SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): **February 25, 2009**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(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:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 2.02. Results of Operations and Financial Condition.

On February 25, 2009, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2008. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses pro forma or non-GAAP results of operations, which are adjusted from GAAP to exclude non-cash compensation related to stock options. The Company is presenting pro forma information excluding the effects of the non-cash compensation expense or benefit because the Company believes it is useful for investors in assessing the Company's operating results compared to the prior year. A copy of the release is furnished with this report as an exhibit pursuant to "Item 2.02. Results of Operations and Financial Condition" of Form 8-K in accordance with SEC Release Nos. 33-8216 and 34-47583.

The information in this Current Report on Form 8-K and the Exhibit attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, regardless of any general incorporation language in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated February 25, 2009.

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: February 24, 2009

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

INDEX TO EXHIBITS

99.1 Press Release dated February 25, 2009.

ISIS REPORTS STRONG FINANCIAL RESULTS AND HIGHLIGHTS FOR FISCAL YEAR 2008

- **Exceeds 2008 Projections for Net Operating Income and Year-End Cash**
- **Achieves 2008 Positive Pro Forma Net Operating Income and Net Income**
- **Conference Call Webcast Wednesday, February 25, 8:30 a.m. EST at www.isispharm.com**

CARLSBAD, Calif., February 25, 2009 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2008 financial results and business highlights. Isis exceeded its 2008 financial guidance by ending 2008 with positive pro forma net income of $3.1 million and positive pro forma net operating income of $226,000. The considerable improvement in Isis' financial results from 2007 was due to a significant increase in revenue that Isis generated in 2008 from its corporate partnerships. On a GAAP basis, Isis' loss from operations of $13.1 million and net loss of $12.0 million also improved significantly from its 2007 loss from operations and net loss. In addition to creating a continuing revenue base, Isis' corporate partnerships have considerably improved its cash position allowing Isis to finish 2008 with $491 million of cash, which does not include the $175 million that Isis received in January 2009 when it completed the sale of its Ibis Biosciences subsidiary to Abbott Molecular Inc (AMI).

"We believe that we are now at the beginning phase of sustained financial strength as evidenced by our 2008 financial results. With the sale of Ibis at the beginning of 2009, we started the year with more than $650 million in cash. In addition, we ended the year with positive pro forma net operating income and net income, further demonstrating our move toward continued financial strength. We expect to continue to benefit financially from the successful execution of our business strategy in 2009 and to move closer to sustainable profitability, an important goal for us," said B. Lynne Parshall, COO and CFO of Isis.

"We are projecting pro forma net income in 2009 of more than $145 million. The gain we realized from our sale of Ibis is a significant contributor to our projected net income. As we move the Phase 3 program forward for mipomersen, as Regulus continues to grow, and as we expand our research and development efforts into new therapeutic areas, we expect our pro forma net operating loss in 2009 will be slightly higher than our 2008 guidance, and in the low to mid $20 million range, excluding non-cash stock compensation. Additionally, based on our cash and committed cash, we expect to end 2009 with more than $550 million in cash," continued Ms. Parshall. "Our financial performance is evidence of the value we have created in our technology and our pipeline. We are able to maximize this value through our innovative business model, which provides us with a continuing stream of revenue that we believe will continue to drive our financial success as our pipeline matures and our partnerships continue to succeed."

Upcoming Key Milestones

- Report data from a Phase 3 study evaluating mipomersen in homozygous Familial Hypercholesterolemia (FH) patients and from additional mipomersen studies in other patient populations
- Report data from a Phase 2 study evaluating ISIS 113715 in combination with sulfonylureas in patients with type 2 diabetes
- Begin clinical trials on three to five drugs per year
- Expand pipeline by moving three to five new drugs into the development pipeline per year in a diverse set of new diseases

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Financial Results

As a result of selling Ibis to AMI, Ibis' financial results are considered discontinued operations. Accordingly, the operating results of Ibis for 2008 and all prior periods are presented in Isis' financial statements separately as discontinued operations.

