such Person or entities.

"***Amended and Restated Research and Development Agreement***" means the Amended and Restated Research and Development Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis.

"***ApoB***" means apolipoprotein B.

"***ApoB Product***" means a pharmaceutical composition comprising an ASO that targets ApoB.

"***ApoB Program***" means the identification, development, manufacture and/or use of any ApoB Product in accordance with the Development Plan.

"***ASO***" means an oligonucleotide or analog, mimic or mimetic thereof having a sequence that selectively modulates protein synthesis via the binding, partially or wholly, of such oligomeric compound to a complementary nucleic acid sequence encoding, directly or indirectly, said protein.

"***Asset Value***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Auditors***" means an independent certified public accounting firm of recognized national standing.

"***Balance Sheet Deficiency Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Bankruptcy Code***" means the United States Bankruptcy Code.

"***Business Day***" means any day other than Saturday, Sunday or any other day on which commercial banks in The City of New York or the City of San Francisco are authorized or required by law to remain closed.

"***Capital Contributions***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Capitalized Leases***" means all leases that have been or should be, in accordance with GAAP, recorded as capitalized leases.

"***Cash Available for Distribution***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Chair***" has the meaning set forth in Paragraph 4 of Annex B to the Amended and Restated Research and Development Agreement.

"***Change of Control***" means and includes the occurrence of any of the following events, but specifically excludes (i) acquisitions of capital stock directly from Isis for cash, whether in a public or private offering, (ii) sales of capital stock by stockholders of Isis, and (iii) acquisitions of capital stock by or from any employee benefit plan or related trust:

(a) the merger, reorganization or consolidation of Isis into or with another corporation or legal entity in which Isis' stockholders holding the right to vote with respect to matters generally immediately preceding such merger, reorganization or consolidation, own less than fifty

percent (50%) of the voting securities of the surviving entity; or

(b) the sale of all or substantially all of Isis' assets or business.

"***Class A Member***" means a holder of a Class A Membership Interest.

"***Class A Membership Interest***" means a Class A Membership Interest in Holdings.

"***Class B Member***" means a holder of a Class B Membership Interest.

"***Class B Membership Interest***" means a Class B Membership Interest in Holdings.

"***Class C Member***" means a holder of a Class C Membership Interest.

"***Class C Membership Interest***" means a Class C Membership Interest in Holdings.

"***Client Schedules***" has the meaning set forth in Section 5(b) of the RRD Services Agreement.

"***Clinical Budget Component***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Closing Date***" means April 7, 2006.

"***CMC***" means the chemistry, manufacturing and controls documentation as required for filings with Regulatory Authority relating to the manufacturing, production and testing of drug products.

"***Code***" means the Internal Revenue Code of 1986, as amended from time to time.

"***Committed Capital***" means $75,000,000.00.

"***Common Stock***" means the common stock, par value $0.01 per share, of Symphony GenIsis.

"***Company Expenses***" has the meaning set forth in Section 5.09 of the Holdings LLC Agreement.

"***Company Property***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Confidential Information***" has the meaning set forth in Section 2 of the Confidentiality Agreement.

"***Confidentiality Agreement***" means the Confidentiality Agreement, dated as of the Closing Date, among Symphony GenIsis, Holdings, Isis, SCP, SSP, Investors, Symphony Capital and RRD, as such agreement may be amended or amended and restated from time to time.

"***Conflict Transaction***" has the meaning set forth in Article X of the Symphony GenIsis Charter.

"***Control***" means, with respect to any material, information or intellectual property right, that a Party owns or has a license to such item or right, and has the ability to grant the other Party access, a license or a sublicense (as applicable) in or to such item or right as provided in the Operative Documents without violating the terms of any agreement or other arrangement with any third party.

"***Debt***" of any Person means, without duplication:

(a) all indebtedness of such Person for borrowed money,

(b) all obligations of such Person for the deferred purchase price of property or services (other than any portion of any trade payable obligation that shall not have remained unpaid for 91 days or more from the later of (A) the original due date of such portion and (B) the customary payment date in the industry and relevant market for such portion),

(c) all obligations of such Person evidenced by bonds, notes, debentures or other similar instruments,

(d) all obligations of such Person created or arising under any conditional sale or other title retention agreement with respect to property acquired by such Person (whether or not the rights and remedies of the seller or lender under such agreement in an event of default are limited to repossession or sale of such property),

(e) all Capitalized Leases to which such Person is a party,

(f) all obligations, contingent or otherwise, of such Person under acceptance, letter of credit or similar facilities,

(g) all obligations of such Person to purchase, redeem, retire, defease or otherwise acquire for value any Equity Securities of such Person,

(h) the net amount of all financial obligations of such Person in respect of Hedge Agreements,

(i) the net amount of all other financial obligations of such Person under any contract or other agreement to which such Person is a party,

(j) all Debt of other Persons of the type described in clauses (a) through (i) above guaranteed, directly or indirectly, in any manner by such Person, or in effect guaranteed, directly or indirectly, by such Person through an agreement (A) to pay or purchase such Debt or to advance or supply funds for the payment or purchase of such Debt, (B) to purchase, sell or lease (as lessee or lessor) property, or to purchase or sell services, primarily for the purpose of enabling the debtor to make payment of such Debt or to assure the holder of such Debt against loss, (C) to supply funds to or in any other

manner invest in the debtor (including any agreement to pay for property or services irrespective of whether such property is received or such services are rendered) or (D) otherwise to assure a creditor against loss, and

(k) all Debt of the type described in clauses (a) through (i) above secured by (or for which the holder of such Debt has an existing right, contingent or otherwise, to be secured by) any Encumbrance on property (including accounts and contract rights) owned or held or used under lease or license by such Person, even though such Person has not assumed or become liable for payment of such Debt.

"***Development Budget***" means the budget (comprised of the Management Budget Component and the Clinical Budget Component) for the implementation of the Development Plan (the initial form of which was agreed upon by Isis and Symphony GenIsis as of the Closing Date and attached to the Amended and Restated Research and Development Agreement as Annex D thereto), as may be further developed and revised from time to time in accordance with the Development Committee Charter and the Amended and Restated Research and Development Agreement.

"***Development Committee***" has the meaning set forth in Article 3 of the Amended and Restated Research and Development Agreement.

"***Development Committee Charter***" has the meaning set forth in Article 3 of the Amended and Restated Research and Development Agreement.

"***Development Committee Member***" has the meaning set forth in Paragraph 1 of Annex B to the Amended and Restated Research and Development Agreement.

"***Development Plan***" means the development plan covering all the Programs (the initial form of which was agreed upon by Isis and Symphony GenIsis as of the Closing Date and attached to the Amended and Restated Research and Development Agreement as Annex C thereto), as may be further developed and revised from time to time in accordance with the Development Committee Charter and the Amended and Restated Research and Development Agreement.

"***Development Services***" has the meaning set forth in Section 1(b) of the RRD Services Agreement.

"***Director(s)***" means the Persons identified as such in the Preliminary Statement of the Indemnification Agreement (including such Persons as may become parties thereto after the date hereof).

"***Disclosing Party***" has the meaning set forth in Section 3 of the Confidentiality Agreement.

"***Discontinuation Closing Date***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinuation Date***" means any date designated by Symphony GenIsis which shall occur on or after the 90th day following the receipt by Isis of notice from Symphony GenIsis of Symphony GenIsis' intent to discontinue a Program in accordance with the terms of the Amended and Restated Research and Development Agreement.

"***Discontinuation Option***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinuation Price***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinued Program***" has the meaning set forth in Section 2.12 of the Novated and Restated Technology License Agreement.

"***Disinterested Directors***" has the meaning set forth in Article IX of the Symphony GenIsis Charter.

"***Distribution***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Early Purchase Option Exercise***" has the meaning set forth in Section 1(c)(iv) of the Purchase Option Agreement.

"***Effective Registration Date***" has the meaning set forth in Section 1(b) of the Registration Rights Agreement

"***Encumbrance***" means (i) any security interest, pledge, mortgage, lien (statutory or other), charge or option to purchase, lease or otherwise acquire any interest, (ii) any adverse claim, restriction, covenant, title defect, hypothecation, assignment, deposit arrangement, license or other encumbrance of any kind, preference or priority, or (iii) any other security agreement or preferential arrangement of any kind or nature whatsoever (including, without limitation, any conditional sale or other title retention agreement).

"***Enhancements***" means findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Intellectual Property and/or Regulatory Files, in each case whether or not patentable.

"***Equity Securities***" means, with respect to any Person, shares of capital stock of (or other ownership or profit interests in) such Person, warrants, options or other rights for the purchase or other acquisition from such Person of shares of capital stock of (or other ownership or profit interests in) such Person, securities convertible into or exchangeable for shares of capital stock of (or other ownership or profit interests in) such Person or warrants, rights or options for the purchase or other acquisition from such Person of such shares (or such other interests), and other ownership or profit interests in such Person (including, without limitation, partnership, member or trust interests therein), whether voting or nonvoting, and whether or not such shares, warrants, options, rights or other interests are authorized or otherwise existing on any date of determination.

"***ERISA***" means the United States Employee Retirement Income Security Act of 1974, as amended.

"***Excepted Debt***" has the meaning set forth in Section 5(c)(iii) of the Purchase Option Agreement.

"***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

"***Exclusive Field***" means human therapeutics, but does not include the Nonexclusive Field.

"***Existing NDA***" has the meaning set forth in Section 2 of the Confidentiality Agreement.

"***Expert***" has the meaning set forth in Section 11.1(c) of the Amended and Restated Research and Development Agreement.

"***External Directors***" means, at any time, up to two (2) Persons elected to the Symphony GenIsis Board after the Closing Date (who shall be neither employees of the Symphony Capital nor of Isis) in accordance with the Symphony GenIsis Charter, the Symphony GenIsis By-laws and Section 4(b)(iv) of the Purchase Option Agreement.

"***FDA***" means the United States Food and Drug Administration or its successor agency in the United States.

"***FDA Sponsor***" has the meaning set forth in Section 5.1 of the Amended and Restated Research and Development Agreement.

"***Final Termination Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Financial Audits***" has the meaning set forth in Section 6.6 of the Amended and Restated Research and Development Agreement.

"***Financing***" has the meaning set forth in the Preliminary Statement of the Purchase Option Agreement.

"***Fiscal Year***" has the meaning set forth in each Operative Document in which it appears.

"***Form S-3***" means the Registration Statement on Form S-3 as defined under the Securities Act.

"***FTE***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Funds Termination Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Funds Termination Notice***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***GAAP***" means generally accepted accounting principles in effect in the United States of America from time to time.

"***GCCR***" means a glucocorticoid receptor.

"***GCCR Product***" means a pharmaceutical composition comprising an ASO that targets GCCR.

"***GCCR Program***" means the identification, development, manufacture and/or use of any GCCR Product in accordance with the Development Plan.

"***GCGR***" means a glucagon receptor.

"***GCGR Product***" means a pharmaceutical composition comprising an ASO that targets GCGR.

"***GCGR Program***" means the identification, development, manufacture and/or use of any GCGR Product in accordance with the Development Plan.

"***GenIsis Relevant Action***" means an action against others in the courts, administrative agencies or otherwise to prevent or terminate infringement, misappropriation, illegal use or misuse of the Licensed Patent Rights or other Licensed Intellectual Property due to the manufacture, use, sale or importation of an ASO that targets ApoB, GCCR or GCGR, as applicable, in the Exclusive Field.

"***Governmental Approvals***" means authorizations, consents, orders, declarations or approvals of, or filings with, or terminations or expirations of waiting periods imposed by any Governmental Authority.

"***Governmental Authority***" means any United States or non-United States federal, national, supranational, state, provincial, local, or similar government, governmental, regulatory or administrative authority, agency or commission or any court, tribunal, or judicial or arbitral body.

"***Governmental Order***" means any order, writ, judgment, injunction, decree, stipulation, determination or award entered by or with any Governmental Authority.

"***Hedge Agreement***" means any interest rate swap, cap or collar agreement, interest rate future or option contract, currency swap agreement, currency future or option contract or other similar hedging agreement.

"***Holdings***" means Symphony GenIsis Holdings LLC, a Delaware limited liability company.

"***Holdings Claims***" has the meaning set forth in Section 5.01 of the Warrant Purchase Agreement.

"***Holdings LLC Agreement***" means the Amended and Restated Limited Liability Company Agreement of Holdings dated as of the Closing Date.

"***HSR Filings***" means the pre-merger notification and report forms required under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended.

"***IND***" means an Investigational New Drug Application, as described in 21 U.S.C. § 355(i)(1) and 21 C.F.R. § 312 in the regulations promulgated by the United States Food and Drug Administration, or any foreign equivalent thereof.

"***Indemnification Agreement***" means the Indemnification Agreement among Symphony GenIsis and the Directors named therein, dated as of the Closing Date, as such agreement may be amended or amended and restated from time to time.

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

"***Indemnified Party***" has the meaning set forth in each Operative Document in which it appears.

"***Indemnified Proceeding***" has the meaning set forth in each Operative Document in which it appears.

"***Indemnifying Party***" has the meaning set forth in each Operative Document in which it appears.

"***Initial Development Budget***" means the initial development budget prepared by representatives of Symphony GenIsis and Isis prior to the Closing Date, and attached to the Amended and Restated Research and Development Agreement as Exhibit D thereto.

"***Initial Development Plan***" means the initial development plan prepared by representatives of Symphony GenIsis and Isis prior to the Closing Date, and attached to the Amended and Restated Research and Development Agreement as Exhibit C thereto.

"***Initial Holdings LLC Agreement***" means the Agreement of Limited Liability Company of Holdings, dated March 8, 2006.

"***Initial Investors LLC Agreement***" means the Agreement of Limited Liability Company of Investors, dated March 8, 2006.

"***Initial LLC Member***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Interest Certificate***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Investment Company Act***" means the Investment Company Act of 1940, as amended.

"***Investment Overview***" means the investment overview describing the transactions entered into pursuant to the Operative Documents.

"***Investment Policy***" has the meaning set forth in Section 1(a)(vi) of the RRD Services Agreement.

"***Investors***" means Symphony GenIsis Investors LLC.

"***Investors LLC Agreement***" means the Amended and Restated Agreement of Limited Liability Company of Investors dated as of the Closing Date

"***IRS***" means the U.S. Internal Revenue Service.

"***Isis***" means Isis Pharmaceuticals, Inc., a Delaware corporation.

"***Isis 2005 10-K***" means the annual report for fiscal year 2005 filed by Isis on Form 10-K on March 16, 2006, pursuant to the Exchange Act.

"***Isis Accounting Advisor***" means Ernst & Young LLP or Deloitte & Touche USA LLP.

"***Isis Common Stock***" means the common stock, par value $0.001 per share, of Isis.

"***Isis Commitment Amount***" has the meaning set forth in Paragraph 14 of Annex B to the Amended and Restated Research and Development Agreement.

"***Isis Common Stock Valuation***" has the meaning set forth in Section 2(e) of the Purchase Option Agreement.

"***Isis Funding Notice***" has the meaning set forth in Section 2 of the Research Cost Sharing and Extension Agreement.

"***Isis Obligations***" has the meaning set forth in Section 6.1 of the Amended and Restated Research and Development Agreement.

"***Isis Personnel***" has the meaning set forth in Section 8.4 of the Amended and Restated Research and Development Agreement.

"***Isis Subcontractor***" has the meaning set forth in Section 6.2 of the Amended and Restated Research and Development Agreement.

"***Key Personnel***" means those Isis Personnel listed on Schedule 6.4 to the Amended and Restated Research and Development Agreement, as such schedule may be updated from time to time by mutual agreement of the parties to the Amended and Restated Research and Development Agreement.

"***Knowledge***" means the actual (and not imputed) knowledge of the executive officers of Isis, without the duty of inquiry or investigation.

"***Law***" means any law, statute, treaty, constitution, regulation, rule, ordinance, order or Governmental Approval, or other governmental restriction, requirement or determination, of or by any Governmental Authority.

"***License***" has the meaning set forth in the Preliminary Statement of the Purchase Option Agreement.

"***Licensed Intellectual Property***" means the Licensed Patent Rights, Symphony GenIsis Enhancements, Licensor Enhancements and the Licensed Know-How.

"***Licensed Know-How***" means any and all proprietary technology that is Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option that relates to, or is exploitable in connection with, the Licensed Patent Rights, Regulatory Files, Products or the Programs, including without limitation, manufacturing processes or protocols, know-how, writings, documentation, data, technical information, techniques, results of experimentation and testing, diagnostic and prognostic assays, specifications, databases, any and all laboratory, research, pharmacological, toxicological, analytical, quality control pre-clinical and clinical data, and other information and materials, whether or not patentable.

"***Licensed Patent Rights***" means:

(a) any and all patents, patent applications and invention disclosures Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option and relating to, or exploitable in connection with, any Product and/or any Program;

(b) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) filed prior to the unexercised expiration or termination of the Purchase Option; and

(c) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) or (b) filed after the unexercised expiration or termination of the Purchase Option but solely to the extent the subject matter in any such continuation-in-part embodies Licensed Know-How or has been disclosed in the patents or patent applications described in (a) or (b).

Licensed Patent Rights include any and all patents and patent applications that claim Licensor Enhancements or Symphony GenIsis Enhancements and Program-Specific Patents.

"***Licensor***" means Isis.

"***Licensor Enhancements***" means all findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Know-How, Regulatory Files, Products or the Programs, in each case, developed by Licensor during the Term (in each case whether or not patentable), to the extent such items do not otherwise qualify as Symphony GenIsis Enhancements hereunder, regardless of whether such work is funded by Symphony GenIsis or Isis.

"***Lien***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Liquidating Event***" has the meaning set forth in Section 8.01 of the Holdings LLC Agreement.

"***LLC Agreements***" means the Initial Holdings LLC Agreement, the Holdings LLC Agreement, the Initial Investors LLC Agreement and the Investors LLC Agreement.

"***Loss***" has the meaning set forth in each Operative Document in which it appears.

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

"***Management Budget Component***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Management Fee***" has the meaning set forth in Section 6(a) of the RRD Services Agreement.

"***Manager***" means (i) for each LLC Agreement in which it appears, the meaning set forth in such LLC Agreement, and (ii) for each other Operative Document in which it appears, RRD in its capacity as manager of Symphony GenIsis.

"***Management Services***" has the meaning set forth in Section 1(a) of the RRD Services Agreement.

"***Manager Event***" has the meaning set forth in Section 3.01(g) of the Holdings LLC Agreement.

"***Material Adverse Effect***" means, with respect to any Person, a material adverse effect on (i) the business, assets, property or condition (financial or otherwise) of such Person or, (ii) its ability to comply with and satisfy its respective agreements and obligations under the Operative Documents or, (iii) the enforceability of the obligations of such Person of any of the Operative Documents to which it is a party.

"***Material Subsidiary***" means, at any time, a Subsidiary of Isis having assets in an amount equal to at least 5% of the amount of total consolidated assets of Isis and its Subsidiaries (determined as of the last day of the most recent reported fiscal quarter of Isis) or revenues or net income in an amount equal to at least 5% of the amount of total consolidated revenues or net

income of Isis and its Subsidiaries for the 12-month period ending on the last day of the most recent reported fiscal quarter of Isis.

"***Medical Discontinuation Event***" means (a) as specified in each Protocol, those data that, if collected in such Protocol, demonstrate that such Protocol should not be continued or (b) a series of adverse events, side effects or other undesirable outcomes that, when collected in a Protocol, would cause a reasonable FDA Sponsor to discontinue such Protocol.

"***Membership Interest***" means (i) for each LLC Agreement in which it appears, the meaning set forth in such LLC Agreement, and (ii) for each other Operative Document in which it appears, the meaning set forth in the Holdings LLC Agreement.

"***MOE Gapmer***" means a single stranded antisense oligonucleotide of less than [***] nucleotides (i) wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (phosphorothioate) and (ii) comprising a region of at least [***] unsubstituted 2′-deoxy nucleotides with the remaining nucleotides contain a 2′-O-(methoxyethyl) substitution at the 2′ position.

"***NASDAQ***" means the National Association of Securities Dealers Automated Quotation System.

"***NDA***" means a New Drug Application, as defined in the regulations promulgated by the United States Food and Drug Administration, or any foreign equivalent thereof.

"***Nonexclusive Field***" means (i) manufacturing (including analytical methods) ASOs, (ii) formulating ASOs, (iii) conducting Research on ASOs and/or (iv) supplying ASOs solely to conduct Research.

"***Non-Isis Capital Transaction***" means any (i) sale or other disposition of all or part of the Symphony GenIsis Shares or all or substantially all of the operating assets of Symphony GenIsis, to a Person other than Isis or an Affiliate of Isis or (ii) distribution in kind of the Symphony GenIsis Shares following the expiration of the Purchase Option.

"***Novated and Restated Technology License Agreement***" means the Novated and Restated Technology License Agreement, dated as of the Closing Date, among Isis, Symphony GenIsis and Holdings.

