Current Agreements

Dealdoc

Co-development, co-promotion and licensing agreement for Apixaban Factor Xa inhibitor

Pfizer
Bristol-Myers Squibb

Apr 26 2007

Co-development, co-promotion and licensing agreement for Apixaban Factor Xa inhibitor

Companies:	Pfizer Bristol-Myers Squibb
Announcement date:	Apr 26 2007
Deal value, US$m:	1000.0 : sum of upfront and milestone payments

Details

Announcement date:	Apr 26 2007
Industry sectors:	Bigpharma Pharmaceutical
Therapy areas:	Cardiovascular » Angina Cardiovascular » Arrhythmia » Atrial fibrillation Cardiovascular » Coronary artery disease Cardiovascular » Peripheral arterial disease Cardiovascular » Thrombus (blood clot) Central Nervous System » Stroke Hematology » Hemophilia Respiratory » Pulmonary embolism
Technology types:	Small molecules
Deal components:	Co-development Co-promotion Licensing
Stages of development:	Phase III
Geographic focus:	Worldwide

Financials

Deal value, US$m:	1000.0 : sum of upfront and milestone payments
Upfront, US$m:	250.0 : upfront payment
Milestones, US$m:	750.0 : based on development and regulatory milestones
Royalty rates, %:	50.0 : share commercialization expenses and profits/losses equally on a global basis
Funding, US$m:	n/d : Pfizer will fund 60% of all planned development costs effective January 1, 2007 going forward, and Bristol-Myers Squibb will fund 40%

Termsheet

Worldwide collaboration to develop and commercialize apixaban, an anticoagulant discovered by Bristol-Myers Squibb being studied for the prevention and treatment of a broad range of venous and arterial thrombotic conditions.

Terms of the apixaban agreement include an upfront payment of $250 million by Pfizer to Bristol-Myers Squibb.

Pfizer will fund 60% of all planned development costs effective January 1, 2007 going forward, and Bristol-Myers Squibb will fund 40%.

Bristol-Myers Squibb may also receive additional payments of up to $750 million based on development and regulatory milestones.

The companies will jointly develop the clinical and marketing strategy of apixaban, and will share commercialization expenses and profits/losses equally on a global basis.

Press Release

07 May 2013

Bristol-Myers Squibb and Pfizer Announce Publication of ARISTOTLE Subanalysis in Circulation

Subgroup analysis demonstrates that the treatment effects of Eliquis® (apixaban) vs. warfarin, across a broad range of warfarin control, are consistent with primary results of ARISTOTLE

ARISTOTLE studied Eliquis vs. warfarin for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

PRINCETON, N.J. & NEW YORK--Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) today announced that results from a prespecified subanalysis of the ARISTOTLE trial were published in Circulation, the peer-reviewed journal of the American Heart Association. Results from this subanalysis showed that the reductions in stroke or systemic embolism, number of major bleeding events and mortality demonstrated with Eliquis® (apixaban) compared to warfarin in the ARISTOTLE trial were consistent across subgroups defined based on levels of International Normalized Ratio (INR) control in patients with nonvalvular atrial fibrillation.

“Concerning the quality of warfarin treatment, there is a large variation in time in therapeutic range among different countries and centers, which affects outcomes. This subanalysis was conducted to determine whether the treatment effects of apixaban were similar in centers and patients with high quality warfarin care”

“Concerning the quality of warfarin treatment, there is a large variation in time in therapeutic range among different countries and centers, which affects outcomes. This subanalysis was conducted to determine whether the treatment effects of apixaban were similar in centers and patients with high quality warfarin care,” said study lead author Dr. Lars Wallentin of Uppsala University in Uppsala, Sweden. “These additional analyses supported that the primary results of ARISTOTLE were consistent across a broad range of quality of warfarin management.”

