# Isis Pharmaceuticals Reports an Update on ISIS-TTR Rx, Including Positive Data from Multiple Clinical Studies, Presented Today at the EC-ATTR Meeting

November 3, 2015

**Disease stabilization observed in patients with TTR amyloid cardiomyopathy**
**Robust and sustained reductions in TTR protein observed in patients with familial amyloid polyneuropathy**
**GSK to initiate a broad Phase 3 program in patients with TTR amyloid cardiomyopathy**

CARLSBAD, Calif., Nov. 3, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today positive preliminary results from an ongoing investigator sponsored, open-label Phase 2 study in patients with TTR amyloid cardiomyopathy, which included patients with familial amyloid cardiomyopathy (FAC) and patients with wild-type transthyretin amyloidosis (wt-TTR amyloidosis, previously referred to as senile systemic amyloidosis, or SSA). In this study, patients receive one injection of ISIS-$TTR_{Rx}$ once a week. The study will continue for 24 months. Data from patients treated for 12 months were presented today (abstract # PM14) by the lead investigator, Merrill D. Benson, M.D., at the First European Congress on Hereditary ATTR amyloidosis in Paris, France. Isis will review these data and the overall development plan for ISIS-$TTR_{Rx}$ in a webcast scheduled for Tuesday, Nov. 3 at 8:00 a.m. Eastern Time.

"Data from our study is encouraging. The study is designed to monitor progression of cardiomyopathy in patients treated with ISIS-$TTR_{Rx}$. The MRI data measured left ventricular mass for the first three patients to complete 12 months on therapy. These data show evidence of disease stabilization when compared to baseline. These observations compare favorably to those from our previously published natural history data. In the natural history study[1], using the same measurements, we observed disease progression at 12 months," said Merrill D. Benson, M.D., professor of pathology and lab medicine, medical and molecular genetics at Indiana University School of Medicine. "Our previously reported echocardiographic measurements in these patients also showed disease stabilization after six months of ISIS-$TTR_{Rx}$ treatment. The MRI data from longer term treatment I reported today support our earlier observations."

- Patients in Dr. Benson's previously published natural history study with an interventricular septum thickness (IVS) $\geq$1.3cm (mean =1.9) at study entry had a mean ***increase*** of 14 percent in left ventricular mass as measured by MRI at 12 months.
- Patients entering the Phase 2 ISIS-$TTR_{Rx}$ study had baseline IVS $\geq$ 1.3cm (mean =2.03). The first three patients treated with ISIS-$TTR_{Rx}$ had a mean ***decrease*** of 1.9 percent in left ventricular mass from baseline as measured by MRI at 12 months.
- No discontinuations and injection site reactions occurring in less than two percent of all injections, which were predominantly mild. The safety and tolerability profile of ISIS-$TTR_{Rx}$ supports continued development.

Isis Pharmaceuticals also announced new data from the ongoing open-label extension (OLE) study of ISIS-$TTR_{Rx}$ in patients with familial amyloid polyneuropathy (FAP) who have completed the Phase 3 study. An analysis conducted on the first 38 patients to reach at least three months of treatment in the OLE study showed a maximum reduction in TTR protein levels of up to 92 percent with a mean maximum (nadir) reduction of 76 percent as compared to patients' baseline TTR levels at entry into the Phase 3 study. Patients continue to be enrolled in the OLE as they complete the Phase 3 study. In addition, a blinded analysis of the Phase 3 study showed injection site reactions occurring in approximately one percent of all injections, which were predominantly mild. The Phase 3 study is expected to complete enrollment by the end of the year.

"We are encouraged by the substantial reductions in TTR protein we have observed in patients who have a variety of variants of the TTR gene. We believe that the observed tolerability profile and the convenience of dosing ISIS-$TTR_{Rx}$ (one low volume, (1.5 mL) once weekly, subcutaneous injection that enables at home administration) contribute significantly to the high rate of patient retention in our Phase 3 FAP study and the high (100 percent) rate of eligible patients enrolling in the OLE study," said Brett Monia, senior vice president of drug discovery and franchise leader for oncology and rare diseases at Isis Pharmaceuticals. "The substantial reduction in TTR protein together with our tolerability profile suggests that ISIS-$TTR_{Rx}$ has the potential to be an attractive treatment for all forms of TTR amyloidosis."

