Current Agreements

Dealdoc

Licensing agreement for ISIS-FXIRx (updated)

Bayer Healthcare
Ionis Pharmaceuticals

May 04 2015

Licensing agreement for ISIS-FXIRx (updated)

Companies:	Bayer Healthcare Ionis Pharmaceuticals
Announcement date:	May 04 2015
Amendment date:	Feb 14 2017
Deal value, US$m:	375 : sum of upfront and milestone payments

Details

Announcement date:	May 04 2015
Amendment date:	Feb 14 2017
Termination date:	Nov 04 2022
Industry sectors:	Bigpharma Pharmaceutical
Compound name:	Fesomersen (formerly IONIS-FXI-LRx)
Exclusivity:	Exclusive
Asset type:	Compound
Therapy areas:	Cardiovascular » Thrombus (blood clot)
Technology types:	Biological compounds
Deal components:	Licensing Termination
Stages of development:	Preclinical Phase I Phase II
Geographic focus:	Worldwide

Financials

Deal value, US$m:	375 : sum of upfront and milestone payments
Upfront, US$m:	100 : upfront payment 75 : upfront payment received on February 2017
Milestones, US$m:	55 : payment upon advancement of the program following a Phase II study in patients with compromised kidney function n/d : milestone payments as the drug advances toward the market
Royalty rates, %:	n/d : tiered royalties on gross margins of ISIS-FXIRx

Termsheet

November 2022

Ionis Pharmaceuticals announced positive results from the Phase 2b RE-THINC ESRD study of fesomersen (formerly IONIS-FXI-LRx), an investigational antisense medicine designed to reduce the production of Factor XI for the prevention of thrombosis, were presented by Bayer at the American Society of Nephrology's (ASN) Kidney Week 2022.

The RE-THINC ESRD study evaluated fesomersen in patients with end-stage renal disease (ESRD) on hemodialysis.

Ionis to regain rights to fesomersen from Bayer.

February 2017

Ionis Pharmaceuticals, Inc. announced the advancement of IONIS-FXIRx in clinical development under an existing exclusive license agreement with Bayer.

Under this agreement, Ionis will also initiate development of IONIS-FXI-LRx, which uses Ionis' proprietary LIgand Conjugated Antisense, or LICA, technology.

In conjunction with the decision to advance these programs, Ionis will receive a $75 million payment from Bayer.

Under the agreement, Ionis plans to conduct a Phase 2b study evaluating IONIS-FXIRx in approximately 200 patients with end-stage renal disease on hemodialysis to finalize dose selection.

Additionally, Ionis plans to rapidly develop IONIS-FXI-LRx 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.

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5 June 2015

Isis Pharmaceuticals announced that its license agreement with Bayer HealthCare (Bayer) to develop and commercialize ISIS-FXIRx has received clearance under the Hart-Scott-Rodino Antitrust Improvements Act.

Based on this approval, Bayer will pay Isis an immediate $100 million up-front payment.

In total, Isis is eligible to receive up to $375 million in payments, including the upfront payment and a $55 million near-term milestone payment upon advancement of the program following the Phase 2 study in patients with compromised kidney function.

In addition, Isis is eligible to receive tiered royalties in the low to high twenty percent range on gross margins of ISIS-FXIRx.

After completion of ongoing activities at Isis, Bayer will assume all global clinical development as well as worldwide regulatory and commercialization responsibilities for ISIS-FXIRx.

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4 May 2015

Bayer HealthCare has entered into an exclusive license agreement with Isis Pharmaceuticals on ISIS-FXIRx, an antisense investigational drug in clinical development for the prevention of thrombosis.

Under the agreement Bayer will further develop and commercialize ISIS-FXIRx in areas of high unmet medical need.

As part of the clinical development program, Bayer plans to evaluate the therapeutic profile of ISIS-FXIRx in an appropriate patient community.

Isis is eligible to receive near-term payments, including an up-front payment and 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 on gross margins of ISIS-FXIRx.

After completion of ongoing activities at Isis, Bayer will assume all global clinical development as well as worldwide regulatory and commercialization responsibilities for ISIS-FXIRx.

Press Release

November 2022

Ionis announces positive results from fesomersen development program

Positive Phase 2b data from RE-THINC ESRD study of fesomersen in patients on hemodialysis presented at Kidney Week 2022

Ionis to regain rights to fesomersen from Bayer

CARLSBAD, Calif., Nov. 4, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive results from the Phase 2b RE-THINC ESRD study of fesomersen (formerly IONIS-FXI-LRx), an investigational antisense medicine designed to reduce the production of Factor XI (FXI) for the prevention of thrombosis, were presented by Bayer at the American Society of Nephrology's (ASN) Kidney Week 2022. The RE-THINC ESRD study evaluated fesomersen in patients with end-stage renal disease (ESRD) on hemodialysis.

In the study, fesomersen achieved its primary endpoint, demonstrating no increase in the incidence of the composite of major bleeding and clinically relevant non-major (CRNM) bleeding with 24 weeks of treatment. Fesomersen also achieved dose-dependent and sustained median reductions in steady-state FXI levels of 53.1%, 72.2% and 86.6% in the 40 mg, 80 mg, and 120 mg doses of fesomersen, respectively, administered once every 4 weeks. Incidences of dialysis circuit clotting and AV-access thrombosis diminished significantly with decreasing FXI levels, both of which were exploratory efficacy endpoints. Fesomersen showed favorable safety and tolerability with 48 weeks of treatment in this study.

