

## Isis Pharmaceuticals Earns \$1 Million Milestone Payment From Eyetech Related to Filing of Macugen(TM) New Drug Application

June 24, 2004

Company's Leading Intellectual Property Position in RNA-Based Drug Discovery and Development has Generated Approximately \$40 Million in Revenue

CARLSBAD, Calif., June 24 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it has earned a \$1 million milestone from Eyetech Pharmaceuticals, Inc. (Nasdaq: EYET) associated with Eyetech's filing of a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) for Macugen™ (pegaptanib sodium injection) for the treatment of wet age-related macular degeneration (AMD). Macugen is a non-antisense, investigational treatment for ophthalmic diseases, including wet AMD and diabetic macular edema. In 2002, Eyetech licensed from Isis specific patents necessary to develop, manufacture and commercialize Macugen. Under the terms of the agreement, Isis may earn additional milestone and royalty payments from Eyetech.

"This milestone demonstrates the value of our large patent estate, and reflects our ongoing efforts to capture the many near and long-term opportunities our intellectual property provides," said B. Lynne Parshall, Executive Vice President and Chief Financial Officer. "In actively creating opportunities for the industry to access our patents, we are generating revenue for the continued development of our strong product portfolio, while supporting other companies in bringing important new products to market."

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 therapeutic target regions for physiologically relevant genes; antisense drug discovery (multiple mechanisms); antisense therapeutics; manufacturing; formulations, and delivery of oligonucleotide therapeutics and Ibis' 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 position in this field. While Isis continues to patent its inventions, the company actively defends its intellectual property rights and seeks licensing partners. Most recently, in March 2004, Isis and Alnylam Pharmaceuticals established an alliance that combines Isis' intellectual property and development expertise with Alnylam's intellectual property and research expertise in RNAi therapeutics. This alliance is an example of the company's strategy to participate in all areas of RNA-based drug discovery directly and through collaborations with companies focused in specific areas, such as antisense mechanisms and chemistry.

### About Wet AMD

Wet age-related macular degeneration (wet AMD) is the leading cause of severe vision loss in patients older than 50 years of age in the developed world. 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. Macugen is also in Phase 2 clinical trials for diabetic macular edema.

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 1,400 issued patents worldwide. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com)

This press release contains forward-looking statements concerning Isis Pharmaceuticals and the potential of the company's intellectual property position and potential 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 systems used to identify infectious agents, 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 and services. 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 March 31, 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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