Antisense Drug Demonstrates Potential to Treat Progressive Form of ALS

April 27, 2004

- Distinguished Neurologist Presents Research Findings at The American Academy of Neurology Meeting -

SAN DIEGO, April 27 /PRNewswire-FirstCall/ -- In preclinical studies, an antisense drug suppressed the production of the mutant protein Cu/Zn superoxide dismutase (SOD1), a molecule associated with an aggressive form of amyotrophic lateral sclerosis (ALS). Researchers believe that decreasing the amount of mutant SOD1 in the brain of patients with this condition could potentially modify or halt the progression of the disease. Previous attempts to specifically inhibit SOD1 expression using traditional inhibition technology have proven unsuccessful. Leading neurodegenerative investigators Richard A. Smith, M.D., Center for Neurologic Study, and Don Cleveland, Ph.D., UCSD Ludwig Institute for Cancer Research, San Diego, conducted this study with funding from The ALS Association. Dr. Smith presented the findings today at the 56th Annual Meeting of the American Academy of Neurology.

In the study, Drs. Smith and Cleveland administered the antisense inhibitor intraperitoneally (directly into the abdomen) and intraventricularly (directly into the brain) to rodents expressing SOD1 over a period of weeks. Rodents receiving the antisense inhibitor intraperitoneally showed a 90% reduction in SOD1 messenger RNA (mRNA) expression in the liver, an organ in which antisense drugs readily accumulate. Animals receiving the inhibitor intraventricularly showed a 50% reduction in SOD1 mRNA levels in brain and spinal cord tissues, accompanied by a significant reduction in SOD1 protein levels. Based on these findings, researchers concluded antisense drugs targeting SOD1 could potentially benefit people with ALS. Drs. Smith and Cleveland collaborated with Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) to develop the proprietary antisense inhibitor.

"If these drugs work as well in humans as they do in the laboratory, there is a good chance we can come up with a molecular therapy for familial ALS as well as for other neurodegenerative disorders," said Dr. Smith. "Although a relatively small group of patients have this much more aggressive form of ALS, they typically have shorter survival rates than the majority of ALS patients. It is our hope that we could slow or arrest disease progression using an antisense therapeutic in this subgroup of patients."

"This study is an excellent example of the versatility of antisense to target disease-associated proteins that cannot be approached with other technologies due to lack of specificity," said Frank Bennett, Ph.D., Vice President of Antisense Research for Isis. "Drs. Smith and Cleveland's findings are encouraging and we hope to move these compounds forward in order to better understand their potential for treating this form of ALS and to broaden the application of antisense into numerous neurodegenerative disorders."

About the Investigators

Dr. Don Cleveland is in the Ludwig Institute for Cancer Research and Professor of Medicine, Neurosciences and Cellular and Molecular Medicine at the University of California, San Diego. Dr. Richard Smith is Director of the Center for Neurologic Study in San Diego and a Skaggs Clinical Scholar at Scripps Research Institute. Both are members of the Laboratory for ALS Research in San Diego. (http://ludwig.ucsd.edu/ClevelandLabCMM/ALSgroup.html).

About ALS

Amyotrophic lateral sclerosis (ALS), often referred to as "Lou Gehrig's disease," is a progressive fatal neurodegenerative disease that attacks nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually lead to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With all voluntary muscle action affected, patients in the later stages of the disease become totally paralyzed. Nearly a decade ago, ALS researchers showed that genetic mutations affecting the SOD1 protein contribute to familial ALS (FALS). While researchers understand that mutant SOD1 is detrimental, its specific biological role in ALS is yet unidentified.

It is estimated that as many as 30,000 Americans may have the disease at any given time with more than 5,000 new cases in the U.S. diagnosed each year. More people die each year of ALS than of Huntington's disease or multiple sclerosis. Life expectancy of ALS patients averages about 2-5 years from the time of diagnosis.

About The ALS Association

ALSA is the only national not-for-profit voluntary health organization dedicated solely to the fight against ALS. The mission of The ALS Association is to find a cure for amyotrophic lateral sclerosis and improve living with ALS. ALSA is one of the largest sources of private funding for ALS-specific scientific research around the world.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 11 antisense products in development to treat metabolic, cardiovascular, inflammatory and viral diseases and cancer. Through its Ibis Therapeutics® program, Isis is developing a biosensor to identify infectious organisms, and discovering small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,300 issued patents worldwide. Additional information about Isis is available at www.isispharm.com

This press release contains forward-looking statements concerning the development, therapeutic potential and safety of antisense inhibitors targeting SOD1 and in treating ALS. 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. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in Isis' Annual Report on form 10-K for the year ended December 31, 2003, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

SOURCE Isis Pharmaceuticals, Inc.