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Findings Released from NAXOS, a French Real-World Data Analysis and the Largest Real-World Data Analysis on Oral Anticoagulant Effectiveness and Safety in Europe Among Patients with Non-Valvular Atrial Fibrillation

Sunday, September 01, 2019 - 09:19am

- Eliquis® (apixaban) was associated with a lower rate of major bleeding, stroke and systemic thromboembolic events compared to a vitamin K antagonist
- Results show Eliquis was associated with a lower rate of major bleeding and comparable rates of stroke and systemic thromboembolic events versus dabigatran or rivaroxaban
- This late-breaking presentation is one of 11 Bristol-Myers Squibb-Pfizer Alliance abstracts being presented at the European Society of Cardiology Congress 2019

PRINCETON, N.J., and NEW YORK, N.Y., September 1, 2019 – The Bristol-Myers Squibb-Pfizer Alliance today announced findings from NAXOS (EvaluatioN of ApiXaban in strOke and Systemic embolism prevention in patients with nonvalvular atrial fibrillation in the real-life setting in France), the largest real-world data analysis on oral anticoagulant (OAC) effectiveness and safety in Europe among patients with non-valvular atrial fibrillation (NVAF). NAXOS is a retrospective cohort analysis including nearly all patients in France aged 18 years or older with NVAF newly initiating one of the OACs between 2014 and 2016 (n=321,501). In this analysis, *Eliquis*® (apixaban) use was associated with a lower rate of major bleeding compared to a vitamin K antagonist (VKA) (hazard ratio [HR]: 0.49, 95% confidence interval [CI]: 0.46-0.52), rivaroxaban (HR: 0.63, 95% CI: 0.58-0.67) and dabigatran (HR: 0.85, 95% CI: 0.76-0.95). These data were featured as a late-breaking oral presentation at the European Society of Cardiology (ESC) Congress 2019 in Paris, France (Abstract 1362). Anticoagulants, including *Eliquis*, increase the risk of bleeding and can cause serious, potentially fatal bleeding. Please see important safety information below for *Eliquis*, including BOXED WARNINGS.

In this analysis, *Eliquis* was also associated with lower rates of stroke and systemic thromboembolic events compared to VKA (HR: 0.67, 95% CI: 0.62-0.72) and rates similar to rivaroxaban (HR: 0.97, 95% CI: 0.89-1.05) or dabigatran (HR: 0.92, 95% CI: 0.81-1.06). *Eliquis* was associated with a lower rate of all-cause mortality compared to VKA (HR: 0.56, 95% CI: 0.54-0.58) and rivaroxaban (HR: 0.89, 95% CI: 0.85-0.93) and rates similar to dabigatran (HR: 0.94, 95% CI: 0.87-1.01). It is important to note that there are no head-to-head clinical trials comparing non-vitamin K antagonist OACs.

“The large-scale NAXOS retrospective observational analysis is significant because it included nearly the entire French population with NVAF and is the first nationwide analysis that has evaluated the effectiveness and safety of all available OACs in France,” said Professor Philippe Gabriel Steg, M.D., FESC, FACC, Head of Cardiology Department at Hôpital Bichat, Assistance Publique-Hôpitaux de Paris and Professor at Université de Paris.

“Being able to analyze data from routine clinical practice from a large patient population may help characterize the effectiveness and safety of available anticoagulants.”

Real-world data have the potential to complement randomized controlled clinical trial data by providing additional information about how a medicine performs in routine medical practice. Real-world data analyses also have several limitations. For example, the source and type of data used may limit the generalizability of the results and endpoints. Observational real-world studies can only evaluate association and not causality, and despite the use of methods to address measured confounding, residual confounding may still be present. Due to its limitations, real-world data analyses are not used as stand-alone evidence to validate the efficacy and/or safety of a treatment.

In this analysis, although propensity score adjustment was used to control for multiple confounders, there is still potential for residual bias. Claims for a filled prescription do not indicate that the medication was consumed or taken as prescribed. Also, over-the-counter medications, such as aspirin, and prescription medications provided as samples are not captured in the claims data.

The NAXOS analysis included nearly all patients in France aged 18 years or older with NVAF newly initiating one of the OACs between 2014 and 2016. Patients were identified in the French national health insurance database, SNIIRAM, which covers almost the entire population living in France.[i] The primary objectives were to describe the real-world use of *Eliquis* and the other OACs available in France, and to evaluate the comparative rates of major bleeding (safety), stroke and systemic thromboembolic events (effectiveness), and all-cause mortality in patients with NVAF initiating OAC treatment. Three sensitivity analyses were performed using adjustment on confounding factors, propensity score matching and high-dimensional propensity score matching.

