

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K/A

(Amendment No.1)

CURRENT REPORT

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

Date of report (Date of earliest event reported): **September 28, 2007**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(IRS Employer Identification No.)

1896 Rutherford Road

Carlsbad, CA 92008

(Address of Principal Executive Offices and Zip Code)

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Explanatory Note

Isis Pharmaceuticals, Inc. filed a Current Report on Form 8-K, dated September 28, 2007, announcing that it had completed its acquisition of Symphony GenIsis, Inc. on September 27, 2007. Until the acquisition of Symphony GenIsis, Isis identified Symphony GenIsis as a variable interest entity for which Isis was the primary beneficiary. Isis' historical consolidated financial statements leading up to the acquisition date include the financial condition and results of operations of Symphony GenIsis. Effective on September 27, 2007, Symphony GenIsis became a wholly owned subsidiary of Isis. The purpose of this amendment is to file various financial statements relating to the business of the acquired company.

Item 9.01 Financial Statements and Exhibits

(a) Financial Statements of Business Acquired

Audited annual financial statements of Symphony GenIsis, Inc.

- (i) Report of Independent Auditors
- (ii) Balance Sheet as of December 31, 2006
- (iii) Statement of Operations for the period from March 8, 2006 (inception) to December 31, 2006
- (iv) Statement of Stockholders' Equity for the period from March 8, 2006 (inception) to December 31, 2006
- (v) Statement of Cash Flows for the period from March 8, 2006 (inception) to December 31, 2006
- (vi) Notes to Financial Statements

Unaudited interim financial statements of Symphony GenIsis, Inc.

- (i) Balance Sheet as of June 30, 2007

- (ii) Statements of Operations for the six months ended June 30, 2007 and 2006
 - (iii) Statements of Cash Flows for the six months ended June 30, 2007 and 2006
 - (iv) Notes to Financial Statements
- (b) Pro Forma Financial Information (Unaudited)
- (i) Introduction to Pro Forma Condensed Consolidated Financial Information
 - (ii) Pro Forma Consolidated Statement of Operations for the year ended December 31, 2006 and accompanying notes
 - (iii) Pro Forma Condensed Consolidated Statement of Operations for the nine months ended September 30, 2007 and accompanying notes
- (d) The exhibits required by this item are listed on the Exhibit Index hereto.

Report of Independent Auditors

Board of Directors and Stockholders
Symphony GenIsis, Inc.

We have audited the accompanying balance sheet of Symphony GenIsis, Inc. (a wholly owned subsidiary of Symphony GenIsis Holdings LLC) (a Development Stage Company) as of December 31, 2006, and the related statements of operations, stockholders' equity, and cash flows for the period from March 8, 2006 (inception) through December 31, 2006. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Symphony GenIsis, Inc. at December 31, 2006, and the results of its operations and its cash flows for the period from March 8, 2006 (inception) through December 31, 2006, in conformity with accounting principles generally accepted in the United States.

/s/ Ernst & Young LLP

San Diego, California
March 2, 2007

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Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Balance Sheet

December 31, 2006

Assets	
Current assets:	
Cash and cash equivalents	\$ 54,867,700
Other current assets	1,223,316
Total current assets	56,091,016
Total assets	\$ 56,091,016
Liabilities and stockholders' equity	
Current liabilities:	
Accounts payable	\$ 447,407
Accrued expenses	1,593,386
Total current liabilities	2,040,793
Total liabilities	2,040,793
Commitments and contingencies	

Stockholders' equity:	
Common stock, \$0.01 par value, 100,000 shares authorized, 50,000 shares issued and outstanding at December 31, 2006	500
Additional paid-in capital	74,999,500
Deficit accumulated during the development stage	(20,949,777)
Total stockholders' equity	54,050,223
Total liabilities and stockholders' equity	\$ 56,091,016

See accompanying notes.

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Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Statement of Operations

Period from March 8, 2006 (inception) to December 31, 2006

Revenues	\$ —
Expenses:	
Research and development	22,277,982
General and administrative	742,628
Total operating expenses	23,020,610
Operating loss	(23,020,610)
Other income – interest	2,070,833
Net loss	\$ (20,949,777)

See accompanying notes.

