

## Isis Announces Antisense Targeting Of HBV Produces Dose-Dependent Reductions In Hepatitis B Virus In An Animal Model Of HBV

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**Data to be presented in April at the European Association for the Study of the Liver Meeting  
Isis' antisense drug targeting HBV, ISIS-HBV<sub>Rx</sub>, in an ongoing Phase 1 study planned to complete this year**

CARLSBAD, Calif., March 24, 2014 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced that treatment with an antisense compound targeting hepatitis B virus (HBV) produced dose-dependent reductions in all measured liver and serum viral markers of HBV infection in animal models of HBV infection. These data will be presented at the 49<sup>th</sup> annual meeting of the European Association for the Study of the Liver (EASL) by Dr. Gaetan Billioud, from the Scripps Research Institute in London, England. Isis is currently evaluating antisense targeting of HBV with ISIS-HBV<sub>Rx</sub> in a Phase 1 study in healthy volunteers.



"Hepatitis B virus infection is a serious health problem that can lead to significant and potentially fatal health conditions, including cirrhosis, liver failure and liver cancer. Chronic HBV infection is one of the most common persistent viral infections in the world. Currently available therapies, although effective in reducing circulating HBV in the blood, do not efficiently inhibit HBV antigen production and secretion, which are associated with poor prognosis and increased risk of liver cancer," said Dr. Stefan Wieland, assistant professor of experimental virology at The Scripps Research Institute. "These data are encouraging as they demonstrate that antisense drugs are able to efficiently reduce HBV-associated antigens as well as circulating HBV in an animal model of disease. As such, these results provide support for the development of ISIS-HBV<sub>Rx</sub> for the treatment of patients with chronic HBV infection."

These preclinical data, which will be presented by Dr. Gaetan Billioud from The Scripps Research Institute during a presentation on April 12 at EASL, demonstrate that antisense targeting of HBV RNA could be an effective approach to treating patients with chronic HBV infection. In this study, an antisense compound targeting HBV produced dose-dependent reductions of HBV-associated antigens, including HBsAg (hepatitis B surface antigen), which is present in both acute and chronic infections and is associated with a poor prognosis in patients with chronic HBV infection. In addition, other measures of viral infection were reduced in both the liver and serum in this mouse model of disease.

"While chronic hepatitis B virus is currently treated with oral antiviral agents or injectable interferons, these treatments do not clear HBV and do not effectively clear HBV antigens from these patients. As a result, patients are unable to fully control HBV infection and achieve sustained disease remission. Many of these patients are at elevated risk for severe liver complications such as cirrhosis and primary liver cancer. By targeting and suppressing viral mRNAs in the liver, treatment with ISIS-HBV<sub>Rx</sub> added to current therapies could result in greater viral inhibition and permit greater immune system activity against the virus," said Richard Geary, Ph.D., senior vice president, development at Isis. "Based on all of the preclinical data, including the animal data that will be presented at EASL, we initiated a Phase 1 study of ISIS-HBV<sub>Rx</sub> late last year, which we plan to complete this year."

The Phase 1 study of ISIS-HBV<sub>Rx</sub> is a randomized, placebo-controlled, dose-escalation study in approximately 30 healthy volunteers. This study is designed to evaluate the safety, tolerability, and pharmacokinetics of single and multiple doses of ISIS-HBV<sub>Rx</sub>. ISIS-HBV<sub>Rx</sub>, formerly referred to as ISIS-GSK3<sub>Rx</sub>, is an investigational drug that is designed to target viral mRNA and reduce the production of viral proteins associated with HBV infection and replication. ISIS-HBV<sub>Rx</sub> is part of Isis' alliance with GSK. Isis will develop ISIS-HBV<sub>Rx</sub> to completion of Phase 2 proof-of-concept, after which GSK has an exclusive option to in-license and further develop and commercialize ISIS-HBV<sub>Rx</sub>. Isis has already earned \$10 million in milestone payments from GSK for ISIS-HBV<sub>Rx</sub> and is eligible to earn additional pre-licensing milestone payments from GSK as ISIS-HBV<sub>Rx</sub> advances in development. Isis is also eligible to receive double-digit royalties on sales of ISIS-HBV<sub>Rx</sub>.

### **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 31 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO<sup>®</sup>, in the United States and other countries for the treatment of patients with homozygous FH. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

### **ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT**

This press release includes forward-looking statements regarding Isis' collaboration with GSK, the discovery, development, activity, therapeutic potential and safety of ISIS-HBV<sub>Rx</sub> and the therapeutic potential of discovering a drug to treat chronic HBV infection. 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. 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, 2013, which is on file with the SEC. Copies of this 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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