Isis Pharmaceuticals Reports Positive Data From ISIS-TTR Rx in Patients With TTR Amyloidosis

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Up to 92 percent reduction in transthyretin protein in patients with familial amyloid polyneuropathy

CARLSBAD, Calif., April 22, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive data from an ongoing open-label extension (OLE) study of ISIS-TTR_{Rx} in patients with familial amyloid polyneuropathy (FAP). FAP patients completing the ongoing Phase 3 study are eligible to enroll in this OLE study in which all patients receive ISIS-TTR_{Rx}. An analysis conducted on the first group of patients to reach three months of treatment in the OLE study showed a reduction in transthyretin (TTR) protein levels up to 92 percent with a median reduction of 78 percent compared to patients' baseline TTR levels at entry into the Phase 3 study. Patients continue to be enrolled as they complete dosing in the Phase 3 study. These data will be presented today at the American Academy of Neurology meeting in Washington, DC.

"TTR amyloidosis is a devastating progressive and fatal disease. FAP is a genetic disease in which mutations in the TTR gene cause the TTR protein to accumulate as amyloid in tissues, peripheral nerves and major organs, and impair their function. The substantial reduction in TTR protein observed in this study suggests that ISIS-TTR_{Rx} could potentially be an important new treatment option for patients with TTR amyloidosis who have very limited therapeutic options," said Merrill D. Benson, M.D., professor of medical genetics at Indiana University.

"We are encouraged by the high rate of patient retention observed in our Phase 3 registration study and by the high rate of enrollment in the OLE study. We believe that the convenience of a once weekly, at home subcutaneous injection of ISIS-TTR_{Rx} is a significant contributing factor for the high retention rate of our Phase 3 study and for the robust enrollment of our OLE study. In addition, a blinded safety analysis of the ongoing Phase 3 study shows the safety and tolerability profile we have observed to date with ISIS-TTR_{Rx} supports continued development. Notably, the injection site reactions were predominantly mild and infrequent, occurring in only about 1% of all injections," said Brett Monia, senior vice president of drug discovery at Isis Pharmaceuticals. "The substantial reduction in TTR protein together with our safety profile and our high patient retention rate gives us confidence that ISIS-TTR_{Rx} may have a significant impact on the treatment of this disease."

In a platform presentation titled, 'A Phase 3 Study to Evaluate ISIS-TTR_{Rx} in Patients with Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP): Study Design and Baseline Demographics', Dr. Benson reported that in the first thirteen patients to enter the OLE study, reductions of up to 92 percent in TTR protein after thirteen weeks of treatment with ISIS-TTR_{Rx} were observed. Across all patients enrolled in the Phase 3 study, 27 TTR mutations were represented to date, including the Val30Met mutation, which is the most common mutation found in patients with FAP. ISIS-TTR_{Rx} is designed to reduce all forms of TTR, including both mutant and wild type, and therefore should provide therapeutic benefit to any FAP patient regardless of that patient's individual TTR mutation.

ISIS-TTR_{Rx} was also highlighted in a second platform presentation titled, 'Development of ISIS-TTR_{Rx} for Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP)'. In this presentation, Dr. Fred Derosier, executive director of clinical development at Isis Pharmaceuticals, provided an overview of the ISIS-TTR_{Rx} program including:

- The Phase 1 study, in which ISIS-TTR_{Rx} achieved reductions of up to 96 percent in TTR protein levels.
- The ongoing Phase 3 study is designed to assess the effects of ISIS-TTR_{Rx} on neurological dysfunction and on quality of life in patients with FAP. Data from this study is planned for the first half of 2017.
- The open-label extension study of ISIS-TTR_{Rx} in patients with FAP who have completed all fifteen months of dosing in the Phase 3 study.
- An investigator-initiated open-label study being conducted by Dr. Merrill Benson in patients with familial cardiomyopathy (FAC) and senile systemic amyloidosis (SSA). This ongoing study is designed to assess the safety, tolerability and efficacy of ISIS-TTR_{Rx} in these patients.
- A Phase 3 study in patients with TTR-related cardiomyopathy that GSK anticipates initiating later this year.
- A Phase 3 study in Japan in patients with FAP that GSK anticipates initiating later this year.

About TTR Amyloidosis and ISIS-TTR_{Rx}

ISIS-TTR_{Rx} is a gen 2.0+ antisense drug Isis is developing with GSK for the treatment of TTR amyloidosis. ISIS-TTR_{Rx} is administered as a once weekly subcutaneous injection and is designed to inhibit the production of all forms of TTR protein, including both mutant and wild type, offering a unique approach to treat all types of TTR amyloidosis.

The Phase 3 study of ISIS-TTR_{Rx} is a randomized, double-blind, placebo-controlled, international study designed to support an application for marketing approval of ISIS-TTR_{Rx} in patients with FAP. The fifteen month study will measure the effects of ISIS-TTR_{Rx} on neurological dysfunction and on quality-of-life. For further study information, please visit www.clinicaltrials.gov and search for the identifier number NCT01737398.

TTR amyloidosis is a severe, genetic and fatal disease in which patients with TTR amyloidosis experience TTR build up in major organs, including peripheral nerves, heart, intestinal tract, kidney and bladder. Patients with FAP experience ongoing debilitating nerve damage throughout their body

resulting in the progressive loss of motor functions, such as walking. These patients also accumulate TTR in major organs, which progressively impacts their function and eventually leads to death. Therapeutic options for the treatment of FAP are very limited and there are currently no drugs approved for the treatment of FAP in the United States.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 38 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe/rare diseases and cardiovascular diseases. These include ISIS-APOCIII$_{Rx}$, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and partial lipodystrophy; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy and cardiomyopathy forms of TTR amyloidosis; and ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. 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' strategic alliance with GSK, and the development, activity, therapeutic and commercial potential and safety of ISIS-TTR$_{Rx}$. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs 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, 2014, which is on file with the SEC. Copies of this 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.

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