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Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Statement of Stockholders' Equity

Period from March 8, 2006 (inception) to December 31, 2006

	Common Stock		Additional Paid-in Capital	Deficit Accumulated during the Development Stage	Total
	Shares	Amount			
Balance at March 8, 2006	—	\$ —	\$ —	\$ —	\$ —
Issuance of common stock in April 2006	50,000	500	74,999,500	—	75,000,000
Net loss and comprehensive loss	—	—	—	(20,949,777)	(20,949,777)
Balance at December 31, 2006	50,000	\$ 500	\$ 74,999,500	\$ (20,949,777)	\$ 54,050,223

See accompanying notes.

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Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Statement of Cash Flows

Period from March 8, 2006 (inception) to December 31, 2006

Operating activities	
Net loss	\$ (20,949,777)
Adjustment to reconcile net loss to net cash used by operating activities:	

Change in operating assets and liabilities:	
Other current assets	(1,223,316)
Accounts payable	447,407
Accrued expenses	1,593,386
Net cash used by operating activities	(20,132,300)
Financing activities	
Issuance of common stock	75,000,000
Net cash provided by financing activities	75,000,000
Net increase in cash and cash equivalents	54,867,700
Cash and cash equivalents at beginning of period	—
Cash and cash equivalents at end of period	\$ 54,867,700

See accompanying notes.

Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Notes to Financial Statements

December 31, 2006

1. Organization and Significant Accounting Policies

Organization and Basis of Presentation

Symphony GenIsis, Inc. (the “Company”) was organized as a Delaware Corporation on March 8, 2006 (“inception”). The Company is a wholly owned subsidiary of Symphony GenIsis Holdings LLC (“Holdings”).

The Company is a biopharmaceutical company formed to collaborate with Isis Pharmaceuticals, Inc. (“Isis”) on the development of three clinical stage programs, one of which utilizes the compound Isis 301012 in Phase II studies for the treatment of high cholesterol, and two other programs study the effects of the compounds GCGR and GCCR for the treatment of diabetes in Phase I trials.

The Company began operations on April 7, 2006 and is currently in the development stage, consisting primarily of research, development and clinical activities. The Company expects to incur losses over the next several years as it continues to develop its technologies. There can be no assurance that the Company’s efforts with regard to these matters will be successful.

Symphony GenIsis Investors LLC and three other minor investors have contributed to Holdings initial funds in an aggregate amount of approximately \$75,000,000.

RRD International, LLC (“RRD”) manages the Company (see Note 2 (c) below), and Isis is primarily responsible for the Company’s Development Plan and Development Budget (see Note 2 (b) below).

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions regarding certain types of assets, liabilities, revenues and expenses. Such estimates primarily relate to unsettled transactions and events as of the date of the financial statements. Accordingly, upon settlement, actual results may differ from estimated amounts.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with an original maturity of three months or less to be cash equivalents. Investments are made solely in money market funds which are subject to minimal credit and market risk. All marketable securities are classified as available-for-sale and are carried at fair value. Unrealized gains or losses, if any, are recorded within accumulated other comprehensive income (loss). As of December 31, 2006, there were no unrealized gains or losses on these investments.

Comprehensive Loss

To date, there are no items of other comprehensive loss other than net loss.

Research and Development

Costs incurred for research and development are expensed as incurred.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash and cash equivalents. The Company maintains cash equivalents in bank accounts that, at times, may exceed federally insured limits. The Company has not experienced any losses on such accounts. The Company has invested its excess cash in mutual funds with maturities of 90 days or less.

Income Taxes

Income taxes have been recorded using the liability method. Accordingly, any income tax provision includes federal and state income taxes both currently payable and changes in deferred taxes due to differences between financial reporting and tax bases of assets and liabilities. Deferred tax liabilities are recorded using the anticipated tax rates that will be in effect when the differences are expected to reverse.

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Risks and Uncertainties

The Company is subject to various risks common to companies within the pharmaceutical and biotechnology industries. These include, but are not limited to, development by competitors of new technological innovations; dependence on key personnel and outside relationships; risks inherent in the research and development of pharmaceutical and biotechnology products; protection of proprietary technology; estimation by the Company of the size and characteristics of the market for the Company's products; acceptance of the Company's products by the country's regulatory agencies in which the Company may choose to sell its products, as well as acceptance by customers; health care cost containment initiatives; and product liability and compliance with government regulations and agencies, including the U.S. Food and Drug Administration ("FDA"). None of these risks resulted in an adjustment to the financial statements as of December 31, 2006.

