New Data on Capsule Form of ISIS 104838 Demonstrate Antisense Drugs Can Be Administered Orally Orasense Joint Venture Makes Fundamental Advance in Antisense Technology

November 12, 2002

TORONTO, Nov. 12 /PRNewswire-FirstCall/ -- In a Phase I study, a proprietary solid oral formulation of ISIS 104838 achieved drug plasma concentrations sufficient to support further clinical development of oral antisense drugs. This is the first human clinical trial to demonstrate the feasibility of solid oral dosing for this class of drugs. The study was conducted by Orasense™, a joint venture of Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and Elan Corporation plc. (NYSE: ELN) of Dublin, Ireland. Based on the new data, Orasense has selected a lead oral formulation that it will further optimize and advance into Phase II clinical trials. Orasense presented these findings today at the 2002 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition in Toronto, Ontario. ISIS 104838 is an antisense inhibitor of tumor necrosis factor-alpha (TNF-alpha), which is a naturally occurring cytokine that is involved in the development and progression of many inflammatory diseases, including rheumatoid arthritis (RA).

In a randomized Phase I clinical trial involving 12 evaluable healthy volunteers, scientists from Isis and Elan studied the oral bioavailability, or the fraction of a drug dose absorbed, of four novel capsule formulations of ISIS 104838. The goal of the study was to identify a lead formulation to be used for oral development of Isis' proprietary antisense drugs. The best performing capsule formulation achieved a predicted average tissue bioavailability of 10%-15%, based on a mean of 7.1% plasma bioavailability. Cumulative data from multiple animal studies demonstrate plasma bioavailability underpredicts tissue bioavailability. These results indicate that this formulation is likely to achieve sufficient antisense drug concentrations in target tissues to produce therapeutic benefit in a patient convenient form.

"Our work dramatically broadens the therapeutic and commercial potential of antisense technology. Thanks to improved patient convenience, this advance makes antisense drugs a practical treatment for a much wider range of conditions, such as diabetes and cardiovascular diseases," said Stanley T. Crooke, M.D., Ph.D., Isis' Chairman and CEO. "We will take the top performing solid formulation into necessary safety studies and manufacturing development so that we can expeditiously move into Phase II efficacy trials. The creation of an oral formulation for antisense drugs has been and continues to be a top priority for Isis."

"Orasense is the first antisense research program to overcome what was once thought to be a significant technical hurdle," said Greg Hardee, Ph.D., Isis' Vice President, Pharmaceutical Development. "We believe that our ongoing research will result in further advances in oral delivery."

Isis and Elan recently extended their collaboration in the Orasense joint venture through the end of 2002. Orasense was created in 1999 to develop an oral delivery platform for Isis' second-generation antisense drugs, and to create an oral formulation of ISIS 104838 for the treatment of RA.

Isis is currently conducting two Phase II studies of ISIS 104838 administered subcutaneously and intravenously in patients with RA. ISIS 104838 is based on Isis' proprietary second-generation antisense chemistry. Currently, Isis has five additional second-generation products in its development pipeline to treat diabetes, diabetic retinopathy, multiple sclerosis and cancer.

According to the Arthritis Foundation, RA affects 2.1 million Americans, predominately women. RA is a systemic disease that affects the entire body and is one of the most common forms of arthritis. RA is characterized by the inflammation of the membrane lining in the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling. The synovium can invade locally and causes damage to bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement.

Isis will conduct a live webcast conference call to discuss this release today, Tuesday, November 12 at 5:00 p.m. Eastern time. To participate over the Internet go to www.isispharm.com or http://www.firstcallevents.com/service/ajwz370079792gf12.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 104838 and plans for and prospects of oral formulations of antisense drugs. 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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