

Isis Reports Financial Results and Highlights for 2012

February 28, 2013

- Conference Call Webcast Thursday, February 28, 12:00 p.m. ET at www.isispharm.com

CARLSBAD, Calif., Feb. 28, 2013 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2012 financial results and reviewed the highlights of the year. Isis ended the year in a strong financial position significantly outperforming both its pro forma net operating loss (NOL) guidance and its cash guidance for the year. For the year ended December 31, 2012, Isis had an NOL of \$60.4 million compared to \$61.3 million for 2011. Isis added a substantial amount of cash to its balance sheet throughout 2012, ending the year with nearly \$375 million. On a GAAP basis, Isis reported a loss from operations of \$26.1 million and \$68.9 million for the three and twelve months ended December 31, 2012, respectively, compared to \$18.6 million and \$71.1 million for the same periods in 2011.

"Last month the FDA approved KYNAMRO™. KYNAMRO is the first systemic antisense drug to be sold commercially. This is an important event for patients with homozygous familial hypercholesterolemia, for Isis, and for our antisense technology. KYNAMRO's approval for chronic use in patients who have a severe and fatal disease highlights the potential of our technology to create drugs that could provide benefit for patients," said B. Lynne Parshall, chief operating officer of Isis. "In addition to KYNAMRO, we have a number of promising new drugs that will report later-stage clinical data this year, setting us up for an exciting year of pipeline activity."

"2012 was a strong year for Isis. We begin 2013 in a significantly improved financial position with nearly \$375 million in cash. Since the beginning of 2013, we have already received a \$25 million milestone payment from Genzyme and a \$7.5 million milestone payment from GSK. With the commercial launch of KYNAMRO and a maturing pipeline of drugs, we have many opportunities for significant near-term revenue from partnerships while we are also setting the stage for significant future revenue growth," said Elizabeth L. Hougen, chief financial officer of Isis.

"In 2013, we are predicting another year of strong financial performance while continuing to advance our pipeline. Although we are planning to have more than a dozen drugs in later-stage clinical studies throughout the year, we are projecting only a slight increase in our 2013 spending compared to 2012. As such, we expect to end 2013 with a pro forma NOL in the mid \$60 million range. We are also projecting to end the year with more than \$325 million in cash. Our guidance is supported by our partnering successes in 2012. Because most drugs are not profitable in their first year of commercialization, and because it is too early in the year to predict the revenue trajectory of KYNAMRO, we are being conservative in our projections by not including KYNAMRO profit share revenue this year. We are pleased with the significant investment Genzyme is making to ensure a successful KYNAMRO launch. This investment should support strong revenue growth in the future. We are fortunate to have Genzyme with its expertise in selling and marketing orphan drugs commercializing KYNAMRO and we look forward to providing updates throughout the year on KYNAMRO's commercial success," concluded Ms. Hougen.

Upcoming Key Milestones

- Receive KYNAMRO marketing opinion from the European regulatory agency
- Initiate a Phase 2/3 program of ISIS-SMN_{Rx} in infants with spinal muscular atrophy
- Report clinical data on ISIS-SMN_{Rx} at the American Academy of Neurology meeting in March
- Report clinical data on ISIS-CRP_{Rx} in patients with rheumatoid arthritis
- Report clinical data on ISIS-APOCIII_{Rx} in patients with high triglycerides

Financial Results

All pro forma amounts referred to in this press release exclude non-cash compensation expense related to equity awards. Please refer to the reconciliation of pro forma and GAAP measures, which is provided later in this release.

Revenue

Revenue for the three and twelve months ended December 31, 2012 was \$19.9 million and \$102.0 million, respectively, compared to \$32.4 million and \$99.1 million for the same periods in 2011. Isis' revenue fluctuates based on the nature and timing of payments under agreements with Isis' partners, including license fees, milestone-related payments and other payments. For example, in 2012, Isis recognized revenue from new sources in connection with the license for ISIS-STAT3_{Rx} which Isis granted to AstraZeneca under its recently announced strategic alliance on RNA therapeutics for cancer, its three new collaborations with Biogen Idec and the KYNAMRO FDA acceptance milestone from Genzyme. At the same time, in 2012, Isis' revenue from amortization of the upfront payments associated with the Genzyme collaboration ended as planned midyear.