“Results from the NAXOS real-world data analysis of NVAF patients in France add to the growing body of real-world evidence for *Eliquis*, which now includes a sample size of over two million lives globally,” said Dr. Rory O’Connor, Chief Medical Officer, Pfizer Internal Medicine. “We are committed to gaining additional insights about how a treatment performs in the real world to help practicing physicians around the world make informed decisions.”

The prevalence of atrial fibrillation in France was estimated to be between 600,000 and one million people in 2011, according to the most recent available data. [ii]

“As the real-world evidence landscape continues to advance, we are able to provide additional insights from a growing amount of patient data from around the world,” said Mary Beth Harler, Head of Innovative Medicines Development, Bristol-Myers Squibb. “Healthcare practices and patient demographics can differ across geographies, and real-world data from the French NAXOS analysis can help provide healthcare practitioners in the region with relatable insights for their patients with NVAF.”

At this year’s ESC Congress, the BMS-Pfizer Alliance presented a total of 11 abstracts, including the NAXOS oral presentation and NAXOS moderated ePoster, presented on September 1, 2019. For a searchable list of abstracts presented during ESC Congress 2019 visit: http://spo.escardio.org/default.aspx?eevtid=1423&_ga=2.264500296.639120494.1560966763-2024847696.1548859184&_gac=1.19911754.1560284117.Cj0KCQjwov3nBRDFARIsANgsdoF-d-kMh-PnVKRDOSa7eZMk8x0Y4Zik2EYQijWPMmrIghMPnRWy_XwaAt6eEALw_wcB

BMS-Pfizer Alliance Real-Word Data Program: NAXOS is part of the Bristol-Myers Squibb-Pfizer Alliance global real-world data 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. These analyses 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. The ACROPOLIS program currently includes analyses of patients from more than 20 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 two million lives spanning more than 10 countries.

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. The approval of Eliquis for stroke risk reduction in patients with NVAF is based on data from the Phase 3 ARISTOTLE and AVERROES studies of Eliquis in patients with NVAF.

U.S. FDA-Approved Indications for Eliquis: Eliquis is a prescription medicine indicated in the U.S. to reduce the risk of stroke and systemic embolism in patients with 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.
- **Patients with Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs) including ELIQUIS are not recommended for patients with a history of thrombosis who are diagnosed with APS. The efficacy and safety of ELIQUIS in patients with APS have not been established.

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
  Although 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 placebocontrolled 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

- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
  - Labor or delivery: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

Please see full Prescribing Information, including BOXED WARNINGS 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 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.: Breakthroughs that change patients' lives
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, including innovative medicines and vaccines. 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 @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Bristol-Myers Squibb Forward-Looking Statement
This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that future study results will be consistent with the results to date, that Eliquis may not achieve its primary study endpoints or receive regulatory approval for the additional indication described in this release in the currently anticipated timeline or at all and, if approved, whether such product candidate for such additional indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol-Myers Squibb's business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2018, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol-Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

Pfizer Disclosure Notice:The information contained in this release is as of September 1, 2019. 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 endpoints, commencement and/or completion dates for our clinical trials, as well as the possibility of unfavorable clinical trial results, including the possibility of unfavorable new clinical data and

further analyses of existing clinical data; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or 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, 2018 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 Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Available from: https://www.researchgate.net/publication/318736432_Value_of_a_national_administrative_database_to_guide_public_d _to_the_systeme_national_des_donnees_de_sante_S [accessed Jun 07 2019] ii Epidemiology of atrial fibrillation in France: Extrapolation of international epidemiological data to France and analysis of French hospitalization data. (2011, March 02). Retrieved from https://www.sciencedirect.com/science/article/pii/S1875213611000209 Contact: Bristol-Myers Squibb Media: Chrissy Trank, 609-252-5609, christina.trank@bms.com Investors: Timothy Power, 609-252-7509, timothy.power@bms.com Pfizer Inc. U.S. Media: Steven Danehy 212-733-1538, steven.danehy@pfizer.com E.U. Media: Andrew Widger +44 1737330909, Andrew.Widger@pfizer.com Investors: Ryan Crowe, 212-733-8160, ryan.crowe@pfizer.com