

FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date: 8 September 2011

NDA: 202439

Sponsor: Janssen Pharmaceuticals

Drug: XARELTO® (rivaroxaban) Tablets

Indication for Use: Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Title of Study: The **ROCKET AF** Trial (**R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition Compared with Vitamin **K** Antagonism for Prevention of Stroke and **E**mbolism **T**rial in Atrial **F**ibrillation)

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This document is based on the applicant's information as submitted up to 9 August 2011

CLINICAL REVIEW

Application Type	NDA Type 1 -- (505(b)(1))
Application Number(s)	202439
Priority or Standard	Standard
Submit Date(s)	4 January 2011
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Division / Office	DCRP/ODE 1
Reviewer Name(s)	Nhi Beasley, Preston Dunnmon (safety); Martin Rose (efficacy)
Review Completion Date	10 August 2011
Established Name	Rivaroxaban
Trade Name	Xarelto®
Therapeutic Class	Anticoagulant (factor Xa inhibitor)
Applicant	Johnson & Johnson Pharmaceutical Research & Development, LLC
Formulation(s)	Oral tablets – 15 & 20 mg
Dosing Regimen	15 or 20 mg once daily, based on renal function
Indication(s)	Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Intended Population(s)	Adults

Template Version: March 6, 2009

Note to Readers

In this review, a high level summary of the efficacy, safety and risk-benefit data is found in Section 1.2. Individual summaries of the efficacy and safety data are found at the beginning of Section 6 and Section 7, respectively. Internal hyperlinks to other parts of the review are in [blue font](#). The Tables of Contents, Tables, and Figures are also hyperlinked to their targets.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on our review of the clinical data, we recommend a complete response.
Reasons for this recommendation include:

1. There is a lack of substantial evidence that rivaroxaban will have its desired effect when used as recommended in labeling. (21 CFR 314.125(b)(5)). The data from the Sponsor's Phase 3 ROCKET trial comparing rivaroxaban to warfarin are not adequate to determine whether rivaroxaban is as effective for its proposed indication in comparison to warfarin when the latter is used skillfully (e.g., TTR >~68%, near the midpoint of center based TTR in the RE-LY study, and the US median TTR of 65% in ROCKET). In order for atrial fibrillation (AFib) patients to be protected from the risk of thrombotic events, a new drug for this indication should be demonstrated to be as effective as warfarin when it is used skillfully. This requirement is based on an FDA policy that requires drugs for conditions that are "life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack)...." to be shown to as effective as approved agents (see Sec. 6.1.10.2.1. This issue also implicates 21 CFR 314.125(b)(4), described in the next paragraph, because of the potential risk of additional strokes in patients who might receive rivaroxaban instead of approved treatment should rivaroxaban be approved. The FDA policy cited above and other aspects of this issue are discussed in further in Sec. 6.1.10.2.
2. There is insufficient information about the drug to determine whether it is safe for use with its proposed labeling (21 CFR 314.125(b)(4)). In the ROCKET study there was an excess of strokes in the rivaroxaban arm during the transition from blinded study drug to open label warfarin at the end of the study. The Sponsor's proposed instructions for the transition from rivaroxaban to warfarin, developed after ROCKET was completed, have not been evaluated or shown to be safe in terms of bleeding risk or embolic risk in a clinical study. Such a study must be performed prior to approval in this case (see Section 6.1.10.3.7 for a discussion of this issue). The study of the transition regimen could be performed as part of the study needed to satisfy the deficiency cited in paragraph 1, above.

There are no additional issues that preclude rivaroxaban's US approval on safety grounds. The principal safety concern with rivaroxaban was its potential to cause major bleeding, as defined in the ROCKET protocol, in excess of that seen with warfarin. This did not occur in ROCKET. There are no novel safety concerns.

1.2 Risk Benefit Assessment

Rivaroxaban is an orally available, reversible, direct inhibitor of Factor Xa. The sponsor's agent, Johnson and Johnson Pharmaceutical Research and Development, LLC, has submitted NDA 202439 for rivaroxaban on behalf of Janssen Pharmaceuticals, Inc, a subsidiary of J&J and the Sponsor of this application. Rivaroxaban was developed by J&J and its partner, Bayer, for the proposed indication of "the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation."

Efficacy Overview

In support of this indication, the sponsor conducted the global ROCKET trial, a large (>14,000 subjects) randomized, double blind (double dummy) event-driven non-inferiority trial in adults with non-valvular AFib at high risk for thrombotic events. ROCKET compared rivaroxaban 20 mg once daily (15 mg in patients with CrCl 30-49 mL/min) to warfarin, which was to be titrated to a target range of 2.0 to 3.0. The primary endpoint was time to a composite of stroke and systemic embolism. The sponsor's designated primary endpoint analysis was in the per-protocol population "on treatment" (including events to the last dose + 2 days); this analysis supports efficacy and nominally found superiority for rivaroxaban. However, reflecting imbalances in the number of post-treatment events in the treatment arms that favored warfarin, multiple analyses (including several ITT analyses) with longer event windows had larger point estimates for their hazard ratios and 95% CIs that all crossed 1.0, and thus did not support superiority of rivaroxaban over warfarin. However, in no case was the upper limit of the 95 % CI more than 1.08 for any analysis of the primary endpoint in the overall patient population. Thus, these analyses support non-inferiority of rivaroxaban to warfarin, but do not take into account other factors, such as the quality of anticoagulation in the warfarin arm.

These efficacy findings appeared to be preserved in nearly all major subgroups of patients, including each gender, the elderly, subjects previously treated with a VKA, subjects in each of the 5 specified geographic regions, and those enrolled from US sites. However, efficacy was substantially reduced in the large subset of patients with a prior history of stroke/TIA/systemic embolism, which comprised about 55% of all patients globally. The hazard ratios for the primary endpoint in patients with and without a baseline history of stroke/TIA/systemic embolism were 0.92 and 0.59, respectively ($p = 0.035$ for the treatment by subgroup interaction). This finding represents a labeling issue if this drug is approved. The primary endpoint findings were also supported by numerical imbalances for important secondary efficacy endpoints that each favored rivaroxaban over warfarin in on-treatment analyses in the safety population. These endpoints included the rates of strokes (all types combined), hemorrhagic strokes, disabling strokes, fatal strokes, systemic emboli, vascular deaths, and non-vascular deaths. The results for myocardial infarction also favored rivaroxaban, unlike in the RE-LY trial of dabigatran.

There was a modest imbalance of ischemic stroke in favor of rivaroxaban in the on treatment safety population analysis (149 vs. 161 patients with ischemic stroke, 1.34 vs. 1.42 events per 100 patient-years). The difference between the treatment arms in the number and rate of hemorrhagic stroke was considerably larger (29 vs. 50 patients, 0.26 vs. 0.44 events per 100 patient-years). Thus, the advantage of rivaroxaban over warfarin in terms of strokes on treatment was driven largely by the results for hemorrhagic stroke.

The following issues are relevant to the interpretation of the efficacy results of the trial:

Superiority to warfarin:

The sponsor has requested language relating to superiority to warfarin. There are several reasons why this is not appropriate in labeling. In the opinion of this reviewer, each of these reasons is sufficient on its own to support a decision to reject a superiority claim:

- Only the on-treatment analyses of the safety and per-protocol populations support superiority. All analyses that include follow-up of patients for at least 7 days after the last dose of study, and all ITT analyses do not support superiority. We generally prefer an ITT analysis as the basis of a superiority claim.
- Overall TTR in the ROCKET study was relatively poor (55%). Thus, the comparison to warfarin may have been biased in favor of rivaroxaban because poor INR control is associated with reduced efficacy of warfarin. As noted below, ROCKET does not show convincingly that rivaroxaban is as effective as warfarin when the latter is used skillfully. This makes a superiority claim based on the results of ROCKET misleading.
- Superiority language in labeling might induce physicians to switch patients who are doing well on warfarin to rivaroxaban. However, the study data do not support an advantage for such a switch. Patients who were VKA experienced at study entry had similar event rates in either arm after 180 days of double blind treatment; nearly all the observed benefit of rivaroxaban in terms of thrombotic event prevention accrued in the first 180 days in this population, during which TTR improved from low levels in the first 30 days on study (48%) to about 60%. Thus, there would be no reason other than convenience to switch most such patients to rivaroxaban, making a superiority claim misleading.

Adequacy of anticoagulation in the warfarin treatment arm:

This reviewer believes that the constancy assumption has been reasonably satisfied and that the sponsor has established that rivaroxaban maintains a substantial fraction of the efficacy of warfarin for its target indication (see Sec. 6.1.10.1). Thus, one can conclude that rivaroxaban is active as an anticoagulant and is clinically superior to the

imputed results for placebo for its target indication. However, the interpretation of ROCKET is complicated by the relatively poor degree of INR control in the study. This has potential implications that will be explored below and in greater detail in Section [6.1.10.2](#).

FDA has a policy stating that, “It is essential that a new therapy must be as effective as alternatives that are already approved for marketing when the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g. stroke or heart attack)” The policy is intended to protect public health when less effective treatments could present a danger to the patients that receive them by keeping patients from receiving more effective treatments (see Section 6.1.10.2.1).

The policy is broadly written and lacks a discussion of operational details. For example, it does not state whether comparable effectiveness to an approved therapy used in an unskilled manner would be adequate for approval. However, if it is essential for a therapy to be as effective as an approved therapy to protect public health, it is logical that the new therapy should be as effective as the approved therapy **when the approved therapy drug is used skillfully**. Otherwise, the public health protection afforded by this policy might be weakened or negated completely. It also does not explain the implications of ambiguous data or data that are insufficient to determine whether the new therapy is as effective as approved therapy. Again, if the underlying goal of protecting public health is to be advanced, the logical course is to reject the new therapy because it has not been convincingly demonstrated to be as effective as approved therapy.

ROCKET was a warfarin controlled study. To interpret the efficacy findings, one must understand the expected benefit of warfarin as it was given in this trial. Warfarin has been demonstrated to be highly effective in preventing strokes in AFib patients in placebo-controlled trials. However, the efficacy of warfarin in this setting is dependent on the quality of control of INR, which should be targeted to the range of 2.0 to 3.0 for patients with non-valvular atrial fibrillation.

Time in therapeutic range (TTR) is a commonly used measure of the adequacy of INR control in studies with a warfarin arm. It is calculated based on observed INR values; INR values are imputed for days in between days with actual values. In ROCKET, the mean overall INR in the warfarin arm was 55%, i.e., the mean individual INR (the imputed percentage of days on study spent in the INR therapeutic range of 2.0 to 3.0 for each patient) was 55%. This contrasts with TTR in recent warfarin-controlled studies of other agents, which ranged from 63% to 73%.

TTR in ROCKET varied widely over regions and countries. The mean TTR of centers in the US was 63%. National TTR ranged from 36% in India to 75% in Sweden. In general, TTR was high in Western Europe (especially in Scandinavia), North America (i.e., Canada and the US), and some locations in the Pacific basin (Australia, New Zealand, Singapore and Hong Kong).

There are other metrics of the quality of control of warfarin dosing, such as the stroke or primary endpoint event rate in the warfarin arm. However, there are no modern warfarin-controlled studies with a study population nearly as high-risk for stroke as the one in ROCKET, making cross study comparisons of stroke rates difficult. Accordingly, TTR will be stressed here as a metric of warfarin control.

At global centers in ROCKET where warfarin was used skillfully, e.g., centers with mean TTR above ~68%, the study data suggest that patients had a numerically greater rate of primary endpoint events (stroke and systemic emboli, but most events were strokes) in the rivaroxaban arm. Such centers constituted about a quarter of the total in ROCKET, but the number of subjects at those centers was only about 15% of the total. The confidence interval around the point estimate for the hazard ratio in this subset of patients is quite wide, so there is a substantial measure of uncertainty about these data. Such uncertainty about comparability to approved therapy for stroke prevention argues strongly for the need for additional data to support approval.

This situation in ROCKET contrasts sharply with the warfarin-controlled RE-LY study of dabigatran, which was conducted globally in over 18,000 AFib patients. In RE-LY, about half of the study patients were at centers where TTR was ≥ 67 , and there was a reasonable degree of confidence about the primary endpoint hazard ratio for dabigatran vs. warfarin in this subgroup. Thus, RE-LY shows that it is possible for the results of a study of thrombotic event prevention in AFib patients to provide reasonably robust and interpretable data regarding the effect of an experimental drug at centers where warfarin is used skillfully, but ROCKET does not provide such robust data.

Thus, the data do not convincingly demonstrate that rivaroxaban is as effective in preventing strokes and systemic emboli as warfarin when warfarin is used skillfully. This suggests that rivaroxaban should only be used in patients whose INR cannot be well controlled on warfarin or are unwilling to take it. However, such patients have an alternative, dabigatran, which is approved for rivaroxaban's proposed indication. Dabigatran was shown to be superior to warfarin in preventing stroke and systemic emboli in the overall results of the large global RE-LY trial (with a median TTR of about 67%), and it was robustly non-inferior to warfarin at RE-LY centers with TTR above the median. Rivaroxaban has not been compared to dabigatran.

Nonetheless, if rivaroxaban is approved, patients taking it might be at greater risk of harm from stroke and/or bleeding than if they were treated with warfarin used skillfully. In the opinion of this reviewer, rivaroxaban should not be approved unless the sponsor submits convincing information that it is as safe and effective for its target indication as warfarin when it is used skillfully (e.g., in the subgroup of patients at centers where TTR $\geq \sim 67\%$), or that it is as safe and effective as another approved agent, such as dabigatran.

However, if the medical community is currently in great need of an additional oral anticoagulant for use in AFib patients, it might not be unreasonable to approve

rivaroxaban as second or third line treatment. It might be useful in patients who are poorly controlled on warfarin or refuse to take it. However, given that dabigatran has been shown to be superior to warfarin when it is used reasonably well, and robustly non-inferior to warfarin when it is used extremely well, it seems advisable to make rivaroxaban a third-line agent, behind both warfarin and dabigatran. This issue is discussed further in Section 6.1.10.2.

Efficacy events occurring after discontinuation of study drug:

Approximately 2/3 of patients in ROCKET in each arm continued taking study drug until the end of this event-driven study. In these patients, blinded study medication was stopped, and the investigator was to transition patients to alternative anticoagulant therapy, usually a vitamin K antagonist such as warfarin. Unlike other recent trials of novel anticoagulants in AFib patients (the Sportif V trial of ximelagatran, the RE-LY trial of dabigatran, and the ARISTOTLE trial of apixaban) no provisions were made for a short period of dual therapy with study drug and open-label warfarin for patients in the rivaroxaban arm to continue anticoagulation during the lag period of INR control at the start of warfarin therapy. Note that rivaroxaban has an elimination half-life of approximately 6-8 hrs in healthy subjects and 11-13 hrs in the elderly, suggesting that a patient started on warfarin the day after the last dose of study drug (the usual time of the end of study visit) would not be adequately anticoagulated for about 5 days (assuming 5 days for the patient to reach an INR of 2), during which time rivaroxaban levels would be expected to be grossly sub-therapeutic.

Possibly as a result of this study design feature, in patients who completed the study on treatment, there was a statistically significant increase in the rate of strokes in the rivaroxaban arm compared to warfarin (22 vs. 6 patients with events) from the end of the “on treatment” period (2 days after the last dose of study drug) up to day 30 after the last dose of study drug. Most of the events in rivaroxaban arm patients occurred in the first half of this period. There was also an excess of strokes in rivaroxaban arm patients who completed the smaller (~1200 patients), warfarin-controlled J ROCKET trial, conducted exclusively in Japan, where the transition to warfarin therapy was handled the same way as in ROCKET.

The ROCKET study data suggests that while > 90% of completing patients received a VKA in the 30 day period following the last dose of study drug, INR control may not have been good, suggesting a possible cause for the strokes in these high-risk patients. However, the sponsor has not performed the studies necessary to exclude the existence of a hypercoagulable state in these patients.

To ameliorate the risk of events after discontinuation of rivaroxaban, the sponsor has submitted proposed labeling with instructions for the transition from rivaroxaban to warfarin therapy. These instructions call for a period of concomitant treatment with both drugs under INR control (with INR measured at the end of the rivaroxaban dosing interval). The instructions are based on PK/PD modeling; they have not been evaluated in a

clinical study. However, given that both ROCKET and J ROCKET identified a serious safety risk of rivaroxaban, it seems prudent to require the sponsor to demonstrate in a clinical study in AFib patients receiving rivaroxaban therapy that the proposed transition regimen is safe and effective.

There was a slight excess of primary endpoint events in the period from day 3 to day 30 after the last dose of study drug in the rivaroxaban arm in patients who discontinued study drug early. However, the difference between the treatment arms was small. Also, death in this subgroup of patients numerically favored rivaroxaban.

More information regarding the rate of events after discontinuation of study drug in ROCKET and the sponsor's proposed instructions for the transition from rivaroxaban to warfarin are found in Section 6.1.10.3.

Dosing regimen:

The sponsor evaluated one dosing regimen in its pivotal trial, 20 mg of rivaroxaban once daily (15 mg once daily for patients with CrCl 30-59 mL/min). The sponsor established that this regimen is non-inferior to warfarin as it was used in ROCKET.

However, the sponsor's rationale for evaluating only once daily dosing in Phase 3 is not strong. Most importantly, there is clinical information from Phase 2 trials in the sponsor's ACS and VTE programs (including a direct comparison in VTE Study 11223 of once daily vs. twice daily dosing at the same total dose that favored the latter in terms of VTE treatment, and another direct comparison favoring twice daily dosing at the same total daily dose in the overall results of ATLAS ACS TIMI 46). There is also information from clinical pharmacology studies suggesting that twice daily dosing would produce substantially lower peak blood levels and substantially higher trough blood levels of rivaroxaban than once daily dosing, which might have been associated with a better safety profile. It might also be associated with improved efficacy, such as lower primary efficacy endpoint rate in patients with a prior history of stroke, a high-risk group that might benefit from better round-the-clock anticoagulation. There is also information from the DVT program suggesting that a lower total daily dose might have been as effective as 20 mg. The data are complex and are explored in greater depth in Section 6.1.8. This reviewer recommends that the sponsor must perform a clinical study to evaluate the efficacy and safety of a lower dose and/or additional dosing regimens, including at least one BID regimen, before this product is approved (Section 1.3). This dose finding work could be incorporated into the required study described on page 14.

Safety Overview

With respect to safety, the single issue weighing on the approval decision for rivaroxaban is bleeding risk.

In ROCKET, bleeding was defined by severity categories as follows:

- Major Bleeding – a decrease in hemoglobin of 2 g/dL or more, or transfusion of 2 or more units of packed red blood cells or whole blood, or critical site bleeding (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or a fatal outcome
- Non-Major Clinically Relevant Bleeding – overt bleeding not meeting major criteria but associated with medical intervention, unscheduled physician contact, temporary interruption of drug, subject discomfort
- Minimal Bleeding - all other overt bleeding.

ROCKET bleeding incidence and event rates were assessed during two different time frames (data scopes):

- LD+2: (AKA the on-treatment data scope) the time from randomization to last dose of study drug plus 2 days, and
- LD+30: the time from randomization to last dose plus 30 days.

Because of the five day window around the day 30 visit, where appropriate, the sponsor also performed a variant of the LD+30 analysis so that patients who came in several days later during the protocol-allowed window around the day 30 follow-up visit could have data included in follow-up period analyses. Analyses using this LD+30 variant time frame were thus referred to simply as “to-follow-up” analyses. Differences in analysis outcomes between LD+30 and to-follow-up were small.

The ROCKET safety population consisted of all intent-to-treat (ITT) patients who took at least 1 dose of study medication after randomization.

Major bleeding rates on rivaroxaban versus warfarin remained essentially unchanged comparing the LD+2 to the LD+30 (or to follow-up visit) time periods, both globally and in the US sub-population. Therefore, this reviewer’s safety analyses concentrate on the LD+2 data scope from the safety populations, with separate consideration given to the Day 3 to Day 30 post-dosing period (i.e., the additional 28 days of the LD+30 data was considered separately). This was done to assess rivaroxaban transition to warfarin after patients withdrew from study drug.

This reviewer’s conclusions regarding safety are based on the following observations from the global ROCKET on-treatment (LD+2) safety population:

- The global ROCKET population demonstrates bleeding parity with warfarin with respect to major bleeding (HR 1.04 (0.90, 1.20), p=0.58), non-major but clinically relevant bleeding (HR 1.04 (0.96, 1.13), p=0.34), the trial’s predefined “principal safety endpoint” (the composite of major and non-major clinically relevant bleeding, HR 1.03 (0.96, 1.11), p=0.44), and minimal bleeding (HR 1.16 (0.97, 2.39), p=.102).

- With respect to the four subcomponents of major bleeding, the excess in 2g/dL hemoglobin drops and 2 unit blood transfusion requirements noted with rivaroxaban were offset by statistically significantly fewer major bleeds of the most serious nature, intracranial hemorrhages and fatal bleeding.
- The findings of decreased critical organ bleeding and decreased fatal bleeding are present in every analytic subset that this reviewer assessed, either as a statistically significant finding when the subsets were large, or as a trend when they were small.
- Within the “major bleeding” category, there were more serious treatment emergent GI bleeding adverse events on rivaroxaban than on warfarin (80(1.13%) versus 60 (0.84%), respectively) , and the vast majority of major bleeding on rivaroxaban involved “mucosal bleeding” (GI bleeding, GU bleeding, hemoptysis, and/or epistaxis). Yet, there were significantly fewer intracranial hemorrhages and hemorrhagic strokes. That rivaroxaban has a short half-life and that coagulation PD parameters essentially normalize every 24 hours following rivaroxaban dosing suggests a mechanism of “biologic plausibility” for this finding.

With respect to the finding of parity between rivaroxaban and warfarin in all bleeding categories in ROCKET (major, non-major clinically relevant, and minimal), the argument could certainly be made that rivaroxaban achieved bleeding parity in the global trial only because warfarin was managed poorly, with an overall trial TTR (INR 2.0 to 3.0) of only 55.2%. Furthermore, that argument would be supported by the fact that unlike the global trial (where TTR was relatively low and major bleeding equal between the rivaroxaban and warfarin arms), in the United States sub-analysis where TTR was high, there was statistically significantly more major bleeding with rivaroxaban as compared to warfarin that is not explained by improved compliance in the North American region compared to other regions, nor by exposure-influencing demographic factors ([Table 101](#) and [Table 102](#)). However, even in the relatively small US sub-population analysis, rivaroxaban-treated patients experienced numerically fewer critical organ bleeds, intracranial hemorrhages, hemorrhagic strokes, and fatal bleeds compared to their warfarin-treated counterparts, a finding that was concordant with the overall trial results.

Benefit-Risk

While US major bleeding results may have been due to a small sample in a post-hoc subgroup analysis, for the purposes of a risk-benefit assessment, this reviewer took the most conservative approach in assuming that increased major bleeding noted in the US subgroup might be real because of some undetermined influence(s), and so examined risk-benefit analyses for both the global ROCKET on-treatment safety population, as well as the US on-treatment sub-population. Given that the primary safety concern was bleeding, a composite endpoint approach for Risk-Benefit was foregone in favor of a risk-benefit ratio calculation for major bleeding versus efficacy endpoint events

(ischemic strokes + non-CNS systemic emboli). Specifically, for this risk-benefit ratio approach, differences between rivaroxaban and warfarin major bleeding rates were calculated for the numerator, and then differences between rivaroxaban and warfarin ischemic strokes/non-CNS systemic emboli event rates calculated for the denominator (global and US LD+2 safety populations). The analysis was performed both by TTR quartile, and for the overall population to assess the influence that warfarin management may have had on the overall results. Negative numbers for this analysis are point estimates for the number of additional bleeds suffered by patients in the rivaroxaban arm for each ischemic stroke prevented as compared to warfarin. Positive values indicate that there were fewer major bleeds (as well as fewer ischemic strokes) in the rivaroxaban arm in the relevant subgroup of patients. The results are displayed for the global and US data set in [Table 1](#) and [Table 2](#).

Table 1. Major Bleeds Incurred Per Stroke/SE Prevented By TTR Quartile – Global Safety Population On-Treatment

TTR Quartile	Patients Rivaroxaban / Warfarin (n)	Major Bleeds per Stroke/NCSE Prevented
0.00 – 46.8	1765 / 1725	1.78 (-2.02, 5.56)
46.8 – 55.9	1724 / 1764	0.32 (-1.87, 2.51)
55.9 – 63.9	1709 / 1787	0.58 (-2.80, 3.96)
63.9 - 100	1690 / 1803	-3.67 (-9.28, 1.95)
Overall	7111 / 7125	-0.33 (-1.46, 0.80)

Table 2. Major Bleeds Incurred Per Stroke/SE Prevented By TTR Quartile – US (LD+2)

TTR Quartile	Patients Rivaroxaban / Warfarin (n)	Major Bleeds per Stroke/NCSE Prevented
0.00 – 57.21	227 / 239	-0.47 (-5.30, 4.36)
57.21 – 64.75	241 / 228	1.47 (-4.52, 7.47)
64.75 – 70.39	220 / 247	-3.66 (-9.72, 2.39)
70.39 - 100	219 / 250	-2.49 (-5.30, 0.32)
Overall	962 / 964	-3.35 (-7.32, 0.63)

From these analyses of the global versus US risk-benefit profiles, note that:

- Quartile four of the global population is essentially quartile three of the US population, both of which demonstrate a cost of approximately 3 – 4 major bleeds per ischemic stroke prevented using rivaroxaban as opposed to warfarin.

- The point estimate for the ratio of major bleeds per stroke prevented is very similar in the US population and the Global population, when comparing equivalent quartiles with TTR above about 64% (i.e., Global quartile 4 and US quartiles 3 and 4). This result is a consequence of the fact that while the hazard ratio for major bleeding was higher in the US, the hazard ratio for the primary efficacy endpoint of ischemic stroke and systemic embolization was lower in the US than for the global population overall
- From the previously described analysis of major bleeding subtypes, the excess of major bleeds is driven by hemoglobin drops and transfusions, which is offset by fewer critical organ bleeds, intracranial hemorrhages, hemorrhagic strokes, and fatal bleeds,

Therefore, it is this review's conclusion that considering the on-treatment (LD+2) data scope of the safety population as the principle indicator of the expected patient experience with rivaroxaban therapy relative to warfarin, there is not a rationale with respect to major bleeding that would prevent an approval decision.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no such recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

We have no such recommendations at this time, assuming this application is not approved. If it is ultimately determined that rivaroxaban can be approved for the AFib indication on the basis of ROCKET, then a REMS to evaluate and minimize thromboembolic events during a transition from rivaroxaban to warfarin is recommended by the reviewers due to the demonstrated, heightened risk of ischemic stroke during the transition.

2 Introduction and Regulatory Background

2.1 Product Information

Rivaroxaban (Xarelto®) is an orally available direct inhibitor of activated Factor X (Factor Xa or FXa). Its proposed indication is the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The product is being developed through a joint collaboration between Bayer HealthCare and Johnson Pharmaceutical Research and Development.

The chemical structure of rivaroxaban and its key attributes are provided below.

Figure 1. Chemical structure of rivaroxaban

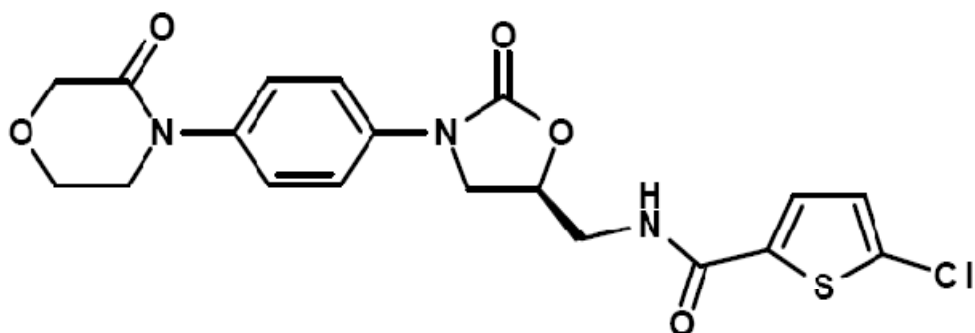


Table 3. Rivaroxaban product information

Attribute	Description
Chemical Name	5-Chloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-ylmethyl)-2-thiophene-carboxamide
Appearance	White to yellowish solid
Molecular Formula	C ₁₉ H ₁₈ ClN ₃ O ₅ S
Molecular Weight	435.89 Daltons
Stereochemistry	Pure (S) enantiomer
Dosing Regimen	For patients with CrCl ≥ 50 mL/min, 20 mg orally once daily with food; for patients with CrCl 30 to < 50 mL/min, 15 mg once daily with food.
Proposed Age Group	Adults (a complete Pediatric Waiver has been requested)
Dosage Forms	Oral film-coated tablets, 15 and 20 mg

2.2 Tables of Currently Available Treatments for Proposed Indication

2.2.1 Overview of Atrial Fibrillation and Stroke

Atrial fibrillation (AFib) is the most common cardiac arrhythmia. It is estimated that 2.5 million Americans have AFib.¹ The rate of hospitalization for AFib has increased in recent years, possibly due to the aging of the population and an increased prevalence of chronic heart disease. AFib prevalence rises with age, and reaches about 8% after

the age of 80, with a somewhat higher rate in men than women. The median age of AFib patients is about 75 years.²

The rate of ischemic stroke in AFib patients is ~5% year, 2 to 7 times the rate of persons without AFib.² Thirty-day stroke mortality in AFib patients has been estimated at 24%¹. Non-cerebral embolic events also occur at an increased rate.

There is a body of literature on the risk factors for stroke in patients with AFib. Probably the most widely recognized risk factors are the 5 that are components of the CHADS₂ risk score: **C**ongestive heart failure, **H**ypertension, **A**ge > 75 years, **D**iabetes mellitus, and prior history of **S**troke or TIA. The last factor is worth 2 points in the score, and the other 4 are worth one point; the CHADS₂ score thus ranges from 0 to 6. More recently identified risk factors include female gender, age > 65 years, and history of vascular disease other than stroke.³

The most common source of emboli in AFib patients is believed to be the left atrial appendage.²

2.2.2 Currently Available Treatments

The only approved oral agents for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation are warfarin (a pre-1962 product with broad labeling as an anti-coagulant that encompasses the proposed indication for rivaroxaban) and dabigatran, a Factor IIa inhibitor that was approved in October, 2010 based on the results of the global RE-LY warfarin-controlled trial in over 18,000 patients with AFib. For additional information on the conduct of RE-LY and how it is relevant to approval of rivaroxaban, see Section 6.1.10.2. This was a three arm trial with a 1:1:1 randomization that compared warfarin titrated to an INR of 2.0 to 3.0 to dabigatran at two doses: 110 mg. bid and 150 mg bid. Warfarin and dabigatran were given in an open-label manner, but the study personnel and patients were blinded with respect to which dabigatran dose was assigned. Relevant results for the primary study endpoint, time to the composite event of stroke or systemic embolism, are displayed in [Table 4](#) and [Table 5](#):

Table 4. Overall Primary Endpoint Results of RE-LY

	Dabigatran 110 vs. warfarin	Dabigatran 150 vs. warfarin
Hazard Ratio (95% CI)	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)
P-value non-inferiority using 1.38	<0.0001	<0.0001
P-value superiority	0.29	0.0001

Source: Dabigatran NDA 022512 clinical review by Drs. Beasley and Thompson.

Table 5. Relative Risk of Stroke/SE by Center-Level INR Control in RE-LY

	Centers with INR control < median of 67%		Centers with INR control ≥ median of 67%	
	D110 vs. warfarin	D150 vs. warfarin	D110 vs. warfarin	D150 vs. warfarin
HR	0.86	0.57	0.96	0.77
95% CI	0.66, 1.12	0.42, 0.76	0.71, 1.30	0.56, 1.06
p-value	0.26	0.0002	0.78	0.10
P-value superiority	0.29		0.0001	

Source: Dabigatran NDA 022512 clinical review by Drs. Beasley and Thompson.

In addition to the above center-level data, in the 4th (best) quartile of center-level INR control, with center INR ≥ 74.2, the HR (and 95% CI) for dabigatran 110 mg and dabigatran 150 mg vs. warfarin, respectively, were 0.92 (0.59, 1.44) and 0.90 (0.57, 1.41). Results with the 150 mg bid dose were superior to the 110 mg bid dose (data not shown). Bleeding risk with dabigatran 150 mg bid was comparable to warfarin, while the 110 mg bid was superior to warfarin.

On the basis of these data, we approved the 150 mg bid dose for patients with CrCl > 30 mg/min, along with a dose of 75 mg bid for patients with CrCl 15-30 mg/min. The 110 mg bid dose was not approved for use in the US. The rationale for the non-approval of 110 mg bid was that the higher dose was as follows: The higher dabigatran dose was clearly superior to the lower dose in terms of efficacy (i.e., stroke/SE prevention). Composite net benefit outcomes that included both stroke and medically important bleeding events did not clearly favor the lower dose, meaning that even if one gave equal weight to strokes and bleeds, the results do not tilt in favor of the lower dose. Since stroke is generally thought to be worse than bleeding, even a near worst case analysis for the higher dose did not negate its superiority. Thus, only the higher dose of dabigatran was approved for all but patients but those with severe renal dysfunction.

There has been considerable development activity recently in this therapeutic area. A number of unapproved oral agents have been evaluated in completed trials with warfarin comparators, including the factor IIa inhibitor ximelagatran (Sportif III and Sportif V trials), the factor Xa inhibitor apixaban (the unpublished, just completed ARISTOTLE trial), and dual antiplatelet therapy with clopidogrel and aspirin (ACTIVE-W). There have also been aspirin-controlled trials of apixaban (AVERROES) and clopidogrel + aspirin (ACTIVE-A). Finally the injectable factor Xa inhibitor idraparinux has been evaluated against warfarin (AMADEUS).

2.3 Availability of Proposed Active Ingredient in the United States

Rivaroxaban was approved on July 1, 2011, by the Division of Hematology Products "...for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery." Relevant information from the approved package insert follows:

The recommended dose of rivaroxaban for DVT prevention is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery, once hemostasis stasis has been established. For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended. For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended. A 10 mg tablet is available.

Contraindications include hypersensitivity to the product and active major bleeding.

Warnings/precautions include:

- Hematoma following spinal/epidural anesthesia or puncture
- Risk of major hemorrhage
- Risk of pregnancy related hemorrhage
- Avoid use in severe renal impairment (Cr CL < 30 mL/min)
- Avoid use in patients with moderate or severe hepatic impairment (C-P Class B or C)

Adverse Reactions:

Bleeding was by far the most important AR. Major bleeding events occurred in 0.3% of patients taking rivaroxaban vs. 0.2% of those taking enoxaparin or placebo in the controlled trials. Non-bleeding ARs mentioned in labeling with an incidence in trials of at least 1% include wound secretion, extremity pain, muscle spasm, syncope, purities, and blister; the only AR mentioned which occurred at an incidence less than 1% was dysuria. Analysis of clinical laboratory results showed no notable excess of hepatic enzyme abnormalities compared to enoxaparin/placebo. Post marketing event data from other nations identified the following non-hemorrhagic adverse reactions: agranulocytosis, jaundice, cholestasis, cytolytic hepatitis, hypersensitivity, anaphylactic reaction, anaphylactic shock, hemiparesis (it is not stated if this was related to CNS bleeding, which did occur postmarketing), and Stevens-Johnson syndrome.

Drug interactions:

PK interactions:

- Avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole,

lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

- Avoid concomitant use of rivaroxaban with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Consider increasing the rivaroxaban dose if these drugs must be co administered.
- Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure.

PD interactions:

- Avoid concurrent use of rivaroxaban with other anticoagulants due to the increased bleeding risk other than during therapeutic transition periods where patients should be observed closely.
- Concurrent use of NSAIDs/ASA may increase bleeding risk.
- Avoid use of rivaroxaban with clopidogrel unless the benefit outweighs the risk of increased bleeding.

Use in Special Populations:

- Pregnancy category C.
- Use in labor & delivery has not been studied. Bleeding may occur.
- It is not known if rivaroxaban is excreted in human milk.
- Pediatric studies have not been performed.
- There has been ample geriatric use. Elderly subjects may have increased exposure due to changes in renal function. Assessment of renal function is advised before starting therapy in patients ≥ 65 years old.
- Females of reproductive potential should discuss pregnancy planning with their physician.
- Even mild renal impairment substantially increases exposure and PD parameters, but patients with mild and moderate renal impairment tolerated rivaroxaban well. Avoid use in pts with severe renal impairment ($\text{CrCl} < 30$ mL/min). Patients with any degree of renal impairment with concurrent use of P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk.
- Hepatic impairment: See Warnings.

Additional Clinical Pharmacology information is discussed in Section [4.4](#).

2.4 Important Issues with Consideration to Related Drugs

The most important safety risk of anticoagulant drugs is pathological bleeding. Anticoagulant agents affecting the intrinsic and/or extrinsic coagulation cascade may have their bleeding risks potentiated by anti-platelet co-therapies. For a discussion of this topic with rivaroxaban, see Bleeding Safety – Concomitant Aspirin in Section 7.3.4.

Ximelagatran, an oral thrombin inhibitor, was also associated with hepatotoxicity, and a possible increased risk of serious coronary events, and was not approved in the United States. Bleeding and hepatotoxicity are discussed extensively in the review of safety in Section 7

Concomitant use of warfarin has been associated with increased accumulation of the hypoglycemic agents chlorpropamide and tolbutamide and the anticonvulsants phenytoin and phenobarbital. An unusually large number of drugs have PK or PD interactions with warfarin that may result in over- or under-anticoagulation and associated problems of bleeding or thrombosis, respectively.⁴ These interactions are relevant to the use of warfarin.

Maintenance of target levels of anticoagulation in patients taking warfarin is highly variable across regions, individual study sites or practices, and patients. In the global RE-LY trial of dabigatran vs. warfarin, which supported approval of dabigatran for the rivaroxaban proposed indication, an analysis of quartiles of site-specific levels of time in therapeutic range (TTR) of INR showed an inverse relationship between quartiles of TTR (with the 4th quartile having the highest TTR) and the rate of efficacy events in the warfarin study arm. The relationship between bleeding rates and INR control was not as clear.⁵ A similar inverse relationship between INR control and efficacy event rate has been reported in the literature.⁶ The efficacy of warfarin therapy for the rivaroxaban proposed indication is discussed in Section 6.1.10.3.1.1 and 6.1.10.3.6.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Following review of the sponsor's proposed development program for Rivaroxaban's use to prevent stroke and systemic emboli in patients with AFib, DCRP issued an advice letter to the sponsor(s) in Sep 2006 in which areas of developmental agreement were noted, as follows:

- Single Study Approval – FDA agreed that robust findings from VTE prevention studies could support single study approval for embolic stroke (ES) and systemic embolization (SE) prevention in patients with AFib. The sponsor has since submitted the Record serious of VTE/PE prevention studies, and approval is anticipated for this indication has been granted.

- Proposed Efficacy Endpoints – FDA agreed that the sponsor’s proposed primary and secondary efficacy endpoints and their definitions were acceptable.
- Proposed Safety Endpoints – FDA agreed that the sponsor’s definitions of bleeding (major, non-major clinically relevant, minimal) were acceptable, and that the proposed principal safety endpoint composite of major and non-major clinically relevant (NMCR) bleeding was acceptable.
- Proposed Comparator – FDA agreed that warfarin (INR 2.5, range 2.0 to 3.0 inclusive) was acceptable comparator.

However, there were two elements of the proposed development program about which FDA either did not agree, or pointed to the lack of data to support specific design elements, as follows:

- Trial Population – FDA did not agree with the sponsors proposal to study a much sicker population (CHADS₂ Score > 3, prior history of stroke) than had been studied in historical SPAF (Stroke Prevention in Atrial Fibrillation) trials that compared the efficacy of warfarin to placebo because:
 - There was sparse evidence for the safety and efficacy of warfarin in preventing strokes and systemic emboli in this much sicker population
 - It was possible that non-embolic and/or non-AFib CVAs might be more frequent in this very sick population, and
 - Warfarin efficacy for non-embolic CVAs had not been demonstrated.

In its Sep 2006 advice letter, the agency stated, *“Therefore, we believe that the population to be studied in your proposed Phase 3 study should closely match the population studied in historical studies to increase the likelihood that the constancy assumption is satisfied.”*

- Dose – FDA did not agree that the selection of the 20 mg once daily dose of Rivaroxaban had been justified. Specifically, the OCP reviewer noted in Sep 2006 that:
 - *“Both Factor 10a inhibition and prothrombin time show a dependency on the plasma concentration of the drug. What degree of Factor Xa inhibition and prothrombin prolongation does the sponsor consider to be effective and safe? This information would be crucial for determining the appropriate dose and interval to be used for the Phase 3 trial.”*
 - Rivaroxaban doses of 2.5, 5, 10, 20 and 30 mg bid and 5, 10, 20, 30 and 40 mg QD were investigated in the lead up to the VTE prevention trials,

and demonstrated flat efficacy and safety dose-response relationships. Therefore, the OCP reviewer felt that the sponsor should explain why 5 mg bid was not considered for the proposed Phase III trial (ROCKET).

Accordingly, the sponsor was advised to justify the 20 mg daily dose in the Sep 2006 advice letter. Agreement was not prospectively achieved on the dose(s) to be tested prior to the execution of the ROCKET trial. In the current submission, the 20-mg dose selection was justified with the following arguments:

- 11223 (ODIXa-DVT) assessed safety, tolerability, and efficacy of rivaroxaban at oral doses of 10, 20, and 30 mg twice-daily and 40 mg once-daily compared with enoxaparin/vitamin K antagonist (VKA)
- Study 11528 (EINSTEIN DVT) assessed safety, tolerability, and efficacy of rivaroxaban at oral doses of 20, 30, and 40 mg once-daily compared with low molecular weight heparin (LMWH)/VKA
- It was appreciated that dose-finding studies in patients with AFib may not be feasible as they carry a high risk of stroke for patients with potentially too low doses of the investigational anticoagulant
- The relative safety in terms of bleeding compared to the within-study standard of care was better for all once-daily regimens compared to the twice-daily regimens for which a trend toward slightly increased risk of bleeding was observed for the 20 mg and the 30 mg doses.
- The 10 mg twice-daily dose in study 11223 was comparable to the once-daily doses in Study 11528 in terms of safety
- Based on these clinical observations, it was concluded that the lowest once-daily dose studied, 20 mg, should be selected for the proposed Phase 3 SPAF study ROCKET
- Given the overall relatively flat dose-response for both efficacy and safety, this dose (20 mg once daily) could potentially have been used as the sole dose in the AFib trial in all patients subgroups. However, certain covariates, e.g., renal function, could raise the exposure to a level of 30 mg once daily dose, as also investigated in the VTE treatment trials and shown to be effective and not different in terms of safety from 20 mg once daily.

2.6 Other Relevant Background Information

2.6.1 Foreign Approvals

Rivaroxaban has been approved in the EU since September 30 2008 for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery. The recommended dose is 10 mg once daily (as a 10 mg tablet), starting 6-10 hours after surgery, providing hemostasis has been established. The recommended duration of therapy is 35 days for hip replacement and 14 days for knee replacement. It may be taken with or without food. Dosing for special populations is similar to US recommendations. The SPC states that “There is no need for monitoring coagulation parameters during treatment...”, but the relationship of PT to plasma concentration of rivaroxaban is described.

Contraindications include those in the US as well as:

- hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- pregnancy and lactation

Warnings/precautions are not notably different from the US labeling. However, there is a precaution regarding syncope and dizziness that may affect the ability to drive or use machines.

In addition to bleeding, nausea, fever, edema, increased GGT & transaminases are listed as common ARs.

The overdose section recommends use of recombinant FVIIa on the basis of pre-clinical data, if other measures cannot control bleeding.

The discussion of pre-clinical safety data included reproductive toxicity in rats relating to hemorrhagic complications, as well as embryo-fetal toxicity (post-implantation loss, ossification abnormalities, and hepatic light colored spots. Offspring had reduced viability at doses that were toxic to the dams.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The following issues have arisen during the course of the review. They do not rise to the level of integrity issues, but are related to definitional issues that were not clearly explained by the sponsor in its initial submission.

- Some patients who were lost to follow-up or who withdrew consent to follow-up were later learned to have died, either from personal contacts or through death registries. Even though these patients were lost to follow-up for non-fatal study outcomes, upon obtaining information about death they were classified as being in the study until the date of death. Thus their censoring date changed for efficacy analyses, and they were not counted as being lost to follow-up or withdrawing consent.
- As noted in Sec 5, the sponsor elected to provide unblinded study data to the DSMB, instead of sending blinded data that would be processed by the data managers of the contractor, DCRI. The company statistician who prepared the unblinded data was ostensibly firewalled. We have no evidence that the firewall was breached, although it could have been breached through informal communications without our knowledge. Complicating the picture is the fact that the SAP was not drafted until almost a year after the start of enrollment. The SAP was then revised several times, with the last revision occurring shortly before data lock. These practices create opportunities for unblinding.

3.2 Compliance with Good Clinical Practices

No GCP violations were identified by the in-house reviewers or at the clinical site inspections.

3.3 Financial Disclosures

The only trial providing efficacy data is ROCKET, performed globally at more than 100 centers. No single investigator provided a meaningful fraction of the safety data. Out of thousands of principal and sub-investigators in ROCKET, only 7 disclosed a financial interest, which consisted of a substantial equity interest in each case. These 7 investigators worked at a total of 8 sites that enrolled a total of 25 subjects (range, 0-9 subjects per site; the 2 sites that were associated with one investigator enrolled one patient in total). These 25 subjects represent 0.18% of the 14,264 subjects who enrolled in ROCKET (ITT population). The sponsor notes that the investigators and patients were blinded to treatment assignment and the study had many sites (1187 sites enrolled at least 1 subject), and argues that 0.18% is a *de minimus* fraction of the total patient population.¹ Accordingly, bias by the potentially conflicted investigators (which was not established or even alleged) could not have affected the outcome of the study in a meaningful way.

¹ The study utilized a double dummy. On visual and tactile inspection of the placebo and active tablets for rivaroxaban by this reviewer (MR), the tablets were indistinguishable; the same was true for warfarin and its placebo. However, as noted in the review, patients who bled or who were about to undergo invasive procedures might have had an open INR performed, the results of which might have unblinded the investigator to study drug assignment.

Reviewer Comment: This reviewer agrees with the sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls

No significant efficacy/safety issues outstanding. The CMC status at this time is as follows:

- Sites for DS, DP manufacturing, packaging, release and stability testing are found to be acceptable by ORC (based on profile).
- Need clarifications from sponsor if (b) (4) is used for ID test
- Will decide on the shelf life to be granted for the blister package. (b) (4) M open dish and (b) (4) M in blister package stability data has been provided.
- The in-vitro dissolution profiles used to demonstrate equivalence of 15 and 20 mg tablets manufactured at pilot and commercial scale is under review by OCP.

4.2 Clinical Microbiology

Not applicable to this submission – no clinical microbiology data submitted.

4.3 Preclinical Pharmacology/Toxicology

Preclinical Pharmacology/Toxicology review has identified two topics of concern, both of which have been explored and addressed internally and with the sponsor:

1. Repro-tox: Review of the reproductive toxicology information available from animal models, as well as consideration of very limited human experience, and in consultation with maternal-fetal health, has resulted in a Pregnancy Category C designation in the rivaroxaban label for the DVT/PE prophylaxis indication.
2. Cardiac valvular fibrosis: a DR letter was issued to the sponsor early in this review cycle requesting clarity on what appeared to be dose-responsive valvular fibrosis in Wistar rats. Review of these cases by FDA pharmacology-toxicology, including incidence analyses of valvular fibrosis in Wistar control rats from

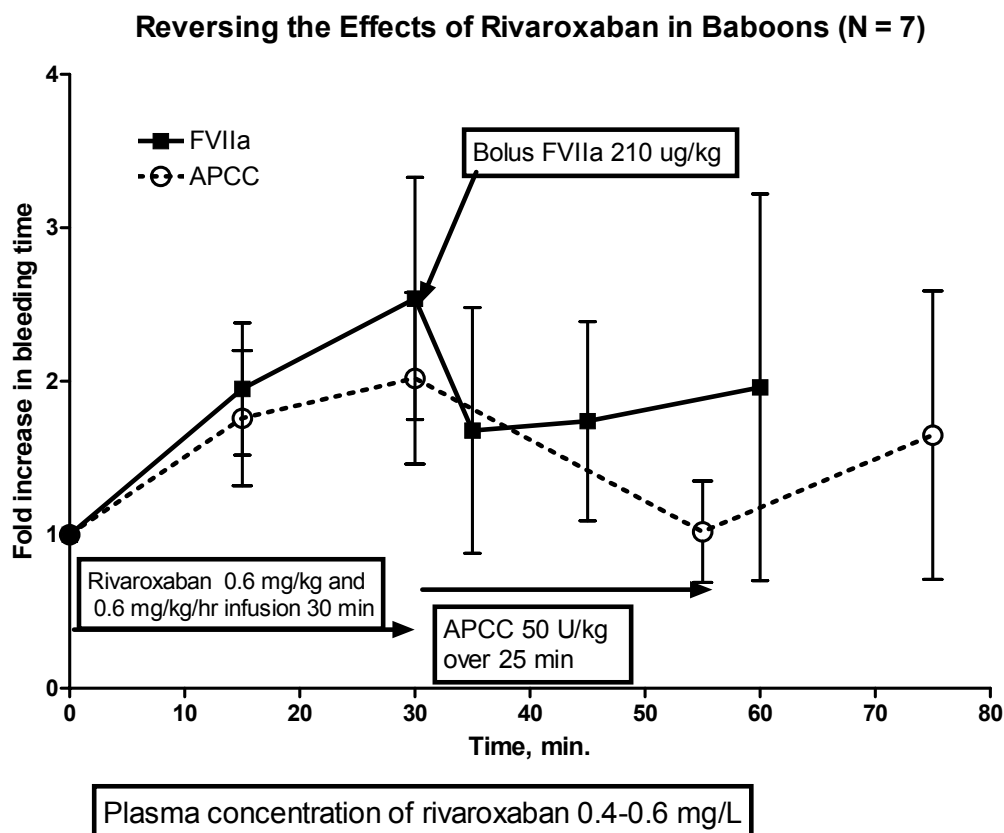
historical studies, lead to the conclusion that valvular fibrosis in the 2-year carcinogenicity study in rats is not the result of treatment with rivaroxaban, but is due to common physiological changes in aging rats. Furthermore, the sponsor noted that rivaroxaban had been inactive in a cell-based assay specific for the human 5-HT_{2B} receptor subtype compared to a positive antagonist control compound. This analysis is still in Pharm/tox review. A MedDRA based interrogation of the clinical trial and post-market databases for the development or worsening of valvular heart disease (VHD) and VHD follow by CHF was unremarkable, demonstrating no indication from human data of rivaroxaban-associated cardiac valvulopathy.