Isis earned a \$25 million milestone payment from Genzyme in January 2013 for FDA approval of KYNAMRO and a \$7.5 million milestone payment from GSK in February 2013 for the initiation of the Phase 2/3 study of ISIS-TTR_{Rx}. Isis will reflect both of these milestone payments in its first quarter 2013 financial results.

Operating Expenses

On a pro forma basis, operating expenses for the three and twelve months ended December 31, 2012 were \$44.2 million and \$162.4 million, respectively, compared to \$48.8 million and \$160.3 million for the same periods in 2011. In 2012, Isis was able to advance and expand its pipeline while maintaining its operating expenses essentially flat to 2011.

On a GAAP basis, Isis' operating expenses for the three and twelve months ended December 31, 2012 were \$46.0 million and \$171.0 million, respectively, compared to \$51.0 million and \$170.2 million for the same periods in 2011.

Early Retirement of Debt

In August 2012, Isis issued \$201.3 million of 2 ¾% convertible senior notes due 2019 (2 ¾% Notes). In September 2012, Isis used a substantial portion of the net proceeds from the issuance of these notes to redeem the entire \$162.5 million of the Company's 2 ½% convertible subordinated notes (2 ½% Notes). As a result of the early redemption of the 2 ¾% Notes, Isis recognized a \$4.8 million loss primarily related to a non-cash write-off of the unamortized portion of the debt discount and debt issuance costs.

Gain on Investment in Regulus Therapeutics Inc.

In October 2012, Regulus Therapeutics, Inc., a company Isis co-founded, completed an initial public offering. In the fourth quarter, as a result of the IPO, Isis recorded an \$18.4 million gain to reflect the Company's change in its ownership percentage in Regulus. Also in the fourth quarter, Isis stopped using the equity method to account for its investment in Regulus and instead began accounting for it at fair value. Isis now owns approximately seven million shares, or 17%, of Regulus' common stock on a fully diluted basis.

Net Loss

Isis reported a net loss of \$2.6 million and \$65.5 million for the three and twelve months ended December 31, 2012, respectively, compared to \$20.0 million and \$84.8 million for the same periods in 2011. Basic and diluted net loss per share for the three and twelve months ended December 31, 2012 was \$0.03 per share and \$0.65 per share, compared to \$0.20 per share and \$0.85 per share for the same periods in 2011. In 2012, Isis' net loss was significantly lower than 2011 primarily due to the \$18.4 million gain from its investment in Regulus and the related \$9.1 million tax benefit offset, in part, by an increase in Isis' net operating loss, the \$4.8 million loss on Isis' early retirement of its 2 5/8% Notes, and an increase in interest expense. Isis' interest expense was higher than in 2011 due to additional non-cash interest expense Isis recorded for the long-term liability associated with its primary research and development facility and slightly higher interest expense related to Isis' 2 3/4% Notes.

Balance Sheet

As of December 31, 2012, Isis had cash, cash equivalents and short-term investments of \$374.4 million compared to \$343.7 million at December 31, 2011 and had working capital of \$349.1 million at December 31, 2012 compared to \$284.0 million at December 31, 2011. During 2012, Isis received a substantial amount of cash, including \$96 million in upfront payments from Biogen Idec and AstraZeneca, a \$25 million milestone payment from Genzyme for FDA acceptance of the KYNAMRO NDA and approximately \$30 million in net proceeds from Isis' issuance of its 2 3/4% Notes. Isis' working capital increased significantly in 2012 primarily due to the cash Isis received in 2012 and an increase in current assets resulting from Isis' investment in Regulus because Isis is now recording its investment at fair value. At December 31, 2012, the carrying value of Isis' investment in Regulus was \$33.6 million.

2013 Goals

"We expect 2013 to be a year of substantial growth and maturation for Isis. We believe that the initial commercial launch of KYNAMRO will be successful and we support Genzyme's ongoing development efforts for KYNAMRO with the FOCUS FH study, which Genzyme is conducting under a special protocol assessment with the FDA," continued Ms. Parshall. "Beyond KYNAMRO, we have a number of drugs in our pipeline that will complete later-stage clinical studies, which are designed to provide clear evidence that these drugs have the potential to work in patients in numerous different diseases. In addition, we plan to advance many other drugs in our pipeline, creating additional opportunities for significant long-term revenue. And finally, we expect to explore partnering opportunities that are the right fit for Isis and designed to provide the most benefit to our programs and drugs, the best balance of risk and commercial participation, while allowing us to continue to do what we do best, drug discovery and early drug development."

