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# Investor News

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Antisense Approach for Clotting Disorders:

## Bayer Licenses ISIS-FXI$_{Rx}$ from Isis Pharmaceuticals to Develop and Commercialize for the Prevention of Thrombosis

**Leverkusen, Germany, May 4, 2015** – Bayer HealthCare (Bayer) has entered into an exclusive license agreement with Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) on ISIS-FXI$_{Rx,}$ an antisense drug in clinical development for the prevention of thrombosis. Under the agreement Bayer will further develop and commercialize ISIS-FXI$_{Rx}$ in areas of high unmet medical need. As part of the clinical development program, Bayer plans to evaluate the therapeutic profile of ISIS-FXI$_{Rx}$ in patients for whom currently available anticoagulants may not be used, such as in patients with a high risk of bleeding due to multiple co-morbidities.

“This first-in-class FXI inhibitor perfectly complements our in-house thrombosis pipeline and is an innovative development candidate for a variety of anti-coagulation needs,” said Dr Joerg Moeller, Member of the Bayer HealthCare Executive Committee and Head of Global Development. “We believe the novel mechanism of Factor XI inhibition may offer an additional pathway for treating patients for whom there are currently no suitable therapeutic options available. We share a common vision with Isis in developing ISIS-FXI$_{Rx}$.”

“We believe Bayer, a leading pharmaceutical company in the treatment of thrombotic disease, is the ideal partner for ISIS-FXI$_{Rx}$. This transaction further demonstrates Bayer’s commitment to the field. Bayer has the expertise, commitment and resources to develop ISIS-FXI$_{Rx}$ in areas where unmet medical needs exist. We are pleased with the value of this partnership, which supports a robust development program to maximize the value of ISIS-FXI$_{Rx}$ globally and which allows us to participate significantly in future commercial success,” said Stanley Crooke, Ph.D, M.D., Chief Executive Officer at Isis

Pharmaceuticals. “We believe that this transaction represents the right deal, with the right partner and the right development plan.”

Under the terms of the agreement, Isis is eligible to receive up to USD155 million in near-term payments, including an immediate USD100 million up-front payment and a USD55 million payment upon advancement of the program following a Phase II study in patients with compromised kidney function. Isis is also eligible to receive milestone payments as the drug advances toward the market. In addition, Isis is eligible to receive tiered royalties in the low to high twenty percent range on gross margins of ISIS-$FXI_{Rx}$. After completion of ongoing activities at Isis, Bayer will assume all global clinical development as well as worldwide regulatory and commercialization responsibilities for ISIS-$FXI_{Rx.}$

This transaction is subject to clearances under the Hart-Scott Rodino Antitrust Improvements Act.

**About ISIS-$FXI_{Rx}$**

ISIS-$FXI_{Rx}$ is an antisense drug in development for the prevention of clotting disorders. Antisense drugs are single-stranded RNA molecules that are complementary to a messenger RNA (mRNA) strand which was transcribed from the DNA strand as part of the protein expression machinery within a cell. Antisense drugs bind to the target mRNA molecules in the cell and inhibit the production of disease-causing proteins. ISIS-$FXI_{Rx}$ targets 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 thrombosis, a process involving aberrant blood clot formation that can be responsible for heart attacks and strokes, while Factor XI deficiency results in a lower incidence of thromboembolic events with minimal increase in bleeding risk. In a Phase II comparator-controlled study evaluating the incidence of venous thromboembolism, or VTE, in patients treated with ISIS-$FXI_{Rx}$ undergoing total knee replacement surgery, patients treated with 300 mg of ISIS-$FXI_{Rx}$ experienced a seven-fold lower rate of VTE as compared with those treated with enoxaparin (4.2% and 30.4%, respectively; $p<0.001$). In this study, ISIS-$FXI_{Rx}$ was generally well tolerated with no observed differences in safety outcomes compared with enoxaparin. The data from this study was published in the New England Journal of Medicine in December 2014.

**About Isis Pharmaceuticals, Inc.**

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis’ broad pipeline

consists of 38 drug candidates to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis has numerous drug candidates in Phase III development in severe/rare diseases and cardiovascular diseases. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

**About Bayer HealthCare**

The Bayer Group is a global enterprise with core competencies in the fields of health care, agriculture and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of around EUR 20.0 billion (2014), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover, develop, manufacture and market products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 60,700 employees (Dec 31, 2014) and is represented in more than 100 countries. More information is available at www.healthcare.bayer.com.

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