For a more in depth summary of the reviews of these two issues, see the completed pharmacology/toxicology review.

Reversing the effects of Rivaroxaban in Baboons:

One small baboon study demonstrated that rivaroxaban effects may be reversed with FVIIa bolus and infusion or APCC, but that the reversal effects may be short-lived as shown in [Figure 2](#):

Figure 2. Incomplete and transient reversal in non-human primates



Pharm-Tox Conclusion:

- NDA 202439 is approvable with appropriate labeling regarding bleeding during pregnancy and delivery.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Activation of Factor X is the initial step in the final common coagulation pathway. FXa cleaves prothrombin to generate thrombin, which triggers the conversion of fibrinogen to fibrin, the fibrous protein that polymerizes to form a clot in conjunction with platelets. The activity of FXa is greatly increased when it is complexed with activated co-factor V in the prothrombinase complex. By inhibiting FXa, rivaroxaban inhibits the formation of thrombin from prothrombin and the downstream formation of fibrin and blood clots. Because of the functional location of FXa at the top of the final common coagulation pathway, rivaroxaban affects clotting induced through both the intrinsic and extrinsic clotting cascades. Studies of the FXa inhibitory action of rivaroxaban are discussed in Section. [4.4.3](#).

4.4.2 Pharmacodynamics

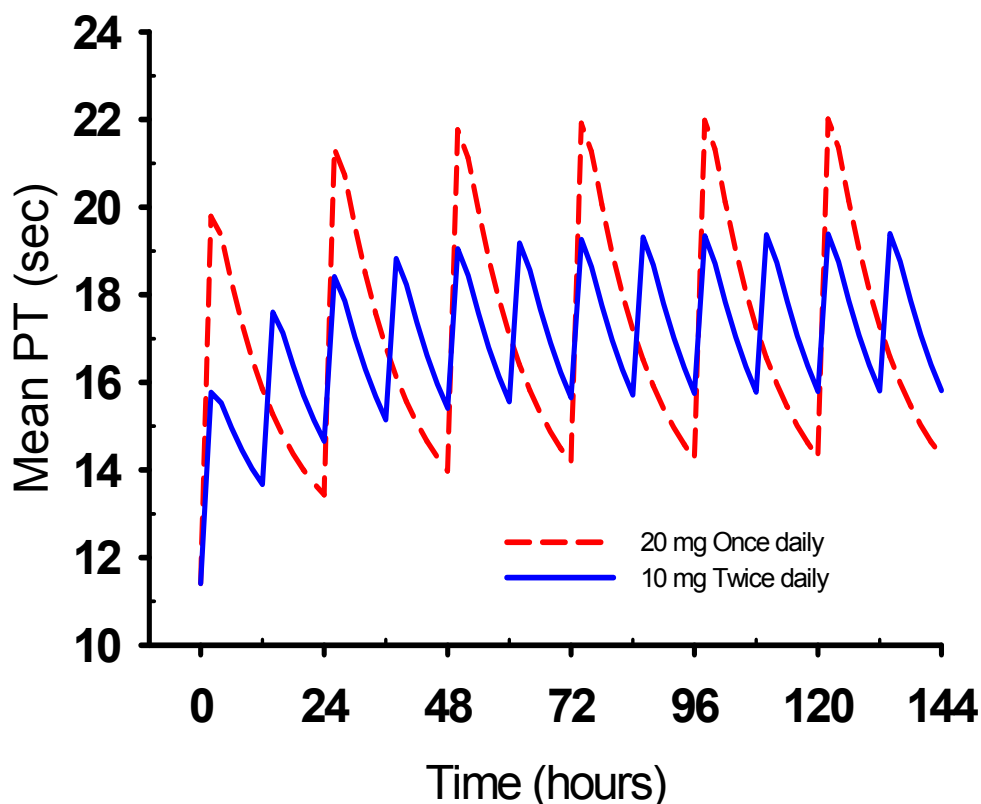
The recently approved labeling for rivaroxaban for use in DVT prevention indicates that, “Dose-dependent inhibition of factor Xa activity was observed in humans and the Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban. There are no data on the use of the International Normalized Ratio (INR). The predictive value of these coagulation parameters for bleeding risk or efficacy has not been established.”

Reviewer Comment: Data relating the relationship of coagulation parameters to efficacy and bleeding events in the ROCKET trial are discussed below. Information on the choice of dose for the ROCKET trial is discussed in Section [6.1.8](#).

Incorporated into ROCKET was a PK-PD sub-study in which approximately 161 patients were assessed with a Rivaroxaban level, prothrombin time, FXa activity, and PiCT at weeks 12 and 24. The PD data from that sub-study was utilized to construct a comparison between a simulated 10-mg BID regimen versus the observed PK-PD relationship for the 20-mg QD regimen that was observed in ROCKET. This simulation

demonstrates the expected lower fluctuation for the BID regimen as compared to the QD regimen, as seen in [Figure 3](#).

Figure 3. Simulation - 20 Mg QD vs. 10 Mg BID



Because neither a BID regimen nor a lower total daily rivaroxaban dose was tested in ROCKET, the implications of these two different PD profiles with respect to efficacy and/or bleeding cannot be assessed. Specifically, the increase in non-major clinically relevant bleeding in comparison to warfarin that was seen in ROCKET could be a result of the higher C_{max} of the daily dosing regimen that was tested in ROCKET. Alternatively, a BID dosing schedule with its higher trough values might exacerbate this bleeding proclivity if the same total daily dose is used.

See Section [4.4.3](#) for a thorough discussion of the PK-PD-Clinical outcomes relationships.

4.4.3 Pharmacokinetics

The approved labeling includes the following information about the PK of rivaroxaban:

Absorption

- The absolute bioavailability of rivaroxaban is estimated to be 80% to 100%) for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.
- Bioavailability of a 20 mg dose is reduced somewhat, but is increased when rivaroxaban is given with food.
- Rivaroxaban pharmacokinetics are linear with no relevant accumulation beyond steady-state after multiple doses. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.
- The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH.
- Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon.

Distribution

- Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component.
- The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

- Approximately 51% of an orally administered [¹⁴C]-rivaroxaban dose was recovered as metabolites in urine (30%) and feces (21%).
- Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation.
- Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

- Following oral administration of a [¹⁴C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug).
- Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio).

- Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated BCRP). Rivaroxaban's affinity for influx transporter proteins is unknown.
- Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following IV administration.
- The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Special Populations

- Gender did not influence the pharmacokinetics or pharmacodynamics of rivaroxaban.
- Healthy Japanese subjects were found to have 50% higher exposures compared to other ethnicities including Chinese.
- In clinical studies, elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being approximately 50% higher, mainly due to reduced (apparent) total body and renal clearance. Age related changes in renal function may play a role in this age effect. The terminal elimination half-life is 11 to 13 hours in the elderly.

Body Weight

- Extremes in body weight (<50 kg or >120 kg) did not influence rivaroxaban exposure.

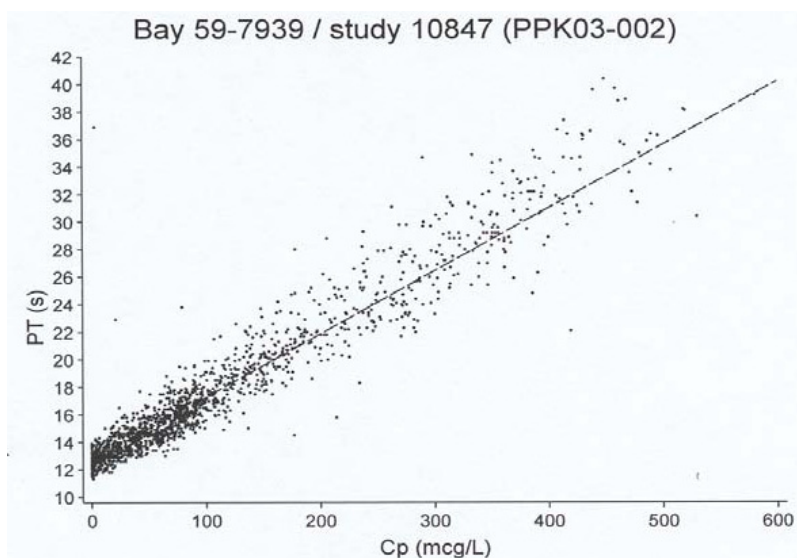
Drug Interactions

- In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4 nor induces CYP1A2, 2B6, 2C19, or 3A4.
- In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.
- There were no significant pharmacokinetic interactions observed in studies comparing concomitant rivaroxaban 20 mg and 7.5 mg single dose of midazolam (substrate of CYP3A4), 0.375 mg once-daily dose of digoxin (substrate of P-gp), or 20 mg once daily dose of atorvastatin (substrate of CYP3A4 and P-gp) in healthy volunteers.

PK – PD Relationships

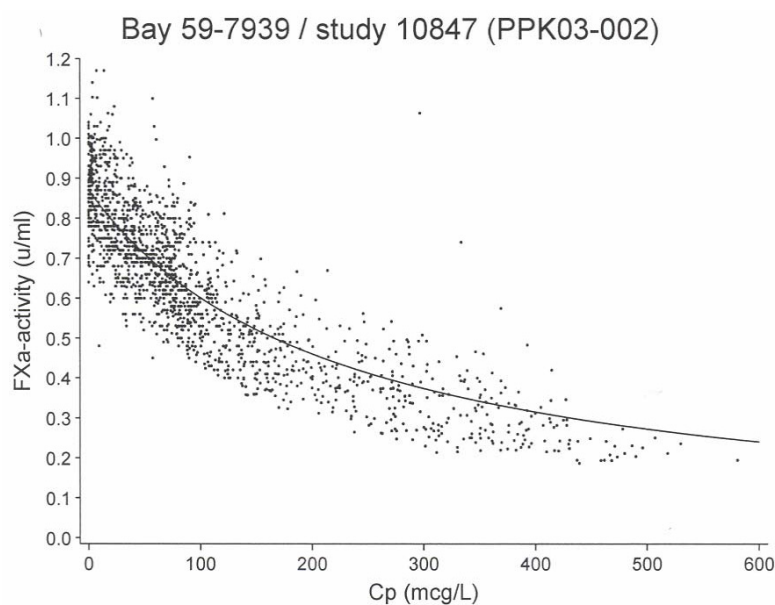
With respect to the PK-PD relationship, there is a direct linear relationship between serum concentrations of Rivaroxaban expected in human use at the doses used in ROCKET, as demonstrated by the results of PK study 10847 (PPK03-002), as seen in [Figure 4](#) below:

Figure 4. Rivaroxaban plasma concentration vs. PT



Similarly, this study also demonstrated an inverse curvilinear relationship between rivaroxaban concentrations in this range and FXa activity, as seen in [Figure 5](#) below:

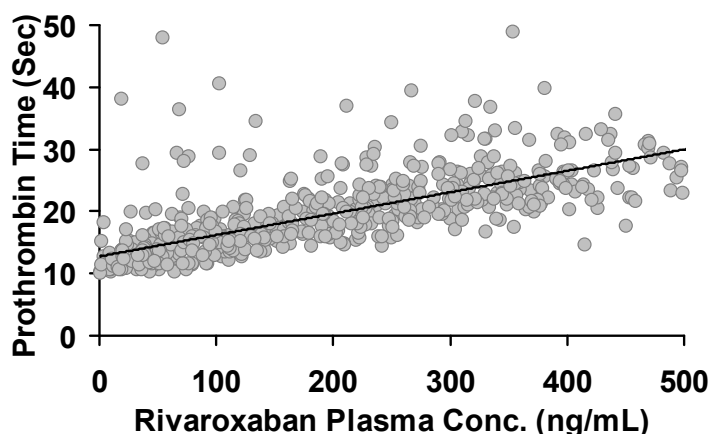
Figure 5. Rivaroxaban plasma concentration vs. FXa-activity



Incorporated into ROCKET was a PK-PD substudy in which approximately 161 patients were assessed with a Rivaroxaban level, prothrombin time, FXa activity, and PiCT. In addition, all subjects had samples drawn for PD assessment at weeks 12 and 24. Based on these data, the four key questions of interest to the agency were as follows:

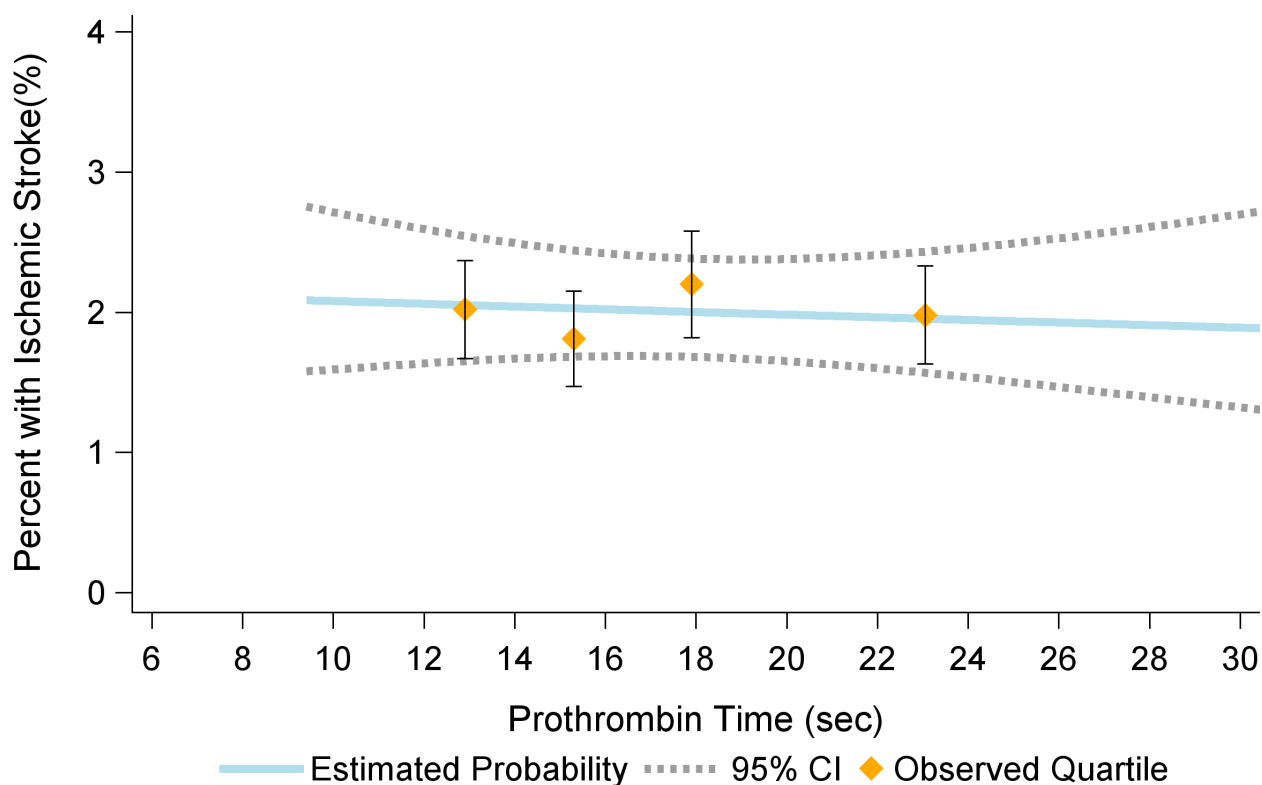
1. Can Prothrombin Time (PT) be used as a surrogate for PK? The PK data from 161 ROCKET patients confirms the linear relationship between the plasma concentration of rivaroxaban, and the PT, as demonstrated in [Figure 6](#) below:

Figure 6. ROCKET prothrombin time vs. rivaroxaban plasma concentration



2. Is there a PT-ischemic stroke relationship? PT data from 7008 patients in the ROCKET per protocol analysis dataset demonstrates that the occurrence of ischemic strokes was independent of PT over the range of 10 to 30 sec, as can be seen from [Figure 7](#) below:

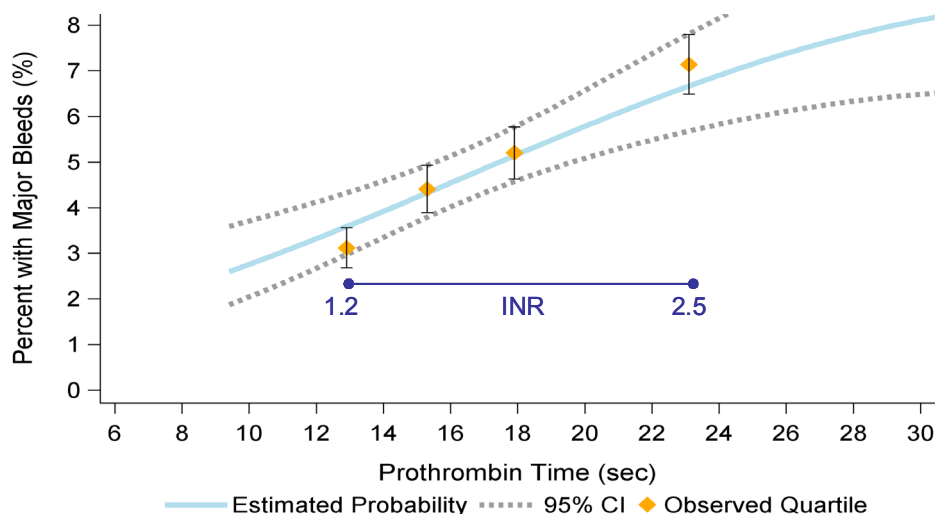
Figure 7. ROCKET ischemic stroke vs. PT (LD+2, pp pop)



	N	N of Event
Per-Protocol Analysis Set	7008	150
PT-outcome subset	6193 (88%)	124 (83%)

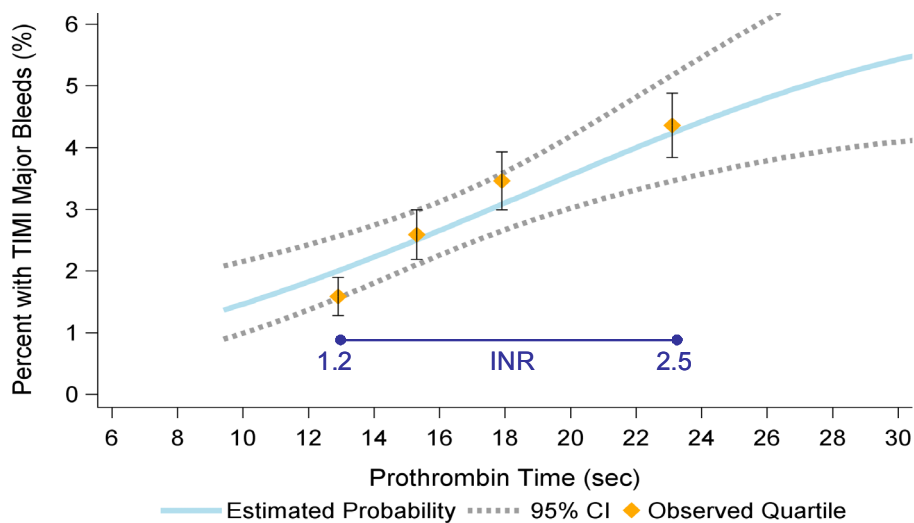
3. Is there a PT-Bleeding relationship? PT data from the 7008 patients in the ROCKET per protocol analysis dataset demonstrates that the risk of major bleeds increases with PT, regardless of whether major bleeding defined as ISTH major bleeding per the ROCKET protocol, or as TIMI major bleeding, as can be seen from [Figure 8](#) and [Figure 10](#) , respectively, below:

Figure 8. ROCKET ISTH major bleeds vs. PT (LD+2, pp pop)



	N	N of Event
Per-Protocol Analysis Set	7008	392
PT-outcome subset	6172 (88%)	306 (78%)

Figure 9. ROCKET TIMI Major Bleeds (LD+2, Pp Pop)



	N	N of Event
Per-Protocol Analysis Set	7008	245
PT-outcome subset	6183 (88%)	185 (76%)

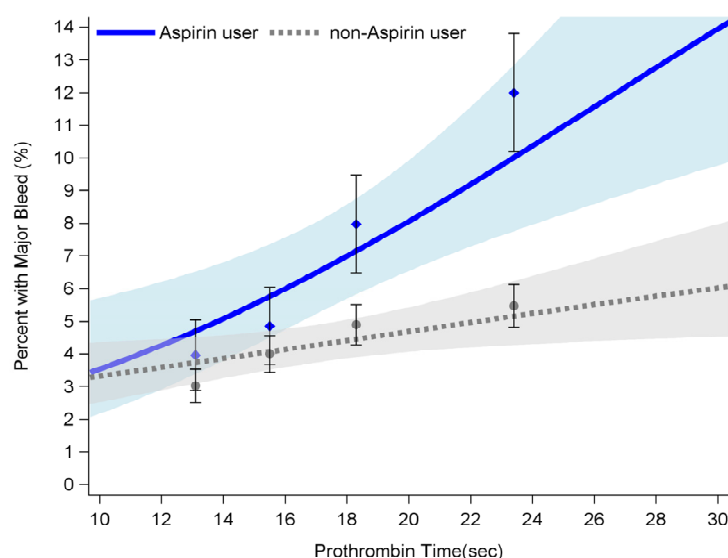
It is reassuring that for the overall population, there does not appear to be a shift from lesser severities of ISTH major bleeding (i.e. hemoglobin drops and transfusions) to the more severe forms (i.e. critical organ bleeding and fatal bleeding) as a function of PT prolongation with rivaroxaban, as can be seen in the FDA analysis in [Table 6](#):

Table 6. ROCKET ISTH Major Bleeding Type vs. PT

PT Quartiles	Rivaroxaban (PT-Major bleeding subset) N=6172			
	Hemoglobin drop, n (%)	2U blood transfusion, n (%)	Critical organ bleed, n (%)	Bleed result in death, n (%)
Q1 (<14.2 sec)	35/1573 (2.23)	16/1573 (1.02)	15/1573 (0.95)	1/1573 (0.06)
Q2 (14.2-<16.6 sec)	49/1543 (3.18)	24/1543 (1.56)	20/1543 (1.30)	8/1543 (0.52)
Q3 (16.6-<19.8 sec)	58/1501 (3.86)	33/1501 (2.20)	25/1501 (1.67)	6/1501 (0.40)
Q4 (≥19.8 sec)	88/1555 (5.66)	61/1555 (3.92)	19/1555 (1.22)	7/1555 (0.45)

The relationship between PT prolongation and major bleeding is exacerbated in patients taking concomitant ASA at least 50% of the time, and attenuated in patients not taking ASA (FDA analysis, [Figure 10](#) below).

Figure 10. ROCKET ISTH major bleeding vs. PT by ASA use

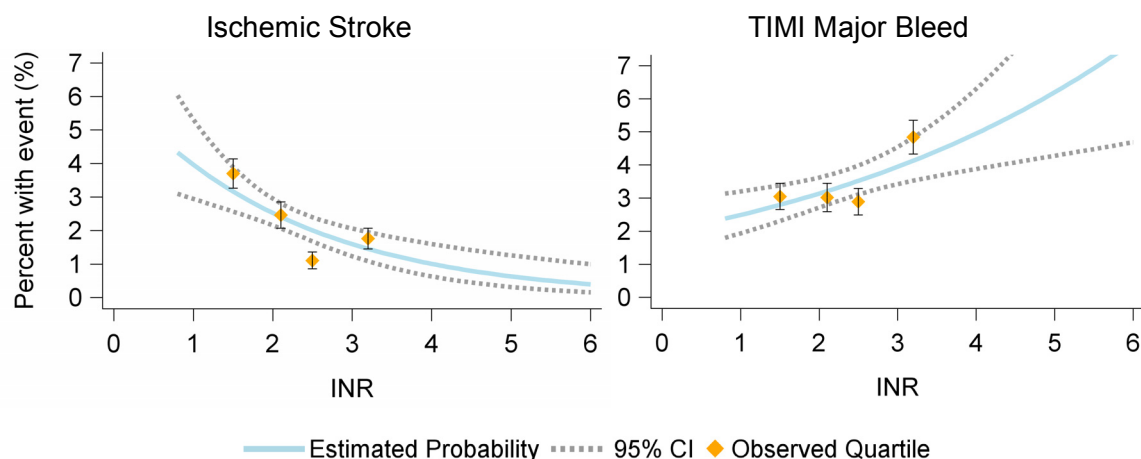


PT Quartiles	Rivaroxaban (PT-Major bleeding subset) N=6172	
	Incidence n (%)	Event Rate (100 pt-yrs)
Q1 (<14.2 sec)	49/1573 (3.12)	1.88
Q2 (14.2-<16.6 sec)	68/1543 (4.41)	2.54
Q3 (16.6-<19.8 sec)	78/1501 (5.20)	2.95
Q4 (≥19.8 sec)	111/1555 (7.14)	4.29

It is important to acknowledge that a similar relationship between ASA co-therapy with warfarin and major bleeding is demonstrated, as would be expected (FDA analysis, [Figure 11](#) below). As was seen with rivaroxaban, aspirin co-therapy with warfarin increases the risk of major bleeding. Aspirin increased the 100 p-y event rate for major bleeding in rivaroxaban-treated patients from 3.02 to 5.82. However, ASA similarly increased the 100 p-y event rate of major bleeding in patients taking warfarin from 3.03 to 4.76.

In this circumstance where 20-mg rivaroxaban demonstrates PT independent occurrence of ischemic stroke events, while simultaneously demonstrating a linear (or curvilinear) increase in the risk of major bleeding with increasing coagulation PD parameters (regardless of which definition of major bleeding is used, or which coagulation PD parameter is assessed, FXa-activity and PiCT data not show) dose optimization can only be performed for decreasing the risk of major bleeding. This is unlike the situation with warfarin, in that the ROCKET warfarin data demonstrates the expected balance of benefit and risk with respect to ischemic strokes and TIMI major bleeding between an INR of 2.0 to 3.0, as calculated from the last observed PT, as shown below in [Figure 11](#):

Figure 11. ROCKET Warfarin Patients - stroke / TIMI major bleeds vs. INR



Of note, approximately 10% of PT measurements from ROCKET patients at week 12 shift to extreme quartiles by week 24, as shown in Table 7 below:

Table 7. Comparisons of Week 12 vs. Week 24 Pt Values In ROCKET

		Week 24			
	PT sec (n = 5280)	Q1 9.4-14.1s	Q2 14.2-16.4s	Q3 16.5-19.6s	Q4 ≥19.7s
Week 12	Q1 8.2-14.1	56%	22%	13%	9%
	Q2 14.2-16.3	26%	37%	26%	10%
	Q3 16.4-19.5	13%	24%	37%	26%
	Q4 ≥ 19.6	7%	14%	25%	54%

4. How does QD compare to BID regimen? See Section [4.4.2](#)

Reviewers' Conclusions: PK-PD-Clinical Outcomes Relationships

- *PT can be used as a surrogate for PK in the range of plasma rivaroxaban concentrations demonstrated from this sample of patients in ROCKET.*
- *No PT-dependent reduction in ischemic stroke is demonstrated over the range of PT data*
- *The risk for Major Bleeding is dependent on PT (both sponsor-fined and TIMI Major Bleeding*
- *Similar safety and efficacy relationships are demonstrated for quartiles of PiCT and/or FXa inhibition (data not shown)*
- *BID dosing provides less PT fluctuation compared to QD in simulation modeling but the impact on efficacy and/or bleeding cannot be assessed due to lack of multiple dosing strategies in ROCKET*
- *10% of PT values in rivaroxaban treated patients shift to extreme quartiles between weeks 12 and 24. The implication of this finding is that a single PT (or*

INR) measurement will not consistently predict future bleeding risk in approximately 10% of patients, as this value may importantly shift with time.

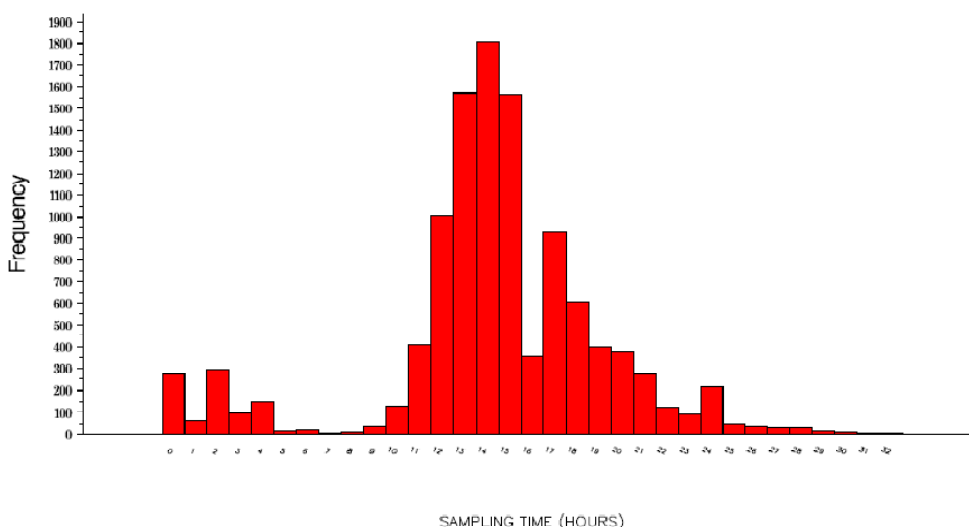
- *Monitoring rivaroxaban therapy with sequential prothrombin times to optimize safety outcomes cannot be recommended due to a lack of information regarding:*
 - *within-patient variability of PT measurements on this drug in the setting of a short half-life and rapidly changing PD effects over each 24 hour period, and*
 - *What action to recommend to the medical provider based on PT results, given that only a single dose was tested in ROCKET*
- *Stroke reduction and bleeding risk for warfarin are dependent upon the last observed INR, and demonstrate the expected optimization in the INR range of 2.0 to 3.0.*

For a thorough discussion of the PK-PD-Clinical outcomes relationships observed in ROCKET, see section 7.3.4, sub-section titled, “Bleeding Occurrences in ROCKET Subgroups: The PK-PD Relationship, and the PD Relationship to Major Bleeding.”

The INR-Clinical Outcome Relationship with Rivaroxaban

The ROCKET protocol stipulated that rivaroxaban should be taken in the evening, and that all INRs were to be obtained by the point of care device at their investigator’s sites. Given the realities of this timing, the majority of the INRs from ROCKET were likely measured between 12 and 18 hours post dosing. Indeed, at weeks 12 and 24 when all patients were to have a PT drawn, most of the samples were obtained between 13 and 15 hours post dose, as seen in the distribution in [Figure 12](#) below:

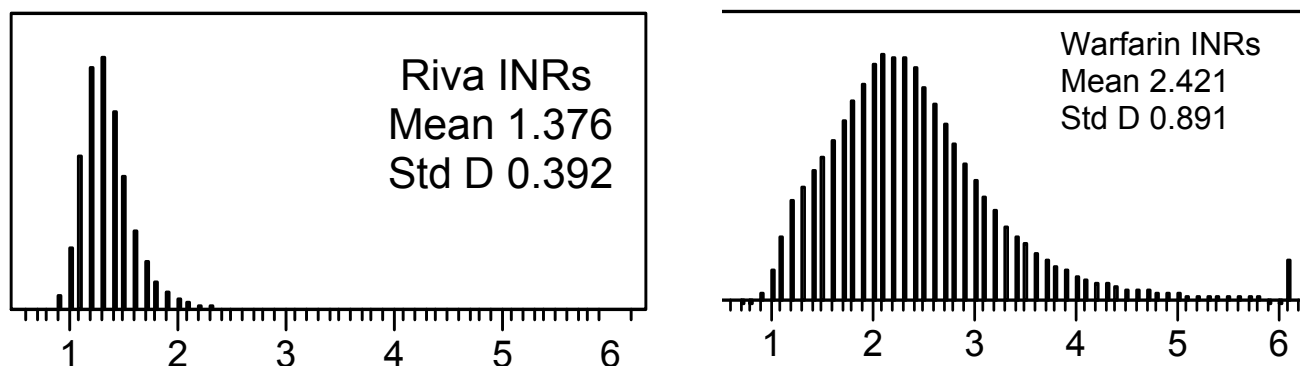
Figure 12. ROCKET – Timing of INR Blood Draws After Dosing



Over the course of ROCKET, there were 175,881 INR measurements performed on patients taking rivaroxaban (as opposed to 190,663 INR measurements performed on patients taking warfarin). A distribution analysis of those INR results in the two patient arms is demonstrated in [Figure 13](#) below:

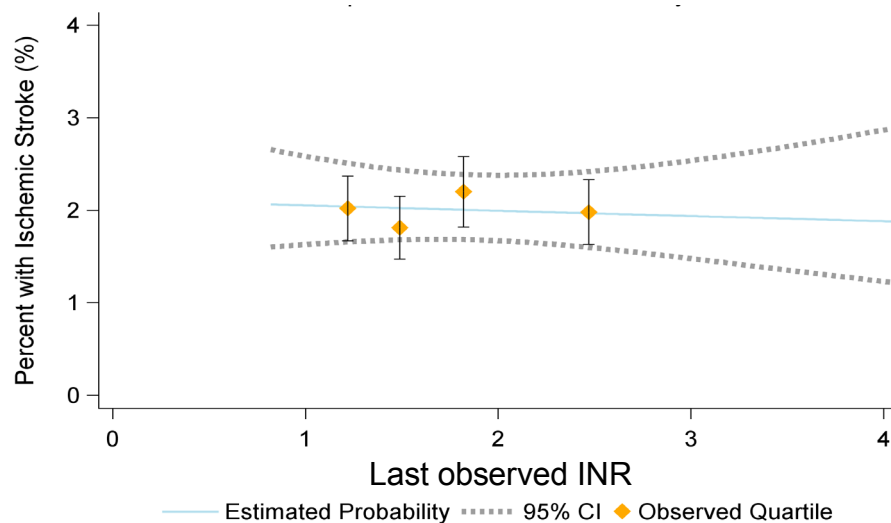
Figure 13. ROCKET INR distributions

INR	Rivaroxaban n (%)	Warfarin n (%)
≥ 3	1239 (0.70)	39,796 (20.9)
≥ 4	757 (0.43)	10,891 (5.71)
≥ 5	570 (0.32)	4,088 (2.14)
≥ 6	458 (0.26)	1,961 (1.03)



While the rivaroxaban INRs were tightly clustered around a mean value of 1.376, there existed a demonstrable right skew in the rivaroxaban INR distribution, raising the question as to whether this tail represented just those patients who happened to have their INRs drawn relatively close to when they took their drug (e.g., they may have taken the drug in the morning before coming to the site for an INR), or, given the PT-Major bleeding relationship that has already been demonstrated, that a similar PT-Major bleeding relationship could be demonstrated for the entire rivaroxaban-treated arm in ROCKET. Accordingly, a similar PD-Major bleeding analysis was performed based on the rivaroxaban INRs, which demonstrated almost identical results to the weeks 12 and 24 coagulation PD parameter analysis above. Specifically, the risk for ischemic stroke was not dependent on the last observed INR for rivaroxaban, as demonstrated in [Figure 14](#) below:

Figure 14. ROCKET ischemic stroke vs. last observed INR

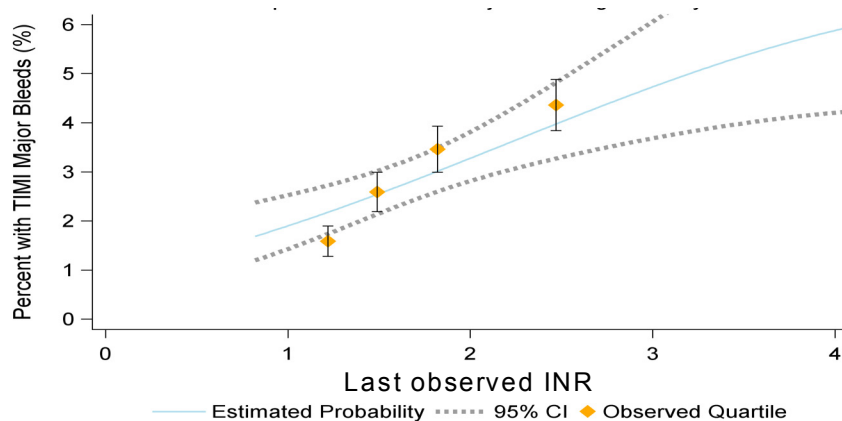


Events: 145/6870

INR measured using point of care device at study centers

In contrast, the occurrence of TIMI major bleeds increased with the last observed INR for rivaroxaban, as shown in [Figure 15](#) below:

Figure 15. ROCKET TIMI major bleeds vs. last observed INR



Events: 241/6966

INR measured using point of care device at study centers

Reviewers' Conclusions: INR-Clinical Outcomes Relationship

- *There is no INR dependent reduction in ischemic stroke over the range of data*
- *The risk for TIMI major bleeding is dependent on INR.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The sponsor's tabular listing of clinical trials and studies of rivaroxaban includes 73 trials and studies. To date, Bayer or the development partnership (Bayer + Johnson & Johnson) has completed 65 clinical trials, including:

1 absolute BA trial in healthy volunteers (HV)
19 comparative BA/BE trials in HV
1 PK/tolerability trials in CHF patients
3 PK/tolerability trials in HV
12 "intrinsic factor" PK trials (i.e., trials to observe the effect of various demographic and organ function related factors on PK)
15 "extrinsic factor" PK trials (i.e., DDI trials) in HV
4 PD or PK/PD trials in health volunteers
2 Phase 3 stroke and SEE prevention trials in AFib patients (i.e., ROCKET-AFib and J ROCKET-AFib)
7 other trials in various patient populations (VTE (4 trials), ACS (1 trial) and AFib (3 safety trials)).

A total of an additional 7 prospective clinical trials were ongoing at the time of the NDA submission, including:

- 2 trials in HV
- 1 VTE prevention trial in at-risk patients
- 1 trial in patients with acute PE
- 1 3-month trial in patients with acute proximal VTE or PE who are receiving a strong CYP 3A4 inducer for the duration of the trial.
- 1 ACS trial
- 1 VTE prevention trial in orthopedic patients examining transition to rivaroxaban from LMWH

There is also one additional, ongoing, observational cohort study of the prevention of VTE in patients with elective hip and knee arthroplasty (rivaroxaban vs. "current standard of care" for VTE prevention).

The sponsor's tabular listing of trials and studies is reproduced in Appendix 1, [List of Trials of Rivaroxaban](#)

5.2 Review Strategy

The clinical review is split between one reviewer focusing on efficacy and two reviewers focusing on safety. The reviews are combined in this document.

The efficacy review focuses primarily on the ROCKET-AFib (ROCKET) trial, the only trial performed by the sponsor intended to evaluate the clinical efficacy of rivaroxaban in preventing strokes and SEE in patients with non-valvular AFib. The J ROCKET-AFib (J ROCKET) trial (performed only in Japan), was less than 10% the size of ROCKET and was not powered to show efficacy. In addition, it used lower doses of rivaroxaban and a different (lower) INR target range in patients age 70 and above and thus is not useful to inform US efficacy labeling. The design features of both these trials are described in Section 5.3. Sec 5.3 also includes the efficacy results of J ROCKET.

The results of ROCKET and J ROCKET were not pooled by the sponsor for the ISE, thus the efficacy results of ROCKET, which is the only efficacy study in the submission, stand alone in Section 6. The data supporting the dose of rivaroxaban used in ROCKET, which come from a DVT treatment dose ranging trial, are also discussed in Section 6. The efficacy data from DVT and PE Phase 3 trials are discussed briefly in Section 6.

The safety review is found in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

The evidence for the efficacy of rivaroxaban in the prevention of strokes and SEE in patients with non-valvular AFib comes primarily from the sponsor's global study No. 39039039AFL3001 (BAY59-7939/11630), "A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation." The study acronym, ROCKET AFib (also known as simply "ROCKET") , is derived from the alternative study name, **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared with Vitamin **K** Antagonism for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation.

5.3.1 ROCKET

Because ROCKET is the only study submitted to establish the efficacy of rivaroxaban for its proposed indication and its safety with respect to US medical practice, the study protocol and statistical plan will be described in considerable detail.

5.3.1.1 Study Design and Objectives

ROCKET was a randomized, parallel-group, active-controlled, double-blind, multicenter, event-driven non-inferiority trial comparing warfarin titrated to the target INR (2.5, range, 2.0 to 3.0) vs. fixed dose rivaroxaban given once daily, using a classic double-dummy design to maintain the blind. The primary objective was to demonstrate that the efficacy of rivaroxaban is non-inferior to that of dose-adjusted warfarin for the prevention of thromboembolic events in subjects with non-valvular atrial fibrillation as measured by the composite of stroke and non-central nervous system (CNS) systemic embolism. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose-adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

5.3.1.2 Geographic Scope

ROCKET was performed at 1187 enrolling sites (i.e., sites with at least one randomized patient) in 45 countries (46, if Hong Kong is considered separately from China). There were enrolling sites on each of the 6 continents with permanent residents (i.e., all continents except Antarctica). The US had more enrolling sites (263) than any other country.

For administrative purposes and for many analyses, the countries where the trial was conducted were organized into 5 regions – North America, Latin America, Western Europe, Eastern Europe, and Asia Pacific. The national makeup of these regions is described in Appendix 6, [Geographic Regions in ROCKET](#)

5.3.1.3 Study Duration/Dates

The protocol anticipated that patients who survived and did not drop out would be followed for 14 to 32 months, based on 18 months to reach full enrollment and another 14 months to reach the event target. The study's actual dates of first and last patient randomized were 18 December 2006 and 17 June 2009, respectively. The final patient contact occurred on 15 September 2010. The database was locked on 20 October 2010.

The study was planned to end shortly after the event target of 405 adjudicated primary endpoint events was reached. Attainment of the event target was to trigger "site notification," i.e., the sites were notified that the event target had been reached and they

were directed to (1) contact all study patients regardless of whether they were taking study drug, (2) collect endpoint data by phone for the final time from those not taking study drug, and (3) schedule the end-of-study (EOS) visit for those patients still taking study drug (see Section 5.3.1.7.2. for additional information). Site notification occurred on 01 April 2010 for the 22 sites in South Africa and on 28 May 2010 for all other sites.²

5.3.1.4 Patients

Patients who met each of the inclusion criteria below could enroll:

- Men or women aged ≥ 18 years with non-valvular atrial fibrillation
- Atrial fibrillation was to be documented by ECG evidence (e.g., 12-lead ECG, rhythm strip, Holter, pacemaker interrogation) within 30 days before randomization.
 - Subjects had medical evidence of atrial fibrillation within 1 year before and at least one day before the qualifying ECG evidence. This could be obtained from a notation in the subject's record (e.g., medical chart, hospital discharge summary).
 - However, subjects with newly diagnosed atrial fibrillation were eligible provided that:
 - there was evidence that the atrial fibrillation was non-valvular
 - cardioversion was not planned
 - There was ECG evidence on 2 occasions 24 hours apart demonstrating atrial fibrillation
- Subject were to have a history of prior ischemic stroke, TIA or non-CNS systemic embolism believed to be cardioembolic in origin OR had 2 or more of the following risk factors:
 - Heart failure and/or left ventricular ejection fraction $\leq 35\%$
 - Hypertension (defined as use of antihypertensive medications within 6 months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg)
 - Age ≥ 75 years
 - Diabetes mellitus (defined as a history of type 1 or type 2 diabetes mellitus or use of antidiabetic medications within 6 months before screening visit)
- Female subjects were to be postmenopausal (for at least 2 years), surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control.

² The reason for the somewhat earlier site notification date for South African sites is relates to events in South Africa at the expected time of study end. In January 2010, as ROCKET neared its end, it was expected that the study's event target would be reached in May or June of 2010. This suggested that end-of-study procedures might overlap with the 2010 FIFA (soccer) World Cup, which was held in various locations throughout South Africa from June 11 through July 11, 2010. The sponsor was advised that patients and site personnel in South Africa might "not be available" to complete study-related procedures during the World Cup. Accordingly, site notification in South Africa alone was moved up to April 1 so that end-of-study procedures could be completed prior to the World Cup events.

Reviewer comment: From the inclusion criteria as noted, the ROCKET population was selected to be a group that was at high risk for stroke or non-CNS embolic events as a consequence of their atrial fibrillation. The at-risk nature of the population was further increased by the protocol-driven stipulation that after enrollment of subjects with only 2 risk criteria (other than subjects with a prior stroke, TIA, or non-CNS systemic embolism) could account for only 10% of the study population in each region, meaning that 90% of patients were to have either a history of stroke/TIA/systemic embolism or have 3 other risk factor. We learned in a separate communication that the 10% limit was based on the assumption that there would be 3 regions, each with 4666 enrolled patients: North America; Europe + South America; and Asia. At some point, the globe was split into 5 regions by the sponsor, but the 10% limits were implemented based on the original 3 regions and the original estimates of enrollment in those regions. Thus, the North American limit on patients with 2 (non-stroke/TIA/systemic emboli) risk factors was 10% of 4666, or 467, which was much greater than 10% of North American enrollment.

Medically important patient exclusions were:

Cardiac-Related Conditions

- Hemodynamically significant mitral valve stenosis
- Prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted)
- Planned cardioversion (electrical or pharmacological)
- Transient atrial fibrillation caused by a reversible disorder (e.g., thyrotoxicosis, PE, recent surgery, MI)
- Known presence of atrial myxoma or left ventricular thrombus
- Active endocarditis

Criteria Related to Hemorrhage Risk

- Active internal bleeding
- History of or condition associated with increased bleeding risk including, but not limited to:
 - Major surgical procedure or trauma within 30 days before the randomization visit
 - Clinically significant gastrointestinal bleeding within 6 months before the randomization visit
 - History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding
 - Chronic hemorrhagic disorder
 - Known intracranial neoplasm, arteriovenous malformation, or aneurysm
- Planned invasive procedure with potential for uncontrolled bleeding, including major surgery

- Platelet count <90,000/ μ L at the screening visit
- Sustained uncontrolled hypertension: systolic blood pressure \geq 180 mmHg or diastolic blood pressure \geq 100 mmHg

Concomitant Conditions and Therapies

- Severe, disabling stroke (modified Rankin score of 3 to 5, inclusive (Attachment 2) within 3 months or any stroke within 14 days before the randomization visit
- Transient ischemic attack within 3 days before the randomization visit
- Indication for anticoagulant therapy for a condition other than atrial fibrillation (e.g., VTE)
- Treatment with:
 - Aspirin >100 mg daily
 - Aspirin in combination with thienopyridines within 5 days before randomization
 - Intravenous antiplatelet therapy within 5 days before randomization
 - Fibrinolytics within 10 days before randomization
 - Note: Aspirin \leq 100 mg monotherapy was allowed and thienopyridine monotherapy was allowed.
- Anticipated need for chronic treatment with a non-steroidal anti-inflammatory drug
- Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization, or planned treatment during the time period of the study
- Treatment with a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin, within 4 days before randomization, or planned treatment during the time period of the study
- Anemia (hemoglobin <10 g/dL) at the screening visit
- Pregnancy or breast-feeding
- Any other contraindication to warfarin
- Known HIV infection at time of screening
- Calculated CLCR <30 mL/min at the screening visit
- Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3 x the ULN

Reviewer comment: Enrollment criteria seem appropriate for a study with the stated objectives of ROCKET.

