# Isis Pharmaceuticals Reports Positive Phase 1 Data On Three Drugs In Development To Treat Metabolic Disorders

December 7, 2012

**Conference Call and Slide Presentation December 7th, 12:00 p.m. EST at www.isispharm.com**

CARLSBAD, Calif., Dec. 7, 2012 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive results from Phase 1 studies of three drugs, ISIS-PTP1B$_{Rx}$, ISIS-GCGR$_{Rx}$ and ISIS-GCCR$_{Rx}$, in development to treat metabolic disorders, including type 2 diabetes. In all three Phase 1 studies, the drugs were safe and well tolerated with early encouraging data that supports the unique mechanism of each drug. All three drugs are part of Isis' metabolic franchise and are designed to act through distinct mechanisms to improve insulin sensitivity and/or reduce glucose production.

"Our goal is to develop safe, effective drugs with unique mechanisms of action that can provide significant therapeutic benefit for patients with metabolic disorders, including type 2 diabetes. This year we have moved closer to this goal with the completion of our initial clinical studies on three promising drugs from our metabolic franchise. These drugs are uniquely positioned to fill the critical voids in diabetes therapy," said Stanley T. Crooke, M.D., Ph.D., chief executive officer at Isis. "While these drugs may be beneficial as single agents, our goal is to develop them as adjuncts to existing diabetes therapies. We believe that each drug has the potential to address a distinct and significant commercial market in patients with type 2 diabetes."

**ISIS-PTP1B$_{Rx}$**

ISIS-PTP1B$_{Rx}$ targets protein tyrosine phosphatase-1B (PTP-1B) and is designed to increase the body's sensitivity to insulin, resulting in better glucose control for patients with type 2 diabetes. Because of its unique mechanism, ISIS-PTP1B$_{Rx}$ has the potential to help patients achieve glucose control without weight gain or hypoglycemia. In the Phase 1 study of ISIS-PTP1B$_{Rx}$ in obese healthy volunteers, Isis observed encouraging data in measures of insulin sensitivity and in a biomarker associated with weight loss. Previous clinical experience with the PTP-1B inhibitor ISIS 113715 demonstrated that PTP-1B inhibition improved glucose control and reduced LDL-cholesterol without causing weight gain. "These new ISIS-PTP1B$_{Rx}$ data are consistent with our findings from the earlier Phase 2 studies of ISIS 113715. It is also important to note that ISIS-PTP1B$_{Rx}$ is a significantly more potent PTP-1B inhibitor than our earlier inhibitor, ISIS 113715, and, as such, we expect more robust effects in clinical trials," said Sanjay Bhanot, M.D., Ph.D., vice president, clinical development and translational medicine at Isis. "We believe that ISIS-PTP1B$_{Rx}$ has the potential to be broadly useful in combination with most of the other commonly used drugs to treat patients with diabetes, including insulin, glucagon-like peptide (GLP-1) agonists, and more traditional drugs like metformin."

**ISIS-GCGR$_{Rx}$**

ISIS-GCGR$_{Rx}$ targets the glucagon receptor (GCGR) and is designed to reduce the effects of glucagon, a hormone that causes increased glucose production in the liver. In patients with advanced diabetes, uncontrolled glucagon action leads to a significant increase in blood glucose levels. Therefore, attenuating glucagon action could have a significant glucose lowering effect in patients with severe diabetes. "Although small molecule inhibitors of GCGR have demonstrated glucose-lowering effects in diabetic patients, they also have produced limiting side effects, including increases in lipids and blood pressure. In contrast, in our Phase 1 study ISIS-GCGR$_{Rx}$ displayed a good safety profile with no clinically significant increases in blood pressure or lipids and with no hypoglycemia. In addition, we observed an increase in active GLP-1, a hormone that preserves pancreatic function and enhances insulin secretion, that confirmed the activity we observed in our preclinical studies," continued Dr. Bhanot. "Given the unique mechanism of action and potentially favorable safety profile observed in the Phase 1 study, we believe that ISIS-GCGR$_{Rx}$ could be valuable for diabetic patients with severe hyperglycemia who are not controlled with current treatments by not only controlling glucose, but also preserving pancreatic function, which would enhance endogenous insulin activity."

**ISIS-GCCR$_{Rx}$**

ISIS-GCCR$_{Rx}$ targets the glucocorticoid receptor (GCCR) and is designed to reduce the effects of glucocorticoids, hormones that promote liver glucose production and fat storage in the liver and fat tissues. Because excessive GCCR activity in the liver and fat is associated with obesity, insulin resistance and glucose intolerance, ISIS-GCCR$_{Rx}$ has the potential to improve glycemic and lipid control in patients with type 2 diabetes. "Reduction of GCCR in tissues other than the liver and fat, such as the brain, can result in many unwanted and potentially toxic side effects, as has been reported with small molecule inhibitors of GCCR. Because ISIS-GCCR$_{Rx}$ reduces GCCR activity only in liver and fat tissues, we avoid these unwanted side effects. In preclinical studies, we demonstrated that antisense reduction of GCCR was limited to the liver and fat tissues and produced robust lowering of glucose and lipid levels. Results from our ISIS-GCCR$_{Rx}$ Phase 1 study were consistent with the liver- and fat-specific activity we observed in our preclinical studies, and also provided early encouraging data on the drug's therapeutic activity," concluded Dr. Bhanot. "Given the mechanism of action, we believe that ISIS-GCCR$_{Rx}$ could be particularly useful for diabetic patients with moderate to severe hyperglycemia who are also obese or have high levels of cholesterol and triglycerides."

**CONFERENCE CALL**

At 12:00 p.m. Eastern Standard Time today, December 7$^{th}$, Isis will conduct a live webcast and slide presentation. Interested parties may listen to the call by dialing 866-362-4831 and refer to the passcode "ISIS 2012" or access the webcast with or without audio 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 25 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, plans to commercialize Isis' lead product, KYNAMRO™, irthe United States and Europe following regulatory approval. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at **www.isispharm.com**.

**ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT**

This press release includes forward-looking statements regarding the development, activity, therapeutic potential and safety of the drugs in Isis'

metabolic pipeline. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization 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.



SOURCE Isis Pharmaceuticals, Inc.

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