The considerable improvement in the Company's pro forma and GAAP operating results was driven primarily by the significant increase in revenue in 2008 from Isis' corporate partnerships. This was offset, in part, by higher expenses associated with the expansion of the Company's programs and, for Isis' GAAP results, an increase in non-cash stock compensation expense reflecting the increase in Isis' stock price over the same periods. Please refer to the reconciliation of pro forma and GAAP measures, which are explained later in this release.

Revenue

Revenue from continuing operations for the year ended December 31, 2008 was $107.2 million compared to $58.3 million in 2007. Isis' revenue nearly doubled in 2008 compared to 2007 as a result of the Company's collaborations including its strategic alliances with Genzyme Corporation (Genzyme), Ortho-McNeil-Janssen Pharmaceuticals Inc. and Bristol-Myers Squibb Company (BMS). Also contributing to the increase was the revenue Regulus Therapeutics (Regulus) earned from its strategic alliance with GlaxoSmithKline (GSK). Since these strategic alliances include ongoing research and development activities, Isis will continue to recognize significant amounts of revenue from these collaborations in the future. In addition to revenue from its pharmaceutical alliances, Isis' satellite company strategy has made significant contributions to Isis' revenue. For example, in 2007, Isis earned $26.5 million of sublicensing revenue from Alnylam Pharmaceuticals, Inc. (Alnylam). In 2008, Isis continued to earn substantial revenue from its satellite companies, including $6.1 million in sublicensing revenue from Alnylam and Antisense Therapeutics Limited (ATL).

Operating Expenses

On a pro forma basis, operating expenses from continuing operations for the year ended December 31, 2008 were $107.0 million compared to $83.0 million for 2007. The higher expenses in 2008 compared to 2007 were primarily due to the expansion of the Company's clinical development programs, including additional expenses associated with the development of mipomersen, the lead drug in Isis' cardiovascular franchise, increased activity levels related to Isis' planned investment to fill its pipeline, increased expenses to manufacture drug supplies for Isis' corporate partners and its internal drug development programs, and expenses for Regulus, which began operations in September 2007. On a GAAP basis, Isis' operating expenses from continuing operations for the year ended December 31, 2008 were $120.3 million compared to $91.3 million for 2007, including non-cash compensation expense related to stock

options of $13.3 million and $8.3 million, respectively. Going forward, Isis' operating expenses will increase modestly as Isis continues the development of mipomersen, as Regulus continues to build its core team, and as Isis expands its research and development efforts in different disease areas.

Net Loss from Continuing Operations

Net loss from continuing operations for the year ended December 31, 2008 was $3.6 million compared to a net loss of $5.0 million in 2007. In 2007, Isis recognized a $23.2 million benefit in the loss attributed to the noncontrolling interest in Symphony GenIsis. Excluding this item, the improvement in Isis' net loss from continuing operations was primarily driven by the improvement in net operating results, illustrating Isis' progression towards sustained profitability.

Net Loss from Discontinued Operations

The net loss from discontinued operations represents the operating results of Ibis that are presented separately in Isis' financial statements as a result of the sale of Ibis to AMI in January 2009. The increase in net loss from discontinued operations from $6.0 million for the year ended December 31, 2007 to $8.4 million in 2008 reflected an increase in expenses to support the growth of Ibis' commercial business

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including selling and support costs for the Ibis T500™ Biosensor System and the cost to achieve milestones as part of the AMI transaction partly offset by the gain recognized for the revaluation of the subscription right and call option granted to AMI.

Net Loss and Net Loss Applicable to Common Stock

Isis' net loss applicable to common stock for the year ended December 31, 2008 and 2007 was $12.0 million, or $0.13 per share, and $136.3 million, or $1.63 per share, respectively. Isis' net loss in 2008 was significantly lower than 2007 primarily due to the $125.3 million that Isis recognized when it acquired Symphony GenIsis in 2007. Also contributing to the decrease was the improvement in the net loss from continuing operations offset by the increase in net loss from discontinued operations.