Variations in time in therapeutic range (TTR) can affect outcomes for atrial fibrillation patients being treated with Vitamin K antagonists such as warfarin for stroke prevention, leading to an increased risk of stroke when INR levels are below, or bleeding when INR levels are above, the therapeutic range. For patients in the ARISTOTLE trial, the quality of warfarin management was defined by TTR, with a target INR of 2.0 – 3.0. In the ARISTOTLE trial, patients in the warfarin group had an INR in the therapeutic range (2.0 to 3.0) for a median of 66.0% of the time. For context, the median time for INR in the therapeutic range varies across the globe. In clinical practice settings in the United States, it is approximately 57-59%.

The ARISTOTLE trial randomized 18,201 patients from 1,034 clinical centers in 39 countries. In this subanalysis, for each patient, a center average TTR (cTTR) was estimated using a linear mixed model based on the real TTRs in warfarin treated patients with a fixed effect for country and random effect for center. Study centers were placed into one of four similarly sized quartile groups based on cTTR (<60.5%; 60.6%-66.3%; 66.4%-71.1%; and >71.2%). The rates of stroke or systemic embolism, major bleeding and mortality were consistently lower with Eliquis than warfarin across the cTTR quartiles. Similar results were seen when an individual TTR (iTTR), predicted using a model including patient characteristics, was examined in a post-hoc analysis.

While demonstrating consistency across a broad range of warfarin control, results of this subanalysis suggest a trend toward reduction of the treatment effects at centers and in patients with predicted excellent INR control. In these centers, interaction tests are less reliable because of low numbers of events, and thereby lack statistical power.

Based on the results of the subanalysis, the benefits of Eliquis compared with warfarin for stroke or systemic embolism, bleeding, and mortality appear similar across the range of centers’ and patients’ quality of INR control.

About ARISTOTLE Trial Design The ARISTOTLE study was designed to demonstrate the efficacy and safety of Eliquis versus warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation. In ARISTOTLE, 18,201 patients were randomized (9,120 patients to Eliquis and 9,081 to warfarin). ARISTOTLE was an active-controlled, randomized, double-blind, multi-national trial in patients with nonvalvular atrial fibrillation or atrial flutter, and at least one additional risk factor for stroke. Patients were randomized to treatment with Eliquis 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, representing 4.7 percent of all patients) or warfarin (target INR range 2.0-3.0), and followed for a median of 1.8 years.

About Atrial Fibrillation Atrial fibrillation is the most common cardiac arrhythmia (irregular heart beat). It is estimated that more than 5.8 million Americans and 6 million individuals in Europe have atrial fibrillation. Nonvalvular atrial fibrillation, or NVAF, is the most common type of atrial fibrillation. The lifetime risk of developing atrial fibrillation is estimated to be approximately 25 percent for individuals 40 years of age or older. One of the most serious medical concerns for individuals with atrial fibrillation is the increased risk of stroke, which is five times higher in people with atrial fibrillation than those without atrial fibrillation. In fact, 15 percent of all strokes are attributable to atrial fibrillation in the U.S. Additionally, strokes due to atrial fibrillation are more burdensome than strokes due to other causes. Atrial fibrillation-related strokes are more severe than other strokes, with an associated 30-day mortality of 24 percent and a 50 percent likelihood of death within one year in patients who

are not treated with an antithrombotic.

About Eliquis® Eliquis® (apixaban) is an oral direct Factor Xa inhibitor. By inhibiting Factor Xa, a key blood clotting protein, Eliquis prevents thrombin generation and blood clot formation. Eliquis is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in the United States, European Union, Canada, Japan, Korea, Mexico, Columbia, Russia, Israel and Australia. Eliquis is approved for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery in a total of 17 regions: Argentina, Australia, Brazil, Canada, Colombia, European Union (which includes 27 member states plus Iceland and Norway), Hong Kong, India, Indonesia, Israel, Peru, Russia, South Korea, Switzerland, Thailand, Turkey and the United Arab Emirates.

IMPORTANT SAFETY INFORMATION FOR ELIQUIS

BOXED WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE.

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (apixaban) (i.e., anaphylactic reactions)

WARNINGS AND PRECAUTIONS Increased Risk of Stroke with Discontinuation of ELIQUIS: Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal bleeding. Concomitant use of drugs affecting hemostasis increases the risk of bleeding including aspirin and other anti-platelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage. There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.