"***Operative Documents***" means, collectively, the Indemnification Agreement, the Holdings LLC Agreement, the Purchase Option Agreement, the Warrant Purchase Agreement, the Registration Rights Agreement, the Subscription Agreement, the Technology License Agreement, the Novated and Restated Technology License Agreement, the RRD Services Agreement, the Research and Development Agreement, the Research Cost Sharing and Extension Agreement, the Amended and Restated Research and Development Agreement, the Confidentiality Agreement, and each other certificate and agreement executed in connection with any of the foregoing documents.

"***Organizational Documents***" means any certificates or articles of incorporation or formation, partnership agreements, trust instruments, bylaws or other governing documents.

"***Partial Stock Payment***" has the meaning set forth in Section 3(a)(iii) of the Purchase Option Agreement.

"***Party(ies)***" means, for each Operative Document or other agreement in which it appears, the parties to such Operative Document or other agreement, as set forth therein. With respect to any agreement in which a provision is included therein by reference to a provision in another agreement, the term "Party" shall be read to refer to the parties to the document at hand, not the agreement that is referenced.

"***Payment Terms***" has the meaning set forth in Section 8.2 of the Amended and Restated Research and Development Agreement.

"***Percentage***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Permitted Investments***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Permitted Lien***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Person***" means any individual, partnership (whether general or limited), limited liability company, corporation, trust, estate, association, nominee or other entity.

"***Personnel***" of a Party means such Party, its employees, subcontractors, consultants, representatives and agents.

"***Prime Rate***" means the quoted "Prime Rate" at JPMorgan Chase Bank or, if such bank ceases to exist or is not quoting a base rate, prime rate reference rate or similar rate for United States dollar loans, such other major money center commercial bank in New York City selected by the Manager.

"***Products***" means an ApoB Product, a GCCR Product and/or a GCGR Product.

"***Profit***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Programs***" means the ApoB Program, the GCCR Program and/or the GCGR Program.

"Program-Specific Patents" means

(a) any and all patents, patent applications and invention disclosures Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option that claim any composition of matter comprising, or method of using, an ASO targeting any of ApoB, GCCR or GCGR, including but not limited to, the patents and patent applications listed on Annex C to the Novated and Restated Technology License Agreement;

(b) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) filed prior to the unexercised expiration or termination of the Purchase Option; and

(c) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) or (b) filed after the unexercised expiration or termination of the Purchase Option but solely to the extent the subject matter in such any continuation-in-part embodyies Licensed Know-How or has been disclosed in the patents or patent applications described in (a) or (b).

"***Protocol***" means a written protocol that meets the substantive requirements of Section 6 of the ICH Guideline for Good Clinical Practice as adopted by the FDA, effective May 9, 1997 and is included within the Development Plan or later modified or added to the Development Plan pursuant to the Amended and Restated Research and Development Agreement.

"***Public Companies***" has the meaning set forth in Section 5(e) of the Purchase Option Agreement.

"***Purchase Option***" has the meaning set forth in Section 1(a) of the Purchase Option Agreement.

"***Purchase Option Agreement***" means this Purchase Option Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis.

"***Purchase Option Closing***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Closing Date***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Commencement Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Purchase Option Exercise Date***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Exercise Notice***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Interim Date***" has the meaning set forth in Section 2(b)(i) of the Purchase Option Agreement.

"***Purchase Option Period***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Purchase Price***" has the meaning set forth in Section 2(b) of the Purchase Option Agreement.

"***Put Option***" has the meaning set forth in Section 2A of the Purchase Option Agreement.

"***Put Option Exercise Notice***" has the meaning set forth in Section 2A of the Purchase Option Agreement.

"***QA Audits***" has the meaning set forth in Section 6.5 of the Amended and Restated Research and Development Agreement.

"***Quarterly Price***" has the meaning set forth in Section 2(b)(i) of the Purchase Option Agreement.

"***Registration Rights Agreement***" means the Registration Rights Agreement dated as of the Closing Date, between Isis and Holdings.

"***Registration Statement***" has the meaning set forth in Section 1(b) of the Registration Rights Agreement.

"***Regulatory Authority***" means the United States Food and Drug Administration, or any successor agency in the United States, or any health regulatory authority(ies) in any other country that is a counterpart to the FDA and has responsibility for granting registrations or other regulatory approval for the marketing, manufacture, storage, sale or use of drugs in such other country.

"***Regulatory Allocation***" has the meaning set forth in Section 3.06 of the Holdings LLC Agreement.

"***Regulatory Files***" means any IND, NDA or any other filings filed with any Regulatory Authority with respect to the Programs.

"***Representative***" of any Person means such Person's shareholders, principals, directors, officers, employees, members, managers and/or partners.

"***Research***" means research, including gene function, gene expression and target validation research, which may include small pilot toxicology studies but excludes IND-Enabling Studies or dosing humans. Research does not include commercialization.

"***Research Cost Sharing and Extension Agreement***" means the Research Cost Sharing and Extension Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis, Inc..

"***Research and Development Agreement***" means the Research and Development Agreement dated as of the Closing Date, between Isis and Holdings.

"***RRD***" means RRD International, LLC, a Delaware limited liability company.

"***RRD FTE Budget***" means the budget attached to the RRD Services Agreement as Exhibit 3 thereto.

"***RRD Indemnified Party***" has the meaning set forth in Section 10(a) of the RRD Services Agreement.

"***RRD Investment Personnel***" has the meaning set forth in Section 1(a)(v) of the RRD Services Agreement.

"***RRD Loss***" has the meaning set forth in Section 10(a) of the RRD Services Agreement.

"***RRD Personnel***" has the meaning set forth in Section 1(a)(ii) of the RRD Services Agreement.

"***RRD Services Agreement***" means the RRD Services Agreement between Symphony GenIsis and RRD, dated as the Closing Date, 2006.

"***Schedule K-1***" has the meaning set forth in Section 9.02(a) of the Holdings LLC Agreement.

"***Scheduled Meeting***" has the meaning set forth in Paragraph 6 of Annex B of the Amended and Restated Research and Development Agreement.

"***Scientific Discontinuation Event***" has the meaning set forth in Section 4.2(c) of the Amended and Restated Research and Development Agreement.

"***SCP***" means Symphony Capital Partners, L.P., a Delaware limited partnership.

"***SEC***" means the United States Securities and Exchange Commission.

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

"***Selling Stockholder Questionnaire***" has the meaning set forth in Section 4(a) of the Registration Rights Agreement.

"***Shareholder***" means any Person who owns any Symphony GenIsis Shares.

"***Solvent***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***SSP***" means Symphony Strategic Partners, LLC, a Delaware limited liability company.

"***Stock Payment Date***" has the meaning set forth in Section 2 of the Subscription Agreement.

"***Stock Purchase Price***" has the meaning set forth in Section 2 of the Subscription Agreement.

"***Subcontracting Agreement***" has the meaning set forth in Section 6.2 of the Amended and Restated Research and Development Agreement.

"***Sublicensed Intellectual Property***" has the meaning set forth in Section 3.2 of the Novated and Restated Technology License Agreement.

"***Sublicense Obligations***" has the meaning set forth in Section 3.2 of the Novated and Restated Technology License Agreement.

"***Subscription Agreement***" means the Subscription Agreement between Symphony GenIsis and Holdings, dated as the Closing Date.

"***Subsidiary***" of any Person means any corporation, partnership, joint venture, limited liability company, trust or estate of which (or in which) more than 50% of (a) the issued and outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether at the time capital stock of any other class or classes of such corporation shall or might have voting power upon the occurrence of any contingency); (b) the interest in the capital or profits of such partnership, joint venture or limited liability company; or (c) the beneficial interest in such trust or estate is at the time directly or indirectly owned or controlled by such Person, by such Person and one or more of its other Subsidiaries or by one or more of such Person's other Subsidiaries.

"***Surviving Entity***" means the surviving legal entity which is surviving entity to Isis after giving effect to a Change of Control.

"***Symphony Capital***" means Symphony Capital LLC, a Delaware limited liability company.

"***Symphony Fund(s)***" means Symphony Capital Partners, L.P., a Delaware limited partnership, and Symphony Strategic Partners, LLC, a Delaware limited liability company.

"***Symphony GenIsis***" means Symphony GenIsis, Inc., a Delaware corporation.

"***Symphony GenIsis Auditors***" has the meaning set forth in Section 5(b) of the RRD Services Agreement.

"***Symphony GenIsis Board***" means the board of directors of Symphony GenIsis.

"***Symphony GenIsis By-laws***" means the By-laws of Symphony GenIsis, as adopted by resolution of the Symphony GenIsis Board on the Closing Date.

"***Symphony GenIsis Charter***" means the Amended and Restated Certificate of Incorporation of Symphony GenIsis, dated as of the Closing Date.

"***Symphony GenIsis Director Event***" has the meaning set forth in Section 3.01(h)(i) of the Holdings LLC Agreement.

"***Symphony GenIsis Enhancements***" means findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Know-How, Regulatory Files, Products or the Programs, made by or on behalf of Symphony GenIsis during the Term, in each case whether or not patentable, including any such findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes related to data and information generated or derived by RRD and assigned to Symphony GenIsis pursuant to Section 12 of the RRD Services Agreement.

"***Symphony GenIsis Equity Securities***" means the Common Stock and any other stock or shares issued by Symphony GenIsis.

"***Symphony GenIsis Loss***" has the meaning set forth in Section 10(b) of the RRD Services Agreement.

"***Symphony GenIsis Shares***" has the meaning set forth in Section 2.02 of the Holdings LLC Agreement.

"***Tangible Materials***" means any tangible documentation, whether written or electronic, existing as of the Closing Date or during the Term, that is Controlled by the Licensor, embodying or relating to the Licensed Intellectual Property, Regulatory Files, Products or the Programs, including, but not limited to, safety, efficacy or other data related to the Products or Programs, documentation, patent applications and invention disclosures.

"***Tax Amount***" has the meaning set forth in Section 4.02 of the Holdings LLC Agreement.

"***Technology License Agreement***" means the Technology License Agreement, dated as of the Closing Date, between Isis and Holdings.

"***Term***" has the meaning set forth in Section 4(b)(iii) of the Purchase Option Agreement, unless otherwise stated in any Operative Document.

"***Territory***" means the world.

"***Third Party IP***" has the meaning set forth in Section 2.9 of the Novated and Restated Technology License Agreement.

"***Third Party Licensor***" means a third party from which Isis has received a license or sublicense to Licensed Intellectual Property.

"***Transfer***" has for each Operative Document in which it appears the meaning set forth in such Operative Document.

"***Transferee***" has, for each Operative Document in which it appears, the meaning set forth in such Operative Document.

"***Voluntary Bankruptcy***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Warrant Closing***" has the meaning set forth in Section 2.03 of the Warrant Purchase Agreement.

"***Warrant Date***" has the meaning set forth in Section 2.02 of the Warrant Purchase Agreement.

"***Warrant Purchase Agreement***" means the Warrant Purchase Agreement, dated as of the Closing Date, between Isis and Holdings.

"***Warrant Shares***" has the meaning set forth in Section 2.01 of the Warrant Purchase Agreement.

"***Warrant Surrender Price***" has the meaning set forth in Section 7.08 of the Warrant Purchase Agreement.

"***Warrants***" has the meaning set forth in Section 2.01 of the Warrant Purchase Agreement.

ANNEX B

[RESERVED]

ANNEX C

CERTAIN PROGRAM-SPECIFIC PATENTS

[***]

ANNEX D

CERTAIN ROYALTY AND MILESTONE PAYMENTS

[***]

SCHEDULE 2.2

CERTAIN RESTRICTIONS RELATING TO LICENSED INTELLECTUAL PROPERTY LICENSED TO LICENSOR BY A THIRD PARTY

[***]

Exhibit 10.5

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

EXECUTION COPY

AMENDED AND RESTATED
RESEARCH AND DEVELOPMENT AGREEMENT

among

ISIS PHARMACEUTICALS, INC.,

SYMPHONY GENISIS HOLDINGS LLC

and

SYMPHONY GENISIS, INC.

Dated as of April 7, 2006

TABLE OF CONTENTS

AMENDED AND RESTATED
RESEARCH AND DEVELOPMENT AGREEMENT

This AMENDED AND RESTATED RESEARCH AND DEVELOPMENT AGREEMENT (this "***Agreement***") is entered into as of April 7, 2006 (the "***Closing Date***") by and among ISIS PHARMACEUTICALS, INC., a Delaware corporation ("***Isis***"), SYMPHONY GENISIS, INC., a Delaware corporation ("***Symphony GenIsis***") (each of Isis and Symphony GenIsis being a "***Party***," and collectively, the "***Parties***"), and SYMPHONY GENISIS HOLDINGS LLC, a Delaware limited liability company ("***Holdings***") (which shall be a Party to this Agreement solely with respect to Articles 1 and 14 and Sections 5.3, 6.3, 6.4, 6.7 and 7.5). Capitalized terms used herein and not defined herein shall have the meanings assigned to such terms in Annex A attached hereto.

PRELIMINARY STATEMENT

Isis and Holdings have entered into that certain Research and Development Agreement, dated as of April 7, 2006 (the "***Research and Development Agreement***"). Pursuant to this Agreement, Holdings desires to assign all of its rights and delegate its obligations under the Research and Development Agreement to Symphony GenIsis, and Isis and Symphony GenIsis desire to amend and restate the terms and conditions of the Research and Development Agreement.

In the Novated and Restated Technology License Agreement, Isis grants Symphony GenIsis an exclusive license to develop and commercialize certain compounds. Symphony GenIsis wishes for Isis to continue to develop such compounds. Symphony GenIsis and Isis desire to establish, and agree on the responsibilities of, a Development Committee to oversee such development. Isis and Symphony GenIsis further desire to comply with and perform certain agreements and obligations related thereto.

The Parties hereto agree as follows:

1. **Assignment.** The Parties agree that from and after the Closing Date, all of the rights and obligations of Holdings under the Research and Development Agreement will be assigned and transferred to, and assumed by, Symphony GenIsis.

2. **Overview of Development.**

(a) The Parties shall develop the Programs in a collaborative and efficient manner. Representatives of the Parties shall engage in joint decision-making for the Programs as set forth in Articles 3 and 4 hereof. Symphony GenIsis shall have overall responsibility for all matters set forth in the Development Plan (pursuant to Article 7 hereof), and shall engage Isis (pursuant to Article 6 hereof), RRD International LLC ("***RRD***") (pursuant to the RRD Services Agreement), and such independent contractors and agents as RRD and Isis may retain on Symphony GenIsis' behalf, to act on behalf of Symphony GenIsis and carry out the duties set forth therein and herein, including management, supervisory and accounting functions, pre-clinical and clinical

development, scientific and technical services associated with such development, and patent work under the Programs.

(b) Isis hereby acknowledges and agrees to Symphony GenIsis' engagement of RRD to act on its behalf and to carry out the duties set forth herein and in the RRD Services Agreement, including, but not limited to (i) the management and administration of Symphony GenIsis, (ii) providing personnel and support to the Development Committee and the Symphony GenIsis Board, (iii) hiring, on Symphony GenIsis' behalf, independent contractors and vendors, (iv) supervising and monitoring the development of the Programs, and (v) such other development-related work as Symphony GenIsis may reasonably delegate to RRD.

(c) With respect to the ApoB Program, the GCGR Program and the GCCR Program, Isis shall be responsible for the execution of all pre-clinical and clinical development, all scientific and technical services associated with such development, and all patent work, including all related matters set forth in the Development Plan for such Programs.

(d) Nothing in clause (c) shall in any way limit the authority of the Development Committee (as defined below) or the Symphony GenIsis Board hereunder, and the engagements and delegations set forth therein shall be subject to the terms and conditions of this Agreement and the RRD Services Agreement, and the satisfactory performance by RRD and Isis of their obligations pursuant hereto and thereto. The allocations of responsibility described in this Article 2 shall remain subject to further modification in accordance with the terms and conditions of this Agreement and the RRD Services Agreement.

3. **Development Committee.** The Parties shall establish and maintain a committee (the "***Development Committee***") to oversee the development of the Programs (including the continued development and refinement of the Development Plan and the Development Budget). The Development Committee shall be established, operated and governed in accordance with the policies and procedures set forth in Annex B hereto (the "***Development Committee Charter***"). The Development Committee Charter may be amended only with the unanimous approval of the Development Committee Members and the consent of the Symphony GenIsis Board and Isis. In no event shall the Development Committee have the power to amend the terms of any Operative Document.

4. **Development Plan and Development Budget.**

4.1 **Generally.** The Parties have agreed, as of the Closing Date, to an Initial Development Plan and an Initial Development Budget, which are attached hereto and incorporated herein as Annex C and Annex D, respectively, and which shall be further developed and refined from time to time in accordance herewith. The Initial Development Plan consists (and the Development Plan shall consist) of detailed provisions governing all pre-clinical, clinical, scientific, technical, regulatory and patent work to be performed under the Operative Documents. Following the Closing Date, the Development Committee shall, on an ongoing basis, further develop the Development

Plan to include, without limitation, (i) an outline of the plan for the development of each Program; (ii) detailed Protocols for each Program; and (iii) outlines of non-clinical activities, key regulatory and quality activities, and CMC activities for each Program. The Initial Development Budget consists (and the Development Budget shall consist) of two (2) components: (x) a budget for the Development Plan (the "***Clinical Budget Component***"), and (y) a budget for the management and administrative functions of Symphony GenIsis, as set forth in Section 1(a) of the RRD Services Agreement (the "***Management Budget Component***"). The Clinical Budget Component shall be further divided into separate budgets for each Program, and, following the Closing Date, the Development Committee shall further develop and refine the Clinical Budget Component to include, without limitation, (1) budget spreadsheets summarizing anticipated costs of engaging third party service providers for each Protocol and the scope of Protocol-related work to be performed by such third parties; and (2) the number of full-time equivalents ("***FTEs***") to be dedicated to the Programs (by function and work responsibilities, on a Program-by-Program basis). All presently anticipated or actual expenditures of Symphony GenIsis, including without limitation, compensation of members of the Symphony GenIsis Board, are included in the Initial Development Budget attached hereto as Annex D, and will continue to be included in any amendments thereof. The Development Committee shall, at the request of the Symphony GenIsis Board, submit the Development Plan and the Development Budget (as each shall have been developed and refined up to such point) to the Symphony GenIsis Board for its review at the first meeting of the Symphony GenIsis Board. Following the Symphony GenIsis Board's review, the Development Committee shall work diligently to incorporate the comments generated by the Symphony GenIsis Board's review and update the Development Plan and the Development Budget as soon as practicable, and submit the updated Development Plan and the Development Budget to the Symphony GenIsis Board for further review; provided that (x) in no event shall the aggregate total amount of the Development Budget be increased to an amount that is greater than [***]. without the consent of Isis (such consent to be given or withheld in Isis' sole discretion), and (y) any amendments to or revisions of the Development Budget shall be made in accordance with Paragraph 14 of the Development Committee Charter and Section 2 of the Research Cost Sharing and Extension Agreement.

4.2 Amendments.

(a) All amendments of and, all material deviations from, the Development Plan and Development Budget (including amendments or deviations made at the request of Isis or RRD, in accordance with Section 8.3 hereof or Section 2(b) of the RRD Services Agreement, respectively) shall be made in accordance with the procedures described in this Article 4 and in the Development Committee Charter, including obtaining the approval of the Symphony GenIsis Board, as may be required by the Development Committee Charter.

(b) The Development Committee shall review the Development Plan and Development Budget in their entirety on an annual basis to determine whether any changes are required, and shall comply with all procedures required to amend the Development Plan or Development Budget to implement such changes. Furthermore,

following the Closing Date, the Development Committee shall, on an ongoing basis, continue to develop the Development Plan, including, without limitation, as set forth in Section 4.1 and in response to requests, proposals or reports from Isis and RRD to the Development Committee.

(c) A Program may only be discontinued in the event that either (i) the Parties mutually agree to discontinue such Program based on (A) a Medical Discontinuation Event, or (B) scientific evidence (regardless of whether such evidence is generated by a Party or a third party) that the likelihood of success for a particular Program is not enough to warrant further development (a "***Scientific Discontinuation Event***") that arises in the course of developing such Program; or (ii) the Symphony GenIsis Board by (x) if the Symphony GenIsis Board shall have less than five (5) members, the unanimous consent of all the members of the Symphony GenIsis Board, or (B) if the Symphony GenIsis Board shall have five (5) members, an affirmative vote of four-fifths (4/5ths) of the members of the Symphony GenIsis Board, resolves to discontinue such Program. The Development Committee shall promptly thereafter amend the Development Plan to reflect such discontinuation and amend the Development Budget to reallocate to any or all of the remaining Programs the funds previously allocated to the discontinued Program (with any funds not then allocated to be held for reallocation by the Development Committee).