Recently Issued Accounting Standards

In July 2006, the Financial Accounting Standards Board ("FASB") issued FASB Interpretation ("FIN") No. 48, *Accounting for Uncertainty in Income Taxes – an interpretation of FASB Statement No. 109*, which clarifies the accounting for uncertainty in tax positions. FIN No. 48 requires that the Company recognize the impact of a tax position in its financial statements if that position is more likely than not of being sustained on audit, based on the technical merits of the position. The provisions of FIN No. 48 are effective as of the beginning of the Company's 2007 fiscal year, with the cumulative effect of the change in accounting principle recorded as an adjustment to opening retained earnings. The Company does not expect the adoption of FIN No. 48 to have a material impact on its results of operations and financial position, and the Company is continuing to evaluate the impact, if any, the adoption of FIN No. 48 will have on its disclosure requirements.

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2. Related Party Transactions

The Company has entered into several agreements with related parties in the ordinary course of business to license intellectual property, to procure administrative and clinical development support services, to conduct clinical trials, to enter into a purchase option and to obtain funding.

(a) Technology License Agreement and Novated and Restated Technology License Agreement

On April 7, 2006, Isis and Holdings entered into a Technology License Agreement, which was subsequently superseded by a Novated and Restated Technology License Agreement (the "Novated TLA") among the Company, Isis and Holdings. The Novated TLA granted the Company the exclusive right to use technology, know-how, patents and other intellectual property rights related to the design, development, manufacture and use of the relevant compounds and products which contain these compounds, with an exclusive sublicense back to Isis for the limited purposes of developing, making, using and importing said compounds.

This agreement shall remain in force until terminated as provided for in the agreement. Per the agreement, either party may terminate if the other is in breach of this agreement.

(b) Research and Development Agreement and Amended and Restated Research and Development Agreement

On April 7, 2006, Isis and Holdings entered into a Research and Development Agreement, which was subsequently superseded by an Amended and Restated Research and Development Agreement among the Company, Isis and Holdings, whereby all the initial rights and obligations of Holdings under the Research and Development Agreement were assigned and transferred to, and assumed by the Company. Under the agreement, Isis is primarily responsible for implementation of the Company's Development Plan in accordance with the Development Budget, subject to oversight of a joint development committee. Isis also acts as the Company's FDA sponsor for each of the research programs.

For 2006, the Company recognized \$22,277,982 in total expenses under this agreement. At December 31, 2006, amounts totaling \$158,613 and \$1,548,386 payable to Isis were included in accounts payable and accrued expenses, respectively, in the balance sheet.

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(c) RRD Services Agreement

On April 7, 2006, the Company entered into a Services Agreement with RRD, a related party (the "RRD Agreement"). Under this agreement, RRD provides overall management and supervision of the Company, including hiring and discharging vendors, compensating Isis for its fees and expenses

under the Amended and Restated Research and Development Agreement, providing employees to serve as officers of the Company, maintaining the Company's financial records and performing all day-to-day administrative functions of the Company. RRD is also required to provide services to the Company in support of the implementation of its Development Plan, including, but not limited to, the appointment of certain RRD executive staff members to serve on the joint development committee.

Under the RRD Agreement, the Company must pay RRD a service fee equivalent to \$54,000 per month in 2006 and \$51,750 per month beginning January 1, 2007. The Company must also reimburse RRD for all reasonable out-of-pocket expenses, including travel. Additionally, RRD arranges for the provision of legal, audit, income tax preparation, and other professional services to the Company by independent contractors, the billings for which the Company pays directly.

The RRD Agreement shall be in full force and effect until the earlier of (i) the fourth anniversary of the closing date (April 7, 2010), (ii) the expiration of the term (the period starting on the closing date and ending upon the termination or expiration of the purchase option period), or (iii) the purchase option closing date (Note 2(d)). The term may be renewed upon written agreement between the Company's Board of Directors and RRD.

During 2006, the Company incurred \$540,000 in total fees under the RRD Agreement. At December 31, 2006, amounts totaling \$265,957 payable to RRD were included in accounts payable in the balance sheet.

(d) Purchase Option

On April 7, 2006, the Company entered into a purchase option agreement (the "Purchase Option Agreement") with Isis and Holdings, pursuant to which, among other things, Holdings granted Isis an option to purchase all of the equity securities of the Company on terms specified in the Purchase Option Agreement. This option is

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exercisable by Isis during the period commencing on and including April 7, 2007 and ending on and including the earlier of (i) April 7, 2010; (ii) the 90th calendar day immediately following the first date on which an internally prepared, unaudited balance sheet of the Company (prepared in accordance with GAAP) is delivered to Isis stating that the aggregate amount of cash and cash equivalents held by the Company is less than \$5,000,000; and (iii) the delivery by the development committee to Isis of an Isis Funding Notice stating that the Company's remaining balance of cash and cash equivalents will not be sufficient to complete the development of the Programs. With certain limitations, Isis may elect to extend the purchase option exercise period, but not beyond April 7, 2010, by providing additional funding ("Extension Funding") to the Company to cover any shortfall pursuant to (ii) or (iii) above (see Note 2(e) below).

