Synopsis

Title of Study: A Phase 4 Trial to Assess the Effectiveness of Apixaban Compared With Usual Care Anticoagulation in Subjects With Nonvalvular Atrial Fibrillation Undergoing Cardioversion

Investigators: National coordinating investigators were: [redacted] (Belgium), [redacted] (Germany), [redacted] (Denmark), [redacted] (Sweden), [redacted] (Israel), [redacted] (Italy), [redacted] (Spain), [redacted] (Romania), [redacted] and [redacted] (United States), and [redacted] (Japan).

Study Centers: This was a multicenter study conducted in 35 centers in the United States, 24 centers in Germany, 14 centers in Israel, 12 centers in the Republic of Korea, 8 centers in Belgium, 8 centers in Italy, 8 centers in Romania, 7 centers in Spain, 7 centers in Sweden, 4 centers in Denmark, 4 centers in Japan, and 3 centers in Canada.

Publications: Ezekowitz MD, Pollack CV, Sanders P, et al. Apixaban compared with parenteral heparin and or Vitamin K antagonist in patients with non-valvular atrial fibrillation undergoing cardioversion: Rationale and design of the EMANATE Trial, AmHeart J (2016), doi: 10.1016/j.ahj.2016.06.008.[1]

Study Period: 14 Jul 2014 (First subject first visit) to 08 Feb 2017 (Last subject last visit)

Drug Development Phase: 4

Objectives: The study objective was to assess the occurrence of clinical endpoints in nonvalvular atrial fibrillation (AF) subjects (ie, without rheumatic mitral valve disease, a prosthetic heart valve, or valve repair) indicated for cardioversion and treated with apixaban or usual care (parenteral heparin and/or oral anticoagulation with vitamin K antagonist [VKA], excluding other novel oral anticoagulants).

Clinical endpoints included stroke, systemic embolism, major bleeding, clinically relevant nonmajor bleeding, and all-cause death.

Methodology: This was a randomized, active-controlled, parallel-group, single-period open-label study. Subjects were randomly assigned 1:1 to apixaban or usual care, which was

administered as per local practice and/or approved label. Apixaban or usual care was administered from randomization up to 30 days after cardioversion (or 30 days following Visit 2 in the event a subject spontaneously reverted to normal sinus rhythm before cardioversion) or up to 90 days after randomization if cardioversion was not performed.

Number of Subjects (Planned and Analyzed): Approximately 1500 subjects were planned, and 1500 subjects were randomly assigned to apixaban or usual care. A total of 44 subjects withdrew from the study before the first dose of study drug: 24 subjects withdrew consent, 12 subjects did not meet (or no longer met) the inclusion/exclusion criteria, 2 subjects were discontinued by the investigator, 2 subjects were discontinued by their physician, 1 subject's heart spontaneously returned to a normal sinus rhythm, 1 subject was confirmed to have atrial flutter (not AF), 1 subject was discontinued before dosing due to an AE, and 1 subject was discontinued before dosing due to inability to undergo transesophageal echocardiography [TEE]. The number of subjects analyzed in each of the analysis sets is presented below:

	Number (%) of Subjects		
	Apixaban	**Usual Care**	**Total**
Full analysis set[a]	753	747	1500
Modified full analysis set[b]	739 (98.1)	717 (96.0)	1456 (97.1)
Safety analysis set[c,h]	735 (97.6)	721 (96.5)	1456 (97.1)
Full prevention-evaluable analysis set[d]	723 (96.0)	717 (96.0)	1440 (96.0)
Safety prevention-evaluable analysis set[e]	706 (93.8)	690 (92.4)	1396 (93.1)
Thrombus-positive full analysis set[f]	30 (4.0)	31 (4.1)[i]	60 (4.0)
Thrombus-positive safety analysis set[g]	29 (3.9)	32 (4.3)[i]	60 (4.0)

The denominator to calculate each percentage is the total number of subjects in the full analysis set within each treatment group.

a. The full analysis set contained all randomized subjects and was used under the intent-to-treat principle (ie, subjects were categorized to the treatment group to which they were assigned by the interactive voice response system, regardless of the treatment actually received).

b. The modified full analysis set is the subset of the full analysis set in which the subjects received at least 1 study drug dose. Subjects were summarized according to the treatment they were randomly assigned to.