5.3.1.5 Treatments

After meeting the study enrollment criteria, eligible subjects were randomized to treatment with rivaroxaban or warfarin. A classic double dummy design was employed. Subjects in the rivaroxaban arm received placebo for warfarin, and subjects in the

warfarin arm received placebo for rivaroxaban. All study medications were to be taken orally in the evening with food.

Rivaroxaban treatment varied with renal function, as follows:

- In subjects with CrCl ≥ 50 mL/min, the dose was one 20 mg tablet daily,
- In subjects with CrCl 30 to < 50 mL/min, the dose was one 15 mg tablet daily.

The dose of rivaroxaban was otherwise fixed and not dependent on any measured coagulation parameters.

Warfarin was administered as tablets containing 1, 2.5 or 5 mg, taken in the evening with food. The dose of warfarin was to be titrated to an INR target of 2.5 (range 2.0 to 3.0, inclusive). No dosing algorithm other guidance regarding maintenance dosing was provided; investigators used their clinical judgment as to how to dose warfarin (or warfarin placebo) to attain and then maintain INR in the target range. This is discussed further below.

5.3.1.5.1 Warfarin Dosing Based on Routine INR Measurements

During the study, with exceptions noted below, INR was to be measured using a point-of-care (POC) device provided to the site. The device and associated procedures were designed to minimize the likelihood of unblinding based on INR data. After analyzing a blood sample, this device displayed a code number instead of the actual INR value. This code number was entered into the telephonic IVRS by site staff along with the subject's study identification number. The IVRS decoded the INR code number and then issued a standardized report which contained either:

- the actual ("decoded") INR value if the subject was assigned to warfarin or
- a sham ("randomly generated") value if the subject was assigned to rivaroxaban.

The site was notified of the sham or true INR during the phone call; a fax of the result was also generated by the IVRS and sent to site. The INR was not entered into the CRF, but was kept separately at the site. There was a data transfer from the IVRS to the study database of the INR information, including the coded ("encrypted") INR, the "decoded" (true) INR and the "randomly generated" (sham) INR. The database contains all versions of the INR for each measurement, but only the true INR was reported to the site by the IVRS for warfarin arm patients and only the sham INR was reported to the site for rivaroxaban arm patients.

Decoded (true) INR values were reported to the site for warfarin arm patients as follows:

- INR values less than 1 were reported as "less than 1.0", but the true value is in the study database
- INR values >6.0 were all reported as "greater than 6.0" and entered into the database as "6.1".

FDA was informed that the true values for INR > 6 are not available from the sponsor or the IVRS vendor.³ INR values from 1.0 to 6.0 were reported and entered into the database as the obtained value for warfarin arm patients.

For patients in the rivaroxaban arm, the sham INR values reported to the sites ranged from “less than 1.0” to 4.0. It was recognized that the lack of reported INR values above 4 might potentially unblind a patient in the rivaroxaban arm. However, the upper limit of 4 was imposed to reduce the possibility that a rivaroxaban patient with a high sham INR would be treated with a pro-coagulant as a rescue measure, which might make the patient prone to thrombosis. The true INR values for rivaroxaban-treated patients were in the study database, subject to the same data recording rules as for the warfarin arm.

It was recommended that INR monitoring using the POC device be performed as clinically indicated, but at least every 4 weeks. While on study drug, unblinded INR measurements were not to be performed at the study center except in case of a medical emergency. The sites were instructed on the importance of limiting the knowledge of any emergency, unblinded INR values to as few staff as possible and of otherwise always using the special study point-of-care device to measure the INR to ensure consistency of warfarin dosing and maintenance of the study blind.

Specific maintenance warfarin dosing instructions were not provided to the enrolling sites. However, an unblinded monitor was employed to review INR data and ascertain if subjects were frequently out of range. This monitor could consult with an unblinded physician at the DCRI to discuss specific cases, if needed. Occasionally and as a result of these surveillance efforts, specific investigators whose patients were found to be persistently below or above the target range received correspondence reminding them of the importance of achieving the INR target. The unblinded monitor was also available to answer questions about individual INR results, in a blinded fashion, from investigators, through local medical monitors. The sponsor states that at no time did the unblinded monitor evaluate aggregate INR time in therapeutic range.

Reviewer comment: The blinding procedures on their face seem appropriately rigorous. However, the lack of a standardized algorithm for maintenance warfarin dose adjustment may have contributed to the overall mediocre TTR for INR in this study, as discussed in Section 6. In RE-LY, in which the sites dosed warfarin using an algorithm provided by the sponsor (i.e., a set of detailed instructions regarding what actions to take in response to INR values in specified ranges), overall TTR was substantially better than in ROCKET. Other warfarin dosing procedures, such as the use of centralized unblinded experts to determine dose (as in SPORTIF V and AMADEUS, have been associated with study TTRs substantially better than what was achieved in ROCKET.

³ We were informed that values > 6.0 were recorded only as “6.1” because if the true value for these elevated INRs were to be recorded, the additional values would have required additional digits in the coded INR. Multiple codes were assigned to each true INR level to foil de-encryption of the code at the sites. The INR device could provide a coded INR with no more than 7 digits, which limited the number of available codes and thus the number of true INR values that could be handled by the system.

5.3.1.5.2 Duration of Treatment

Except has provided below, treatment with blinded study drug was to continue until the end of the study, which was to occur following attainment of the target number of endpoint events. Patients could withdraw from treatment at their discretion, but would have been followed as described in Section 5.3.7.1 unless they specifically withdrew from follow-up. For procedures regarding temporary discontinuation of study drug, see information below in Section [5.3.1.5.3](#) under the heading Interruption of Study Drug. For information on the last study visit and follow-up of patients ending blinded study drug, see Section [5.3.1.7.2](#).

The protocol indicated that double-blind treatment was to be discontinued for the following reasons (non-discretionary reasons are bolded and underlined):

- The investigator believed that for safety reasons (e.g., adverse event) it was in the best interest of the subject to stop treatment
- **Pregnancy**
- If at any time, in the investigator's opinion, the subject no longer required anti-coagulation treatment
- Non-compliance with study drug
- **Stroke or non-CNS systemic embolism (i.e., a primary endpoint event)**
- **Diagnosis of HIV**
- **Abnormal LFTs (consisting any one or more of the following) --**
 - **Clinical manifestation of liver injury (e.g., jaundice) in association with abnormal LFTs**
 - **Concurrent combined increase of ALT >3 x ULN plus total bilirubin >2 x ULN and the ratio of direct to total bilirubin is ≥50% ("concurrent" was not defined here)**
 - **Persistent ALT elevation of >3 x ULN for 4 weeks or longer**
 - **ALT between 3 and 5 x ULN, and an increase of more than 1 x ULN of the previous value observed on reconfirmation within 5 days (e.g., from 3.5 to 4.5 x ULN)**
 - **ALT level >5 x ULN that was confirmed within 5 days**
- **Creatinine clearance <25 mL/min on 2 consecutive occasions**
- **Need for excluded concomitant medication**

A number of concomitant medications were prohibited during study treatment, including ASA > 100 mg/day, strong CYP3A4 inhibitors or inducers, ASA + a thienopyridine (except "as appropriate after vascular intervention"), or fibrinolytics (except in the case of a STEMI when primary percutaneous intervention could not be performed). Open-label warfarin was **not** a prohibited medication, and a small number of patients in each treatment arm received this medication. This is discussed further in Section [7](#).

5.3.1.5.3 Special Dosing Procedures

The protocol specified dosing instructions for several types of special circumstances, as follows.

Initiation of Study Drug in Subjects Receiving a Vitamin K Antagonist Before Study Entry

In this case, the subject was to be instructed to discontinue his/her VKA. Unblinded INRs (i.e., obtained not using the point-of-care device) were to be performed every 1 to 2 days based on the initial INR. Randomization of the subject was to occur as soon as possible when the INR was ≤ 3.0 . Investigators were encouraged to randomize subjects before the INR fell below 2.0. Randomization was to occur within 36 hours of the last unblinded INR.

Interruption of Study Drug

Study drug could be interrupted as necessary for invasive procedures or as medically needed (e.g., in the setting of a bleeding event or a required prohibited therapy), but these interruptions were to be kept to the minimum period possible.

Bleeding Events

For clinically significant bleeding events, the protocol recommended that study drug should be stopped and the subject managed according to guidelines in the protocol. The blind was to be maintained. The decision to restart or permanently withdraw study drug after resolution of a bleeding event was at the discretion of the investigator. If study drug was restarted, frequent INRs using the point-of-care device were to be performed until INR reached the target range 2.0 to 3.0, after which routine monitoring with the point-of-care device was to proceed per the protocol.

Switching from Blinded Study Drug to Open-Label VKA or Other Appropriate Therapy

Transition from blinded study drug to open-label warfarin (or other VKA) was to be done without breaking the study blind. The recommended procedure was to start open-label VKA at its anticipated maintenance dose after discontinuing blinded study drug. The study report (but not the protocol) offers more information. It indicates that for subjects who were receiving a VKA prior to the start of the study, it was suggested by the Executive Committee (EC) that physicians resume open-label therapy at the dose used before the study. For subjects who were VKA naive at the start of the study, the EC suggested that physicians start with a modest dose of open-label VKA, such as 5 mg warfarin daily. However, there was no requirement to start open-label anticoagulant therapy when study drug was discontinued.

Both the protocol and the study report indicate that to maintain the integrity of the blind, local unblinded INR measurements were discouraged for at least 3 days after the start of open-label VKA therapy. After 3 days, VKA dosing was to be managed using unblinded local INR measurements. If necessary, for subjects with high risk of thromboembolism, bridging LMWH therapy could be administered during this transition period.

Reviewer comment: the above instructions for switching to open label VKA applied to patients who dropped out during the study and the greater number of patients who stayed in the study until it was closed. Like for use of warfarin during double blind treatment, there was no dosing algorithm for VKAs. There was also no established INR target, although physicians might pick the study target of 2-3. As noted in Section 6, the timing of attainment of target INR values was not optimal in the rivaroxaban group patients who started open VKA treatment. This may have contributed to the high initial stroke rate in the rivaroxaban arm patients after discontinuation of study drug (see Sec 6). Note that all study patients (except a trivial number of protocol violators) had a CHADS₂ score of at least 2 at entry, 87% had a CHADS₂ score of 3 or more, and about 55% had a prior history of stroke, TIA, or systemic embolism. Essentially all patients should have been received anticoagulant therapy if US guidelines had been followed.

Changes in Renal Function

If the calculated CrCl became <25 mL/min (confirmed by repeat assessment) during the study then study medication was to be discontinued. For subjects who started with a calculated CrCl of ≥50 mL/min and the CrCl decreased to below 50 mL/min during the study, no dose adjustment or discontinuation was to be performed.”

Reviewer comment: The rationale for not reducing the rivaroxaban dose to 15 mg/day in patients whose CrCl dropped below 50 mL/min after randomization is not provided in the protocol or study report. If the 15 mg dose provides therapeutic blood levels of rivaroxaban in patients with mild renal dysfunction (as claimed by the sponsor), then the use of the 20 mg dose in these patients might provide a super-therapeutic dose, and possibly increase the risk of bleeding.

See Appendix 3 for information on [Special Dosing Instructions – Elective Invasive and Emergency Procedures](#)

5.3.1.6 Randomization and Blinding

Subjects were randomly assigned in a 1:1 ratio to rivaroxaban or warfarin based on a computer-generated randomization schedule prepared by the sponsor before the study. The randomization was stratified by country, prior VKA use (defined as VKA use for 6 weeks or longer at the time of screening), and history of a prior stroke, TIA, or non-CNS systemic embolism (3 binary yes/no variables), but not by site. Central randomization with an IVRS was used in this study.

The investigator was not provided with randomization codes. The codes were maintained within the IVRS. Under normal circumstances, the blind was not to be broken until all subjects had completed the study and the database was finalized. However, the blind could be broken for an individual subject if the choice of specific emergency treatment was dependent upon knowing the treatment status of the subject. In such cases, the investigator was to contact the sponsor. Additional details about blinding are discussed in Section 5.3.1.5.1.

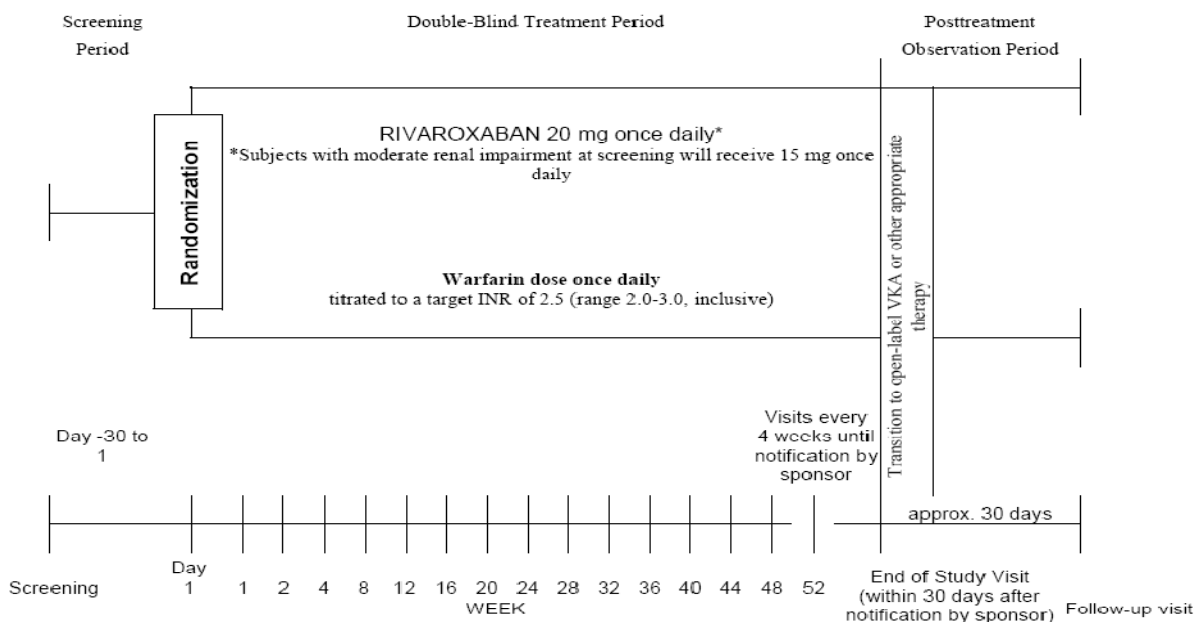
5.3.1.7 Study Plan and Procedures

The study was divided into a screening period, a double-blind treatment period that closed with an end-of-study or early study medication discontinuation visit and a post-treatment observation period. At the early study medication discontinuation or end-of-study visit, subjects were transitioned from study drug to an open-label VKA or other appropriate therapy. At the end of the post-treatment observation period, a follow-up visit occurred. This was planned as the last contact with the subject for patients who completed the study. Figure 16 is a simple schematic figure of the trial plan. Note that some patients were in the study for more than 3 years.

All randomized subjects were to be followed until the study end trigger (the occurrence of 405 adjudicated endpoint events) and the subsequent procedures, even if they did not ever take study drug or prematurely discontinued study drug. Efforts were to be made to contact any subjects lost to follow-up and collect information on the occurrence of efficacy endpoint events and the reason for discontinuation. This might include the use of subject locator agencies where allowed.

4 If the investigator was unable to contact the sponsor, the investigator could in an emergency determine the identity of the treatment by telephoning IVRS. The sponsor then was to be informed as soon as possible by the investigator that this occurred. The date, time, and reason for the unblinding were to be documented in the appropriate section of the CRF and in the source document.

Figure 16. Study flow diagram



5.3.1.7.1 Study Visits and Information Collected

Written informed consent was to be obtained before any study-specific procedure occurred. There was a separate informed consent form for the pharmacogenetic aspect of the study.

Screening procedures were to be performed within 30 days of randomization. Patients determined to be eligible for the study on the basis of screening procedures were asked to return for the Baseline (Day 1) visit, when randomization and dispensing of study drug were to occur. However, if the patient was taking a VKA at baseline, the relevant procedures in Section 5.3.1.5.3 were followed prior to randomization.

In general, during the double-blind treatment period, there were 2 types of visits: Brief Visits and Full Visits. The time points for these visits are detailed in Table 8. These visits included, but were not limited to, the following assessments.

Brief Visit

- Assessed efficacy endpoint events
- INR using the specially programmed point-of-care device
- Adverse event assessment
- Dispensed study drug, as needed

- Drug accountability

Full Visit

- Liver function tests - ALT, total and direct bilirubin
- Assessed efficacy endpoint events
- INR using the specially programmed point-of-care device
- Adverse event assessment
- Dispense study drug, as needed
- Drug accountability
- Anti-Clot Treatment Scale (self-reported) for a subset of subjects at Weeks 4, 8, 12 and 24
- Treatment Satisfaction Questionnaire for Medication (TSQM) (version II) (self-reported) at selected visits for a subset of subjects at Weeks 4 and 24.

Subjects returned for visits at Week 1, 2, 4 and then every 4 weeks thereafter for the duration of the double-blind treatment period. After Week 1, all visits during the first year were to be Full Visits. Double-blind treatment visits occurring after 1 year took place every 4 weeks and either a Brief Visit or a Full Visit was performed according to the Schedule for Brief and Full Clinic Visits provided in the Time and Events Schedule ([Table 8](#)). A 12-lead ECG and clinical laboratory tests were to be performed annually. Unscheduled visits for INR measurement or evaluation of efficacy or safety events could occur at any time during the study.

Non-fasting blood samples were drawn at various times throughout the study for laboratory evaluations ([Table 8](#)). A PK/PD substudy included matched evaluations of blood levels of rivaroxaban and three coagulation tests: FXa activity, prothrombin time (PT) and prothrombinase-induced clotting time (PiCT, see [ATTACHMENT 3](#)).

Table 8. ROCKET -- Schedule For Brief And Full Clinic Visits

Schedule for Brief and Full Clinic Visits			
Study Week	Brief Visit	Full Visit	Additional Tests
1	X		
2, 4, 8, 12, 16, 20		X	Blood sample for sparse PD (Week 12)
24		X	Clinical laboratory tests, risk markers/ proteomics, blood sample for sparse PD (Week 24)
28, 32, 36, 40, 44, 48		X	
52		X	12-lead ECG, clinical laboratory tests
56, 60	X		
64,		X	
68, 72	X		
76		X	
80, 84	X		
88		X	
92, 96, 100	X		
104		X	12-lead ECG, clinical laboratory tests
108, 112	X		
116		X	
120, 124	X		
128		X	
132, 136	X		
140		X	
144, 148, 152	X		
156		X	12-lead ECG, clinical laboratory tests
160, 164	X		
168		X	
172, 176	X		
180		X	
184, 188	X		
192		X	
196, 200, 204	X		
208		X	12-lead ECG, clinical laboratory tests

Additional information on safety monitoring is found in Section [5.3.1.9.2](#).

Health care resource utilization data were to be collected in all subjects during the double-blind treatment phase of the study and for efficacy endpoint events only during the post-treatment observation period. Only the occurrence of these events (with identifying information such as types of procedures) was to be collected, but no cost data were collected.

In a subset of subjects from the United States, Germany and Netherlands, subject satisfaction with therapy was to be assessed using the ACTS (Anti-Clot Treatment Scale). To avoid potential selection bias the subset was to be selected either from a subset of clinics recruiting all their subjects or at random without the influence or discretion of treatment provider. An attempt to validate the ACTS, which was under development, was made by also administering the Treatment Satisfaction Questionnaire for Medication (TSQM) Version II, an older instrument. The TSQM is not specific for anti-coagulants, and the sponsor claims that it can be applied across drug classes.

See Appendix 3 for additional [Time and Event Information](#)

5.3.1.7.2 Procedures for discontinuation of study drug

Procedures were specified for discontinuation of study drug at the end of the study as well as for early discontinuation of study drug.

The end-of-study (EOS) visit was to be scheduled when the sponsor notified the sites that the prespecified number of adjudicated primary endpoint events had occurred (“site notification”). The EOS visit was the last visit in the double-blind treatment period for subjects on study drug at that time. Once notified about the end of study, the study center was to contact each subject on the study who was still taking double-blind study drug and schedule this visit as soon as possible but within 30 days of the notification. Subjects were to continue to take study drug until they returned for the EOS visit. Because study drug was to be taken in the evening, the last dose of study drug ordinarily should have been taken the evening before the EOS visit.

Investigators were encouraged, but not required, to transition patients to open-label anticoagulant therapy at the EOS visit (see the discussion under the heading, [Switching from Blinded Study Drug to Open-Label VKA or Other Appropriate Therapy](#)). Unlike the transition from VKA therapy to blinded study drug, which was subject to specified procedures, management of the transition from blinded study drug to open-label anticoagulant therapy was largely left to the investigator’s discretion.

Reviewer comment: The lack of direction in the protocol regarding how to transition the study patients off of study drug was associated with a sharp increase in the rate of stroke in rivaroxaban patients.

Following the EOS visit there was to be an observation period to follow subjects after transition from study drug to open-label VKA or other appropriate therapy. In addition to ad hoc return visits to assess INR control (scheduled at the investigators’ discretion), subjects were to return to the clinic for a “follow-up visit” approximately 30 days (±5 days) after the permanent discontinuation of study drug. For subjects who completed the scheduled double-blind treatment period, this was the final subject contact.

Subjects who had prematurely discontinued study drug (or who were planning to discontinue) were to have a site visit (the early study medication discontinuation visit, or ESMDV). If appropriate, study drug was to be continued until the ESMDV. At this visit, they were to be started on open-label VKA treatment or other appropriate therapy using the same procedures as those patients who completed the study, including visits for INR measurements. After the ESMDV, patients were to have a final site visit 30 days later. They were then followed up by phone every 12 weeks for the occurrence of efficacy endpoints until site notification of attainment of the target number of primary efficacy endpoints. Such subjects were to be contacted for the last time after site notification.

The following table summarizes planned study drug discontinuation and end of study procedures.

Table 9. ROCKET – Early Termination And End Of Study Procedures

Patients with Early Termination of Study Drug	Patients who Completed the Study
1. Decision by subject or investigator to terminate study drug ↓ ↓	1. Sponsor notifies sites that the target number of primary adjudicated primary endpoints have occurred (“site notification”), triggering the end-of-study procedures ↓
2. If possible, continue study drug, with last dose taken the evening before the early study medication discontinuation visit (ESMDV) ↓	2. Site schedules end-of-study visits to occur within 30 days of site notification; subjects to continue study drug, with last dose taken the evening before the end-of-study visit ↓
3. <u>ESMDV</u> Unused study drug returned to site; begin open label anticoagulation at investigator’s discretion ↓	3. <u>End of study visit</u> Unused study drug returned to site; begin open label anticoagulation at investigator’s discretion ↓
4. Other discretionary visits for monitoring anti-coagulation therapy. Follow up site visit in 30 days (intended as the last in-person site visit). ↓	4. Other discretionary visits for monitoring of anti-coagulation therapy. Follow up site visit in 30 days (intended as the final planned contact). ↓
5. Phone contacts q 12 weeks until the end of the study. Upon “site notification” (see event No. 1 in the next column), a final phone contact is made. ↓	5. Efficacy endpoint information to be collected through final contact
6. Efficacy endpoint information to be collected through final contact	

5.3.1.8 Efficacy Endpoints

5.3.1.8.1 Primary Endpoint

The primary efficacy outcome was the composite of stroke and non-CNS systemic embolism. Adjudicated results were to be used for the final analysis.

5.3.1.8.2 Secondary Endpoints

“Major” secondary efficacy endpoints included:

1. Composite of stroke, non-CNS systemic embolism, and vascular death
2. Composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death

Other secondary efficacy endpoints included:

- Individual components of the composite primary and major secondary endpoints
- Disabling stroke
- All-cause mortality

5.3.1.8.3 Endpoint Definitions

The following definitions were used in assessing efficacy endpoints:

Stroke was defined as “a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause such as a tumor or seizure.” Such an event lasting less than 24 was considered a TIA. Stroke was sub-categorized as:

- Primary hemorrhagic – stroke with focal collections of intracerebral blood. Events of subarachnoid, subdural, and epidural hemorrhage were to be recorded, but these events were not to be considered part of the primary efficacy endpoint.
- Primary ischemic infarction – stroke without focal collections of intracranial blood. The occurrence of hemorrhagic conversion of a primary ischemic infarction was to be recorded including whether it was symptomatic or asymptomatic. Stroke subtype was to be assessed as cardioembolic, non-cardioembolic (e.g., atherothrombotic, lacunar, other known cause) and uncertain.
- Uncertain – no imaging or autopsy data available.

Non-CNS systemic embolism was defined as “abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms, (e.g., trauma, atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities was to be made with caution and required angiographic demonstration of abrupt arterial occlusion.

All strokes were sent to the Clinical Endpoint Committee (CEC) for adjudication and categorization. A stroke was considered disabling if the subject's modified Rankin score (Attachment 2) was between 3 and 5, inclusive. The investigator or designee was to perform the Rankin evaluation 3 months after the onset of a stroke. For events occurring at the end of the study this evaluation was to occur at least 1 month after the onset of the stroke.

A fatal stroke was one that produced death within 30 days of the onset of the stroke.

Myocardial infarction (MI) definitions varied with the patient's procedural history:

- In the absence of a PCI or CABG, myocardial infarction was defined as “clinical symptoms consistent with myocardial ischemia and cardiac biomarker elevation (Troponin I or T, creatine kinase-muscle and brain subunit [CK-MB]) greater than the site's ULN or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram or autopsy confirmation.”
- For subjects having a PCI, a myocardial infarction was defined as: “CK-MB (or CK in the absence of CK-MB) >3 x ULN for samples obtained within 24 hours of the procedure if the baseline values were normal or at least a 50% increase over elevated baseline values that were stable or decreasing or development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram. Symptoms of cardiac ischemia were not required.
- After coronary artery bypass graft surgery, a myocardial infarction was defined as either:
 - CK-MB (or CK in the absence of CK-MB) >5 x ULN for samples obtained within 24 hours of the procedure with development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram OR
 - CK-MB (or CK in the absence of CK-MB) >10 x ULN for samples obtained within 24 hours of the procedure with or without development of new pathological Q waves in at least 2 contiguous leads on the electrocardiogram.

Myocardial infarction caused by a coronary artery embolus was considered a type of non-CNS systemic embolism. Other types of MIs were not primary endpoints, but were components of secondary efficacy endpoints. No specific guidance was provided with respect to diagnosis of coronary artery embolism.

Vascular death was defined as follows: “Any death that is not clearly non-vascular. For example this includes deaths due to spontaneous bleeding, myocardial infarction, stroke, heart failure and arrhythmias.”

5.3.1.9 Safety Endpoints and Procedures

5.3.1.9.1 Safety Endpoints

The principal safety endpoint was the composite of major and non-major clinically relevant bleeding events. These were defined as follows:

Major bleeding was defined as clinically overt bleeding associated with:

- A fall in hemoglobin of 2 g/dL or more,
- A transfusion of 2 or more units of packed red blood cells or whole blood,
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

Non-major clinically relevant bleeding was defined as s overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life. Examples of non-major clinically relevant bleeding are:

- Epistaxis, if lasting more than 5 minutes, if it was repetitive (i.e., 2 or more episodes of true bleeding, i.e., not spots on a handkerchief, within 24 hours), or led to an intervention (packing, electrocautery, etc.),
- Gingival bleeding, if occurring spontaneously (i.e., unrelated to tooth brushing or eating), or if lasting for more than 5 minutes,
- Hematuria, if macroscopic, and either spontaneous or lasting for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract,
- Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent,
- Rectal blood loss, if more than a few spots,
- Hemoptysis, if more than a few speckles in the sputum,
- Intramuscular hematoma,
- Subcutaneous hematoma, if the size was larger than 25 cm² or larger than 100 cm² if provoked, or
- Multiple source bleeding

All other overt bleeding episodes not meeting the criteria for major or non-major clinically relevant bleeding were classified as minimal bleeding.

5.3.1.9.2 Safety Procedures

The ROCKET trial included the following evaluations of safety and tolerability at the indicated timing and frequency specified:

Table 7. ROCKET – Schedule Of Safety Assessments

Safety Assessment	Screen	Brief Visits	Full Visits	Discontinuation Visit	EOS Visit	FU Visit
12-lead ECG ^a	X			X	X	
Physical examination	X			X	X	
Vital signs	X			X	X	
INR	X	X	X	X	X	
Hematology and Chemistry ^{a,b}	X			X	X	
Liver-related laboratory tests ^c	X		X	X	X	X ^d
Adverse events ^a	X	X	X	X	X	X

Key: ECG = electrocardiogram; EOS = end of study; FU = follow-up; INR=international normalized ratio;

Adverse Events

Adverse events were reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events were to be followed by the investigator for a length of time as determined by the sponsor. The protocol did not provide specific directions on how to solicit adverse events.

Serious adverse events were to be immediately reported (within 24 hours of the investigator's awareness) and from the interval that commenced with the signing of the informed consent and ended after the completion of the Post Treatment Observation Period. When required, and according to applicable local law and regulations, serious adverse events were reported to the IRB or Ethics Committee and Regulatory Authorities. All SAE reports were reviewed by J&JPRD with a primary focus on subjects who experienced serious adverse events of special interest: bleeding events, liver-related events, pancreatitis, hypersensitivity reactions and other potential safety issues (e.g., organ toxicity, renal toxicity).

See Appendix 3 for information on **Clinical Laboratory Tests**

AE reporting of study endpoints

In ROCKET, the clinical efficacy endpoint events of myocardial infarction, ischemic stroke, and non-CNS systemic embolism were not to be considered adverse events or serious adverse events; they were to be captured on the CRF as endpoint events only.

All bleeding events (including CNS bleeds) were to be reported as adverse events or serious adverse events, as appropriate. The protocol stated that an “untoward medical occurrence” that “results in death” is an SAE. This suggests that deaths, even though they were considered efficacy endpoint events, should have been also captured as SAEs.

5.3.1.9.3 Monitoring and Evaluation of Liver Function

Special procedures were created for evaluation of liver function abnormalities. Initially, a Liver Advisory Panel (LAP) was available for consultation as necessary and to assess liver-related cases of interest. Adjudications of drug relatedness were made by consensus. This group did not have a charter or operations manual that was submitted with the study report.

In September 2009, the LAP was replaced by the Hepatic Event Assessment Committee (HEAC), which was organized and run under an Operations Manual. This was an external group of drug-induced liver injury (DILI) experts (3 clinicians and 2 pathologists) whose purpose was to independently review individual hepatic event cases that met any of 5 pre-defined criteria (based on either central or local labs):

- Concurrent combined ALT >3x ULN with total bilirubin >2x ULN (defined by occurrence on the same calendar day)
- Non-concurrent combined ALT >3x ULN with total bilirubin >2x ULN, if the total bilirubin elevation occurred within the first 30 days after the ALT elevation
- ALT > 8xULN
- Deaths with ALT >3x ULN within 30 days of death
- Other (includes cases of possible concern not meeting any of the 4 categories listed above). Cases under ‘Other’ were identified using 28 hepatic disorder adverse event terms that might indicate acute liver injury.

In addition to cases from ROCKET, the HEAC adjudicated cases arising in J ROCKET and several studies of rivaroxaban in patients with or at risk for venous or pulmonary thromboembolic events.

The assessments by the HEAC were performed in a blinded fashion for individual cases on an ongoing basis during clinical study conduct. The 3 HEAC clinical reviewers independently completed a clinical evaluation form and provided a written narrative for each case. The primary information collected was their assessment of the relationship of the causality of the study drug to the liver event using the categories of definite, probable, possible, unlikely, excluded and not assessable. The review team, including pathologists, also provided a description of the type of hepatic injury.

All cases of ALT and/or bilirubin elevation that occurred from the beginning of the study until September of 2009 (the time during which the LAP was the liver consultation panel) that met HEAC evaluation criteria were referred to the HEAC for adjudication. Therefore, all cases from ROCKET that met HEAC adjudication criteria were indeed adjudicated by the HEAC. In some instances, there may have been both LAP and HEAC evaluations.

5.3.1.9.4 Additional data to be collected

Additional data were collected during the study, included information on the following parameters:

- health care utilization
- patient satisfaction
- risk markers
- proteomics
- pharmacogenomics

Information on the plans to collect these data are found in Attachment 3 - **Health Economic Data and Patient Satisfaction Data**

5.3.1.10 Adjudication of Endpoints by the Clinical Endpoint Committee

An independent Clinical Endpoint Committee (CEC), which operated under a charter, was created to adjudicate the endpoints described below. The CEC was comprised of members of the Duke Clinical Research Institute (DCRI) and Duke University who were not otherwise involved in the study, and was blinded to treatment assignment. Physicians from outside of the Duke community could also be selected for membership. The adjudicated endpoints were:

- Stroke
- Non-CNS systemic embolism
- Death
- Myocardial infarction
- Transient ischemic attack
- Major bleeding event
- Non-major clinically relevant bleeding event

5.3.1.10.1 CEC structure and responsibilities

CEC members were to have clinical and research experience; the charter suggests that both cardiologists and neurologists were members. The DCRI CEC Director, Dr. Ken Mahaffey, was responsible for the “initial selection” of the CEC members, subject to approval of the sponsor. There were to be no sponsor representatives on the CEC.

The CEC Chair was responsible for presiding over CEC meetings and conference calls, the finalization and dissemination of endpoint criteria, the assurance of quality of the adjudication process through ongoing QC reviews, and participation in the adjudication process.

The CEC Coordinator, from DCRI, played a central in the adjudication process. Among other responsibilities, the Coordinator was to:

- collaborate with the sponsor in designing the eCRF to include and facilitate the collection of ancillary data required for event adjudication,
- collaborate with the sponsor in providing the sites with the necessary tools and training to provide the CEC with complete data required for event adjudication,
- train and oversee the day-to-day work of the CEC team members,
- organize and participate in the CEC meetings,
- facilitate the collection of additional source documents and any additional data requested from the committee by posting the query directly in the electronic data capture system, and
- review all endpoint specific source documents and eCRF data to ensure that data required by the CEC physicians was complete capture

Data managers at DCRI collaborated with the sponsor to develop data specifications for various listings, forms, and reports involved in the adjudication process, to design the eCRF, and to develop the definitions and specifications for the “event triggers” discussed below.

The Charter suggests that the CEC had oversight from an “Executive Operations Committee” (which may have been the same as another group mentioned in the Charter, the “Study Operations Committee”), which monitored the progress of the CEC, approved CEC members, ensured that CEC recommendations to improve quality were implemented by the sponsor, and informed the CEC of the study’s progress. The composition of this committee was not described in the Charter.

5.3.1.10.2 Ascertainment of events for adjudication

All events brought for adjudication were identified by a computer program that queried key data fields on the eCRF determined to be CEC-critical variables. Once all eCRF

data fields necessary for CEC review were query-clean, the case was ready for adjudication. As noted earlier, it was the responsibility of the Coordinator to ensure that records were complete enough for adjudication. Specified source documents were required for adjudication of stroke/TIA (imaging study reports, discharge summary), non-CNS systemic embolism (imaging study reports, discharge summary), and myocardial infarction (ECGs at baseline, event, and post-event).

See Appendix 3 for information on the [Triggers for CEC Review](#).

5.3.1.10.3 Adjudication procedures

Adjudication was performed in “phases”. Phase I adjudication for deaths, non-CNS embolic events, and MIs involved independent adjudication by two physicians. If they agreed, the event was resolved. If they disagreed, the event went to the Phase II Committee (which contained at least 2 board eligible or certified cardiologists) for consensus adjudication.

All triggered stroke events were adjudicated by consensus agreement of the Phase II Committee for strokes, which included at least 2 cardiologists and at least 1 neurologist, all board certified or board eligible.

Phase I for bleeding events started with review of the event by either the CEC Coordinator or a physician to classify the bleeding event as minimal, non-major clinically relevant, or major. All bleeding events determined to be minimal or non-major clinically relevant were to be reviewed in full by the CEC Coordinator or a physician. A random 10% sample these bleeding events were to be sent to the Phase II Committee for a QC review initially. All bleeding events determined to be major were to be reviewed by two reviewers: the CEC Coordinator or physician and a physician reviewer. If the two reviewers agreed that an event did or did not occur, then the suspected event was considered resolved. If the two reviewers disagreed, the event was adjudicated by consensus agreement of the Phase II Committee, which included at least 2 board certified or board eligible cardiologists.

Reviewer comment: These automated, two-level event screening procedures and adjudication procedures seem very-well thought out. While it might have been preferable to adjudicate all hospitalizations, to find efficacy and safety events, the algorithms used in ROCKET appear to be unbiased and quite inclusive, and it seems unlikely that a meaningful number of endpoint events were missed.

5.3.1.11 Statistical Plan

5.3.1.11.1 Sample Size

This study was planned to stand alone as support of efficacy of rivaroxaban for the target indication, with a primary analysis involving non-inferiority to warfarin for the time to the primary endpoint. The statistical assumptions were:

- Non-inferiority margin of 1.46 for the risk ratio (rivaroxaban/warfarin)
- Two-sided significance level of 0.05 (1-sided significance level of 0.025)
- Power of >95% when the true risk ratio is 1
- Exponential distributions for time from randomization to event

Using East 4.0 statistical software, the Sponsor calculated that 363 events in the per-protocol population would provide 95% power to demonstrate non-inferiority. The Sponsor increased the target number of events to 405 to “assess consistency across important subgroups.”

The event rate in the control arm was based on data from recent trials of warfarin treatment of the target indication. The assumed event rate was 2.3% per patient-year. Other assumptions were an enrollment period of 1.5 years, yearly dropout of 14% (this included lost to follow-up, premature discontinuation of study drug and withdrawal of consent). The expected study duration from first patient in to the 405th event was 32 months. It was expected that 14,000 patients would be enrolled to achieve the event target. Up to 16,000 patients could be enrolled if events were not as frequent as anticipated.

For the principal safety endpoint, the composite of major and non-major clinically relevant bleeding events, assuming that there was 10% bleeding rate per year in the warfarin group, the study would have had approximately 80% and 95% power to detect 15% and 20% relative risk reductions at a 1-sided significance level 0.025, respectively.

Reviewer comment: The proposed non-inferiority margin of 1.46 for efficacy is higher (more permissive) than the 1.38 margin that the Division favors and which was explicitly recommended to the sponsor. In addition, using a significance level of 0.05 in a sample size calculation for the only study intended to support efficacy is risky. However, if the true HR was < 1, the study might have good power to achieve an observed a p value for non-inferiority substantially less than 5%.

5.3.1.11.2 Analysis Plan

Analysis sets

The primary time to event analysis (using adjudicated primary endpoint events of stroke or systemic embolism) was performed in the per-protocol population on treatment. “On treatment” was defined as the period from randomization to the earliest of the Trial reference end date (i.e., the overall end of the study), the date/time of death, or the date/time of the last double-blind study medication administration + 2 days. The Per Protocol population was all randomized subjects excluding those with pre-defined major protocol violations that occurred while on treatment and before the occurrence of the primary endpoint event. These protocol violations included:

- Inadequate documentation of atrial fibrillation at the time of enrollment into the study
- Prosthetic heart valve at the time of enrollment into the study
- Documented atrial myxoma at the time of enrollment into the study (not including subjects with a history of atrial myxoma that has been resected in the past)
- Documented active endocarditis at the time of enrollment into the study
- Receiving study medication different from that assigned by the IVRS/IWRS during the double-blind treatment period
- Not receiving any study medication during the double-blind treatment period
- No proper informed consent
- Documented left ventricular thrombus at the time of enrollment into the study
- CHADS₂ score = 0 or 1 at the time of enrollment into the study
- Compliance with study drug lower than 60%

The last 4 bullets were added to the list of protocol violations in the first amendment to the SAP (dated June 30, 2009, prior to data lock).

The safety population was all randomized subjects who received at least one dose of blinded study medication.

The ITT population was all randomized subjects.

Efficacy Endpoint Analyses

The primary analysis was performed in the Per-Protocol population, on treatment (as defined above). The aim of the primary analysis was “to establish that rivaroxaban is non-inferior to warfarin by a non-inferiority margin of 1.46 in terms of risk ratio rivaroxaban / warfarin.” The analysis performed was a 1-sided test of the time to event at the 0.025 level. The 2 sided 95% CI of the hazard ratio was obtained using the non-stratified Cox Proportional Hazards model with treatment as a covariate.

If the upper limit of the 2-sided CI of the HR was below the non-inferiority margin of 1.46, then non-inferiority on the Primary Efficacy Endpoint would be declared.

A similar analysis in the ITT on treatment population was planned as a supportive analysis. An analysis aimed at testing the robustness of the primary efficacy endpoint analysis was planned that included 3 randomization stratification factors as strata in the Cox Model: region, prior VKA use, and history of a prior stroke, TIA or non-CNS systemic embolism. Otherwise the analysis would be similar the primary endpoint analysis.

Reviewer comment: The ITT population includes patients who are not on treatment, so an analysis in the ITT population “on treatment” would be either have an identical number of events as the Safety population on treatment analysis or the analysis would need to have 2 sets of censoring rules: one for patients who received randomized study treatment, and one for those who were randomized but took no study drug at all.

If non-inferiority was declared in the primary analysis, the sponsor intended to test superiority of rivaroxaban on the primary efficacy endpoint in the safety population on treatment. If the upper limit of the two sided CI of the HR was below 1, then superiority would be declared. As a supportive analysis for superiority, an analysis of primary endpoint events from randomization to the follow-up visit in the ITT population was planned. An enhanced Cox Model superiority analysis analogous to the robustness analysis described in the previous paragraph was planned to investigate robustness of the superiority finding.

Reviewer Comment: Because of an analysis of results in the safety population on treatment to assess superiority might be confounded by informative censoring, the ITT analysis and other analyses that count at least some events occurring after discontinuation of study drug should be given substantial weight.

Hierarchical Analysis Plan

To control the family-wise type I error rate strongly, a closed testing procedure in the following specific order was to be conducted. This included the primary efficacy endpoint analysis and an additional 5 analyses in a specified order. Each individual test in the multiple testing procedure was to be performed at a 2-sided significance level of 0.05. If an individual test during any step is not statistically significant, later tests were not to be declared to be statistically significant.

1. Non-inferiority on the Primary Efficacy Endpoint (based on on-treatment data from the PP population)
2. Superiority on the Primary Efficacy Endpoint (based on on-treatment data from the safety population)

3. Superiority on Major Secondary Efficacy Endpoint 1 (based on on-treatment data from the safety population)
4. Superiority on Major Secondary Efficacy Endpoint 2 (based on on-treatment data from the safety population)
5. Superiority on On-Treatment All-Cause Mortality (based on on-treatment data from the safety population)
6. Superiority on All-Cause Mortality (based on the ITT population regardless of treatment exposure)

The SAP provides that for the purposes of completeness, all the above specified tests would also be performed regardless of the above hierarchy of testing.

Reviewer comment: The hierarchical procedure seems acceptable, but we should seek the views of the statistical reviewer.

Interim Analysis for Futility

A prespecified interim analysis was performed when approximately 50% (202) of the required total primary efficacy events occurred, to assess the option of stopping early for futility of success for the primary endpoint. Futility would have been declared if the point estimate of the HR for the primary endpoint was more than 1.64. The futility boundary was not reached and the trial continued.

There was also a stopping rule for attainment of “overwhelming superiority” of rivaroxaban over warfarin at the same interim analysis (using the on treatment safety population). The study was to be stopped if the one-sided p for superiority was <0.001 . There was no stated plan to adjust the final p value for this early look. The stated p was not attained and the study continued.

Safety Analysis Plan

Safety analyses, including data from the Czech Republic site closed for GCP violations (042012) were conducted. Supplemental key safety summaries and listings of subjects from Site 042012, per the unanimous vote of the Executive Committee, were also conducted.

Primary Safety Analysis

The principal safety endpoint was the composite of major and non-major clinically relevant bleeding events. The hypothesis of superiority on the Principal Safety Endpoint of rivaroxaban over warfarin was tested at a 1-sided significance level of 0.025 based on on-treatment data from the safety population. Time from the first study medication administration to the first occurrence of the principal safety endpoint was analyzed using the same approach as in the Primary Efficacy Analysis based on on-treatment data from the safety population. The 2-sided 95% confidence interval for hazard ratio

(rivaroxaban/warfarin) was provided. If the upper limit of the 2-sided confidence interval was below 1, then Superiority on the Principal Safety Endpoint of rivaroxaban over warfarin was declared. The model assumptions made in the principal safety analysis were assessed using the same approaches as those in the Primary Efficacy Analysis.

For further information on planned analyses, see Appendix 3, [Additional Information Regarding the Statistical Plan](#)

Evolution of the statistical plan

The study protocol contained fairly detailed information about the statistical analysis plan. Some statistical material was missing from the protocol, which referenced the Statistical Analysis Plan (SAP). Notably, the protocol violations that would exclude patients from the per-protocol population (and thus the sponsor's primary endpoint analysis) and details of the definition of "on treatment" (a definition that could affect the primary endpoint analysis) were not specified in the protocol.

All of the material above reflects the final statistical analysis plan. However, there were several iterations of the sponsor's SAP document. All were dated prior to the stated date for database lock, which was October 20, 2010.

Reviewer comment: However, the statistical plan was not finalized prior to the target specified in the DSMB charter, which was prior to the study's interim analysis, which was reviewed by the IDMC on August 12, 2009. In addition, the first draft of the SAP is dated 11/27/2007. While this date is well before the date of the interim analysis, it is very close to the date of the first IDMC meeting for which unblinded safety and efficacy data were provided by J&J prior to the meeting, which was held on December 12, 2007. Substantial amounts of blinded data were available to the sponsor at that time (the meeting minutes note that they had data for 1655 patients in the safety analysis set and unblinded data for efficacy endpoints and bleeding events). However the number of events at this time, including events occurring after discontinuation of treatment, was uninformative.

In addition, at least one person in J&J was unblinded with respect to critical safety and efficacy data that were to be provided for closed review at each IDMB meeting. Thus, there is a possibility that blinded or perhaps even unblinded study data informed the design key provisions of the SAP that could have affected important analyses. However as noted above, when the key provisions in the SAP that could have influenced the important efficacy analyses were drafted, the number of efficacy events was uninformative, meaning that no useful knowledge could have been passed on to the statistical plan authors.

Table 10. ROCKET – History Of The Sponsor’s SAP With Other Relevant Events

SAP Version or Relevant Event	Date	Comments
First patient randomized	12/18/2006	-
Original SAP	11/27/2007	See text
1 st DSMB meeting	12/12/2007	Unblinded data prepared by Sponsor and provided to DCRI in advance of meeting
SAP Amendment 1	6/30/2009	See text
SAP Amendment 2	10/1/2010	See text
“Supplemental” SAP	10/15/2010	This is a very short document that describes only new exploratory analyses relating to the effects of specified concomitant medications on bleeding risk and efficacy endpoints
Database lock	10/20/2010	--

Amendments 1 and 2 to the SAP were stated by the Sponsor to be “planned” amendments. The protocol states that the SAP “... will be finalized before unblinding of treatment assignment. The SAP will accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses, and will provide more details on the analytic approaches, coding guidelines, censoring of time-to-event variables, and output tables and figures.”

Amendment 1, completed more than 1 year prior to data base lock and about 6 weeks prior to the first and only interim analysis of the study results, provided for the following important provisions:

- Contacting patients who discontinued prematurely every 12 weeks until the final assessment.
- A uniform definition of “on treatment” for efficacy and safety events, clinical laboratory assessments and vital signs. However, in the event that the timing of an event was unclear due to missing data, safety events or abnormalities would be considered on treatment if it was logically possible for the event to fall within the on treatment window. Efficacy endpoint events would be considered on treatment only if it was logically impossible for the event to fall outside the on treatment window. The rationale for the higher burden for classifying an efficacy event as occurring on treatment was not stated. The definition of “on-treatment” for the efficacy and bleeding event analyses was not changed from its original version as stated in the initial SAP: last dose of double-blinded study drug + 2 days.
- Sites or subjects who do not meet GCP standards could be excluded from some analysis sets on a case by case basis, provided that the decision to exclude was made before unbinding.

- Four additional protocol deviations were added to the list of those that would exclude a patient from the per-protocol population. These are noted in the discussion of this issue on page 95.
- “Superiority on all-cause mortality” in the ITT population, regardless to drug exposure, was added as a statistical hypothesis for analysis at the end of the chain of hierarchical analyses.