(d) The Development Plan shall never be amended in any manner that would require Isis or Symphony GenIsis (or any Person acting on behalf of Isis or Symphony GenIsis (including RRD and its RRD Personnel)) to perform any assignments or tasks in a manner that would violate any applicable law or regulation. In the event of a change in any applicable law or regulation, the Development Committee shall consider amending the Development Plan to enable Isis or Symphony GenIsis (or any Person acting on behalf of Isis or Symphony GenIsis (including RRD and its RRD Personnel)), as the case may be, to comply fully with such law or regulation. If such amendment is not approved, the affected Party shall be excused from performing any activity specified herein or in the Development Plan that would violate or result in a violation of any applicable law or regulation.

5. Regulatory Matters.

5.1 FDA Sponsor. Notwithstanding any governance provision contained herein or in any Operative Document, the Parties agree that, until the termination or unexercised expiration of the Purchase Option, Isis shall be the FDA Sponsor for the Programs (except any Programs which were the subject of a Discontinuation Option that was not exercised by Isis). Isis shall have the responsibility and the authority to act as the sponsor and make those decisions and take all actions necessary to assure compliance with all regulatory requirements. Isis agrees to be bound by, and perform all obligations set forth in, 21 C.F.R. § 312 related to its role as the FDA sponsor for the Programs (the "***FDA Sponsor***"). Notwithstanding anything to the contrary in Article 4 or the Development Committee Charter, Isis, in its capacity as FDA Sponsor, may discontinue or modify any Program without the approval of the Development Committee or the Symphony GenIsis Board in the event such actions are: (a) triggered by an event that is reportable to the

FDA; and (b) reasonably necessary to avoid the imposition of criminal or civil liability; provided, however, that to the extent commercially reasonable, Isis shall (i) pursuant to Section 5.2, advise and consult with the Development Committee prior to taking such action and (ii) forward a copy of all such correspondence to the members of the Symphony GenIsis Board.

5.2 Correspondence. Each Party hereto acknowledges that Isis, in its capacity as FDA Sponsor, shall be the Party responding to any regulatory correspondence or inquiry. Each Party shall: (a) notify the other Parties promptly of any FDA or other governmental or regulatory inspection or inquiry concerning any study or project under the Programs, including, but not limited to, inspections of investigational sites or laboratories; and (b) forward to the other Parties copies of any correspondence from any regulatory or governmental agency relating to such a study or project, including, but not limited to, Form FD-483 notices and FDA refusal to file, action or warning letters, even if they do not specifically mention the other Parties. Symphony GenIsis shall obtain the written consent of Isis, which consent will not be unreasonably withheld, before referring to Isis or its Affiliates in any regulatory correspondence, except to the extent that such reference is required by law or simply refers to the existence of this Agreement or any of the other Operative Documents. Furthermore, Isis shall be the Party responsible for responding to or handling any FDA or regulatory inspection; provided, that Isis shall notify the Development Committee (i) within twenty-four (24) hours of the commencement of a clinical hold for any Protocol, and (ii) concurrently with its submission to the FDA of any IND safety reports for the Programs.

5.3 Inspections and Meetings. Each Party agrees that, during an inspection by the FDA or other Regulatory Authority concerning any study or project under the Programs, it will not disclose information and materials (including but are not limited to (x) financial data and pricing data including, but not limited to, budget and payment schedules, (y) sales data (other than shipment data), and (z) personnel data (other than data as to qualification of technical and professional persons performing functions subject to regulatory requirements)) to such agency without the prior consent of the other Parties, which consent shall not be unreasonably withheld or delayed, except to the extent that such Party may be required to disclose such information and materials or such Party determines, in its reasonable judgment, that it is prudent to disclose such materials or information at such time. Furthermore, each Party shall promptly inform each other Party of any meetings concerning the Programs between its personnel and any Regulatory Authority or other outside personnel or agencies, and shall, upon a request from such other Party or Parties, and to the extent reasonably possible, facilitate the attendance at such meetings of a Development Committee Member nominated (x) by Holdings if Isis was the notifying Party, or (y) by Isis if Holdings or Symphony GenIsis was the notifying Party.

5.4 Transfer of FDA Sponsorship.

(a) On or prior to the thirtieth (30^{th}) day after the unexercised expiration or termination of the Purchase Option, Isis shall cease to act as the FDA sponsor for the Programs for which Isis has not exercised the Discontinuation Option, and Isis and

Symphony GenIsis shall, at Symphony GenIsis' expense, take all actions necessary to effect the transfer of (x) the Regulatory Files solely related to such Programs to Symphony GenIsis or its designee in accordance with Section 2.7 of the Novated and Restated Technology License Agreement, and (y) any and all materials necessary for Symphony GenIsis to practice or exploit the license granted to it under the Novated and Restated Technology License Agreement, by such date. In conjunction with such transfer, Isis hereby assigns to Symphony GenIsis or its designee, as of the date specified in the first sentence of this Section 5.4(a), all of the material agreements to which Isis is a Party and that: (i) are related to such Programs; (ii) provide Isis with goods and services (clinical and manufacturing) from third party suppliers and subcontractors; and (iii) are assignable to Symphony GenIsis or its designee. Isis shall provide copies of all such contracts to Symphony GenIsis in connection with such transfer. Isis shall use commercially reasonable efforts to cause the transfer of any non-assignable material agreements meeting the criteria set forth in (i) and (ii) above, or if such agreements are not assignable, Isis shall act as agent of Symphony GenIsis in processing all goods and services under such agreements. Isis agrees to take such commercially reasonable actions as Symphony GenIsis may request in furtherance of the foregoing at the expense of Symphony GenIsis Such efforts shall not include any obligation for Isis to incur any out-of-pocket costs in connection with such transfer.

(b) Upon the discontinuation of any of the Programs pursuant to Section 4.2(c), Isis shall have no further obligations with respect to such Programs under the Operative Documents. If such Programs are transferred or licensed to a third party in accordance with Section 11.1 (such third party, the "***Transferee***"), then Isis shall cooperate with Symphony GenIsis and the Transferee to effect the assignment to the Transferee of the sponsorship to the Regulatory Files with respect to the Program for which Transferee has acquired rights; provided, however, that Isis shall not be obligated to take any action pursuant to this Section 5.4(b) for which it will not receive full reimbursement from Symphony GenIsis or another party. The assignment of such Regulatory Files to the Transferee does not include an assignment of any Licensed Intellectual Property.

6. Isis' Obligations.

6.1 Generally.

(a) Isis shall be responsible for (i) the execution of all matters set forth in the Development Plan for the ApoB Program, the GCGR Program and the GCCR Program, and (ii) the execution of all other matters set forth in the Development Plan that have been delegated to Isis by Symphony GenIsis (collectively, the "***Isis Obligations***"); provided, however that, following the Closing Date, the Development Committee shall be responsible for any decision to delegate additional matters or responsibilities to Isis.

(b) Isis agrees that it will work diligently and use commercially reasonable efforts to discharge the Isis Obligations in a good scientific manner and in accordance with the Development Plan, the Development Budget, and the terms of this Agreement. In the event that Isis is unable to execute any of the aforementioned development

activities which comprise the Isis Obligations in accordance with the standard established in the preceding sentence, as determined by the Development Committee, Symphony GenIsis shall re-assign such development activities in a manner to be determined by the Development Committee, and Isis shall transfer and deliver to Symphony GenIsis (or RRD on behalf of Symphony GenIsis) any and all materials, documents, files

and other information relating to such development activities; provided, that Isis shall be permitted to retain copies of such transferred materials, documents, files and other information relating to such development activities as necessary in order to comply with any requirements of a Governmental Authority.

6.2 Subcontracting. All agreements between Isis and third parties (including without limitation clinical research organizations and contract manufacturers) for such third parties to perform any Isis Obligations (each such third party, an "***Isis Subcontractor***" and each such agreement, a "***Subcontracting Agreement***") entered into by Isis prior to the Closing Date (except for those master service agreements executed prior to the Closing Date that, only through the subsequent addition of a new work order, change order, project or the like after the Closing Date, become Subcontracting Agreements) shall be deemed to be acceptable to the Parties in all respects. Following the Closing Date, Isis shall obtain the approval of the Development Committee prior to entering into any Subcontracting Agreement or amending or terminating any Subcontracting Agreement. Isis shall provide the Development Committee with a copy of each draft Subcontracting Agreement at a monthly Development Committee meeting, or at such other time as may be agreed among the Parties, prior to the execution of such Subcontracting Agreement. The terms of any such Subcontracting Agreements shall be deemed the Confidential Information of Isis and be subject to the rights and obligations set forth in the Confidentiality Agreement. Isis shall monitor the performance of its Isis Subcontractors and shall promptly notify the Development Committee with respect to any Isis Subcontractor performance issues that may have a material adverse effect on the Programs. The Development Committee shall have the authority to direct Isis to terminate any Subcontracting Agreement pursuant to the terms thereof.

6.3 Reports. Isis shall keep the Development Committee informed of its activities under the Development Plan through regular reports. At each Scheduled Meeting of the Development Committee, Isis shall, to the extent reasonably required by the Development Committee, provide the Development Committee with a summary of Isis' activities and developments with respect to the Programs for the period following the most recent preceding Scheduled Meeting. Such summary shall include: (i) a copy of each new Protocol for the Programs being drafted by Isis; (ii) a copy of each standard clinical study progress report for the Programs received by Isis during the preceding month from any of the clinical research organizations engaged by Isis pursuant to any Subcontracting Agreements; (iii) updates regarding (A) CMC status, non-clinical program status, regulatory and quality program status, communications with regulatory agencies, results of meetings of Isis' Clinical Advisory Board for a particular Program, and results of meetings with consultants for the Programs, all to the extent related to Isis' activities under the Development Plan, and (B) patient enrollment, any adverse events (to the extent Isis has been notified of such adverse events) or serious adverse events, any added or terminated clinical trial sites, any significant Protocol deviation and any interim

analyses or statistical reports, all to the extent relating to clinical trials under the Development Plan; (iv) a financial report, in a format agreed upon by the Development Committee, itemizing actual spending under the Development Plan as well as any variation from planned spending; (v) if the portion of the Development Budget related to a particular Program is altered to the extent that available funding for such Program no longer appears to be adequate to complete the Program, an updated budget forecast; and (vi) such other information as the Development Committee may reasonably request.

6.4 Staffing. Isis shall provide such sufficient and competent staff and Personnel (including, without limitation, such employees or agents of, or independent contractors retained by, Isis) that have the skill and expertise necessary to perform the Isis Obligations. Isis shall notify Symphony GenIsis in advance, if practicable, and in any event promptly thereafter, of any change in Key Personnel involved in the Programs.

6.5 QA Audit. During the Term, Isis will permit Symphony GenIsis' representatives, such representatives to be identified by Symphony GenIsis in advance and reasonably acceptable to Isis, to examine and audit the work performed by Isis hereunder and the Isis facilities at which such work is conducted to determine that the project assignment is being conducted in accordance with the agreed upon services ("***QA Audits***") during regular business hours. Symphony GenIsis shall give Isis reasonable advance notice of such QA Audits specifying the scope of the audit. Symphony GenIsis shall reimburse Isis for its time associated with QA Audits; provided, however, that should a particular QA Audit reveal a material deficiency, then Symphony GenIsis will not be responsible for costs associated with such QA Audit, the work to be re-performed or the costs or expenses associated with curing any material deficiencies. Symphony GenIsis and Isis shall meet to discuss the results of the QA Audit and, if required, jointly agree upon any actions that will be required as a result of such audits including defining material deficiencies to be addressed. Isis shall make commercially reasonable efforts to reconcile all such deficiencies found by Symphony GenIsis during such QA Audit.

6.6 Financial Audit. During the Term, Isis will permit Symphony GenIsis' representatives (such representatives to be identified by Symphony GenIsis in advance and reasonably acceptable to Isis), to verify Isis' invoices, other receipts, and FTE records that are related to Isis' performance of the work under the Programs ("***Financial Audits***"), which review shall be conducted during regular business hours will take place no more than once per year, unless otherwise agreed to by the Parties. Symphony GenIsis shall give Isis reasonable advance notice of such Financial Audits specifying the scope of the audit, which shall not include work that has previously undergone Financial Audits. Symphony GenIsis shall reimburse Isis for its time associated with Financial Audits; provided, however, that should a particular Financial Audit reveal an aggregate variance of more than 5% between such financial records and the reports submitted by Isis to Symphony GenIsis for reimbursement purposes, then Symphony GenIsis will not be responsible for costs associated with such Financial Audit. Symphony GenIsis and Isis shall meet to discuss the results of the Financial Audit and, if required, jointly agree upon any actions that will be required as a result of such audits including defining material discrepancies to be addressed. Isis shall make commercially reasonable efforts to reconcile all such discrepancies found by Symphony GenIsis during such Financial

Audit. In addition, Isis shall, during regular business hours, cooperate with, and promptly respond to inquiries from, the Symphony GenIsis Auditors, if the Symphony GenIsis Auditors shall reasonably conclude that they require additional information or clarification regarding any invoices, other receipts or FTE records submitted by Isis.

6.7 Insurance.

(a) Subject to Section 6.7(b), Isis shall, at all times and at Isis' own expense, cause, to the extent available on a commercially reasonable basis, clinical trials and product liability insurance with respect to bodily injury or property damage, and with respect to such other risks as are covered by insurance maintained by Isis in connection with other medical technology, in an amount not less than [***] per occurrence and

[***] in the aggregate, to be carried and maintained with financially sound insurers of recognized standing; provided, that, following the submission by Isis of the applicable invoices for such coverage, Symphony GenIsis shall reimburse Isis for [***] of the cost of obtaining and maintaining such insurance. The deductible for the insurance policy shall not exceed [***] per occurrence and [***] in the aggregate. Subject to Section 6.7(d), the terms and conditions of such liability insurance shall be no less favorable to Symphony GenIsis than the liability insurance maintained by Isis as of the Closing Date.

(b) Isis shall not be required to maintain the liability insurance required by this section if and to the extent that Isis furnishes to each of Symphony GenIsis and Holdings a written report of an independent insurance advisor of recognized national standing acceptable to Symphony GenIsis and Holdings confirming in reasonable detail that such insurance, in respect of amount or scope of coverage, is not available on a commercially reasonable basis. In such event Isis shall maintain liability insurance to the extent it is available on a commercially reasonable basis. If the insurance which was previously discontinued because of its commercial unavailability later becomes available on a commercially reasonable basis, Isis shall reinstate such insurance.

(c) Prior to the expiration of the liability insurance required to be carried hereunder, Isis shall make a good faith effort to renew or replace such policy, and furnish to each of Symphony GenIsis and Holdings a certificate of insurance evidencing that such insurance has been replaced or renewed in compliance with this Section 6.7.

(d) Each insurance policy required by this Section 6.7 shall, to the extent available on a commercially reasonable basis:

(i) name Symphony GenIsis, along with Symphony GenIsis' affiliates, subsidiaries, directors, officers, partners, employees, advisers and any other individual or organization for which Symphony GenIsis is obligated to provide insurance, and RRD, along with RRD's affiliates, subsidiaries, directors, officers, partners, employees, advisers and any other individual or organization for which RRD is obligated to provide insurance, to the extent that such parties are engaged in activities contemplated by the Development Plan, as the only additional insureds (the "***Additional Insureds***"). Symphony GenIsis may also add other entities or individuals as additional insureds in good faith as part of the

continued development of the Programs as contemplated by the Development Plan;

(ii) exclusively cover Symphony GenIsis' participation in the transactions and activities set forth in the Operative Documents to which Symphony GenIsis is a party;

(iii) require thirty (30) days prior notice to Symphony GenIsis and Holdings of cancellation for any reason;

(iv) not require contributions from other policies held by the Additional Insureds;

(v) waive any right of set-off, counterclaim, deduction or subrogation of the insurers against the Additional Insureds;

(vi) continue to cover the Additional Insureds regardless of any breach or violation of any warranty, declaration or condition contained in such policy by Isis;

(vii) waive any right to claim any premium or commissions against the Additional Insureds;

(viii) require that the exclusions are reasonably acceptable to Symphony GenIsis and Holdings;

(ix) require that a copy of the insurance policy, all policy amendments, and any notices of cancellation or non-renewal, be sent to each of Symphony GenIsis and Holdings;

(x) have an order of payments provision requiring the insurer to pay any covered loss of the Additional Insureds first; and

(xi) require that the Additional Insureds shall also have the right to purchase the extended reporting period that is available in such policy.

(e) If Isis is in default of its obligation to obtain or maintain the insurance coverage specified herein when such coverage is available on a commercially reasonable basis, Symphony GenIsis may, at its option, but shall not be required to, provide such insurance, and in such event, Isis shall, upon demand from time to time, reimburse Symphony GenIsis for any incremental costs incurred by Symphony GenIsis in obtaining insurance coverage to replace the insurance coverage which Isis shall have failed to maintain.

(f) Isis shall provide each of Symphony GenIsis and Holdings with a blind copy of all material correspondence between Isis, the insurer and/or the insurance broker relating to the insurance policies discussed in this Section 6.7.

(g) Isis shall provide each of Symphony GenIsis and Holdings with a copy of the insurance policy upon receipt from the insurer.

(h) In the event of a circumstance, occurrence, claim or suit that may be covered under the insurance policy, Isis shall promptly provide notice of such event to each of Symphony GenIsis and Holdings.

(i) Nothing in this Section 6.7 shall prohibit Symphony GenIsis from obtaining insurance for its own account as contemplated in the Operative Documents, and any proceeds payable thereunder shall be as provided in the insurance policy relating thereto.

(j) Once in any twelve (12) month period, at Symphony GenIsis' request, Isis shall provide certificates of insurance to each of Symphony GenIsis and Holdings, evidencing that the insurance required by this Section 6.7 is in effect.

(k) If for any reason Isis cancels or fails to renew any liability insurance policy required by this Section 6.7, then Symphony GenIsis shall have the option to purchase the longest extended reporting period that is available on a commercially reasonable basis under such policy.

7. Symphony GenIsis' Obligations.

7.1 Generally. Symphony GenIsis shall have overall responsibility for all matters set forth in the Development Plan, and shall be responsible for (i) executing or delegating its management and administration responsibilities; and (ii) executing or delegating the clinical development activities set forth in the Development Plan. Symphony GenIsis shall, and shall instruct all Persons whom it engages pursuant to Section 2 hereof to, perform its obligations hereunder and under Development Plan acting in good faith and in accordance with the applicable provision of the Development Plan, the Development Budget, and the terms of this Agreement.

7.2 Subcontracting. Symphony GenIsis is subcontracting, and will in the future subcontract, certain of its responsibilities under the Development Plan to RRD (pursuant to the RRD Services Agreement), to Isis (pursuant hereto) and to other vendors and service providers (pursuant to subcontracting agreements to be approved by the Development Committee); provided, that Symphony GenIsis shall remain responsible for the performance of its obligations hereunder notwithstanding any such arrangement. Any subcontracting agreement entered into by Symphony GenIsis (including such contracts as RRD may negotiate on its behalf) shall include a provision permitting assignment at any time of the subcontracting agreement from Symphony GenIsis to Isis without the subcontractor's consent.

7.3 Insurance. Symphony GenIsis shall maintain insurance with creditworthy insurance companies against such risks and in such amounts as are usually maintained or insured against by other companies of established repute engaged in the same or a similar business.

7.4 Staffing. Symphony GenIsis shall use commercially reasonable efforts to provide, or cause to be provided on its behalf (including Personnel retained by RRD), sufficient and competent staff and Personnel that have the skill and expertise necessary to perform Symphony GenIsis' obligations under this Agreement, the RRD Services Agreement, the Development Plan and the Development Budget, including, but not limited to, (i) carrying out its management and administrative functions pursuant to the RRD Services Agreement, and (ii) and carrying out its clinical development duties in accordance with this Agreement, the Development Plan and the Development Budget.

7.5 Audit. Symphony GenIsis shall permit each of Isis, Holdings, Investors and each Symphony Fund and their duly authorized representatives at all reasonable business hours to inspect (1) Symphony GenIsis' books, records and other reasonably requested materials and (2) any and all properties of Symphony GenIsis, and it shall provide to each of Isis, Holdings, Investors and each Symphony Fund all books, records and other materials related to any meeting of the Symphony GenIsis Board and to permit Holdings, Investors and each Symphony Fund to make copies or extracts therefrom; provided, that each aforementioned party may conduct one such inspection in each calendar year without cost to such party, and that any party conducting additional inspections shall reimburse the Manager for its reasonable costs and expenses in facilitating such inspection. Symphony GenIsis and Isis shall meet to discuss the results of the audit and, if required, jointly agree upon any actions that will be required as a result of such audits including defining material discrepancies to be addressed. Symphony GenIsis shall make commercially reasonable efforts to reconcile all such discrepancies found by Isis, Holdings, Investors or any Symphony Fund during such audit.

