



## **Isis Initiates Phase 1 Study of ISIS 325568 Targeting Glucagon Receptor to Treat Type 2 Diabetes**

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### **\*Isis Now Has Two Drugs From Its Metabolic Disease Program In Clinical Development**

CARLSBAD, Calif., Sept 04, 2007 /PRNewswire-FirstCall via COMTEX News Network/ --

Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today it has initiated a Phase 1 study of ISIS 325568, an antisense drug designed to improve blood glucose control in patients with type 2 diabetes by inhibiting production of the glucagon receptor (GCGR). GCGR is a receptor that binds glucagon, a hormone that opposes the action of insulin. The Phase 1 trial of ISIS 325568 is designed to assess the drug's activity, including its effect on liver glucose production, as well as safety and pharmacokinetic profiles, providing the opportunity to demonstrate proof-of-concept in this first human trial. The study is a randomized, placebo-controlled, dose-escalation study conducted in healthy volunteers.

"We are excited by the preclinical profile of ISIS 325568, a novel first-in-class drug that has demonstrated excellent glucose control and improved pancreatic function through a dual mechanism of action in insulin-resistant animal models. Furthermore, the favorable effects on GLP-1 that we have seen exceed those observed with DPP IV inhibitors, and there was no evidence of hypoglycemia or GI side effects. These preclinical findings suggest that ISIS 325568 could offer disease modifying effects and long-term disease control both as a single agent and in combination with other diabetes treatments," said Sanjay Bhanot, M.D., Ph.D., Vice President of Metabolic Diseases Research & Development, Isis Pharmaceuticals. "In addition to demonstrating safety and tolerability in this study, we will be closely monitoring a number of biomarkers that could provide evidence for the drug's activity as well as help inform dose selection for future studies."

#### **ISIS 325568 Targets the Glucagon Receptor (GCGR)**

Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. In type 2 diabetes, unopposed action of glucagon can lead to increased blood glucose levels. Reducing the expression of liver GCGR using antisense inhibitors, and thereby reducing excessive liver glucose production, is expected to lower blood glucose levels and help control type 2 diabetes. In preclinical studies, antisense inhibitors of GCGR led to improved glucose control and reduced levels of blood triglycerides without producing hypoglycemia. In addition, treatment with ISIS 325568 led to an increase in circulating glucagon-like peptide, or GLP-1, which is a hormone that helps to preserve pancreatic function, thereby enhancing insulin secretion.

#### **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 17 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing drugs for cancer, and inflammatory and other diseases. Ibis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000 Biosensor System, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at <http://www.isispharm.com>.

This press release includes forward-looking statements regarding Isis' discovery and development of drugs for diabetes and metabolic diseases, and the potential of the antisense drug ISIS 325568 for type 2 diabetes. 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 December 31, 2006, and its quarterly report on Form 10-Q for the quarter ended June 30, 2007, 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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