"We are very pleased with the efficacy and safety data seen in the Phase 2b study of fesomersen in patients with ESRD, which we believe supports continued advancement of this potential novel anti-thrombotic therapy for patients with renal and cardiovascular diseases," said Richard S. Geary, Ph.D., executive vice president and chief development officer at Ionis. "We thank Bayer for their partnership in the development of fesomersen. We are focused on getting fesomersen into the hands of a new partner to deliver it to the market and patients in need."

About the RE-THINC ESRD Study

RE-THINC ESRD (NCT04534114) is a randomized, double-blind, placebo-controlled study evaluating the safety, pharmacokinetics and pharmacodynamics of multiple doses of fesomersen in 307 patients with end-stage renal disease on hemodialysis. Study participants were randomized to each of 3 dose cohorts or placebo administered subcutaneously every four weeks for up to 48 weeks. The RE-THINC ESRD study was conducted by Bayer, which licensed fesomersen from Ionis.

About Thrombosis

Thrombosis is the formation of blood clots inside blood vessels. Blood clots can obstruct blood flow to prevent sufficient oxygen flow to tissues and organs. In addition, clot fragments can break off from the blood clot and travel to occlude other parts of the circulation. Thrombosis is responsible for many heart attacks and strokes and is the leading cause of morbidity and mortality worldwide. Current anti-thrombotic treatments include anticoagulants such as warfarin, Factor Xa inhibitors and thrombin inhibitors. Although these therapies are effective at lowering the risk of thrombosis, they can place patients at significant risk of bleeding because they target factors required for normal coagulation.

About Fesomersen

Fesomersen, (formerly IONIS-FXI-LRx) is an investigational antisense medicine designed by Ionis 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 anti-thrombotic medicine because of the potential to separate anti-thrombotic 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.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry-leading cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming a leading, fully integrated biotechnology company.

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

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14 February 2017

CARLSBAD, Calif., Feb. 14, 2017 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) announced today the advancement of IONIS-FXIRx in clinical development under an existing exclusive license agreement with Bayer. Under this agreement, Ionis will also initiate development of IONIS-FXI-LRx, which uses Ionis' proprietary LIgand Conjugated Antisense, 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-FXIRx with Bayer. IONIS-FXIRx 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-FXIRx 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-FXIRx in approximately 200 patients with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, Ionis plans to rapidly develop IONIS-FXI-LRx 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-FXIRx and IONIS-FXI-LRx IONIS-FXIRx and IONIS-FXI-LRx 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 LIgand Conjugated Antisense, 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-TTRRx, 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.

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5 June 2015

Isis Pharma (ISIS)' License Agreement With Bayer (BAY) For ISIS-FXI Rx Receives Hart-Scott-Rodino Approval

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6/5/2015 6:37:05 AM

CARLSBAD, Calif., June 5, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today announced that its license agreement with Bayer HealthCare (Bayer) to develop and commercialize ISIS-FXIRx has received clearance under the Hart-Scott-Rodino Antitrust Improvements Act. Based on this approval, Bayer will pay Isis an immediate $100 million up-front payment. In total, Isis is eligible to receive up to $375 million in payments, including the upfront payment and a $55 million near-term milestone payment upon advancement of the program following the Phase 2 study in patients with compromised kidney function. In addition, Isis is eligible to receive tiered royalties in the low to high twenty percent range on gross margins of ISIS-FXIRx. After completion of ongoing activities at Isis, Bayer will assume all global clinical development as well as worldwide regulatory and commercialization responsibilities for ISIS-FXIRx.

Isis Pharmaceuticals, Inc. ABOUT ISIS-FXIRx

ISIS-FXIRx is an antisense drug in development for the prevention of clotting disorders. It 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 2 comparator-controlled study evaluating the incidence of venous thromboembolic events, or VTEs, in patients treated with ISIS-FXIRx undergoing total knee replacement surgery, patients treated with 300 mg of ISIS-FXIRx 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-FXIRx 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 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.

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 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe/rare diseases and cardiovascular diseases. These include ISIS-APOCIIIRx, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and partial lipodystrophy; ISIS-TTRRx, a drug Isis is developing with GSK to treat patients with the polyneuropathy and cardiomyopathy forms of TTR amyloidosis; and ISIS-SMNRx, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

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4 May 2015

Bayer HealthCare (BAY) Licenses Investigational ISIS FXI(Rx) From Isis Pharma (ISIS) To Develop And Commercialize For The Prevention Of Thrombosis

WHIPPANY, N.J., May 4, 2015 /PRNewswire/ -- Bayer HealthCare (Bayer) has entered into an exclusive license agreement with Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) on ISIS-FXIRx, an antisense investigational drug in clinical development for the prevention of thrombosis. Under the agreement Bayer will further develop and commercialize ISIS-FXIRx in areas of high unmet medical need. As part of the clinical development program, Bayer plans to evaluate the therapeutic profile of ISIS-FXIRx in an appropriate patient community.

"Bayer is committed to developing therapies in areas of patient need and we share a common vision with Isis in developing ISIS-FXIRx," said Dr Joerg Moeller, Member of the Bayer HealthCare Executive Committee and Head of Global Development.

"We believe Bayer, a leading pharmaceutical company in the treatment of thrombotic disease, is the ideal partner for ISIS-FXIRx. This transaction further demonstrates Bayer's commitment to the field. Bayer has the expertise, commitment and resources to develop ISIS-FXIRx 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-FXIRx 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 near-term payments, including an up-front payment and 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 on gross margins of ISIS-FXIRx. After completion of ongoing activities at Isis, Bayer will assume all global clinical development as well as worldwide regulatory and commercialization responsibilities for ISIS-FXIRx.

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

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.

Filing Data

Not available.

Contract

Not available.