The purchase price is \$112,500,000 if the purchase option is exercised at any time between April 7, 2007 and June 30, 2007, and increases to a maximum of \$195,000,000 on or after January 1, 2010. At Isis' sole discretion, a portion of the option price may be paid in shares of its common stock, but only to the extent that said stock component does not exceed the lower of (i) 33% of the purchase option price and (ii) 10% of the then outstanding shares of Isis common stock.

(e) Stock Subscription and Research Cost Sharing and Extension Agreement

Holdings purchased 50,000 shares of the Company's common stock on April 7, 2006 for \$75,000,000. In addition, the Company has entered into a Research Cost Sharing and Extension Agreement with Holdings and Isis, whereby Isis, with certain limitations, may elect to provide supplemental funding for one or more of the Programs in order to increase the Company's total available funding to an amount not to exceed the original development budget of \$83,241,426. Thus, Isis' supplemental funding may not exceed \$8,241,426, and may not expand the development plan beyond its original scope nor extend Isis' Purchase Option exercise period beyond April 7, 2010.

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3. Income Taxes

As of December 31, 2006, the Company had deferred tax assets of approximately \$9.2 million before a valuation allowance. A valuation allowance of \$9.2 million has been recognized to offset the deferred tax assets at December 31, 2006 as realization of the deferred tax assets is uncertain. Deferred tax assets relate primarily to net operating loss carryforwards and R&D credits.

As of December 31, 2006, the Company has federal and state net operating loss carryforwards of approximately \$20.9 million, and \$20.9 million, respectively. The federal and state net operating loss carryforwards will expire in 2026. The company also has federal research credit of approximately \$0.9 million which will expire in 2026 unless utilized.

Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of the Company's net operating loss and credit carryforwards may be limited due to cumulative changes in ownership of more than 50%.

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Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Balance Sheet
June 30, 2007

Assets	
Current assets:	
Cash and cash equivalents	\$ 42,987,127
Other current assets	1,519,214
Total current assets	<u>44,506,341</u>
Total assets	<u>\$ 44,506,341</u>
Liabilities and stockholders' equity	
Current liabilities:	
Accounts payable	\$ 2,956,823
Accrued expenses	634,549
Total current liabilities	<u>3,591,372</u>
Total liabilities	<u>3,591,372</u>
Commitments and contingencies	—
Stockholders' equity:	
Common stock, \$0.01 par value, 100,000 shares authorized, 50,000 shares issued and outstanding at June 30, 2007	500
Additional paid-in capital	74,999,500
Deficit accumulated during the development stage	<u>(34,085,031)</u>
Total stockholders' equity	<u>40,914,969</u>
Total liabilities and stockholders' equity	<u>\$ 44,506,341</u>

See accompanying notes.

Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Statement of Operations
(Unaudited)

	Six Months Ended June 30,	
	2007	2006
Revenues	\$ —	\$ —
Expenses:		
Research and development	14,015,630	13,364,152
General and administrative	393,411	243,751
Total operating expenses	<u>14,409,041</u>	<u>13,607,903</u>
Operating loss	(14,409,041)	(13,607,903)
Other income – interest	1,273,787	558,268
Net loss	<u>\$ (13,135,254)</u>	<u>\$ (13,049,635)</u>

See accompanying notes.

Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Statement of Cash Flows
(Unaudited)

	Six Months Ended June 30,	
	2007	2006
Net cash used by operating activities	\$ (11,880,573)	\$ (10,562,383)
Financing activities		
Issuance of common stock	—	75,000,000
Net cash provided by financing activities	<u>—</u>	<u>75,000,000</u>
Net (decrease) increase in cash and cash equivalents	(11,880,573)	64,437,617

Cash and cash equivalents at beginning of period	54,867,700	—
Cash and cash equivalents at end of period	<u>\$ 42,987,127</u>	<u>\$ 64,437,617</u>

See accompanying notes.