The second SAP amendment is dated less than one month prior to database lock and unblinding. This amendment calls for the following significant changes, among others:

- Hypotheses of non-inferiority on Major Secondary Efficacy Endpoints 1 and 2 in the hierarchical chain were removed. This deletion had the effect of making superiority for the primary efficacy endpoint the second analysis in the hierarchical endpoint chain.
 - *Reviewer comment: Analyses of both these endpoints on treatment (Safety population) showed superiority of rivaroxaban over warfarin; thus, removal of these endpoints from the hierarchical analysis did not affect the validity of considering the significance of analyses below them in the original hierarchy.*
- A change was made to the method of imputing INR values in between known INR values (based on the Rosendaal method): In the event of a study drug interruption of 7 days or more, neither imputed or actual values would be used in the various analyses of INR for days the drug was discontinued.
- Efficacy analyses excluding and including the closed site in the Czech Republic (closed due to GCP violations) would be performed. The analyses excluding that site would be in the “primary package;” analyses including that site would be considered supportive. This action was taken “per the unanimous vote of the Executive Committee.” Safety analyses with and without this site would be done, but the ones with the site would be considered primary and the ones without the site, supportive.
- Language was added regarding the replacement of the “liver advisory panel” with the Hepatic Event Advisory Committee (HEAC). The composition and duties of the HEAC were described.
- All summaries and analyses of efficacy in Section 2.2.9 based on on-treatment data from the ITT population were replaced with similar summaries and analyses based on on-treatment data from the safety population.
 - *Reviewer comment: The only difference between the ITT population and the safety population is that the ITT population includes 28 additional patients who never received study drug; the notion of “on-treatment” for these 28 patients is an oxymoron. As a practical matter, the on treatment ITT and safety populations are congruent, so this amendment to the SAP has no real effect except possibly to decrease modestly the denominator in a calculation involving patient-years of data.*

- New language on net clinical benefit (NCB) was added. NCB was to be based on on-treatment data in the safety population as well as all data up the follow-up visit in the ITT population. The endpoints to be analyzed included:
 - The composite endpoint of death, stroke, MI, major bleeding, and non-CNS systemic embolism
 - The composite endpoint of death, stroke, MI, major bleeding, non-CNS systemic embolism, and pulmonary embolism
 - The composite endpoint of vascular death, stroke, MI, major bleeding, and non-CNS systemic embolism
 - The composite endpoint of vascular death, stroke, MI, major bleeding, non-CNS systemic embolism, and pulmonary embolism.

5.3.1.12 Study Committees

The study protocol described the following committee structure:

Executive Committee (EC): The EC consisted of members of the academic leadership of the study and one member from each sponsoring company. The EC was ultimately responsible for the conduct of the study, including addressing any DMC recommendations and overseeing publication of the results. The study report indicates that the SC approved such decisions as the decision to perform certain analyses with and without data from one site with important GCP violations.

Steering Committee (SC): The SC consisted of the lead investigators from each country/region. The SC was to advise and assist the EC with regard to the scientific and operational aspects of the study.

Independent Data Monitoring Committee (IDMC): The IDMC was established pursuant to a charter to monitor the progress of the study and ensure that the safety of subjects. The DMC was to include, but was not limited to, a clinical chairman, physician(s) experienced in clinical trials but not participating in this study, and at least one statistician.

Reviews of unblinded data reviews were to be conducted on an ongoing basis. The unblinded reports reviewed by the IDMC were to include (at a minimum) the following study information:

- Summary of bleeding events
- Summary of clinical outcomes
 - Strokes (non-hemorrhagic / hemorrhagic / unknown)
 - Death / Cause of death
 - Myocardial ischemia/MI
- Summary of Serious Adverse Events

- Permanent discontinuation of double-blind study drug
- Laboratory tests and abnormalities (including LFT and amylase abnormalities, calculated creatinine clearance, complete blood count)
- INR

Reviewer comment: Because the vast majority of primary efficacy endpoint events were strokes, the IDMC was essentially unblinded with respect to the primary endpoint starting no later than their first meeting in December, 2007, when the study N was 3146, about 22% of the total enrolled at study end.

The flow of data to the IDMC bears discussion. Blinded study data held at J&J PRD by the study project team were transferred to a designated “independent and unblinded programmer” at J&J PRD, who ran SAS programs on the blinded data to generate unblinded analysis data sets and output (tables, listings, and graphics) with actual treatment codes. These were provided to the Statistics Reporting Group at DCRI, who confirmed the output and provided data monitoring reports to the IDMC members. The Charter documents indicated that within J&J, access to the data directory with the unblinded data will be restricted to the independent programmer, but no other information on separation of the independent programmer from others in the company was provided.

After each meeting of the IDMC, the clinical IDMC chair (Joseph Alpert, MD) communicated the IDMC recommendation to the study leadership at DCRI. In each case, the recommendation was that the trial should continue as currently implemented. Dr. Alpert’s final communication to the study leadership, dated March 17, 2011, stressed the issue of risk to patients upon discontinuation of study drug and appropriate transition to warfarin or, in some cases, parenteral anticoagulation. The final communication of the DSMB, following the March 17, 2011 telecon of the IDMC, stressed the issue of risk to patients upon discontinuation of study drug and appropriate transition to warfarin or, in some cases, parenteral anticoagulation. This was identified as an issue that should be handled by the “steering committee.”

Clinical Endpoint Committee (CEC): The composition and functions of the CEC are described above in Section [5.3.1.10](#).

Liver Advisory Panel (LAP)/Hepatic Events Assessment Committee (HEAC): The composition and functions of the LAP and HEAC are described above in Section [5.3.1.9.3](#).

5.3.1.13 Protocol Amendments

There were two protocol amendments. Note that the discussion above describes the final protocol as amended twice. See Appendix 3 for information on the [Protocol Amendments](#)

Reviewer comment: None of these changes appear to impair the integrity of the study.

5.3.2 Supporting Study: J ROCKET

ROCKET had no study sites in Japan. J ROCKET refers to a study performed by the Bayer subsidiary in Japan entitled, “Evaluation of the efficacy and safety of Rivaroxaban (BAY 59-7939) for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation.” The study was performed entirely in Japan, using a protocol that was similar in many ways to the ROCKET protocol, but with some key differences, described below, that reduce the value of J ROCKET in shaping US labeling.

5.3.2.1 Design of J ROCKET and contrasts with ROCKET

Similarities and differences between the ROCKET protocol and the J ROCKET in terms of design features, enrollment data, and several key patient baseline characteristics affecting stroke risk, are described in the following table, including design features. I

Table 11. Features of ROCKET And J ROCKET

	ROCKET	J ROCKET
Basic design	Randomized, prospective, double-blind (double dummy) warfarin-controlled, event-driven, parallel trial	Same, except that the trial was not event-driven.
Primary objective	Demonstrate non-inferiority of rivaroxaban to warfarin in terms of prevention of primary endpoint events (stroke, SEE)	Demonstrate non-inferiority of rivaroxaban to warfarin in terms of bleeding events
Geographic scope	1187 enrolling sites on 6 continents, including 263 sites in the US	165 sites, all in Japan
Patients	Adults (≥18 yrs) with atrial fibrillation and a prior h/o stroke, TIA or SEE, or with 2 of 4 other stroke risk factors	Same, except all subjects were to be “Japanese” and ≥ 20 yrs old.
Planned sample size	About 14,000	About 1,200
Enrolled	14,264	1280
Study drug	Rivaroxaban 20 mg po once daily (15 mg for those with Cr CL 30-49) vs. warfarin tablets once daily	Rivaroxaban 15 mg po once daily (10 mg for those with Cr CL 30-49) vs. warfarin tablets once daily
Warfarin dosing	Based on INR target of 2.5 (range, 2.0-3.0) for all ages; blinded INR results obtained from point-of-care device	Same, except that patients age ≥ 70 years had INR target range of 1.6 – 2.6
Warfarin dosing algorithm used during double blind treatment?	No – Doses used to achieve target INR were at the investigator’s discretion	Same
Warfarin strengths	1, 2.5, and 5 mg	0.5, 1 and 2 mg

Clinical Review: Nhi Beasley, Preston Dunnmon and Martin Rose
Application type: Standard, NDA 22-439
Xarelto (rivaroxaban)

Planned duration of treatment	Until study termination for all surviving subjects, except those with primary endpoint events and a few others – estimated maximum treatment of 32 months for completers who enrolled at the start of the study	Same, except the estimated maximum treatment was 28-30 months
Follow up of completers	30 days after end-of-study (EOS) visit	Same
Follow-up of those with premature discontinuation	30 days after EOS visit, then phone follow-up q 12 weeks until overall end of study	Same
Anticoagulation required after study drug d/c'ed?	No – Institution of anticoagulation was at the investigator's discretion	Same
Primary study endpoint based on -	Efficacy	Safety
Primary efficacy endpoint analysis	Non-inferiority to warfarin for time to first stroke or SEE in per-protocol population on treatment	Same
Primary safety endpoint analysis	Non-inferiority to warfarin for time to first major or non-major clinically relevant bleeding event in safety population on treatment	Same
Non-inferiority margin for primary study endpoint analysis (per sponsor):	1.46 (for primary efficacy endpoint events)	2.0 (for primary safety endpoint events)
Important endpoints adjudicated?	Yes	Yes
PK/PD data collected?	Yes	Yes
First patient entered	Dec 2006	Jun 2007
Last patient entered	Jun 2009	Nov 2008
Last patient visit	Sept 2010	Jan 2010
Median Days F/U	Riva -- 572.2 Warf -- 579.9	Riva -- 498.9 Warf -- 481.1
Baseline CHADS2 ≥ 3	Riva – 87% Warf – 87%	Riva – 85% Warf – 82%
Prior Stroke/TIA	Riva – 55% Warf – 55%	Riva – 64% Warf – 63%
Prior Use of VKA	Riva – 90% Warf – 90%	Riva – 90% Warf – 90%

Given the important differences between the trials, including in J ROCKET the use of a substantially lower target INR in patients age ≥ 70 years (about 60% of the study population in J ROCKET), use of lower doses of rivaroxaban than in ROCKET in patients with or without moderate renal insufficiency, the lack of US sites and persons of any racial background other than Japanese, and differing primary objectives, the efficacy results of J ROCKET cannot be considered definitive for regulatory purposes in the US.

Differences between the studies are also relevant to the assessment of safety. These differences include:

- Global/multinational participation (ROCKET) versus single country enrollment (J-ROCKET)
- Lower dosing in J-ROCKET to achieve similar exposures in the Japanese population as are seen in non-Japanese patients
- A split INR target range based in age in J-ROCKET that is substantially lower than the US target INR range in patients over the age of 70 (77% of ROCKET patients were $>$ age 65, 44% were $>$ age 75)
- Thienopyridine monotherapy excluded in J-ROCKET, but allowed in ROCKET (though both allowed with ASA after PCI)
- Only two “as-treated” data scopes in J-ROCKET (LD+2 AND LD+30), but no “regardless of treatment duration” data scope, as no patient from J-ROCKET was followed past LD+30 for adjudicated safety or efficacy endpoints. Patients in ROCKET were followed until the trial ended
- A notably higher prior stroke incidence in J-ROCKET (Riva/Warfarin: 54.3%/54%) as compared to ROCKET (Riva/Warfarin 34% / 34%).

Due to differences in con-med rules, dose, data scopes, and INR target ranges, as well as the fact that the patient population of ROCKET was approximately 11 times that of J-ROCKET, bleeding analyses in the safety section will focus on the ROCKET dataset, though integrated outcomes for LD+2 and LD+30 for the primary efficacy and principal safety outcomes of the two trials will be presented.

5.3.2.2 Efficacy Results of J ROCKET

Efficacy results of J ROCKET are provided in this section. The reader desiring to understand the data supporting the efficacy of rivaroxaban in the US population may elect to proceed directly to Section 6, which contains the results of the single definitive

study, ROCKET, and then return here to review the abbreviated efficacy results of J ROCKET in Japanese subjects. Safety results of J ROCKET and ROCKET are discussed in Section 7.

5.3.2.2.1 **Demographics**

Demographic data for the Safety population (N=1278, with 639 in each treatment arm), which includes all randomized patients who received at least one dose of study drug, are provided here. Note only two patients (one in each treatment arm) in the ITT population (all randomized patients, N=1280) failed to receive study drug. The per-protocol population is only slightly smaller (N= 1274).

In general, the treatment arms in the Safety Population were quite well balanced at baseline. Each arm had a mean age of 71 years, with 39% and 38% with age ≥ 75 years in the rivaroxaban and warfarin arms, respectively. All patients were Asian. Women comprised 17% and 22% of the rivaroxaban and warfarin arms, respectively. Mean height was 162 cm and 161 cm in the rivaroxaban and warfarin arms, respectively. Mean weight was 64 kg in each arm. Mean creatinine clearance (CrCl) was 68 mL/min in each arm, and 22% in each arm had CrCl of 30 to 49 mL/min, the range specified to receive the lower rivaroxaban dose of 10 mg daily.

Table 12 is a display of relevant medical history at baseline in the treatment arms. There were no notable differences.

Table 12. J ROCKET – Baseline Medical History

Condition, risk factor, treatment, or substance use (N, %)	Rivaroxaban n = 639 N (%)	Warfarin N = 639 N (%)
Congestive Heart Failure	264 (41)	257 (40)
Hypertension	508 (80)	508 (80)
CHADS ₂ ≥ 3	542 (85)	524 (82)
Past or present smoker	439 (69)	402 (63)
Abstains from alcohol	252 (40)	271 (42)
Heavy alcohol consumption	5 (0.8)	2 (0.3)
Prior use of VKA	577 (90)	573 (90)
Prior use of aspirin	243 (38)	222 (34)
h/o Stroke, TIA, embolism	408 (64)	405 (63)
h/o Liver disease	124 (19)	105 (16)

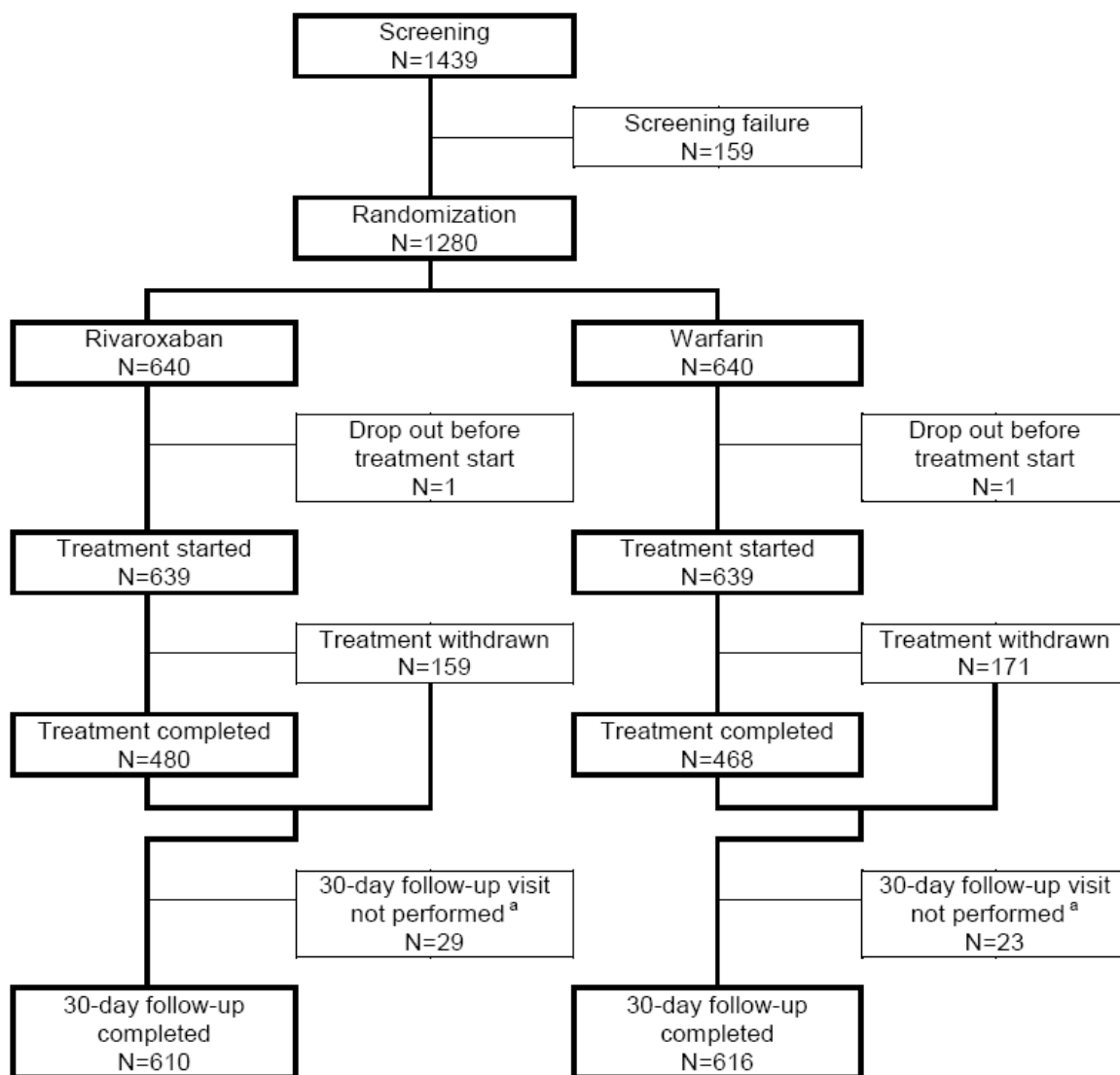
5.3.2.2.2 Subject Disposition

[Figure 17](#) provides an overview of disposition in J ROCKET.

Of the 639 patients who received study treatment in each arm, study drug was discontinued prematurely in 159 (25%) and 171 (27%) in the rivaroxaban and warfarin arms, respectively. However, only 29 (5%) and 23 (4%) of patients in the rivaroxaban and warfarin arms, respectively, failed to complete the study's 30 day post treatment follow-up visit.

Information regarding patients who discontinued treatment during double-blind therapy is provided in [Table 13](#), and details regarding the patients who failed to have the 30 day follow up visit are provided in [Table 14](#).

Figure 17. J ROCKET patient disposition



- a A total of 52 subjects (29 rivaroxaban; 23 warfarin) did not have 30-day follow up visit because of the following reasons: death (n=25), consent withdrawn (n=10), lost to follow-up (n=8), clinical endpoint reached (n=5), adverse event (n=2), investigator decision-not protocol driven (n=1), and protocol violation (n=1).

Table 13. J ROCKET - Reasons For Failure To Complete Double-Blind Treatment

	Rivaroxaban n = 639 N (%)	Warfarin N = 639 N (%)
Total who failed to complete	159 (25)	171 (27)
Adverse event	73 (11)	70 (11)
Clinical endpoint reached	18 (3)	28 (4)
Consent withdrawn ¹	26 (4)	35 (5)
Death	8 (1)	3 (0.5)
Lost to follow-up	4 (0.6)	1 (0.2)
Protocol violation	9 (1)	9 (1)
Investigator decision (unspecified)	4 (0.6)	13 (2)
Other reason (site closed, "protocol driven decision point" ² , non- compliant with study medication)	14 (2)	12 (2)

^{1*} Includes withdrawal of consent to treatment only and also consent to treatment and follow-up.

² Includes discontinuation for a protocol defined event requiring withdrawal or one allowing withdrawal at the discretion of the investigator.

Roughly ¾ of subjects completed treatment during the double blind period of the study. The median duration of double-blind treatment was 499 and 481 days in the rivaroxaban and warfarin arms, respectively. The leading causes of discontinuation (> 10% of subjects in either treatment arm) during this phase of the study was occurrence of an adverse event, followed by occurrence of a clinical endpoint and withdrawal of consent (either to study treatment or to both study treatment and follow-up). However, the data in [Table 14](#) indicate that withdrawal of consent to follow-up was quite uncommon.

Table 14. J ROCKET - Reasons For Failure To Complete 30 Day Follow-Up Visit

	Rivaroxaban n = 639 N (%)	Warfarin N = 639 N (%)
Total who failed to complete	29 (4.5)	23 (3.6)
Adverse event	1 (0.2)	1 (0.2)
Clinical endpoint reached	3 (0.5)	2 (0.3)
Consent to follow-up withdrawn	5 (0.8)	5 (0.8)
Death	13 (2)	12 (2)
Lost to follow-up	6 (0.9)	2 (0.3)
Protocol violation	1 (0.2)	0
Investigator decision (unspecified)	0	1 (0.2)

[Table 14](#) indicates that in general, follow-up was good in this study, with a low lost-to-follow-up rate (<1% in each arm). As for patients who were not lost to follow-up, less than 1% of subjects in each arm withdrew consent to follow-up. A few additional

patients were not followed up due to having clinical endpoints, adverse events, protocol violations, or for unspecified reasons (< 1% in total in each arm).

Table 15 is a display of the number of subjects in the various study populations used in the efficacy analyses described under the next heading.

Table 15. J ROCKET -- Analysis Populations

Population ¹	Rivaroxaban	Warfarin	Total
ITT	640	640	1280
Safety	639	639	1278
Per-Protocol	637	637	1274
Per-Protocol (restrictive definition)	637	637	1274

¹ ITT Population – All randomized patients

Safety Population – Randomized patients who took at least one dose of study drug

Per-Protocol Populations – Safety population minus patients with important protocol violations

5.3.2.2.3 Analysis of Efficacy Endpoints

The primary endpoint in J ROCKET was the time to an adjudicated first major or non-major clinically relevant bleeding event in the safety population, on treatment. These data and other safety information are discussed in Section 7.

Primary Efficacy Endpoint

The primary efficacy endpoint was the time to the first stroke or non-cerebral systemic embolic event in the per-protocol population, on treatment. “On treatment” includes an additional two days beyond the day of the last dose of double-blind study medication. Results for the analysis of the protocol-specified primary efficacy endpoint are displayed in the first data row in Table 16, which is highlighted. Other data rows show results for this endpoint in additional analysis populations and event windows.

Information on rates of the individual components of the primary endpoint and other secondary endpoints are discussed below.

Displays of the Kaplan-Meier curves for time to first primary efficacy event in the protocol-specified primary efficacy analysis (Per-Protocol population, on treatment) and in the ITT population, to 30 days after last treatment, are shown in Figure 18 and Figure 19, respectively. Note that “on treatment” includes the two days after the last dose of study drug.

Table 16. J ROCKET – Primary Efficacy Endpoint Results

Analysis Method	Rivaroxaban		Warfarin		Hazard Ratio (95% CI)
	Num/Den	/100PY	Num/Den	/100PY	
PP, on treatment	11/637	1.26	22/637	2.61	0.49 (0.24 – 1.00)
PP, on treatment (restrictive definition)	11/637	1.26	22/637	2.61	0.49 (0.24 – 1.00)
PP, last dose plus 30 days	22/637	2.40	25/637	2.81	0.85 (0.48 – 1.51)
Safety, on treatment	11/639	1.26	22/639	2.60	0.48 (0.23 – 1.00)
ITT, follow-up visit	22/640	2.38	26/640	2.91	0.82 (0.46 – 1.45)

Primary efficacy endpoint is the composite of adjudicated stroke and non-CNS systemic embolism.

"PP, on treatment" is the main efficacy analysis.

On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days.

On treatment (restrictive definition): if the subject has a temporary stop of the study medication before the efficacy endpoint event and re-starts the study medication after the efficacy endpoint event, the event is considered to occur while on treatment only if additionally its date is definitively within 2 calendar days from that temporary stop of the study medication.

Analysis of "Follow-up visit" is based on time to event from randomization, ie, only events that occurred between randomization and the maximum of End of Post-Treatment Observation 30-day follow-up visit.

100PY=100 patient-years; Numerator (Num)=number of subjects with events; Denominator (Den)=number of subjects in the subgroup

Event rate (/100 patient-years) was calculated as: $([\text{number of subjects with events}]/[\text{sum of each total observation days}]) \times 100 \times 365.25$

CI=confidence interval; ITT=intention-to-treat; PP=per protocol

Figure 18. J ROCKET -- Time To First Primary Endpoint Event

(Per-Protocol Population on Treatment)

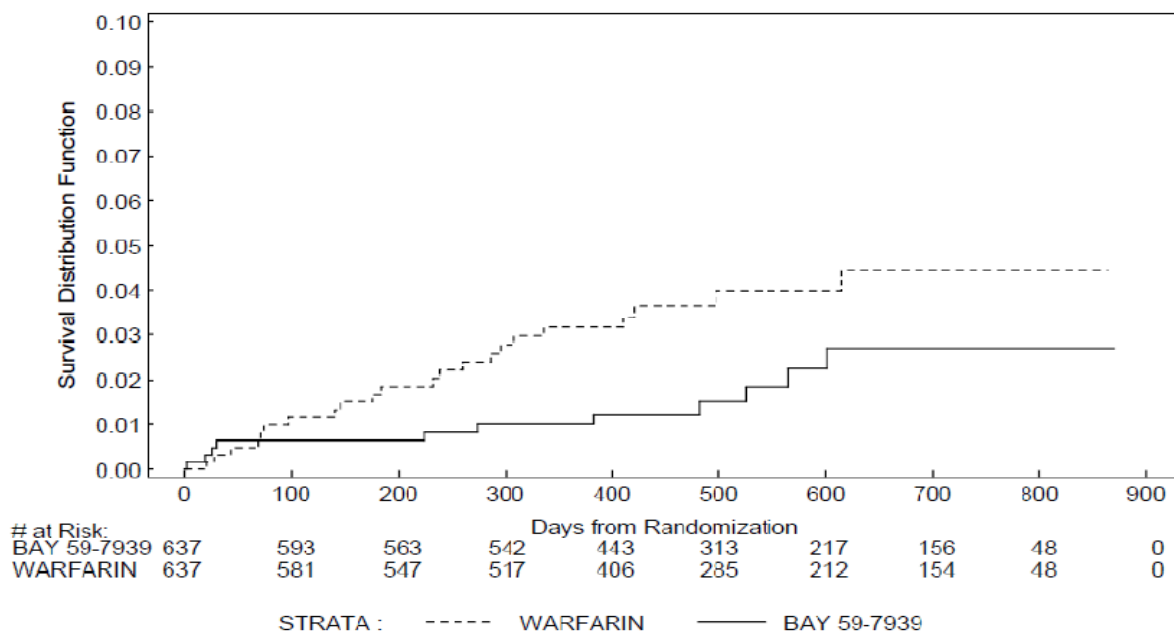
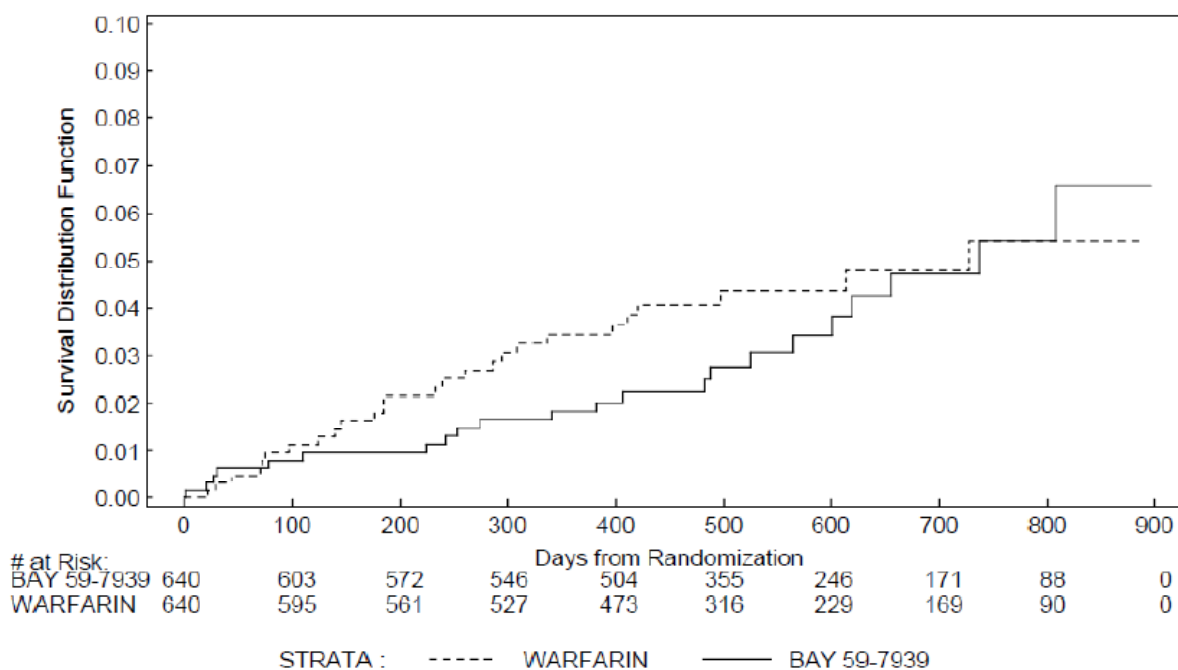


Figure 19. J ROCKET -- Time To First Primary Endpoint Event

(ITT Population to Follow-up Visit)



The data indicate that rivaroxaban was associated with numerically better outcomes in each analysis population, with results marginally attaining marginal statistical significance in the PP, PP restrictive definition, and Safety populations, all “on-treatment” (i.e., counting events occurring from the first day of double blind study drug treatment to the 2 days after the last day of treatment, inclusive). The best results were achieved in the Safety population with 11 vs. 22 events in the rivaroxaban and warfarin arms, respectively, corresponding to 1.26 vs. 2.61 events per 100 patient/years (PY) and a HR of 0.48 (95% CI. 0.23 – 1.00). Results in the PP population were only trivially different.

While the analyses that included events occurring “on treatment” are quite favorable for rivaroxaban, those that include events occurring as late as 30 days after study drug discontinuation or up to the follow-up visit are much less favorable. In the Per Protocol analysis that included events up to 30 days after the last dose of dose drug, there were 22 vs. 25 events in the rivaroxaban and warfarin arms, respectively, corresponding to 2.40 vs. 2.81 events per 100 PY and a HR of 0.85 (95% CI. 0.48 – 1.51). The ITT analysis that included events to the follow-up visit was quite similar (HR = 0.82, 95% CI 0.46 – 1.45).

Subtraction of the event counts in the two Per Protocol analyses in [Table 16](#) (the on treatment (+ 2 days) analysis and the analysis including events up to 30 days after the last dose of study drug) indicates that in the 28 days between the ends of the two counting periods, there were 11 additional events in the rivaroxaban arm and 3 additional events in the warfarin arm, a difference that came close to equalizing the event rates in the arms. For further discussion of this observation, along with a similar observation in the much larger ROCKET trial, see Section [6.1.10.3](#)

Secondary Endpoints

Rates for the occurrence of secondary endpoints in the Safety Population, on treatment (last dose of study medication + 2 days) are displayed in [Table 17](#). These endpoints include the individual components of the primary endpoint (stroke and systemic embolism), as well as sub-categories of stroke, MI, vascular death, and all-cause death. There was also a composite Major Secondary Endpoint 1 (adjudicated stroke, non-CNS systemic embolism, and vascular death) and a composite Major Secondary Endpoint 2 (adjudicated stroke, non-CNS systemic embolism, MI, and vascular death). The data indicate the dominant component of the primary endpoint was stroke and in particular, ischemic stroke (as expected), and that both occurred more frequently in the warfarin arm, with a confidence interval of the HR for each just barely less than 1.0. The two Major Secondary Endpoints both numerically favored rivaroxaban, due to the dominance of the stroke data. Other secondary endpoints occurred at low rates and favored the warfarin arm numerically, except for stroke with serious residual disability, which numerically favored rivaroxaban.

Table 17. J ROCKET – Rates Of Secondary Efficacy Endpoints

(Safety Population on Treatment)

	Rivaroxaban (N=639) n (/100PY)	Warfarin (N=639) n (/100PY)	Hazard Ratio (95% CI)
Major secondary efficacy endpoint 1	16 (1.83)	24 (2.84)	0.65 (0.34 – 1.22)
Major secondary efficacy endpoint 2	19 (2.17)	25 (2.96)	0.74 (0.41 – 1.34)
Other secondary efficacy endpoints			
Stroke	10 (1.14)	21 (2.48)	0.46 (0.22 – 0.98)
Primary hemorrhagic stroke	3 (0.34)	4 (0.47)	0.73 (0.16 – 3.25)
Primary ischemic stroke	7 (0.80)	17 (2.01)	0.40 (0.17 – 0.96)
Non-CNS systemic embolism	1 (0.11)	1 (0.12)	0.99 (0.06 – 15.83)
Myocardial infarction	3 (0.34)	1 (0.12)	2.92 (0.30 – 28.12)
Vascular death	6 (0.68)	2 (0.24)	2.96 (0.60 – 14.69)
Stroke with serious residual disability	5 (0.57)	10 (1.18)	0.48 (0.16 – 1.39)
All-cause death	7 (0.80)	5 (0.59)	1.37 (0.43 – 4.31)

100PY=100 patient-years

Event rate (/100 patient-years) was calculated as: ([number of subjects with events]/[sum of each total observation days]) x 100 x 365.25

Major secondary efficacy endpoint 1 is the composite of adjudicated stroke, non-CNS systemic embolism, and vascular death

Major secondary efficacy endpoint 2 is the composite of adjudicated stroke, non-CNS systemic embolism, myocardial infarction, and vascular death

CI=confidence interval; CNS=central nervous system; PP=per protocol

Subgroups

Interactions between treatment and subgroup for the primary efficacy endpoint in the Per Protocol Population (on treatment) were examined in a wide of subgroups based on various parameters, including demographic features, CHADS₂ score, medical history, and prior medication use (warfarin or aspirin). Only two such parameters yielded interaction p-values values less than 0.2: creatinine clearance and prior aspirin usage.

Data for event rates in subgroups based on creatinine clearance and prior aspirin use are displayed in [Table 18](#).

Table 18. J ROCKET -- Subgroup Analyses For The Primary Efficacy Endpoint

(Groups with Interaction p-values < 0.2, Per Protocol Population, On Treatment)

Variable Subgroup	Rivaroxaban (N=637) N/n (/100PY)	Warfarin (N=637) N/n (/100PY)	Hazard Ratio (95% CI)	Interaction p- value
Creatinine clearance (mL/min)				0.0884
<50	5/141 (2.77)	6/143 (3.34)	0.82 (0.25 – 2.69)	
50 to 80	2/338 (0.43)	13/335 (2.96)	0.15 (0.03 – 0.64)	
>80	4/158 (1.78)	3/159 (1.34)	1.32 (0.30 – 5.91)	
Prior aspirin use				0.1912
No	5/395 (0.92)	16/416 (2.89)	0.32 (0.12 – 0.87)	
Yes	6/242 (1.83)	6/221 (2.06)	0.88 (0.28 – 2.73)	

For creatine clearance, the subgroup with CrCl 50 to 80 mL was the largest and had the most favorable HR for rivaroxaban (0.15, 95% CI 0.03 – 0.64). In the subgroup with the best CrCl, the results numerically favored warfarin. For aspirin, the lowest HR was in patients with no prior aspirin use (0.32, 95% CI 0.12 – 0.87), but the HR was also numerically favorable in patients with prior aspirin use (0.88, 95% CI 0.28 – 2.73). These interaction results are probably not meaningful unless replicated in other studies.

Control of INR

The ROCKET study report included information on overall study performance in warfarin arm subjects with respect to time in therapeutic range (TTR) for INR. In this study, consistent with Japanese anticoagulation treatment guidelines, the target INR range for adults < 70 years old with atrial fibrillation requiring warfarin treatment was 2.0 to 3.0, as in the US. While the US guidelines recommend the same target range for all adult age groups, the Japanese guidelines recommend an INR target range of 1.6 to 2.6 in patients ≥ 70 years old.

Results for study-wide percentage of INR values in the warfarin group are displayed in Table 19.

Table 19. J ROCKET – Percentage Of Warfarin Arm INR Values In The Target Range

(Overall and by age group during treatment, Per Protocol population)

All warfarin subjects (639 subjects)	Days of Exposure	INR Below target (%)	INR Within target (%)	INR Above target (%)
Total treatment duration ^a	327352	28.0	65.0	6.9
<3 months	55747	38.9	54.6	5.8
3 to <6 months	52612	30.6	63.0	6.4
6 to <9 months	49893	28.2	65.9	5.9
9 to <12 months	47155	24.9	67.4	7.8
12 to <15 months	41296	25.0	67.1	7.9
15 to <18 months	28989	22.9	70.5	6.5
18 to <21 months	21814	22.6	71.3	6.1
21 to <24 months	16625	20.5	70.6	8.8
24 to <27 months	10937	20.3	70.5	9.2
27 to <30 months	2284	19.6	65.7	14.7
≥70 years (389 subjects) (Target INR: 1.6 to 2.6)	Days of Exposure	INR <1.6 (%)	INR 1.6 to 2.6 (%)	INR >2.6 (%)
Total treatment duration ^a	195371	17.3	74.0	8.8
<3 months	33869	28.0	63.9	7.4
3 to <6 months	31483	19.2	72.4	8.4
6 to <9 months	29743	16.6	75.9	7.4
9 to <12 months	27814	14.7	75.2	10.1
12 to <15 months	24351	13.2	76.4	10.4
15 to <18 months	17089	12.4	79.6	8.0
18 to <21 months	13105	12.2	80.6	7.2
21 to <24 months	10200	11.4	78.4	10.2
24 to <27 months	6488	13.9	75.5	10.7
27 to <30 months	1229	12.4	76.5	11.1
<70 years (250 subjects) (Target INR: 2 to 3)	Days of Exposure	INR <2 (%)	INR 2 to 3 (%)	INR >3 (%)
Total treatment duration ^a	131981	43.8	51.8	4.2
<3 months	21878	55.8	40.2	3.2
3 to <6 months	21129	47.7	48.9	3.4
6 to <9 months	20150	45.2	51.1	3.7
9 to <12 months	19341	39.6	56.1	4.4
12 to <15 months	16945	41.8	53.8	4.3
15 to <18 months	11900	38.1	57.6	4.4
18 to <21 months	8709	38.3	57.2	4.5
21 to <24 months	6425	35.1	58.3	6.6
24 to <27 months	4449	29.6	63.3	7.1
27 to <30 months	1055	28.0	63.2	18.9

Note: INR values were imputed based on linear interpolation of the two consecutive data points where INR values are measured.

a Duration of treatment is from first dose to last dose

PT-INR=prothrombin time-international normalized ratio (PT-INR values measured by the point-of-care device were used for the analysis.)

Source: Table 14.1.2A, Table 14.1.6, Table 14.1.18-1 (Note: All warfarin subjects, additional analysis)

Overall TTR was fair, at 66%. The expected time trend of improving TTR the first year of the study was observed. The best results were observed in the patients treated for 18 to 21 months, who had a TTR of 71%. Below-target values were generally much more frequent than above-target values in the various time cuts.

The best results were observed in the subgroup of patients age ≥ 70 , who had an INR target of 1.6 to 2.6, with 74% of values in the target range. The subgroup age < 70 , with the same target range as in the US, was in-range for 52% of INR values. It is interesting that when this subgroup was assessed using the same target range as subjects ≥ 70 , the TTR performance overall quite similar to the older age group, at 73%, but the percentage of above range values was higher in the younger patients.

The hazard ratios (rivaroxaban vs. warfarin) for the primary efficacy endpoint (Per Protocol, on treatment) were similar in age groups of <70 (N=509), 70 to 75 (N=353), and >75 years (N=412), being 0.47, 0.51, and 0.49, respectively. This is consistent with the data indicating that there were not marked differences in TTR (by US standards) in patients age <70 vs. those ≥ 70 years.

The sponsor did not perform an analysis of the event rates in quartiles based on site-specific TTR. However, due to the small number of primary endpoint event in this trial on treatment (11 vs. 22 in the rivaroxaban and warfarin arms, respectively) such an analysis may not have been informative.

Reviewer comment: The results of J ROCKET cannot be considered as definitive support for the indication proposed in the sponsor's NDA for rivaroxaban for several important reasons, including: the patient population in J ROCKET does not match the US population; the dosing regimen of rivaroxaban used in J ROCKET is different than the one proposed for use in the US; and the dosing of the warfarin control arm is different (and probably results in higher event rates) than the warfarin dosing paradigm recommended in the US. However, the study results are not inconsistent with ROCKET.

6 Review of Efficacy

Efficacy Summary

In support of rivaroxaban's proposed indication for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the sponsor conducted the global ROCKET trial, a large ($>14,000$ subjects) randomized, double blind (double dummy), event-driven non-inferiority trial in adults with non-valvular AFib at high risk for thrombotic events. ROCKET compared rivaroxaban 20 mg once daily (15 mg in patients with CrCl 30-49 mL/min) to warfarin, which was to be titrated to a target range of 2.0 to 3.0. The primary endpoint was time to a composite of stroke and systemic embolism. The sponsor's designated primary endpoint analysis was for non-inferiority in the per-protocol population "on treatment" (including events to the last dose + 2 days). This analysis yielded event rates of 1.71 and 2.16 events per 100 patient-years in the rivaroxaban and warfarin arms, respectively, and a hazard ratio of 0.79 (95% CI 0.66,

0.96, superiority $p = 0.018$). Thus the test for non-inferiority was satisfied using FDA's preferred margin of 1.38. The next test in the pre-specified event hierarchy was for superiority in the safety population on treatment; the results were trivially different from the previous analysis, yielding a hazard ratio of 0.79 (95% CI 0.65, 0.95, $p = 0.015$) and a finding of superiority, without regard to such interpretative issues as the adequacy of INR control in the comparator arm.

However, superiority was not supported by any analysis that included events occurring more than 2 days after the last dose of study drug, which was the end of the "on treatment" period. These included per-protocol and safety populations with event windows extending to 7, 14, or 30 days after the last dose of study drug, and several ITT analyses. Hazard ratios ranged from 0.88 (safety population and per-protocol population, last dose + 7 days) to 0.91 (ITT population, regardless of treatment, i.e., to the overall data cut-off date). All 95% confidence intervals for these analyses crossed 1.0. Thus none of these analyses supported superiority. However, none had an upper limit of the 95% CI of HR > 1.08; thus all analyses supported non-inferiority, again without regard to other issues such as the adequacy of INR control in the warfarin arm. Moreover, the poor warfarin control, as evidenced by the overall TTR in ROCKET of 55%, biased the study in favor of rivaroxaban. The study results do not convincingly demonstrate the non-inferiority, much less the superiority, of rivaroxaban to warfarin when the latter is used skillfully (see discussion on page 97 and Section 6.1.10.2

The overall efficacy findings appeared to be preserved in nearly all major subgroups of patients, including each gender, the elderly, subjects previously treated with a VKA, subjects in each of the 5 specified geographic regions, and those enrolled from US sites. However, efficacy was substantially reduced in the large subset of patients with a prior history of stroke/TIA/systemic embolism, which comprised about 55% of all patients globally. The hazard ratios for the primary endpoint in patients with and without a baseline history of stroke/TIA/systemic embolism were 0.92 and 0.59, respectively ($p = 0.035$ for the treatment by subgroup interaction).

The primary endpoint findings were also supported by numerical imbalances (which in a few cases reached statistical significance) for secondary efficacy endpoints that each favored rivaroxaban over warfarin in on-treatment analyses in the safety population. These endpoints included the rates of strokes of all kinds combined, hemorrhagic strokes, disabling strokes, fatal strokes, systemic emboli, vascular deaths, non-vascular deaths, and several composites of vascular endpoints. The results for myocardial infarction also favored rivaroxaban, unlike in the RE-LY trial of dabigatran.

However, the difference favoring rivaroxaban in the incidence of ischemic of ischemic strokes on treatment (i.e., up to the last dose of study drug + 2 days) was quite modest and not statistically significant. In the rivaroxaban and warfarin arms, respectively, there were 149 vs. 161 patients with ischemic stroke, (1.34 vs. 1.42 events per 100 patient-years). The difference between the treatment arms in the number and rate of hemorrhagic stroke was considerably larger (29 vs. 50 patients, 0.26 vs. 0.44 events

per 100 patient-years, $p < 0.05$)). Thus, the advantage of rivaroxaban over warfarin in terms of strokes on treatment was driven largely by the results for hemorrhagic stroke.

Notably, the modest imbalance noted above in favor of rivaroxaban in ischemic strokes on treatment (149 vs. 161) was reversed in the last dose + 7 day analysis, which followed patients for an additional 5 days: 173 vs. 171 patients with ischemic stroke, 1.54 vs. 1.50 events per 100 patient-years. This suggests that with better control of the warfarin dose, the observed difference between in the rate of strokes favoring rivaroxaban may have been reduced or eliminated.

The following issues are important and relevant to the interpretation of the efficacy results of the trial:

Adequacy of anticoagulation in the warfarin treatment arm:

ROCKET was a warfarin controlled study. Thus, to interpret the efficacy findings, one must understand the expected benefit of warfarin as it was given in this trial. Warfarin has been demonstrated to be highly effective in preventing strokes in AFib patients in 6 placebo-controlled trials conducted before the turn of the century, including one with enrollment limited to patients with a prior history of stroke or TIA. However, the efficacy of warfarin in preventing strokes in AFib patients is dependent on the quality of control of INR, which should be targeted to the range of 2.0 to 3.0 for patients with non-valvular atrial fibrillation.

Time in therapeutic range (TTR) is a commonly used measure of the adequacy of INR control in studies with a warfarin arm. It is calculated based on observed INR values; INR values are imputed for days in between days with actual values. In ROCKET, the mean overall INR in the warfarin arm was 55%; this represents the mean of the individual TTRs in the warfarin arm patients (i.e., the percentage of days when actual or imputed INR values were in the target range of 2.0 – 3.0). This contrasts with TTR in recent warfarin-controlled trials of other agents that was uniformly above 60% and in one case above 70%.

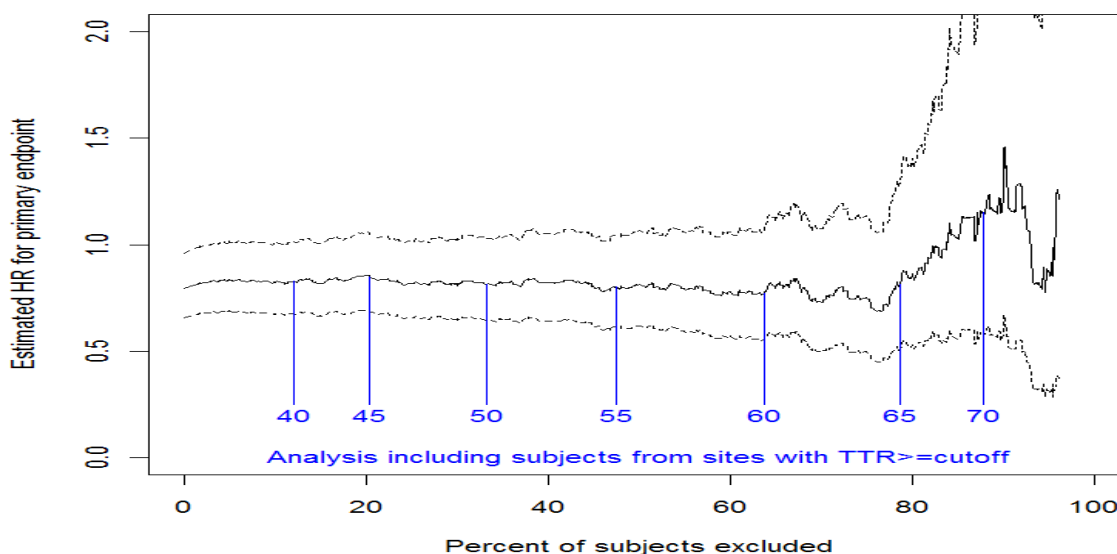
There are other metrics of the adequacy of control of warfarin dosing, including the warfarin arm event rate in clinical studies. However, the ROCKET study population was substantially different from other modern AFib trials in with a warfarin arm, making cross study comparisons problematic. Thus, TTR will be stressed here as a measure of adequacy of the control of warfarin dose.

TTR in ROCKET varied widely over regions and countries. The mean TTR in the US was 63%, with a median center TTR of 65%. Globally, national TTR ranged from 36% in India to 75% in Sweden. In general, TTR was higher in Western Europe (especially in the UK and Scandinavia), North America (i.e., Canada and the US), and some areas in the Pacific basin (Australia, New Zealand, Singapore and Hong Kong), and tended to be low in Eastern Europe, South America, and with a few notable exceptions, the Asia-

Pacific region. Analyses of the HR for the primary endpoint over the range of center TTR revealed that the HR tended to increase sharply as center TTR increased over about 65%, and crossed 1.0 at about 67%. (see Figure 20). There were relatively few patients in ROCKET with this high level of control, and the confidence interval of the HR is quite wide at these levels of TTR. This is in contrast to RE-LY, where the median center TTR was 67%. Thus the ROCKET study data indicate that a substantial question remains about the efficacy of rivaroxaban compared to warfarin when warfarin is used skillfully.

Figure 20: Hazard Ratio For The Primary Efficacy Endpoint Analysis As A Function Of Center TTR

Per Protocol Population, On Treatment ¹



¹ Plot of $y = f(x)$ where $f(x)$ = HR for all centers with TTR in the interval of x to 100%. The dark, unbroken central line represents the HR; dotted lines below the central line the 5th and 95th CI of the HR.

FDA's policy regarding comparative risk-benefit indicates states it is essential for the approval of a new therapy for condition such as stroke prevention to be as effective as previously approved therapy (see Section 6.1.10.2.1). In the opinion of this reviewer, the lack of convincing evidence that rivaroxaban is as effective as warfarin when it is used skillfully means that it should not be approved.