Balance Sheet

As of December 31, 2008, Isis had cash, cash equivalents and short-term investments of $491.0 million compared to $193.7 million at December 31, 2007. In 2008 and early 2009, Isis received a significant amount of cash from its partners including:

- $325 million from Genzyme
- $20 million from GSK (for its transaction with Regulus)
- $215 million from AMI (for its transaction with Ibis)

As of December 31, 2008, Isis had consolidated working capital of $393.7 million compared to $147.7 million at December 31, 2007. The cash Isis received in 2008 primarily led to the increase in Isis' consolidated working capital, offset by $68.9 million of deferred revenue from Genzyme and GSK that is included in current liabilities.

Regulus Therapeutics

Regulus' revenue for the year ended December 31, 2008 was $2.1 million compared to $119,000 in 2007. The increase was primarily related to revenue from its collaboration with GSK.

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were $7.6 million for the year ended December 31, 2008 compared to $612,000 in 2007. With the strategic alliance with GSK, it is anticipated that Regulus' expenses will increase over its run rate in 2008 as Regulus advances its research and development activities. Regulus generated a loss from operations, excluding non-cash compensation expense related to stock options, of $5.5 million for the year ended December 31, 2008 compared to $493,000 in 2007.

Business Highlights

"Our pipeline has matured significantly in the past year. Together with our partner, Genzyme, we initiated four new studies that will expand our experience with mipomersen. Mipomersen continues to be well tolerated, and our level of confidence with mipomersen's safety profile continues to grow as our clinical and preclinical experience increases. In addition, our partners have reported encouraging clinical data on a number of antisense drugs in our pipeline, including OGX-011 in patients with prostate cancer and ATL/TV1102 in patients with multiple sclerosis. Positive clinical results for the drugs in our pipeline increase the value of all the drugs and add to a growing body of evidence demonstrating the therapeutic benefit of antisense drugs in a variety of diseases. The efficiency of our antisense technology enables us to expand ours and our partner's pipelines with promising new therapies. Furthermore, our strong financial position provides us the freedom to pursue additional therapeutic areas where we feel antisense can offer new treatment options," added Ms. Parshall.

"We believe that we have just begun to benefit from the efficiency of our technology. The successes that we have had in the past two years have generated more than $650 million in cash with the potential for us

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to earn future milestones and royalties as drugs from our collaborations progress. The most tangible recent example of the success of our business strategy is the sale of our Ibis subsidiary to AMI for a total purchase price of $215 million and the ability to continue to participate in Ibis' commercial success through an earn out as AMI sells Ibis products," added Ms. Parshall.

"We have many key milestones to look forward to in 2009, with the most significant being the data from our Phase 3 study evaluating mipomersen in patients with homozygous FH. Also we and our partners expect to report data from some of the other drugs in our pipeline in a number of different diseases, including metabolic diseases. We will aggressively grow our pipeline, adding 3 to 5 new drugs per year and advancing the drugs currently in our pipeline. In

short, 2008 was a remarkable year for us. Our successes this past year bring our drugs closer to commercialization and reflect the type of shareholder value we can create. We look forward to another exciting year," concluded Ms. Parshall.

Drug Development Highlights

Isis and Genzyme made substantial progress defining the safety and activity profile of mipomersen and moving the drug toward the market including,

- Completing enrollment in a Phase 3 mipomersen study in homozygous FH subjects.
- Initiating four additional mipomersen studies in high risk patients, including three Phase 3 studies in heterozygous FH subjects, high-risk hypercholesterolemia and severe hypercholesterolemia patients and a Phase 2 study in statin-intolerant patients.
- Reporting additional safety data including mipomersen data from a Phase 2 mipomersen liver imaging study in heterozygous FH subjects and long-term dosing data in FH patients exposed to mipomersen from three to 23 months.
- Publishing preclinical data showing that lowering of apoB-100 resulted in significant reduction of atherosclerotic plaques in murine models of atherosclerosis.