Prosthetic Heart Valves: The safety and efficacy of ELIQUIS has not been studied in patients with prosthetic heart valves and is not recommended in these patients.

ADVERSE REACTIONS The most common and most serious adverse reactions reported with ELIQUIS (apixaban) were related to bleeding.

DISCONTINUATIONS FOR SURGERY AND OTHER INTERVENTIONS ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.

DRUG INTERACTIONS Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Decrease the dose of ELIQUIS to 2.5 mg twice daily when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.

Strong Dual Inducers of CYP3A4 and P-gp: Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke. Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban.

Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see full Prescribing Information including BOXED WARNING and Medication Guide available at www.bms.com.

About the Bristol-Myers Squibb/Pfizer Collaboration In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize Eliquis, an investigational oral anticoagulant discovered by Bristol-Myers Squibb. This global alliance combines Bristol-Myers Squibb's long-standing strengths in cardiovascular drug development and commercialization with Pfizer's global scale and expertise in this field.

About Bristol-Myers Squibb Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit http://www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

Pfizer Inc.: Working together for a healthier world™ At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more, please visit us at www.pfizer.com.

---

26 April 2007

Bristol-Myers Squibb and Pfizer Announce Worldwide Collaboration to Develop and Commercialize Anticoagulant and Metabolic Compounds

-Apixaban Currently in Phase III Trials for Prevention of Venous Thromboembolism and Prevention of Stroke Associated With Atrial Fibrillation-

-Advanced Pre-Clinical Compounds Being Studied in Treatment of Metabolic Disorders-

PRINCETON, N.J., and NEW YORK, April 26 /PRNewswire-FirstCall/ -- Bristol- Myers Squibb Company (NYSE: BMY) and Pfizer Inc (NYSE: PFE) ("companies") today announced a worldwide collaboration to develop and commercialize apixaban, an anticoagulant discovered by Bristol-Myers Squibb being studied for the prevention and treatment of a broad range of venous and arterial thrombotic conditions. In a separate agreement, the companies will also collaborate on the research, development and commercialization of a Pfizer discovery program which includes advanced pre-clinical compounds with potential applications for the treatment of metabolic disorders, including obesity and diabetes.

Phase III trials are currently underway investigating the potential use of apixaban in the prevention of venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of stroke in patients with atrial fibrillation (AF). Phase II trials are studying apixaban in the treatment of acute symptomatic DVT and for the secondary prevention of cardiovascular events in patients with acute coronary syndrome.

Terms of the apixaban agreement include an upfront payment of $250 million by Pfizer to Bristol-Myers Squibb. Pfizer will fund 60% of all planned development costs effective January 1, 2007 going forward, and Bristol-Myers Squibb will fund 40%. Bristol-Myers Squibb may also receive additional payments of up to $750 million based on development and regulatory milestones. The companies will jointly develop the clinical and marketing strategy of apixaban, and will share commercialization expenses and profits/losses equally on a global basis.

Pfizer will be responsible for all research and early-stage development activities for the metabolic disorders program, and the companies will jointly conduct Phase III development and commercialization activities. Bristol-Myers Squibb will make an upfront payment of $50 million to Pfizer as part of this agreement. The companies will share all development and commercialization expenses along with profits/losses on a 60%-40% basis, with Pfizer assuming the larger share of both expenses and profit/losses.

"By combining our company's long-standing strengths in cardiovascular drug development and commercialization with Pfizer's global scale and expertise in this field, we can maximize the potential benefits of apixaban for patients. In addition, the metabolic disorders program complements existing research efforts in another area of significant unmet medical need where Bristol-Myers Squibb is quite active," said Jim Cornelius, chief executive officer, Bristol- Myers Squibb. "This collaboration supports our strategy to focus on serious diseases, maintain commercial emphasis on specialists and high-prescribing primary care physicians, and work with partners to offset the risks inherent with developing certain medicines."