However, if the medical community is currently in great need of an additional oral anticoagulant for use in AFib patients, it might not be unreasonable to approve rivaroxaban as second or third line treatment. It might be useful in patients who are poorly controlled on warfarin or refuse to take it. However, given that dabigatran has been shown to be superior to warfarin when it used reasonably well, and robustly non-

inferior to warfarin when it is used extremely well, it seems advisable to make rivaroxaban a third-line agent, behind both warfarin and dabigatran.

The issue of the quality of control of INR in ROCKET, including information about the FDA policy mentioned above, is discussed further in Section [6.1.10.2](#)

Efficacy events occurring after discontinuation of study drug:

Approximately 2/3 of patients in ROCKET in each arm continued taking study drug until the end of this event-driven study. In these patients, blinded study medication was stopped, and the investigator was to transition patients to alternative anticoagulant therapy, usually a vitamin K antagonist such as warfarin. Unlike other recent trials of novel anticoagulants in AFib patients (the Sportif V trial of ximelagatran, the RE-LY trial of dabigatran, and the ARISTOTLE trial of apixaban) no provisions were made for a short period of dual therapy with study drug and open-label warfarin for patients in the rivaroxaban arm to continue anticoagulation during the lag period of INR control at the start of warfarin therapy. In contrast to warfarin which has long half life, rivaroxaban has a terminal elimination half-life of approximately 5-9 hours in healthy subjects aged 20 - 45 years, and somewhat longer half-life in the elderly.

Possibly as a result of this study design feature, in patients who completed the study, there was a statistically significant difference in the rate of strokes in the rivaroxaban arm compared to warfarin from the end of the “on treatment” period (the last dose + 2 days) up to day 30 after the last dose of study drug (which was the last study visit for completers). The event rate for primary endpoint events, all of which were strokes in this period, was 6.42 vs. 1.73 events per 100 patient-years in the rivaroxaban and warfarin arms, respectively (HR = 3.72 (95% CI, 1.51, 9.16, p= 0.004). While the event rate in the rivaroxaban arm is more 3X the event rate on treatment in the same arm, the event rate in the warfarin arm is less than on treatment. There was a directionally similar but even more dramatic finding in the much smaller J-ROCKET trial, conducted only in Japan. Study data from ROCKET indicate that while > 90% of completing patients received a VKA in this period, INR control may not have been good, suggesting a possible cause for the strokes in these patients. However, the sponsor has not performed the studies necessary to exclude the existence of a hypercoagulable state in these patients.

There was also a modest excess of primary endpoint events in rivaroxaban patients who discontinued study drug early in ROCKET from day 3 to day 30 after the last dose of study drug. However, the hazard ratio vs. warfarin was not nearly as large as in completers (1.10, 95% CI, 0.71, 1.71). In addition, deaths in this period favored rivaroxaban.

To ameliorate the risk of events after discontinuation of rivaroxaban, the sponsor has submitted proposed labeling with instructions for the transition from rivaroxaban to

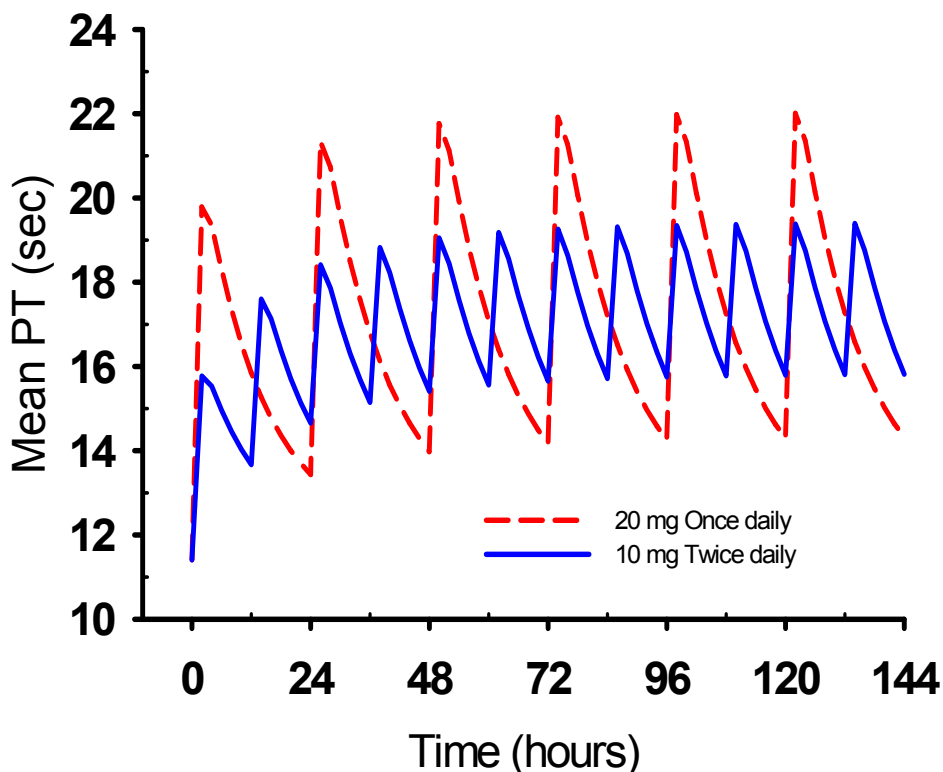
warfarin therapy. These instructions call for a period of concomitant treatment with both drugs under INR control for at least 2 days (with INR measured at the end of the rivaroxaban dosing interval). The instructions are based on PK/PD modeling. However, the proposed transition regimen has not been demonstrated in a clinical study for bleeding risk or thrombotic event risk. Because a substantial safety risk of transitioning completing patients from rivaroxaban to warfarin has been observed in a clinical trial, the sponsor must demonstrate the safety of the transition regimen in terms of bleeding risk and thrombotic event risk in a clinical trial in AFib patients before this drug can be approved in the opinion of this reviewer.

More information regarding the rate of events after discontinuation of study drug in ROCKET and the sponsor's proposed instructions for the transition from rivaroxaban to warfarin are found in Section [6.1.10.3](#)

Choice of dosing regimen:

The sponsor evaluated one dosing regimen in its pivotal trial, 20 mg of rivaroxaban once daily (15 mg once daily for patients with CrCl 30-59 mL min). The sponsor established that this regimen is non-inferior to warfarin as it was used in ROCKET. However, the sponsor's rationale for evaluating only once daily dosing in Phase 3 is not strong. Most importantly, there is clinical information from Phase 2 trials in the sponsor's ACS program and the VTE program and from clinical pharmacology studies suggesting that twice daily dosing, which would produce lower peak blood levels and higher trough blood levels of rivaroxaban, might have been associated with greater efficacy and/or a better safety profile. There is also information suggesting that a lower total daily dose might have been as effective as 20 mg. Modeling results for the kinetics of once vs. twice daily dosing are depicted in Figure 21. The data relating to the issue of dose are complex and are explored in greater depth in Section [6.1.8](#). This reviewer recommends that a study must be performed to evaluate one or more additional dosing regimens, including at least one BID regimen before this product is approved (Section [1.3](#)).

Figure 21. Modeling of Once vs. Twice Daily Dosing with Rivaroxaban



6.1.1 Indication

The Sponsor's proposed indication is prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

6.1.2 Methods

The sponsor provided an ISE, but did not pool the results of the two ROCKET studies. The designs of the two studies have already been described. Because the results of J ROCKET are not useful to shape efficacy labeling in the US, only the results of ROCKET are discussed here. The efficacy results of J ROCKET are found at the end of the preceding section on page 95.

Analysis populations for the ROCKET efficacy analyses are shown in Table 20. Note that nearly all analyses of efficacy provided by the sponsor exclude site 042012 in the Czech Republic. This was done pursuant to a unanimous vote of the study Executive Committee, based on evidence that source documents had been modified so subjects

appeared to meet study inclusion/exclusion criteria. Data from the site were deemed not to be reliable. The site enrolled 93 patients; 50 and 43 patients were randomized to rivaroxaban warfarin, respectively. Two patients in each arm had a CEC-adjudicated primary endpoint, indicating that exclusion of this site would not bias the efficacy results. Safety data from this site were included in the various safety analyses.

Table 20. ROCKET – Efficacy Analysis Populations

Population ^{1, 2}	Rivaroxaban	Warfarin	Total
ITT	7081	7090	14,171
Safety	7061	7082	14,143
Per-Protocol	6958	7004	13,962

1 Excluding site 042012 (see text)

2 ITT Population – All randomized patients

Safety Population – Randomized patients who took at least one dose of study drug

Per-Protocol Populations – Safety population minus patients with important protocol violations

6.1.3 Demographics

Baseline data for demographic and disease-related parameters are displayed in [Table 21](#) for the ITT population (all randomized patients, N=14,264).

As expected in a study of this size, the treatment arms were well balanced for all important demographic and prevalent disease specific features. About 60.3% of subjects in each arm were male. The mean age in both arms was 71.2 years. About 81% in each arm had persistent AFib (as defined by the sponsor). About 62% had a history of prior VKA use at baseline. About 21% in each arm had creatinine clearance <50 mL/min, meaning they qualified for the lower dose of rivaroxaban (15 mg daily), if randomized to that arm.

Notably, about 55% of subjects in each arm had a prior history of stroke, TIA, or non-CNS systemic embolism, while 62% in each arm had heart failure at baseline. The distribution of NYHA HF class was similar in the two arms (data not shown). About 17 – 18% in the rivaroxaban and warfarin arms, respectively, had a prior history of MI. The mean CHADS₂ score in each arm was 3.5, and about 87% in each arm had a CHADS₂ score ≥ 3.

Table 21. ROCKET – Baseline Demographics And Disease-Related Parameters

(ITT population)

Characteristic	Rivaroxaban 20 mg N=7131	Warfarin N=7133	Total N=14,264
Male	4301 (60.31)	4303 (60.3)	8604 (60.3)
Age			
Mean (SD)	71.2 (9.5)	71.2 (9.4)	71.2 (9.4)
18 to <65	1651 (23.2)	1643 (23.0)	3294 (23.1)
65≤ to <75	2360 (33.1)	2381 (33.4)	4741 (33.2)
≥75	3120 (43.8)	3109 (43.6)	6229 (43.7)
Race, N (%)			
White	5922 (83.0)	5957 (83.5)	11879 (83.3)
Black	94 (1.3)	86 (1.2)	180 (1.3)
Asian	897 (12.6)	889 (12.5)	1786 (12.5)
Other	218 (3.1)	201 (2.8)	419 (2.9)
Ethnicity, N (%)			
Hispanic or Latino	1166 (16.4)	1168 (16.4)	2334 (16.4)
Body metrics, Mean (SD)			
Weight (kg)	82.1 (19.1)	81.6 (19.0)	81.9 (19.0)
Height (cm)	167.7 (10.0)	167.7 (10.2)	167.7 (10.1)
BMI	29.1 (5.7)	29.0 (7.2)	29.0 (6.5)
AFib type, N (%)			
Persistent (lasting > 7 days at any time)	5786 (81.1)	5762 (80.8)	11548 (81.0)
Paroxysmal (lasting ≤ 7 days at any time)	1245 (17.5)	1269 (17.8)	2514 (17.6)
Newly diagnosed	100 (1.40)	102 (1.4)	202 (1.4)
Prior VKA use, N (%)			
Yes	4443 (62.3)	4461 (62.5)	8904 (62.4)
Prior chronic aspirin use, N (%)			
Yes	2586 (36.3)	2619 (36.7)	5205 (36.5)
Creatine clearance, mean (SD) and stratum			
Mean (SD)	72.9 (29.3)	72.5 (29.3)	72.8 (29.3)

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<30, (N (%))	4 (0.06)	4 (0.06)	8 (0.06)
30 to <50	1503 (21.1)	1475 (20.7)	2978 (20.9)
50 to ≤ 80	3321 (46.6)	3414 (47.9)	6735 (47.3)
>80	2295 (32.2)	2231 (31.3)	4526 (31.7)
Prior Stroke/TIA/Non-CNS Systemic Embolism, N (%)			
Yes	3916 (54.9)	3895 (54.6)	7811 (54.7)
Prior MI, N (%)			
Yes	1182 (16.6)	1286 (18.0)	2468 (17.3)
Baseline hypertension, N (%)			
Yes	6436 (90.3)	6474 (90.8)	12910 (90.5)
Baseline diabetes mellitus, N (%)			
Yes	2878 (40.4)	2817 (39.5)	5695 (39.9)
Baseline heart failure, N (%)			
Yes	4467 (62.6)	4441 (62.3)	8908 (62.5)
Baseline CHADS ₂ score			
Mean (SD)	3.5 (0.94)	3.5 (0.95)	3.5 (0.94)
Median	3.0	3.0	3.0
Score -- N, (%)			
0	0	0	0
1	1 (0.01)	2 (0.02)	3 (0.02)
2	925 (13.0)	934 (13.1)	1859 (13.0)
3	3058 (42.9)	3158 (44.3)	6216 (43.6)
4	2092 (29.3)	1999 (28.0)	4091 (28.7)
5	932 (13.1)	881 (12.4)	1813 (12.7)
6	123 (1.7)	159 (2.2)	282 (2.0)

Reviewer comment: These data suggest that virtually all subjects were candidates for anticoagulant therapy and would have been at moderate to high risk of stroke or other serious events if they discontinued study therapy without some kind of anti-coagulant coverage.^{7, 8} Patients with a prior history of stroke or TIA would have been at particularly high risk. The rate of stroke on placebo in the EAFT secondary prevention trial was 12%/year and the primary event rate (stroke + MI + systemic embolism + vascular death) was 17% year.⁷ In EAFT, all subjects had a history of ischemic stroke or TIA at entry.

An analysis of medications received prior to baseline reveals no imbalances between the groups in the use of any of the classes of medications expected to be used by the enrolled patients, many of whom had hypertension and heart failure. The most commonly used medication classes (> 30% of subjects) were beta blockers, diuretics, ACE inhibitors, statins, digitalis glycosides, and aspirin (Table 22).

Table 22. ROCKET -- Medications Received Prior To Baseline

(Safety population)

	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Relevant Medications			
Total no. subjects with relevant medications received prior to Baseline	6981 (98.17)	7015 (98.46)	13996 (98.31)
Beta Blockers	4631 (65.12)	4686 (65.77)	9317 (65.45)
Diuretics	4289 (60.32)	4248 (59.62)	8537 (59.97)
Angiotensin Converting Enzyme Inhibitors	3915 (55.06)	3845 (53.96)	7760 (54.51)
Statins	3055 (42.96)	3077 (43.19)	6132 (43.07)
Digitalis Glycosides	2758 (38.78)	2768 (38.85)	5526 (38.82)
Aspirin	2726 (38.33)	2759 (38.72)	5485 (38.53)
Calcium Channel Blockers	2045 (28.76)	1973 (27.69)	4018 (28.22)
Oral Antidiabetics	1696 (23.85)	1714 (24.06)	3410 (23.95)
Angiotensin Receptor Blockers	1609 (22.63)	1626 (22.82)	3235 (22.72)
Organic Nitrates	950 (13.36)	1035 (14.53)	1985 (13.94)
Proton Pump Inhibitors	918 (12.91)	889 (12.48)	1807 (12.69)
Antiarrhythmics, Class III	622 (8.75)	616 (8.65)	1238 (8.70)
Anticoagulants, Excluding VKA	170 (2.39)	176 (2.47)	346 (2.43)

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: Prior to baseline refers to any relevant medication received prior to the first study medication administration.

Note: Sorted in descending order of incidence based on Total.

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6.1.4 Subject Disposition and Compliance with Study Drug

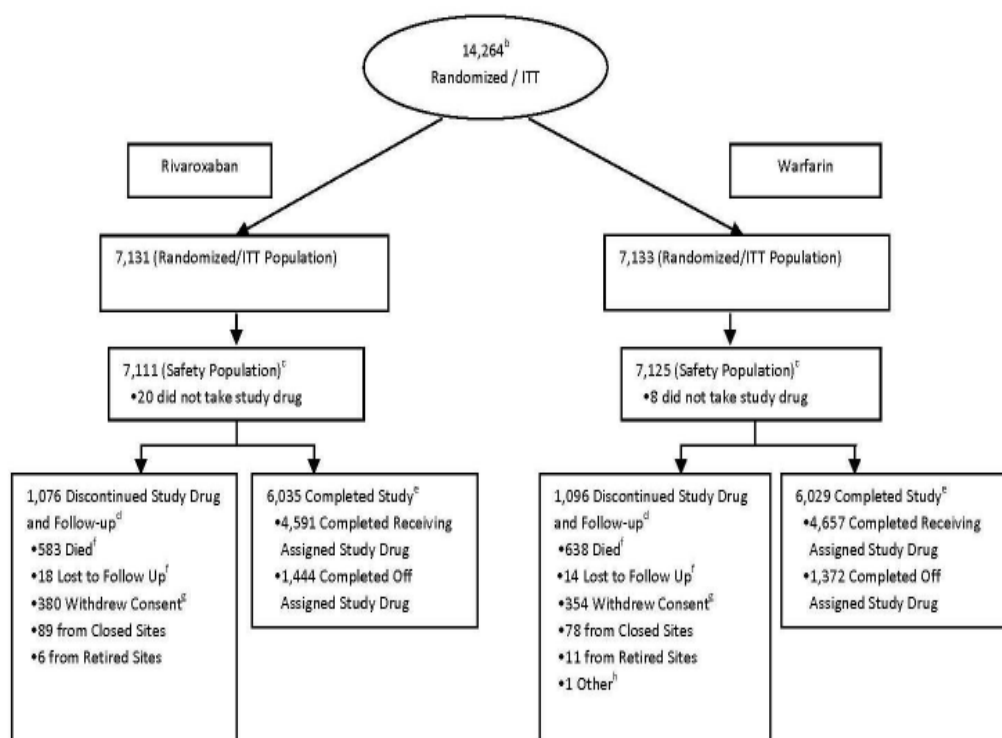
6.1.4.1 Disposition

There were 17,232 subjects screened for entry into ROCKET; 14,269 were randomized, yielding 2963 screen failures and a screen failure rate of 17.2%. Note that in the previous sentence both the number screened and the number randomized represent the total of times any subject was screened or randomized; some individuals were screened or randomized more than once were counted each time. The number of unique individuals randomized was 14,264; 5 individuals were randomized twice. Two were initially randomized to rivaroxaban and 3 were initially randomized to warfarin. For the various efficacy analyses, only data resulting from the first randomization were included. Likewise, safety analyses only include data resulting from the first randomization unless otherwise stated.

All screen failures signed consent forms. Reasons for the 2963 screen failures, in decreasing order of frequency, included violation of the one of the inclusion/exclusion criteria (N=1816, 10.5% of all subjects screened), withdrawal of consent (N=771, 4.5%), lost to follow-up during screening period (N=255, 1.5%) and an adverse event occurring during the screening period (N=114, 0.7%). Case records for seven subjects (<0.1%) included no reason for why they were not randomized.

[Figure 22](#) provides data on patient flow in ROCKET. The ITT population, including all 14,264 individual randomized subjects, included 7131 and 7133 subjects in the rivaroxaban and warfarin arms, respectively. Twenty and 8 of the randomized subjects in the rivaroxaban and warfarin arms, respectively did not receive any study medication, leaving 7111 and 7125 subjects (for a total 14,236) in the Safety population of subjects who received at least one dose of study medication. Note that the follow-up information in the figure has been revised. Corrected data are provided in [Table 24](#).

Figure 22. ROCKET – Subject Disposition



^a As of the site notification date (28-May-2010 for all countries except South Africa [1-April-2010])

^b Intent to Treat (ITT) population constitutes all uniquely randomized subjects. Five subjects were randomized twice. Only the data associated with the first randomizations were used for the analysis of the ITT group

^c Safety Population equals all subjects in the ITT population who had a least one dose of study drug

^d Discontinued Study Drug and Follow-up: Subjects who permanently discontinued study drug before the site notification date and last contact was before the site notification date

^e Completed Study: Last contact with the subject (regardless of whether study drug was being taken or not) was on or after the site notification date

^f Subjects from closed sites are included.

^g Subjects from closed sites are excluded

^h One subject in the warfarin group who discontinued due to Clinical Efficacy Endpoint and last contact was 3 days prior to site notification date of 28-May-2010 (Subject 105680)

Closed Sites: Sites closed by sponsor for GCP violation(s): Site numbers: 063011, 001512, 042012, 055033, 031029, 039003, 002529, 051018, 886012, 886015, 001353, 011608

Retired Sites: Sites closed before the site notification date and were unavailable for further subject information (i.e., 001032, 001529, 001541, 011015, 011058, 049031, 056019, 061017)

Reviewer Comment: The Sponsor has updated the follow-up information in the above figure. The updated data, which indicate that additional patients discontinued follow-up before the notification date, are reflected in Table 24. Data provided in text prior to the table are correct.

Of the patients in the Safety Population, 9248 subjects (about 65% in each arm) “completed” study medication, meaning that their last dose of study drug occurred no

earlier than the day the sites were notified that the study had reached its event target and that end-of-study visits should be scheduled. The remaining 4988 subjects, about 35% of each arm, discontinued study medication prematurely, i.e., before site notification. Reasons for premature discontinuation of study drug are displayed in [Table 23](#). Note that many of the discontinued patients were followed up. Details regarding follow-up information are provided in [Table 24](#).

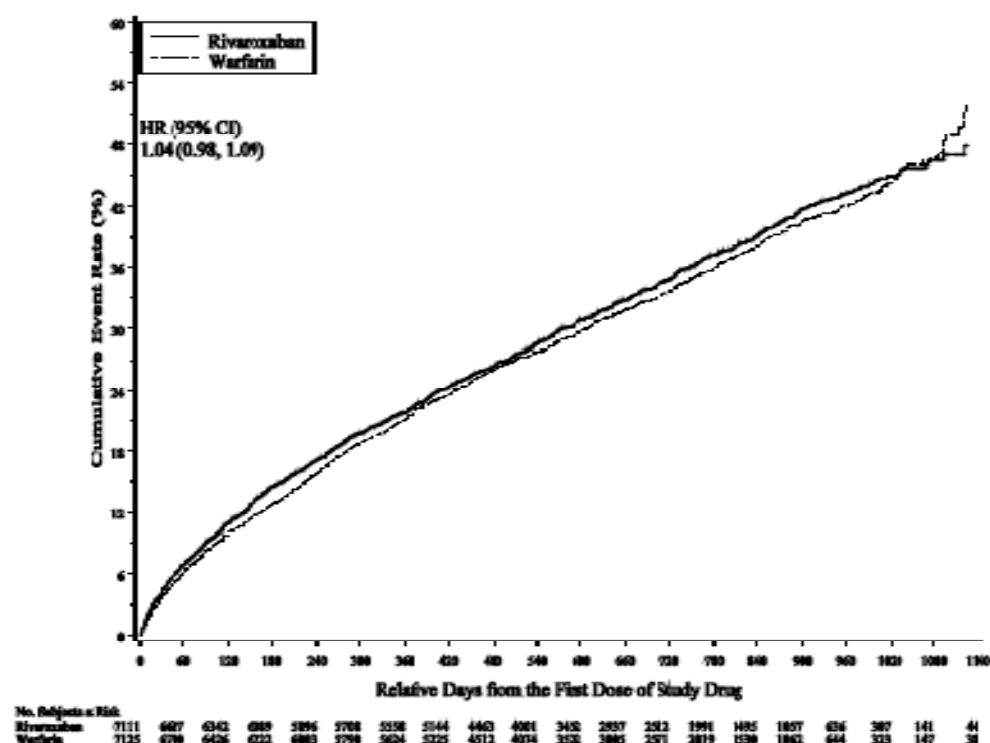
Table 23. ROCKET -- Reasons For Early Discontinuation Of Study Drug

(Prior to Site Notification to Schedule End-of-Study Visits, Safety Population)

Status Discontinuation Reason	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Completed Study Medication	4591 (64.56)	4657 (65.36)	9248 (64.96)
Early Study Medication Discontinuation	2520 (35.44)	2468 (34.64)	4988 (35.04)
Adverse Event	993 (13.96)	919 (12.90)	1912 (13.43)
-Bleeding	304 (4.28)	219 (3.07)	523 (3.67)
-Non-bleeding	689 (9.69)	699 (9.81)	1388 (9.75)
-Missing/incomplete data	0	1 (0.01)	1 (0.01)
Non-Compliant with Study Medication	134 (1.88)	164 (2.30)	298 (2.09)
Consent Withdrawn	671 (9.44)	673 (9.45)	1344 (9.44)
Investigator Decision, Not Protocol Related	191 (2.69)	178 (2.50)	369 (2.59)
Lost to Follow-Up	6 (0.08)	8 (0.11)	14 (0.10)
Protocol Violation	142 (2.00)	124 (1.74)	266 (1.87)
Clinical Efficacy Endpoint Reached	300 (4.22)	332 (4.66)	632 (4.44)
Study Terminated by Sponsor	82 (1.15)	69 (0.97)	151 (1.06)
Missing/Incomplete Data	1 (0.01)	1 (0.01)	2 (0.01)

[Figure 23](#) is a display of time to discontinuation of study drug during the double-blind period. The curves for the two arms are nearly superimposed, and the HR for rivaroxaban vs. warfarin is 1.04 (95% CI, 0.98 – 1.09).

Figure 23. ROCKET -- Time To Discontinuation Of Study Drug



Not all of the patients who discontinued study drug also discontinued follow-up. In the Safety population, about 7.4% and 7.0% of subjects in the rivaroxaban and warfarin arms, respectively, discontinued both study drug and follow-up alive prematurely. Reasons for discontinuation of follow-up are displayed in [Table 24](#). Most patients represented in the row labeled “Other” were at study sites that were closed early.

Table 24. ROCKET -- Reasons For Early Discontinuation Of Follow-Up

(Prior to Site Notification, Safety Population)

Status Discontinuation Reason	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Completed Study	5987 (84.19)	5974 (83.85)	11961 (84.02)
Died on Study	599 (8.42)	650 (9.12)	1249 (8.77)
Discontinued Follow-up Alive	525 (7.38)	501 (7.03%)	1026 (7.26)
Consent Withdrawn ¹	406 (5.71)	390 (5.47)	796 (5.59)
Lost to Follow-up	18 (0.25)	15 (0.21)	33 (0.23)
Other	101 (1.42)	96 (1.35)	117 (1.38)

¹ Includes 3 and 8 patients in the rivaroxaban and warfarin arms, respectively who discontinued follow-up early and later died; news of their death eventually reached their study centers. However, these patients were lost to follow-up for non-fatal endpoints. These patients are not counted in the row of “Death” in this table.

In order to evaluate the potential effects on the primary endpoint results of patients lost to follow-up, we performed a near worst case analysis with differing assumptions about the fates of persons lost to follow-up alive in the two treatment arms (525 of 7111 patients in the rivaroxaban arm (7.38%) and 501 of 7125 patients in the warfarin arm (7.03%). We assumed that rivaroxaban arm patients had primary event rates after discontinuation of follow-up similar to those of patients who discontinued study drug early and were followed for 28 days after the end of the on-treatment period, i.e., 25.60 events per 100 patient-years (see [Table 62](#)). We assumed that warfarin arm patients who discontinued early had such events at the same rate as they did on treatment, 2.15 events per 100 patient-years. We calculated that over the 28 days following discontinuation of follow up, there would be 10.31 events vs. 0.82 events in the rivaroxaban and warfarin arms, respectively, for a difference of about 9.48 events favoring warfarin. This would not negate non-inferiority. In the highly unlikely event that these event rates continued held for a mean of 180 days after discontinuation of follow-up, there would be a difference of about 61 events favoring warfarin. Again this would not upset the finding of non-inferiority (see [Table 29](#) for information regarding the number of events needed to negate non-inferiority for the primary endpoint analysis).

As noted earlier, site notification was the trigger for scheduling end-of-study visits for subjects still taking study medication, and was also the trigger for a last telephone contact for discontinued patients who were being followed by phone. About 30 days after the end-of-study visit, there was to be a follow-up clinical visit. Likewise, 30 days after an early discontinuation visit, there was to be a follow-up clinic visit.

[Table 25](#) is a display of the reasons for failure to complete the 30-day follow-up visit in the ITT population, including completers and those with early discontinuation of study drug. Note that unlike previous table, the time window is up to the follow-up visit, which is specific to each patient and may have been well before the study-wide “site notification” for patients who discontinued study drug early. Thus, the percentage of patients with a follow-up visit is larger than the percentage with no early discontinuation of follow-up in the previous table.

About 87% of subjects in each arm had a post-treatment follow-up visit performed, either in person (about 76%) in each arm or by phone (about 10.5%). Phone contacts were made using the same CRF to ascertain efficacy events as the clinic visits; in theory, data on all the relevant efficacy endpoints could have been collected with either type of contact (i.e., stroke, systemic embolism, MI, and death). However, patient memory may be faulty, and a face-to-face visit with a just a cursory examination (or merely just watching and listening to the patient as she walks and talks) has a greater chance of picking up an event, especially a subtle neurological event, than a phone contact.

Table 25. ROCKET -- Reasons For Lack Of 30-Day Follow-Up Visit (ITT Population)

Status/Type of Contact Discontinuation Reason	Rivaroxaban (N=7131) n (%)	Warfarin (N=7133) n (%)	Total (N=14,264) n (%)
Post Treatment Follow-up Visit Performed?			
Yes	6215 (87.15)	6170 (86.50)	12385 (86.83)
Clinic Visit	5453 (76.47)	5416 (75.93)	10869 (76.20)
Phone Contact	762 (10.69)	754 (10.57)	1516 (10.63)
No	916 (12.85)	963 (13.50)	1879 (13.17)
Alive but Missed Clinic Visit	228 (3.20)	230 (3.22)	458 (3.21)
Lost to Follow-up	4 (0.06)	3 (0.04)	7 (0.05)
Withdrew Consent for Follow-up	247 (3.46)	224 (3.14)	471 (3.30)
Death or missing reason	437 (6.13)	506 (7.19)	943 (6.61)

Slightly over 3% of subjects in each arm were known to be alive but missed their last visit, and were not contacted by phone. About 3% of patients withdrew consent for follow-up or were lost to follow up. Overall, about 7% and 6% of subjects in the rivaroxaban and warfarin arms, respectively might have been followed up but were not. Another 6 to 7% were dead or have missing data regarding the follow-up visit, adding up to close to about 13% in each arm who did not have a documented follow-up visit or phone contact.

6.1.4.2 Compliance with Study Drug

The sponsor provided several sets of compliance information, obtained using different methods. Data shown here are for a method based on returned tablet count information to calculate the number of doses taken and which excludes from the denominator days of missed doses due to physician-driven dosing interruptions. Data for the study's 5 regions indicate that within each region, compliance rates for the two treatment arms were similar. Mean compliance rates ranged from a low of 95.2% (North America, warfarin arm) to a high of 97.1% (Eastern Europe, rivaroxaban arm). The rank order of compliance in regions was Eastern Europe > Western Europe > Latin America > Asia Pacific > North America (see [Table 26](#)).

Reviewer Comment: The review team has concerns about the compliance data. It seems paradoxical that North America, which had the highest overall TTR, would have the lowest compliance rate, and Eastern Europe, with the lowest overall TTR, would have the highest compliance rate. It is possible that the returned tablet count data were not representative of the number of tablets actually taken by the some patients.

Table 26. Compliance By Region And Treatment

REGION	Treatment	N	Mean Compliance (%) ¹
ASIA PACIFIC	Rivaroxaban	1052	95.726
	Warfarin	1052	95.969
EASTERN EUROPE	Rivaroxaban	2746	97.055
	Warfarin	2747	96.790
LATIN AMERICA	Rivaroxaban	939	95.582
	Warfarin	938	95.681
NORTH AMERICA	Rivaroxaban	1334	95.461
	Warfarin	1339	95.247
WESTERN EUROPE	Rivaroxaban	1040	96.131
	Warfarin	1049	96.026

¹ Percentage compliance calculated as: total days receiving treatment based on counts of returned tablets and intervals between dispensing dates / (((first dose date – last dose date) + 1) – days of physician-driven treatment interruptions).

6.1.5 Analysis of Primary Endpoint

The primary efficacy endpoint was the composite of stroke (ischemic, hemorrhagic or of unknown type) or non-CNS systemic embolism. The primary efficacy analysis was the time to the first occurrence of a primary endpoint event in the Per-Protocol population, on-treatment (defined as the time from randomization up to the date of the last dose of study drug + 2 days). The sponsor's intent was to establish that rivaroxaban is non-inferior to warfarin, using a non-inferiority (NI) margin of 1.46 for the hazard ratio. FDA prefers a NI margin of 1.38. However, all NI analyses of the primary endpoint demonstrate NI with margins considerably below 1.37, and some show nominal superiority.

The results for the primary endpoint analysis are shown below in [Table 27](#) and [Figure 24](#). Data in these analyses, as well as other efficacy analyses (unless otherwise specified) exclude all of the 93 patients who were enrolled at site 042012 in the Czech Republic (50 and 43 patients randomized to rivaroxaban warfarin, respectively). Inclusion of data from this site in the efficacy analyses does not result in meaningful differences in the results (data not shown). Unless otherwise specified, all efficacy analyses pool data from patients with estimated CrCl ≥50 mL/min at baseline (who were to receive rivaroxaban 20 mg if randomized to rivaroxaban) and patients with CrCl 30 to < 50 mL/min (who were to receive rivaroxaban 15 mg).

There were 188 and 241 first primary efficacy events in the rivaroxaban and warfarin arms, respectively, yielding respective event rates of 1.71 and 2.16 events per 100 patient-years and a hazard ratio of 0.79 (95% CI 0.66 to 0.96). The p for non-inferiority was highly significant using the sponsor's preferred NI margin of 1.46, but would be significant using any margin greater than 1.0. The p for superiority was also significant, with a value of 0.018.

Table 27. ROCKET -- Primary Efficacy Endpoint Results

Time to first event – stroke or non-CNS systemic embolism (Adjudicated data, Per-Protocol Population, On-Treatment)

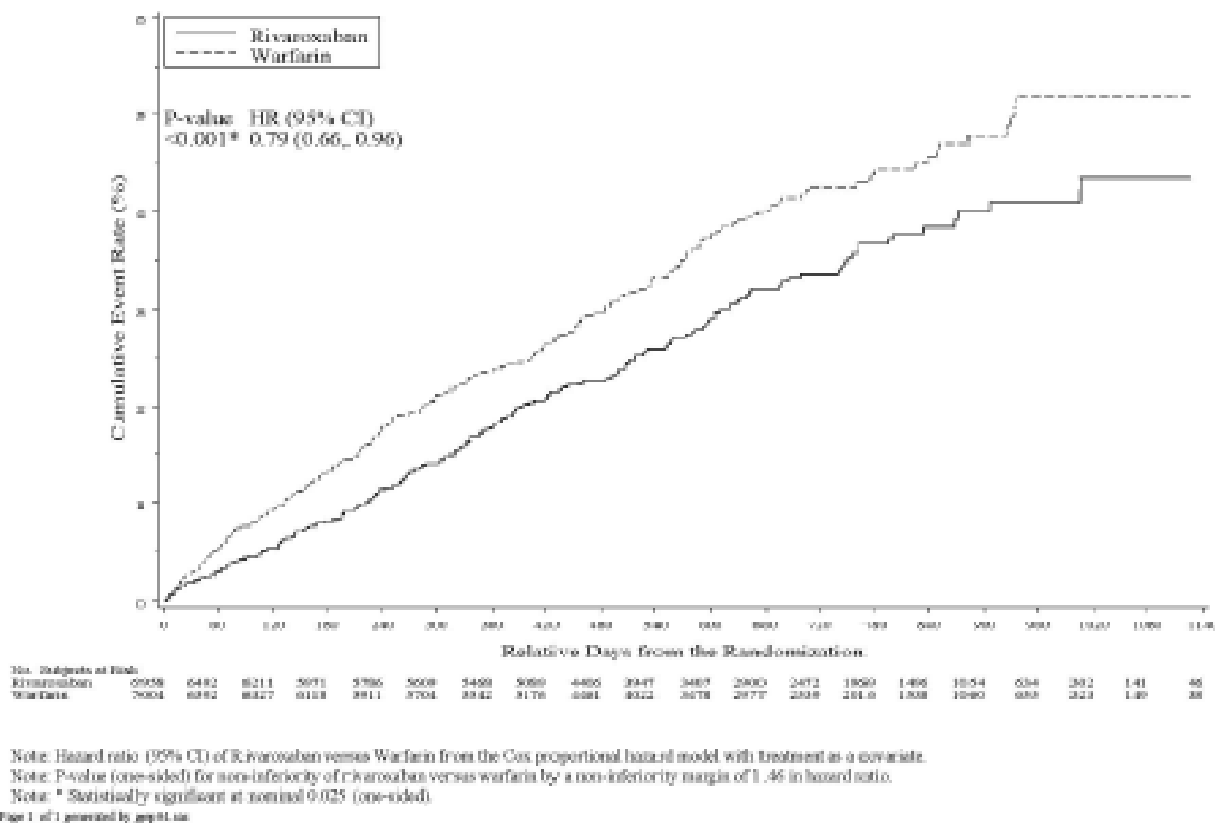
Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin			
n/N	Event Rate ¹	n/N	Event Rate ¹	Hazard Ratio	(95% CI)	p (non-Inferiority) ²	p (superiority)
188/6958	1.71	241/7004	2.16	0.79	(0.66,0.96)	<0.001	0.018

¹ Events/100 patient-years

² The p value was calculated using the sponsor's specified margin of 1.46. FDA's preferred margin is 1.38, which was met.

Figure 24. ROCKET -- Kaplan-Meier Plots Of Primary Efficacy Endpoint Results

Time to first event – stroke or non-CNS systemic embolism (Adjudicated data, Per-Protocol Population, On-Treatment)



Note that in the above figure, the curves for the event rate in the treatment arms tend to diverge from Day 0 (randomization until about Day 180, when the rate of divergence decreases, suggesting a narrowing of the difference in event rates for the primary endpoint after about 6 months of treatment. This phenomenon is examined further in [Section 6.1.5.1](#).

Sensitivity analyses of the primary analyses were performed by the sponsor and are reproduced below in [Table 28](#). These range (in terms of the total number of events) from a more restrictive version of the Per-protocol analysis on treatment to the ITT analysis regardless of treatment exposure, which included all randomized patients and all primary efficacy endpoint events occurring up to the last known study observation, whether or not patients were taking (or ever took) study medication. This last analysis included a total of 613 primary endpoint events, compared to 439 such events in the primary efficacy analysis. The event rate comparisons are numerically favorable for rivaroxaban in all the analyses, and that the 95% CI for the hazard ratio did not exceed 1.08 in any of the analyses, indicating that the non-inferiority finding of the primary

efficacy analysis is statistically robust. However these analyses do not take into account possible deficiencies of the comparator.

Table 28. ROCKET – Additional Analyses Of The Primary Efficacy Endpoint Results

Time to first event – stroke or non-CNS systemic embolism (adjudicated data, various populations and observation periods)

Analysis Method	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin		
	n/N	Event Rate (100 Pt-Yr)	n/N	Event Rate (100 Pt-Yr)	Hazard Ratio(95% CI)	P-Value ^a	P-Value ^b
Per protocol, on treatment	188/6958	1.71	241/7004	2.16	0.79 (0.66,0.96)	<0.001*	0.018*
Per protocol, on treatment (restrictive definition)	186/6958	1.70	239/7004	2.14	0.79 (0.65,0.96)	<0.001*	0.017*
Per protocol, last dose plus 7 days	219/6958	1.98	253/7004	2.25	0.88 (0.74,1.06)	<0.001*	0.172
Per protocol, last dose plus 14 days	233/6958	2.08	269/7004	2.36	0.88 (0.74,1.05)	<0.001*	0.159
Per protocol, last dose plus 30 days	247/6958	2.16	279/7004	2.39	0.90 (0.76,1.07)	<0.001*	0.230
Safety, on treatment	189/7061	1.70	243/7082	2.15	0.79 (0.65,0.95)	<0.001*	0.015*
Safety, last dose plus 7 days	220/7061	1.96	255/7082	2.24	0.88 (0.73,1.05)	<0.001*	0.149
Safety, last dose plus 14 days	235/7061	2.07	271/7082	2.35	0.88 (0.74,1.05)	<0.001*	0.150
Safety, last dose plus 30 days	251/7061	2.16	281/7082	2.38	0.91 (0.76,1.07)	<0.001*	0.252
ITT - follow-up visit	257/7081	2.18	285/7090	2.39	0.91 (0.77,1.08)	<0.001*	0.286
ITT - site notification	269/7081	2.12	306/7090	2.42	0.88 (0.74,1.03)	<0.001*	0.117
ITT - regardless of treatment exposure	293/7081	2.20	320/7090	2.40	0.91 (0.78,1.07)	<0.001*	0.263

Notes: p^a is the p for non-inferiority, based on a margin of 1.46.
p^b is the p for superiority
Populations and time periods are described in Section 5.

Reviewer comment: In the above table, the various time cuts for events in the per-protocol population and the safety population show a sharp increase in the number of events in the rivaroxaban arm in the 5 day interval between the end of the on treatment analysis and the last dose + 7 days analysis. The number of additional events over the same period on the warfarin arm is substantially smaller. For example, in the safety population there were 31 vs. 12 events that occurred during this 5 day period in the rivaroxaban and warfarin arms, respectively. This finding is explored in Section 6.1.10.3.

In addition to the analyses, described above, we asked the Sponsor to perform a hybrid analysis in all randomized patients with differing event windows for different subgroups of patients, all starting at randomization and ending: 30 days after randomization for patients who never took study drug; 30 days after the last dose of study drug for patients who discontinued study drug early; and 2 days after the last dose of study drug (identical to the “on treatment” event window) for patients who completed the study. The reasoning for these disparities was based on the fact that the first two of these

subgroups were, at least to some extent, subject to informative censoring and should be followed for some period of time after treatment, such as 30 days. The last subgroup, those who completed the trial, were not subject to informative censoring, and following them for 30 days might resulting in confounded results by such factors the occurrence of events associated with poor anticoagulation control after discontinuation of study drug. This “hybrid” analysis yielded event rates of 2.04 and 2.40 events per 100 patient-years in the rivaroxaban and warfarin arms, respectively, and a hazard ratio of 0.85 (95% CI, 0.71, 1.01, p=0.065).

While the randomization was stratified by 3 factors (geographic region, prior VKA use (yes or no), and prior history of stroke, TIA or non-CNS systemic embolism (yes or no), the primary endpoint analysis did not take these factors into account. As one might expect, analyses that adjusted for these factors produced results identical or trivially different in terms of hazard ratios and p values for the specified primary analysis (per-protocol, on treatment) and four other analyses of the primary endpoint (safety, on treatment; ITT, to the follow-up visit; ITT, to site notification; and ITT, regardless of treatment exposure) that are displayed in [Table 28](#) (data not shown for adjusted analyses).

FDA performed an analysis of how many additional primary endpoint events would be required in the rivaroxaban arm to negate the findings of non-inferiority and superiority in the sponsor’s primary efficacy analysis (Depending on the non-inferiority analysis, from 80 to 95 additional events would be required to produce a margin (i.e., the maximum of the 95% CI for the hazard ratio) greater than 1.38. This analysis supports the statistical robustness of the non-inferiority finding of the primary efficacy analysis. For the two superiority analyses that were evaluated, 13 additional events in the rivaroxaban would negate superiority in each analysis (see [Table 29](#)).

Table 29. Sensitivity Analyses Of Non-Inferiority And Superiority Of Rivaroxaban

Analysis Method (observed events/N in rivaroxaban arm)	Additional Events in Rivaroxaban arm needed to negate finding of:	
	Non-inferiority ¹	Superiority
Per protocol, on treatment (188/6958)	91	13
Safety, on treatment (189/7061)	95	13
ITT, to follow-up visit (257/7081)	80	NA ²
ITT, regardless of exposure (293/7081)	88	NA ²

¹ Based on NI margin of 1.38

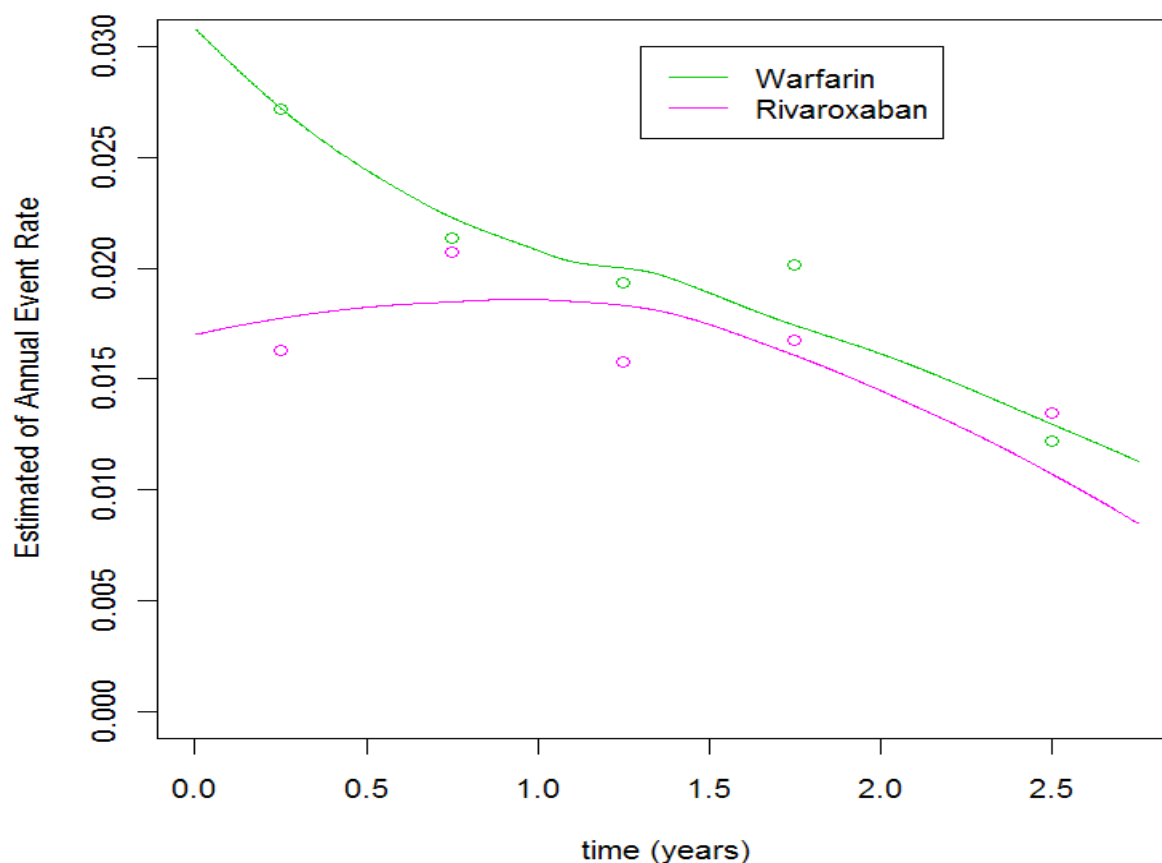
² NA = not applicable because superiority was not attained in the base case of the relevant analysis

6.1.5.1 Effect of Time after Randomization

As note earlier, in the Kaplan-Meier plot of the primary endpoint, [Figure 24](#), much of the divergence in the curves for the event rates occurs in the 180 day of treatment. After that time, the curves tend to stay about the same distance apart, suggesting a convergence of the event rates after the first 6 months of treatment.

Accordingly, we asked our colleagues in the Davison of Biometrics I to examine the relationship of time after randomization to the event rates and hazard ratio (rivaroxaban vs. warfarin) for primary endpoint events. [Figure 25](#) is a plot of the annual event rate over time since randomization in each treatment arm. The curve for warfarin (in green) is above the curve for rivaroxaban (in pink) at all time points, but the distance between the curves decreases sharply from randomization until about 1 year of treatment. After that, the curves remain close together as the rate falls over time in each arm.

Figure 25. Estimated Hazard Functions over Time since Randomization



The curves in both [Figure 24](#) and [Figure 25](#) suggest that the event rates in the two treatment arms approach each other over the first six months of treatment and become nearly similar after one year. Using the Cox proportional hazards model, the HR for

event occurring up to Day 180 was calculated as 0.69 (95% CI, 0.432, 0.860). Starting at Day 180, the HR and CI are 0.895 (0.710, 1.13), consistent with the suggestion in the two figures.

We asked the sponsor to confirm these findings. The sponsor determined that the on treatment primary efficacy endpoint event rates in the rivaroxaban and warfarin arms (safety population), in the first 180 days after randomization, were, respectively, 1.66 and 2.66 events per hundred patient years, yielding a hazard ratio of 0.62 (95% CI, 0.44, 0.88). For days 181 on, the analogous rates were 1.71 and 1.96 with a hazard ratio of 0.87 (95% CI, 0.70, 1.10), very similar to the rates obtained by FDA. The sponsor's event rate data for these and other time periods are shown in [Table 30](#). The data show a progressive increase in the hazard ratio over the first year of the study to 0.89, with stabilization after that.