Symphony GenIsis, Inc.
(a Wholly Owned Subsidiary of Symphony GenIsis Holdings LLC)
(a Development Stage Company)

Notes to Financial Statements
June 30, 2007
(Unaudited)

1. Organization and Significant Accounting Policies

Organization and Basis of Presentation

Symphony GenIsis, Inc. (the “Company”) was organized as a Delaware Corporation on March 8, 2006 (“inception”). As of June 30, 2007, the Company is a wholly owned subsidiary of Symphony GenIsis Holdings LLC (“Holdings”).

The Company is a biopharmaceutical company formed to collaborate with Isis Pharmaceuticals, Inc. (“Isis”) on the development of three clinical stage programs, one of which utilizes the compound ISIS 301012 in Phase II studies for the treatment of high cholesterol, and two other programs study the effects of the compounds GCGR and GCCR for the treatment of diabetes in Phase I trials.

The Company began operations on April 7, 2006 and is currently in the development stage, consisting primarily of research, development and clinical activities. The Company expects to incur losses over the next several years as it continues to develop its technologies. There can be no assurance that the Company’s efforts with regard to these matters will be successful.

Symphony GenIsis Investors LLC and three other minor investors have contributed to Holdings initial funds in an aggregate amount of approximately \$75,000,000.

RRD International, LLC (“RRD”) manages the Company (see Note 2 (c) below), and Isis is primarily responsible for the Company’s Development Plan and Development Budget (see Note 2 (b) below).

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions regarding certain types of assets, liabilities, revenues and expenses. Such estimates primarily relate to unsettled transactions and events as of the date of the financial statements. Accordingly, upon settlement, actual results may differ from estimated amounts.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with an original maturity of three months or less to be cash equivalents. Investments are made solely in money market funds which are subject to minimal credit and market risk. All marketable securities are classified as available-for-sale and are carried at fair value. Unrealized gains or losses, if any, are recorded within accumulated other comprehensive income (loss). For the six months ended June 30, 2007 and 2006, there were no unrealized gains or losses on these investments.

Comprehensive Loss

To date, there are no items of other comprehensive loss other than net loss.

Research and Development

Costs incurred for research and development are expensed as incurred.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash and cash equivalents. The Company maintains cash equivalents in bank accounts that, at times, may exceed federally insured limits. The Company has not experienced any losses on such accounts. The Company has invested its excess cash in mutual funds with maturities of 90 days or less.

Income Taxes

Income taxes have been recorded using the liability method. Accordingly, any income tax provision includes federal and state income taxes both currently payable and changes in deferred taxes due to differences between financial reporting and tax bases of assets and liabilities. Deferred tax liabilities are recorded using the anticipated tax rates that will be in effect when the differences are expected to reverse.

Risks and Uncertainties

The Company is subject to various risks common to companies within the pharmaceutical and biotechnology industries. These include, but are not limited to, development by competitors of new technological innovations; dependence on key personnel and outside relationships; risks inherent in the research and development of pharmaceutical and biotechnology products; protection of proprietary technology; estimation by the Company of the size and characteristics of the market for the Company's products; acceptance of the Company's products by the country's regulatory agencies in which the Company may choose to sell its products, as well as acceptance by customers; health care cost containment initiatives; and product liability and compliance with government regulations and agencies, including the U.S. Food and Drug Administration ("FDA"). None of these risks resulted in an adjustment to the financial statements as of June 30, 2007 and 2006.

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2. Related Party Transactions

The Company has entered into several agreements with related parties in the ordinary course of business to license intellectual property, to procure administrative and clinical development support services, to conduct clinical trials, to enter into a purchase option and to obtain funding.

(a) Technology License Agreement and Novated and Restated Technology License Agreement

On April 7, 2006, Isis and Holdings entered into a Technology License Agreement, which was subsequently superseded by a Novated and Restated Technology License Agreement (the "Novated TLA") among the Company, Isis and Holdings. The Novated TLA granted the Company the exclusive right to use technology, know-how, patents and other intellectual property rights related to the design, development, manufacture and use of the relevant compounds and products which contain these compounds, with an exclusive sublicense back to Isis for the limited purposes of developing, making, using and importing said compounds.

This agreement shall remain in force until terminated as provided for in the agreement. Per the agreement, either party may terminate if the other is in breach of this agreement.

