Isis Pharmaceuticals Demonstrates The Potential Of Single-Stranded RNA-Like Antisense Technology To Activate The RNAi Pathway

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CARLSBAD, Calif., Aug. 30, 2012 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today the publication of two papers in the journal *Cell* demonstrating that single-stranded short interfering RNA (ss-siRNA) molecules distributed broadly, activated the RNA interference (RNAi) pathway and reduced expression of targeted genes in animal models. The RNAi pathway is a mechanism that can be used to inhibit expression of genes. The RNAi pathway has typically been engaged by short double-stranded RNAs (dsRNA). Once engaged, the RNAi mechanism removes the 'sense' strand of the dsRNA leaving a functional 'antisense' single-stranded RNA to bind to the target mRNA and cause degradation. In these studies, Isis scientists and collaborators demonstrated that ss-siRNA molecules can effectively trigger the RNAi pathway and selectively inhibit the expression of a targeted gene.

In the published study titled 'Single-stranded siRNAs activate RNAi in animals', Isis scientists evaluated the absorption, distribution, metabolism and activity of the ss-siRNAs designed to utilize the RNAi pathway. These data show that single-stranded RNA-like antisense oligonucleotides are broadly distributed to and active in multiple organs and effectively engage and trigger the RNAi pathway without the need for complex formulations or delivery vehicles typically necessary for double-stranded RNAi molecules.

"Double-stranded siRNA drugs require complex formulations to achieve sufficient delivery for systemic activity. This requirement has severely limited the development of safe and effective drugs that work through the RNAi pathway. In contrast, single-stranded RNA-like antisense drugs can be administered subcutaneously and distribute to tissues without the need for formulations. In addition, approaching RNAi with single-stranded drugs eliminates the need for the complementary strand, the 'sense' strand, which limits the risk of adverse effects, and reduces the cost of manufacturing," said Stanley T. Crooke, M.D., Ph.D., Chairman of the Board and Chief Executive Officer of Isis. "At Isis, we have made significant breakthroughs in oligonucleotide chemistry developing single-stranded RNA-like antisense drugs that can work through many different antisense mechanisms, including RNaseH, splicing, and now RNAi."

In a separate study also published today in *Cell* titled 'Single-stranded RNAs act through RNAi, allele-selectively target expanded CAG repeats, and potently inhibit huntingtin expression', Isis and collaborators from University of Texas Southwest Medical Center and University of California, San Diego (UCSD) designed ss-siRNA molecules to mimic microRNA activity and selectively inhibit the production of a specific mutant, disease-causing HTT protein that is associated with the cause and progression of Huntington's disease. These data showed that ss-siRNAs engaged the RNAi pathway to produce selective silencing of the huntingtin gene in an animal model of Huntington's disease.

"Together, these data provide compelling evidence that single-stranded oligonucleotides can be designed to exploit the RNAi pathway and silence gene expression of specific mRNAs in target tissues. In our initial experiments with animals, the compounds were well-tolerated even when used at high doses," said David Corey, Ph.D., Professor of Pharmacology at University of Texas, Southwestern Medical Center. "Single-stranded antisense technology provides a new strategy for harnessing the RNAi pathway. It combines the potential of RNAi with the favorable drug properties of single-stranded nucleic acids."

"Working with our colleagues at the University of Texas Southwestern and UCSD, we showed that, using ss-siRNAs, we could selectively target and specifically silence the gene responsible for the disease-causing form of huntingtin protein and exploit the RNAi pathway to produce microRNA-like effects," continued Dr. Crooke. "We believe that this work lays the foundation for the development of a robust, drug discovery platform that takes advantage of using single-stranded RNA-like antisense drugs that harness the power of the RNAi pathway for gene silencing."

The journal articles titled, "Single-Stranded siRNAs Activate RNAi in Animals" and "Single-Stranded RNAs Use RNAi to Potently and Allele-Selectively Inhibit Mutant Huntingtin Expression" and a leading edge preview titled "Singles Engage the RNA Interference Pathway" by Davidson, B.L. and Monteys A.M. are available in the August 31, 2012 edition of Cell.

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 25 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, plans to commercialize Isis' lead product, KYNAMRO™, following regulatory approval. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT
This press release includes forward-looking statements regarding Isis' antisense technology, the discovery, development and therapeutic potential of Isis' antisense drugs and the potential for Isis to develop antisense drugs that work through the RNAi pathway. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, 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, 2011 and its most recent quarterly report on Form 10-Q, 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, including Regulus Therapeutics Inc., its jointly owned subsidiary.

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