

Ionis Earns \$28 Million from AstraZeneca for a New Drug to Treat Cancer

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- AstraZeneca Exercises Option to License IONIS-KRAS-2.5 Rx (AZD4785)

CARLSBAD, Calif., Dec. 16, 2016 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today that it has earned \$28 million from AstraZeneca (NYSE:AZN) following AstraZeneca's completion of IND-supporting studies and license of IONIS-KRAS-2.5_{Rx}, or AZD4785. IONIS-KRAS-2.5_{Rx} is a Generation 2.5 antisense drug discovered by Ionis designed to directly target *KRAS*, one of the most frequently mutated genes in cancer. *KRAS* mutations are thought to underlie the pathogenesis of up to 30% of human tumors. The *KRAS* protein is involved in regulating cell division and tumor cell survival. However, developing therapeutics using traditional drug modalities to block *KRAS* activity has proven difficult. IONIS-KRAS-2.5_{Rx} will be the first drug to enter clinical development that directly targets *KRAS*, regardless of mutation type. AstraZeneca will be responsible for further developing and commercializing IONIS-KRAS-2.5_{Rx}.



Brett Monia, Ph.D., senior vice president of drug discovery at Ionis, said: "We and AstraZeneca are uniquely positioned to advance the first antisense drug in development to target *KRAS* as this is a very challenging target to engage with other therapeutic modalities. Our partner AstraZeneca has extensive experience in successfully developing and commercializing drugs to treat cancer and we look forward to working with them to advance this innovative cancer treatment through clinical development."

As IONIS-KRAS-2.5_{Rx} advances in development, Ionis is eligible to receive up to \$137 million for additional development and regulatory milestone payments. In addition, Ionis is eligible to receive up to low double-digit royalties from sales of the drug.

ABOUT IONIS AND ASTRAZENECA

Ionis and AstraZeneca are collaborating to discover and develop antisense drugs to treat cancer under a Collaboration, License and Development Agreement entered into in December 2012. The collaboration combines AstraZeneca's experience and expertise in developing anti-cancer agents with Ionis' antisense technology platform to broaden Ionis' cancer franchise. With the completion of the IND-supporting studies for IONIS-KRAS-2.5_{Rx}, Ionis has received more than \$85 million in upfront and milestone payments from its oncology collaboration with AstraZeneca and is eligible to earn additional milestone payments as the drug progresses in development as well as royalties on sales of IONIS-KRAS-2.5_{Rx} if it is commercialized. AstraZeneca is also evaluating, as part of the oncology collaboration, another drug to treat cancer, AZD9150 (IONIS-STAT3-2.5_{Rx}), in combination with durvalumab, AstraZeneca's investigational anti-PD-L1 antibody, in patients with head and neck cancer and in patients with diffuse large B-cell lymphoma. The two companies have also formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular, metabolic and renal diseases.

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 TTR amyloidosis; and SPINRAZA™ (nusinersen), a drug licensed by Biogen to treat infantile and later-onset 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.

ABOUT ASTRAZENECA

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three main therapy areas - Oncology, Cardiovascular & Metabolic Diseases and Respiratory. The Company also is selectively active in the areas of autoimmunity, neuroscience and infection. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit www.astrazeneca.com.

IONIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' alliance with AstraZeneca. 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 of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZA™ is a trademark of Biogen.

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Ionis Pharmaceuticals Investor and Media Contact, D. Wade Walke, Ph.D., Vice President, Corporate Communications and Investor Relations, 760-603-2741