8. Funding and Payments.

8.1 Use of Proceeds. Symphony GenIsis shall use any and all (x) net proceeds received by Symphony GenIsis as a result of the Financing, (y) indemnity payments received by Symphony GenIsis, and (z) payments received by Symphony GenIsis pursuant to first and third party covered insurance claims, for the development of the Programs and general corporate purposes, including the payment of all fees and expenses in accordance with the Development Plan and the Development Budget, as may be modified from time to time pursuant to Section 4.2 and the payment of any indemnification obligations of Symphony GenIsis under the Operative Documents and agreements with third party contractors. Notwithstanding the foregoing, Symphony GenIsis agrees that any agreement under which Symphony GenIsis indemnifies any Person shall contain appropriate provisions to cause such Person who receives payments from Symphony GenIsis as a result of Symphony GenIsis' indemnification obligations under the Operative Documents, and who is subsequently reimbursed from insurance proceeds with respect to such losses, costs, interest, awards, judgments, fees liabilities, damages and expenses for which such Person received the indemnity payments from Symphony GenIsis, to then reimburse Symphony GenIsis the amounts paid to such Person by Symphony GenIsis to the extent of the insurance proceeds. Symphony GenIsis further agrees to use all commercially reasonable means to enforce such provisions.

8.2 Reimbursement. Symphony GenIsis shall compensate Isis and RRD fully for their respective Development Plan-associated activities, including without limitation its research, clinical and manufacturing services, and any other activities delegated to Isis or RRD by Symphony GenIsis or the Development Committee. Such compensation shall be made to (a) Isis in accordance with the provisions of this Article 8 and the payment terms attached hereto as Annex E (the "***Payment Terms***"), the terms of which are hereby adopted and incorporated herein, and (b) RRD in accordance with the payments terms of Section 6 of the RRD Services Agreement and Annex C thereto.

8.3 Budget Allocation and Deviations. Isis shall have the discretion to incur out-of-pocket fees, expenses and costs and allocate Isis resources in a manner consistent with the Development Plan and the Development Budget. If Isis reasonably anticipates that the actual cost for any particular activity will exceed the greater of (i) [***] of that portion of the Development Budget allocated for such activity, and (ii) [***] of that portion of the Development Budget allocated for such activity (or such greater amount as the Symphony GenIsis Board may subsequently determine), then Isis may request that the Development Committee amend the Development Budget, either at its next Scheduled Meeting or at an Ad Hoc Meeting, to reflect such cost increase. Isis shall not be reimbursed for such additional expenditure without the prior approval of the Development Committee.

8.4 Employee Benefits. Symphony GenIsis shall not be responsible for providing or paying any benefits (including, but not limited to, unemployment, disability, insurance, or medical, and any pension or profit sharing plans) to Isis or to any employees of Isis or any persons retained or used by Isis to perform activities pursuant to the Development Plan, including independent contractors, Subcontractors and agents (collectively, "***Isis Personnel***"). As to Isis or any Isis Personnel, Symphony GenIsis shall not be responsible for: (a) any federal, state or local income tax withholding; (b) "FICA" contributions; (c) contributions to state disability funds or liability funds or similar withholdings; (d) payment of any overtime wages; (e) workers' compensation; or (f) compliance with any laws, rules or regulations governing employees. Isis agrees that, as between Symphony GenIsis and Isis, Isis is and will continue to be solely responsible for: (i) all matters relating to the payment of compensation and provision of benefits to Isis Personnel; and (ii) compliance with all applicable laws, rules and regulations governing Isis' employees.

9. Covenants.

9.1 Mutual Covenants. Each of Isis and Symphony GenIsis covenants and agrees that, with respect to the Programs and any other rights and obligations set forth in the Operative Documents, it shall:

(a) perform all of its obligations pursuant to this Agreement in material compliance with: (i) all applicable federal and state laws, statutes, rules, regulations and orders (including all applicable approval and qualification requirements thereunder), including, without limitation, the Federal Food, Drug and Cosmetic Act and the regulations promulgated pursuant thereto; (ii) all applicable good clinical practices and

guidelines; (iii) all applicable standard operating procedures; (iv) all applicable Protocols; and (v) the provisions of this Agreement;

(b) keep complete, proper and separate books of record and account, including a record of all costs and expenses incurred, all charges made, all credits made and received, and all income derived in connection with the operation of its business, all in accordance with GAAP;

(c) not employ (or, to the best of its knowledge without further duty of inquiry, shall not use any contractor or consultant that employs) any individual or entity debarred by the FDA (or subject to a similar sanction of any other Regulatory Authority), or, to the best of its knowledge without further duty of inquiry, any individual who or entity which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of any other Regulatory Authority), in the conduct of the Programs;

(d) promptly deliver to the other, upon receipt thereof, notice of all actions, suits, investigations, litigation and proceedings before any Governmental Authority, which would reasonably be expected to affect such Party's ability to perform its obligations under this Agreement;

(e) upon it receiving Knowledge of (i) a material event or development with respect to any Program or (ii) a breach of any covenant or representation of such Party in any material respect, such Party shall notify the other Party in writing within three (3) Business Days of the receipt of such Knowledge by any executive officer of such Party, provided that the failure to provide such notice shall not impair or otherwise be deemed a waiver of any rights any Party may have arising from such material event or breach; and

(f) with reasonable promptness, deliver to the other such data and information relating to the ability of such Person to perform its obligations hereunder as from time to time may be reasonably requested by the other (subject to the maintenance of the confidentiality of any such information by the receiving Party). For the avoidance of doubt, this Section 9.1(f) includes Isis' obligations to provide financial and other necessary information to Symphony GenIsis and RRD to enable Symphony GenIsis to fulfill its obligations to Isis under Section 5(d) of the Purchase Option Agreement, and to enable RRD to fulfill its obligations to Symphony GenIsis and Isis under Sections 5(a) and 5(b) of the RRD Services Agreement.

10. Confidentiality.

10.1 Confidentiality Agreement. It is understood that during the course of this Agreement each of the Parties shall be bound by the terms of the Confidentiality Agreement. In addition, the Parties' employees, subcontractors and agents shall be bound by terms substantially similar to the Confidentiality Agreement. The foregoing shall not be construed to (a) require Isis to amend or supplement any of the agreements it entered into prior to the Closing Date, or (b) apply to future agreements Isis may enter into with any Isis Accounting Advisor, even if the confidentiality provisions in such agreements do not satisfy the foregoing requirement.

10.2 Permitted Disclosure of Information. The Parties agree that Isis shall have access to, and may use and disclose the Development Plan and any existing or newly generated data or intellectual property developed with respect to the Programs (i) to obtain the assistance of one or more third parties to develop and/or commercialize the Programs subject to the terms of this Agreement, the other Operative Documents and appropriate confidentiality agreements pursuant to Section 10.1 or as approved by Symphony GenIsis, (ii) to use such intellectual property for all purposes not licensed exclusively to Symphony GenIsis under the Novated and Restated Technology License Agreement, and (iii) through press releases, in public presentations or as part of other appropriate public disclosures; provided that all such disclosure under this Section 10.2 shall be subject to the terms of the Confidentiality Agreement.

11. Discontinuation Option.

11.1 Discontinuation Option.

(a) A Program may only be discontinued in accordance with Section 4.2(c). In the event of such a Program discontinuation during the Term, (i) Symphony GenIsis shall so notify Isis promptly and in writing of such discontinuation, and (ii) Isis shall have the right and option (a "***Discontinuation Option***"), exercisable for [***] days after receipt of such written notice from Symphony GenIsis of such discontinuation, to buy back the Licensed Intellectual Property related to such discontinued Program for a price (payable by wire transfer to Symphony GenIsis) that is the sum of (x) the funds expended on such discontinued Program and (y) a share of all non-Program-specific expenditures that is in the same proportion

to the total of all non-Program-specific expenditures as the amount in clause (x) of this sentence is to the aggregate of all Program-specific expenditures (the "***Discontinuation Price***"), to be reasonably determined between the Parties, or, if the Parties are unable to come to a resolution, for a Discontinuation Price determined in accordance with Section 11.1(c) hereof. If the Discontinuation Price is determined in accordance with Section 11.1(c), then such [***] day period shall be extended by the time needed by the Experts for such determination. Any Discontinuation Price paid to Symphony GenIsis under this Section 11.1(a) and subsequently dividended or otherwise distributed to Holdings shall reduce the Purchase Option Exercise Price in the amount of such dividends or other distributions.

(b) Following the expiration of the Discontinuation Option without exercise by Isis, if Symphony GenIsis transfers or licenses such Program rights to a third party before the termination of the Term, all payments and other consideration that Holdings receives directly from such third party or that Symphony GenIsis receives from such third party in connection with such transfer or license prior to the termination of the Term, and subsequently dividends or otherwise distributes to Holdings, shall reduce the Purchase Option Exercise Price in the amount of such dividends or other distributions. During the Term, under no circumstances may Symphony GenIsis or Isis (unless Isis has exercised a Discontinuation Option in respect of such Program) reinitiate work on a discontinued Program.

(c) If Isis and Symphony GenIsis cannot agree on the Discontinuation Price, with respect to Section 11.1(a), Isis and Symphony GenIsis shall each appoint a nationally recognized expert in the field of pharmaceutical technology and licensing (each, an "***Expert***") (that, in each case, has had no prior dealings with either of Isis and Symphony GenIsis in the preceding twelve (12) months), and such two (2) Experts shall appoint a third Expert. In accordance with this Section 11.1(c), such three (3) Experts shall jointly determine, or, if all three (3) Experts shall not be able to agree on such Discontinuation Price as applicable, two (2) of such three (3) Experts shall jointly determine, the Discontinuation Price, which determination shall be made within thirty (30) days of the appointment of the third Expert and, absent manifest error, shall be (i) binding and conclusive and (ii) the Discontinuation Price at which the Discontinuation Option shall be exercised by Isis. All costs and expenses incurred in appointing the Experts shall be shared equally between Isis and Symphony GenIsis.

12. Representations and Warranties.

12.1 Isis Representations and Warranties. Isis hereby represents and warrants to Symphony GenIsis and Holdings that, as of the Closing Date:

(a) Organization. Isis is a corporation, duly organized, validly existing and in good standing under the laws of the State of Delaware.

(b) Authority and Validity. Isis has all requisite corporate power and authority to execute, deliver and perform its obligations under this Agreement and the Novated and Restated Technology License Agreement and to consummate the transactions contemplated thereby. The execution, delivery and performance by Isis of this Agreement and the Novated and Restated Technology License Agreement and the consummation of the transactions contemplated thereby have been duly and validly authorized by all necessary action required on the part of Isis, and no other proceedings on the part of Isis are necessary to authorize this Agreement or the Novated and Restated Technology License Agreement or for Isis to perform its obligations under this Agreement or the Novated and Restated Technology License Agreement. This Agreement and the Novated and Restated Technology License Agreement constitute the lawful, valid and legally binding obligations of Isis, enforceable in accordance with their terms, except as the same may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the enforcement of creditors' rights generally and general equitable principles regardless of whether such enforceability is considered in a proceeding at law or in equity.

(c) No Violation or Conflict. The execution, delivery and performance of this Agreement and the Novated and Restated Technology License Agreement and the transactions contemplated thereby do not and will not (i) violate, conflict with or result in the breach of any provision of the Organizational Documents of Isis, (ii) conflict with or violate any law or Governmental Order applicable to Isis or any of its assets, properties or businesses, or (iii) conflict with, result in any breach of, constitute a default (or event that with the giving of notice or lapse of time, or both, would become a default) under, require any consent under, or give to others any rights of termination, amendment, acceleration,

suspension, revocation or cancellation of, or result in the creation of any Encumbrance on any of the assets or properties of Isis, pursuant to, any note, bond, mortgage or indenture, contract, agreement, lease, sublease, license, permit, franchise or other instrument or arrangement to which Isis is a party except, in the case of clauses (ii) and (iii), to the extent that such conflicts, breaches, defaults or other matters would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis or a material adverse effect on the Programs.

(d) Governmental Consents and Approvals. The execution, delivery and performance of this Agreement and the Novated and Restated Technology License Agreement by Isis do not, and the consummation of the transactions contemplated thereby do not and will not, require any Governmental Approval which has not already been obtained, effected or provided, except with respect to which the failure to so obtain, effect or provide would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis or a material adverse effect on the Programs.

(e) Litigation. Except as disclosed on the Isis 2005 10-K, there are no actions by or against Isis pending before any Governmental Authority or, to the knowledge of Isis, threatened to be brought by or before any Governmental Authority, that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis. There are no pending or, to the knowledge of Isis, threatened actions, to which Isis is a party (or is threatened to be named as a party) to set aside, restrain, enjoin or prevent the execution, delivery or performance of this Agreement or the Operative Documents or the consummation of the transactions contemplated hereby or thereby by any party hereto or thereto. Isis is not subject to any Governmental Order (nor, to the knowledge of Isis, is there any such Governmental Order threatened to be imposed by any Governmental Authority) that would, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Isis or a material adverse effect on the Programs.

(f) No Contracts. Except as disclosed on Schedule 12.1(f) hereto, there are no material contracts between Isis and any third party (other than licenses of intellectual property that is in turn licensed to Symphony GenIsis under the Novated and Restated Technology License Agreement), including contractors, manufacturers or suppliers, used with or otherwise necessary for the Programs, and all such contracts are assignable to Symphony GenIsis. With respect to the contracts disclosed on Schedule 12.1(f) hereto, the absence of such contracts (due to the inability or impracticability of assigning such contracts to Symphony GenIsis following a termination of this Agreement without the exercise of the Purchase Option) would not have a material adverse effect on any of the Programs or on Symphony GenIsis' rights under the Novated and Restated Technology License Agreement.

12.2 Symphony GenIsis Representations and Warranties. Symphony GenIsis hereby represents and warrants to Isis that, as of the Closing Date:

(a) Organization. Symphony GenIsis is a corporation, duly organized, validly existing and in good standing under the laws of the State of Delaware.

(b) Authority and Validity. Symphony GenIsis has all requisite corporate power and authority to execute, deliver and perform its obligations under this Agreement and the Novated and Restated Technology License Agreement and to consummate the transactions contemplated thereby. The execution, delivery and performance by Symphony GenIsis of this Agreement and the Novated and Restated Technology License Agreement and the consummation of the transactions contemplated thereby have been duly and validly authorized by all necessary action required on the part of Symphony GenIsis, and no other proceedings on the part of Symphony GenIsis are necessary to authorize this Agreement or the Novated and Restated Technology License Agreement or for Symphony GenIsis to perform its obligations under this Agreement or the Novated and Restated Technology License Agreement. This Agreement and the Novated and Restated Technology License Agreement constitute the lawful, valid and legally binding obligations of Symphony GenIsis, enforceable in accordance with its terms, except as the same may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the enforcement of creditors' rights generally and general equitable principles regardless of whether such enforceability is considered in a proceeding at law or in equity.

(c) No Violation or Conflict. The execution, delivery and performance of this Agreement and the Novated and Restated Technology License Agreement and the transactions contemplated thereby do not and will not (i) violate, conflict with or result in the breach of any provision of the Organizational Documents of Symphony GenIsis, (ii) conflict with or violate any law or Governmental Order applicable to Symphony GenIsis or any of its assets, properties or businesses, or (iii) conflict with, result in any breach of, constitute a default (or event that with the giving of notice or lapse of time, or both, would become a default) under, require any consent under, or give to others any rights of termination, amendment, acceleration, suspension, revocation or cancellation of, or result in the creation of any Encumbrance on any of the assets or properties of Symphony GenIsis, pursuant to, any note, bond, mortgage or indenture, contract, agreement, lease, sublease, license, permit, franchise or other instrument or arrangement to which Symphony GenIsis is a party except, in the case of clauses (ii) and (iii), to the extent that such conflicts, breaches, defaults or other matters would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(d) Governmental Consents and Approvals. The execution, delivery and performance of this Agreement and the Novated and Restated Technology License Agreement by Symphony GenIsis do not, and the consummation of the transactions contemplated thereby do not and will not, require any Governmental Approval which has not already been obtained, effected or provided, except with respect to which the failure to so obtain, effect or provide would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect on Symphony GenIsis.

(e) Litigation. There are no actions by or against Symphony GenIsis pending before any Governmental Authority or, to the knowledge of Symphony GenIsis, threatened to be brought, by or before any Governmental Authority that would, individually or in the aggregate, reasonably be expected to have a Material Adverse

Effect on Symphony GenIsis. There are no pending or, to the knowledge of Symphony GenIsis, threatened actions to which Symphony GenIsis is a party (or is threatened to be named as a party) to set aside, restrain, enjoin or prevent the execution, delivery or performance of this Agreement or the Operative Documents or the consummation of the transactions contemplated hereby or thereby by any party hereto or thereto. Symphony GenIsis is not subject to any Governmental Order (nor, to the knowledge of Symphony GenIsis, is there any such Governmental Order threatened to be imposed by any Governmental Authority) that would, individually or in the aggregate reasonably be expected to have a Material Adverse Effect on Symphony GenIsis or a material adverse effect on the Programs.

13. Relationship Between Isis and Symphony GenIsis. Nothing contained in this Agreement or any acts or omissions hereunder shall constitute or be construed so as to create any joint venture or partnership relationship between Isis and Symphony GenIsis, and the Parties acknowledge and agree that Isis is acting as an independent contractor in the performance of its obligations under this Agreement.

14. Change of Control. Isis will not, at any time during the Term, undergo a Change of Control, unless:

(a) the Surviving Entity remains Isis; or

(b) such Surviving Entity shall (i) have executed and delivered to Symphony GenIsis and Holdings instruments, in form and substance reasonably acceptable to Symphony GenIsis and Holdings, expressly assuming all of the obligations of Isis hereunder and under each other Operative Document to which Isis is a party; and (ii) have provided to Symphony GenIsis and Holdings an opinion of nationally recognized outside counsel to the effect that (A) the instruments referred to in clause (i) above are valid and binding obligations of such Surviving Entity, enforceable in accordance with their terms, except as the same may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the enforcement of creditors' rights generally or general equitable principles regardless of whether such enforceability is considered in a proceeding at law or in equity, and except as may be set forth in any express representation and warranty of Isis in this Agreement, and (B) such Change of Control does not violate any material term of the Operative Documents; (iii) ensure that all material applications and filings have been

made to, and all material consents have been received from, the United States Food and Drug Administration, and any applicable foreign equivalent thereof, necessary for the Surviving Entity to satisfy all of its material obligations under the Operative Documents, except to the extent that failure to make such applications or filings or receive such consents would not reasonably be expected to have a material adverse effect on the Programs or Symphony GenIsis' rights under the Operative Documents; and (iv) have arranged for an appropriate senior executive of the Surviving Entity to discuss in good faith and reasonable detail with a representative of the Symphony GenIsis Board the Surviving Entity's ongoing operations, including, but not limited to, the Surviving Entity's commitment to Isis' obligations under the Operative Documents, Holdings' Put Option pursuant to Section 2A of the Purchase Option Agreement, and the strategic importance of the Programs to the Surviving Entity.

15. No Restrictions; Indemnification.

15.1 No Restrictions. Nothing in this Agreement shall limit or restrict the right of any director, officer or employee of Isis or any director, officer, or employee of any of its subsidiaries or its Affiliates to engage in any other business or to devote his or her time and attention to the management or other aspects of any other business, whether of a similar or dissimilar nature, nor limit or restrict the right of Isis or any of its affiliates to engage in any other business or to render services of any kind to any other Person.

15.2 Indemnification.

(a) To the greatest extent permitted by applicable law, Isis shall indemnify and hold harmless Symphony GenIsis and RRD and each of their respective Affiliates, officers, directors, employees, agents, members, managers, successors and assigns (each, a "***Symphony Indemnified Party***"), and Symphony GenIsis shall indemnify and hold harmless Isis, and its Affiliates and each of their respective officers, directors, employees, agents (other than Isis Subcontractors), members, managers, successors and assigns (each, an "***Isis Indemnified Party***"), from and against any and all claims, losses, costs, interest, awards, judgments, fees (including reasonable fees for attorneys and other professionals), court costs, liabilities, damages and expenses with an aggregate value of at least [***] (as determined by the applicable Indemnified Party acting in good faith), incurred by any Symphony Indemnified Party or Isis Indemnified Party (irrespective of whether any such Indemnified Party is a party to the action for which indemnification hereunder is sought) (hereinafter, a "***Loss***") to the extent resulting from, arising out of, or relating to any and all third party suits, claims, actions, proceedings or demands based upon:

(i) in the case of Isis being the Indemnifying Party, (A) any breach of any representation or warranty made by Isis herein or in any other Operative Document, (B) any breach of any covenant, agreement or obligation of Isis contained herein or in any other Operative Document, except to the extent such covenant, agreement or obligation relates to Isis' performance under the Development Plan, (C) any gross negligence or willful misconduct of Isis (and not that of any Isis Subcontractors) in connection with Isis' performance of its obligations under this Agreement (including the Development Plan), (D) any action undertaken or performed by or on behalf of Isis prior to, and including, the Closing Date that relates to the Programs or the Products, or (E) in the event Isis exercises a Discontinuation Option for a Program, any action undertaken and/or performed by or on behalf of Isis after the Discontinuation Closing Option Date and relating to the Product that was the subject of such Program (including the development, manufacture, use, handling, storage, sale or other disposition of such Product); in each case, except (1) with respect to Losses for which Isis is entitled to indemnification under this Article 15 or (2) to the extent such Loss arises from the gross negligence or willful misconduct of a Symphony Indemnified Party; and

(ii) in the case of Symphony GenIsis being the Indemnifying Party, (A) any breach of any representation or warranty made by Symphony GenIsis herein or in any other Operative Document, (B) any breach of any covenant, agreement or

obligation of Symphony GenIsis contained herein or in any other Operative Document, (C) any gross negligence or willful misconduct of Symphony GenIsis (and not that of its direct subcontractors) in connection with Symphony GenIsis' performance of its obligations under this Agreement, or (E) the development, manufacture, use, handling, storage, sale or other disposition of the Products (including in the course of conducting the Programs) during the Term (except with respect to the development, manufacture, use, handling, storage, sale or other disposition, after Isis' exercise of the Discontinuation Option, of Products covered under Section 15.2(a)(i)(E)); in each case, except (1) with respect to Losses for which Symphony GenIsis is entitled to indemnification under this Article 15, or (2) Losses deemed to have arisen from the breach by Isis of any covenant, agreement or obligation under this Agreement that relates to Isis' performance under the Development Plan, as determined by a court, arbitrator or pursuant to a settlement agreement, or (3) to the extent such Loss arises from the gross negligence or willful misconduct of an Isis Indemnified Party.