c. The safety analysis set (as-treated) consisted of all treated subjects (randomized subjects who received at least 1 dose of study drug). For the purpose of safety analyses, subjects were categorized according to the treatment received. Subjects who received both treatments were counted as apixaban-treated.

d. The full prevention-evaluable analysis set is the subset of the full analysis set from which the thrombus-positive subjects are removed.

e. The safety prevention-evaluable analysis set is the subset of the safety analysis set from which the thrombus-positive subjects are removed.

f. The thrombus-positive full analysis set is the complement of the full prevention-evaluable analysis set with only the thrombus-positive subjects included.

g. The thrombus-positive safety analysis set is the complement of the safety prevention-evaluable analysis set with only the thrombus-positive subjects (per investigators' assessments) included.

h. Six subjects were entered in the case report form as having been dispensed incorrect study drug. One of these subjects was randomly assigned to usual care but received apixaban by mistake. The other 5 subjects who were randomly assigned to apixaban discontinued from the study before commencing apixaban dosing, and subsequently received usual care treatment. Thus, a net of 4 subjects were removed from the apixaban group and added to the usual care group in the safety analysis set.

i. For 1 subject, the "no thrombus" checkboxes on the CRF were marked in error. Adjudicators verified this patient did have an atrial thrombus; therefore, the number of thrombus positive usual care patients should be 31 (instead of 30) in the thrombus-positive full analysis set, and 32 (instead of 31) in the thrombus-positive safety analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects aged ≥18 years (≥19 years for the Republic of Korea only and ≥20 years for Japan only) with nonvalvular AF indicated for cardioversion and initiation of anticoagulation in accordance with the approved local label.

Subjects presenting with atrial flutter with no evidence of AF were not eligible for enrollment.

Test Product, Dose and Mode of Administration, Lot Numbers: Apixaban (supplied by the sponsor as 2.5-mg and 5-mg film-coated tablets) was administered orally and dose adjusted as per local label for the prevention of stroke and systemic embolism in subjects with nonvalvular AF. Lot numbers for 5-mg apixaban were: 4B82124, 4G82460, and AAB2726. Lot numbers for 2.5-mg apixaban were: 4B82126, 4G82335, and AAB2730.

Reference Therapy, Dose and Mode of Administration: Usual care treatment (parenteral heparin and/or oral anticoagulation with VKA, excluding other novel oral anticoagulants) was administered as per local label/practice/guidelines. The dosing of VKA was to be individualized according to the subject's sensitivity to the drug as indicated by their international normalized ratio (INR). International normalized ratio monitoring followed the investigator's usual practice. The target therapeutic range for INR was 2.0 to 3.0, per standard practice guidelines. Usual care treatment was locally sourced, and commercial drug supply was provided by the investigator site; no study-related packaging or labeling was performed unless required by local country regulations (South Korea, Romania, Spain, and Italy).

Duration of Treatment: Up to 30 days after cardioversion (or 30 days following Visit 2 in the event a subject had spontaneously reverted to normal sinus rhythm before cardioversion) or 90 days after randomization if cardioversion was not performed.

Criteria for Evaluation: Clinical Endpoints: Clinical endpoints included stroke, systemic embolism, major bleeding, clinically relevant nonmajor bleeding, and all-cause death. Potential clinical endpoints were assessed by the investigator, with respect to the endpoint definitions specified in the protocol, and were recorded on the case report form. Potential clinical endpoints were adjudicated by the independent endpoint adjudication committee. Death events were not required to be adjudicated.

Additional information was collected on cardioversion details (timing, type, attempts, and rhythm status), length of in-hospital stay, and use of image guidance.

Statistical Methods: The study was intended to be descriptive only and randomized 1500 subjects in a 1:1 ratio to apixaban and usual care. There was no hypothesis testing in this study and no power calculation was performed but with a sample size of 1500 subjects, and based upon a randomized, double-blind, Phase 3 trial (ARISTOTLE) warfarin-naïve cohort of subjects (the closest analogous data set to this study design), the predicted incidence of stroke and systemic embolism within 30 days after cardioversion was approximately 0.3% (1 event on apixaban and 3 events on usual care treatment expected). Similarly, the predicted event rate for major bleeding was approximately 0.45% (2 events on apixaban and 5 events on usual care treatment expected).