(b) Research and Development Agreement and Amended and Restated Research and Development Agreement

On April 7, 2006, Isis and Holdings entered into a Research and Development Agreement, which was subsequently superseded by an Amended and Restated Research and Development Agreement among the Company, Isis and Holdings, whereby all the initial rights and obligations of Holdings under the Research and Development Agreement were assigned and transferred to, and assumed by the Company. Under the agreement, Isis is primarily responsible for implementation of the Company's Development Plan in accordance with the Development Budget, subject to oversight of a joint development committee. Isis also acts as the Company's FDA sponsor for each of the research programs.

For the six months ended June 30, 2007 and 2006, the Company recognized \$14,015,630 and \$13,364,152, respectively, in total expenses under this agreement. At June 30, 2007, amounts totaling \$2,914,032 and \$634,549 payable to Isis were included in accounts payable and accrued expenses, respectively, in the balance sheet.

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(c) RRD Services Agreement

On April 7, 2006, the Company entered into a Services Agreement with RRD, a related party (the "RRD Agreement"). Under this agreement, RRD provides overall management and supervision of the Company, including hiring and discharging vendors, compensating Isis for its fees and expenses under the Amended and Restated Research and Development Agreement, providing employees to serve as officers of the Company, maintaining the Company's financial records and performing all day-to-day administrative functions of the Company. RRD is also required to provide services to the Company in support of the implementation of its Development Plan, including, but not limited to, the appointment of certain RRD executive staff members to serve on the joint development committee.

Under the RRD Agreement, the Company must pay RRD a service fee equivalent to \$54,000 per month in 2006 and \$51,750 per month beginning January 1, 2007. The Company must also reimburse RRD for all reasonable out-of-pocket expenses, including travel. Additionally, RRD arranges for the provision of legal, audit, income tax preparation, and other professional services to the Company by independent contractors, the billings for which the Company pays directly.

The RRD Agreement shall be in full force and effect until the earlier of (i) the fourth anniversary of the closing date (April 7, 2010), (ii) the expiration of the term (the period starting on the closing date and ending upon the termination or expiration of the purchase option period), or (iii) the purchase option closing date (Note 2(d)). The term may be renewed upon written agreement between the Company's Board of Directors and RRD.

During the first six months ended June 30, 2007 and 2006, the Company incurred \$310,500 and \$216,000, respectively, in total fees under the RRD Agreement. At June 30, 2007, amounts totaling \$42,791 payable to RRD were included in accounts payable in the balance sheet.

(d) Purchase Option

On April 7, 2006, the Company entered into a purchase option agreement (the "Purchase Option Agreement") with Isis and Holdings, pursuant to which, among other things, Holdings granted Isis an option to purchase all of the equity

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securities of the Company on terms specified in the Purchase Option Agreement. This option is exercisable by Isis during the period commencing on and including April 7, 2007 and ending on and including the earlier of (i) April 7, 2010; (ii) the 90th calendar day immediately following the first date on which an internally prepared, unaudited balance sheet of the Company (prepared in accordance with GAAP) is delivered to Isis stating that the aggregate amount of cash and cash equivalents held by the Company is less than \$5,000,000; and (iii) the delivery by the development committee to Isis of an Isis Funding Notice stating that the Company's remaining balance of cash and cash equivalents will not be sufficient to complete the development of the Programs. With certain limitations, Isis may elect to extend the purchase option exercise period, but not beyond April 7, 2010, by providing additional funding ("Extension Funding") to the Company to cover any shortfall pursuant to (ii) or (iii) above (see Note 2(e) below).

The purchase price is \$112,500,000 if the purchase option is exercised at any time between April 7, 2007 and June 30, 2007, and increases to a maximum of \$195,000,000 on or after January 1, 2010. At Isis' sole discretion, a portion of the option price may be paid in shares of its common stock, but only to the extent that said stock component does not exceed the lower of (i) 33% of the purchase option price and (ii) 10% of the then outstanding shares of Isis common stock.

(e) Stock Subscription and Research Cost Sharing and Extension Agreement

Holdings purchased 50,000 shares of the Company's common stock on April 7, 2006 for \$75,000,000. In addition, the Company has entered into a Research Cost Sharing and Extension Agreement with Holdings and Isis, whereby Isis, with certain limitations, may elect to provide supplemental funding for one or more of the Programs in order to increase the Company's total available funding to an amount not to exceed the original development budget of \$83,241,426. Thus, Isis' supplemental funding may not exceed \$8,241,426, and may not expand the development plan beyond its original scope nor extend Isis' Purchase Option exercise period beyond April 7, 2010.