In addition, Isis and its partners showed encouraging clinical results in a broad range of diseases including,

- Encouraging Phase 2 data of OGX-011 in prostate cancer patients showing survival advantage, durable reductions in pain, and declines in PSA.
- Positive Phase 2 results showing that ATL/TV1102 demonstrated a highly significant effect on disease activity in patients with multiple sclerosis.
- Interim data from an ongoing Phase 1 study showing that iCo-007 appears to be well tolerated in patients with diffuse diabetic macular edema.

Isis broadened its pipeline with the addition of new drugs that Isis' partners are developing including,

- An antisense drug that targets PCSK9, BMS-PCSK9$_{Rx}$.
- An antisense drug for the local treatment of fibrosis and scarring, EXC001.
- A novel aminoglycoside drug, ACHN-490, which Achaogen is developing to treat bacterial infections.

Isis' pipeline matured with the initiation of clinical trials in multiple drugs including,

- ISIS-CRP$_{Rx}$ to treat coronary artery disease, inflammation and end stage renal disease.
- ISIS-SGLT2$_{Rx}$ to treat type 2 diabetes.
- AIR645 to treat asthma.
- LY2181308 to treat cancer.

Corporate Highlights

Isis continued to execute its successful business strategy by monetizing key assets with partners to continue the development and commercialization of the assets with lucrative terms in upfront payments, milestones and participation in the commercial success of each asset.

- Licensed mipomersen to Genzyme and received $325 million in an upfront license fee and equity investment with the potential to earn over $1.5 billion in potential commercial and developmental milestone payments, and a share of profits for Isis on mipomersen ranging from 30 to 50%.

- Sold its Ibis subsidiary to AMI for a total purchase price of $215 million, plus a 5% earn out on sales of assay kits and services.

Isis benefits financially as its partners advance drugs in development while also receiving upfront and royalty payments. This strategy provides cash to the Company while the drugs in Isis' pipeline mature in clinical development.

- ATL licensed ATL/TV1102 to Teva in a deal with a potential $100 million value in which Isis will receive one-third of licensing fees plus significant royalties.
- Isis received a $2 million milestone payment from BMS for the selection of a development candidate, BMS-PCSK9$_{Rx}$.
- Isis received a $1 million milestone payment from Achaogen for the IND of Achaogen's aminoglycoside drug.
- Regulus entered into a strategic alliance with GSK with an upfront payment of $20 million and the potential to earn up to nearly $600 million in milestone payments plus royalties.

Isis has significantly strengthened the Company's financial position.

- Isis exceeded its 2008 net operating loss guidance of less than $15 million and ended 2008 with positive pro forma net operating income and net income.
- Isis exceeded its 2008 cash guidance of $450 million by ending 2008 with over $490 million in cash.
- During 2008, Isis reported multiple profitable quarters.

Conference Call

At 08:30 a.m. Eastern Time today, February 25, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may access the webcast at www.isispharm.com, or listen to the call by dialing 877-852-6543. A webcast replay will be available for a limited time at the same address.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis is a joint owner of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott Molecular Inc. are commercializing. As an innovator in

RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis as well as Regulus its majority-owned subsidiary, and the therapeutic and commercial potential of the Company's technologies and products in development. Any statement describing Isis' goals, expectations, financial or other projections, 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, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended

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December 31, 2007, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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ISIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION

Condensed Consolidated Statements of Operations
(In Thousands, Except Per Share Data)

