



Ionis Earns \$75 Million from Bayer for Advancing IONIS-FXI_{Rx} and IONIS-FXI-L_{Rx}

CARLSBAD, Calif., February 14, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today the advancement of IONIS-FXI_{Rx} in clinical development under an existing exclusive license agreement with Bayer. Under this agreement, Ionis will also initiate development of IONIS-FXI-L_{Rx}, which uses Ionis' proprietary **L**igand **C**onjugated **A**ntisense, or LICA, technology. In conjunction with the decision to advance these programs, Ionis will receive a \$75 million payment from Bayer.

"We look forward to continuing the development of IONIS-FXI_{Rx} with Bayer. IONIS-FXI_{Rx} was the first antithrombotic in development to demonstrate the potential to separate antithrombotic activity from bleeding risk. We recently completed a Phase 2 study in patients with end-stage renal disease on hemodialysis, in which IONIS-FXI_{Rx} demonstrated robust reductions in FXI activity and no treatment-related major bleeding," said B. Lynne Parshall, chief operating officer at Ionis Pharmaceuticals. "We are pleased that Bayer has decided to expand our collaboration and initiate development of a LICA antisense drug targeting Factor XI. Our LICA technology enables flexible, low and infrequent doses and dose regimens, which may be preferred for a drug targeting broad indications."

Under the agreement, Ionis plans to conduct a Phase 2b study evaluating IONIS-FXI_{Rx} in approximately 200 patients with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, Ionis plans to rapidly develop IONIS-FXI-L_{Rx} through Phase 1. Following these Ionis-conducted studies and Bayer's decision to further advance these programs, Bayer will be responsible for all subsequent global clinical development activities as well as worldwide regulatory and commercialization activities for both drugs. Ionis is eligible to receive additional milestone payments as each drug advances toward the market. Ionis is also eligible to receive tiered royalties in the low to high twenty percent range on gross margins of both drugs combined.

ABOUT IONIS-FXI_{Rx} and IONIS-FXI-L_{Rx}

IONIS-FXI_{Rx} and IONIS-FXI-L_{Rx} are antisense drugs designed to reduce the production of Factor XI. Factor XI is a clotting factor produced in the liver that is an important component of the coagulation pathway. High levels of Factor XI increase the risk of thrombosis, a process involving aberrant blood clot formation that can be responsible for heart attacks and strokes. People who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleeding risk. Factor XI deficiency results in a lower incidence of thromboembolic events with minimal increase in bleeding risk.

ABOUT LICA

Ionis' proprietary **L**igand **C**onjugated **A**ntisense, or LICA, technology conjugates specific chemical structures or molecules to antisense drugs to increase the efficiency of drug uptake in a particular tissue and increasing drug potency from 20 to over 30 fold compared to non-conjugated antisense drugs. Currently, Ionis has multiple drugs in their pipeline that contain Ionis' most advanced liver-targeting conjugate, an N-acetyl galactosamine, or GalNAc molecule that interact specifically with receptors present on the surface of important liver cells, which increases uptake of the antisense drug in these cells. The higher potency of Ionis' LICA drugs, compared to their non-LICA forms, enables lower and less frequent doses to be used in patients, which has the potential to reduce side effects and improve patient convenience.

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 three dozen drugs in development. SPINRAZA™ (nusinersen) is a drug that has been approved in the U.S. for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. Biogen is responsible for commercialization of SPINRAZA. 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; and IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with TTR amyloidosis. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

IONIS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' alliance with Bayer, the development, activity, therapeutic potential, commercial potential and safety of IONIS-FXI_{Rx} and IONIS-FXI-L_{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, 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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