New England Journal of Medicine publishes study results evaluating Ionis antisense therapy in treatment of patients with hereditary angioedema

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- Compassionate-use study supports continued development of IONIS-PKK-LRx as an experimental treatment to reduce acute attacks of hereditary angioedema

CARLSBAD, Calif., Sept. 2, 2020 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced the publication today of the results from a compassionate-use study evaluating IONIS-PKK$_{Rx}$ and IONIS-PKK-L$_{Rx}$ in patients living with severe bradykinin-mediated angioedema in *The New England Journal of Medicine* (NEJM). IONIS-PKK$_{Rx}$ and IONIS-PKK-L$_{Rx}$ are investigational antisense medicines designed to reduce the production of prekallikrein, or PKK, which plays a key role in the activation of inflammatory mediators associated with acute attacks of hereditary angioedema (HAE). In the study, researchers found that the drugs reduced plasma prekallikrein activity levels and showed evidence of clinical efficacy in reducing the number of breakthrough attacks per month in patients over the course of the treatment, including complete resolution in a patient with Type 1 HAE. To view the published study, please visit NEJM.org.

Hereditary angioedema is a rare autosomal dominant disease that results in recurrent, painful attacks of swelling affecting the arms, legs, face, intestinal track and airway. Without preventive treatment, attacks can be frequent and severe and, in some patients, life-threatening. The majority of HAE cases are caused by genetic mutations that lead to either a deficiency (Type 1 HAE) or dysfunction (Type 2 HAE) of C1 esterase inhibitor (C1-INH), which regulates multiple pathways, including the kallikrein-kinin and contact system. In the third, especially rare form of the disorder (Type 3 HAE or HAE-nC1-INH), which occurs predominantly in women, and in which the cause is often unknown, patients have a higher frequency of facial, pharyngeal and tongue swelling.

"The results of this study are encouraging and support continued development of IONIS-PKK-L$_{Rx}$ as a potential treatment in patients with severe hereditary angioedema for whom current therapies offer limited therapeutic benefit. The study also highlights the progress we continue to make advancing investigational medicines that are wholly owned by Ionis," said Richard S. Geary, Ph.D., Ionis' executive vice president of Development and a co-author on the paper published in NEJM.

In the study, two patients – Patient 1 with Type 1 HAE and Patient 2 with Type 3 HAE – were first treated with IONIS-PKK$_{Rx}$ for a period of 12 to 16 weeks, after which they received IONIS-PKK-L$_{Rx}$ at a dose of 80 mg every three to four weeks for seven to eight months at the time of data analysis. During treatment with the ligand-conjugated IONIS-PKK-L$_{Rx}$ and the unconjugated parent drug, IONIS-PKK$_{Rx}$, there was a clinically meaningful reduction in HAE attack rates in both patients. Plasma prekallikrein activity levels decreased substantially following treatment.

Physicians have long prescribed prophylactic treatment approaches, including C1-INH replacement therapies and more recently inhibitors of plasma kallikrein, to prevent and reduce the severity of HAE attacks. IONIS-PKK-L$_{Rx}$ is an investigational antisense medicine that is being developed because it has the potential to provide significant efficacy with the convenience of once per month low volume subcutaneous injections.

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' business and the therapeutic potential of IONIS-PKK-L$_{Rx}$, IONIS-PKK$_{Rx}$ and Ionis' technologies and 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, 2019, and the most recent Form 10-Q quarterly filing, 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.

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About Ionis Pharmaceuticals

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs. We created the first and only approved treatment for children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to potentially treat a broad range of disease, including neurological, cardio-renal, metabolic, infectious, and pulmonary diseases.

To learn more about Ionis visit www.ionispharma.com or follow us on twitter @ionispharma.

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