These data confirm that once patients are stabilized on warfarin therapy, event rates with rivaroxaban and warfarin are quite similar.

Table 30: Primary Event Rates In Various Time Periods

Safety Population, On Treatment

Time Interval from Random- ization	----- Rivaroxaban ----		----- Warfarin -----		Rivaroxaban vs. Warfarin	
		Event Rate		Event Rate		
	n/N	(100 pt-yr)	n/N	(100 pt-yr)	Hazard Ratio (95% CI)	p-value
1-30	13/7061	2.29	20/7082	3.50	0.65 (0.33,1.31)	0.233
31-60	7/6766	1.28	16/6830	2.89	0.44 (0.18,1.08)	0.072
61-90	10/6585	1.87	15/6664	2.77	0.67 (0.30,1.50)	0.334
91-180	24/6439	1.56	35/6518	2.24	0.70 (0.41,1.17)	0.173
181-360	56/6058	1.97	64/6190	2.21	0.89 (0.62,1.27)	0.524
≥ 361	80/5546	1.57	95/5613	1.84	0.86 (0.64,1.15)	0.304
1-180	53/7061	1.66	86/7082	2.66	0.62 (0.44,0.88)	0.007
≥ 181	136/6058	1.71	158/6190	1.96	0.87 (0.70,1.10)	0.253

A likely explanation for the rising HR over time is sub-optimal TTR in the warfarin arm in the early weeks of study treatment. [Table 31](#) is a display of the mean and SD of global INR at weekly intervals until week 4, then 4 week intervals until week 56, and then 8 week intervals until week 180, when only 1 subject had INR data. The data indicate that the mean (SD) INR over the course of the study was 2.40 (0.38). During the first week, mean INR was 2.26 (1.09), but by week 2 it was 2.26 (1.06). By week 4, mean INR was 2.38 (0.86) and the mean remained near that value for most of the next three years of treatment. However, the SD fell gradually over this period, suggesting less variance,

which might explain the narrowing difference in the event rates over time, as INR below 2 and above 3 would be associated with increased primary efficacy event risk. Analysis of only mean INR could obscure important temporal trends in the data, and we plan to examine other approaches to evaluating INR control.

Table 31. Mean INR Over The Course Of ROCKET

Time since Random-ization	N	INR Mean (SD)		Time since Random-ization	N	INR Mean (SD)
Entire Study	7025	2.40 (0.38)		WEEK 56	5343	2.40 (0.73)
WEEK 1	6672	2.26 (1.09)		WEEK 64	4731	2.42 (0.73)
WEEK 2	6351	2.49 (1.06)		WEEK 72	4200	2.43 (0.75)
WEEK 3	1669	2.43 (1.02)		WEEK 80	3803	2.41 (0.73)
WEEK 4	6576	2.38 (0.86)		WEEK 88	3249	2.44 (0.71)
WEEK 8	6630	2.34 (0.81)		WEEK 96	2811	2.43 (0.73)
WEEK 12	6487	2.38 (0.81)		WEEK 104	2355	2.43 (0.71)
WEEK 16	6358	2.40 (0.80)		WEEK 112	1860	2.41 (0.72)
WEEK 20	6246	2.40 (0.77)		WEEK 120	1406	2.40 (0.70)
WEEK 24	6130	2.41 (0.80)		WEEK 128	1037	2.46 (0.68)
WEEK 28	6041	2.40 (0.76)		WEEK 136	664	2.43 (0.65)
WEEK 32	5931	2.40 (0.75)		WEEK 144	343	2.38 (0.68)
WEEK 36	5813	2.42 (0.75)		WEEK 152	163	2.50 (0.60)
WEEK 40	5734	2.40 (0.74)		WEEK 160	56	2.45 (0.46)
WEEK 44	5653	2.42 (0.75)		WEEK 168	13	2.46 (0.54)
WEEK 48	5577	2.42 (0.70)		WEEK 172	8	2.59 (0.63)
WEEK 52	5501	2.44 (0.74)		WEEK 180	1	1.5

We asked the Sponsor to provide tables of mean time in ranges on INR during specified intervals of treatment in the warfarin arm overall and the subsets of patients were VKA experienced and VKA naïve at baseline. These data are displayed in [Table 32](#), [Table 33](#), and [Table 34](#), respectively.

Table 32. Mean Time In Specified Ranges Of INR During Intervals Of Treatment

Safety Population

Analysis Set: Safety

Time Period		Average Percentage of INR values in Ranges						
		<1.5	1.5-<1.8	1.8-<2	2-3	>3-3.2	>3.2-5	>5
Entire Study On Treatment	(N=7003)	8.18	10.38	10.27	55.43	4.80	9.91	1.03
Day 1-30	(N=7003)	16.58	12.50	8.60	41.39	4.60	13.47	2.87
Day 31-60	(N=6829)	11.06	12.21	10.42	50.22	4.78	10.39	0.94
Day 61-90	(N=6681)	8.79	11.83	11.31	52.93	4.67	9.63	0.84
Day 91-180	(N=6541)	6.94	10.34	10.75	56.57	4.95	9.65	0.78
Day 181-360	(N=6217)	5.97	9.48	10.44	59.08	5.09	9.38	0.56
Day 361-540	(N=5618)	5.28	9.15	10.90	59.80	4.97	9.37	0.53
Day 541-720	(N=4068)	4.94	8.92	10.61	61.15	4.80	9.03	0.54
Day 721-900	(N=2563)	5.57	9.11	10.45	60.60	4.96	8.65	0.50
Day 901-1080	(N=1053)	4.91	9.59	10.68	61.80	4.43	8.33	0.25
Day 1081-1260	(N=146)	3.86	4.68	6.75	69.53	8.30	6.86	0.03
Day 1261-1440	(N=1)	0.00	100.00	0.00	0.00	0.00	0.00	0.00

Table 33. Mean Time In Specified Ranges Of INR During Intervals Of Treatment

Safety Population, Patients with VKA use at Baseline

Analysis Set: Safety

Prior VKA Use: YES

Time Period		Average Percentage of INR values in Ranges						
		<1.5	1.5-<1.8	1.8-<2	2-3	>3-3.2	>3.2-5	>5
Entire Study On Treatment	(N=4399)	5.18	9.00	9.93	59.93	5.23	9.96	0.77
Day 1-30	(N=4399)	11.51	11.24	8.94	47.72	5.20	13.36	2.02
Day 31-60	(N=4320)	7.09	10.00	9.75	55.70	5.49	11.15	0.83
Day 61-90	(N=4253)	5.79	9.85	10.57	57.64	5.17	10.19	0.79
Day 91-180	(N=4176)	4.35	8.96	10.45	60.51	5.39	9.70	0.65
Day 181-360	(N=4000)	3.97	8.42	10.07	62.58	5.34	9.19	0.43
Day 361-540	(N=3648)	3.76	8.00	10.58	62.88	5.20	9.12	0.46
Day 541-720	(N=2701)	3.72	7.92	10.04	63.84	5.18	8.92	0.38
Day 721-900	(N=1772)	4.09	8.37	9.95	63.32	5.10	8.78	0.39
Day 901-1080	(N=792)	3.19	8.54	10.36	64.86	4.90	7.88	0.27
Day 1081-1260	(N=127)	4.44	3.98	6.63	70.68	8.23	6.00	0.04
Day 1261-1440	(N=1)	0.00	100.00	0.00	0.00	0.00	0.00	0.00

Table 34. Mean Time In Specified Ranges Of INR During Intervals Of Treatment

Safety Population, Patients with No VKA use at Baseline

Analysis Set: Safety
Prior VKA Use: No

Time Period		Average Percentage of INR values in Ranges					
		<1.5	1.5-<1.8	1.8-<2	2-3	>3-3.2	>3.2-5
Entire Study On Treatment	(N=2604)	13.24	12.72	10.84	47.81	4.09	9.83
Day 1-30	(N=2604)	25.15	14.63	8.01	30.68	3.58	13.66
Day 31-60	(N=2509)	17.89	16.02	11.57	40.77	3.55	9.08
Day 61-90	(N=2428)	14.03	15.30	12.60	44.70	3.78	8.65
Day 91-180	(N=2365)	11.51	12.78	11.30	49.62	4.19	9.57
Day 181-360	(N=2217)	9.58	11.41	11.12	52.77	4.62	9.71
Day 361-540	(N=1970)	8.11	11.27	11.50	54.09	4.53	9.84
Day 541-720	(N=1267)	7.27	10.90	11.76	55.92	4.02	9.26
Day 721-900	(N=791)	8.88	10.76	11.56	54.78	4.65	8.36
Day 901-1080	(N=261)	10.12	12.81	11.67	52.53	3.01	9.69
Day 1081-1260	(N=19)	0.00	9.30	7.54	61.83	8.75	12.58

The VKA naïve patients had a time in the INR therapeutic range of 2 to 3 (TTR) of 31% from day 1-30 and did not exceed 50% until the period from day 181-360, despite substantial attrition. Out of range values were mostly on the low side (i.e., <2), but about 21% were > 3 in the first 30 days. The VKA experience patients started with a TTR of 48% in the first 30 days and reached 63% in the period from day 181-360. At all time points until the very last days of the study when one VKA experienced patient remained on treatment, TTR was substantially lower in the VKA naïve patients than in the VKA experienced patients.

Consistent with the TTR data, the primary efficacy event rate data show a substantial difference between the VKA experienced patients and the VKA naïve patients in the pattern of event rates and rivaroxaban vs. warfarin arm hazard ratios over the course of the study. Data for the overall population, VKA experienced, and VKA naïve patients are summarized in for the periods from Day 1 to 180 and Day 181 and beyond for the safety population on treatment in [Table 35](#).

Table 35. Primary Efficacy Endpoint Events By Baseline VKA Status And Time Period

Safety Population, On Treatment						
Population and Time Interval From Randomization	---- Rivaroxaban ----		----- Warfarin -----		Rivaroxaban vs. Warfarin	
	n/N	Event Rate (100 pt-yr)	n/N	Event Rate (100 pt-yr)	Hazard Ratio (95% CI)	p-value
All patients						
1-180	53/7061	1.66	86/7082	2.66	0.62 (0.44,0.88)	0.007
≥ 181	136/6058	1.71	158/6190	1.96	0.87 (0.70,1.10)	0.253
VKA Experienced						
1-180	25/4401	1.24	47/4437	2.28	0.54 (0.33,0.88)	0.014
≥ 181	89/3839	1.71	93/3985	1.73	0.99 (0.74,1.32)	0.948
VKA Naïve						
1-180	28/2660	2.37	39/2645	3.33	0.71 (0.44,1.16)	0.171
≥ 181	47/2219	1.72	65/2205	2.43	0.71 (0.49,1.03)	0.072

In both VKA naïve patients VKA experienced patients, the warfarin arm event rate falls by roughly 25% from the 0-180 day period to the ≥ day 181 period, but the rates are higher in the VKA naïve patients in both periods. The absolute reduction in rates between the two periods is also somewhat larger in the VKA naïve patients (a reduction of 0.7 vs. 0.55 events per 100 patient-years).

In the rivaroxaban arm, the event rate falls from the earlier to later period in the VKA naïve patients, but moves in the opposite direction in the VKA experienced patients. Overall there is only a small rise in the event rate in the rivaroxaban arm from the earlier to later period.

Thus, most of the observed increase in the hazard ratio from the early period to the later period in the “all patients” rows of Table 33 results from the decrease in the warfarin arm event rate over time, which was larger in the VKA naïve patients in absolute terms. This suggests that poor warfarin control played in role in the relative poor results for warfarin from day 0 to 180, but that reductions in event rates in both the VKA naïve and experienced patients contributed to the overall reduction. The differing patterns of change in the event rates over time in the VKA naïve and experienced subgroups in the events rates in the rivaroxaban arm are difficult to explain, and may be due to chance.

Reviewer Comment: The fact that patients who were VKA experienced at baseline therapy had similar event rates after 180 days on study regardless of treatment arm suggests that such patients may have little to gain (except perhaps convenience) from switching to rivaroxaban. This is another argument

against suggesting in labeling that rivaroxaban is superior to warfarin in preventing thrombotic events in non-valvular AFib patients.

6.1.6 Other Efficacy Endpoints

Table 36 is a display of event rates, hazard ratios, and p-values (superiority) for secondary endpoint data, including the components of the primary endpoint, various categories of stroke, all-cause death and several categories of cause-specific death, myocardial infarction, and 2 composite "Major Secondary Endpoints (defined below).

Table 36. ROCKET – Secondary Endpoint Data

Safety Population, On Treatment

Endpoints	----- Rivaroxaban -----		----- Warfarin -----		Rivaroxaban vs. Warfarin	
	N= 7061 n (%)	Event Rate (100 Pt-yr)	N= 7082 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	189 (2.68)	1.70	243 (3.43)	2.15	0.79 (0.65,0.95)	0.015*
Major Secondary Efficacy Endpoint 1	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74,0.99)	0.034*
Major Secondary Efficacy Endpoint 2	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74,0.96)	0.010*
Other Efficacy Endpoints						
Stroke Type	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70,1.03)	0.092
Primary Hemorrhagic Stroke	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37,0.93)	0.024*
Primary Ischemic Stroke	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75,1.17)	0.581
Unknown Stroke Type	7 (0.10)	0.06	11 (0.16)	0.10	0.65 (0.25,1.67)	0.366
Stroke Outcome	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70,1.03)	0.092
Stroke Outcome Death	47 (0.67)	0.42	67 (0.95)	0.59	0.71 (0.49,1.03)	0.075
Disabling Stroke	43 (0.61)	0.39	57 (0.80)	0.50	0.77 (0.52,1.14)	0.188
Nondisabling Stroke	88 (1.25)	0.79	87 (1.23)	0.77	1.03 (0.76,1.38)	0.863
Stroke Outcome Missing Rankin	7 (0.10)	0.06	12 (0.17)	0.11	0.59 (0.23,1.50)	0.271
Non-CNS Systemic Embolism	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09,0.61)	0.003*
Myocardial Infarction	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63,1.06)	0.121
All Cause Mortality	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70,1.02)	0.073
Vascular Death	170 (2.41)	1.53	193 (2.73)	1.71	0.89 (0.73,1.10)	0.289
Non-vascular Death	21 (0.30)	0.19	34 (0.48)	0.30	0.63 (0.36,1.08)	0.094
Unknown Death	17 (0.24)	0.15	23 (0.32)	0.20	0.75 (0.40,1.41)	0.370

Notes: p value is for superiority

Disabling stroke = Modified Rankin score of 3 - 5

There were significant differences favoring rivaroxaban for rates of each of the two Major Secondary Endpoints (MSE). For MSE 1 (time to first event of stroke, non-CNS systemic embolism, and vascular death), event rates were 3.11 and 3.63 per 100 patient-years in the rivaroxaban and warfarin arms, respectively, with a HR of 0.86 (95% CI, 0.74, 0.99, unadjusted p=0.034). For MSE 2 (which is time to MSE1 or myocardial infarction), event rates were 6.13 and 7.33 per 100 patient-years in the rivaroxaban and warfarin arms, respectively, with a HR of 0.86 (95% CI 0.74, 0.96, unadjusted p=0.010). Non-CNS systemic embolism was uncommon but more frequent in the warfarin arm; the event rates were 0.07 and 0.31 per 100 patient-years in the rivaroxaban and warfarin arms, respectively, with a HR of 0.23 (95% CI 0.09, 0.61, unadjusted p=0.003). Rates of stroke (as well as the individual subcategories of primary hemorrhagic stroke, , fatal

stroke, and disabling stroke), MI, all-cause death, vascular death, and non-vascular death, all numerically favored the rivaroxaban arm.

There was a modest and non-significant imbalance of ischemic stroke in favor of rivaroxaban in the on treatment safety population analysis (149 vs. 161 patients with ischemic stroke, 1.34 vs. 1.42 events per 100 patient-years (HR= 0.94, 95% CI 0.75, 1.17)). The difference between the treatment arms in the number and rate of hemorrhagic stroke was considerably larger (29 vs. 50 patients, 0.26 vs. 0.44 events per 100 patient-years (HR= 0.59, 95% CI, 0.37, 0.93)). Thus, the advantage of rivaroxaban over warfarin in terms of strokes on treatment was driven largely by the results for hemorrhagic stroke.

Notably, the modest imbalance noted above in favor of rivaroxaban in ischemic strokes on treatment (149 vs. 161) was reversed in the last dose + 7 day analysis, which followed patients for an additional 5 days: 173 vs. 171 patients with ischemic stroke, 1.54 vs. 1.50 events per 100 patient-years. Thus, the entire advantage of rivaroxaban over warfarin in terms of stroke prevention at this time point (a total of 21 strokes) was due to a reduced rate of hemorrhagic stroke. By contrast, in the ITT analysis of RE-LY, the advantages of dabigatran 150 mg over warfarin for hemorrhagic stroke (a difference of 32 strokes) and ischemic / unknown stroke (a difference in of 31 strokes) were similar in magnitude on an absolute basis.⁹

The statistical plan included a hierarchical analysis plan. Below is a display of the plan, along with symbols depicting success (✓) or failure (X) in the specified analysis (at the level of $p < 0.05$ for non-inferiority or superiority, as specified), starting at the top.

1. ✓ Non-inferiority on the Primary Efficacy Endpoint (based on on-treatment data from the PP population)
 2. ✓ Superiority on the Primary Efficacy Endpoint (based on on-treatment data from the safety population)
 3. ✓ Superiority on Major Secondary Efficacy Endpoint 1 (based on on-treatment data from the safety population)
 4. ✓ Superiority on Major Secondary Efficacy Endpoint 2 (based on on-treatment data from the safety population)
-
5. X Superiority on On-Treatment All-Cause Mortality (based on on-treatment data from the safety population)
 6. X Superiority on All-Cause Mortality (based on the ITT population regardless of treatment exposure)

Note that success in the hierarchy means that there is no increase in alpha error inherent in moving down to the next analysis in the hierarchy. It does not necessarily imply regulatory recognition of the finding for the purposes of labeling.

6.1.7 Subpopulations

6.1.7.1 Subpopulations of the global study population

Results for the primary efficacy endpoint were analyzed in various subgroups of patients, based on geographic region, demographic factors, disease-related factors, and prior medication use. The results in the Per-Protocol population on treatment will be emphasized here.

Figure 26. ROCKET -- Primary Endpoint Results by Patient Subgroup

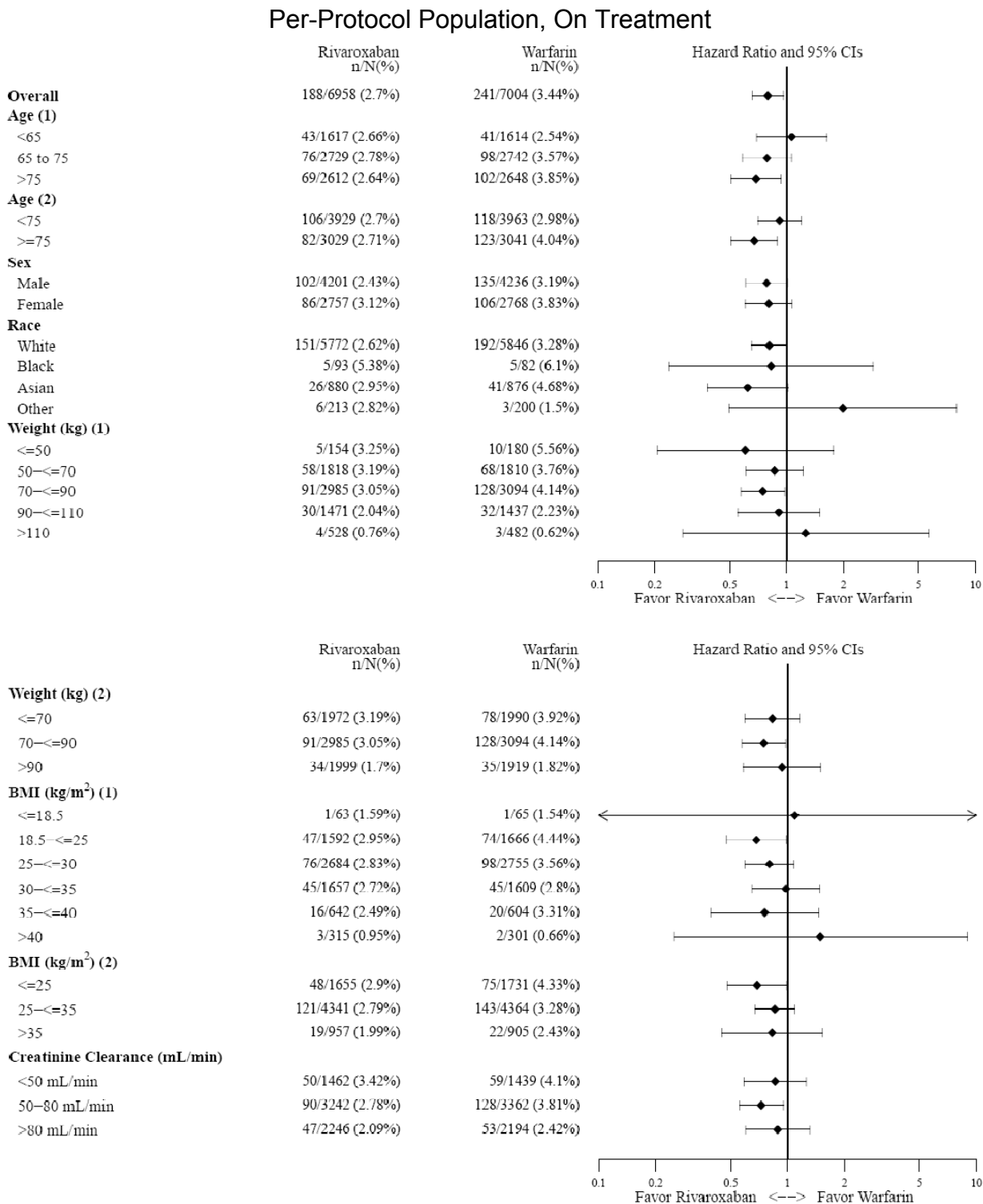
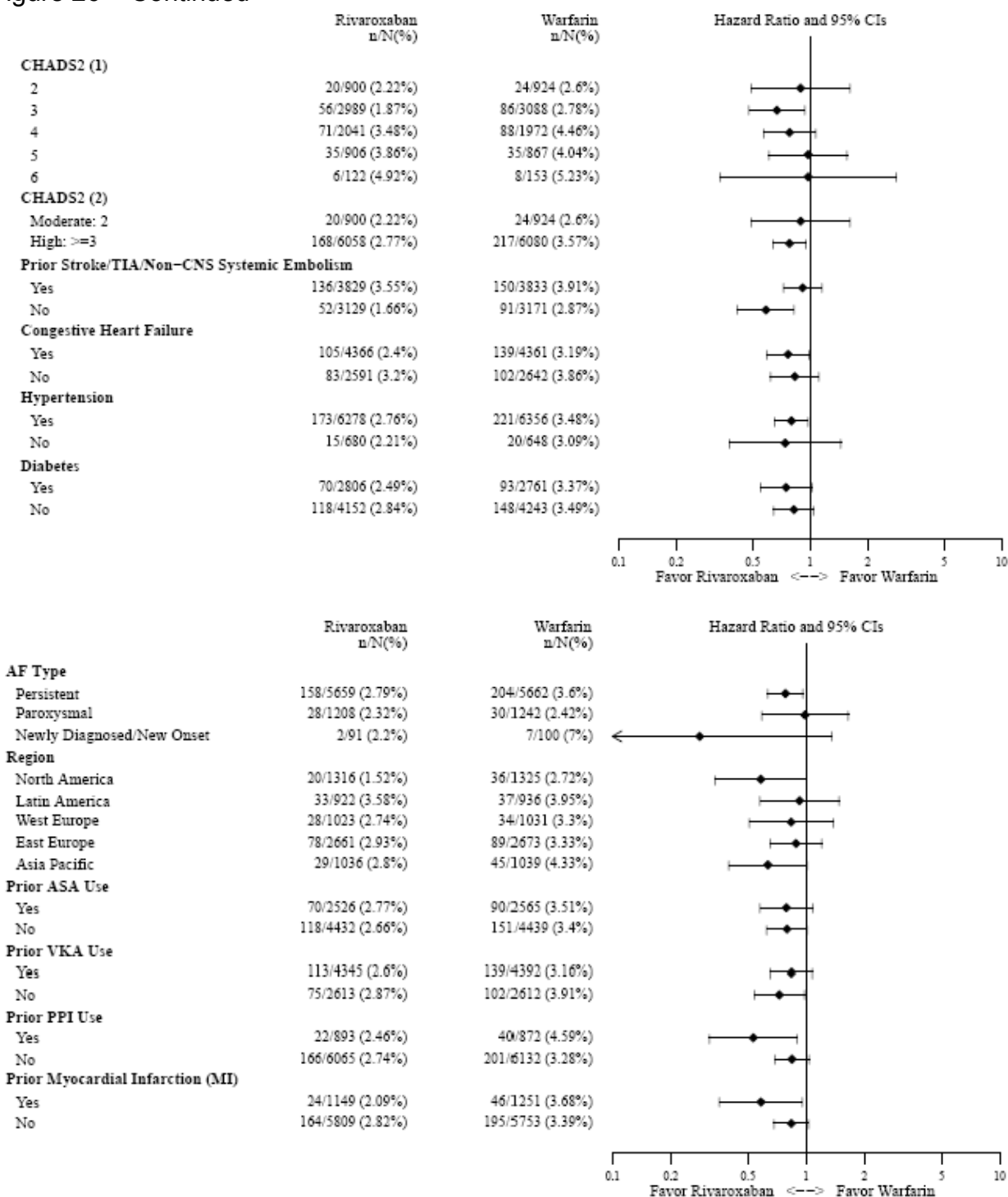


Figure 26 – Continued



Tables of the same data depicted in [Figure 26](#) indicate that the only statistically significant treatment by subgroup interaction was for prior history of stroke, TIA, or non-CNS systemic embolism ($p=0.035$). The point estimate for the hazard ratio of rivaroxaban vs. warfarin was lower in the 45% of patients with no prior history of stroke/TIA/non-CNS systemic embolism than in those with such a history (HR of 0.59 (95% CI 0.42, 0.83) vs. 0.92 (95% CI 0.73, 1.15), but the confidence intervals for the hazard ratios overlap. As expected, event rates were substantially higher in both treatment arms in the stratum of patients with a positive history than in those with a negative history. Data for the two history-based strata are shown below:

Table 37. ROCKET -- Primary Efficacy Endpoint Results – Subgroup Interaction

Effect of Prior History of Stroke/TIA/Non-CNS Systemic Embolism
Per-Protocol Population, On Treatment

Prior History	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	n/N	Event Rate ¹	n/N	Event Rate ¹	Hazard Ratio (95% CI)	p ²
Yes	126 / 3829	2.30	150 / 3875	2.51	0.92 (0.73, 1.15)	0.035
No	52 / 3129	1.03	91 / 3171	1.75	0.59 (0.42, 0.83)	

¹ Events/100 patient-years

² p value is for the treatment by subgroup interaction

The analysis of the effects of baseline renal function is important because subjects with “moderate” renal dysfunction (estimated CrCl 30 to < 50 mL/min) were to be treated with rivaroxaban 15 mg if randomized to rivaroxaban, while patients with CrCl ≥ 50 mL/min were to receive 20 mg rivaroxaban; patients with CrCl < 30 mL/min were excluded. The results, displayed below, show no significant interaction of treatment with renal function ($p=0.632$) and numerical benefit of rivaroxaban over warfarin in all strata, with hazard ratios between 0.73 and 0.88 and broadly overlapping confidence intervals ([Table 38](#)).

Table 38. ROCKET -- Primary Efficacy Endpoint Results – Subgroup Interaction

Effect of Renal Function, Per-Protocol Population, On Treatment

Baseline Estimated CrCl ¹ (mL/min)	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	n/N	Event Rate ²	n/N	Event Rate ²	Hazard Ratio (95% CI)	p ³
< 50	50/1462	2.38	59/1439	2.77	0.86 (0.59, 1.25)	0.632
50 to 80	90/3242	1.75	128/3362	2.41	0.73 (0.55, 0.95)	
> 80	47/2246	1.27	53/2194	1.42	0.88 (0.60, 1.31)	

¹ Creatinine clearance

² Events/100 patient-years

³ p value is for the treatment by subgroup interaction

One might expect a treatment by subgroup interaction in the subgroups of patients with and without a baseline history of VKA use, especially in a study where time in therapeutic range varied widely among regions. However, the hazard ratios for the two subgroups did not differ substantially, the confidence intervals overlapped broadly, and the interaction term was not significant ([Table 39](#)).

Table 39. ROCKET -- Primary Efficacy Endpoint Results – Subgroup Interaction

Effect of Prior VKA Use, Per-Protocol Population, On Treatment

Prior use of VKA	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin		
	n/N	Event Rate ²	n/N	Event Rate ²	Hazard Ratio	(95% CI)	p ³
Yes	114/4401	1.58	140/4437	1.88	0.84	(0.66, 1.08)	0.42
No	75/2660	1.92	103/2645	2.68	0.72	(0.53, 0.97)	

A numerical benefit of rivaroxaban over warfarin was observed in all 5 pre-specified geographic regions (North America, Latin America, Western Europe, Eastern Europe, and Asia Pacific). The hazard ratio was most favorable for rivaroxaban in the North American region, which for the purposes of this study was the US and Canada only. The US results are discussed immediately below.

6.1.7.2 US patients only

6.1.7.2.1 Demographics

Study centers in the US provided 13.5% of patients in the global ITT population. Demographic data are provided in [Table 40](#).

Table 40. ROCKET – US Patients – Key Baseline Demographics And Disease-Related Parameters

(ITT population)

Characteristic	Rivaroxaban N=965	Warfarin N=966	Total N=1931
Male	657 (68.08)	606 (62.73)	1263 (65.41)
Age			
Mean (SD)	74.10 (9.26)	74.27 (8.88)	74.18 (9.07)
≥75 (%)	568 (58.86)	575 (59.52)	1143 (59.19)
Race, N (%)			
White	901 (93.37)	895 (92.65)	1796 (93.01)
Black	44 (4.56)	44 (4.55)	88 (4.56)
Asian	4 (0.41)	3 (0.31)	7 (0.36)
Other	16 (1.66)	24 (2.48)	40 (2.07)
Ethnicity, N (%)			
Hispanic or Latino	32 (3.32)	40 (4.14)	72 (3.73)
Body metrics, Mean (SD)			
Weight (kg)	93.20 (23.50)	91.45 (23.48)	92.32 (23.50)
BMI	31.48 (6.89)	31.48 (14.05)	31.48 (11.06)
Prior VKA use, N (%)			
Yes	871 (90.26)	880 (91.10)	1751 (90.68)
Prior chronic aspirin use, N (%)			
Yes	353 (36.58)	336 (34.78)	689 (35.68)
Creatine clearance, mean (SD) and stratum (mL/min)			
Mean (SD)	79.26 (36.56)	76.13 (37.20)	77.69(36.90)
30 to <50, N (%)	194 (20.12)	209 (21.68)	403 (20.90)
Prior Stroke/TIA/Non-CNS Systemic Embolism, N (%)			
Yes	364 (37.72)	361 (37.37)	725 (37.55)
Prior MI, N (%)			
Yes	227 (23.52)	206 (21.33)	433 (22.42)
Baseline hypertension, N (%)			
Yes	903 (93.58)	911 (94.31)	1814 (93.94)

Baseline diabetes mellitus, N (%)			
Yes	462 (47.88)	465 (48.14)	927 (48.01)
Baseline heart failure, N (%)			
Yes	533 (55.29)	511 (52.90)	1044 (54.09)
Baseline CHADS ₂ Score			
Mean (SD)	3.32 (0.99)	3.31 (0.98)	3.32 (0.99)
Median	3.0	3.0	3.0
Score, N (%)			
2	200 (20.73)	189 (19.57)	389 (20.15)
3	402 (41.66)	431 (44.62)	833 (43.14)
4	234 (24.25)	227 (23.50)	461 (23.87)
5	108 (11.19)	94 (9.73)	202 (10.46)
6	21 (2.18)	25 (2.59)	46 (2.38)

Overall, the US population differed somewhat from the global population. US patients were older; with a mean age of 74 vs. 71 years, and a larger percentage of US patients were at least 75 years old, 59% vs. 44%. This would suggest higher risk for stroke. A greater percentage of US patients were men, 65% vs. 60%. This might tend to reduce stroke risk in the US population, as female gender has been identified as a risk factor for stroke in AFib patients, and is element of the CHA₂DS₂-VASc (Birmingham) score.³ Mean BMI was also higher in the US, 31.5 vs. 29.0. Baseline VKA use was substantially higher in the US, 91% vs. 62%, suggesting that INR control might be better in the warfarin arm due to established warfarin control for a higher percentage of individual patients as well the likelihood of greater familiarity and skill in warfarin use by US investigators, compared to investigators globally. The percentage of patients with the classic stroke risk factors of hypertension, and diabetes (considered separately) were each higher in the US than globally, suggesting greater stroke risk (94% vs. 90% and 48% vs. 40%, respectively). However, there was a lower percentage of heart failure patients in the US, 54% vs. 62%. Notably, fewer patients in the US had a prior history of stroke/TIA/systemic embolism, 38% vs. 55%, suggesting a substantially reduced risk of stroke. The mean baseline CHADS₂ score was lower in the US, 3.3 vs. 3.5, and a substantially greater percentage of patients had a CHADS₂ score of 2, 20% vs. 13%, also suggesting a reduced stroke risk. Note that no US patients entered the study with a CHADS₂ score less than 2.

In the subpopulation of US patients, the treatment arms were well-balanced for most demographic and disease-related factors that might influence study outcomes. There was one notable exception: the percentage of women was lower in the rivaroxaban arm than in the warfarin arm, 32% vs. 37%. As noted in the previous paragraph, female

gender has been identified as a risk for stroke in AFib patients, and the observed imbalance would tend to favor the rivaroxaban arm.

Thus, although not all relevant risk factors trended in the same direction, several important ones, the percentage of patients with a prior history of stroke/TIA/systemic embolism, the distribution of CHADS₂ scores, and the percentage use of VKA at baseline, suggested that the overall risk for the primary endpoint would be lower in the US than globally. With regard to differences between the treatment arms in the US, the lower percentage of female patients in the rivaroxaban arm compared to the warfarin arm would tend to favor the former in terms of stroke risk.

6.1.7.2.2 Disposition

Information on patients who discontinued treatment early is found in [Table 41](#). About 43% of US patients discontinued study drug early, compared to about 35% globally. The most common reason for early discontinuation of study medication was an adverse event (22% vs. 18% in the rivaroxaban and warfarin arms, respectively). Bleeding AEs were more commonly associated with discontinuation in the rivaroxaban arm (8.4% vs. 4.5%). About 9% of patients in each arm withdrew consent for continuing with study medication. More warfarin arm subjects discontinued because a clinical efficacy endpoint had been reached (3.2% vs. 4.0%).

Table 41. ROCKET – US Patients - Reasons For Early Discontinuation Of Study Drug

(Prior to Site Notification to Schedule End-of-Study Visits, Safety Population)

Status Discontinuation Reason	Rivaroxaban (N=962) n (%)	Warfarin (N=964) n (%)	Total (N=1926) n (%)
Completed Study Medication	546 (56.76))	556 (57.68)	1102 (57.22)
Early Study Medication Discontinuation	416 (43.24)	408 (42.32)	824 (42.78)
Adverse Event	213 (22.14)	169 (17.53)	382 (19.83)
-Bleeding	81 (8.42)	43 (4.46)	124 (6.44)
-Non-bleeding	132 (13.72)	126 (13.07)	258 (13.40)
Non-Compliant with Study Medication	17 (1.77)	26 (2.70)	43 (2.23)
Consent Withdrawn	85 (8.84)	90 (9.34)	175 (9.09)
Investigator Decision, Not Protocol Related	35 (3.64)	44 (4.56)	79 (4.10)
Lost to Follow-Up	1 (0.10)	0	1 (0.05)
Protocol Violation	27 (2.81)	26 (2.70)	53 (2.75)
Clinical Efficacy Endpoint Reached	31 (3.22)	39 (4.05)	70 (3.63)
Study Terminated by Sponsor	6 (0.62)	14 (1.45)	20 (1.04)
Missing/Incomplete Data	1 (0.10)	0	1 (0.05)

[Table 42](#) provides information on patients who discontinued follow-up early. The number of such patients is considerably smaller than those who discontinued study drug. Overall, excluding patients who died, about 8.8% and 8.3% of US patients discontinued follow-up early in the rivaroxaban and warfarin arms, respectively, compared to about 7% globally. US death rates during the trial (11-12%) were higher than global death rates (8-9%).

Table 42. ROCKET – US Patients - Reasons For Early Discontinuation Of Follow-Up

(Prior to Site Notification, Safety Population)

Status Discontinuation Reason	Rivaroxaban (N=962) n (%)	Warfarin (N=964) n (%)	Total (N=1926) n (%)
No Early Discontinuation of Follow-up	771 (80.15)	772 (81.02)	1554 (80.69)
Early Discontinuation of Follow-up	191 (19.85)	192 (19.92)	383 (19.89)
Death	106 (11.02)	112 (11.62)	218 (11.32)
Discontinued Follow-up Alive	85 (8.84)	80 (8.30)	165 (8.57)
Consent Withdrawn	63 (6.55)	56 (5.81)	119 (6.18)
Lost to Follow-up	1 (0.1)	0	1 (0.05)
Other	21 (2.18)	24 (2.49)	45 (2.34)

Thus, the number of patients effectively lost to follow-up alive, and thus not available for ascertainment of endpoint events, was slightly larger in the rivaroxaban arm (85 vs. 80).

6.1.7.2.3 Efficacy results

The US data for control of INR were better than the global results. Mean overall (imputed) INR was 63.29%, and the median was 65.13%. About 20.34% of days on warfarin were associated with INR values < 2.0, including 3.45% of days associated with values < 1.5. About 16.37% of days were associated with INR values > 3.0, including 10.18% of days, with INR values >3.2 to 5 and 0.68% of days with values > 5.0.

Efficacy results for the US population are shown in [Table 43](#).

Table 43. US Patients – Efficacy Results For Primary Endpoint

Population and Event Window	Rivaroxaban		Warfarin		HR (95% CI)
	n/N	Event Rate ¹	n/N	Event Rate ¹	
Per Protocol, On Treatment	15 / 950	0.95	29 / 956	1.76	0.54 (0.29,1.01)
Per Protocol, Last Dose + 30 Days	24 / 950	1.46	34 / 956	1.99	0.74 (0.44,1.24)
Safety, On Treatment	15 / 962	0.94	29 / 964	1.75	0.54 (0.29,1.01)
Safety, Last Dose + 7 Days	20 / 962	1.24	31 / 964	1.86	0.67 (0.38,1.18)
Safety, Last Dose + 14 Days	21 / 962	1.29	34 / 964	2.02	0.64 (0.37,1.11)
Safety, Last Dose + 30 Days	24 / 962	1.44	34 / 964	1.97	0.73 (0.44,1.24)
ITT - Follow-Up Visit	25 / 965	1.48	35 / 966	2.0	0.74 (0.44,1.24)
ITT - Site Notification	34 / 965	1.78	41 / 966	2.12	0.84 (0.53,1.32)
ITT - Regardless of Treatment Exposure	36 / 965	1.81	42 / 966	2.09	0.87 (0.56,1.35)

¹ Events per 100 pt-years.

All the displayed analyses, including the ITT analysis regardless of treatment exposure, favor rivaroxaban. The on treatment (last dose + 2 days) analyses strongly favor rivaroxaban, each with an HR of 0.54 and a CI that barely crosses 1.0. The rivaroxaban event rate in those analyses is less than 1 per 100 patient years, but increases (and eventually nearly doubles in the rivaroxaban arm in the ITT/regardless of treatment exposure analysis, with a much smaller increase in the warfarin arm. The ratios for the event rates for the ITT/regardless of treatment exposure over the safety/on treatment analysis were 1.93 and 1.19, in the rivaroxaban and warfarin arms, respectively. This indicates that a substantially higher percentage of patients in the rivaroxaban arm had post-discontinuation primary efficacy events.

In the safety population, there were 14 primary endpoint events that occurred in the 28 days between the of the on treatment period (last dose + 2 days) and the last dose + 30 days; 9 and 5 of these events occurred in rivaroxaban and warfarin arm patients, respectively. All of but one of these post-treatment events occurred in patients who discontinued treatment early; the one completing patient with a post-treatment primary endpoint event was in the rivaroxaban arm.

Results for secondary endpoint analyses are shown in [Table 44](#). Results for the two major secondary endpoints (defined in the table), strokes (all types combined), fatal strokes, hemorrhagic stroke, ischemic stroke, systemic emboli, MI, all-cause mortality, vascular death and non-vascular death all favor rivaroxaban, although some only slightly. All-cause mortality, death of unknown cause, and disabling stroke rates favor warfarin.

Table 44. US Patients – Efficacy Results For Secondary Endpoints

Safety Population, On Treatment

Population and Event Window	Rivaroxaban N=962		Warfarin N=964		HR (95% CI)
	n (%)	Event Rate ¹	n (%)	Event Rate ¹	
Major Secondary Efficacy Endpoint 1 ¹	30 (3.12)	1.88	46 (4.77)	2.77	0.68 (0.43, 1.08)
Major Secondary Efficacy Endpoint 2 ²	50 (5.20)	3.15	70 (7.26)	4.28	0.74 (0.51, 1.06)
All Strokes	14 (1.46)	0.88	24 (2.49)	1.45	0.61 (0.32, 1.18)
Primary Hemorrhagic Stroke	6 (0.62)	0.38	8 (0.83)	0.48	0.79 (0.27, 2.28)
Primary Ischemic Stroke	8 (0.83)	0.5	16 (1.66)	0.96	0.52 (0.22, 1.22)
Unknown Stroke Type	0	0	0	0	-
Stroke Outcome Death	4 (0.42)	0.25	11 (1.14)	0.66	0.38 (0.12, 1.20)
Disabling Stroke	5 (0.52)	0.31	4 (0.41)	0.24	1.30 (0.35, 4.85)
Non-disabling Stroke	4 (0.42)	0.25	7 (0.73)	0.42	0.60 (0.18, 2.04)
Stroke Outcome Missing Rankin	1 (0.10)	0.06	2 (0.21)	0.12	0.52 (0.05, 5.77)
Non-CNS Systemic Embolism	1 (0.10)	0.06	5 (0.52)	0.3	0.21 (0.02, 1.77)
Myocardial Infarction	22 (2.29)	1.39	24 (2.49)	1.46	0.95 (0.53, 1.69)
All-Cause Mortality	26 (2.70)	1.63	28 (2.90)	1.69	0.97 (0.57, 1.65)
Vascular Death	17 (1.77)	1.06	20 (2.07)	1.2	0.88 (0.46, 1.69)
Non-vascular Death	3 (0.31)	0.19	5 (0.52)	0.3	0.62 (0.15, 2.59)
Unknown Death	6 (0.62)	0.38	3 (0.31)	0.18	2.08 (0.52, 8.33)

¹ Composite of stroke, TIA, systemic embolism and vascular death

² Composite of stroke, TIA, systemic embolism, vascular death and MI

In summary, the US results for primary efficacy endpoint strongly favored rivaroxaban on treatment. Secondary endpoint results on treatment are mixed. There was a marked excess of post-treatment primary endpoint events in the rivaroxaban arm compared to warfarin. However, all analyses of the primary endpoint starting at randomization, regardless of patient population and data cutoff, numerically favored rivaroxaban.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen of rivaroxaban was evaluated in ROCKET, the sole study supporting efficacy for the proposed indication. The regimen was 20 mg rivaroxaban

once daily for patients with baseline CrCl ≥ 50 mL/min and 15 mg rivaroxaban for patients with baseline CrCl 30 to < 50 mL/min; study drug was to be taken by mouth in the evening with food. There is no information in the NDA on the effects of other dosing regimens on the outcomes of interest in patients with atrial fibrillation other than the results of J ROCKET. However these results are not useful in understanding the appropriate dose to be used in the US due to the design of J ROCKET, as discussed in Section 5.3.2.

As noted below, there is information from the sponsor's development program for other indications suggesting that twice daily dosing may have efficacy and safety advantages to once daily dosing at same total daily dose.

The dosing regimen proposed for use is similar to the ROCKET dosing regimen. The sponsor states that two dose-ranging Phase 2 venous thromboembolism (VTE) treatment studies, ODIXa-DVT (11223) and Einstein-DVT (11528) support the ROCKET dosing regimen. The sponsor's rationale for proceeding forward with the 20 mg once daily dose in ROCKET was summarized in the ISS of this submission by the following points:

- 11223 (ODIXa-DVT) assessed safety, tolerability, and efficacy of rivaroxaban at oral doses of 10, 20, and 30 mg twice-daily and 40 mg once-daily compared with enoxaparin/vitamin K antagonist (VKA)
- Study 11528 (EINSTEIN DVT) assessed safety, tolerability, and efficacy of rivaroxaban at oral doses of 20, 30, and 40 mg once-daily compared with low molecular weight heparin (LMWH)/VKA
- The relative safety in terms of bleeding compared to the within-study standard of care was better for all once-daily regimens compared to the twice-daily regimens for which a trend toward slightly increased risk of bleeding was observed for the 20 mg and the 30 mg doses
- The 10 mg twice-daily dose in study 11223 was comparable to the once-daily doses in Study 11528 in terms of safety
- Dose-finding studies in patients with AFib may not be feasible as they carry a high risk of stroke for patients with potentially too low doses of the investigational anticoagulant
- Based on these clinical observations, it was concluded that the lowest once-daily dose studied, 20 mg, should be selected for the proposed Phase 3 SPAF study ROCKET, with a down-dosing to 15 mg daily for patients with CrCl 30 to < 50 mL/min to achieve an equivalent exposure in patients with moderately depressed renal function.

However, at the time of FDA's 2006 review of the proposed ROCKET protocol, the rationale for dose selection was of concern. It was noted that there is a direct linear relationship between serum concentrations of rivaroxaban expected in patients at the doses used in ROCKET and prothrombin time, as well as an inverse curvilinear relationship between rivaroxaban concentrations in this range and FXa activity (see section 4.4.3, pharmacokinetics). In the September 2006 advice letter to the sponsor regarding the ROCKET trial design, based on the PK, PD, and Clinical outcomes data, the clinical pharmacology reviewer noted the following:

“Both Factor 10a inhibition and prothrombin time show a dependency on the plasma concentration of the drug. What degree of Factor Xa inhibition and prothrombin prolongation does the sponsor consider to be effective and safe? This information would be crucial for determining the appropriate dose and interval to be used for the Phase 3 trial.”

FDA requested that the sponsor justify the 20-mg daily dose selected by the sponsor for testing in ROCKET.

The sponsor claims that in study 11223, the only study in which once daily and twice daily regimens at the same total dose were compared (40 mg), all total daily doses (20 to 60 mg) were associated with comparable safety and efficacy. Efficacy and safety data from this study are displayed in

Table 45 and Table 46, respectively. The efficacy data are not consistent with the sponsor's claims, in that the response rate (percentage of patients improved) is somewhat higher in the 20 mg bid arm than in the 40 mg od arm (59% vs. 44%, respectively). In fact, the 40 mg od arm had the lowest response rate of the 5 study arms (Table 45). The rate of major bleeding was similar in the 20 mg bid and 40 mg od arms (1.7% in each arm), and the overall rate of bleeding was slightly less in the 20 mg bid arm (9.4% vs. 11.6%). The 10 mg bid arm had the lowest rates of major bleeding and overall bleeding (5% and 1.7%, respectively, Table 46).

Table 45. DVT Treatment Study 11223 – Efficacy Results

	Rivaroxaban				Enox/ VKA (N = 109)
Overall response at Week 12 ¹	10 mg bid (N = 100)	20 mg bid (N = 98)	40 mg od (N = 112)	30 mg bid (N = 109)	
Improved	53 (53%)	58 (59%)	49 (44%)	62 (57%)	50 (46%)
Unchanged	46 (46%)	39 (40%)	63 (56%)	47 (43%)	59 (54%)
Deterioration	0	0	0	0	0
Missing	1 (1%)	1 (1%)	0	0	0

Source: Table 5-29 of Investigator brochure from original IND 75,238 submission (dated 13 June 2006).

¹ For the primary endpoint: the response to treatment (i.e., thrombus regression) as determined by compression ultrasound (CUS) after 3 weeks of treatment

Table 46. DVT Treatment Study 11223 – Safety Results

	Rivaroxaban				Enox/ VKA (N = 126)
	10 mg bid (N = 119)	20 mg bid (N = 117)	40 mg od (N = 121)	30 mg bid (N = 121)	
Any bleeding event	6 (5%)	11 (9.4%)	14 (11.6%)	13 (10.7%)	8 (6.3%)
Major bleeding	2 (1.7%)	2 (1.7%)	2 (1.7%)	4 (3.3%)	0

Source: Table 5-31, Investigator brochure in original IND 75,238 submission (dated 13 June 2006).

