First Patient Enrolled in Pivotal Study of RG6042 (IONIS-HTT Rx) for People with Huntington's Disease

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First of 4+ Ionis programs expected to advance to pivotal studies this year
Ionis earns $35 million milestone payment

CARLSBAD, Calif., Jan. 28, 2019 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in antisense therapeutics, today announced that its partner Roche, also known as Genentech in the United States, has enrolled the first patient in a pivotal study of RG6042 (IONIS-HTT_{Rx}) for people living with symptoms of Huntington's disease (HD), a hereditary neurodegenerative disorder for which there is currently no approved disease-modifying treatment. RG6042 is the first therapy in pivotal trials designed to target the underlying cause of HD by reducing production of the toxic mutant huntingtin protein (mHTT). Ionis has earned a $35 million milestone payment for the initiation of the study.

"We are pleased that RG6042 has progressed to a Phase 3 study. It is the first of four or more Ionis programs that we anticipate will advance to pivotal studies this year, further proof that we are realizing the potential of our novel antisense technology to deliver transformative medicines to those who need them," said Brett P. Monia, Ph.D., Ionis' chief operating officer. "Our commitment to developing antisense medicines for neurological diseases has led to the commercialization of SPINRAZA, the standard of care treatment for people with all forms of spinal muscular atrophy. Enrollment of the first patient in this pivotal trial represents substantial hope for people living with Huntington's disease and their families."

HD is a devastating and ultimately fatal, hereditary disease resulting in deterioration in mental abilities and physical control. In the U.S., there are approximately 30,000 people with symptomatic HD and more than 200,000 people at risk of having inherited HD.

About Ionis/Roche Collaboration

Roche and Ionis are collaborating to develop antisense drugs to treat HD. In December 2017, Roche licensed IONIS-HTT_{Rx} from Ionis and has renamed the investigational molecule RG6042. In total, Ionis has generated $135 million in up-front, milestone and license payments and is eligible to receive additional milestone payments as RG6042 progresses in development, as well as royalties on sales of the medicine if it is commercialized. Roche is responsible for all RG6042 development, regulatory and commercialization activities and costs. Additional information about clinical trials of RG6042 may be found at https://clinicaltrials.gov/ct2/show/NCT03761849.

In October 2018, Ionis and Roche announced a collaboration to develop IONIS-FB-L_{Rx}, an antisense medicine using Ionis' advanced **LI**gand **C**onjugated **A**ntisense (LICA) technology, for the treatment of complement-mediated diseases. Ionis is eligible to earn additional payments as IONIS-FB-L_{Rx} progresses in development, as well as royalties on sales of the medicine if it is commercialized.

About Ionis Pharmaceuticals

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, proprietary antisense technology platform with the potential to 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 – such as children and adults with spinal muscular atrophy (SMA). We created SPINRAZA® (nusinersen)* and are proud to have brought new hope to the SMA community by developing the first and only approved treatment for this disease.

Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 drugs with the potential to treat patients with cardiovascular disease, rare diseases, neurological diseases, infectious diseases and cancer. We created TEGSEDI™ (inotersen) the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy of hereditary transthyretin (TTR) amyloidosis (ATTR) in adult patients that our affiliate Akcea Therapeutics is commercializing. Together with Akcea, we are also bringing new medicines to patients with cardiometabolic lipid disorders.

To learn more about Ionis follow us on twitter @ionispharma or visit http://ir.ionispharma.com/.

*Spinraza is marketed by Biogen.

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' alliance with Roche and the development, activity, therapeutic potential, commercial potential and safety of IONIS-HTT_{Rx} (RG6042). 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, 2017, and its most recent Form 10-Q quarterly filing, which are 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, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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