Adverse events (AEs) and adjudicated bleeding endpoints (major bleeding and clinically relevant nonmajor bleeding) were reported based on the safety analysis set. All other data were reported based on the full analysis set. Full and safety prevention-evaluable analysis data sets were created to exclude subjects identified as already having a thrombus.

The following time periods were defined for reporting clinical endpoints: precardioversion, postcardioversion, and total. The clinical endpoint summaries included individual event rates and their exact 95% confidence intervals (CIs); exact risk ratios and corresponding *P* values from a Fisher's exact test comparing the treatment arms were also presented without any formal testing.

For continuous data, frequencies, means and medians were reported by treatment arms; time-to-event data summaries included tabular and graphical summaries of Kaplan-Meier estimates by treatment, hazard ratios of the treatment effect or other covariates, their 95% CIs and *P* values. For binary endpoints, 95% exact CIs of each event rate were reported by treatment group. The relative risk (ie, risk ratios) was also reported. In the SAS® language, the RELRISK with FMSCORE method option was used in the EXACT statement of PROC FREQ to provide exact unconditional confidence limits for the relative risk.

All safety analyses were conducted on the safety analysis set. All AEs were presented in a data listing. The overall incidence of treatment-emergent AEs (TEAEs) was presented, as was the incidence of TEAEs by early cardioversion (defined as cardioversion that occurred within 7 days from randomization), image guidance at Visit 2, age category, and gender and TEAEs leading to study drug discontinuation. Summary tables for TEAEs were also

presented for relationship to study drug and severity. Treatment-emergent serious AEs (SAEs) were summarized in a table by treatment. All SAEs were presented in the data listings.

All vital sign measurement data were presented in a data listing.

Electrocardiogram results were summarized and presented by treatment. All electrocardiogram data were presented in a data listing. Actual results were summarized by parameter and time point.

Physical examination data were summarized by treatment group and overall and were presented in data listings.

The independent data monitoring committee, in collaboration with the sponsor (Pfizer/Bristol-Myers Squibb) and the executive committee, created a charter that outlined the membership and activities of the data monitoring committee.

Results: A total of 1522 subjects were assessed for eligibility and 1500 subjects were randomly assigned to apixaban or usual care treatment. Overall, 1335 subjects (89.0%) completed the study; 678 (90.0%) in the apixaban group and 657 (88.0%) in the usual care group. The most common reason for not completing the study was withdrawal of consent. Demographics, pertinent medical history, and prior antithrombotic medication history were balanced between the apixaban and usual care treatment groups.

Clinical Endpoints Results: Overall, there were few clinical endpoint events. In the full analysis set, no subjects presented with a stroke in the apixaban group during the study (through study completion/discontinuation), compared with 6 subjects (0.8%) presenting with a stroke in the usual care group (nominal *P*=0.0151). The timing of INR assessments coincided with onset of stroke in 2 of these subjects: in 1 subject INR results were 1.2, 1.4, and 2.8 and in the other subject INR was 1.9. The INR was not recorded at the time of stroke in the remaining 4 subjects. In the full analysis set, all-cause death occurred in 2 subjects (0.27%) in the apixaban group and 1 subject (0.13%) in the usual care group. The relative risk for stroke and all-cause death was zero and 1.9841, respectively. One of the 2 subjects randomly assigned to apixaban died of acute [redacted] on the day of randomization

before receiving the study drug; therefore, this subject was not in the modified full analysis set. No systemic embolisms were reported.

In the safety analysis set, there were numerically fewer major bleeding events in the apixaban treatment group (3 subjects [0.41%]) than in the usual care treatment group (6 subjects [0.83%]). There were also numerically fewer clinically relevant nonmajor bleeding events in apixaban treatment group (11 subjects [1.5%]) than in the usual care treatment group (13 subjects [1.8%]).

