Phase 1b/2 Data of Durvalumab Plus Danvatirsen Presented at European Society for Medical Oncology

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Response rate approximately doubled compared to previous studies with durvalumab alone in refractory head and neck cancer

Danvatirsen, Ionis' most advanced Generation 2.5 antisense drug, demonstrated potential to treat intractable cancers

CARLSBAD, Calif., Oct. 22, 2018 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) reported new data today on danvatirsen (formerly IONIS-STAT3-2.5$_{Rx}$, also known as AZD9150) presented at the 2018 European Society for Medical Oncology (ESMO) Annual Congress. The study showed clinical and safety results from a phase 1b/2 trial evaluating danvatirsen, a Generation 2.5 antisense therapy targeting signal transducer and activator of transcription 3 (STAT3), in combination with durvalumab, AstraZeneca's anti-PD-L1 (programmed death ligand-1) antibody, in recurrent metastatic head and neck cancer. The combination treatment resulted in 7% of patients achieving a complete tumor response and 23% achieving either a partial or complete tumor response. This response rate is estimated to be double that with durvalumab alone, based on previous studies in this difficult to treat patient population.

"At AstraZeneca, we are exploring new modalities such as antisense oligonucleotides to expand the range of druggable targets. Our strategy is also to develop novel combinations to overcome key immunosuppressive mechanisms, and thereby expand the potential for anti-tumour activity of immune checkpoint inhibition," said Susan Galbraith, Senior Vice President and Head of Oncology, Innovative Medicines and Early Development Biotech Unit at AstraZeneca. "We are encouraged by the results observed in the SCORES trial of patients with head and neck cancer and remain excited about the potential for this combination."

"AstraZeneca has made important progress in advancing the danvatirsen clinical program. The clinical responses observed in this study along with the strong safety profile exhibited by danvatirsen hold great promise for patients with head and neck cancer and other intractable cancers," said Brett P. Monia, Ph.D., Ionis' chief operating officer. "The results from this study provide additional evidence that our antisense platform can address previously undruggable targets and difficult to reach cell types in the tumor microenvironment. We believe that our Generation 2.5 chemistry will one day deliver new, potent treatment options to patients suffering from a variety of cancers."

AstraZeneca is evaluating danvatirsen in a range of cancer types as part of a broader oncology partnership evaluating Generation 2.5 antisense therapies against undruggable targets either alone or in combination with immuno-oncology agents, including in non-small cell lung cancer, bladder cancer and head and neck cancer. Ionis earned a $17.5 million milestone payment from AstraZeneca for advancing the phase 2 program for danvatirsen. Ionis is eligible for additional developmental and regulatory milestone payments from AstraZeneca, plus royalties on commercial sales of the drug.

About danvatirsen

Danvatirsen is Ionis' most advanced antisense therapy containing Generation 2.5 chemistry. The Generation 2.5 antisense chemistry was developed to increase the potency of antisense drugs. Danvatirsen inhibits the production of signal transducer and activator of transcription 3 (STAT3), a previously undruggable target and an important regulator of immune responses to cancer cells. Inhibition of STAT3 has been shown to broadly enhance the activity of several immune check point therapies in preclinical studies.

About Ionis Pharmaceuticals, Inc.

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 AstraZeneca and the therapeutic and commercial potential of

danvatirsen (formerly known as IONIS-STAT3-2.5$_{Rx}$). 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 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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