Our concerns about the efficacy results of 11223 and their implications for ROCKET dosing regimen were communicated to the sponsor. At the EOP2 meeting held on Sept. 12, 2006, the sponsor requested our agreement with the rivaroxaban dosing regimen proposed for use in ROCKET (which was the regimen later used in the trial). In our response in the EOP2 meeting minutes, we stated: “In study 11223, there was some

suggestion that a twice daily dosing regimen was more effective compared to a once daily dosing regimen. Please provide your rationale for a once daily dosing regimen.”
The sponsor has not provided information to allay concerns.

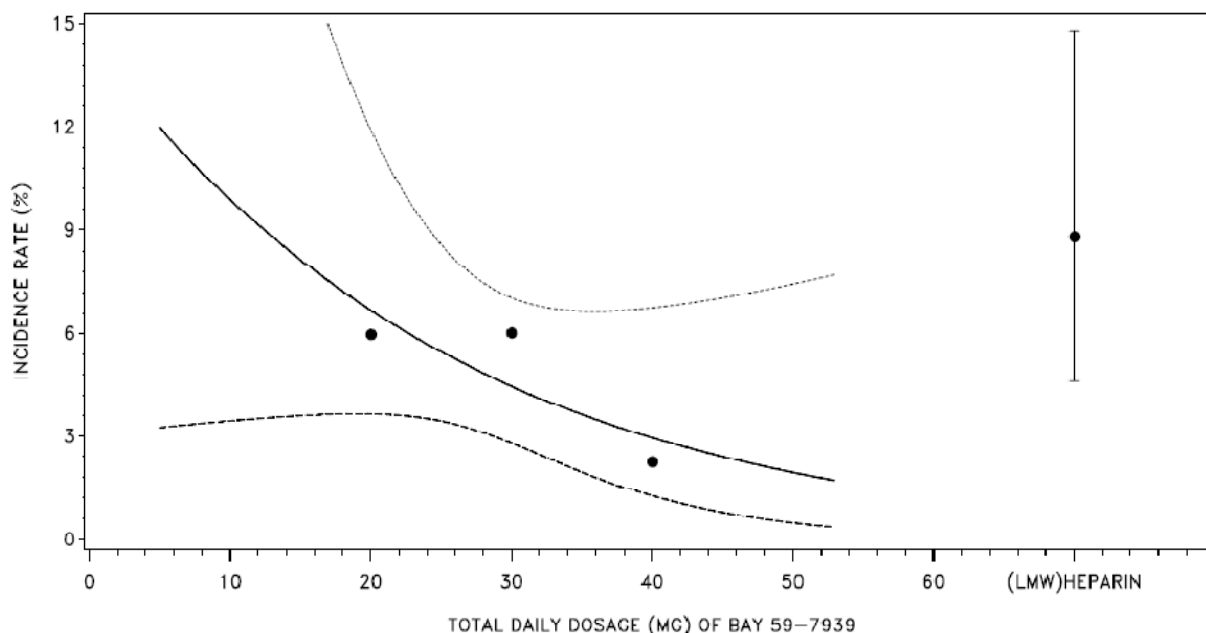
The sponsor claims in the ISS that “The relative safety in terms of bleeding compared to the within-study standard of care was better for all once-daily regimens compared to the twice-daily regimens for which a trend toward slightly increased risk of bleeding was observed for the 20 mg and the 30 mg doses. The 10 mg twice-daily dose in study 11223 was comparable to the once-daily doses in Study 11528 in terms of safety.” However, in the cited studies, the only twice daily regimen were in study 11233, where single comparison of once to twice daily dosing at the same total favored twice daily in terms of efficacy and leaned slightly toward favoring twice daily dosing in terms of safety. Efficacy and safety information from Study 11528 are displayed in [Table 47](#) and [Figure 27](#), respectively.

Reviewer Comment: The within-study comparison, which favors twice daily dosing is more relevant to dose selection than the sponsor’s cross-study comparison.

Table 47. DVT Treatment Study 11528 – Efficacy Results

	Rivaroxaban			LMWH/ VKA N=101
	20 mg od N=115	30 mg od N=112	40 mg od N=121	
Incidence (%) ¹	6.1	5.4	6.6	9.9
95% CI (%)	2.5, 12.1	2.0, 11.3	2.9, 12.6	4.9, 17.5
¹ Of primary endpoint: the composite of symptomatic recurrent DVT or fatal and non-fatal PE at Week 12 and deterioration in thrombotic burden, as assessed by ultrasonography and perfusion lung scan at baseline and at Week 12.				

Figure 27. DVT Treatment Study 11528 – Safety Results



Source: Clinical Pharmacology Review

Reviewer Comment: In addition to the foregoing, the Clinical Pharmacology Review of September 2006 indicated that there was a flat efficacy and safety dose response relationship for doses of 2.5, 5, 10, 20 and 30 mg bid and 5, 10, 20, 30 and 40 mg od in VTE prevention trials. The sponsor was asked to explain why 5 mg bid was not being considered for Phase 3 trials. However, trough levels with this regimen might be as low as with 20 mg once daily, which might be problematic in terms of prevention of thrombosis.

Information from the ACS development program for ROCKET is also relevant to the issue of the merits of once vs. twice daily dosing. ATLAS TIMI 46 (Protocol 39039039ACS2001-11898) was a phase 2, multicenter, randomized, double-blind, placebo-controlled dose-finding study in recent (i.e. with symptoms within 7 days) ACS patients (STEMI, NSTEMI, or UA) taking concomitant ASA or ASA + a thienopyridine. The study used a dose escalation design based on total daily dose. The study had two planned phases, but Phase 2 was not performed. Phase 1, had a dose escalation design. The initial rivaroxaban total daily dose (TDD) was 5 mg/day. Patients were randomized 1:1:1 to placebo, once daily (OD) rivaroxaban, or BID rivaroxaban at the assigned total daily dose for a 6 month treatment period, with a final follow-up at seven months. Randomization was stratified by the intent to use thienopyridine therapy. Dose escalation decisions were made by an unblinded, "independent" Operations Committee that reviewed the study data after the follow-up visit. Subsequent TDD levels were planned to be 10 mg and then 20 mg, with the same randomization scheme as at a TTD

of 5 mg. Initially 225 patients were to be randomized at each TTD level, but the decision was made to expand Phase 1 and drop Phase 2, which was intended to be the dose confirmation phase.

The primary efficacy endpoint was the time to the EC adjudicated composite of all-cause death, MI, or stroke (ischemic, hemorrhagic or unknown) or severe recurrent ischemia requiring revascularization through 6 months. The composite of ACD, MI or stroke was one of several secondary endpoints.

The primary safety endpoint was the incidence of clinically significant bleeding, defined as:

- TIMI Major bleeding,
- TIMI Minor bleeding
- Bleeding requiring medical attention not satisfying the requirements of TIMI Major or Minor bleeding

A total of 3491 patients were randomized, 761 in stratum 1 (concomitant ASA alone) and 2730 in stratum 2 (ASA + thienopyridine). Efficacy results are for all randomized patients followed for 6 months; safety data are for the safety population; varying data cutoffs were used.

Data for the composite of death, MI, and stroke are shown in [Table 48](#) and [Table 49](#).

Table 48. ATLAS-ACS TIMI 46 – Rates Of MACE ¹

ITT population followed for 6 months

	n/N (%)	HR vs. placebo (95% CI)	HR for OD vs. BID (95% CI)
STRATUM 1 ²	<i>(Concomitant ASA)</i>		
Pooled Placebo	29/253 (11.5)	--	--
ALL OD rivaroxaban	17/254 (6.7)	0.54 (0.31,0.95)	0.95 (0.49,1.85)
ALL BID rivaroxaban	18/254 (7.1)	0.60 (0.35,1.03)	
STRATUM 2 ²	<i>(Concomitant ASA + Thienopyridine)</i>		
Pooled Placebo	37/907 (4.1)	--	--
ALL OD rivaroxaban	37/912 (4.1)	1.00 (0.63,1.57)	1.27 (0.78,2.07)
ALL BID rivaroxaban	29/911 (3.2)	0.78 (0.48,1.27)	
POOLED STRATA			
Pooled Placebo	66/1160 (5.7)	--	--
ALL OD rivaroxaban	54/1166 (4.6)	0.81 (0.56,1.16)	1.15 (0.78,1.7)
ALL BID rivaroxaban	47/1165 (4.0)	0.70 (0.48,1.02)	

¹ Time to the composite of all-cause death, stroke or MI

² Stratum 1 is patients taking concomitant ASA; Stratum 2 is patients taking concomitant ASA + a thienopyridine.

Table 49. ATLAS ACS TIMI 46 – Rates Of MACE

TDD	Pooled placebo KM rate (n/N)	Once daily dosing		Twice daily dosing	
		KM rate (n/N)	HR (95% CI)	KM rate (n/N)	HR (95% CI) ²
Pooled Strata					
5 mg	5.5% (62/1160)	6.7% (10/155)	0.90 (0.46–1.78)	4.0% (6/153)	0.52 (0.23–1.22)
10 mg	5.5% (62/1160)	3.9% (20/529)	0.74 (0.45–1.22)	3.0% (15/527)	0.56 (0.32–0.98)
20 mg	5.5% (62/1160)	2.8% (8/304)	0.46 (0.22–0.95)	4.1% (12/307)	0.69 (0.37–1.28)
Stratum 1					
5 mg	11.9% (29/253)	9.4% (7/77)	0.80 (0.35–1.82)	6.6% (5/77)	0.54 (0.21–1.40)
10 mg	11.9% (29/253)	7.3% (7/99)	0.62 (0.27–1.41)	6.7% (6/97)	0.54 (0.22–1.29)
20 mg	11.9% (29/253)	2.7% (2/78)	0.21 (0.05–0.88)	6.7% (5/80)	0.52 (0.20–1.36)
Stratum 2					
5 mg	3.8% (33/907)	4.0% (3/78)	1.04 (0.32–3.39)	1.4% (1/76)	0.35 (0.05–2.58)
10 mg	3.8% (33/907)	3.2% (13/430)	0.84 (0.44–1.59)	2.2% (9/430)	0.58 (0.28–1.21)
15 mg	3.8% (33/907)	4.0% (7/178)	1.07 (0.47–2.42)	5.3% (9/178)	1.42 (0.68–2.97)
20 mg	3.8% (33/907)	2.8% (6/226)	0.73 (0.31–1.74)	3.2% (7/227)	0.86 (0.38–1.94)

¹ Time to the composite of all-cause death, stroke, or MI

² Rivaroxaban vs. placebo

Source: Mega et al.¹⁰

The data in [Table 48](#) show numerical superiority for twice daily dosing over once daily dosing at the same TDD for the pooled strata. The data in [Table 49](#) suggest a flat dose response curve for the MACE endpoint in stratum 2 over TDD from 5 mg to 20 mg. In Stratum 1, there was a strong trend indicating improved responses as dose increased to 20 mg. However, there was a substantially increased risk of bleeding above a TDD of 10 mg. Rates for clinically significant bleeding at TIMI 46 are shown in [Table 50](#).

Table 50. ATLAS ACS TIMI 46 – Rates Of Clinically Significant Bleeding

TDD	Pooled placebo KM rate (n/N)	Once daily dosing		Twice daily dosing	
		KM rate (n/N)	HR (95% CI) ¹	KM rate (n/N)	HR (95% CI) ¹
Pooled Strata					
5 mg	3.3% (37/1153)	7.4% (11/155)	2.73 (1.38–5.37)	4.8% (7/152)	1.71 (0.76–3.85)
10 mg	3.3% (37/1153)	10.8% (55/527)	3.35 (2.21–5.09)	11.0% (55/519)	3.36 (2.21–5.09)
20 mg	3.3% (37/1153)	16.0% (47/301)	5.32 (3.46–8.18)	14.6% (43/302)	4.80 (3.09–7.45)
Stratum 1					
5 mg	1.7% (4/252)	2.9% (2/77)	1.67 (0.31–9.14)	1.4% (1/77)	0.81 (0.09–7.23)
10 mg	1.7% (4/252)	7.6% (7/99)	4.74 (1.39–16.19)	5.5% (5/96)	3.40 (0.91–12.65)
20 mg	1.7% (4/252)	10.6% (8/78)	6.69 (2.01–22.21)	10.7% (8/79)	6.43 (1.94–21.37)
Stratum 2					
5 mg	3.8% (33/901)	11.7% (9/78)	3.28 (1.57–6.84)	8.2% (6/75)	2.17 (0.91–5.18)
10 mg	3.8% (33/901)	11.6% (48/428)	3.21 (2.06–5.00)	12.2% (50/423)	3.34 (2.15–5.19)
15 mg	3.8% (33/901)	13.1% (23/178)	3.69 (2.17–6.29)	12.3% (21/175)	3.41 (1.97–5.89)
20 mg	3.8% (33/901)	17.8% (39/223)	5.12 (3.22–8.14)	16.0% (35/223)	4.56 (2.83–7.33)

¹ Rivaroxaban vs. placebo
Source: Mega et al.¹⁰

There was more bleeding in stratum 2 than stratum1, and there was a dose response for bleeding in both strata. Differences between once and twice daily dosing were generally not marked, but favored BID dosing for the 5 mg dose and the 20 mg dose in both strata.

Based on these data, the doses chosen for evaluation in the placebo-controlled Phase 3 ACS trial (ATLAS-ACS 2 TIMI 51) were rivaroxaban 2.5 mg bid and 5 mg bid.¹¹

Thus the information from ACS studies (where rivaroxaban is given to prevent arterial circulation thrombotic events, as in ROCKET) is consistent with the data from the VTE studies suggesting that bid dosing may have a better benefit/risk profile than once daily dosing at the same TDD.

Dose in renal failure patients and other subgroups: Based on PK modeling, subjects with CrCl between 30 and 49 mL/min taking 15 mg daily would have similar exposure to those with normal renal function taking 20 mg daily, so 15 mg daily was in ROCKET patients with CrCl 30 to < 50 mL/min.

In the ISE, in Section 4, the sponsor argues that the ROCKET results demonstrate the efficacy of the rivaroxaban 20/15 mg once daily regimen overall, and that results were not dependent on age, gender, race, BMI, body weight, baseline CHADS₂ score, or history of prior stroke, TIA or non-CNS systemic embolism. Accordingly, there would be no need to adjust the dose for any of these factors. As was done in ROCKET, rivaroxaban should be taken with food to augment absorption.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan Meier curve for time to the primary efficacy endpoint in ROCKET suggests that efficacy is maintained with continued treatment for over to 3 years ([Figure 24](#)).

There is no diminution of the apparent treatment effect during the on-treatment period as the study progressed to its end. However, there was an excess of events in the rivaroxaban arm when study treatment was discontinued (see [Section 6.1.10.3](#)).

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Constancy assumption issues

[Table 51](#) provides information on the demographics, control of INR in the warfarin arm, and results of the six published placebo controlled trials of warfarin therapy in atrial fibrillation patients at risk for stroke and systemic embolism. These studies were conducted in the 1990s. In five of these studies, most (> 90%) of patients did not have a prior history of stroke. In the sixth, the EAFT study, 100% of patients had a prior history of recent stroke or TIA; 76% of these had had a stroke. No CHADS₂ score data are available for the historical studies.

The table indicates that the studies utilized a broad range of INR targets. In the US studies, INR had not yet been adopted widely, and the INR target (and its attainment) was back-calculated from the PT target and the assumed ISI of the thromboplastin used in the PT assay. The INR target range of ROCKET, 2.0 to 3.0, falls within the range of INR targets for the placebo-controlled trials. Similarly, the mean time in therapeutic range, 55%, falls within the range of mean TTR or % of INRs in range in the placebo controlled trials. Thus, it seems that constancy holds for the issue of control of anticoagulation as an isolated question. Moreover, the upper boundary of the 95% CI of the hazard ratio for the primary endpoint was not more than 1.08 in any of the analyses of the overall study results, meaning that the finding of non-inferiority margin was quite robust.

Table 51. ROCKET vs. 6 Placebo-Controlled Warfarin Trials

Selected Parameters

Study name and agents compared → Study Parameter 1	ROCKET (rivaroxaban vs. W) ¹	5 Primary Prevention Studies (W vs. placebo)	EAFT (W vs. placebo)
N (ITT)	14,171	2461	439
% female	40	0-47	43
% with h/o stroke/TIA/SE	55	6	100
Target INR (range)	2.5 (2.0-3.0)	(1.4-2.8 to 2.0-4.5)	(2.5-4.0)
Mean TTR or % in range*	55	42-83	59*
Endpoint	Stroke + SE	Ischemic stroke to Stroke + TIA + SE	Stroke
Event Rate Warfarin	2.42	0.62 - 3.08	4
Event Rate Rivaroxaban or Placebo	2.12	2.99 – 8.20	12
HR (95% CI)	0.88 (0.74, 1.03)	0.21 – 0.65	0.34 (0.20, 0.57)
FDA meta-analysis of 6 placebo-controlled studies (random effects model) --		HR for W vs. Placebo = 0.36 (0.24, 0.53)	

¹ ROCKET event rates and hazard ratio are for ITT population, with event window up to site notification

The question of constancy for the patient population is less clear. In ROCKET, 55% of patients had a prior history of stroke, TIA or systemic embolism; a stroke history was the most common in these patients. Of the historical trials, only EAFT had a population with more than 10% of patients with such a history. The hazard ratio for the effect of warfarin vs. placebo on stroke for EAFT was in line with the 5 other trials. However, the INR target for warfarin in EAFT was high, 2.5 to 4.0, and the mean INR overall was 2.9; it was 2.4 in ROCKET. One could question whether patients with a prior history of stroke or TIA were somewhat under-anticoagulated in ROCKET. Nonetheless, the event rate in the ROCKET warfarin arm was about 2.4%, in the range of the event rates in the primary prevention trials (~1-3%) other trials, and lower than the warfarin arm event rate in EAFT (4%). It was much lower than the placebo arm event rate in EAFT (12%). This suggests that the efficacy of warfarin was substantially maintained in ROCKET, and supports the conclusion that rivaroxaban was non-inferior to warfarin as it was used in this study.

6.1.10.2 Adequacy of comparator

6.1.10.2.1 Standards for approval of therapies to prevent stroke

However, non-inferiority to warfarin as it was used in ROCKET may not enough to support approval an additional product to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation. There are already two product indicated for this use: warfarin and dabigatran. The availability of other approved products for the target indication of rivaroxaban brings into play an Agency policy described in a 1995 Federal Register notice regarding several issues relating to FDA's evaluation of efficacy.⁵ The notice explains that in general, drug and devices usually are required to show superiority to placebo, without regard to comparisons to other approved products. However, the notice describes an important exception related to risk of harm:

“In certain circumstances, however, it may be important to consider whether a new product is less effective than available alternative therapies, when less effectiveness could present a danger to the patient or to the public. For example, it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when: (1) The disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack)” [Emphasis added, see [ATTACHMENT 4](#)]

The notice goes on state that a product otherwise subject to the previous paragraph that was developed for a particular subpopulation for which no effective therapy is available might be approved for use in that subpopulation despite lack of evidence that the product is as effective as an approved competitor in the overall population. For example, a drug might be approved for use in patients who cannot tolerate an approved therapy or therapies.

The quoted language above seems clearly to apply to rivaroxaban. It suggests two possible comparisons in terms of efficacy: rivaroxaban vs. warfarin, and rivaroxaban vs. dabigatran. However, dabigatran was not available for use as a comparator when ROCKET was started in 2006, leaving warfarin as the only feasible comparator.

Reviewer comment: The 1995 Federal Register notice cited above is written broadly, like most policy documents. It lacks operational details, such as what to do when two potential comparators are approved. The underlying goal of the policy, to prevent harm from the use of inferior therapies, suggests that the most effective therapy that is feasible to use should be the comparator. Another missing operational detail concerns the situation of insufficient data or data too ambiguous to allow confidence as to whether the new agent is as effective as the comparator. Again, the fundamental basis of the policy, to prevent harm from the

⁵ 60 Fed. Reg. 39180 (1 August 1995).

use of inferior therapies, suggests that the proper course is to reject the new therapy if there is not convincing data to support that it is effective as the best feasible comparator.

6.1.10.2.2 Importance of the quality of warfarin management

The consensus guidelines for the management of patients with AFib recognize that the efficacy of warfarin in preventing thrombotic events is dependent on the quality of INR control,² a conclusion also reached in other publications describing the inverse relationship between center TTR and event rate in warfarin-treated patients in studies of stroke prevention in AFib patients.^{5, 6} The recommended target range in the guidelines for patients with non-valvular AFib in need of anticoagulation with a VKA is 2.0 to 3.0.

Quality of INR control is usually assessed by calculating imputed percentage time in therapeutic range (TTR)¹², is a critical factor in interpreting a trial in which warfarin is used as an active control, and data for this parameter has been often in reports of clinical trials of warfarin performed in recent years. For additional information regarding the methods used by FDA and the Sponsor to calculate TTR, see [ATTACHMENT 6](#).

6.1.10.2.3 INR in ROCKET

In ROCKET, the target therapeutic range of INR was 2 – 3, consistent with the recommendation in the consensus guidelines. Data on overall TTR in the warfarin arm of ROCKET is displayed in [Table 52](#).

Table 52. ROCKET – Percent Time In INR Range In Warfarin Arm

INR Range	Mean	SD	Med
<1.5	8.47	15.68	2.73
1.5 - <1.8	10.38	10.56	7.88
1.8 - <2	10.26	7.61	9.07
2 – 3	55.16	21.25	57.83
>3 - 3.2	4.76	4.23	4.03
>3.2 - 5	9.94	9.96	7.94
>5	1.03	4.85	0.00

TTR was first calculated within individuals and then summarized over all subjects. The method of Rosendaal was used to impute INR values over the course of treatment.

Imputed INR was in the target range or 2 to 3 about 55% of the time in ROCKET. Of the 45% of time spent outside the therapeutic range, about 29% was spent below range (meaning that there was an increased risk of ischemic stroke over the risk when in range) and the remainder, about 14%, was spend above the therapeutic range (meaning that there was an increased risk of hemorrhagic stroke over the risk when in range).

Reviewer comment: The Sponsor has suggested that an time in expanded INR range, extending from 1.8 to 3.2, was about 70% (the expanded range includes the cells highlighted in gray in Table 52), and that this should allay concerns about the overall TTR data. However, this argument has no merit.

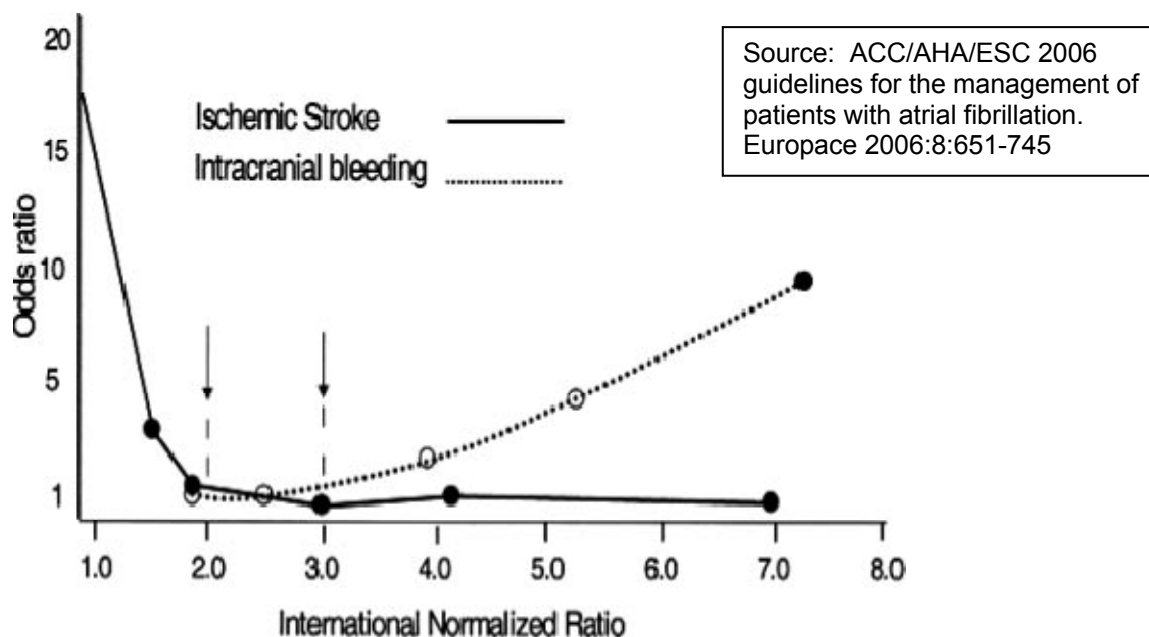
In the Sponsor's suggested expanded range of acceptable INR, more than 2/3 of the added time in "range" is spent in the INR range of 1.8 - <2. Hylek et. al. have published data indicating that the rate of ischemic stroke increases steeply at INR levels below 2. An INR of 1.8 is associated with a 1.5 X risk of ischemic stroke compared to an INR of 2.0¹³ (see Table 53 and Figure 28). They performed a case control study in 69 patients with a diagnosis of ischemic stroke hospitalized from January 1989 through December 1994 at a large academic medical center, who also had non-valvular AFib and were taking warfarin at the time of the stroke. Their INR on admission for stroke was used for comparison. Their mean yearly admission INR was 1.58. Matched controls were selected from among the patients attending the center's anticoagulation therapy unit in 1994; a control patient's INR value used for comparison was the one closest in time to the month and day of admission for the matched case. Odds ratios for the risk of stroke at various levels of INR less than 2 were calculated; the rate at INR = 2 was normalized to 1.0.

In a subsequent publication, Hylek et al. studied 596 patients with acute ischemic stroke and non-valvular AFib from a large HMO population.¹⁴ The 30 day mortality rate in patients taking warfarin with a INR ≥ 2.0 at the time of the stroke was 6%. The 30 day mortality rates in patients taking warfarin with INR between 1.9 to 1.5 and those with INR < 1.5 were similar – 18% and 15%, respectively. The HR for 30 day mortality for patients taking warfarin with INR <2.0 vs. INR ≥ 2.0 was 1.9 (95% CI, 1.1, 3.4, p=0.03). Hylek's findings have been cited in the 2006 consensus guidelines on the management of AFib to support the current recommendation of maintenance of an INR range of 2.0 - 3.0 for non-valvular AFib patients taking warfarin.² Accordingly, the sponsor's suggestion that consideration of an expanded INR therapeutic range is appropriate should be rejected.

Table 53: Ischemic Stroke Risk For INR < 2.0

Adjusted OR for Ischemic Stroke (vs. INR of 2.0)	
INR	Odds Ratio (95% CI)
1.9	1.2 (1.2–1.3)
1.8	1.5 (1.4–1.7)
1.7	2.0 (1.6–2.4)
1.6	2.5 (1.9–3.3)
1.5	3.3 (2.4–4.6)
1.4	4.4 (2.9–6.6)
1.3	6.0 (3.6–9.8)
1.2	8.3 (4.6–15.0)
1.1	11.9 (6.0–23.8)
1.0	17.6 (7.9–39.3)
Source: Hylek EM et. al., NEJM 1996; 335:540-46.	

Figure 28. INR vs. Risks Of Ischemic And Hemorrhagic Stroke



TTR varied widely across the study's five geographic regions. [Table 54](#) is a display of mean time in various INR ranges by region. TTR ranged from a high of 64.1% in North

America to a low of 49.7 % in Eastern Europe. The rank order of TTR was North America > Western Europe > Latin America > Asia Pacific > Eastern Europe.

Table 54. ROCKET – Mean Percentage Time In INR Categories By Region

	Region					
	NA	LA	WE	EE	AP	TOTAL
N	1327	924	1033	2705	1036	7025
Category (%)						
<1.5	3.54	7.73	4.61	11.98	10.10	8.47
1.5 to <1.8	7.22	9.84	8.11	12.19	12.48	10.38
1.8 to <2	9.15	9.85	9.16	10.98	11.28	10.26
2 to 3	64.13	55.19	60.62	49.73	52.38	55.16
>3 to 3.2	5.50	5.05	5.73	4.24	3.96	4.76
>3.2 to 5	9.87	10.96	10.90	9.82	8.44	9.94
>5	0.59	1.39	0.87	1.05	1.35	1.03

Note: NA-'North America' LA-'Latin America' WE-'West Europe' EE-'East Europe' AP-'Asia Pacific'

Note: The percentage is calculated within each subject firstly and then average is calculated across all subjects within each region

Table 55 (which has 2 parts) provides information on design features and results, including TTR data, for ROCKET and recent trials of warfarin vs. various anticoagulants in patients with atrial fibrillation. All of the recent trials were phase 3 outcome studies with endpoints of stroke and sometime additional events comparing warfarin to a non-VKA anticoagulant or a an antiplatelet regimen, except for EMBRACE AC, which was a phase 2 study comparing warfarin to a novel VKA antagonist. All trials were open label except for ROCKET, SPORTIF V and EMBRACE AC.

Table 55. ROCKET vs. Modern Warfarin-Controlled Trials

Selected Parameters – Part 1

Study name and agents compared	ROCKET (rivaroxaban vs. W)	RE-LY (dabigatran 150 mg vs. W)	SPORTIF III (ximelagatran vs. W)	SPORTIF V (ximelagatran vs. W)
Study Parameter				
N (ITT)	14,171	12,098	3397	3922
% female	40	37	30	31
% with h/o stroke/TIA/SE	55	22	29	22
Mean CHADS2 score (SD)	3.5	2.1	-	-
% w prior VKA therapy	62	61	73	85
Target INR (range)	2.5 (2.0-3.0)	(2.0-3.0)	(2.0 – 3.0)	(2.0-3.0)
Mean TTR (%)	55	64	66	68
Primary endpoint	Stroke + SE	Stroke + SE	Stroke + SE	Stroke + SE
Event rate warfarin	2.42	1.71	2.29	1.16
Event rate test agent	2.12	1.11	1.64	1.61
HR or Δ (95% CI)	0.88 (0.74, 1.03)	0.65 (0.52, 0.81)	-0.66%/yr (-1.45, 0.13)	0.45%/yr (-0.13, 1.03)

(See Part 2 on next page)

Table 55. ROCKET vs. Modern Warfarin-Controlled Trials
Selected Parameters – Part 2

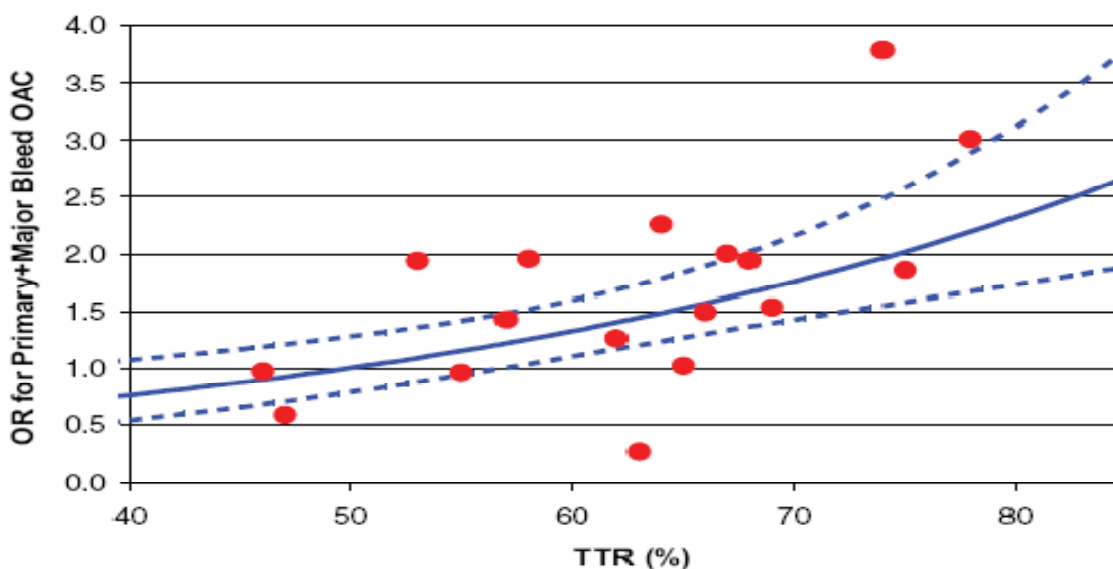
Study name and agents compared	ACTIVE W (clopidogrel + ASA vs. W or other OAC)	AMADEUS (idraparinux vs. W)	AFFIRM (rate vs. rhythm control)	EMBRACE AC (tecarfarin vs. W, phase 2) ⁸
Study Parameter				
N (ITT)	6706	4576	4060	612
% female (overall)	34	34	39	-
% with h/o stroke/TIA/SE	18	24	-	-
Mean CHADS2 score (SD)	2.0 (1.1)	(41% had score of 0-1)	-	-
% w prior VKA therapy	77	76	-	-
Target INR (range)	(2.0-3.0)	(2.0-3.0)	(2.0-3.0)	(2.0-3.0)
Mean TTR or % in range *	64	63	62*	74 vs. 73
Endpoint	Stroke	Stroke + SE	Mortality	TTR
Event rate warfarin	1.40	1.3	Ischem. stroke rate ~ 1%/yr	-
Event rate test agent	2.39	0.9	Same as above	-
HR (95% CI)	1.72 (1.24, 2.37)	0.71 (0.39, 1.30)	-	-

With the exception of ROCKET, all the trials had a mean TTR (or time in range for AFFIRM) for warfarin of 62% to 73%. Note that in the trials for which demographic data are available, the percentage of patients with a baseline history of stroke/TIA/systemic embolism ranges from 18% to 29%, considerably less than the analogous level in ROCKET, 55%.

The available data suggest that control of INR in the warfarin arm in ROCKET was considerably below what was achieved in other modern studies.

Connolly et al have published data showing that country level TTR (CLTTR) in ACTIVE W was significantly correlated with outcome across a broad range of TTR⁶ (see [Figure 29](#)). ACTIVE W was an international trial in non-valvular AFib patients comparing the effects of warfarin titrated to an INR target of 2.0-3.0 vs. clopidogrel + aspirin on stroke, other major CV outcomes and bleeding. The trial was terminated early because of clear evidence of the superiority of warfarin to dual antiplatelet therapy. The authors analyzed the relationship of country level TTR to the hazard ratio for the composite outcome of stroke, systemic embolism, MI, vascular death or major bleeding. They found a significant relationship and derived a regression equation of $HR = -1.40 + (0.28 \times CLTTR)$. The TTR equivalent of clopidogrel + aspirin overall was 50%. Overall TTR in this study was 64% and the overall HR for the composite endpoint was 1.44. Although the authors did not do a similar analysis of the ROCKET primary endpoint (stroke + systemic embolism), the TTR quartile data for stroke + systemic embolism are similar in pattern to the TTR quartile data for the composite endpoint from which the regression equation was derived. If the ROCKET mean TTR value of 55% is entered into the regression equation of Connolly et al., a hazard ratio estimate of 1.14 is obtained. This obviously represents a cross study comparison. However, this information suggests that the overall quality of anticoagulation obtained in the ROCKET warfarin arm may have been only slightly better than what one might expect with clopidogrel + aspirin, which was substantially inferior to warfarin.

Figure 29. TTR vs. Hazard Ratio Estimate from ACTIVE-W



Reviewer Comment: In Active W, the relative risk (RR) for the primary endpoint of stroke, systemic embolism, MI, or vascular death (clopidogrel + ASA vs. oral anticoagulation (OAC) was 1.44 (95% CI: 1.18, 1.76, p=0.0003). For stroke alone, the RR was 1.72 (1.24, 2.37, p<0.0001). The overall mean TTR in

ACTIVE W was 64%¹⁵ and the median site TTR was 65%.⁶ These data suggest that if rivaroxaban was determined to be non-inferior to warfarin at a TTR of 55%, it might not be as effective as warfarin as it was used in ACTIVE W. However, this is a cross-study comparison.

6.1.10.2.4 Analyses of center-based TTR in ROCKET

Another way to examine the impact of the quality of warfarin anticoagulation in ROCKET is to examine the results for the primary endpoint in various subsets of the study based on center level TTR. Use of center-level data preserves the effects of randomization and is less prone to bias than simply comparing all patients in the rivaroxaban arm to those with various levels of TTR in the warfarin arm. The latter type of comparison could be greatly confounded by the effects of nationality, region, demography, and general quality of care, which could differ greatly in patients with poor vs. good warfarin control.

Before analyzing the center-based TTR data, it is important to understand how it was calculated.

To our knowledge, all published reports of center-based TTR in trials have utilized the method of Connolly et al. in their secondary publication from the ACTIVE-W trial.¹⁶ We thus used this method, which consists of two steps: first, the TTR for each individual patient at a center is calculated using the method of Rosendaal.¹² Then, the mean of the individual TTRs at the center is calculated; this becomes the mean center TTR. Note that there is no weighting of patients by time on treatment; all patients are weighted equally.

The sponsor used this method to calculate overall study TTR and TTR in the various geographic regions and countries where ROCKET was conducted. However, they used a different method to calculate center-based TTR. Instead of calculating each patient's individual TTR first, they divided the aggregate time in range for all patients by the aggregate amount of time on warfarin for all patients. This is essentially how one calculates TTR for an individual patient. However, each patient's contribution to the center TTR value is directly proportional to the patient's time on treatment.

One would expect warfarin patients who in the study for a long time to tend to have better control of INR than those who discontinue early. Patients who discontinue early would be thus be underrepresented at a center, meaning that the Sponsor's method would tend to narrow the gap in TTR between centers with lower and higher skill at controlling INR.

The following example is illustrative. A hypothetical site enrolls 4 patients into the warfarin arm. One remains on therapy for 36 months and has an TTR of 70%. The other 3 each drop out after 4 months and each have a TTR of 50%. Using the method of Connolly, which was used by FDA and all publications of which we are aware, the

center based TTR would be the mean of the individual TTR values, or 55%. The Sponsor's method would be calculated as $((70 \times 36) + (3 \times 50 \times 4))$ divided by $(36 + (3 \times 4))$, yielding a TTR of 65%, a full 10% higher.⁶ This is an extreme example, but it suggests that TTR might be higher using the Sponsor's method. It turns out that the quartile cutoffs in the sponsor's analysis of center based TTR quartiles are about 2 to 3% higher than FDA's calculated cutoffs.

Notably, we asked the sponsor to provide published literature to support their method of calculating TTR. They sent an article that actually used the method of Connolly, which was cited in the article. We are still not aware on any publication that has used the sponsor's method of calculating center-based TTR.

The Sponsor performed an analysis of the primary endpoint analysis in quartiles of center based TTR, using it's unique method of calculation. The sponsor's data are displayed in [Table 56](#).

Table 56. ROCKET – Sponsor's Analysis Of Primary Endpoint Results By Center TTR Quartile,

Safety population on treatment

Center TTR	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin - Hazard Ratio (95% CI) ²
	N=7061 n/J (%) ¹	Event rate (per 100 pt-yr)	N=7082 n/J (%) ¹	Event rate (per 100 pt-yr)	
0.00 - 50.62%	45/1735 (2.59)	1.77	62/1689 (3.67)	2.53	0.70 (0.48,1.03)
50.71 - 58.54%	53/1746 (3.04)	1.94	63/1807 (3.49)	2.18	0.89 (0.62,1.29)
58.63 - 65.71%	54/1734 (3.11)	1.90	62/1758 (3.53)	2.14	0.89 (0.62,1.28)
65.74 - 100.0%	37/1676 (2.21)	1.33	55/1826 (3.01)	1.80	0.74 (0.49,1.12)

¹ J = number of patients in subgroup

² p value for treatment by site TTR quartile interaction = 0.736

In both treatment arms, there is a downward trend in event rates as center INR control increases. The point estimates for the hazard ratio vary from 0.70 to 0.89, without a

⁶ TTR is actually imputed and calculated on daily basis, but monthly TTR is used here for the sake of simplicity.

clear directional pattern. Note that the TTR in the 4th (best) quartile of INR control starts at about 66%.

FDA did the same type of analysis, but we used the method of Connolly et. al. to calculate center based TTR. We thought it would be more appropriate to follow the published method of Connolly et al. ⁶ (see [Table 57](#)).

As we expected, the quartile boundaries were somewhat lower than in the sponsor's analysis, but the quartile results for the comparison of the treatment arms differed little between the two analyses. In the FDA analysis, the warfarin arm results show roughly similar event rates in the quartiles 1-3, (2.2 to 2.4 events per 100 pt-yr), with a considerably lower rate in the 4th (highest) quartile of center TTR (1.75 events per 100 pt-yr). Event rates in the rivaroxaban arm also show a reduction in the fourth quartile compared to the other 3, although the HR favors rivaroxaban over warfarin in each quartile. The hazard ratios in the 4 quartiles differ little from each other and cluster near the overall HR of 0.79. Note that the fourth quartile of TTR in the FDA analysis starts at 64%, about equal to the average TTR in the RE-LY study of dabigatran, and less than the RE-LY median TTR of 67%.

Table 57. ROCKET – FDA's Analysis Of Primary Endpoint Results By Center TTR Quartile

Safety population on treatment

Center TTR (%)	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin - Hazard Ratio (95% CI)
	N=7061 n/J (%) ¹	Event Rate (per 100 pt-yr)	N=7082 n/J (%) ¹	Event Rate (per 100 pt-yr)	
<46.8	47 / 1765 (2.62)	1.80	56 / 1725 (3.25)	2.24	0.80 (0.54, 1.18)
46.8 - 55.9	50 / 1724 (2.90)	1.89	65 / 1764 (3.68)	2.36	0.80 (0.55, 1.16)
55.9 - 63.9	55 / 1709 (3.22)	1.95	66 / 1787 (3.69)	2.26	0.86 (0.60, 1.24)
> 63.9	37 / 1690 (2.19)	1.30	55 / 1803 (3.05)	1.75	0.75 (0.49, 1.13)

¹ J= Number of patients in subgroup. Quartiles had approximately equal numbers of patients.

This was not our first set of results, however. In our first such analysis, we performed a similar analysis in which we grouped sites in to quartiles with an equal number of *centers* (instead of patients) in each quartile, producing a higher Q4 cut point and a smaller number of patients in the 4th quartile. The results of this analysis are shown in [Table 58](#). Note that the 4th quartile starts at a TTR of about 68%, and the point estimate for HR for this quartile is 1.02 with a wide confidence interval that extends beyond 1.8.

Table 58. ROCKET – FDA’s Analysis Of Primary Endpoint Results By Center TTR Quartile

Safety population on treatment

Center TTR (%)	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin - Hazard Ratio (95% CI)
	N=7061 n/J (%) ¹	Event rate (per 100 pt-yr)	N=7082 n/J (%) ¹	Event rate (per 100 pt-yr)	
<48.3	55 / 2019	1.85	67 / 1980	2.35	0.78 (0.55, 1.12)
48.3 - < 59	64 / 2111	1.90	79 / 2194	2.24	0.85 (0.61, 1.18)
59 - < 67.8	49 / 1671	1.79	73 / 1740	2.50	0.72 (0.50, 1.03)
≥ 67.8	21 / 1087	1.15	23 / 1165	1.14	1.02 (0.56, 1.84)

¹ J= Number of patients in subgroup. Quartiles had approximately equal numbers of centers.

We also did an analysis that split the centers into those with TTR < 65 and those with TTR ≥ 65. Results for the groups with the highest TTR in those analyses are shown in [Table 59](#).

Table 59. ROCKET – FDA’s Analysis Of Primary Endpoint Results By Site TTR Subgroups with TTR ≥ 63.9%

Center TTR	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin - Hazard Ratio (95% CI)
	N=7061 n/J (%) ¹	Event rate (per 100 pt-yr)	N=7082 n/J (%) ¹	Event rate (per 100 pt-yr)	
4 th Quartile ² TTR > 63.9 Safety pop, LD + 2 d	37 / 1690 (2.19)	1.30	55 / 1803 (3.05)	1.75	0.75 (0.49, 1.13)
Center TTR ≥ 65 Safety pop, LD + 2 d	31 / 1444 (2.15)	1.28	41 / 1545 (2.65)	1.54	0.84 (0.53, 1.34)
Center TTR ≥ 65 Safety pop, LD + 30 d	49 / 1444 (3.39)	1.95	49 / 1545 (3.17)	1.76	1.10 (0.75, 1.64)
4 th Quartile ³ TTR ≥ 67.8 Safety pop. LD + 2 d	21 / 1087 (1.93)	1.15	23 / 1165 (1.98)	1.14	1.02 (0.56, 1.84)
4 th Quartile ³ TTR ≥ 67.8 Safety pop. LD + 30 d	34 / 1087 (3.13)	1.78	29 / 1165 (2.48)	1.38	1.30 (0.79, 2.13)

¹ J=No of patients in subgroup.

² Based on quartiles of center TTR, with equal number of patients in each quartile.

³ Based on quartiles of center TTR, with equal number of sites in each quartile.

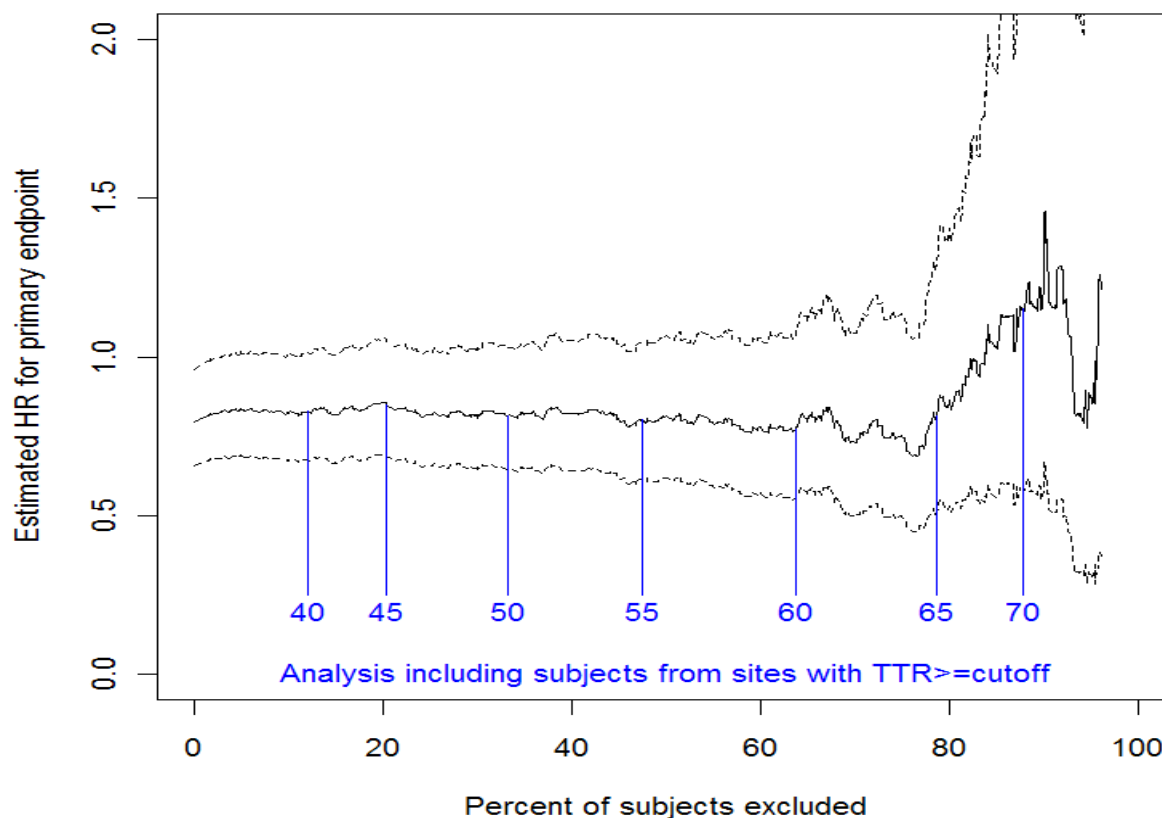
The data suggest that as TTR increases above the low sixties, the hazard ratio for the primary endpoint approaches and eventually crosses one for the last-dose + 2 days analysis. If patients are followed out to 30 days after the last dose, the point estimate for the hazard ratio increases to as high as 1.3 in the analyses we performed. The number of patients in each arm decreases from 1700 to 1800 in the quartile/equal patients analysis to about 1100 in the quartile/equal centers analysis in quartile 4. Confidence intervals expand accordingly.

To further examine efficacy at centers with a high TTR, we asked Division Biometrics I to create a graphical analysis of the primary endpoint (per protocol, last dose + 2 days) in which the x axis is center TTR ranging from 0% to 100% and y axis is the HR for rivaroxaban vs. warfarin (see [Figure 30](#)). Y=f(x) where f(x) was the point estimate for

the HR for primary endpoint for rivaroxaban vs. warfarin at all centers where TTR was in the interval from x to 100%. Thus, for $x=0\%$, the HR corresponded to the HR for the entire study, and for $x=K\%$, the HR was the HR for the centers with TTR ranging from $K\%$ to 100%. As K increases, the number of patients in the analysis decreases, and the CI becomes wider. We also plotted the 5th and 95th percentile for the HR. Note that the HR point estimate curve (the center curve) is fairly flat from $X=0\%$ to about $X=64\%$ and then goes up steeply as X approaches and then exceeds 70%. The HR point estimate crosses 1 at about $X=67-68\%$ and the 95th percentile for the HR crosses 1.38 at a slightly lower value of X .

