

Ionis' Factor XI anti-thrombotic medicine advances with Bayer following positive clinical results

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- IONIS-FXI-L_{Rx} Ionis' first-in-class FXI anti-thrombotic medicine, to potentially treat millions of patients globally

CARLSBAD, Calif., Oct. 9, 2019 /PRNewswire/ --Ionis Pharmaceuticals, Inc. (NASDAQ: IONS), the leader in RNA-targeted therapeutics, announced today that the company has been notified by its partner Bayer about the decision to advance IONIS-FXI-L_{Rx} following positive clinical results. IONIS-FXI-L_{Rx} is an antisense medicine being developed to treat patients with clotting disorders.

IONIS-FXI-L_{Rx} utilizes Ionis' advanced **Ligand Conjugated Antisense (LICA)** technology platform and is designed to reduce the production of Factor XI (FXI), a clotting factor produced in the liver. High levels of FXI increase the risk of thrombosis and can be responsible for heart attacks and strokes. Alternatively, individuals deficient in FXI have a lower incidence of thrombosis-related events and little to no increase in bleeding risk.

"Ionis was first to validate Factor XI and the intrinsic coagulation pathway as a novel antithrombotic strategy. Our antisense medicine targeting Factor XI demonstrates potent antithrombotic activity with little to no bleeding in multiple patient populations. This enables, for the first time, the potential to separate anti-thrombotic activity from bleeding risk," said Brett P. Monia, chief operating officer at Ionis. "Considering their vast experience in developing and commercializing medicines to treat thrombosis, along with the significant unmet medical need and the broad market potential for a Factor XI therapy, we believe Bayer is the perfect partner for IONIS-FXI-L_{Rx}. Bayer's decision to advance IONIS-FXI-L_{Rx} into a phase 2 clinical trial highlights their confidence in our LICA technology."

"Bayer and Ionis have a common vision of bringing innovative therapies to patients," said Dr. Joerg Moeller, Member of the Executive Committee of Bayer AG's Pharmaceuticals Division and Head of Research and Development. "We are driving forward the development of our FXI-program and IONIS' FXI-L_{Rx} offers an additional pathway for treating patients for whom there are currently no suitable therapeutic options available."

In May 2015, Ionis entered into an exclusive license agreement with Bayer to develop and commercialize Ionis' programs targeting FXI for the treatment of clotting disorders. Under the agreement, Ionis has generated more than \$185 million to date, including a \$10 million milestone payment Ionis earned with Bayer's continuation decision. Ionis is eligible to receive additional milestone payments as the medicine advances toward the market, as well as tiered royalties in the low to high twenty percent range on gross margins. Bayer will now assume all development, regulatory and commercialization activities and costs.

Review of the full data package by Ionis and Bayer is ongoing, and the positive clinical results will be presented at an upcoming medical congress.

ABOUT IONIS-FXI-L_{Rx}

IONIS-FXI-L_{Rx} is a Generation 2+ ligand-conjugated antisense (LICA) drug designed to reduce the production of Factor XI, 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 blood clot formation inside blood vessels (thrombosis), which can cause heart attacks and strokes. Alternatively, individuals deficient in Factor XI have a lower incidence of thrombosis-related events and little to no increase in bleeding risk. This makes Factor XI an attractive target for an antithrombotic drug because of the potential to separate antithrombotic activity from bleeding risk. Although currently available anticoagulants reduce the risk of thrombosis, these anticoagulants are associated with increased bleeding risk at therapeutic doses, which can lead to major, sometimes fatal bleeding events. In clinical studies evaluating the safety and efficacy of the non-LICA version of IONIS-FXI-L_{Rx} (IONIS-FXI_{Rx}), dose-dependent inhibition of Factor XI activity was demonstrated, which was associated with significant reductions in clotting events and no increase in major bleeding events. These data coupled with data in humans with little to no Factor XI activity provide evidence that IONIS-FXI-L_{Rx} has the potential to be used broadly as an anti-thrombotic in different therapeutic settings for which additional safe and well tolerated anti-thrombotic drugs are needed, especially in patient populations that are at high risk for thrombosis and are also at high risk for bleeding.

ABOUT IONIS PHARMACEUTICALS, INC.

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can 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. We created the first and only approved treatment for both children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to treat a broad range of diseases including cardiovascular diseases, neurological diseases, infectious diseases, pulmonary diseases and cancer.

To learn more about Ionis visit www.ionispharma.com and follow us on twitter @ionispharma.

IONIS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Ionis' alliance with Bayer and the development, activity, therapeutic potential, commercial potential and safety of Ionis' antisense medicine for people with clotting disorders, 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, 2018, and its most recent Form 10-Q quarterly filing, 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.

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