In a poster presented today titled, 'A phase 3 clinical trial with ISIS-$TTR_{Rx}$, a 2nd-generation antisense oligonucleotide targeting transthyretin (TTR), for the treatment of TTR amyloid cardiomyopathy' (abstract # PM15), GSK provided an overview on the design of the ISIS-$TTR_{Rx}$ Phase 3 study in patients with TTR amyloid cardiomyopathy (CARDIO-TTR). This randomized, double-blind, international, multi-center study will evaluate the efficacy and safety of ISIS-$TTR_{Rx}$ in approximately 500 TTR amyloid cardiomyopathy patients diagnosed with either FAC or wt-TTR amyloidosis. The primary endpoint will be based on clinical composite outcomes that will include mortality, cardiac transplant and cardiovascular hospitalization.

"We are committed to a broad development program for ISIS-$TTR_{Rx}$ to treat all patients who suffer from TTR amyloidosis," said Sarah Boyce, chief business officer at Isis Pharmaceuticals. "This is highlighted by GSK's substantial investment in CARDIO-TTR, which includes both FAC and wt-TTR amyloidosis patients and an additional small Phase 3 FAP study to support regulatory filings in Asia. We are encouraged by the evolving product profile of ISIS-$TTR_{Rx}$ across all forms of TTR amyloidosis as one patient–friendly, once weekly injection, and we believe it has the potential to be the first-in-class and best-in-class RNA-targeted drug. GSK is the right partner for ISIS-$TTR_{Rx}$. They have the resources to support patient diagnosis and access with a global sales effort and operations in over 100 countries. GSK plans to develop ISIS-$TTR_{Rx}$ for TTR amyloidosis patients worldwide."

**ABOUT 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 single 300 mg injection, once weekly, at home self-administered low-volume subcutaneous injection and is designed to inhibit the production of all forms of TTR protein, including both hereditary and wild-type, offering a unique approach to treat all types of TTR amyloidosis. ISIS-TTR$_{Rx}$ has already demonstrated sustained and robust TTR reductions in multiple clinical studies in multiple indications of TTR-related amyloidosis.

ISIS-TTR$_{Rx}$ is currently being evaluated in a Phase 3 randomized, double-blind, placebo-controlled, international study in patients with FAP. The study is 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.

**ABOUT TTR AMYLOIDOSIS**

TTR amyloidosis is a fatal genetic disease in which patients 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. There are an estimated 10,000 FAP patients worldwide.

Patients with FAC experience ongoing debilitating heart damage resulting in progressive heart failure. Therapeutic options for the treatment of FAC are very limited and there are currently no drugs approved for the treatment of FAC. There are an estimated 40,000 FAC patients worldwide.

wt-TTR amyloidosis (previously referred to as senile systemic amyloidosis or SSA) is a form of TTR amyloidosis associated with the aging process and is characterized by deposition of amyloid fibrils derived from normal or wild-type TTR protein. Although the hereditary forms of TTR are more likely to misfold and aggregate in various tissues, the normal or wild-type TTR protein can also cause heart damage. Amyloid deposition is mainly seen in the myocardium, resulting in arrhythmia (atrial fibrillation) and/or heart failure. wt-TTR amyloidosis typically affects male patients over 80 years, but is also indicated in younger patients, with an onset around 50 years. There are an estimated 200,000 patients worldwide.

**Webcast**

At 8:00 a.m. Eastern Time, Nov. 3, 2015, Isis will conduct a webcast to discuss the latest data and overall development plan for ISIS-TTR$_{Rx}$. A live audio webcast of the presentation will be available on the "Investor & Media" section of the Company's website, www.isispharm.com. Interested parties may listen to the call by dialing 877-443-5662. A replay will be available for a limited time. The slides presented on the webcast will be available on Isis' website at www.isispharm.com at the time of the webcast and for a limited time after.

**ABOUT ISIS PHARMACEUTICALS, INC.**

Isis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Isis has created a large pipeline of first-in-class or best-in-class drugs, with over a dozen drugs in mid- to late-stage development. Drugs currently in Phase 3 development include volanesorsen, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and familial partial lipodystrophy; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with all forms of TTR amyloidosis; and ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy. 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 Pharmaceuticals' strategic alliance with GSK, and the development, activity, therapeutic and commercial potential and safety of ISIS-TTR$_{Rx}$ to treat all forms of TTR amyloidosis. 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, 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.



[1]Benson MD et al. Am J Cardiol. 2011 Jul 15;108(2):285-9.

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To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/isis-pharmaceuticals-reports-an-update-on-isis-ttr-rx-including-positive-data-from-multiple-clinical-studies-presented-today-at-the-ec-attr-meeting-300170825.html

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