In 2013, Isis plans to achieve the following goals itself and with its partners:

- Together with Genzyme, Isis will continue to support KYNAMRO development, marketing and commercialization activities.
 - Support commercial launch in the United States for patients with HoFH.
 - Continue enrollment in FOCUS FH.
 - Pursue marketing approval in Europe for HoFH in the first half of 2013.
- Mature its pipeline:
 - Complete and report late-stage clinical data from Phase 2 or Phase 3 studies from up to nine drugs in its pipeline.
 - Initiate Phase 2/3 or Phase 3 studies on two or three drugs for severe and rare diseases.
 - Initiate Phase 2 studies on up to five drugs in its pipeline.
- Broaden its pipeline by adding up to five new drugs.
- Continue to successfully execute its business strategy to generate revenue and cash.

Business Highlights

"2012 was a year of significant achievements for Isis. Together with Genzyme we successfully completed the final steps to bring KYNAMRO to the market in the US for patients with HoFH. We continued to mature and expand our severe and rare disease franchise, receiving orphan drug designation for two of the drugs in this franchise. We reported clinical data on seven drugs in our pipeline and advanced three drugs into Phase 2 clinical studies that we plan to report data from this year, which could support significant licensing opportunities for us," continued Ms. Parshall.

"And finally, we have been successful in implementing our business strategy and establishing strategic partnerships that provide us with significant value. We established three collaborations with Biogen Idec focused on neurologic severe and rare diseases. Biogen Idec's extensive expertise and experience in neurological diseases makes Biogen Idec an ideal partner to work with us to build a neurologic disease franchise. In addition, we established a collaboration with AstraZeneca that allows us to broaden and expand our antisense drug discovery and development efforts and apply our antisense technology to novel oncology targets with a global leader in cancer drug development and commercialization," concluded Ms. Parshall.

Drug Development Highlights for 2012/ Early 2013

- Isis and Genzyme were successful in bringing KYNAMRO to the market for patients with HoFH. These patients are at high cardiovascular risk and may not be able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
 - KYNAMRO was approved for marketing in the United States by the US FDA for the treatment of patients with HoFH.
 - Isis received a total of \$50 million in milestone payments from Genzyme related to the NDA acceptance in 2012 and marketing approval of KYNAMRO by the FDA in 2013.
 - Genzyme continues to enroll the FOCUS FH study, which is designed to provide 60-week safety and efficacy data in FH patients to support an additional regulatory filing. Genzyme reached an agreement with the FDA on the

- design of the FOCUS FH study via a Special Protocol Assessment, or SPA.
- Genzyme submitted a request for re-examination of the EMA's negative opinion on the marketing authorization application for KYNAMRO and expects to report the outcome of the re-examination in the first half of 2013.
- Isis received European GMP certification of its manufacturing facility for production of drug substance to support KYNAMRO commercial launch.
- Clinical investigators presented KYNAMRO data at important cardiovascular medical meetings throughout the year.
 - Dr. Raul Santos presented data from the long-term extension study of KYNAMRO at the International Symposium on Atherosclerosis. These data highlighted the long-term safety and efficacy of KYNAMRO in patients who have been treated with KYNAMRO.
 - Dr. Klaus Parhofer presented an analysis of data from the KYNAMRO Phase 3 study in patients with severe heterozygous FH at the European Society of Cardiology. These data highlighted the potential of KYNAMRO to reduce the need for apheresis by lowering LDL-C values below the thresholds for apheresis eligibility in patients with severe heterozygous FH.
 - Dr. Sotirios Tsimikas presented an analysis of Lp(a) data from the KYNAMRO Phase 3 program at the European Atherosclerosis Society. These data demonstrated sustained reductions of Lp(a), an independent risk factor for cardiovascular disease.
- Isis and its partners reported positive clinical data on seven drugs and Isis added four drugs to its pipeline.
- Isis and its partners initiated Phase 2 or Phase 3 clinical studies on eight drugs.
- Isis received Orphan Drug Designation and Fast Track Status in the US for ISIS-SMN_{Rx} and ISIS-TTR_{Rx}. Isis received Orphan Drug Designation in the EU for ISIS-SMN_{Rx}.