To the extent that the foregoing undertaking by Isis or Symphony GenIsis may be unenforceable for any reason, such Party shall make the maximum contribution to the payment and satisfaction of any Loss that is permissible under applicable law.

(b) Notice of Claims. Any Indemnified Party that proposes to assert a right to be indemnified under this Section 15.2 shall notify Isis or Symphony GenIsis, as applicable (the "***Indemnifying Party***"), promptly after receipt of notice of commencement of any action, suit or proceeding against such Indemnified Party (an "***Indemnified Proceeding***") in respect of which a claim is to be made under this Section 15.2, or the incurrence or realization of any Loss in respect of which a claim is to be made under this Section 15.2, of the commencement of such Indemnified Proceeding or of such incurrence or realization, enclosing a copy of all relevant documents, including all papers served and claims made, but the omission so to notify the applicable Indemnifying Party promptly of any such Indemnified Proceeding or incurrence or realization shall not relieve (x) such Indemnifying Party from any liability that it may have to such Indemnified Party under this Section 15.2 or otherwise, except, as to such Indemnifying Party's liability under this Section 15.2, to the extent, but only to the extent, that such Indemnifying Party shall have been prejudiced by such omission, or (y) any other indemnitor from liability that it may have to any Indemnified Party under the Operative Documents.

(c) Defense of Proceedings. In case any Indemnified Proceeding shall be brought against any Indemnified Party, it shall notify the applicable Indemnifying Party of the commencement thereof as provided in Section 15.2(b), and such Indemnifying Party shall be entitled to participate in, and provided such Indemnified Proceeding involves a claim solely for money damages and does not seek an injunction or other

equitable relief against the Indemnified Party and is not a criminal or regulatory action, to assume the defense of, such Indemnified Proceeding with counsel reasonably satisfactory to such Indemnified Party. After notice from such Indemnifying Party to such Indemnified Party of such Indemnifying Party's election so to assume the defense thereof and the failure by such Indemnified Party to object to such counsel within ten (10) Business Days following its receipt of such notice, such Indemnifying Party shall not be

liable to such Indemnified Party for legal or other expenses related to such Indemnified Proceedings incurred after such notice of election to assume such defense except as provided below and except for the reasonable costs of investigating, monitoring or cooperating in such defense subsequently incurred by such Indemnified Party reasonably necessary in connection with the defense thereof. Such Indemnified Party shall have the right to employ its counsel in any such Indemnified Proceeding, but the fees and expenses of such counsel shall be at the expense of such Indemnified Party unless:

(i) the employment of counsel by such Indemnified Party at the expense of the applicable Indemnifying Party has been authorized in writing by such Indemnifying Party;

(ii) such Indemnified Party shall have reasonably concluded in its good faith (which conclusion shall be determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between the applicable Indemnifying Party and such Indemnified Party in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes of action available to such Indemnified Party (it being agreed that in any case referred to in this clause (ii) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

(iii) the applicable Indemnifying Party shall not have employed counsel reasonably acceptable to the Indemnified Party, to assume the defense of such Indemnified Proceeding within a reasonable time after notice of the commencement thereof; provided, however, that (A) this clause (iii) shall not be deemed to constitute a waiver of any conflict of interest that may arise with respect to any such counsel, and (B) an Indemnified Party may not invoke this clause (iii) if such Indemnified Party failed to timely object to such counsel pursuant to the first paragraph of this Section 15.2(c) above (it being agreed that in any case referred to in this clause (iii) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party); or

(iv) any counsel employed by the applicable Indemnifying Party shall fail to timely commence or reasonably conduct the defense of such Indemnified Proceeding and such failure has prejudiced (or is in immediate danger of prejudicing) the outcome of such Indemnified Proceeding (it being agreed that in any case referred to in this clause (iv) such Indemnifying Party shall not have the right to direct the defense of such Indemnified Proceeding on behalf of the Indemnified Party);

in each of which cases the fees and expenses of counsel for such Indemnified Party shall be at the expense of such Indemnifying Party. Only one counsel shall be retained by all Indemnified Parties with respect to any Indemnified Proceeding, unless counsel for any Indemnified Party reasonably concludes in good faith (which conclusion shall be

determinative unless a court determines that such conclusion was not reached reasonably and in good faith) that there is or may be a conflict of interest between such Indemnified Party and one or more other Indemnified Parties in the conduct of the defense of such Indemnified Proceeding or that there are or may be one or more different or additional defenses, claims, counterclaims, or causes or action available to such Indemnified Party.

(d) Settlement. Without the prior written consent of such Indemnified Party, such Indemnifying Party shall not settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding, unless such settlement, compromise, consent or related judgment (i) includes an unconditional release of such Indemnified Party from all liability for Losses arising out of such claim, action, investigation, suit or other legal proceeding, (ii) provides for the payment of money damages as the sole relief for the claimant (whether at law or in equity), (iii) involves no finding or admission of any violation of law or the rights of any Person by the Indemnified Party, and (iv) is not in the nature of a criminal or regulatory action. No Indemnified Party shall settle or compromise, or consent to the entry of any judgment in, any pending or threatened Indemnified Proceeding (A) in respect of which any payment would result hereunder or under any other Operative Document, (B) which includes an injunction that will adversely affect any Indemnifying Party, (C) which involves a finding or admission of any violation of law or the rights of any Indemnifying Party, or (D) which is in the nature of a criminal or regulatory action, without the prior written consent of the Indemnifying Party, such consent not to be unreasonably conditioned, withheld or delayed.

16. Limitation of Liabilities.

16.1 Between the Parties. TO THE GREATEST EXTENT PERMITTED BY APPLICABLE LAW, NEITHER PARTY NOR ANY OF THEIR RESPECTIVE DIRECTORS, OFFICERS, MEMBERS, MANAGERS, EMPLOYEES, INDEPENDENT CONTRACTORS OR AGENTS (INCLUDING RRD AND ITS MEMBERS, MANAGERS, EMPLOYEES, INDEPENDENT CONTRACTORS AND AGENTS) SHALL HAVE ANY LIABILITY OF ANY TYPE (INCLUDING, BUT NOT LIMITED TO, CLAIMS IN CONTRACT, NEGLIGENCE AND TORT LIABILITY) FOR ANY SPECIAL, INCIDENTAL, INDIRECT OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, THE LOSS OF OPPORTUNITY, LOSS OF USE OR LOSS OF REVENUE OR PROFIT IN CONNECTION WITH OR ARISING OUT OF THIS AGREEMENT OR THE SERVICES PERFORMED HEREUNDER, EVEN IF SUCH DAMAGES MAY HAVE BEEN FORESEEABLE. THE FOREGOING SHALL NOT LIMIT EITHER PARTY'S INDEMNIFICATION OBLIGATIONS PURSUANT TO SECTION 15.2 AND SHALL NOT APPLY TO BREACHES OF ITS CONFIDENTIALITY OBLIGATIONS PURSUANT TO ARTICLE 10.

16.2 Pursuant to the RRD Services Agreement. Each Party hereby acknowledges and agrees that, pursuant to Sections 9(f) and (g) of the RRD Services Agreement, RRD has expressly disclaimed all liability for (a) any claim arising out of, or allegedly arising out of the activities carried out by (or within the authority of) Isis (and such Isis

Subcontractors and vendors it may retain) hereunder, or for any liability arising under the Novated and Restated Technology License Agreement with respect to any license or sublicense thereunder in relation to the activities carried out by (or within the authority of) Isis (and such Isis Subcontractors and vendors it may retain) hereunder, and (b) supervising, compensating or discharging, or any other liability to or with respect to, any vendor retained by Isis (or, in the case of a vendor engaged by both RRD and Isis, to and for such vendor to the extent that such vendor performs services for Isis), except that RRD shall make payments from Symphony GenIsis' funds to reimburse Isis, in accordance with Article 8 and Annex E of this Agreement, for costs and expenses incurred by Isis in connection with the engagement of such vendors by Isis for the performance of services contemplated under the Development Plan.

17. Term and Termination.

17.1 Term. This Agreement shall be effective as of the Closing Date and shall expire on the last day of the Term, unless the Agreement is earlier terminated as specified in this Article 17.

17.2 Termination for Isis' Breach.

(a) Symphony GenIsis may terminate this Agreement at any time upon written notice to Isis if Isis is in material default or breach of this Agreement, and such material default or breach continues unremedied for a period of sixty (60) days after written notice thereof is delivered to Isis. Such cure period may be extended if (i) Isis reasonably believes such breach can be cured within ninety (90) days of Isis' receipt of Symphony GenIsis' written notice of such breach (and notifies Symphony GenIsis in writing of such belief and the basis for such belief), and (ii) Symphony GenIsis, acting reasonably, agrees. If Isis fails to remedy the default or breach within the applicable cure period, Symphony GenIsis may by final notice of termination to Isis terminate this Agreement.

(b) In the event that Symphony GenIsis terminates this Agreement pursuant to Section 17.2(a) above, Isis may exercise its Purchase Option, pursuant to Section 1(c)(v) of the Purchase Option Agreement, within five (5) Business Days of receiving such notice of termination from Symphony GenIsis; provided, that if such termination occurs after a Change of Control with respect to Isis has occurred, and if the successor entity chooses not to exercise its Purchase Option, then Holdings may exercise its Put Option pursuant Section 2A of the Purchase Option Agreement.

17.3 Termination for Symphony GenIsis' Breach. Isis may terminate this Agreement at any time upon written notice to Symphony GenIsis if Symphony GenIsis is in material default or breach of this Agreement, and such material default or breach continues unremedied for a period of sixty (60) days after written notice thereof is delivered to Symphony GenIsis. Such cure period may be extended if (i) Symphony GenIsis reasonably believes such breach can be cured within ninety (90) days of Symphony GenIsis' receipt of Isis' written notice of such breach (and notifies Isis in writing of such belief and the basis for such belief), and (ii) Isis, acting reasonably,

agrees. If Symphony GenIsis fails to remedy the default or breach within the applicable cure period, Isis may by final notice of termination to Symphony GenIsis terminate this Agreement.

17.4 Termination of License Agreement. This Agreement shall automatically terminate upon the termination of the Novated and Restated Technology License Agreement.

17.5 Survival.

(a) The agreements and covenants of the Parties set forth in Articles 10, 11, 15, 16 and 18, and Sections 6.7 and 17.5 shall survive the expiration or termination of this Agreement. In addition, Section 8.2 shall, to the extent that the costs and expenses reimbursable thereunder have been incurred or become uncancellable prior to such termination, also survive such expiration.

(b) If Isis does not exercise the Purchase Option, in addition to the provisions specified in Section 17.5(a), then Section 5.4 shall also survive such unexercised expiration.

18. Miscellaneous.

18.1 No Petition. Isis covenants and agrees that, prior to the date which is one (1) year and one (1) day after the expiration of the Term, Isis will not institute or join in the institution of any bankruptcy, insolvency, reorganization or similar proceeding against Symphony GenIsis. The provisions of this Section 18.1 shall survive the termination of this Agreement.

18.2 Notices. Any notice, request, demand, waiver, consent, approval or other communication which is required or permitted to be given to any Party shall be in writing and shall be deemed given only if delivered to the Party personally or sent to the Party by facsimile transmission (promptly followed by a hard-copy delivered in accordance with this Section 18.2), by next Business Day delivery by a nationally recognized courier service, or by registered or certified mail (return receipt requested), with postage and registration or certification fees thereon prepaid, addressed to the Party at its address set forth below:

Isis:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: B. Lynne Parshall
Facsimile: (760) 603-4652

With a copy to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: General Counsel
Facsimile: (760) 268-4922

Symphony GenIsis:

Symphony GenIsis, Inc.
7361 Calhoun Place, Suite 325
Rockville, MD 20850
Attn: Charles W. Finn, Ph.D.
Facsimile: (301) 762-6154

Holdings:

Symphony GenIsis Holdings LLC
7361 Calhoun Place, Suite 325
Rockville, MD 20850
Attn: Joseph P. Clancy
Facsimile: (301) 762-6154

with copies to:

Symphony Capital Partners, L.P.
875 Third Avenue
18th Floor
New York, NY 10022
Attn: Mark Kessel
Facsimile: (212) 632-5401

and

Symphony Strategic Partners, LLC
875 Third Avenue
18th Floor
New York, NY 10022
Attn: Mark Kessel
Facsimile: (212) 632-5401

or to such other address as such Party may from time to time specify by notice given in the manner provided herein to each other Party entitled to receive notice hereunder.

18.3 Governing Law; Consent to Jurisdiction and Service of Process.

(a) This Agreement shall be governed by, and construed in accordance with, the laws of the State of New York.

(b) Each of the Parties hereby irrevocably and unconditionally submits, for itself and its property, to the nonexclusive jurisdiction of any New York State court or federal court of the United States of America sitting in The City of New York, Borough of Manhattan, and any appellate court from any jurisdiction thereof, in any action or proceeding arising out of or relating to this Agreement, or for recognition or enforcement of any judgment, and each of the Parties hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in any such New York State court or, to the fullest extent permitted by law, in such federal court. Each of the Parties agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. Nothing in this Agreement shall affect any right that any Party may otherwise have to bring any action or proceeding relating to this Agreement.

(c) Each of the Parties irrevocably and unconditionally waives, to the fullest extent it may legally and effectively do so, any objection that it may now or hereafter have to the laying of venue of any suit, action or proceeding arising out of or relating to this Agreement in any New York State or federal court. Each of the Parties hereby irrevocably waives, to the fullest extent permitted by law, the defense of an inconvenient forum to the maintenance of such action or proceeding in any such court.

18.4 WAIVER OF JURY TRIAL. EACH OF THE PARTIES HERETO IRREVOCABLY WAIVES ALL RIGHT TO TRIAL BY JURY IN ANY ACTION, PROCEEDING OR COUNTERCLAIM (WHETHER BASED ON CONTRACT, TORT OR OTHERWISE) ARISING OUT OF OR RELATING TO THIS AGREEMENT.

18.5 Entire Agreement. This Agreement (including any Annexes, Schedules, Exhibits or other attachments hereto) constitutes the entire agreement between the Parties with respect to the matters covered hereby, and no oral or written statement may be used to interpret or vary the meaning of the terms and conditions hereof. This Agreement supersedes all prior agreements and understanding with respect to such matters between the Parties, including the Research and Development Agreement but excluding the Operative Documents.

18.6 Amendment; Successors; Assignment; Counterparts.

(a) The terms of this Agreement shall not be altered, modified, amended, waived or supplemented in any manner whatsoever except by a written instrument signed by each of the Parties.

(b) Nothing expressed or implied herein is intended or shall be construed to confer upon or to give to any Person, other than the Parties (and, to the extent of Section 18.8, RRD), any right, remedy or claim under or by reason of this Agreement or of any

term, covenant or condition hereof, and all the terms, covenants, conditions, promises and agreements contained herein shall be for the sole and exclusive benefit of the Parties (and, to the extent of Section 18.8, RRD) and their successors and permitted assigns.

(c) This Agreement may not be assigned by either Party hereto without the prior written consent of the other part; provided that, in the event Isis undergoes a Change of Control in compliance with Article 14 hereof, Isis may assign this Agreement to its Successor Entity.

(d) This Agreement may be executed in one or more counterparts, each of which, when executed, shall be deemed an original but all of which taken together shall constitute one and the same Agreement.

18.7 Severability. If any term or other provision of this Agreement is invalid, illegal or incapable of being enforced by any rule of law or public policy, all other conditions and provisions of this Agreement shall nevertheless remain in full force and effect so long as the economic or legal substance of the transactions contemplated hereby is not affected in a manner materially adverse to either party. Upon such determination that any term or other provision is invalid, illegal or incapable of being enforced, the parties hereto shall negotiate in good faith to modify this Agreement so as to effect the original intent of the parties as closely as possible in an acceptable manner to the end that the transactions contemplated hereby are fulfilled to the extent possible.

18.8 Third Party Beneficiary. Each of the Parties agrees that RRD shall be a third party beneficiary of Articles 2, 8 and 16, and Sections 4.1, 4.2(a), 4.2(b), 7.1, 7.4, 9.1(f), 15.2 and 18.6(b) of this Agreement.

[SIGNATURES FOLLOW ON NEXT PAGE]

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed as of the day and year above written.

SYMPHONY GENISIS HOLDINGS LLC

By: Symphony Capital Partners, L.P.,
its Manager

By: Symphony Capital GP, L.P.,
its general partner

By: Symphony GP, LLC,
its general partner

By: /s/ Mark Kessel
Name: Mark Kessel
Title: Managing Member

SYMPHONY GENISIS, INC.

By: /s/ Neil J. Sandler
Name: Neil J. Sandler
Title: Chairman of the Board

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall, J.D.
Name: B. Lynne Parshall, J.D.
Title: Executive Vice President, Chief Financial Officer and Secretary

ANNEX A

CERTAIN DEFINITIONS

CERTAIN DEFINITIONS

"***$***" means United States dollars.

"***Accredited Investor***" has the meaning set forth in Rule 501(a) of Regulation D promulgated under the Securities Act of 1933, as amended.

"***Act***" means the Delaware Limited Liability Company Act, 6 Del. C. § 18-101 et seq.

"***Ad Hoc Meeting***" has the meaning set forth in Paragraph 6 of Annex B of the Amended and Restated Research and Development Agreement.

"***Additional Party***" has the meaning set forth in Section 13 of the Confidentiality Agreement.

"***Additional Regulatory Filings***" means such Governmental Approvals as required to be made under any law applicable to the purchase of the Symphony GenIsis Equity Securities under the Purchase Option Agreement.

"***Adjusted Capital Account Deficit***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Affected Member***" has the meaning set forth in Section 27 of the Investors LLC Agreement.

"***Affiliate***" means, with respect to any Person (i) any Person directly or indirectly controlling, controlled by or under common control with such Person, (ii) any officer, director, general partner, member or trustee of such Person, or (iii) any Person who is an officer, director, general partner, member or trustee of any Person described in clauses (i) or (ii) of this sentence. For purposes of this definition, the terms "controlling," "controlled by" or "under common control with" shall mean the possession, direct or indirect, of the power to direct or cause the direction of the management and policies of a Person or entity, whether through the ownership of voting securities, by contract or otherwise, or the power to elect at least 50% of the directors, managers, general partners, or persons exercising similar authority with respect to such Person or entities.

"***Amended and Restated Research and Development Agreement***" means the Amended and Restated Research and Development Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis.

"***ApoB***" means apolipoprotein B.

"***ApoB Product***" means a pharmaceutical composition comprising an ASO that targets ApoB.

"***ApoB Program***" means the identification, development, manufacture and/or use of any ApoB Product in accordance with the Development Plan.

"***ASO***" means an oligonucleotide or analog, mimic or mimetic thereof having a sequence that selectively modulates protein synthesis via the binding, partially or wholly, of such oligomeric compound to a complementary nucleic acid sequence encoding, directly or indirectly, said protein.

"***Asset Value***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Auditors***" means an independent certified public accounting firm of recognized national standing.

"***Balance Sheet Deficiency Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Bankruptcy Code***" means the United States Bankruptcy Code.

"***Business Day***" means any day other than Saturday, Sunday or any other day on which commercial banks in The City of New York or the City of San Francisco are authorized or required by law to remain closed.

"***Capital Contributions***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Capitalized Leases***" means all leases that have been or should be, in accordance with GAAP, recorded as capitalized leases.

"***Cash Available for Distribution***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Chair***" has the meaning set forth in Paragraph 4 of Annex B to the Amended and Restated Research and Development Agreement.

