Pfizer Logo

Real-World Evidence on Patients Aged 80 and Older Presented From ARISTOPHANES, the Largest Real-World Data Study Evaluating Oral Anticoagulants Among Patients with Non-Valvular Atrial Fibrillation

Sunday, November 11, 2018 - 12:45pm

- *Eliquis® (apixaban) was associated with lower rates of stroke or systemic embolism and major bleeding in elderly patient populations when compared to rivaroxaban and dabigatran*
- *This oral presentation is one of 16 Bristol-Myers Squibb-Pfizer Alliance-sponsored abstracts featured at the American Heart Association Scientific Sessions 2018*

[PRINCETON, N.J. & NEW YORK] November 11, 2018 – The Bristol-Myers Squibb-Pfizer Alliance today presented new real-world evidence (RWE) from a sub-analysis of the ARISTOPHANES study comparing the safety and effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs), including Eliquis® (apixaban), in non-valvular atrial fibrillation (NVAF) patient populations aged 80 and older (n=46,208). In the analysis, apixaban use was associated with lower rates of both stroke/systemic embolism (S/SE) and major bleeding (MB) compared to dabigatran ([S/SE hazard ratio (HR): 0.65, 95% confidence interval (CI): 0.47-0.89]; [MB HR: 0.60, 95% CI: 0.49-0.73]) or rivaroxaban ([S/SE HR: 0.72, 95% CI: 0.59-0.86]; [MB HR: 0.50, 95% CI: 0.45-0.55]). i Dabigatran was associated with lower rates of MB compared to rivaroxaban (HR: 0.77, 95% CI: 0.67-0.90). [i] Comprehensive details of this retrospective database analysis are included in the study details section below. Please note that Eliquis increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

In this sub-analysis of the ARISTOPHANES study (NCT03087487), patients aged 80 years and older with NVAF who initiated NOACs (apixaban, dabigatran, rivaroxaban) between January 1, 2013 and September 30, 2015 were identified using CMS Medicare and three U.S. commercial claims databases. These four databases cover more than 123 million beneficiaries annually (~38 percent of U.S. population). This analysis included pre-specified outcomes and utilized a statistical method called propensity score matching designed to help balance the characteristics in each treatment group. However, as with all real-world data analyses, the source and type of RWE may limit how results and outcomes can be applied to other patient populations. RWE studies should be used in conjunction with clinical trial evidence to support healthcare decision making. See additional RWE limitations and Eliquis indications and Important Safety Information below.

“Practicing physicians, like myself, are often faced with making a treatment decision for patient populations with limited clinical trial data available,” said Dr. Steven Deitelzweig, one of the lead investigators for the ARISTOPHANES study and Medical Director of Regional Business Development, System Chairman of Hospital Medicine and Associate Professor of Medicine at Ochsner Clinical School. “Real-world evidence

provides additional information that may help inform treatment decisions for select patient sub-populations, such as these patients 80 years of age and older with non-valvular atrial fibrillation."

Under-treatment with anticoagulants is frequently seen among elderly populations, perhaps due to the increased bleeding risk that accompanies aging. [ii,iii] Additional RWE from a sub-analysis of the ARISTOPHANES study comparing the safety and effectiveness of apixaban, rivaroxaban and dabigatran to warfarin in NVAF patients 80 years of age and older were also presented as a moderated poster.[iv]

"Studies such as ARISTOPHANES aim to provide a clearer understanding of the effectiveness and safety associated with a treatment option in elderly non-valvular atrial fibrillation populations in routine clinical practice," said Dr. Christoph Koenen, Head of Cardiovascular Development, Bristol-Myers Squibb. "Real-world data allow us to look at a larger group of patients than those included in the pivotal clinical trials – thereby offering additional insight into everyday clinical questions."

"The BMS-Pfizer Alliance is proud to work with medical experts to share additional insights from the ARISTOPHANES study," said Dr. Rory O'Connor, Chief Medical Officer, Pfizer Internal Medicine. "Our ongoing real-world data program, ACROPOLIS, encompasses analyses that are designed with pre-specified outcomes and methodologies to ensure analyses are transparent and meaningful – ultimately contributing to the medical community's understanding of anticoagulant use."

At this year's AHA Scientific Sessions, the BMS-Pfizer Alliance sponsored a total of 16 abstracts. For a full list of abstract titles and authors being presented, visit: http://www.abstractsonline.com/pp8/#!/4682

The aforementioned study details and observations are as follows:

Lip GYH, et al. Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants Among Very Elderly Patients with Non-Valvular Atrial Fibrillation: An Observational Study.[i]

