



## **Ionis Announces Submission of New Drug Application (NDA) for Inotersen to the U.S. FDA**

November 6, 2017

CARLSBAD, Calif., Nov. 6, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that the company submitted a new drug application (NDA) to the U.S. Food and Drug Administration for inotersen, an investigational medicine for the treatment of patients with hereditary TTR amyloidosis (hATTR).



"The filing of the NDA for inotersen in the U.S. is an important milestone for Ionis. We would like to thank the patients suffering with hATTR, their families and the healthcare professionals who participated in the NEURO-TTR study and were instrumental in reaching this goal. In the Phase 3 NEURO-TTR study, inotersen-treated patients experienced significant benefit in their quality of life and in measures of neurological disease compared to placebo-treated patients, and 50% of inotersen-treated patients improved in their quality of life from baseline. We believe that the benefit seen with inotersen treatment in the NEURO-TTR study, combined with its superior convenience, could make inotersen the treatment of choice for this patient population," said Sarah Boyce, chief business officer of Ionis Pharmaceuticals. "As part of our commitment to patients with this devastating, progressive and fatal disease, we have initiated our plan to open an expanded access program for eligible patients, with the first wave of sites to open in the U.S. in the coming months. We are also making substantial progress in advancing inotersen to market and are in advanced discussions with potential partners who could work with us to commercialize inotersen outside of North America while we commercialize or co-commercialize inotersen in North America. We believe the right partner can maximize the commercial success of inotersen."

"Today, patients with hATTR have no approved therapeutic options in the U.S. and are often misdiagnosed over the course of many years because symptoms of the disease overlap with other, more common conditions. This can lead to ineffective, costly and often unnecessary invasive treatment," said Dr. Morie A. Gertz, Roland Seidler Jr. Professor of the Art of Medicine and Chair of the Department of Internal Medicine Mayo Clinic in Rochester, Minnesota and study author. "I am encouraged by data from the Phase 3 NEURO-TTR study, which demonstrated substantial benefit in both quality of life and disease progression among inotersen-treated patients compared to placebo-treated patients. As we move closer to having a potential therapeutic option to treat this patient population, I am hopeful that physicians will begin to keep hATTR top-of-mind, so that they can connect seemingly disparate symptoms, speed diagnosis and give patients the opportunity to most fully benefit from therapy."

"We are grateful that today, the amyloidosis community of patients, families, and healthcare professionals are one step closer to having an approved treatment that has the potential to halt the progression of this devastating and fatal disease. We are excited about the NEURO-TTR study results and are equally excited with the potential for many patients to participate in the planned expanded access program in the coming months. Ionis has demonstrated great commitment to the advancement of potential new therapies for hATTR and we are excited to continue to collaborate with them closely to someday, potentially find a cure for this terrible disease," said Isabelle Lousada, president and chief executive officer of the Amyloidosis Research Consortium.

### **ABOUT INOTERSEN**

Inotersen is an antisense drug designed to reduce the production of transthyretin, or TTR, to treat patients with TTR amyloidosis (ATTR), a severe, rare and fatal disease. In patients with ATTR, both the mutant and wild type (wt), TTR builds up as fibrils in tissues, such as the peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. As the TTR protein fibrils enlarge, more tissue damage occurs and the disease worsens, resulting in poor quality of life and eventually death.

Inotersen is under regulatory review for marketing authorization in the U.S. and EU. The U.S. Food and Drug Administration has granted Orphan Drug Designation and Fast Track Status to inotersen for the treatment of patients with polyneuropathy due to hATTR. The European Medicines Agency has granted Accelerated Assessment and Orphan Drug Designation to inotersen for the

treatment of patients with ATTR.

### **ABOUT INOTERSEN PHASE 3 CLINICAL STUDY**

Inotersen completed a Phase 3 study, NEURO-TTR, in patients with polyneuropathy due to hereditary TTR amyloidosis (hATTR) in May 2017. Results from the study demonstrated benefit compared to placebo across both primary endpoints of the study: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) and the modified Neuropathy Impairment Score +7 (mNIS+7) at both eight and 15 months of treatment. In addition, consistent and significant benefit was observed in both the Norfolk-QoL-DN and mNIS+7, independent of disease stage, types of mutation, previous treatment with TTR protein stabilizers or presence of cardiomyopathy. Inotersen-treated patients benefited significantly in the quality of life primary endpoint compared to placebo, with a difference in magnitude of 11.68 points in the Norfolk QoL-DN score at 15 months of treatment (mean change from baseline of 0.99 vs. 12.67,  $p=0.0006$ ). Inotersen-treated patients experienced improvement in the Norfolk QoL-DN score compared to placebo-treated patients at 15 months of treatment, and 50% of inotersen-treated patients saw improvement from baseline in the Norfolk QoL-DN score at 15 months of treatment. In addition, clinically meaningful benefit compared to placebo was observed in the SF-36 physical component score, a measure of general health quality of life. Inotersen-treated patients also benefited significantly in the co-primary endpoint of disease control, mNIS+7, with a mean 19.73-point benefit observed after 15 months of treatment, compared to placebo-treated patients ( $p = 0.00000004$ ).

Two key safety issues were identified during the study: thrombocytopenia and safety signals related to renal function. Enhanced monitoring was implemented during the study to support early detection and management of these issues. Serious platelet and renal events were infrequent and easily managed with routine monitoring, which has proven effective since implementation. Other serious adverse events were observed in 24.1% of inotersen-treated patients and 21.7% of placebo-treated patients. No cumulative toxicities have been identified with long-term exposure.

Adverse events occurring in  $\geq 10\%$  of patients and twice as frequently in inotersen-treated patients compared with placebo-treated patients, included thrombocytopenia/platelet count decreases, nausea, pyrexia, chills, vomiting, and anemia. Injection site reactions accounted for less than 1% of all injections and were mild or moderate in severity. There were no discontinuations due to injection site reactions.

The overall mortality rate in the NEURO-TTR study was 2.9% and was lower than mortality rates reported in other studies in hATTR patients. There was a total of five deaths in the study, five (4.7%) in the inotersen arm and zero in the placebo arm. Four deaths in the inotersen arm were associated with disease progression and considered unrelated to treatment. As previously reported, there was one fatal intracranial hemorrhage in conjunction with serious thrombocytopenia. No serious thrombocytopenia was observed following implementation of more frequent monitoring.

### **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 three dozen drugs in development. SPINRAZA<sup>®</sup> (nusinersen) has been approved in global markets for the treatment of spinal muscular atrophy (SMA). Biogen is responsible for commercializing SPINRAZA. Drugs that have successfully completed Phase 3 studies include inotersen, an antisense drug Ionis is developing to treat patients with hereditary TTR amyloidosis (hATTR), and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy. Akcea, an affiliate of Ionis, is a biopharmaceutical company focused on developing and commercializing drugs to treat patients with serious cardiometabolic diseases caused by lipid disorders. If approved, volanesorsen will be commercialized through Ionis' affiliate, Akcea. Inotersen filings for marketing approval have been submitted in the U.S. and EU. Volanesorsen filings for marketing approval have been submitted in the U.S., EU, and Canada. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at [www.ionispharma.com](http://www.ionispharma.com).

### **IONIS' FORWARD-LOOKING STATEMENT**

This press release includes forward-looking statements regarding the therapeutic and commercial potential of inotersen and other products in development. 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, 2016, 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<sup>™</sup> is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics<sup>™</sup> is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZA<sup>®</sup> is a registered trademark of Biogen.

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