



Isis Pharmaceuticals Earns \$3 Million Milestone Payment from Eyetech for FDA Marketing Clearance of Macugen(TM)

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CARLSBAD, Calif., Dec 20, 2004 /PRNewswire-FirstCall via COMTEX/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it has earned a \$3 million milestone from Eyetech Pharmaceuticals, Inc. (Nasdaq: EYET) associated with the marketing clearance of Macugen™ (pegaptanib sodium injection) by the U.S. Food and Drug Administration (FDA). Macugen, a non-antisense drug, is a treatment for patients with wet age-related macular degeneration (AMD). The drug is also in clinical trials for the treatment of diabetic macular edema. In 2002, Eyetech licensed from Isis specific patents necessary to develop, manufacture and commercialize Macugen. In June 2004, Isis earned a \$1 million milestone payment from Eyetech associated with its submission of a New Drug Application (NDA) for Macugen to the FDA. Under the terms of the agreement, Isis may earn additional milestone payments from Eyetech, and will earn royalties on commercial sales of the drug.

"The \$6 million we have earned thus far from our agreement with Eyetech, and our potential to earn significant revenue from future product sales, validates the near and long-term value of our large patent estate," said B. Lynne Parshall, Isis' Executive Vice President and Chief Financial Officer. "To date, we have earned more than \$45 million from licensing our intellectual property. By successfully commercializing our inventions and innovation, we are generating revenue for the continued advancement of our RNA-based drug pipeline, while supporting other companies in bringing valuable new products to market for the benefit of patients."

Isis' chemistry suite of patents represents a subset of Isis' overall intellectual property estate of more than 1,400 issued patents that the company owns or exclusively licenses covering RNA-based drug discovery and development. More specifically, the estate covers fundamental oligonucleotide chemistries; antisense-based gene functionalization and identification of validated target regions of relevant genes; multiple antisense mechanisms; antisense therapeutics; manufacturing; formulations, and delivery of oligonucleotide therapeutics. Additionally, Isis' patents cover Isis' RNA technology for the identification of infectious biological agents (TIGER).

Isis has taken advantage of its work in RNA-based drug discovery and development to build the industry's leading intellectual property position in this field. While Isis continues to patent its inventions, the company actively leverages its intellectual property rights and seeks licensing partners.

About Wet AMD and Macugen

AMD is the leading cause of severe vision loss in Americans age 65 years and over. The "wet" form of macular degeneration accounts for about 10% of all AMD cases. Macugen is a pegylated anti-vascular endothelial growth factor (VEGF) aptamer (an oligonucleotide) which binds to and thus inhibits the activity of VEGF. VEGF is a protein that plays a critical role in angiogenesis (the formation of new blood vessels) and increased permeability (leakage from blood vessels), two of the primary pathological processes responsible for the vision loss associated with wet AMD.

About Isis Pharmaceuticals, Inc.

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 10 antisense products in development to treat metabolic, cardiovascular, inflammatory and viral diseases, and cancer. Through its Isis 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 1,400 issued patents worldwide. Additional information about Isis is available at <http://www.isispharm.com>

This press release contains forward-looking statements concerning Isis Pharmaceuticals, its business relationship with Eyetech Pharmaceuticals and the potential of the company's intellectual property position and potential for future payments to the company related to the success of Macugen. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology and in discovering and commercializing drugs that are safe and effective for use as human therapeutics and in the endeavor of building a business around such products. Actual results could differ materially from those discussed in this press 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 Isis' Annual Report on Form 10-K for the year ended December 31,

2003, and quarterly report on Form 10-Q for the quarter ended September 30, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.

Macugen® is a trademark of Eyetech Pharmaceuticals, Inc.

Ibis Therapeutics® is a registered trademark of Isis Pharmaceuticals, Inc.

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