"***Change of Control***" means and includes the occurrence of any of the following events, but specifically excludes (i) acquisitions of capital stock directly from Isis for cash, whether in a public or private offering, (ii) sales of capital stock by stockholders of Isis, and (iii) acquisitions of capital stock by or from any employee benefit plan or related trust:

(a) the merger, reorganization or consolidation of Isis into or with another corporation or legal entity in which Isis' stockholders holding the right to vote with respect to matters generally immediately preceding such merger, reorganization or consolidation, own less than fifty

percent (50%) of the voting securities of the surviving entity; or

(b) the sale of all or substantially all of Isis' assets or business.

"***Class A Member***" means a holder of a Class A Membership Interest.

"***Class A Membership Interest***" means a Class A Membership Interest in Holdings.

"***Class B Member***" means a holder of a Class B Membership Interest.

"***Class B Membership Interest***" means a Class B Membership Interest in Holdings.

"***Class C Member***" means a holder of a Class C Membership Interest.

"***Class C Membership Interest***" means a Class C Membership Interest in Holdings.

"***Client Schedules***" has the meaning set forth in Section 5(b) of the RRD Services Agreement.

"***Clinical Budget Component***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Closing Date***" means April 7, 2006.

"***CMC***" means the chemistry, manufacturing and controls documentation as required for filings with Regulatory Authority relating to the manufacturing, production and testing of drug products.

"***Code***" means the Internal Revenue Code of 1986, as amended from time to time.

"***Committed Capital***" means $75,000,000.00.

"***Common Stock***" means the common stock, par value $0.01 per share, of Symphony GenIsis.

"***Company Expenses***" has the meaning set forth in Section 5.09 of the Holdings LLC Agreement.

"***Company Property***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Confidential Information***" has the meaning set forth in Section 2 of the Confidentiality Agreement.

"***Confidentiality Agreement***" means the Confidentiality Agreement, dated as of the Closing Date, among Symphony GenIsis, Holdings, Isis, SCP, SSP, Investors, Symphony Capital and RRD, as such agreement may be amended or amended and restated from time to time.

"***Conflict Transaction***" has the meaning set forth in Article X of the Symphony GenIsis Charter.

"***Control***" means, with respect to any material, information or intellectual property right, that a Party owns or has a license to such item or right, and has the ability to grant the other Party access, a license or a sublicense (as applicable) in or to such item or right as provided in the Operative Documents without violating the terms of any agreement or other arrangement with any third party.

"***Debt***" of any Person means, without duplication:

(a) all indebtedness of such Person for borrowed money,

(b) all obligations of such Person for the deferred purchase price of property or services (other than any portion of any trade payable obligation that shall not have remained unpaid for 91 days or more from the later of (A) the original due date of such portion and (B) the customary payment date in the industry and relevant market for such portion),

(c) all obligations of such Person evidenced by bonds, notes, debentures or other similar instruments,

(d) all obligations of such Person created or arising under any conditional sale or other title retention agreement with respect to property acquired by such Person (whether or not the rights and remedies of the seller or lender under such agreement in an event of default are limited to repossession or sale of such property),

(e) all Capitalized Leases to which such Person is a party,

(f) all obligations, contingent or otherwise, of such Person under acceptance, letter of credit or similar facilities,

(g) all obligations of such Person to purchase, redeem, retire, defease or otherwise acquire for value any Equity Securities of such Person,

(h) the net amount of all financial obligations of such Person in respect of Hedge Agreements,

(i) the net amount of all other financial obligations of such Person under any contract or other agreement to which such Person is a party,

(j) all Debt of other Persons of the type described in clauses (a) through (i) above guaranteed, directly or indirectly, in any manner by such Person, or in effect guaranteed, directly or indirectly, by such Person through an agreement (A) to pay or purchase such Debt or to advance or supply funds for the payment or purchase of such Debt, (B) to purchase, sell or lease (as lessee or lessor) property, or to purchase or sell services, primarily for the purpose of enabling the debtor to make payment of such Debt or to assure the holder of such Debt against loss, (C) to supply funds to or in any other

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manner invest in the debtor (including any agreement to pay for property or services irrespective of whether such property is received or such services are rendered) or (D) otherwise to assure a creditor against loss, and

(k) all Debt of the type described in clauses (a) through (i) above secured by (or for which the holder of such Debt has an existing right, contingent or otherwise, to be secured by) any Encumbrance on property (including accounts and contract rights) owned or held or used under lease or license by such Person, even though such Person has not assumed or become liable for payment of such Debt.

"***Development Budget***" means the budget (comprised of the Management Budget Component and the Clinical Budget Component) for the implementation of the Development Plan (the initial form of which was agreed upon by Isis and Symphony GenIsis as of the Closing Date and attached to the Amended and Restated Research and Development Agreement as Annex D thereto), as may be further developed and revised from time to time in accordance with the Development Committee Charter and the Amended and Restated Research and Development Agreement.

"***Development Committee***" has the meaning set forth in Article 3 of the Amended and Restated Research and Development Agreement.

"***Development Committee Charter***" has the meaning set forth in Article 3 of the Amended and Restated Research and Development Agreement.

"***Development Committee Member***" has the meaning set forth in Paragraph 1 of Annex B to the Amended and Restated Research and Development Agreement.

"***Development Plan***" means the development plan covering all the Programs (the initial form of which was agreed upon by Isis and Symphony GenIsis as of the Closing Date and attached to the Amended and Restated Research and Development Agreement as Annex C thereto), as may be further developed and revised from time to time in accordance with the Development Committee Charter and the Amended and Restated Research and Development Agreement.

"***Development Services***" has the meaning set forth in Section 1(b) of the RRD Services Agreement.

"***Director(s)***" means the Persons identified as such in the Preliminary Statement of the Indemnification Agreement (including such Persons as may become parties thereto after the date hereof).

"***Disclosing Party***" has the meaning set forth in Section 3 of the Confidentiality Agreement.

"***Discontinuation Closing Date***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinuation Date***" means any date designated by Symphony GenIsis which shall occur on or after the 90th day following the receipt by Isis of notice from Symphony GenIsis of Symphony GenIsis' intent to discontinue a Program in accordance with the terms of the Amended and Restated Research and Development Agreement.

"***Discontinuation Option***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinuation Price***" has the meaning set forth in Section 11.1 of the Amended and Restated Research and Development Agreement.

"***Discontinued Program***" has the meaning set forth in Section 2.12 of the Novated and Restated Technology License Agreement.

"***Disinterested Directors***" has the meaning set forth in Article IX of the Symphony GenIsis Charter.

"***Distribution***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Early Purchase Option Exercise***" has the meaning set forth in Section 1(c)(iv) of the Purchase Option Agreement.

"***Effective Registration Date***" has the meaning set forth in Section 1(b) of the Registration Rights Agreement

"***Encumbrance***" means (i) any security interest, pledge, mortgage, lien (statutory or other), charge or option to purchase, lease or otherwise acquire any interest, (ii) any adverse claim, restriction, covenant, title defect, hypothecation, assignment, deposit arrangement, license or other encumbrance of any kind, preference or priority, or (iii) any other security agreement or preferential arrangement of any kind or nature whatsoever (including, without limitation, any conditional sale or other title retention agreement).

"***Enhancements***" means findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Intellectual Property and/or Regulatory Files, in each case whether or not patentable.

"***Equity Securities***" means, with respect to any Person, shares of capital stock of (or other ownership or profit interests in) such Person, warrants, options or other rights for the purchase or other acquisition from such Person of shares of capital stock of (or other ownership or profit interests in) such Person, securities convertible into or exchangeable for shares of capital stock of (or other ownership or profit interests in) such Person or warrants, rights or options for the purchase or other acquisition from such Person of such shares (or such other interests), and other ownership or profit interests in such Person (including, without limitation, partnership, member or trust interests therein), whether voting or nonvoting, and whether or not such shares, warrants, options, rights or other interests are authorized or otherwise existing on any date of determination.

"***ERISA***" means the United States Employee Retirement Income Security Act of 1974, as amended.

"***Excepted Debt***" has the meaning set forth in Section 5(c)(iii) of the Purchase Option Agreement.

"***Exchange Act***" means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

"***Exclusive Field***" means human therapeutics, but does not include the Nonexclusive Field.

"***Existing NDA***" has the meaning set forth in Section 2 of the Confidentiality Agreement.

"***Expert***" has the meaning set forth in Section 11.1(c) of the Amended and Restated Research and Development Agreement.

"***External Directors***" means, at any time, up to two (2) Persons elected to the Symphony GenIsis Board after the Closing Date (who shall be neither employees of the Symphony Capital nor of Isis) in accordance with the Symphony GenIsis Charter, the Symphony GenIsis By-laws and Section 4(b)(iv) of the Purchase Option Agreement.

"***FDA***" means the United States Food and Drug Administration or its successor agency in the United States.

"***FDA Sponsor***" has the meaning set forth in Section 5.1 of the Amended and Restated Research and Development Agreement.

"***Final Termination Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Financial Audits***" has the meaning set forth in Section 6.6 of the Amended and Restated Research and Development Agreement.

"***Financing***" has the meaning set forth in the Preliminary Statement of the Purchase Option Agreement.

"***Fiscal Year***" has the meaning set forth in each Operative Document in which it appears.

"***Form S-3***" means the Registration Statement on Form S-3 as defined under the Securities Act.

"***FTE***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Funds Termination Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Funds Termination Notice***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***GAAP***" means generally accepted accounting principles in effect in the United States of America from time to time.

"***GCCR***" means a glucocorticoid receptor.

"***GCCR Product***" means a pharmaceutical composition comprising an ASO that targets GCCR.

"***GCCR Program***" means the identification, development, manufacture and/or use of any GCCR Product in accordance with the Development Plan.

"***GCGR***" means a glucagon receptor.

"***GCGR Product***" means a pharmaceutical composition comprising an ASO that targets GCGR.

"***GCGR Program***" means the identification, development, manufacture and/or use of any GCGR Product in accordance with the Development Plan.

"***GenIsis Relevant Action***" means an action against others in the courts, administrative agencies or otherwise to prevent or terminate infringement, misappropriation, illegal use or misuse of the Licensed Patent Rights or other Licensed Intellectual Property due to the manufacture, use, sale or importation of an ASO that targets ApoB, GCCR or GCGR, as applicable, in the Exclusive Field.

"***Governmental Approvals***" means authorizations, consents, orders, declarations or approvals of, or filings with, or terminations or expirations of waiting periods imposed by any Governmental Authority.

"***Governmental Authority***" means any United States or non-United States federal, national, supranational, state, provincial, local, or similar government, governmental, regulatory or administrative authority, agency or commission or any court, tribunal, or judicial or arbitral body.

"***Governmental Order***" means any order, writ, judgment, injunction, decree, stipulation, determination or award entered by or with any Governmental Authority.

"***Hedge Agreement***" means any interest rate swap, cap or collar agreement, interest rate future or option contract, currency swap agreement, currency future or option contract or other similar hedging agreement.

"***Holdings***" means Symphony GenIsis Holdings LLC, a Delaware limited liability company.

"***Holdings Claims***" has the meaning set forth in Section 5.01 of the Warrant Purchase Agreement.

"***Holdings LLC Agreement***" means the Amended and Restated Limited Liability Company Agreement of Holdings dated as of the Closing Date.

"***HSR Filings***" means the pre-merger notification and report forms required under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended.

"***IND***" means an Investigational New Drug Application, as described in 21 U.S.C. § 355(i)(1) and 21 C.F.R. § 312 in the regulations promulgated by the United States Food and Drug Administration, or any foreign equivalent thereof.

"***Indemnification Agreement***" means the Indemnification Agreement among Symphony GenIsis and the Directors named therein, dated as of the Closing Date, as such agreement may be amended or amended and restated from time to time.

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

"***Indemnified Party***" has the meaning set forth in each Operative Document in which it appears.

"***Indemnified Proceeding***" has the meaning set forth in each Operative Document in which it appears.

"***Indemnifying Party***" has the meaning set forth in each Operative Document in which it appears.

"***Initial Development Budget***" means the initial development budget prepared by representatives of Symphony GenIsis and Isis prior to the Closing Date, and attached to the Amended and Restated Research and Development Agreement as Exhibit D thereto.

"***Initial Development Plan***" means the initial development plan prepared by representatives of Symphony GenIsis and Isis prior to the Closing Date, and attached to the Amended and Restated Research and Development Agreement as Exhibit C thereto.

"***Initial Holdings LLC Agreement***" means the Agreement of Limited Liability Company of Holdings, dated March 8, 2006.

"***Initial Investors LLC Agreement***" means the Agreement of Limited Liability Company of Investors, dated March 8, 2006.

"***Initial LLC Member***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Interest Certificate***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Investment Company Act***" means the Investment Company Act of 1940, as amended.

"***Investment Overview***" means the investment overview describing the transactions entered into pursuant to the Operative Documents.

"***Investment Policy***" has the meaning set forth in Section 1(a)(vi) of the RRD Services Agreement.

"***Investors***" means Symphony GenIsis Investors LLC.

"***Investors LLC Agreement***" means the Amended and Restated Agreement of Limited Liability Company of Investors dated as of the Closing Date

"***IRS***" means the U.S. Internal Revenue Service.

"***Isis***" means Isis Pharmaceuticals, Inc., a Delaware corporation.

"***Isis 2005 10-K***" means the annual report for fiscal year 2005 filed by Isis on Form 10-K on March 16, 2006, pursuant to the Exchange Act.

"***Isis Accounting Advisor***" means Ernst & Young LLP or Deloitte & Touche USA LLP.

"***Isis Common Stock***" means the common stock, par value $0.001 per share, of Isis.

"***Isis Commitment Amount***" has the meaning set forth in Paragraph 14 of Annex B to the Amended and Restated Research and Development Agreement.

"***Isis Common Stock Valuation***" has the meaning set forth in Section 2(e) of the Purchase Option Agreement.

"***Isis Funding Notice***" has the meaning set forth in Section 2 of the Research Cost Sharing and Extension Agreement.

"***Isis Obligations***" has the meaning set forth in Section 6.1 of the Amended and Restated Research and Development Agreement.

"***Isis Personnel***" has the meaning set forth in Section 8.4 of the Amended and Restated Research and Development Agreement.

"***Isis Subcontractor***" has the meaning set forth in Section 6.2 of the Amended and Restated Research and Development Agreement.

"***Key Personnel***" means those Isis Personnel listed on Schedule 6.4 to the Amended and Restated Research and Development Agreement, as such schedule may be updated from time to time by mutual agreement of the parties to the Amended and Restated Research and Development Agreement.

"***Knowledge***" means the actual (and not imputed) knowledge of the executive officers of Isis, without the duty of inquiry or investigation.

"***Law***" means any law, statute, treaty, constitution, regulation, rule, ordinance, order or Governmental Approval, or other governmental restriction, requirement or determination, of or by any Governmental Authority.

"***License***" has the meaning set forth in the Preliminary Statement of the Purchase Option Agreement.

"***Licensed Intellectual Property***" means the Licensed Patent Rights, Symphony GenIsis Enhancements, Licensor Enhancements and the Licensed Know-How.

"***Licensed Know-How***" means any and all proprietary technology that is Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option that relates to, or is exploitable in connection with, the Licensed Patent Rights, Regulatory Files, Products or the Programs, including without limitation, manufacturing processes or protocols, know-how, writings, documentation, data, technical information, techniques, results of experimentation and testing, diagnostic and prognostic assays, specifications, databases, any and all laboratory, research, pharmacological, toxicological, analytical, quality control pre-clinical and clinical data, and other information and materials, whether or not patentable.

"Licensed Patent Rights" means:

(a) any and all patents, patent applications and invention disclosures Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option and relating to, or exploitable in connection with, any Product and/or any Program;

(b) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) filed prior to the unexercised expiration or termination of the Purchase Option; and

(c) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) or (b) filed after the unexercised expiration or termination of the Purchase Option but solely to the extent the subject matter in any such continuation-in-part embodies Licensed Know-How or has been disclosed in the patents or patent applications described in (a) or (b).

Licensed Patent Rights include any and all patents and patent applications that claim Licensor Enhancements or Symphony GenIsis Enhancements and Program-Specific Patents.

"***Licensor***" means Isis.

"***Licensor Enhancements***" means all findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Know-How, Regulatory Files, Products or the Programs, in each case, developed by Licensor during the Term (in each case whether or not patentable), to the extent such items do not otherwise qualify as Symphony GenIsis Enhancements hereunder, regardless of whether such work is funded by Symphony GenIsis or Isis.

"***Lien***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Liquidating Event***" has the meaning set forth in Section 8.01 of the Holdings LLC Agreement.

"***LLC Agreements***" means the Initial Holdings LLC Agreement, the Holdings LLC Agreement, the Initial Investors LLC Agreement and the Investors LLC Agreement.

"***Loss***" has the meaning set forth in each Operative Document in which it appears.

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

"***Management Budget Component***" has the meaning set forth in Section 4.1 of the Amended and Restated Research and Development Agreement.

"***Management Fee***" has the meaning set forth in Section 6(a) of the RRD Services Agreement.

"***Manager***" means (i) for each LLC Agreement in which it appears, the meaning set forth in such LLC Agreement, and (ii) for each other Operative Document in which it appears, RRD in its capacity as manager of Symphony GenIsis.

"***Management Services***" has the meaning set forth in Section 1(a) of the RRD Services Agreement.

"***Manager Event***" has the meaning set forth in Section 3.01(g) of the Holdings LLC Agreement.

"***Material Adverse Effect***" means, with respect to any Person, a material adverse effect on (i) the business, assets, property or condition (financial or otherwise) of such Person or, (ii) its ability to comply with and satisfy its respective agreements and obligations under the Operative Documents or, (iii) the enforceability of the obligations of such Person of any of the Operative Documents to which it is a party.

"***Material Subsidiary***" means, at any time, a Subsidiary of Isis having assets in an amount equal to at least 5% of the amount of total consolidated assets of Isis and its Subsidiaries (determined as of the last day of the most recent reported fiscal quarter of Isis) or revenues or net income in an amount equal to at least 5% of the amount of total consolidated revenues or net

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income of Isis and its Subsidiaries for the 12-month period ending on the last day of the most recent reported fiscal quarter of Isis.

"***Medical Discontinuation Event***" means (a) as specified in each Protocol, those data that, if collected in such Protocol, demonstrate that such Protocol should not be continued or (b) a series of adverse events, side effects or other undesirable outcomes that, when collected in a Protocol, would cause a reasonable FDA Sponsor to discontinue such Protocol.

"***Membership Interest***" means (i) for each LLC Agreement in which it appears, the meaning set forth in such LLC Agreement, and (ii) for each other Operative Document in which it appears, the meaning set forth in the Holdings LLC Agreement.

"***MOE Gapmer***" means a single stranded antisense oligonucleotide of less than [***] nucleotides (i) wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (phosphorothioate) and (ii) comprising a region of at least [***] unsubstituted 2′-deoxy nucleotides with the remaining nucleotides contain a 2′-O-(methoxyethyl) substitution at the 2′ position.

"***NASDAQ***" means the National Association of Securities Dealers Automated Quotation System.

"***NDA***" means a New Drug Application, as defined in the regulations promulgated by the United States Food and Drug Administration, or any foreign equivalent thereof.

"***Nonexclusive Field***" means (i) manufacturing (including analytical methods) ASOs, (ii) formulating ASOs, (iii) conducting Research on ASOs and/or (iv) supplying ASOs solely to conduct Research.

"***Non-Isis Capital Transaction***" means any (i) sale or other disposition of all or part of the Symphony GenIsis Shares or all or substantially all of the operating assets of Symphony GenIsis, to a Person other than Isis or an Affiliate of Isis or (ii) distribution in kind of the Symphony GenIsis Shares following the expiration of the Purchase Option.

"***Novated and Restated Technology License Agreement***" means the Novated and Restated Technology License Agreement, dated as of the Closing Date, among Isis, Symphony GenIsis and Holdings.

"***Operative Documents***" means, collectively, the Indemnification Agreement, the Holdings LLC Agreement, the Purchase Option Agreement, the Warrant Purchase Agreement, the Registration Rights Agreement, the Subscription Agreement, the Technology License Agreement, the Novated and Restated Technology License Agreement, the RRD Services Agreement, the Research and Development Agreement, the Research Cost Sharing and Extension Agreement, the Amended and Restated Research and Development Agreement, the Confidentiality Agreement, and each other certificate and agreement executed in connection with any of the foregoing documents.

"***Organizational Documents***" means any certificates or articles of incorporation or formation, partnership agreements, trust instruments, bylaws or other governing documents.

"***Partial Stock Payment***" has the meaning set forth in Section 3(a)(iii) of the Purchase Option Agreement.

"***Party(ies)***" means, for each Operative Document or other agreement in which it appears, the parties to such Operative Document or other agreement, as set forth therein. With respect to any agreement in which a provision is included therein by reference to a provision in another agreement, the term "Party" shall be read to refer to the parties to the document at hand, not the agreement that is referenced.