"We're very pleased to collaborate with Bristol-Myers Squibb on the worldwide commercialization of apixaban, which has the potential to be a best- in-class product and would represent an excellent strategic fit with our global cardiovascular franchise," said Jeffrey B. Kindler, chairman and chief executive officer, Pfizer. "We see significant opportunities for an orally active anticoagulant with the clinical profile apixaban has demonstrated to date, particularly because of the clear need for new treatments to combat thrombosis and stroke. This agreement demonstrates our commitment to pursue revenue opportunities both through our business development and external alliances as well as our internal research

and development pipeline."

About Venous Thromboembolism and Atrial Fibrillation

The process by which blood clots occur and travel through the veins is known as venous thromboembolism (VTE), the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). In the U.S., it is estimated that 2 million people develop DVT each year. DVT is the formation of a thrombus (clot) in one of the deep, large veins of the body, such as in the leg or pelvis. A thrombus that breaks free and travels through the circulatory system is called an embolism. An embolism that lodges in a pulmonary artery in the lungs results in pulmonary embolism (PE). PE is a potentially fatal condition if not immediately diagnosed and treated.

Atrial fibrillation (AF) is an abnormal heart rhythm that affects approximately 2.3 million people in North America and 4.5 million people in Europe. The chief hazard of atrial fibrillation is the risk of stroke, which is five times higher in people with AF than in those without AF. AF is responsible for one out of every six ischemic strokes.

About Apixaban

Apixaban is a novel, oral, highly selective, direct factor Xa inhibitor currently in Phase III development. Factor Xa plays a pivotal role in the coagulation cascade and may represent a more targeted approach to anticoagulation therapy compared to current treatments that affect multiple factors in the coagulation pathway. The companies plan to file for U.S. regulatory approval of apixaban for prevention of VTE in the second half of 2009 assuming the successful completion of clinical trials, with filings planned for additional indications beginning in 2010.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global pharmaceutical and related healthcare products company whose mission is to extend and enhance human life.

About Pfizer

Pfizer discovers and develops innovative medicines to treat and help prevent disease for both people and animals. We also partner with healthcare providers, governments and local communities around the world to expand access to our medicines and to provide better quality healthcare and health system support.

Bristol-Myers Squibb And Pfizer Announce Plans To Submit Regulatory Filing For Apixaban In Europe

December 04, 2009

PRINCETON, N.J. & NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer (NYSE: PFE) today announced that the companies are planning to submit an application for regulatory approval of apixaban in Europe for the prevention of venous thromboembolism (VTE) after orthopedic surgery in the first half of 2010. The application will be supported by ADVANCE-2 and ADVANCE-3, two clinical trials that evaluated apixaban versus the European dosing regimen of enoxaparin for prevention of VTE in patients undergoing orthopedic surgery. Results of ADVANCE-2 were first presented in July 2009 at the 22nd Congress of the International Society on Thrombosis and Haemostasis in Boston. The ADVANCE-3 data will be submitted for publication and presentation in 2010.

Apixaban is a novel, oral, highly selective Factor Xa inhibitor, a new class of agents being studied for the potential to prevent and treat blood clots in the veins and arteries.

About the Bristol-Myers Squibb/Pfizer Collaboration

In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize apixaban, an investigational oral anticoagulant discovered by Bristol-Myers Squibb being studied for the prevention and treatment of a broad range of venous and arterial thrombotic conditions. This global alliance combines Bristol-Myers Squibb's long-standing strengths in cardiovascular drug development and commercialization with Pfizer’s global scale and expertise in this field to maximize the potential benefits of apixaban for patients.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company committed to discovering, developing and delivering innovative medicines that help patients prevail over serious diseases. For more information, please visit www.bms.com.

Pfizer Inc: Working together for a healthier world™

At Pfizer, we apply science and our global resources to improve health and well-being at every stage of life. We strive to set the standard for quality, safety and value in the discovery, development and manufacturing of medicines for people and animals. Our diversified global health care portfolio includes human and animal biologic and small molecule medicines and vaccines, as well as nutritional products and many of the world’s best-known consumer products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as the world’s leading biopharmaceutical company, we also collaborate with health care providers, governments and local communities to support and expand access

to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more about our commitments, please visit us at www.pfizer.com

Filing Data

Not available.

Contract

Not available.