Overall, the incidence of major bleeding and clinically relevant nonmajor bleeding, comparing apixaban to usual care, was similar at precardioversion and postcardioversion time points. The relative risk for major bleeding in the early cardioversion subgroup, comparing apixaban to usual care, was 0.9634. For clinically relevant nonmajor bleeding, the relative risk, comparing apixaban to usual care, was 0.4817 in subjects with early cardioversion compared with 1.7795 in subjects who had no cardioversion. When assessed by image guidance, the relative risk, comparing apixaban to usual care, for major bleeding and clinically relevant nonmajor bleeding was 0.5262 and 0.9208, respectively, in subjects who underwent TEE. The event rate for adjudicated major bleeding during the treatment period was 0.30% in subjects who received the 10-mg apixaban loading dose and 0.54% in subjects who received an initial apixaban 5-mg dose (not loaded). For clinically relevant nonmajor bleeding, the event rate during the treatment period was 1.21% in subjects who received the 10-mg apixaban loading dose and 1.88% in subjects who received an initial apixaban 5-mg dose (not loaded). Eleven subjects had a reduced apixaban loading dose (5 mg). None of the subjects with major bleeding and clinically relevant nonmajor bleeding had a 5-mg loading dose.

Clinical endpoint results from the safety, full prevention-evaluable, safety prevention-evaluable, thrombus-positive full, and thrombus-positive safety analysis sets were similar to those obtained from the full analysis set.

Safety Endpoints Results: In the safety analysis set, the proportion of subjects reporting AEs, SAEs, discontinuations due to AEs, and deaths was similar between the apixaban and usual care groups. The most commonly reported TEAEs were in the cardiac disorders system organ class, followed by investigations and respiratory, thoracic, and mediastinal disorders. Atrial

fibrillation (AF that recurred or worsened after successful cardioversion) was the most frequently reported AE, and was reported in a smaller proportion of subjects in the apixaban group (66 subjects [9.0%]) than in the usual care group (80 subjects [11.1%]).

The number (%) of subjects with AEs after early cardioversion was 155 (47.3%) and 129 (40.8%) in the apixaban and usual care groups, respectively; the number (%) of subjects with AEs after no early cardioversion was 76 (39.6%) and 100 (48.8%) in the apixaban and usual care groups, respectively. The incidence of AEs was lower in subjects less than 65 years of age (121 subjects [36.3%] and 124 subjects [37.8%] in the apixaban and usual care groups, respectively) than in subjects 65 years of age and older (181 subjects [45.0%] and 193 subjects [49.1%] in the apixaban and usual care groups, respectively). When assessed by gender, AEs were more frequently reported in females (121 subjects [49.4%] and 116 subjects [48.7%] in the apixaban and usual care groups, respectively) than in males (181 subjects [36.9%] and 201 subjects [41.6%] in the apixaban and usual care groups, respectively). For subjects who underwent TEE image guidance, 190 subjects (47.4%) in the apixaban group and 195 subjects (46.2%) in the usual care group presented with AEs.

Most AEs in the apixaban and usual care groups were mild or moderate in severity. The proportion of subjects presenting with severe and very severe AEs was higher in the usual care group (where 40 subjects [5.5%] and 7 subjects [1.0%] presented with severe and very severe events, respectively) than in the apixaban group (where 23 subjects [3.1%] and 5 subjects [0.7%] presented with severe and very severe events, respectively).

The proportion of subjects presenting with treatment-related AEs was lower in the apixaban group (53 subjects [7.2%]) than in the usual care group (102 subjects [14.1%]). The difference in proportion of subjects presenting with treatment-related AEs was largely due to the events reported in the investigations system organ class, where 3 apixaban-dosed subjects (0.4%) presented with AEs in this category compared with 55 subjects (7.6%) in the usual care group. Most of the AEs reported under “investigations” in the usual care group were INR increased or INR abnormal (either low or high); INR was not assessed in the apixaban group.

Overall, 100 subjects (13.6%) in the apixaban group and 112 subjects (15.5%) in the usual care group presented with SAEs during the treatment period. The percentage of subjects

experiencing an SAE of AF was higher in the usual care group (40 subjects [5.5%]) than in the apixaban group (27 subjects [3.7%]).

Overall, 32 subjects (4.4%) and 23 subjects (3.2%) in the apixaban and usual care groups, respectively, presented with AEs that led to treatment discontinuation. No AEs leading to treatment discontinuation were reported in more than 2 subjects for each preferred term in either group. Most AEs leading to treatment discontinuation were in the cardiac disorders system organ class and were more commonly reported in the apixaban group (10 subjects [1.4%]) than in the usual care group (3 subjects [0.4%]).