"***Payment Terms***" has the meaning set forth in Section 8.2 of the Amended and Restated Research and Development Agreement.

"***Percentage***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Permitted Investments***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Permitted Lien***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Person***" means any individual, partnership (whether general or limited), limited liability company, corporation, trust, estate, association, nominee or other entity.

"***Personnel***" of a Party means such Party, its employees, subcontractors, consultants, representatives and agents.

"***Prime Rate***" means the quoted "Prime Rate" at JPMorgan Chase Bank or, if such bank ceases to exist or is not quoting a base rate, prime rate reference rate or similar rate for United States dollar loans, such other major money center commercial bank in New York City selected by the Manager.

"***Products***" means an ApoB Product, a GCCR Product and/or a GCGR Product.

"***Profit***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Programs***" means the ApoB Program, the GCCR Program and/or the GCGR Program.

"Program-Specific Patents" means

(a) any and all patents, patent applications and invention disclosures Controlled by Licensor prior to the unexercised expiration or termination of the Purchase Option that claim any composition of matter comprising, or method of using, an ASO targeting any of ApoB, GCCR or GCGR, including but not limited to, the patents and patent applications listed on Annex C to the Novated and Restated Technology License Agreement;

(b) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) filed prior to the unexercised expiration or termination of the Purchase Option; and

(c) any and all reissues, continuations, divisionals, continuations-in-part, reexaminations, renewals, substitutes, extensions or foreign counterparts of the patents, patent applications and invention disclosures described in (a) or (b) filed after the unexercised expiration or termination of the Purchase Option but solely to the extent the subject matter in such any continuation-in-part embodyies Licensed Know-How or has been disclosed in the patents or patent applications described in (a) or (b).

"***Protocol***" means a written protocol that meets the substantive requirements of Section 6 of the ICH Guideline for Good Clinical Practice as adopted by the FDA, effective May 9, 1997 and is included within the Development Plan or later modified or added to the Development Plan pursuant to the Amended and Restated Research and Development Agreement.

"***Public Companies***" has the meaning set forth in Section 5(e) of the Purchase Option Agreement.

"***Purchase Option***" has the meaning set forth in Section 1(a) of the Purchase Option Agreement.

"***Purchase Option Agreement***" means this Purchase Option Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis.

"***Purchase Option Closing***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Closing Date***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Commencement Date***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Purchase Option Exercise Date***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Exercise Notice***" has the meaning set forth in Section 2(a) of the Purchase Option Agreement.

"***Purchase Option Interim Date***" has the meaning set forth in Section 2(b)(i) of the Purchase Option Agreement.

"***Purchase Option Period***" has the meaning set forth in Section 1(c)(iii) of the Purchase Option Agreement.

"***Purchase Price***" has the meaning set forth in Section 2(b) of the Purchase Option Agreement.

"***Put Option***" has the meaning set forth in Section 2A of the Purchase Option Agreement.

"***Put Option Exercise Notice***" has the meaning set forth in Section 2A of the Purchase Option Agreement.

"***QA Audits***" has the meaning set forth in Section 6.5 of the Amended and Restated Research and Development Agreement.

"***Quarterly Price***" has the meaning set forth in Section 2(b)(i) of the Purchase Option Agreement.

"***Registration Rights Agreement***" means the Registration Rights Agreement dated as of the Closing Date, between Isis and Holdings.

"***Registration Statement***" has the meaning set forth in Section 1(b) of the Registration Rights Agreement.

"***Regulatory Authority***" means the United States Food and Drug Administration, or any successor agency in the United States, or any health regulatory authority(ies) in any other country that is a counterpart to the FDA and has responsibility for granting registrations or other regulatory approval for the marketing, manufacture, storage, sale or use of drugs in such other country.

"***Regulatory Allocation***" has the meaning set forth in Section 3.06 of the Holdings LLC Agreement.

"***Regulatory Files***" means any IND, NDA or any other filings filed with any Regulatory Authority with respect to the Programs.

"***Representative***" of any Person means such Person's shareholders, principals, directors, officers, employees, members, managers and/or partners.

"***Research***" means research, including gene function, gene expression and target validation research, which may include small pilot toxicology studies but excludes IND-Enabling Studies or dosing humans. Research does not include commercialization.

"***Research Cost Sharing and Extension Agreement***" means the Research Cost Sharing and Extension Agreement dated as of the Closing Date, among Isis, Holdings and Symphony GenIsis, Inc..

"***Research and Development Agreement***" means the Research and Development Agreement dated as of the Closing Date, between Isis and Holdings.

"***RRD***" means RRD International, LLC, a Delaware limited liability company.

"***RRD FTE Budget***" means the budget attached to the RRD Services Agreement as Exhibit 3 thereto.

"***RRD Indemnified Party***" has the meaning set forth in Section 10(a) of the RRD Services Agreement.

"***RRD Investment Personnel***" has the meaning set forth in Section 1(a)(v) of the RRD Services Agreement.

"***RRD Loss***" has the meaning set forth in Section 10(a) of the RRD Services Agreement.

"***RRD Personnel***" has the meaning set forth in Section 1(a)(ii) of the RRD Services Agreement.

"***RRD Services Agreement***" means the RRD Services Agreement between Symphony GenIsis and RRD, dated as the Closing Date, 2006.

"***Schedule K-1***" has the meaning set forth in Section 9.02(a) of the Holdings LLC Agreement.

"***Scheduled Meeting***" has the meaning set forth in Paragraph 6 of Annex B of the Amended and Restated Research and Development Agreement.

"***Scientific Discontinuation Event***" has the meaning set forth in Section 4.2(c) of the Amended and Restated Research and Development Agreement.

"***SCP***" means Symphony Capital Partners, L.P., a Delaware limited partnership.

"***SEC***" means the United States Securities and Exchange Commission.

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

"***Selling Stockholder Questionnaire***" has the meaning set forth in Section 4(a) of the Registration Rights Agreement.

"***Shareholder***" means any Person who owns any Symphony GenIsis Shares.

"***Solvent***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***SSP***" means Symphony Strategic Partners, LLC, a Delaware limited liability company.

"***Stock Payment Date***" has the meaning set forth in Section 2 of the Subscription Agreement.

"***Stock Purchase Price***" has the meaning set forth in Section 2 of the Subscription Agreement.

"***Subcontracting Agreement***" has the meaning set forth in Section 6.2 of the Amended and Restated Research and Development Agreement.

"***Sublicensed Intellectual Property***" has the meaning set forth in Section 3.2 of the Novated and Restated Technology License Agreement.

"***Sublicense Obligations***" has the meaning set forth in Section 3.2 of the Novated and Restated Technology License Agreement.

"***Subscription Agreement***" means the Subscription Agreement between Symphony GenIsis and Holdings, dated as the Closing Date.

"***Subsidiary***" of any Person means any corporation, partnership, joint venture, limited liability company, trust or estate of which (or in which) more than 50% of (a) the issued and outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether at the time capital stock of any other class or classes of such corporation shall or might have voting power upon the occurrence of any contingency); (b) the interest in the capital or profits of such partnership, joint venture or limited liability company; or (c) the beneficial interest in such trust or estate is at the time directly or indirectly owned or controlled by such Person, by such Person and one or more of its other Subsidiaries or by one or more of such Person's other Subsidiaries.

"***Surviving Entity***" means the surviving legal entity which is surviving entity to Isis after giving effect to a Change of Control.

"***Symphony Capital***" means Symphony Capital LLC, a Delaware limited liability company.

"***Symphony Fund(s)***" means Symphony Capital Partners, L.P., a Delaware limited partnership, and Symphony Strategic Partners, LLC, a Delaware limited liability company.

"***Symphony GenIsis***" means Symphony GenIsis, Inc., a Delaware corporation.

"***Symphony GenIsis Auditors***" has the meaning set forth in Section 5(b) of the RRD Services Agreement.

"***Symphony GenIsis Board***" means the board of directors of Symphony GenIsis.

"***Symphony GenIsis By-laws***" means the By-laws of Symphony GenIsis, as adopted by resolution of the Symphony GenIsis Board on the Closing Date.

"***Symphony GenIsis Charter***" means the Amended and Restated Certificate of Incorporation of Symphony GenIsis, dated as of the Closing Date.

"***Symphony GenIsis Director Event***" has the meaning set forth in Section 3.01(h)(i) of the Holdings LLC Agreement.

"***Symphony GenIsis Enhancements***" means findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes to the Licensed Know-How, Regulatory Files, Products or the Programs, made by or on behalf of Symphony GenIsis during the Term, in each case whether or not patentable, including any such findings, improvements, discoveries, inventions, additions, modifications, enhancements, derivative works, clinical development data, or changes related to data and information generated or derived by RRD and assigned to Symphony GenIsis pursuant to Section 12 of the RRD Services Agreement.

"***Symphony GenIsis Equity Securities***" means the Common Stock and any other stock or shares issued by Symphony GenIsis.

"***Symphony GenIsis Loss***" has the meaning set forth in Section 10(b) of the RRD Services Agreement.

"***Symphony GenIsis Shares***" has the meaning set forth in Section 2.02 of the Holdings LLC Agreement.

"***Tangible Materials***" means any tangible documentation, whether written or electronic, existing as of the Closing Date or during the Term, that is Controlled by the Licensor, embodying or relating to the Licensed Intellectual Property, Regulatory Files, Products or the Programs, including, but not limited to, safety, efficacy or other data related to the Products or Programs, documentation, patent applications and invention disclosures.

"***Tax Amount***" has the meaning set forth in Section 4.02 of the Holdings LLC Agreement.

"***Technology License Agreement***" means the Technology License Agreement, dated as of the Closing Date, between Isis and Holdings.

"***Term***" has the meaning set forth in Section 4(b)(iii) of the Purchase Option Agreement, unless otherwise stated in any Operative Document.

"***Territory***" means the world.

"***Third Party IP***" has the meaning set forth in Section 2.9 of the Novated and Restated Technology License Agreement.

"***Third Party Licensor***" means a third party from which Isis has received a license or sublicense to Licensed Intellectual Property.

"***Transfer***" has for each Operative Document in which it appears the meaning set forth in such Operative Document.

"***Transferee***" has, for each Operative Document in which it appears, the meaning set forth in such Operative Document.

"***Voluntary Bankruptcy***" has the meaning set forth in Section 1.01 of the Holdings LLC Agreement.

"***Warrant Closing***" has the meaning set forth in Section 2.03 of the Warrant Purchase Agreement.

"***Warrant Date***" has the meaning set forth in Section 2.02 of the Warrant Purchase Agreement.

"***Warrant Purchase Agreement***" means the Warrant Purchase Agreement, dated as of the Closing Date, between Isis and Holdings.

"***Warrant Shares***" has the meaning set forth in Section 2.01 of the Warrant Purchase Agreement.

"***Warrant Surrender Price***" has the meaning set forth in Section 7.08 of the Warrant Purchase Agreement.

"***Warrants***" has the meaning set forth in Section 2.01 of the Warrant Purchase Agreement.

ANNEX B

DEVELOPMENT COMMITTEE CHARTER

[***]

ANNEX C

INITIAL DEVELOPMENT PLAN

[***]

ANNEX D

INITIAL DEVELOPMENT BUDGET

[***]

ANNEX E

PAYMENT TERMS

[***]

Schedule 6.4

KEY PERSONNEL OF ISIS

[***]

Schedule 12.1(f)

DISCLOSED MATERIAL CONTRACTS

[***]

NEITHER THIS WARRANT NOR THE SECURITIES ISSUABLE UPON EXERCISE HEREOF HAVE BEEN THE SUBJECT OF REGISTRATION UNDER THE SECURITIES ACT OF 1933, AS AMENDED, OR UNDER THE SECURITIES LAWS OF ANY STATE, AND THE SAME HAVE BEEN (OR WILL BE, WITH RESPECT TO THE SECURITIES ISSUABLE UPON EXERCISE HEREOF) ISSUED IN RELIANCE ON EXEMPTIONS FROM THE REGISTRATION REQUIREMENTS OF SAID ACT AND SUCH LAWS. NEITHER THIS WARRANT NOR THE SECURITIES ISSUABLE UPON EXERCISE HEREOF MAY BE SOLD, TRANSFERRED, PLEDGED, HYPOTHECATED OR OTHERWISE DISPOSED OF EXCEPT AS PERMITTED UNDER SUCH SECURITIES LAWS, PURSUANT TO REGISTRATION OR EXEMPTION THEREFROM.

THE WARRANT EVIDENCED BY THIS CERTIFICATE IS SUBJECT TO CERTAIN RESTRICTIONS ON TRANSFER AS SET FORTH IN THE WARRANT PURCHASE AGREEMENT, DATED AS OF APRIL 7, 2006, COPIES OF WHICH ARE ON FILE AT THE PRINCIPAL EXECUTIVE OFFICES OF THE ISSUER. NO REGISTRATION OF TRANSFER OF THIS WARRANT WILL BE MADE ON THE BOOKS OF THE ISSUER UNLESS AND UNTIL SUCH RESTRICTIONS SHALL HAVE BEEN COMPLIED WITH.

ISIS PHARMACEUTICALS, INC.

WARRANT TO PURCHASE COMMON STOCK

No. CW-SG001 **April 7, 2006**

Void After April 7, 2011

THIS CERTIFIES THAT, for value received, **SYMPHONY GENISIS HOLDINGS LLC**, with its principal office at 7361 Calhoun Place, Suite 325, Rockville, MD 20850, or its assigns (the ***"Holder"***), is entitled to subscribe for and purchase at the Exercise Price (defined below) from Isis Pharmaceuticals, Inc., a Delaware corporation, with its principal office at 1896 Rutherford Road, Carlsbad, CA 92008-7208 (the ***"Company"***) up to four million two hundred fifty thousand (4,250,000) shares of the Common Stock of the Company (the ***"Common Stock"***), subject to adjustment as provided herein. This Warrant is being issued pursuant to the terms of the Warrant Purchase Agreement, dated April 7, 2006, by and among the Company and the Holder (the ***"Warrant Purchase Agreement"***). Capitalized terms not otherwise defined herein shall have the respective meanings ascribed to such terms in the Warrant Purchase Agreement.

1. DEFINITIONS. As used herein, the following terms shall have the following respective meanings:

(a) ***"Exercise Period"*** shall mean the period commencing one hundred eighty (180) days after the date hereof and ending April 7, 2011, unless sooner terminated as provided below.

(b) ***"Exercise Price"*** shall mean $8.93 per share, subject to adjustment pursuant to Section 6 below.

(c) ***"Exercise Shares"*** shall mean the shares of the Company's Common Stock issuable upon exercise of this Warrant, subject to adjustment pursuant to the terms herein, including but not limited to adjustment pursuant to Section 6 below.

2. EXERCISE OF WARRANT.

2.1 Method of Exercise. The rights represented by this Warrant may be exercised in whole or in part at any time during the Exercise Period, by delivery of the following to the Company at its address set forth above (or at such other address as it may designate by notice in writing to the Holder):

(a) An executed Notice of Exercise in the form attached hereto;

(b) Payment of the Exercise Price of the Exercise Shares purchased thereby (i) in cash or by check or wire transfer of immediately available funds, (ii) pursuant to a Cashless Exercise, as described below, or (iii) by a combination of (i) and (ii); and

(c) This Warrant.

Upon the exercise of the rights represented by this Warrant, shares of Common Stock shall be issued for the Exercise Shares so purchased, and shall be registered in the name of the Holder or persons affiliated with the Holder, if the Holder so designates, within a reasonable amount of time following receipt by the Company of all of the items designated in clauses (a), (b) and (c) above, but in no event later than thirty (30) days after the date of exercise pursuant to this Section 2.1. The Company shall (i) upon request of the Holder, if available and if allowed under applicable securities laws, use commercially reasonable efforts to deliver Exercise Shares electronically through the Depository Trust Corporation or another established clearing corporation performing similar functions, or (ii) if requested by the Holder, deliver to the Holder certificates evidencing the Exercise Shares.

The person in whose name any Exercise Shares are to be issued upon exercise of this Warrant shall be deemed to have become the holder of record of such shares on the date on which delivery of the Notice of Exercise, delivery of this Warrant and payment of the Exercise Price were made, irrespective of the date of issuance of the shares of Common Stock, except that, if the date of such delivery and payment is a date when the stock transfer books of the Company are closed, such person shall be deemed to have become the holder of such shares at the close of business on the next succeeding date on which the stock transfer books are open.

2.2 Cashless Exercise. Notwithstanding any provisions herein to the contrary, if, at any time during the Exercise Period, the Current Market Price (as defined below) of one share of Common Stock is greater than the Exercise Price (at the date of calculation as set forth below), in lieu of exercising this Warrant by payment of cash, the Holder may exercise this Warrant in whole or part by a cashless exercise by surrender of this Warrant at the principal office of the Company together with the properly endorsed Notice of Exercise and the Company shall issue to the Holder a number of shares of Common Stock computed using the following formula:

$$X = \frac{Y(B-A)}{B}$$

Where: X = the number of shares of Common Stock to be issued to the Holder.

Y = the number of shares of Common Stock purchasable upon exercise of all of the Warrant or, if only a portion of the Warrant is being exercised, the portion of the Warrant being exercised (in each case subject to adjustment pursuant to the terms herein, including but not limited to adjustment pursuant to Section 6 below).

A = the Exercise Price.

B = the Current Market Price of one share of Common Stock.

"Current Market Price" means on any particular date:

(a) if the Common Stock is traded on the Nasdaq SmallCap Market or the Nasdaq National Market, the average of the closing prices of the Common Stock of the Company on such market over the five (5) trading days ending immediately prior to the applicable date of valuation (in the case of a cashless exercise, the date of valuation will be the exercise date);

(b) if the Common Stock is traded on any registered national stock exchange but is not traded on the Nasdaq SmallCap Market or the Nasdaq National Market, the average of the closing prices of the Common Stock of the Company on such exchange over the five (5) trading days ending immediately prior to the applicable date of valuation (in the case of a cashless exercise, the date of valuation will be the exercise date).

(c) if the Common Stock is traded over-the-counter, but not on the Nasdaq SmallCap Market, the Nasdaq National Market or a registered national stock exchange, the average of the closing bid prices over the 30-day period ending immediately prior to the applicable date of valuation (in the case of a cashless exercise, the date of valuation will be the exercise date); and

(d) if there is no active public market for the Common Stock, the value thereof, as determined in good faith by the Board of Directors of the Company upon due consideration of the proposed determination thereof by the Holder.

2.3 Partial Exercise. If this Warrant is exercised in part only, the Company shall, upon surrender of this Warrant, execute and deliver, within ten (10) days of the date of exercise, a new Warrant evidencing the rights of the Holder, or such other person as shall be designated in the Notice of Exercise, to purchase the balance of the Exercise Shares purchasable hereunder. In no event shall this Warrant be exercised for a fractional Exercise Share, and the Company shall not distribute a Warrant exercisable for a fractional Exercise Share. Fractional Exercise Shares shall be treated as provided in Section 5 hereof.

2.4 Legend.

(a) All certificates evidencing the shares to be issued to the Holder may bear the following legend (provided that no such legend shall be borne by Exercise Shares issued following the valid disposition of such shares pursuant to a registration statement which is effective under the Securities Act):

"THE SHARES REPRESENTED BY THIS CERTIFICATE HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, OR UNDER THE SECURITIES LAWS OF ANY STATE, AND THE SAME HAVE BEEN ISSUED IN RELIANCE ON EXEMPTIONS FROM THE REGISTRATION REQUIREMENTS OF SAID ACT AND SUCH LAWS. SUCH SHARES MAY NOT BE SOLD, TRANSFERRED, PLEDGED, HYPOTHECATED OR OTHERWISE DISPOSED OF EXCEPT AS PERMITTED UNDER SUCH SECURITIES LAWS, PURSUANT TO REGISTRATION OR EXEMPTION THEREFROM.**"**

"THE SHARES REPRESENTED BY THIS CERTIFICATE ARE SUBJECT TO CERTAIN RESTRICTIONS ON TRANSFER AS SET FORTH IN ARTICLE VI OF THE WARRANT PURCHASE AGREEMENT, DATED AS OF APRIL 7, 2006, BY AND BETWEEN THE ISSUER HEREOF AND SYMPHONY GENISIS HOLDINGS LLC (COPIES OF WHICH ARE ON FILE AT THE PRINCIPAL EXECUTIVE OFFICES OF THE ISSUER HEREOF), INCLUDING, BUT NOT LIMITED TO, A DAILY SHARE DISPOSITION LIMIT, WHICH IS THE GREATER OF (X) [ ] SHARES OR (Y) [ ]% OF THE AVERAGE DAILY TRADING VOLUME OF ISIS COMMON STOCK OVER THE COURSE OF THE PREVIOUS MONTH (AS REPORTED ON THE NASDAQ NATIONAL MARKET OR SUCH OTHER NATIONAL EXCHANGE REPRESENTING THE PRIMARY EXCHANGE ON WHICH ISIS COMMON STOCK IS LISTED) PER DAY IN RESPECT OF THE WARRANT SHARES OF THE HOLDER HEREOF. UPON A SALE OR OTHER TRANSACTION RESULTING IN A DIVISION OF THE SHARES REPRESENTED HEREBY, SUCH MAXIMUM DAILY DISPOSITION AMOUNT WILL BE DIVIDED *PRO RATA* AMONG SUBSEQUENT HOLDERS OF THE WARRANT SHARES."