	Three months ended, December 31,		Years ended, December 31,	
	2008	2007	2008	2007
	(unaudited)			
Revenue:				
Research and development revenue under collaborative agreements	$ 29,103	$ 13,020	$ 98,853	$ 22,319
Licensing and royalty revenue	546	8,535	8,337	36,025
Total revenue	29,649	21,555	107,190	58,344
Expenses:				
Research and development	33,343	23,583	106,439	78,204
General and administrative	4,382	4,227	13,811	13,059
Total operating expenses	37,725	27,810	120,250	91,263
Loss from operations	(8,076)	(6,255)	(13,060)	(32,919)
Other income (expense):				
Investment income	2,514	2,386	11,318	11,443
Interest expense	(1,306)	(1,441)	(5,603)	(7,573)
Gain (loss) on investments, net	(965)	—	(965)	3,510
Loss on early retirement of debt	—	—	—	(3,212)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	—	—	23,157
Loss attributed to noncontrolling interest in Regulus Therapeutics	1,678	542	4,734	629
Net loss from continuing operations	(6,155)	(4,768)	(3,576)	(4,965)
Net loss from discontinued operations	(2,503)	(2,189)	(8,387)	(6,029)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	—	—	—	(125,311)
Net loss applicable to common stock	$ (8,658)	$ (6,957)	$ (11,963)	$ (136,305)
Basic and diluted net loss per share from continuing operations	$ (0.06)	$ (0.05)	$ (0.04)	$ (0.06)
Basic and diluted net loss per share applicable to common stock	$ (0.09)	$ (0.08)	$ (0.13)	$ (1.63)
Shares used in computing basic and diluted net loss per share	96,889	86,970	94,566	83,739

Isis Pharmaceuticals, Inc.

Reconciliation of GAAP to Pro Forma Basis:
Condensed Consolidated Operating Expenses and Loss From Operations
(In Thousands)

	Three months ended, December 31,		Years ended, December 31,	
	2008	2007	2008	2007
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 37,725	$ 27,810	$ 120,250	$ 91,263
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,852)	(2,302)	(13,286)	(8,298)
Pro forma operating expenses	$ 34,873	$ 25,508	$ 106,964	$ 82,965
As reported loss from operations according to GAAP	$ (8,076)	$ (6,255)	$ (13,060)	$ (32,919)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,852)	(2,302)	(13,286)	(8,298)
Pro forma income (loss) from operations	$ (5,224)	$ (3,953)	$ 226	$ (24,621)
As reported net loss according to GAAP	$ (8,658)	$ (6,957)	$ (11,963)	$ (10,994)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,248)	(2,702)	(15,063)	(9,910)
Pro forma net income (loss)	$ (5,410)	$ (4,255)	$ 3,100	$ (1,084)

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses, pro forma loss from operations and pro forma net income (loss) were adjusted from GAAP to exclude compensation expense related to stock options, which are non-cash. Isis has regularly reported non-GAAP measures for operating expenses and loss from operations as pro forma results. These measures are provided as supplementary information and are not a substitute for financial measures calculated in accordance with GAAP. Isis reports these pro forma results to better enable financial statement users to assess and compare its historical performance and project its future operating results and cash flows. Further, the presentation of Isis' pro forma results is consistent with how Isis' management internally evaluates the performance of its operations.

Regulus Therapeutics
Statements of Operations
(In Thousands)

	Three months ended, December 31,		Years ended, December 31,	
	2008	2007	2008	2007
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 681	$ 78	$ 2,110	$ 119
Total revenue	681	78	2,110	119
Expenses:				
Research and development	2,738	734	8,030	833
General and administrative	673	161	2,001	191
Total operating expenses	3,411	895	10,031	1,024
Loss from operations	$ (2,730)	$ (817)	$ (7,921)	$ (905)

Isis Pharmaceuticals, Inc.
Condensed Consolidated Balance Sheets
(In Thousands)

	December 31, 2008	December 31, 2007
Assets:		
Cash, cash equivalents and short-term investments	$ 490,998	$ 193,719
Other current assets	27,386	16,155
Property, plant and equipment, net	17,371	5,960
Other assets	38,395	43,024
Total assets	$ 574,150	$ 258,858

Liabilities, noncontrolling interest and stockholders' equity:		
Other current liabilities	$ 32,036	$ 30,670
Current portion of deferred contract revenue	92,662	31,535
2 5/8% convertible subordinated notes	162,500	162,500
Long-term obligations, less current portion	9,938	362
Long-term deferred contract revenue	172,766	23,548
Noncontrolling interest in Regulus Therapeutics	4,737	9,371
Noncontrolling interest in Ibis Biosciences, Inc. — held for sale	32,419	—
Stockholders' equity	67,092	872
Total liabilities, noncontrolling interest and stockholders' equity equity	$ 574,150	$ 258,858

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