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3. Income Taxes

In July 2006, the FASB issued FIN 48, *Accounting for Uncertainty in Income Taxes*, which addressed the determination of how tax benefits claimed or expected to be claimed on a tax return should be recorded in the financial statements. Under FIN 48, the Company must recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by the taxing authorities, based on the technical merits of the position. The tax benefits recognized in the financial statements from such a position are measured based on the largest benefit that has a greater than fifty percent likelihood of being realized upon ultimate resolution. The accounting provisions of FIN 48 became effective for the Company beginning January 1, 2007.

As of December 31, 2006, the Company had deferred tax assets of approximately \$9.2 million before a valuation allowance. A valuation allowance of \$9.2 million has been recognized to offset the deferred tax assets at December 31, 2006 as realization of the deferred tax assets is uncertain. Deferred tax assets relate primarily to net operating loss carryforwards and R&D credits.

As of December 31, 2006, the Company has federal and state net operating loss carryforwards of approximately \$20.9 million, and \$20.9 million, respectively. The federal and state net operating loss carryforwards will expire in 2026. The company also has federal research credit of approximately \$0.9 million which will expire in 2026 unless utilized. As a result of the adoption of FIN 48, the Company has not recorded any change to retained earnings at January 1, 2007 and it had no unrecognized tax benefits that, if recognized, would favorably affect the Company's effective income tax rate in future periods. At June 30, 2007, the Company had no unrecognized tax benefits. The Company's continuing practice is to recognize interest and/or penalties related to income tax matters in income tax expense. The Company had no accrued interest or penalties at January 1, 2007 and June 30, 2007.

Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of the Company's net operating loss and credit carryforwards may be limited due to cumulative changes in ownership of more than 50%. The Company has not experienced any cumulative changes in ownership of more than 50% as of June 30, 2007.

4. Subsequent Event

On September 27, 2007, Isis exercised its purchase option and acquired all of the equity of the Company for an aggregate purchase price of \$120 million.

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ISIS PHARMACEUTICALS, INC. INTRODUCTION TO PRO FORMA CONSOLIDATED FINANCIAL INFORMATION

(Unaudited)

On September 27, 2007, Isis purchased all of the equity of Symphony GenIsis for \$120 million, \$80.4 million in cash and the remaining amount in approximately 3.4 million shares of Isis' common stock. Prior to the acquisition of Symphony GenIsis, Isis identified Symphony GenIsis as a variable interest entity for which Isis was the primary beneficiary. Isis' historical consolidated financial statements leading up to the acquisition date include the financial condition and results of operations of Symphony GenIsis. Effective on September 27, 2007, Symphony GenIsis became a wholly owned subsidiary of Isis.

The accompanying unaudited pro forma consolidated statements of operations for the year ended December 31, 2006 and the nine months ended September 30, 2007, give effect to the acquisition as if it had been consummated at the beginning of the periods presented. A pro forma consolidated balance sheet is not provided since the Symphony GenIsis acquisition was reflected in Isis' condensed consolidated balance sheet as of September 30, 2007, which was included in Isis' Form 10-Q filing on November 9, 2007.

The historical financial information on which the pro forma statements are based is included in Isis' Annual Report on Form 10-K for the fiscal year ended December 31, 2006, which was filed on March 16, 2007, Isis' Quarterly Report on Form 10-Q for the quarter ended September 30, 2007, which was filed on November 9, 2007, and Symphony GenIsis' financial statements included in this current report on Form 8-K/A. The pro forma consolidated financial statements and the notes thereto should be read in conjunction with these historical consolidated financial statements.

The unaudited pro forma consolidated financial statements are presented for illustrative purposes only and are subject to a number of assumptions which may not be indicative of the results of operations that would have occurred had the acquisition been completed at the dates indicated or what the results will be for any future periods.