Corporate Highlights for 2012/ Early 2013

- Isis formed three new strategic alliances with Biogen Idec to develop and commercialize antisense drugs for severe and rare and neurologic diseases. In total all three alliances are valued at up to \$1.2 billion.
 - Isis entered into an alliance with Biogen Idec to develop and commercialize its drug, ISIS-SMN_{Rx}, to treat SMA. Isis received a \$29 million upfront payment and is eligible to receive up to an additional \$270 million in a license fee and milestone payments, and double-digit royalties on sales of ISIS-SMN_{Rx}.
 - Isis entered into an alliance with Biogen Idec to develop and commercialize a drug to treat myotonic dystrophy. Isis received a \$12 million upfront payment and is eligible to receive up to an additional \$259 million in a licensing fee and milestone payments. Isis is also eligible to receive double-digit royalties on product sales.
 - Isis entered into an alliance with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. Isis received a \$30 million upfront payment and is eligible to receive up to another \$200 million in a license fee and regulatory milestone payments per program. Isis is also eligible to receive double-digit royalties on product sales for each drug.
- Isis formed a new strategic alliance with AstraZeneca to discover and develop antisense drugs against five cancer targets, which included a license to develop and commercialize ISIS-STAT3_{Rx}.
 - The agreement comprises \$31 million in upfront and near-term payments, including a \$25 million payment Isis has received followed by a \$6 million payment Isis is eligible to receive in the second quarter of 2013 assuming the research program is continuing. Isis is also eligible to receive milestone payments, license fees and royalties.
 - Isis added the first drug from its research collaboration, ISIS-AZ1_{Rx}, to the pipeline.
- Isis and GlaxoSmithKline amended the clinical development plan and financial terms relating to ISIS-TTR_{Rx} to support an accelerated development plan for the drug. As a result of the revised agreement, Isis received a \$2.5 million upfront payment.
 - Isis received a \$7.5 million milestone payment upon initiation of the Phase 2/3 study for ISIS-TTR_{Rx}.
 - Isis is also eligible to earn an additional \$50 million in pre-licensing milestone payments to support the ISIS-TTR_{Rx} Phase 2/3 study.
- Isis benefited as its partners advanced RNA-based technologies and products incorporating its technology.
 - Isis received \$2.7 million from Alnylam as a result of Alnylam's licenses that included Isis' patents.
 - Isis received \$1.3 million from Pfizer triggered by Pfizer's decision to advance EXC 001 into a Phase 2 study.
- Regulus Therapeutics completed an initial public offering and is now traded on The NASDAQ Global Market under the ticker RGLS. Isis purchased \$3 million of Regulus' common stock at the offering price and remains a significant shareholder with approximately 17% ownership on a fully diluted basis, which is valued at approximately \$36 million.
- Isis completed a successful \$201.3 million convertible debt financing. Isis used the majority of the proceeds of this financing to redeem its outstanding \$162.5 million 2 ½% subordinated convertible debt.
- The securities class action lawsuit was voluntarily withdrawn and there are no pending lawsuits related to any violation of securities laws.
- Isis and its collaborators published papers in leading scientific journals demonstrating the broad applicability of its technologies.
 - A paper in Nature demonstrating that an antisense compound selectively and rapidly reduced target RNA in

- skeletal muscle and alleviated disease in animal models of myotonic dystrophy.
- o A paper in Neuron demonstrating that an antisense compound reversed disease in animal models of Huntington's disease.
- o Two papers in the journal Cell demonstrating that single-stranded RNA-like antisense technology can activate the RNAi pathway and inhibit the expression of targeted genes.

