Isis Pharmaceuticals Reports New Data From Phase II Clinical Trial Of ISIS 2503 Plus Chemotherapy in Pancreatic Cancer

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Study Results Support Further Development of Antisense Compound

CARLSBAD, Calif., Dec. 18 /PRNewswire-FirstCall/ -- In a Phase II clinical trial of ISIS 2503 in combination with gemcitabine, median survival time was more than six months in patients with pancreatic cancer, exceeding the primary endpoint of the study. Summary results of the Phase II study were described yesterday at the 6th National Institutes of Health Therapeutic Oligonucleotide Interest Group Symposium in Bethesda, Maryland. The North Central Cancer Treatment Group (NCCTG), a North American cancer cooperative group with its research base located at Mayo Clinic in Rochester, Minnesota, designed and conducted the Phase II trial. Mayo Clinic has submitted complete results from the study to the 2003 Annual Meeting of the American Society of Clinical Oncology (ASCO). Based on the findings of this trial, Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) is considering various strategies for potential Phase III development of ISIS 2503 in pancreatic cancer.

"The survival results from this study are encouraging. Adding ISIS 2503 to gemcitabine appears to be of benefit in pancreatic cancer where new treatment options are much needed," said Steven R. Alberts, M.D., a Mayo Clinic oncologist and lead researcher on the study.

The open-label Phase II trial enrolled 48 patients with locally advanced or metastatic pancreatic cancer, who had not received prior chemotherapy for their disease. Each patient received ISIS 2503 by continuous intravenous infusion for two weeks of a three-week cycle in combination with typical doses of gemcitabine on days one and eight. Gemcitabine is the standard of care worldwide for pancreatic cancer.

In the study, 57.5 percent of patients who received ISIS 2503 in combination with gemcitabine survived six months or longer. This final result is consistent with observations made at the planned interim analysis reported earlier this year. Complete results of the study have been submitted to ASCO for presentation at the 2003 annual meeting. As previously reported at the 93rd Annual Meeting of the American Association for Cancer Research in April, the interim analysis showed that 60 percent of patients (12 of 20) had survived six months or longer, with a median survival time for those 20 patients of 6.7 months. These interim results compared favorably to historical gemcitabine pivotal trial results, which have reported a 46 percent six months survival and median survival time of 5.6 months. In the interim analysis, the safety profile of this combination did not appear to be meaningfully different from that of gemcitabine alone.

"Based on these top-line results, randomized trials are warranted. We are considering various strategies, including partnering, for the development of this compound in pancreatic cancer," said F. Andrew Dorr, M.D., Isis Vice President and Chief Medical Officer. "ISIS 2503 is the second drug in Isis' antisense pipeline to show promising activity in a poorly treated form of cancer."

ISIS 2503, an inhibitor of Harvey-ras or H-ras, is also being studied in two Phase II clinical trials for metastatic breast and non-small cell lung cancer. H-ras is a molecule known to be involved in the development and maintenance of human cancers. H-ras is a member of the ras family of proteins, which regulate the process by which cells receive and send signals that affect their behavior. Through an antisense mechanism, ISIS 2503 binds to a mRNA sequence specific to Ha-ras, and thus selectively inhibits production of this protein without inhibiting production of other proteins in the ras family. The specificity of antisense technology makes it possible to inhibit a single family member that may play a role in disease while allowing other family members to continue to perform normal cellular functions. This high degree of selectivity may provide antisense drugs substantial advantage over traditional small molecule drugs in many difficult to treat diseases.

According to the American Cancer Society (ACS), pancreatic cancer is the fourth leading cause of cancer death in men and women in the United States. The ACS estimates that in 2002, about 30,300 people will be diagnosed with pancreatic cancer and nearly 30,000 will die from the disease. For all stages combined, the 1-year survival rate is only 21 percent.

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. Affinitak™ (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 2503 in the treatment of pancreatic and other types of cancer. 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 September 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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