



# Subanalysis of Phase III ARISTOTLE Trial of Eliquis® (apixaban) Demonstrated Consistent Results Versus Warfarin in Patients with Nonvalvular Atrial Fibrillation with or without Valvular Heart Disease

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Data show consistent results in reductions in stroke or systemic embolism, fewer major bleeding events, and reductions in all-cause death Post-hoc subanalysis of Phase III ARISTOTLE trial presented today at ESC Congress 2013

PRINCETON, N.J. & NEW YORK--Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) today announced at the ESC Congress 2013, organized by the European Society of Cardiology, results of a post-hoc subanalysis from the Phase III ARISTOTLE trial, which was designed to demonstrate the efficacy and safety of Eliquis compared to warfarin for the prevention of stroke or systemic embolism in nonvalvular atrial fibrillation (NVAf) patients. The ARISTOTLE trial excluded patients with clinically significant mitral stenosis, or a mechanical prosthetic heart valve. This subanalysis evaluated Eliquis compared to warfarin in patients with or without other types of valvular heart disease (VHD) who were eligible for enrollment in the ARISTOTLE trial, including mitral regurgitation, mitral stenosis, aortic regurgitation, aortic stenosis, tricuspid regurgitation, or valve surgery. Those 4,808 patients were the focus of this subanalysis.

The results of this subanalysis were consistent with the results of the overall ARISTOTLE trial and demonstrated that Eliquis compared with warfarin reduced stroke or systemic embolism, caused fewer major bleeding events, and reduced all-cause mortality in NVAF patients with or without VHD. These results were presented in an oral session today at the ESC Congress 2013 in Amsterdam, The Netherlands.

“This subanalysis provides better insight into the efficacy and safety of apixaban in nonvalvular atrial fibrillation patients with certain types of valvular heart disease, which are common in an elderly population,” said study lead author Dr. Alvaro Avezum of the Dante Pazzanese Institute of Cardiology in San Paulo, Brazil. “These patients are generally older and considered to be at greater risk for clinical events than NVAF patients without VHD.”

This subanalysis evaluated data from 4,808 NVAF patients (26.4 percent of the ARISTOTLE trial population) who had both VHD and NVAF. For the purpose of this analysis, subjects with VHD were identified by any history of at least moderate mitral regurgitation (N=3,526), mitral stenosis (N=131), aortic regurgitation (N=384), aortic stenosis (N=887), tricuspid regurgitation (N=2,124), or valve surgery (N=251). Note that some of these patients had more than one valvular abnormality.

In this subanalysis, overall patients with these types of VHD had higher rates of stroke or systemic embolism and of major bleeding than patients without VHD, regardless of treatment. Moreover, patients randomized to Eliquis had lower rates of stroke or systemic embolism and of major bleeding compared with patients randomized to warfarin, both among patients with and without VHD. All p-values for interaction (due to presence or absence of VHD) were non-significant for the major outcomes of stroke and systemic embolism, major bleeding, and death. This means that patients in the ARISTOTLE trial had similar outcomes with Eliquis regardless of whether they had VHD, and that the results of this subanalysis were consistent with the overall results of the trial.

## About ARISTOTLE

The ARISTOTLE study was designed to evaluate the efficacy and safety of Eliquis versus warfarin for the prevention of stroke or systemic embolism. 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 approximately 5.8 million Americans and six million individuals in Europe have 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 (which includes 28 member states plus Iceland and Norway), Japan and a number of other countries around the world. Eliquis is approved for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery in the European Union (which includes 28 member states plus Iceland and Norway) and a number of other countries around the world. Eliquis is not approved for this indication in the U.S. or Japan.

## 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](http://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 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](http://www.pfizer.com).

## Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that Eliquis will be approved for the prevention and treatment of VTE in the U.S. Forward-looking statements in this press release should be evaluated together with

the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2012, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

**PFIZER DISCLOSURE NOTICE:**

The information contained in this release is as of September 3, 2013. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Eliquis (apixaban), including its potential benefits, that involves substantial risks and uncertainties. Such risks and uncertainties include, among other things, (i) the uncertainties inherent in research and development; (ii) uncertainties regarding the commercial success of Eliquis; (iii) whether and when Eliquis will be approved in the EU for the treatment of venous thromboembolic events (VTE) or in the U.S. and other markets for the prevention and treatment of VTE, as well as the decisions of regulatory authorities in those jurisdictions regarding labeling and other matters that could affect the availability or commercial potential of those additional indications; and (iv) competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K/A for the fiscal year ended December 31, 2012 and in its reports on Form 10-Q and Form 8-K.

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