Conference Call

At 12:00 p.m. Eastern Time today, February 28, 2013, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may listen to the call by dialing 866-323-2841 and provide the conference identification number "90809537", or access the webcast at www.isispharm.com. A webcast replay will be available for a limited time at the same address.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 28 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO™, in the United States for the treatment of patients with HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets, including Europe. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis Pharmaceuticals' financial position and outlook, Isis' business, and the therapeutic and commercial potential of Isis' technologies and products in development. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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 December 31, 2011 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.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc. Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc. KYNAMRO™ is a trademark of Genzyme Corporation.

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,	
	2012	2011	2012	2011
Revenue:	(unaudited)			
Research and development revenue under collaborative agreements	\$19,015	\$31,682	\$99,100	\$96,190
Licensing and royalty revenue	858	721	2,949	2,896
Total revenue	<u>19,873</u>	<u>32,403</u>	<u>102,049</u>	<u>99,086</u>
Expenses:				
Research and development	42,758	47,219	158,458	157,397
General and administrative	3,234	3,800	12,515	12,789
Total operating expenses	<u>45,992</u>	<u>51,019</u>	<u>170,973</u>	<u>170,186</u>
Loss from operations	(26,119)	(18,616)	(68,924)	(71,100)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	(267)	(1,279)	(1,406)	(3,554)
Investment income	359	518	1,844	2,414
Interest expense	(4,817)	(5,108)	(21,152)	(16,732)
Gain on investments, net	1,446	4,449	1,465	4,182
Gain on investment in Regulus Therapeutics Inc.	18,356	-	18,356	-
Loss on early retirement of debt	-	-	(4,770)	-
Loss before income tax benefit (expense)	<u>(11,042)</u>	<u>(20,036)</u>	<u>(74,587)</u>	<u>(84,790)</u>
Income tax benefit (expense)	<u>8,405</u>	<u>-</u>	<u>9,109</u>	<u>(11)</u>
Net loss	<u><u>\$(2,637)</u></u>	<u><u>\$(20,036)</u></u>	<u><u>\$(65,478)</u></u>	<u><u>\$(84,801)</u></u>
Basic and diluted net loss per share	<u><u>\$(0.03)</u></u>	<u><u>\$(0.20)</u></u>	<u><u>\$(0.65)</u></u>	<u><u>\$(0.85)</u></u>
Shares used in computing basic and diluted net loss per share	101,246	99,763	100,576	99,656

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,	
	2012	2011	2012	2011
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	\$45,992	\$51,019	\$170,973	\$170,186
Excluding compensation expense related to equity awards	(1,811)	(2,249)	(8,571)	(9,845)
Pro forma operating expenses	<u>\$44,181</u>	<u>\$48,770</u>	<u>\$162,402</u>	<u>\$160,341</u>
As reported loss from operations according to GAAP	\$(26,119)	\$(18,616)	\$(68,924)	\$(71,100)
Excluding compensation expense related to equity awards	(1,811)	(2,249)	(8,571)	(9,845)
Pro forma loss from operations	<u>\$(24,308)</u>	<u>\$(16,367)</u>	<u>\$(60,353)</u>	<u>\$(61,255)</u>

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses and pro forma loss from operations were adjusted from GAAP to exclude compensation expense related to equity awards, 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.

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

	December 31, December 31,	
	2012	2011
Assets:		
Cash, cash equivalents and short-term investments	\$374,446	\$343,664
Investment in Regulus Therapeutics Inc.	33,622	-
Other current assets	15,370	16,475
Property, plant and equipment, net	91,084	96,615
Other assets	31,164	28,140
Total assets	<u>\$545,686</u>	<u>\$484,894</u>
Liabilities and stockholders' equity:		
Other current liabilities	\$38,397	\$39,528
Current portion of deferred contract revenue	35,925	36,584
2 3/4% convertible senior notes	143,990	-
2 5/8% convertible subordinated notes	-	141,448
Long-term obligations, less current portion	77,952	74,002
Investment in Regulus Therapeutics Inc.	-	4,424
Long-term deferred contract revenue	66,656	17,474
Stockholders' equity	182,766	171,434
Total liabilities and stockholders' equity	<u>\$545,686</u>	<u>\$484,894</u>

SOURCE Isis Pharmaceuticals, Inc.

D. Wade Walke, Ph.D., Executive Director, Corporate Communications and Investor Relations, +1-760-603-2741, or Amy Blackley, Ph.D., Associate Director, Corporate Communications, +1-760-603-2772