(b) If the certificates representing shares include either or both of the legends set forth in Section 2.4(a) hereof, the Company shall, upon a request from a Holder, or subsequent transferee of a Holder, as soon as practicable but in no event more than thirty (30) days after receiving such request, remove or cause to be removed (i) if the shares cease to be restricted securities, the securities law portion of the legend and/or (ii) in the event of a sale of the shares subject to issuance following the transfer of the shares in compliance with the transfer restrictions, the transfer restriction portion of the legend, from certificates representing the shares delivered by a Holder (or a subsequent transferee).

2.5 Charges, Taxes and Expenses. Issuance of the Exercise Shares shall be made without charge to the Holder for any issue or transfer tax or other incidental expense in respect of the issuance of any electronic or paper certificate, all of which taxes and expenses shall be paid by the Company, and such certificates shall be issued in the name of the Holder or in such name or names as may be directed by the Holder; provided, however, that

in the event Exercise Shares are to be issued in a name other than the name of the Holder, this Warrant when surrendered for exercise shall be accompanied by the Assignment Form attached hereto duly

executed by the Holder; and the Company may require, as a condition thereto, the payment of a sum sufficient to reimburse it for any transfer tax incidental thereto.

3. COVENANTS OF THE COMPANY.

3.1 Covenants as to Exercise Shares. The Company covenants and agrees that all Exercise Shares that may be issued upon the exercise of the rights represented by this Warrant will, upon issuance, be duly authorized and validly issued and outstanding, fully paid and nonassessable, and free from all taxes, liens and charges with respect to the issuance thereof. The Company further covenants and agrees that the Company will at all times during the Exercise Period, have authorized and reserved, free from preemptive rights, a sufficient number of shares of its Common Stock to provide for the exercise of the rights represented by this Warrant. If at any time during the Exercise Period the number of authorized but unissued shares of Common Stock shall not be sufficient to permit exercise of this Warrant, the Company will take such corporate action as may, in the opinion of counsel, be necessary to increase its authorized but unissued shares of Common Stock (or other securities as provided herein) to such number of shares as shall be sufficient for such purposes.

3.2 No Impairment. Except and to the extent as waived or consented to by the Holder in accordance with Section 10 hereof, the Company will not, by amendment of its Certificate of Incorporation (as such may be amended from time to time), or through any means, avoid or seek to avoid the observance or performance of any of the terms to be observed or performed hereunder by the Company, but will at all times in good faith carry out of all the provisions of this Warrant and take all such action as may be necessary or appropriate in order to protect the exercise rights of the Holder against such impairment.

3.3 Notices of Record Date. If at any time:

(a) the Company shall take a record of the holders of Common Stock for the purpose of entitling them to receive a dividend or other distribution, or any right to subscribe for or purchase any evidences of its indebtedness, any shares of stock of any class or any other securities or property, or to receive any other right (other than with respect to any equity or equity equivalent security issued pursuant to a rights plan adopted by the Company's Board of Directors);

(b) there shall be any capital reorganization of the Company, any reclassification or recapitalization of the capital stock of the Company or any consolidation or merger of the Company, or any sale, transfer or other disposition of all or substantially all the property, assets or business of the Company; or

(c) there shall be a voluntary or involuntary dissolution, liquidation or winding up of the Company;

then, in any one or more of such cases, the Company shall use commercially reasonable efforts to give to the Holder, provided that such action is available and permitted under the applicable securities laws, at least ten (10) days' prior written notice of the record date for such dividend, distribution or right or for determining rights to vote in respect of any such reorganization, reclassification, recapitalization, consolidation, merger, sale, transfer, disposition, dissolution,

liquidation or winding up of the Company. Any notice provided hereunder shall specify the date on which the holders of Common Stock shall be entitled to any such dividend, distribution or right, and the amount and character thereof, and the then current estimated date for the closing of the transaction contemplated by any proposed reorganization, reclassification, recapitalization, consolidation, merger, sale, transfer, disposition, dissolution, liquidation or winding up of the Company.

4. REPRESENTATIONS OF HOLDER.

4.1 Acquisition of Warrant for Personal Account. The Holder represents and warrants that it is acquiring the Warrant and the Exercise Shares solely for its account for investment and not with a present view toward the public sale or public distribution of said Warrant or Exercise Shares or any part thereof and has no intention of selling or distributing said Warrant or Exercise Shares or any arrangement or understanding with any other persons regarding the sale or distribution of said Warrant or the Exercise Shares, except as would not result in a violation of the Securities Act. The Holder will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) the Warrant except in accordance with the provisions of Article VI of the Warrant Purchase Agreement and will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) the Exercise Shares except in accordance with the provisions of Article VI of the Warrant Purchase Agreement or pursuant to and in accordance with the Securities Act.

4.2 Securities Are Not Registered.

(a) The Holder understands that the offer and sale of neither the Warrant nor the Exercise Shares has been registered under the Securities Act.

(b) The Holder recognizes that the Warrant and the Exercise Shares must be held indefinitely unless they are subsequently registered under the Securities Act or an exemption from such registration is available. The Holder recognizes that the Company has no obligation to register the Warrant or, except as provided in the Warrant Purchase Agreement and the Registration Rights Agreement, the Exercise Shares, or to comply with any exemption from such registration.

(c) The Holder is aware that neither the Warrant nor the Exercise Shares may be sold pursuant to Rule 144 adopted under the Securities Act unless certain conditions are met, including, among other things, the availability of certain current public information about the Company and

the expiration of the required holding period under Rule 144.

4.3 Disposition of Warrant and Exercise Shares.

(a) The Holder further agrees not to make any disposition of all or any part of the Warrant or Exercise Shares in any event unless and until one of the following occurs:

(i) The Company shall have received a letter secured by the Holder from the SEC stating that no action will be recommended to the Commission with respect to the proposed disposition;

(ii) There is then in effect a registration statement under the Securities Act covering such Warrant or Exercise Shares and such disposition is made in accordance with said registration statement; or

(iii) The Holder shall have furnished the Company with an opinion of counsel, reasonably satisfactory to the Company, for the Holder to the effect that such disposition will not require registration of such Warrant or Exercise Shares under the Securities Act or any applicable state securities laws; *provided*, that so long as the Holder provides the Company with a representation letter in customary form with respect to such Rule 144 disposition, no opinion shall be required for any disposition made or to be made in accordance with the provisions of Rule 144.

5. FRACTIONAL SHARES. No fractional shares shall be issued upon the exercise of this Warrant as a consequence of any adjustment pursuant hereto. All Exercise Shares (including fractions) issuable upon exercise of this Warrant may be aggregated for purposes of determining whether the exercise would result in the issuance of any fractional share. If, after aggregation, the exercise would result in the issuance of a fractional share, the Company shall, in lieu of issuance of any fractional share, pay the Holder otherwise entitled to such fraction a sum in cash equal to the product resulting from multiplying the then Current Market Price (as of the applicable exercise date) of an Exercise Share by such fraction.

6. CERTAIN EVENTS.

6.1 Distribution of Assets. In case the Company shall declare or make any distribution of its assets (or rights to acquire its assets) to holders of Common Stock as a partial liquidating dividend, by way of return of capital or otherwise (including any dividend or distribution to the Company's stockholders of cash or shares (or rights to acquire shares) of capital stock of a subsidiary) (a ***"Distribution"***), at any time after the initial issuance of this Warrant, then the Holder shall be entitled upon exercise of this Warrant for the purchase of any or all of the shares of Common Stock subject hereto, to receive the amount of such assets (or rights) which would have been payable to the Holder had such Holder been the holder of such shares of Common Stock on the record date for the determination of stockholders entitled to such Distribution.

6.2 Dividends, Subdivisions, Combinations and Reclassifications. The number and kind of securities purchasable upon the exercise of this Warrant and the Exercise Price shall be subject to adjustment from time to time upon the happening of any of the following. In case the Company shall (i) pay a dividend in shares of Common Stock or make a distribution in shares of Common Stock to holders of its outstanding Common Stock, (ii) subdivide its outstanding shares of Common Stock into a greater number of shares, (iii) combine its outstanding shares of Common Stock into a smaller number of shares of Common Stock, or (iv) issue any shares of its capital stock in a reclassification of the Common Stock, then the number of Warrant Shares purchasable upon exercise of this Warrant immediately prior thereto

shall be adjusted so that the Holder shall be entitled to receive the kind and number of Warrant Shares or other securities of the Company which it would have owned or have been entitled to receive had such Warrant been exercised in advance thereof. Upon each such adjustment of the kind and number of Warrant Shares or other securities of the Company which are purchasable hereunder, the Holder shall thereafter be entitled to purchase the number of Warrant Shares or other securities resulting from such adjustment at an Exercise Price per Warrant Share or other security obtained by multiplying the Exercise Price in effect immediately prior to such adjustment by the number of Warrant Shares purchasable pursuant hereto immediately prior to such adjustment and dividing by the number of Warrant Shares or other securities of the Company resulting from such adjustment. An adjustment made pursuant to this paragraph shall become effective immediately after the effective date of such event retroactive to the record date, if any, for such event.

6.3 Corporate Transactions. In the event that the Company enters into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than the Company, then the Holder shall either exercise the Warrant or surrender the Warrant in exchange for a new warrant exercisable in return for shares or common stock of the Surviving Entity (as defined in the Warrant Purchase Agreement) (the "***Replacement Warrant***"), provided that:

(a) if the terms of such merger or acquisition shall provide for consideration that consists solely of stock of the Surviving Entity, and such Surviving Entity has a class of common stock (x) registered under Section 12(b) or 12(g) of the Exchange Act and traded on a major national exchange such as the NYSE or NASDAQ, or (y) traded on a major foreign exchange such as the Deutsche Börse or the London Stock Exchange (such a class of common shares, "***Public Common Shares***"), then any Replacement Warrants issued to the holders of the Warrants shall be solely for Public Common Shares of the Surviving Entity, at an exchange ratio reflecting the stock consideration paid by the Surviving Entity at the time of such change in control, and the holders of the Replacement Warrants shall have the registration rights for Public Common Shares issuable upon exercise of the Replacement Warrants as provided under the Registration Rights Agreement; or

(b) if the terms of such merger or acquisition shall provide for consideration that consists of cash or a combination of cash and Public Common Shares of the Surviving Entity, then any Replacement Warrants issued to the holders of the Warrants shall be solely for Public Common Shares of the Surviving Entity, at an exchange ratio reflecting the total consideration paid by the Surviving Entity at the time of such change in control, as if the total consideration (including cash) for each share of Isis Common Stock was instead paid only in Public Common Shares of the Surviving Entity at the time of such change of control (as illustrated on Exhibit C to the Warrant Purchase Agreement), and the holders of the Replacement Warrants shall have the registration rights for Public Common Shares issuable upon exercise of the Replacement Warrants as provided under the Registration Rights Agreement; or

(c) if during the Term, such a merger or acquisition shall occur and the Surviving Entity is a private corporation, closely held company or other entity that does not have a class of Public Common Shares, then the holders of the Warrants shall have the option to elect within twenty (20) Business Days of receiving notice of the public announcement of the merger

or acquisition, to either (A) retain all then outstanding Warrants and exercise such Warrants in accordance with the terms of the Warrants and this Agreement, effective immediately prior to the consummation of such merger or acquisition; or (B) surrender all outstanding Warrants to Isis in consideration of a cash payment for each share of Isis Common Stock subject to purchase under the Warrants in an amount equal to forty percent (40%) of the per share cash consideration to be received by a holder of one share of Isis Common Stock to be tendered in the merger or acquisition (the "***Warrant Surrender Price***"); provided, further, that the aggregate total cash payments to all holders of the Warrants shall not exceed twenty-two million dollars ($22,000,000). The Warrant Surrender Price shall be paid upon the surrender of the Warrants promptly following the closing of a merger or acquisition described in this clause (iii).

The foregoing provisions of this Section 6.3 shall similarly apply to successive mergers, acquisitions, consolidations or disposition of assets.

6.4 Adjustment of Exercise Price. The form of this Warrant need not be changed because of any adjustment in the number, class, and kind of shares subject to this Warrant. The Company shall promptly provide a certificate from its principal accounting officer notifying the Holder in writing of any adjustment in the Exercise Price and/or the total number, class, and kind of shares (and other securities or property) issuable upon exercise of this Warrant, which certificate shall specify the Exercise Price and number, class and kind of shares (and other securities or property) under this Warrant after giving effect to such adjustment and shall set forth a brief statement of the facts requiring such adjustment and setting forth the computation by which such adjustment was made.

7. NO STOCKHOLDER RIGHTS. Except to the extent specified in Section 6, this Warrant in and of itself shall not entitle the Holder to any voting rights or other rights as a stockholder of the Company. Upon the exercise of this Warrant in accordance with Section 2, the Exercise Shares so purchased shall be and be deemed to be issued to such Holder as the record owner of such shares as of the close of business on the date of such exercise.

8. TRANSFER OF WARRANT. Subject to applicable laws, the restriction on transfer set forth on the first page of this Warrant and the provisions of Article VI of the Warrant Purchase Agreement, this Warrant and all rights hereunder are transferable by the Holder, in person or by duly authorized attorney, upon delivery of this Warrant, the Assignment Form attached hereto, to any transferee designated by Holder. The transferee will sign and deliver to the Company an investment letter in a form that is commercially reasonable, customary for use in similar transactions and reasonably satisfactory to the Company. Upon such delivery and, if required, such payment, the Company shall execute and deliver a new Warrant or Warrants in the name of the assignee or assignees and in the denomination or denominations specified in such instrument of assignment, and shall issue to the assignor a new Warrant evidencing the portion of this Warrant not so assigned, and this Warrant shall promptly be cancelled. A Warrant, if properly assigned, may be exercised by a new holder for the purchase of Exercise Shares without having a new Warrant issued.

9. LOST, STOLEN, MUTILATED OR DESTROYED WARRANT. If this Warrant is lost, stolen, mutilated or destroyed, the Company may, on such terms as to indemnity or otherwise as it may reasonably impose (which shall, in the case of a mutilated Warrant, include the surrender

thereof), issue a new Warrant of like denomination and tenor as the Warrant so lost, stolen, mutilated or destroyed. Any such new Warrant shall constitute an original contractual obligation of the Company, whether or not the allegedly lost, stolen, mutilated or destroyed Warrant shall be at any time enforceable by anyone.

10. MODIFICATIONS AND WAIVER. This Warrant and any provision hereof may be changed, waived, discharged or terminated only by an instrument in writing signed by the Company and the Holder.

11. NOTICES, ETC. All notices required or permitted hereunder shall be in writing and shall be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by confirmed facsimile if sent during normal business hours of the recipient, if not, then on the next business day, (c) five days after having been sent by registered or certified mail, return receipt requested, postage prepaid, or (d) one business day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. All communications shall be sent to the Company at the address listed on the signature page and to the Holder at the addresses on the Company records, or at such other address as the Company or Holder may designate by ten days' advance written notice to the other party hereto.

12. ACCEPTANCE. Receipt of this Warrant by the Holder shall constitute acceptance of and agreement to all of the terms and conditions contained herein.

13. GOVERNING LAW. This Warrant and all rights, obligations and liabilities hereunder shall be governed by the laws of the State of New York without regard to the principles of conflict of laws. The Company and, by accepting this Warrant, the Holder, each irrevocably submits and consents to the exclusive jurisdiction of the courts of the State of New York located in New York County and the United States District Court for the Southern District of New York for the purpose of any suit, action, proceeding or judgment relating to or arising out of this Warrant and the transactions contemplated hereby. The Company and, by accepting this Warrant, the Holder, each irrevocably waives any objection to the laying of venue of any such suit, action or proceeding brought in such courts and irrevocably waives any claim that any such suit, action or proceeding brought in any such court has been brought in an inconvenient forum. **EACH OF THE COMPANY AND, BY ITS ACCEPTANCE HEREOF, THE HOLDER HEREBY WAIVES ANY RIGHT TO REQUEST A TRIAL BY JURY IN ANY LITIGATION WITH RESPECT TO THIS WARRANT AND REPRESENTS THAT COUNSEL HAS BEEN CONSULTED SPECIFICALLY AS TO THIS WAIVER.**

14. DESCRIPTIVE HEADINGS. The descriptive headings of the several paragraphs of this Warrant are inserted for convenience only and do not constitute a part of this Warrant. The language in this Warrant shall be construed as to its fair meaning without regard to which party drafted this Warrant.

15. SUCCESSORS AND ASSIGNS. Subject to applicable securities laws, this Warrant and the rights and obligations evidenced hereby shall inure to the benefit of and be binding upon the successors of the Company and the successors and permitted assigns of the Holder.

16. SEVERABILITY. The invalidity or unenforceability of any provision of this Warrant in any jurisdiction shall not affect the validity or enforceability of such provision in any other jurisdiction, or affect any other provision of this Warrant, which shall remain in full force and effect.

17. REGISTRATION RIGHTS. The holder of this Warrant and of the Exercise Shares shall be entitled to the registration rights and other applicable rights as and to the extent set forth in the Warrant Purchase Agreement and the Registration Rights Agreement.

18. ENTIRE AGREEMENT. This Warrant constitutes the entire agreement between the parties pertaining to the subject matter contained in it and supersedes all prior and contemporaneous agreements, representations, and undertakings of the parties, whether oral or written, with respect to such subject matter.

[Signature Page Follows]

IN WITNESS WHEREOF, the Company has caused this Warrant to be executed by its duly authorized officer as of April 7, 2006.

ISIS PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____

Address: 1896 Rutherford Road
Carlsbad, CA 92008-7208
Attn: B. Lynne Parshall
Facsimile: (760) 603-4650

W/copy to: General Counsel
Facsimile: (760) 268-4922

NOTICE OF EXERCISE

NOTICE OF EXERCISE

TO: ISIS PHARMACEUTICALS INC.

(1) The undersigned hereby elects to (check one box only):

o purchase shares of the Common Stock of Isis Pharmaceuticals, Inc. (the ***"Company"***) pursuant to the terms of the attached Warrant, and tenders herewith payment of the exercise price in full for such shares.

o purchase the number of shares of Common Stock of the Company by cashless exercise pursuant to the terms of the Warrant as shall be issuable upon cashless exercise of the portion of the Warrant relating to shares.

(2) Please issue a certificate or certificates representing said shares of Common Stock in the name of the undersigned or in such other name as is specified below:

_____
(Name)

_____
_____
(Address)

(3) If the Warrant is not being exercised in full, please issue a certificate representing a new Warrant evidencing the right of the Holder to purchase the balance of the Exercise Shares purchasable under the Warrant, such certificate to be registered in the name of the undersigned or in such other name as is specified below:

_____
(Name)

(Address)

(4) The undersigned represents that (i) the aforesaid shares of Common Stock are being acquired for the account of the undersigned not with a view to, or for resale in connection with, the distribution thereof in violation of the Securities Act of 1933, as amended (the ***"Securities Act"***) and that the undersigned has no present intention of distributing or reselling such shares in violation of the Securities Act; (ii) the undersigned is aware of the Company's business affairs and financial condition and has acquired sufficient information about the Company to reach an informed and knowledgeable decision regarding its investment in the Company; (iii) the undersigned is experienced in making investments of this type and has such knowledge and background in financial and business matters that the undersigned is capable of evaluating the merits and risks of this investment and protecting the undersigned's own interests; (iv) the undersigned understands that the shares of Common Stock issuable upon exercise of this Warrant must be held indefinitely unless subsequently registered under the Securities Act or an exemption from such registration is

available, and (v) the undersigned agrees not to make any disposition of all or any part of the aforesaid shares of Common Stock unless and until there is then in effect a registration statement under the Securities Act covering such proposed disposition and such disposition is made in accordance with said registration statement, or the undersigned has provided the Company with an opinion of counsel satisfactory to the Company, stating that such registration is not required.

(Date) (Signature)

(Print name)

ASSIGNMENT FORM

(To assign the foregoing Warrant, subject to compliance with section 4.3 hereof, execute this form and supply required information. Do not use this form to purchase shares.)

FOR VALUE RECEIVED, the foregoing Warrant and all rights evidenced thereby are hereby assigned to

Name: (Please Print)

Address: (Please Print)

Dated: , 20

Holder's Signature:

Holder's Address:

NOTE: The signature to this Assignment Form must correspond with the name as it appears on the face of the Warrant, without alteration or enlargement or any change whatever. Officers of corporations and those acting in a fiduciary or other representative capacity should file proper evidence of authority to assign the foregoing Warrant.

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

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

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 10, 2006

/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 consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

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

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 10, 2006

/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 March 31, 2006, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 10, 2006

/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.