Overall, the proportion of subjects with bleeding-related AEs (not adjudicated) was lower in the apixaban group (29 subjects [3.9%]) than in the usual care group (84 subjects [11.7%]). In the usual care group, 10 subjects had INR results of 3 or higher; however, INR was not consistently obtained at the time of bleeding events and there was no clear correlation between the timing of bleeding-related AEs and INR results.

Overall, 13 subjects had additional visits due to bleeding events (3 subjects in the apixaban group and 10 subjects in the usual care group); 5 subjects were admitted to hospital for stroke (1 subject in the apixaban group [adjudicated to have occurred before dosing with apixaban] and 4 subjects in the usual care group). Most reasons for additional visits to the clinic or hospital were categorized as “other” (276 subjects overall, with 129 subjects in the apixaban group and 147 subjects in the usual care group) and included cardioversion, AF, and atrial flutter; 19 subjects in the apixaban group and 35 subjects in the usual care group had additional visits for these reasons. In the usual care group, more subjects had additional visits due to bleeding events than in the apixaban group (10 subjects in the usual care group vs 3 subjects in the apixaban group).

Conclusions:

In subjects with nonvalvular AF requiring cardioversion:

- For the clinical endpoint of stroke, in the full analysis set, there were no strokes in the apixaban treatment group and 6 strokes in the usual care group (nominal *P*=0.0151).
- No systemic embolisms events were reported.

- In the safety analysis set, there were numerically fewer major bleeding events in the apixaban treatment group (3 subjects [0.41%]) than those randomly assigned to usual care (6 subjects [0.83%]), and numerically fewer clinically relevant nonmajor bleeding events in the apixaban treatment group (11 subjects [1.5%]) than those randomly assigned to usual care (13 subjects [1.8%]).

- In the full analysis set, there were 2 all-cause deaths in the apixaban treatment group (1 of which occurred before dosing [acute [redacted]]) and 1 all-cause death in the usual care treatment group.

- In the safety analysis set, the event rate during the treatment period for adjudicated major bleeding was 0.30% in subjects who received the 10-mg apixaban loading dose and 0.54% in subjects who received an initial apixaban 5-mg dose (not loaded). For clinically relevant nonmajor bleeding during the treatment period, the event rate was 1.21% in subjects who received the 10-mg apixaban loading dose and 1.88% in subjects who received an initial apixaban 5-mg dose (not loaded).

- Results of the sensitivity analyses were similar to the results obtained in the full analysis set.

- In the safety analysis set, the incidence of AEs, SAEs, discontinuations due to AEs, and death was similar between apixaban and usual care groups. The incidence of bleeding-related AEs was higher in the usual care group (11.7%) compared with the apixaban group (3.9%).

- The most commonly reported AEs were in the cardiac disorders system organ class. Atrial fibrillation was the most frequently reported AE in the cardiac disorders system organ class and was reported in a smaller proportion of subjects in the apixaban group (66 subjects [9.0%]) than in the usual care group (80 subjects [11.1%]).

- The number (%) of subjects with AEs after early cardioversion was 155 (47.3%) and 129 (40.8%) in the apixaban and usual care groups, respectively; the number (%) of subjects with AEs after no early cardioversion was 76 (39.6%) and 100 (48.8%) in the apixaban and usual care groups, respectively. Age was a factor for the incidence of

AEs, where subjects 65 years of age and older presented with a higher incidence of AEs. When assessed by gender, AEs were more frequently reported in females than in males. Image guidance assessments of AEs demonstrated no obvious difference between the treatment groups.

- Most AEs in the apixaban and usual care groups were mild or moderate in severity. The proportion of subjects presenting with severe and very severe AEs was higher in the usual care group than in the apixaban group.

- The proportion of subjects presenting with treatment-related AEs was lower in the apixaban group than in the usual care group, largely due to INR increased and INR abnormal, which were reported more commonly in the usual care group (INR was not assessed in the apixaban group).

- The proportion of subjects with bleeding-related AEs (not adjudicated) was lower in the apixaban group than in the usual care group. The INR was not consistently obtained at the time of bleeding events and there was no clear correlation between the timing of bleeding-related AEs and INR results.

- More subjects in the usual care group had additional visits due to bleeding-related events and stroke than in the apixaban group. Most reasons for additional visits to the clinic or hospital were categorized as “other” and included cardioversion, AF, and atrial flutter.

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