# New Phase II Data Confirm ISIS 14803 Produces Significant Viral Level Reductions in Patients With Drug-Resistant Hepatitis C

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Clinical Investigators Report Data From Two Clinical Trials

BOSTON, Nov. 5 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc., (Nasdaq: ISIS) announced today that its antisense drug ISIS 14803 demonstrated promising antiviral activity by producing up to 3.8 log reductions in plasma virus levels in patients with chronic hepatitis C virus (HCV), in an ongoing Phase II clinical trial. The majority of patients participating in the three month study are HCV genotype 1, the most common and difficult to treat form of HCV, and all but two had been treated previously with interferon. Clinical investigators presented results from this study as well as final data from a previous Phase I/II trial at the 53rd Annual Meeting of The American Association for the Study of Liver Diseases (AASLD) in Boston, Massachusetts.

"The results from this Phase II trial are encouraging. ISIS 14803 reduces viral burden in patients with chronic HCV, many of whom had received prior treatment. We observed significant viral load reductions in patients that had extremely high viral levels and were genotype 1. These two key factors are important as they represent our most difficult clinical challenge," said Stuart C. Gordon, M.D., of William Beaumont Hospital, Royal Oak, Michigan, and first author of the Phase II study.

Results from the Three Month Phase II Clinical Trial

In the study, two doses and two treatment schedules of ISIS 14803 are being evaluated. A total of 43 patients were enrolled in the trial. All patients initially received 2.5 mg/kg of ISIS 14803 three times a week for two weeks. Patients then received 4 mg/kg or 6 mg/kg of ISIS 14803 either once weekly or twice weekly for 10 weeks. The drug was administered by intravenous infusion. At the time of reporting these data, the majority of patients in the once weekly treatment arm are still early in their treatment courses. Thus, data for these patients are not yet available.

Clinical investigators reported that six of 17 patients receiving 6 mg/kg of ISIS 14803 twice a week experienced viral titer reductions of 1.0 - 3.8 logs, with three of these patients experiencing a greater than 3.0 log reduction. Consistent with data reported from a previous clinical trial, this study suggests that elevated levels of liver function tests, including alanine aminotransferase (ALT), may correlate with antiviral activity of ISIS 14803. In the trial, decreases in viral titers were accompanied by asymptomatic transient increases in ALT levels. The ALT flares resolved while dosing with ISIS 14803 continued.

"In addition to the responses observed in this trial to date, ISIS 14803 treatment has also been well tolerated," said Bruce R. Bacon, M.D., James F. King MD Endowed Chair in Gastroenterology, Professor of Internal Medicine, Director, Division of Gastroenterology and Hepatology, Saint Louis University, Saint Louis. "There are no treatment options for drug resistant HCV patients, so we are encouraged by the data from this Phase II trial of ISIS 14803. We look forward to continuing to evaluate whether ISIS 14803 can be a valuable new addition to the HCV treatment armamentarium."

Final Results from the One Month Phase I/II Trial

ISIS 14803 clinical investigators also presented final results of an initial one month Phase I/II study of the antisense drug in patients with chronic HCV. Twenty-eight patients were enrolled in the study, which was designed to evaluate escalating doses of ISIS 14803 administered three times a week for one month by either intravenous infusion or subcutaneous injection. In the trial, five of 28 patients had meaningful viral reductions. Three of 10 patients that received 2 mg/kg of ISIS 14803 experienced 1.3-2.2 log reductions in viral levels. Reductions in viral titers were maintained for more than 40 days. The majority of patients in this study were genotype 1 and all but three patients had failed previous interferon-based therapy. ISIS 14803 was well tolerated in the Phase I/II clinical trial. Adverse events reported were minor. Isis previously reported preliminary data from this trial in June 2001.

"Data reported from the three month Phase II trial confirm and enhance the results of our earlier clinical experience. We are very encouraged by the activity of ISIS 14803 in drug resistant patients and the safety profile of the drug," said F. Andrew Dorr, M.D., Isis' Vice President and Chief Medical Officer. "We believe that ISIS 14803 is the only agent in development to produce viral titer reductions of this magnitude in this patient group."

Hepatitis C causes chronic inflammation of the liver that can go undetected for months or years but is frequently progressive, resulting in life-threatening impairment of liver function. Persistent liver inflammation causes ongoing injury to the cells of the liver. If left untreated, it can lead to liver scarring called cirrhosis, liver failure, possibly liver cancer and death due to the complications of these hepatic insults. Liver complications of chronic HCV infections are the most frequent indication for liver transplantation.

According to the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), HCV is one of the most important causes of chronic liver disease in the U. S. It accounts for approximately 20 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and 30 percent of cirrhosis, end-stage liver disease, and liver cancer. Nearly four million Americans, or 1.8 percent of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. There are at least six major genotypes and more than 50 subtypes of HCV. Genotypes 1a and 1b are the most common in the U.S. Genotypes 2 and 3 are present in approximately 30 percent of patients. There is little difference in the severity of disease or outcome of patients infected with different genotypes. However, patients with genotypes 2 and 3 are more likely to respond to interferon and ribavirin. HCV causes an estimated 8,000 to 10,000 deaths annually in the U.S.

Isis will conduct a live webcast conference call to discuss this release on Tuesday, November 5, at 10:00 am Eastern time. To participate over the Internet, go to www.isispharm.com or to http://www.firstcallevents.com/service/ajwz369460297gf12.html . A replay of the webcast will be available at this address for up to 30 days.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene® (formivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline, with two in late-stage development and six in Phase II human clinical trials. Affinitac™ (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III human clinical trials for Crohn's disease. Isis has a broad patent estate, as the owner or exclusive licensee of more than 1000 issued patents worldwide. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics™ is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at

www.isispharm.com .

This press release contains forward-looking statements about the potential of the investigational compound ISIS 14803 in the treatment of hepatitis C virus. Any statement describing a goal, expectation, intention or belief of the company 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 financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the company's Annual Report on Form 10-K and quarterly report on Form 10-Q for the periods ended December 31, 2001 and June 30, 2002, respectively, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

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