- One-to-one propensity score matching was conducted between each NOAC cohort, and Cox proportional hazards models were used to estimate the hazard ratios of S/SE and MB
- Apixaban was associated with lower rates of both S/SE (HR: 0.65, 95% CI: 0.47-0.89, p=0.008) and lower rates of MB (HR: 0.60, 95% CI: 0.49-0.73, p<0.001) compared to dabigatran (n=12,954)
- Apixaban was associated with lower rates of both S/SE (HR: 0.72, 95% CI: 0.59-0.86, p<0.001) and lower rates of MB (HR: 0.50, 95% CI: 0.45-0.55, p<0.001) compared to rivaroxaban (n=37,116)
- Dabigatran was associated with lower rates of MB (HR: 0.77, 95% CI: 0.67-0.90, p<0.001) compared to rivaroxaban; there was no statistically significant difference in S/SE rates for dabigatran compared to rivaroxaban (HR: 1.11, 95% CI: 0.84-1.46, p=0.481) (n=13,366)

Limitations of Real-World Data Analyses: Real-world data have the potential to complement randomized controlled trial data by providing additional information about how a medicine performs in routine medical practice. Real-world data analyses have several limitations. For example, the source and type of data used may limit the generalizability of the results and of the endpoints. Observational real-world studies can only evaluate association and not causality. Due to these limitations, real-world data analyses are not used as stand-alone evidence to validate the efficacy and/or safety of a treatment. **It is important to note that, at this time, there are no head-to-head clinical trials comparing direct oral anticoagulants**.

BMS-Pfizer Alliance Real-Word Data (RWD) Program: ARISTOPHANES is part of the Bristol-Myers Squibb-Pfizer Alliance global RWD analysis program, ACROPOLIS™ (**A**pixaban Experien**C**e Through **R**eal-W **O**rld **PO**pu**L**at**I**on **S**tudies), designed to generate additional evidence from routine clinical practice settings to further inform healthcare decision makers, including healthcare providers and payers. The ACROPOLIS

program currently includes analyses of patients from 19 databases around the world, including anonymized medical records, medical and pharmacy health insurance claims data, and national health data systems. To date, the ACROPOLIS program includes a sample size of more than one million lives spanning 11 countries. Analyses of real-world data allow for a broader understanding of patient outcomes associated with Eliquis outside of the clinical trial setting, as well as insight into other measures of healthcare delivery, such as hospitalization and costs.

About Eliquis

Eliquis (apixaban) is an oral selective Factor Xa inhibitor. By inhibiting Factor Xa, a key blood clotting protein, Eliquis decreases thrombin generation and blood clot formation. Eliquis is approved for multiple indications in the U.S. based on efficacy and safety data from multiple Phase 3 clinical trials. Eliquis is a prescription medicine indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF); for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery; for the treatment of DVT and PE; and to reduce the risk of recurrent DVT and PE, following initial therapy.

ELIQUIS Important Safety Information

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures • a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including 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 atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, 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 antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
    - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
    - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours. Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

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

- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION 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. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

Clarithromycin
lthough clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS

- Combined P-gp and Strong CYP3A4 Inducers: Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (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 WARNINGS and Medication Guide, available at www.bms.com.

About ARISTOTL
ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembоLic Events in Atrial Fibrillation) 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, multinational 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 the Bristol-Myers Squibb/Pfizer Collaboration
In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize apixaban, 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 about Bristol-Myers

Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

About 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, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @PfizerNews, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

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 the research, development and commercialization of pharmaceutical products. 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. 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, 2017, 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 November 11, 2018. 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 that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including, without limitation, the ability to meet anticipated clinical trial commencement and completion dates as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of Eliquis; and competitive developments. A further description of risks and uncertainties can be found in Pfizer’s Annual Report on Form 10-K for the fiscal year ended December 31, 2017 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned “Risk Factors” and “Forward-Looking Information and Factors That May Affect Future Results”, as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com. Eliquis® and the Eliquis logo are trademarks of Bristol-Myers Squibb Company. # # # # # i Lip GHY, Keshishian, Li X, et al. Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants Among Very Elderly Patients with Non-Valvular Atrial Fibrillation: An Observational Study. Presented at the American Heart Association (AHA) Scientific Sessions 2018 in Chicago, Illinois. ii Marinigh R, Lip GYH, Fioti N, et al. Age as a Risk Factor for Stroke in Atrial Fibrillation Patients: Implications for Thromboprophylaxis. (J Am Coll Cardiol 2010;56:827–37 iii Xian Y, O’Brien E, et al. Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation. JAMA. 2017;317(10):1057-1067. iv Lip GHY, Keshishian, Li X, et al. Non-Vitamin K Antagonist Oral Anticoagulants Associated with Lower Stroke Rates Compared to Warfarin Among Very Elderly Patients

with Non-Valvular Atrial Fibrillation: An ARISTOPHANES Subgroup Analysis. Presented at the American Heart Association (AHA) Scientific Sessions 2018 in Chicago, Illinois. Contact: Bristol-Myers Squibb Media: Rob Perry, 407-492-4616, rob.perry@bms.com Investors:Timothy Power, 609-252-7509, timothy.power@bms.com Pfizer Inc. Media: Neha Wadhwa, 212-733-2835, neha.wadhwa@pfizer.com Investors: Ryan Crowe, 212-733-8160, ryan.crowe@pfizer.com