ISIS PHARMACEUTICALS, INC.
PRO FORMA CONSOLIDATED STATEMENT OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Historical Isis Pharmaceuticals, Inc. Year Ended December 31, 2006	Historical Symphony GenIsis, Inc. Period from March 8, 2006 (inception) to December 31, 2006	Intercompany Eliminations (Note 1)	Pro Forma Adjustments	Notes	Pro Forma Year Ended December 31, 2006
Revenue	\$ 24,532	\$ —	\$ —	\$ —		\$ 24,532
Expenses:						
Research and development	80,567	22,278	(22,278)	—		80,567
Selling, general and administrative	12,619	743	(743)	—		12,619
Restructuring activities	(536)	—	—	—		(536)
Total operating expenses	92,650	23,021	(23,021)	—		92,650
Loss from operations	(68,118)	(23,021)	23,021	—		(68,118)
Other income (expense):						
Investment income	5,960	2,071	(2,071)	(3,337)	2	2,623
Interest expense	(9,029)	—	—	—		(9,029)
Gain on investments, net	2,263	—	—	—		2,263
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(68,924)	(20,950)	20,950	(3,337)		(72,261)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	23,021	—	—	(23,021)	3	—
Net loss applicable to common stock	\$ (45,903)	\$ (20,950)	\$ 20,950	\$ (26,358)		\$ (72,261)
Basic and diluted net loss per share	\$ (0.62)					\$ (0.94)
Shares used in computing basic and diluted net loss per share	74,308			2,762	4	77,070

Note 1: Since Isis' historical consolidated statements of operations already included the results of operations of Symphony GenIsis, Symphony GenIsis' results of operations are eliminated.

Note 2: This adjustment is recorded to reflect the reduction to interest income assuming that the \$80.4 million cash paid for the acquisition of Symphony GenIsis was made at the beginning of the period presented.

Note 3: This adjustment is recorded to remove the loss attributed to noncontrolling interest in Symphony GenIsis that was recognized on the historical statement of operations as a result of the consolidation of Symphony GenIsis as a variable interest entity.

Note 4: This adjustment is recorded to reflect the additional weighted average shares assuming the 3.4 million shares of common stock issued for the acquisition of Symphony GenIsis was done at the beginning of the period presented.

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

	Historical Isis Pharmaceuticals, Inc. Nine Months Ended September 30, 2007	Historical Symphony GenIsis, Inc. Nine Months Ended September 30, 2007	Intercompany Eliminations (Note 1)	Pro Forma Adjustments	Notes	Pro Forma Nine Months Ended September 30, 2007
Revenue	\$ 44,893	\$ —	\$ —	\$ —		\$ 44,893
Expenses:						
Research and development	64,629	22,586	(22,586)	—		64,629

Selling, general and administrative	10,769	571	(571)	—	10,769	
Total operating expenses	75,398	23,157	(23,157)	—	75,398	
Loss from operations	(30,505)	(23,157)	23,157	—	(30,505)	
Other income (expense):						
Investment income	9,058	1,784	(1,784)	(3,136)	2	5,922
Interest expense	(6,132)	—	—	—	—	(6,132)
Gain on investments	3,510	—	—	—	—	3,510
Loss on early retirement of debt	(3,212)	—	—	—	—	(3,212)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	23,157	—	—	(23,157)	3	—
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	87	—	—	—	—	87
Net loss	(4,037)	(21,373)	21,373	(26,293)	—	(30,330)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	(125,311)	—	—	—	—	(125,311)
Net loss applicable to common stock	\$ (129,348)	\$ (21,373)	\$ 21,373	\$ (26,293)	—	\$ (155,641)
Basic and diluted net loss per share	\$ (1.57)	—	—	—	—	\$ (1.81)
Shares used in computing basic and diluted net loss per share	82,650	—	—	3,347	4	85,997

Note 1: Since Isis' historical consolidated statements of operations already included the results of operations of Symphony GenIsis, Symphony GenIsis' results of operations are eliminated.

Note 2: This adjustment is recorded to reflect the reduction to interest income assuming that the \$80.4 million cash paid for the acquisition of Symphony GenIsis was made at the beginning of the period presented.

Note 3: This adjustment is recorded to remove the loss attributed to noncontrolling interest in Symphony GenIsis that was recognized on the historical statement of operations as a result of the consolidation of Symphony GenIsis as a variable interest entity.

Note 4: This adjustment is recorded to reflect the additional weighted average shares assuming the 3.4 million shares of common stock issued for the acquisition of Symphony GenIsis was done at the beginning of the period presented.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: December 7, 2007

By: /s/ B. Lynne Parshall
B. LYNNE PARSHALL
Executive Vice President,
Chief Financial Officer and Director

EXHIBIT INDEX

Exhibit Number	Description
23.1	Consent of Independent Registered Public Accounting Firm

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777) of Isis Pharmaceuticals, Inc. of our report dated March 2, 2007, with respect to the financial statements of Symphony GenIsis, Inc. included in Isis Pharmaceuticals, Inc.'s Current Report on Form 8-K/A, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

San Diego, California

December 4, 2007
