Ionis and AstraZeneca Advance New Drug for NASH

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Ionis earns $30 million license fee for IONIS-AZ6-2.5-L Rx

Third drug to enter development under strategic cardiovascular-renal-metabolic collaboration with AstraZeneca

CARLSBAD, Calif., April 9, 2018 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in antisense therapeutics, today announced that it has licensed IONIS-AZ6-2.5-L_{Rx}, or AZD2693, to AstraZeneca (NYSE: AZN) following advancement of the drug into development. IONIS-AZ6-2.5-L_{Rx} is designed to inhibit an undisclosed target to treat patients with nonalcoholic steatohepatitis (NASH). In conjunction with this milestone, global, science-led biopharmaceutical company AstraZeneca will pay a $30 million license fee to Ionis. AstraZeneca will be responsible for further development and commercialization of IONIS-AZ6-2.5-L_{Rx}.

"This is the third drug to enter development under our strategic collaboration with AstraZeneca to discover drugs to treat cardiovascular, renal and metabolic diseases. IONIS-AZ6-2.5-L_{Rx} incorporates many of the advancements we have made in antisense technology, including our LIgand-Conjugated Antisense (LICA) and Generation 2.5 chemistry, and is the second drug in our collaboration to incorporate both modifications. By combining Generation 2.5 and LICA, we generate drugs that have the advantages of both higher affinity chemistry and efficient cell-specific targeting. This combination provides us with drugs that are substantially more potent than either Generation 2.5 or LICA alone, and supports administration of infrequent, very low doses, and even enables the potential for oral dosing," said Brett P. Monia, chief operating officer, senior vice president of antisense drug discovery and translational medicine at Ionis Pharmaceuticals. "We are pleased with how quickly we moved IONIS-AZ6-2.5-L_{Rx} from target validation into development, exemplifying the efficiency of our antisense platform. AstraZeneca has played a strategic role in advancing this program forward by providing both preclinical and development expertise in NASH that has contributed to the rapid advance of this drug into development. We look forward to AstraZeneca moving this program swiftly into clinical testing and ultimately to the market."

As IONIS-AZ6-2.5-L_{Rx} advances in development, Ionis may also receive up to $300 million in additional development and regulatory milestone payments, as well as tiered royalties up to the low teens from sales of the drug.

ABOUT IONIS AND ASTRAZENECA

AstraZeneca and Ionis have a strategic alliance focused on leveraging antisense technology to discover and develop antisense therapies for cardiovascular, metabolic and renal diseases. The collaboration builds on a broad existing relationship between the two companies and is supported by Ionis' expertise in cardiovascular disease and antisense technology and AstraZeneca's drug development expertise and infrastructure. In the collaboration, Ionis is primarily responsible for creating development candidates. AstraZeneca paid Ionis an upfront fee of $65 million at the initiation of the collaboration. Beyond AZD2693, AstraZeneca has the option to license additional antisense drugs upon development candidate nomination and will pay a license fee for each drug licensed plus development and regulatory milestones and sales royalties for each program that AstraZeneca advances. Ionis and AstraZeneca are also collaborating to discover and develop antisense drugs to treat cancer.

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 40 drugs in development. SPINRAZA® (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 ATTR (hATTR) amyloidosis, and volanesorsen, an antisense drug discovered by Ionis and co-developed by Ionis and Akcea Therapeutics, Inc. 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 rare diseases. If approved, inotersen and volanesorsen will be commercialized through Ionis' affiliate, Akcea. Inotersen is under regulatory review in the U.S. and EU. Volanesorsen is under regulatory review 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.

IONIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' alliance with AstraZeneca and the therapeutic and commercial potential of IONIS-AZ6-2.5-L_{Rx} (AZD2693). 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, which is 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.

Ionis Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

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