Ionis Pharmaceuticals Reports Positive Clinical Data on IONIS-TTR Rx at the XV International Symposium on Amyloidosis

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Evidence for disease stabilization observed in patients with TTR amyloid cardiomyopathy
Substantial reductions in both mutant and wild-type TTR protein observed in patients with familial amyloid polyneuropathy

CARLSBAD, Calif., July 7, 2016 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONIS) announced today positive results from two ongoing trials with IONIS-TTR$_{Rx}$:

- An ongoing investigator-sponsored, open-label Phase 2 study in patients with TTR amyloid cardiomyopathy, which includes patients with familial amyloid cardiomyopathy (FAC) and patients with wild-type transthyretin amyloidosis (wt-TTR amyloidosis). The data in a subset of patients treated with IONIS-TTR$_{Rx}$ for 12 months were presented today (abstract # O-72) by the lead investigator, Merrill D. Benson, M.D., at the XV International Symposium on Amyloidosis (ISA) in Uppsala, Sweden.
- In addition, new data from the ongoing open-label extension (OLE) study of IONIS-TTR$_{Rx}$ in patients with familial amyloid polyneuropathy (FAP) who have completed dosing in the Phase 3 NEURO-TTR study presented in a poster at ISA on July 5 showed that both wild-type and mutant TTR levels were substantially reduced and that the reductions observed were approximately equal in magnitude regardless of the presence or location of the mutation.

Phase 2 Investigator-initiated (Benson) Open-label Study Results
"Data from multiple endpoints support cardiomyopathy disease stabilization in patients treated with IONIS-TTR$_{Rx}$. The MRI data demonstrated disease stabilization, as measured by left ventricular mass, as compared to both baseline values and from our published[1] natural history data. The observation of disease stabilization in patients treated for 12 months with IONIS-TTR$_{Rx}$, differs from what we observed in our recent natural history study, which used the same MRI measurements to follow disease progression over a year," said Merrill D. Benson, M.D., professor of pathology and lab medicine, medical and molecular genetics at Indiana University School of Medicine. "Last year, we reported similar data on the first three patients in the study to achieve 12 months of dosing with IONIS-TTR$_{Rx}$. These new data, which now include a total of eight patients out of 22 enrolled who have now been treated with IONIS-TTR$_{Rx}$ for 12 months, support and extend our previous observations."

- Patients entering the Phase 2 IONIS-TTR$_{Rx}$ study had baseline interventricular septum thickness (IVS) ≥1.3cm. In this study, patients receive one injection of IONIS-TTR$_{Rx}$ once a week.
- The first eight patients treated with IONIS-TTR$_{Rx}$ had a mean ***decrease*** of 4 percent in left ventricular mass from baseline as measured by MRI at 12 months. This compares favorably to Dr. Benson's published natural history study in similar patients with an IVS ≥1.3cm at study entry who had a mean ***increase*** of 14 percent in left ventricular mass as measured by MRI at 12 months.
- Patients in the Phase 2 IONIS-TTR$_{Rx}$ study also demonstrated evidence for disease stabilization in multiple additional endpoints at 12 months, including, IVS thickness, global strain, the cardiac biomarker B-type natriuretic peptide (BNP) and the functional endpoint, 6-minute walk test (6MWT).
- Safety and tolerability data were presented on all of patients treated with IONIS-TTR$_{Rx}$ in the Phase 2 IONIS-TTR$_{Rx}$ study (n=22). No drug related serious adverse events have been reported. Three patients developed the need for cardiac pacing. Moderate decreases in platelets were observed in some patients, but no serious platelet declines have been observed to date in this study. Injection site reactions were predominantly mild and infrequent, occurring in less than 2% of all injections. Transient pruritus was observed in two patients. Two patients reported fatigue lasting two to four days after dosing.
- The study is progressing and was recently amended to extend treatment from 24 to 36 months.

Phase 3 NEURO-TTR Open-label Extension (OLE) Study Results
New data from the ongoing open-label extension (OLE) study of IONIS-TTR$_{Rx}$ in patients with familial amyloid polyneuropathy (FAP) who have completed the Phase 3 NEURO-TTR study was also presented at the ISA meeting. An analysis conducted on patients with 12 different mutations who reached up to 12 months of treatment in the NEURO-TTR OLE study showed approximately equal reduction of both wild-type and mutant TTR levels as measured by liquid chromatography-mass spectrometry (LC-MS). Patients continue to be enrolled in the OLE as they complete the Phase 3 NEURO-TTR study. The Phase 3 NEURO-TTR study is expected to complete in the first half of 2017.

"TTR amyloidosis is a progressive, debilitating, fatal disease with multi-organ failure and limited treatment options. TTR amyloidosis patients who

have the cardiomyopathy form of the disease progress rapidly and typically die within three to five years. We are pleased by the positive data from Dr. Benson's ongoing investigator initiated study in patients with TTR amyloid cardiomyopathy. We are also encouraged by the substantial reductions in TTR protein we have observed in patients, which appears to be independent of the presence or nature of the mutation in the TTR gene," said Brett Monia, senior vice president of drug discovery and franchise leader for oncology and rare diseases at Ionis Pharmaceuticals. "We believe that the product profile including the convenience of dosing for IONIS-TTR$_{Rx}$ as one subcutaneous injection, once a week with no premedication requirements contributes significantly to the high rate of patient retention in our Phase 3 NEURO-TTR study and the high rate of eligible patients enrolling in the OLE study. Given the potential risk/benefit profile, we believe IONIS-TTR$_{Rx}$ will be the preferred treatment option for patients with TTR amyloidosis."

ABOUT IONIS-TTR$_{Rx}$

IONIS-TTR$_{Rx}$ is a Generation 2+ antisense drug Ionis is developing for the treatment of TTR amyloidosis. IONIS-TTR$_{Rx}$ is administered as one 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. IONIS-TTR$_{Rx}$ has already demonstrated sustained and robust TTR reductions in multiple clinical studies in multiple indications of TTR-related amyloidosis.

IONIS-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 IONIS-TTR$_{Rx}$ in patients with FAP. The fifteen month study will measure the effects of IONIS-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.

ABOUT IONIS PHARMACEUTICALS, INC.

Ionis 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, Ionis 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 Ionis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; IONIS-TTR$_{Rx}$, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and nusinersen, a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' alliance with GSK, and the development, activity, therapeutic and commercial potential and safety of IONIS-TTR$_{Rx}$ to treat all forms of TTR amyloidosis. Any statement describing Ionis' 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. Ionis' 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 Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2015, 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, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals™ is a trademark o**f**onis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark o**f**onis Pharmaceuticals, Inc.

[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/ionis-pharmaceuticals-reports-positive-clinical-data-on-ionis-ttr-rx-at-the-xv-international-symposium-on-amyloidosis-300295098.html

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