Figure 30. Hazard Ratio and 95% CI for the Primary Efficacy Endpoint Analysis as a Function of Center TTR

Per Protocol Population, On Treatment ¹



¹ Plot of $y = f(x)$ where $f(x)$ = HR for all centers with TTR in the interval from x to 100%.

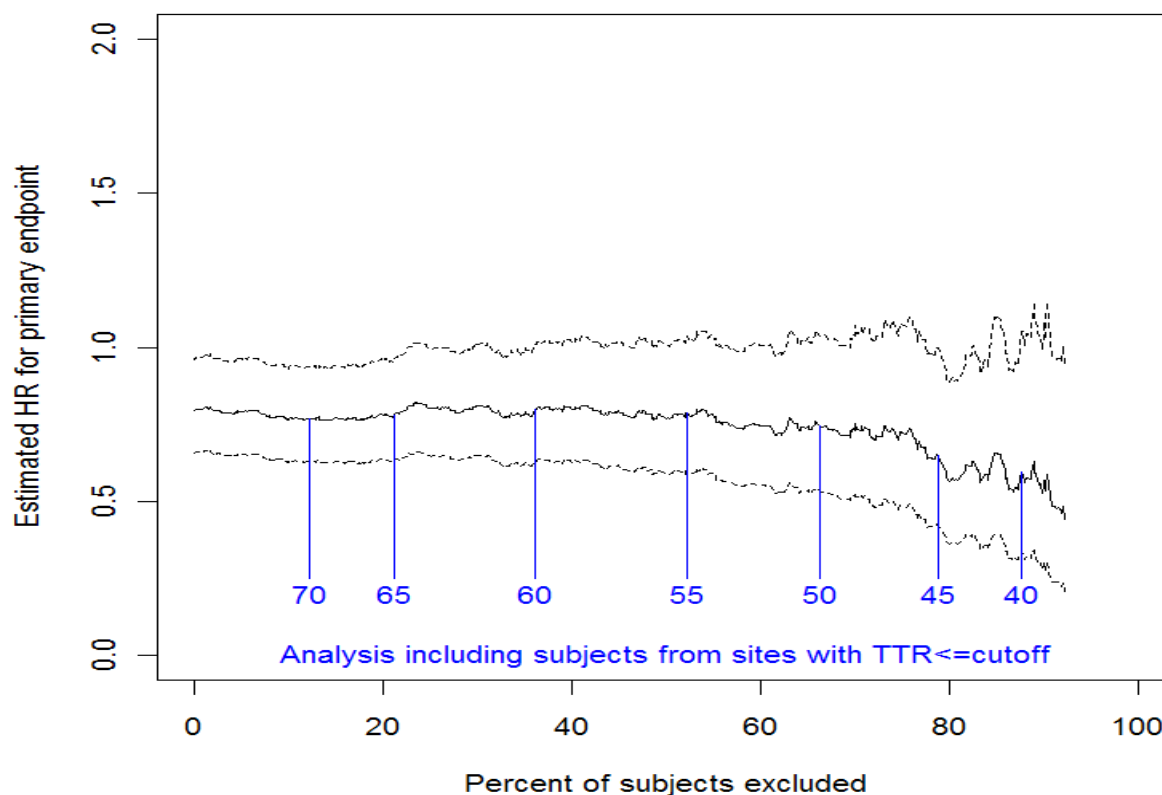
Reviewer comment: The Sponsor has provided a graph like the one in Figure 30, presumably using its own method of calculating TTR, which would shift the curve

to the right on the X axis. Otherwise, the graph is quite similar to FDA's version. Both graphs have wide confidence intervals around TTR values greater than about 65% that generally overlap.

We also performed a graphical analysis where $f(x)$ is the HR for all sites with TTR in the range of 0% to $x\%$ (Figure 31), and the x axis ranges from TTR =100% to TTR=0%. As expected, this analysis shows that as TTR is reduced, the hazard ratio for rivaroxaban vs. warfarin decreases.

Figure 31. Hazard Ratio And 95% CI For The Primary Efficacy Endpoint Analysis As A Function Of Center TTR

Per Protocol Population, On Treatment ¹

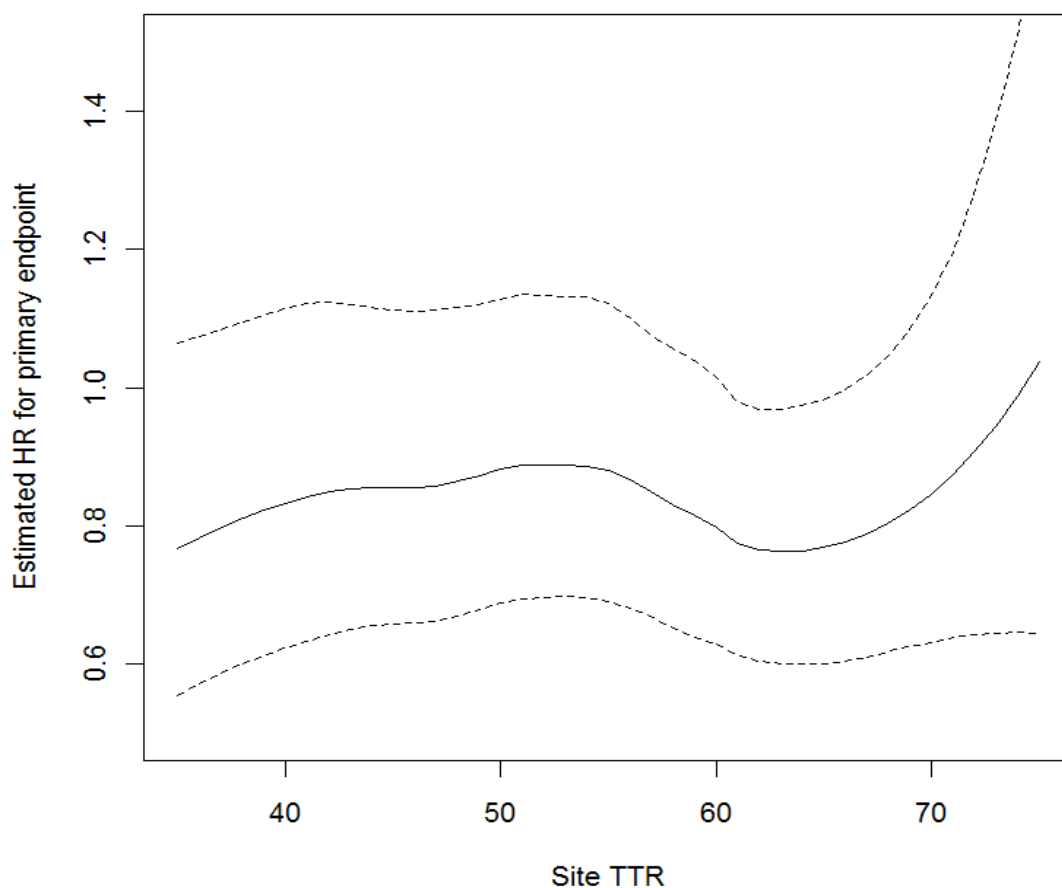


¹ Plot of $y = f(x)$ where $f(x)$ = HR for all centers with TTR in the interval from x to 100%.

OBI staff also plotted the moving average over a window of sites whose TTR values were close to each other (see Figure 32). Note that there were very few events at sites

with TTR > 70, and the confidence interval is quite wide in this region. The data are consistent with the information in [Figure 30](#).

Figure 32. ROCKET - Moving Average of HR vs. TTR



We also performed an exploratory analysis of center-based time *below* therapeutic range (TBTR), defined as time below an INR of 2 ([Table 60](#)).⁷ Note that for TBTR, the

⁷ We hypothesized that quartiles or other subsets based on this parameter might better distinguish centers in terms of primary event rates than a conventional TTR analysis. The underlying rationale is based on the fact that most primary endpoint events are ischemic strokes. The risk of ischemic stroke increases sharply as INR falls below 2. On the other hand, ischemic stroke risk is little affected by INR > 3 compared to INR in the therapeutic range of 2 – 3. The risk of hemorrhagic stroke does increase as INR increases over 3, but the rate of increase is modest, and such strokes are decidedly less common

first (lowest) quartile would expected to have the lowest event rate in the warfarin arm and thus the highest HR; this turned out to be true. The hazard ratios decrease step-wise from quartiles 1 to 4. The spread of event rates in the warfarin arm across the quartiles is somewhat wider than in the TTR analysis, suggesting that the TBTR analysis may be useful in analyzing the effect of center based warfarin control on the rates of thrombotic events in trials of novel anticoagulants with warfarin controls. Notably, in the first quartile, the HR is 0.91, with a 95% CI ranging from 0.59 to 1.41. Subgroups with lower rates of TBTR would be expected to have higher hazard ratios. The data from this analysis suggest that at sites where control of INR is very good, treatment with rivaroxaban may not be as effective as treatment with warfarin.

Table 60. ROCKET – Primary Endpoint Results By Site Mean Time Below Therapeutic Range Quartile

Safety Population, to Last Dose + 2 days – FDA Analysis

Site TBTR ¹ (%)	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin – Hazard Ratio (95% CI)
	N=7061 n/J (%) ²	Event rate (per 100 pt-yr)	N=7082 n/J (%) ²	Event rate (per 100 pt-yr)	
<18.9	37 / 1688 (2.19)	1.33	45 / 1804 (2.49)	1.47	0.91 (0.59, 1.41)
18.9 - 27.1	59 / 1705 (3.46)	2.09	76 / 1790 (4.25)	2.56	0.82 (0.58, 1.15)
27.1 - 37.7	48 / 1731 (2.77)	1.78	61 / 1758 (3.47)	2.22	0.80 (0.55, 1.17)
> 37.7	45 / 1764 (2.55)	1.72	60 / 1727 (3.47)	2.38	0.73 (0.49, 1.07)

¹ TBTR = time below therapeutic range (i.e., INR < 2.0)

² J = number of patients in subgroup

than ischemic strokes in studies in atrial fibrillation patients. Accordingly, while INRs above the therapeutic range count against TTR as it is usually measured, they have only modest effects on primary endpoint rates. This would tend to blunt the power of a primary endpoint analysis that takes into account such INRs to distinguish between subsets based on INR control. Accordingly an analysis that considers only time below the therapeutic range might better distinguish among subgroups of centers with different levels of INR control. However, INRs above therapeutic range would be relevant in an analysis of bleeding risk, and the conventional TTR analysis (or an analysis that considers only time above range) would be expected to be useful in assessing the affects of differences in INR control on bleeding events.

6.1.10.2.5 Effect of patient characteristics on TTR in ROCKET

The ROCKET population was sicker than the population in other recent anticoagulation trials in AFib patients. This might have influenced warfarin control in ROCKET.

There is literature on the effect of patient characteristics on observed TTR. While other publications describe characteristics associated with poor control of INR,^{17 18} the largest and most comprehensive study is by Rose et al., who analyzed data from more than 124,000 VA patients who were anticoagulated with VKA at 100 VA centers from 2006-2008.¹⁹ This is the only study of which we are aware that attempts to quantify the effect on TTR of a large variety of patient characteristics. Rose obtained data from the VA VARIUS database of data from anticoagulated patients. Patients with valvular heart disease, no INR above 1.2, and those at 28 centers (of 128 that were screened) with poor data quality were not analyzed. The authors calculated TTR for each patient separately (if possible) in the first 6 months of anticoagulant therapy (inception phase) and during subsequent therapy (experienced phase). They used linear regression in adjusted models, employing a mixed model (SAS PROC MIXED) with exchangeable correlation structure to account for the correlation of patient outcomes by site of care. ICD-9 codes were used to obtain co-morbid conditions. The output of the model was an expected adjustment to TTR for dozens of patient characteristics, including demographic characteristics, co-morbid conditions, number of concomitant medications, number of hospitalizations, and several residential factors.

To estimate the expected effect on TTR of the differences in the patient populations of RE-LY and ROCKET, we computed the differences between the studies (warfarin arms) in term of the distributions of age, gender, prevalence of the medical components of the CHADS₂ score, baseline “CKD” rate (which we defined as CrCl < 50 mL/min), and history of MI, which we used a surrogate for the term “CAD” used by Rose et al. All but one of these corresponded to factors assessed by Rose et al. History of stroke/TIA/SE was not assessed by Rose; we used the expected effect for “CAD” (-0.6) as a substitute (this was close to the value of the calculated effect for “PVD”, which was -0.5). We calculated the differences between ROCKET and RE-LY in the proportion of patients with each of these characteristics and multiplied each difference by the corresponding effect calculated by Rose et al. for that characteristic in the “experienced” period of VKA administration (i.e., > 6 months after initiation of therapy). Those effects ranged from

-1.6 for CKD (i.e., each 1% increase in the prevalence of CKD would be expected to be associated with a 0.016% decrease in overall TTR) to +1.0 for hypertension (each 1% increase in the incidence of hypertension would be expected to be associated with a 0.01% increase in overall TTR). We then summed all the results. Accounting for all these factors, if the ROCKET population had the same makeup as the RE-LY population with respect to the characteristics we analyzed, we estimate that the overall mean TTR would have increased less than 1%, i.e., from 55.16% to 55.84%.

We also used another method based on data from ROCKET to estimate the ROCKET global mean TTR if the warfarin arm had the same CHADS₂ distribution as RE-LY. Table 20 in the ROCKET study report has the following data for mean TTR for warfarin arm patients with the following baseline CHADS₂ scores: 0 – NA (no patients); 1 – 33.33% (3 patients); 2 – 59.26%; 3 – 55.04%; 4 – 54.36%; 5 – 53.62%; and 6 – 53.49%. The following information on CHADS₂ score distribution in the warfarin arm in RE-LY was obtained from the dabigatran NDA medical

review: 0 – 2.5%; 1 – 28.3%; 2 – 37%; 3 or more – 32%. In our calculation for the estimated TTR we used the following TTRs for the RE-LY CHADS₂ distribution categories: 0, 1, and 2 – 59.26 (the mean TTR for a score of 2 in ROCKET); 3 or more – 54.26 (the mean TTR for a score of 4 in ROCKET). We then multiplied the imputed TTR by the fraction of patients in the relevant CHADS₂ score category in RE-LY, and summed the products to determine an estimate for the ROCKET TTR if the CHADS₂ scores were distributed in the ROCKET warfarin arm as they were in RE-LY. The estimate was 57.6%, compared to the actual ROCKET mean TTR of 55.16%. However the estimated score was still substantially below the observed mean TTR in RE-LY of 64.

Finally, we asked our colleagues in the Division of Biometrics I to perform a logistic regression analysis of various the effects of various demographic, disease-related, and geographic factors on TTR in ROCKET, and model TTR in ROCKET, with baseline characteristics adjusted to match those in RE-LY. The characteristics examined were age, gender, region, baseline use of VKA, CHADS₂ score, and history of heart failure, stroke/TIA/SE, diabetes, or hypertension.

Significant variables in the regression model are shown below

Variable	Estimate	p-value
age	0.1371/yr	4.76 * 10 ⁽⁻⁷⁾
sex == "MALE"	2.1315	2.13 * 10 ⁽⁻⁵⁾
priorvka == "Y"	9.3523	< 2 * 10 ⁽⁻¹⁶⁾
chads == 3	-2.7491	0.000290
chads == 4	-2.7219	0.000798
chads == 5	-3.7257	0.000127
chads == 6	-5.6547	0.001489
region == "WEST EUROPE"	6.1997	< 2 * 10 ⁽⁻¹⁶⁾
region == "NORTH AMERICA"	7.9877	< 2 * 10 ⁽⁻¹⁶⁾
*heart failure	-2.0	0.027
*prior stroke/TIA/SE	3.0	0.043

The observed mean TTR in ROCKET was 55.16%. Based on the variables that are not asterisked, which all had p values <0.0015, the model predicted a TTR of 57.68% if ROCKET patients, in the aggregate, had the same characteristics as RE-LY patients for the modeled variables. When the asterisked variables (history of heart failure and history of stroke/TIA/SE) were included in the model, the model predicted a TTR of 57.74%. The mean TTR in RE-LY (excluding treatment interruptions, as was done in the analysis of ROCKET TTR), was 64%.

Thus, none of the 3 methods used to model the ROCKET mean TTR based on the assumption of a population similar to the one in RE-LY resulted in an estimated mean TTR nearly as high as the one observed in RE-LY, which was 64%. The observed ROCKET mean TTR of 55.16% was no higher than 57.74% after the adjustment that produced the highest estimated TTR.

6.1.10.2.6 Summary of data

Reviewer's conclusion regarding the adequacy of comparator:

- *The number of patients at sites in ROCKET where warfarin was used skillfully (TTR \geq ~68% is comparatively small, about 1000 patients per arm. By contrast, half of the patients in the 18000 patient RE-LY study were at sites with TTR > 67%, and ¼ were at sites with TTR > 74%.*
- *For ROCKET centers with TTR \geq ~68% the point estimate for the HR is >1 and rising as TTR increases; the confidence level is quite wide*
- *It has not been established that rivaroxaban is as effective as warfarin when warfarin is used skillfully*
- *Modeling the TTR data to conform to the makeup of the RE-LY study population suggests that the unusually high risk population of ROCKET did not markedly affect the level of TTR attained.*
- *In RE-LY and other studies, INR control was substantially better than in ROCKET, suggesting that it is feasible to perform studies capable of being informative about the question of whether a new drug is as effective as warfarin when it is used skillfully.*

6.1.10.3 Events Occurring After Discontinuation of Study Drug

6.1.10.3.1 ROCKET

In ROCKET most of the protocol-specified primary and secondary endpoint analyses in the efficacy event hierarchy counted events that occurred in the “on treatment” period, i.e., from randomization to the last dose of study drug + 2 days. However, in ROCKET, the sponsor analyzed both the safety and per-protocol populations with additional “data scopes”, including last dose + 7 days, last dose + 14 days, and last dose + 7 days, as well as ITT analyses that followed all randomized patients to the site notification date, the follow-up visit, or to the last contact with the patient without regard to whether the patient was on treatment. Analyses of the primary endpoint (time to stroke or systemic embolism) in the safety population using various event windows are reproduced in [Table 61](#).

Table 61. Primary Endpoint Results In Various Event Windows

Safety Population excluding site 042012

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p ¹
Event Window	n/N	Event Rate (per 100 pt-yr)	n/N	Event Rate (per 100 pt-yr)		
On treatment ² (Last dose + 2 days)	189 / 7061	1.70	243 / 7082	2.15	0.79 (0.65, 0.95)	0.015
Last dose + 7 days	220 / 7061	1.96	255 / 7082	2.24	0.88 (0.73, 1.05)	0.149
Last dose + 14 days	235 / 7061	2.07	271 / 7082	2.35	0.88 (0.74, 1.05)	0.150
Last dose + 30 days	251 / 7061	2.16	281 / 7082	2.38	0.91 (0.76, 1.07)	0.252

¹ p value for superiority, unadjusted

² This was the designated analysis to assess superiority of rivaroxaban to warfarin

Note that as the event windows include progressively more time after the last dose of study drug, the number of events and the event rates increase steadily in both treatment arms. However, the number of additional events is greater in the rivaroxaban arm, and the statistical significance of the superiority finding that was present in the last dose + 2 day analysis is now longer present in the last dose + 7 day analysis, only 5 days later. In those 5 days, there were an additional 31 primary endpoint events in the rivaroxaban arm, compared to 12 in the warfarin arm. There was also an excess of events in the rivaroxaban arm over the remainder of the period depicted in the table, only not as marked as in the first 5 days.

These post-discontinuation events occurred in two very different populations. About 1/3 of study patients discontinued study drug early; these patients had a very high rate of events over the 28 day post treatment period (from Day 3 to Day 30 after the last dose of study drug), but the difference between primary event rates in the treatment arms over the 28 days was modest. The 2/3 of patients who continued treatment to the end of the study (those whose last dose of study drug was on or after the “notification date” to the sites that the event target had been reached and the end of study procedures should be implemented) had a much lower rate of events, but the difference between the rivaroxaban and warfarin arms was more marked for primary endpoint events.

[Table 62](#) provides information on primary and secondary efficacy endpoint event rates (and their components) over the period from Day 3 to Day 30 in patients who discontinued study drug early. Note that in this population, discontinuations may have been health related reasons that might be associated with an increased the risk of efficacy events, resulting in the possibility of informative censoring. None of the events enumerated in [Table 62](#) were included in the sponsor's on-treatment analyses, including the primary endpoint analyses for non-inferiority or superiority. There were 42 vs. 36 primary endpoint event events over this period in the rivaroxaban and warfarin arms, respectively, yielding respective event rates of about 26 and 23 events per 100 pt-years, about a log increase over the event rates on treatment; the treatment arms did not differ significantly. In the rivaroxaban arm, there were 33 strokes (28 were ischemic and 5 were of unknown type) and 9 systemic embolisms. In the warfarin arm, there were 35 strokes (31 were ischemic and 4 were hemorrhagic) and 2 systemic embolisms. Rates of all-cause mortality were high in both arms but favored rivaroxaban over warfarin: 145 deaths (87 per 100 patient-years) vs. 170 deaths (109 per 100 patient-years). Vascular death rates were likewise high but favored rivaroxaban. There were 13 vs. 10 patients with myocardial infarction in the rivaroxaban and warfarin arms, respectively. Rates for the "Major Secondary Endpoint 1" (time to the composite of stroke, systemic embolism or vascular death) and the "Major Secondary Endpoint 2 (the composite of the foregoing + myocardial infarction) were high in both arms (i.e., ≥ 75 per 100 patient-years in each arm) but favored rivaroxaban. This was clearly a sick population with morbidity from both vascular and non-vascular disease. The extent of anticoagulation in these patients was poorly documented.

Table 62. ROCKET - Efficacy Endpoint Events From Day 3 To Day 30

(After Early Discontinuation of Study Drug)

(Study 39039039AFL3001: Safety (Excluding SITE=042012) Analysis Set)

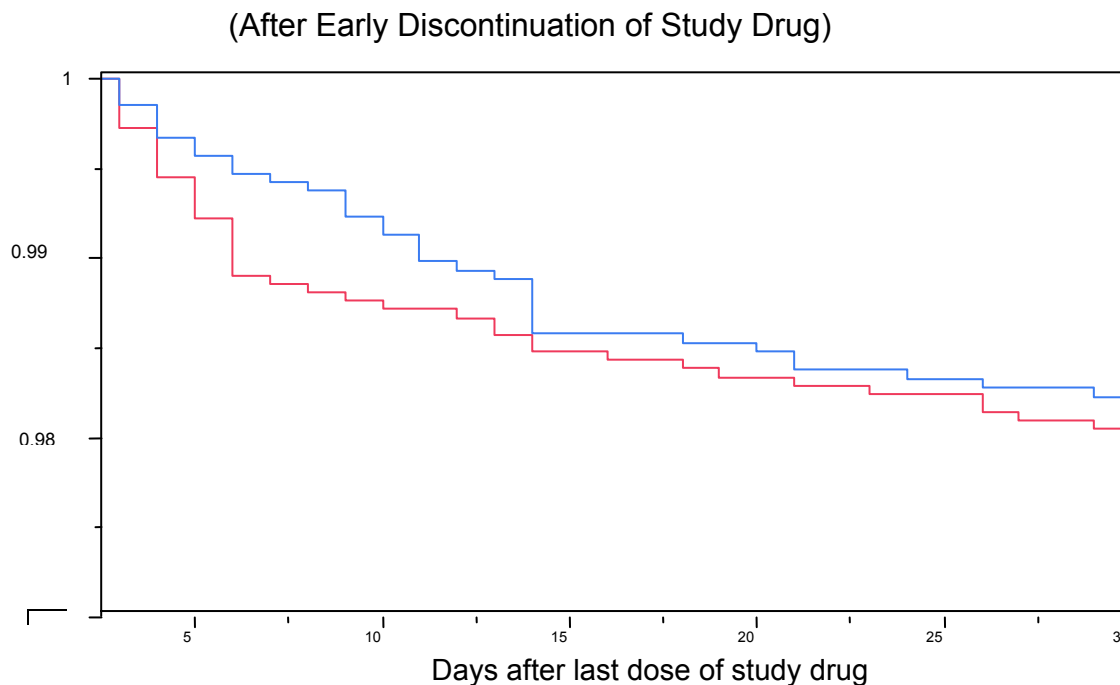
Early Study Medication Discontinuation: Yes

Analysis Set: Safety (Excluding SITE=042012)

Endpoints	----- Rivaroxaban -----		----- Warfarin -----		---- Rivaroxaban vs. Warfarin ----	
	N= 2256 n (%)	Event Rate (100 Pt-yr)	N= 2155 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	42 (1.86)	25.60	36 (1.67)	23.28	1.10 (0.71,1.72)	0.663
Major Secondary Efficacy Endpoint 1	124 (5.50)	75.58	141 (6.54)	91.18	0.83 (0.65,1.06)	0.135
Major Secondary Efficacy Endpoint 2	131 (5.81)	80.01	147 (6.82)	95.28	0.84 (0.67,1.07)	0.154
Other Efficacy Endpoints						
Stroke Type	33 (1.46)	20.06	35 (1.62)	22.62	0.89 (0.55,1.43)	0.636
Primary Hemorrhagic Stroke	0 (0.00)	0.00	4 (0.19)	2.56	0.00	
Primary Ischemic Stroke	28 (1.24)	16.99	31 (1.44)	20.02	0.85 (0.51,1.42)	0.542
Unknown Stroke Type	5 (0.22)	3.02	0 (0.00)	0.00		
Stroke Outcome	33 (1.46)	20.06	35 (1.62)	22.62	0.89 (0.55,1.43)	0.636
Stroke Outcome Death	11 (0.49)	6.64	13 (0.60)	8.34	0.80 (0.36,1.79)	0.587
Disabling Stroke	11 (0.49)	6.65	8 (0.37)	5.13	1.30 (0.52,3.23)	0.572
Nondisabling Stroke	9 (0.40)	5.44	13 (0.60)	8.36	0.65 (0.28,1.53)	0.325
Stroke Outcome Missing Rankin	2 (0.09)	1.21	1 (0.05)	0.64	1.88 (0.17,20.8)	0.605
Non-CNS Systemic Embolism	9 (0.40)	5.43	2 (0.09)	1.28	4.24 (0.92,19.6)	0.064
Myocardial Infarction	13 (0.58)	7.85	10 (0.46)	6.42	1.23 (0.54,2.80)	0.625
All Cause Mortality	145 (6.43)	87.33	170 (7.89)	108.8	0.80 (0.64,1.00)	0.054
Vascular Death	89 (3.95)	53.60	113 (5.24)	72.34	0.74 (0.56,0.98)	0.036*
Non-vascular Death	48 (2.13)	28.91	50 (2.32)	32.01	0.90 (0.61,1.34)	0.620
Unknown Death	8 (0.35)	4.82	7 (0.32)	4.48	1.08 (0.39,2.97)	0.886

Figure 33 depicts the survival curve for primary efficacy curve from Day 3 to Day 30 after early discontinuation of study drug. Note that there are more events in the rivaroxaban arm until about day 6, but over the next enough events accrue in the warfarin arm to nearly equalize event rates in the two arms.

Figure 33. Survival Curve Of Primary Efficacy Endpoint Events From Day 3 To Day 30



[Table 63](#) provides information on primary event rates in the patients who discontinued study drug over segments of the period from Day 3 to Day 30. Consistent with the pattern of events in the previous figure, the event rate is highest in the rivaroxaban arm between Day 3 and Day 7, but there are more warfarin arm events from Day 8 to Day 30.

Table 63. ROCKET - Primary Efficacy Endpoint Events From Day 3 To Day 30

(After Early Discontinuation of Study Drug)
Safety population excluding Site 042012

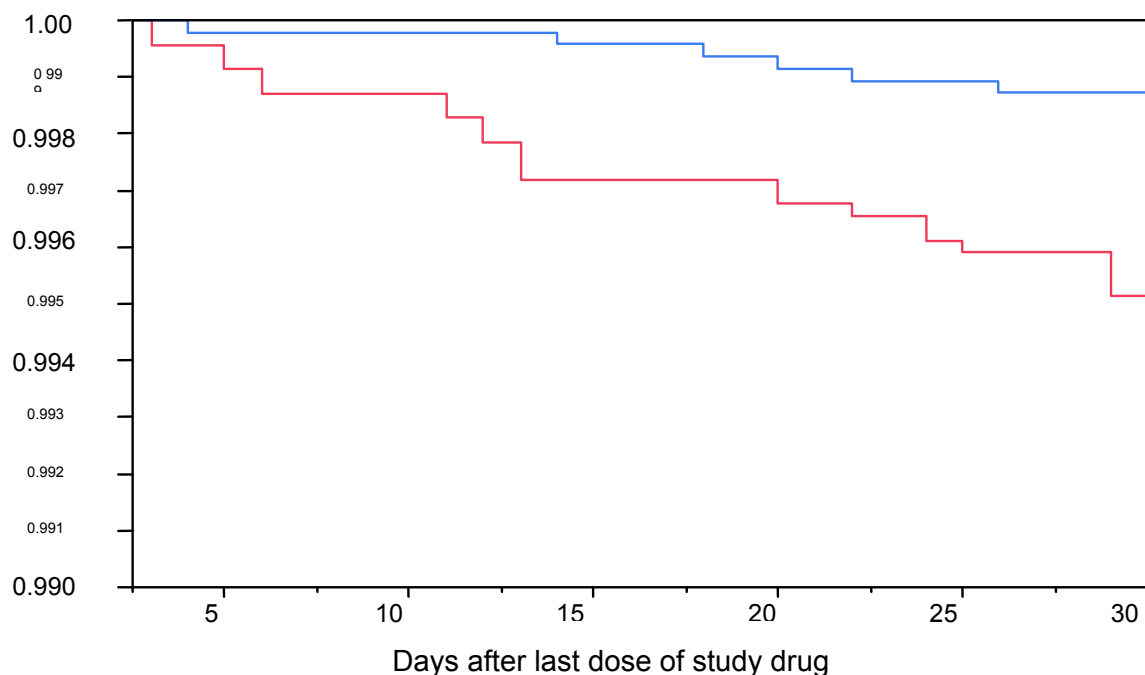
	Rivaroxaban		Warfarin	
Days after last dose (days in period)	n/N	Event Rate ¹	n/N	Event Rate ¹
Days 3-30 (28)	42 / 2206	24.8	36 / 2116	22.1
Days 3-7 (5)	25 / 2206	82.7	12 / 2116	41.4
Days 8-14 (7)	8 / 2128	19.6	17 / 2030	43.7
Days 15-30 (16)	9 / 2095	9.8	7 / 1972	8.1

¹ Events per 100 patient-years, calculated assuming all patients entering a period are at risk throughout the entire period. True event rates would be slightly higher due to attrition of the denominator during the event window.

Figure 34 is KM plot of primary efficacy endpoint events in the period from Day 3 to Day 30 after the last dose of study drug for study completers. Table 64 provides results for all efficacy endpoints for the same population in this period. The rate of primary efficacy events is significantly higher in the rivaroxaban arm than in the warfarin arm, but event rates are low compared to the early discontinuation population. Note that in this population, discontinuation from the study was based on a generalized decision to shut down the study at the site level. Thus informative censoring would not be an issue for these patients.

From Day 3 to Day 30, there were 22 vs. 6 primary endpoint events in the rivaroxaban and warfarin arms, respectively, corresponding to event rates of 6.4 vs. 1.7 events per 100 patient-years ($p=0.004$). The warfarin arm event rate during this period is roughly comparable the warfarin arm event rate during treatment, while the rivaroxaban arm event rate during this period is about 4 fold higher than during treatment (see Table 61). As expected, the data indicate that this population was healthier than patients who discontinued study treatment early.

Figure 34. Survival Curve Of Primary Efficacy Endpoint Events From Day 3 To Day 30



All primary efficacy endpoint events during this period were strokes in the patients who completed therapy. In the rivaroxaban arm, 18 patients had an ischemic stroke and 4 had a hemorrhagic stroke. In the warfarin arm 4 patients had an ischemic stroke and 2 had a stroke of unknown type. There were 14 vs. 8 deaths in the rivaroxaban and warfarin arms, respectively; 12 vs. 7 of these were vascular deaths. There were 1 vs. 2 patients with myocardial infarction in the rivaroxaban and warfarin arms, respectively. Driven by the stroke and vascular death outcomes, the results for both Major Secondary Efficacy Endpoint 1 (composite of stroke, systemic embolism, and vascular death) and Major Secondary Efficacy Endpoint 2 (composite of stroke, systemic embolism, vascular death and myocardial infarction) significantly favored warfarin.

Table 64. ROCKET - Efficacy Endpoint Events From Day 3 To Day 30 After Last Dose Of Study Drug In Completers

(Study 39039039AFL3001: Safety (Excluding SITE=042012) Analysis Set)

Early Study Medication Discontinuation: No
Analysis Set: Safety (Excluding SITE=042012)

Endpoints	----- Rivaroxaban -----		----- Warfarin -----		---- Rivaroxaban vs. Warfarin ----	
	N= 4587 n (%)	Event Rate (100 Pt-yr)	N= 4652 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	22 (0.48)	6.42	6 (0.13)	1.73	3.72 (1.51,9.16)	0.004*
Major Secondary Efficacy Endpoint 1	30 (0.65)	8.76	12 (0.26)	3.45	2.54 (1.30,4.95)	0.006*
Major Secondary Efficacy Endpoint 2	31 (0.68)	9.05	14 (0.30)	4.03	2.24 (1.19,4.22)	0.012*
Other Efficacy Endpoints						
Stroke Type	22 (0.48)	6.42	6 (0.13)	1.73	3.72 (1.51,9.16)	0.004*
Primary Hemorrhagic Stroke	4 (0.09)	1.17	0 (0.00)	0.00		
Primary Ischemic Stroke	18 (0.39)	5.25	4 (0.09)	1.15	4.56 (1.54,13.5)	0.006*
Unknown Stroke Type	0 (0.00)	0.00	2 (0.04)	0.58	0.00	
Stroke Outcome	22 (0.48)	6.42	6 (0.13)	1.73	3.72 (1.51,9.16)	0.004*
Stroke Outcome Death	4 (0.09)	1.17	1 (0.02)	0.29	4.06 (0.45,36.3)	0.210
Disabling Stroke	12 (0.26)	3.50	0 (0.00)	0.00		
Nondisabling Stroke	5 (0.11)	1.46	4 (0.09)	1.15	1.26 (0.34,4.71)	0.726
Stroke Outcome Missing Rankin	1 (0.02)	0.29	1 (0.02)	0.29	1.01 (0.06,16.2)	0.992
Non-CNS Systemic Embolism	0 (0.00)	0.00	0 (0.00)	0.00		
Myocardial Infarction	1 (0.02)	0.29	2 (0.04)	0.58	0.50 (0.05,5.55)	0.575
All Cause Mortality	14 (0.31)	4.08	8 (0.17)	2.30	1.77 (0.74,4.22)	0.197
Vascular Death	12 (0.26)	3.49	7 (0.15)	2.01	1.73 (0.68,4.41)	0.247
Non-vascular Death	2 (0.04)	0.58	0 (0.00)	0.00		
Unknown Death	0 (0.00)	0.00	1 (0.02)	0.29	0.00	

Table 65 provides information on the time course of primary endpoint events over the 28 day period from Day 3 to Day 30 after the last dose of study drug in completers. The warfarin arm event rate was low and consistent throughout this period, ranging from 1.1 to 1.6 events per 100 patient-years in the 3 segments, and was lower than the warfarin arm event rate on treatment (2.16 events per 100 patient-years). In the rivaroxaban arm, the event rate was highest in the first 5 days (9.4 per 100 patient-years) and then dropped, but was numerically higher than the warfarin arm event rate in each of the 3 segments of the overall period. Notably, the event rate in the first five days in the rivaroxaban arm was not higher than the placebo arm stroke event rate in the EAFT trial (12 per 100 patient-years), the only placebo controlled trial of warfarin for stroke prevention in patients with atrial fibrillation that had included an appreciable percentage of patients with a history of stroke at baseline (76%; the remainder had a baseline history of TIA). This suggests that the stroke rate in the rivaroxaban arm in ROCKET during day 3 to 30 after the last dose of study drug may not be inconsistent with sub-therapeutic warfarin levels in a population at high risk for stroke.

Table 65. ROCKET – Primary Efficacy Events From Day 3 To Day 30

(After Last Dose of Study Drug in Completers, (Safety Population)

	Rivaroxaban		Warfarin	
Days after last dose (days in period)	n/N	Event rate¹	n/N	Event Rate¹
Days 3-30 (28)	22 / 4637	6.2	6 / 4691	1.7
Days 3-7 (5)	6 / 4637	9.4	1 / 4691	1.6
Days 8-14 (7)	7 / 4629	7.9	1 / 4688	1.1
Days 15-30 (16)	9 / 4622	4.4	4 / 4687	1.4

The results for the analysis in the previous table were disaggregated by the number of days between the last dose of rivaroxaban and the first dose of VKA (Table 66). In the rivaroxaban arm, there were no events in the 47 patients who received VKA before the last dose of study drug. The data suggest a relationship between the start of VKA relative to the last dose of rivaroxaban and the rate of events from day 3 to 30. There were few events in the warfarin arm, and the event rate ranged from 0 to <2 in the various cohorts.

Table 66. ROCKET – Primary Endpoint Events Day 3-30

(After Last Dose of Study Drug in Completers. Safety Population)

	Rivaroxaban		Warfarin	
Days between last dose and initiation of VKA	n/N	Event rate¹	n/N	Event Rate¹
VKA started before last dose	0 / 47	0	0 / 61	0
0-2 days after last dose	17 / 3992	5.50	6 / 4022	1.93
3-7 days after last dose	2 / 144	17.82	0 / 156	0

Did not start VKA by day 30 ²	2 / 356	7.32	0 / 363	0
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¹ Per 100 pt-years.

² The number of patients in the categories between day 7 and 30 was small, and there was one event in the rivaroxaban arm vs. none in the warfarin arm.

We analyzed the characteristics of the completing patients who had primary endpoint events between day 3 and 30 after the last dose of study drug (Table 67). Patients in the warfarin arm were slightly older (mean age 70.8 vs. 74 years) and had somewhat higher CHADS₂ scores (mean of 4.1 vs. 4.25). Note that the overall study CHADS₂ mean score was 3.5. Notably, patients in both arms had a high rate of prior history of stroke/TIA/SE: over 80% in each treatment arm in this subgroup, compared to 55% for the study as a whole.

Table 67. Characteristics Of Completing Patients With Primary Endpoint Events 3 To 30 Days

(After last dose of study drug, Safety Population)

	Rivaroxaban (N=22)	Warfarin (N=6)
Age (mean)	70.77	74.00
Baseline CHADS₂ score (mean)	4.09	4.25
History of stroke/TIA/SE (N, (%))	19 (86.3)	5 (83.3)
History of no prior VKA use (N, (%))	11 (50)	2 (33.3)

Reviewer Comment: These data suggests that the completers who had events in this period simply may have been a high risk group with a low tolerance for inadequate anticoagulation. Rivaroxaban arm patients may be been at greater risk than those in the warfarin arm simply because of the short half-life of rivaroxaban's PD effect compared to warfarin, which could have increased the degree and duration of inadequate anticoagulation in the rivaroxaban arm.

6.1.10.3.1.1 Extent and Quality of Anticoagulation in ROCKET after discontinuation of study drug

As noted above, the DSMB had information from J ROCKET indicating that the quality of anticoagulation after discontinuation of study drug contributed to the excess of primary endpoint events in the rivaroxaban arm. Patients in the warfarin arm (at least those who were started on open label VKA) would likely have a less marked lapse in anticoagulation, if any, after discontinuation of study drug, and they fared better in J ROCKET.

ROCKET was a much larger study and there are substantially more data on the extent and quality of anticoagulation after discontinuation of study drug than in J ROCKET, so the results from ROCKET will be stressed here.

As one might expect, the percentage of patients who received anticoagulation was lower among patients who discontinued study drug early than in completers. In the former group, slightly more than half of patients in either treatment arm did not receive VKA in the 30 days after the last dose of study drug. Information on time to the first dose of open-label VKA treatment in the early discontinuation patients is displayed in [Table 68](#).

Table 68. ROCKET – Time To First Dose Of VKA Within 30 Days After Last Dose Of Study Drug – Early Discontinuation Patients

Analysis Set: Safety	Rivaroxaban	Warfarin
	(N=2520)	(N=2468)
Time Between Last Dose of Study Drug and Start of Open Label VKA	n (%)	n (%)
0 (DAY)	313 (12.42)	287 (11.63)
1 (DAY)	442 (17.54)	390 (15.80)
2 (DAYS)	77 (3.06)	80 (3.24)
3 (DAYS)	41 (1.63)	43 (1.74)
4 (DAYS)	37 (1.47)	38 (1.54)
5 (DAYS)	23 (0.91)	31 (1.26)
6 (DAYS)	23 (0.91)	29 (1.18)
7 (DAYS)	30 (1.19)	27 (1.09)
8-14 (DAYS)	102 (4.05)	89 (3.61)
15-21 (DAYS)	43 (1.71)	53 (2.15)
22-30 (DAYS)	53 (2.10)	37 (1.50)
0-30 (DAYS)	1184 (46.98)	1104 (44.73)
Did not receive VKA in this period	1336 (53.02)	1364 (55.27)

About 47% and 45% of early discontinuation patients in the rivaroxaban and warfarin arms, respectively, were started on VKA in the 30 days after the last dose of blinded study medication.

In the majority of such patients in each arm, open label VKA therapy was started on the same day or one day after the last dose of study drug. Information on dose of VKA was not provided.

INR information was not routinely collected in patients who discontinued study drug early.

Use of other anticoagulant classes was not common in this cohort. About 12.8% and 12.1% of patients in the rivaroxaban and warfarin arms, respectively, received non-VKA anticoagulants. About 34.0% and 34.8% of patients received one or more anti-platelet agents (aspirin, thienopyridines or “other”) in the rivaroxaban and warfarin arms, respectively.

In the roughly 2/3 of ROCKET patients who completed study drug, the overall rate of anticoagulation was substantially higher than in the early discontinuation patients.

Table 69 provides Information on time to the first dose of open-label VKA treatment in completing patients.

Table 69. ROCKET – Time To First Dose Of VKA Within 30 Days After Last Dose Of Study Drug – Completing Patients

Analysis Set: Safety	Rivaroxaban (N=4591)	Warfarin (N=4657)
Time in Days Between Last Dose of Study Drug and Start of Open Label VKA	n (%)	n (%)
0	518 (11.28)	556 (11.94)
1	3381 (73.64)	3373 (72.43)
2	142 (3.09)	157 (3.37)
3	41 (0.89)	49 (1.05)
4	37 (0.81)	36 (0.77)
5	30 (0.65)	35 (0.75)
6	21 (0.46)	17 (0.37)
7	13 (0.28)	17 (0.37)
8-14	32 (0.70)	30 (0.64)
15-21	9 (0.20)	10 (0.21)
22-30	8 (0.17)	12 (0.26)
0-30	4232 (92.18)	4292 (92.16)
Did not receive VKA in this period	359 (7.82)	365 (7.84)

About 92% of completing patients in each treatment arm received open label VKA in the 30 day period after the last dose of study drug. More than 80% of these patients started open label VKA therapy the same day as their last dose of study drug or one day later. Note that the end of study visit typically occurred on the day after the last dose of study drug, which occurred in the evening; this day was by far the most common day to start VKA in this cohort of patients.

Spotty INR information was collected from these patients. There was no dedicated page in the case record for these data, but the sites were instructed to capture it on the

local laboratory results page. They were also instructed not to use of the point of care device during the post-treatment period and not to get an unblinded INR until the 3rd day after the last dose of study medication.

Table 70 provides information on the last observed INR in the period beginning on day 1 after the last dose of study and ending on either the date of the first primary efficacy endpoint in the post-treatment period (Day 3 to Day 30) or on day 30 after the last dose, which ever occurred first, for completers.

Table 70. ROCKET – Last Observed INR Between Day 1 After Last Dose Of Study Drug And Either The First Primary Efficacy Endpoint (Day 3 To Day 30) Or Day 30, Completing Patients

INR Category	Rivaroxaban			Warfarin		
	Total N=4231	No Event N=4212	With Event N=19	Total N=4291	No Event N=4285	With Event N=6
<1.5	1281 (30.28)	1274 (30.25)	7 (36.84)	413 (9.62)	412 (9.61)	1 (16.67)
1.5 to <1.8	580 (13.71)	575 (13.65)	5 (26.32)	481 (11.21)	479 (11.18)	2 (33.33)
1.8 to <2	304 (7.19)	304 (7.22)	0	474 (11.05)	474 (11.06)	0
2 to 3	1261 (29.80)	1257 (29.84)	4 (21.05)	2149 (50.08)	2147 (50.11)	2 (33.33)
>3 to 3.2	97 (2.29)	97 (2.30)	0	143 (3.33)	143 (3.34)	0
>3.2 to 5	353 (8.34)	352 (8.36)	1 (5.26)	332 (7.74)	332 (7.75)	0
>5	145 (3.43)	144 (3.42)	1 (5.26)	64 (1.49)	64 (1.49)	0
No INR	210 (4.96)	209 (4.96)	1 (5.26)	235 (5.48)	234 (5.46)	1 (16.67)

The overall data for rivaroxaban patients indicate that about 30% of patients had their last INR in the therapeutic range, 51% were below range, 14% were above range, and 5% had no INR. Among those who had events, 13 of 19 were below range and 1 had no INR.

Among the warfarin patients overall, 50% of patients were in range on their last INR, 31% were below range, 13% were above range, and 5% had no INR. Among the 6 patients with events, 2 were in range, 3 were below range and 1 had no INR.

These data suggest that warfarin arm patients were better controlled in the post-treatment period to the extent that INR data are available. Patients who had events tended to be less well controlled than those who did not, but the number of patients with events was small.

Reviewer Comment: The available data suggest that many patients who discontinued early did not receive effective anticoagulant therapy. While > 90% of completers received anticoagulant therapy, most in a timely manner, the

available INR data suggest that patients in the warfarin study arm were better anticoagulated than those in the rivaroxaban arm.

6.1.10.3.2 Comparisons of “VKA naïve” patients at the start and after the end of double blind treatment

ROCKET study patients who entered the study VKA naïve and were randomized into the warfarin arm may be similar in terms of their risk of thrombotic events to rivaroxaban arm patients who completed the study and then started warfarin treatment, since both subgroups of patients were started on warfarin during the study after extended period of time without warfarin treatment. Thus, a comparison of event rates in these subgroups of patients might be useful in assessing the cause of the excess of strokes in rivaroxaban arm completers in the day 3 to 30 period after the last dose of study drug. Similar event rates in the two populations, one transitioning from essentially no anticoagulant therapy to warfarin, and the other transitioning from rivaroxaban therapy to open label VKA therapy, might suggest that the elevated event rate observed in the latter group of patients might simply be due to poor INR control, as was observed in the VKA naïve patients at the start of the study.

We asked the sponsor to perform a time to event analysis for primary efficacy endpoint events in warfarin arm patients covering the first 30 days after randomization, looking at all patients and the subgroups of VKA naïve and experienced patients. Data from these analyses, along with data for rivaroxaban completers in the day 3 to 30 window after the last dose of study drug are displayed in [Table 71](#). Cell of interest are shaded; other cells are provided for completeness, but are not relevant to the comparison of interest.

Table 71. Comparison Of Primary Efficacy Endpoint Event Rates In “VKA Naïve” Patients

Safety Population

		Warfarin		Rivaroxaban	
			Event Rate		Event Rate
		n/N	(100 pt-yr)	n/N	(100 pt-yr)
Start of Treatment	Time Interval after Randomization				
All patients	Days 1-30	20/7082	3.50	13/7061	2.29
VKA Experienced	Days 1-30	12/4437	3.34	8/4401	2.25
VKA Naïve	Days 1-30	8/2645	3.78	5/2660	2.35
After Completion	Time interval after last dose				
All	Days 3-30	6/4652	1.73	22/4587	6.42

completers					
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The primary efficacy endpoint event rate over the 30 days following randomization in warfarin naïve patients who then began blinded VKA therapy was 3.78 events per hundred patient years. At the end of the study, the event rate in rivaroxaban arm patients (all presumably warfarin naïve at the time), more than 90% of whom then began label VKA, was 6.42 per hundred patient years, 1.72 x the rate for the warfarin naïve patients at the start of the study. These data do not allay our concerns about the possible existence of a hypercoagulable state in patients who discontinue from chronic rivaroxaban therapy.

6.1.10.3.3 Events during interruptions of therapy in ROCKET

Patients with temporary interruptions of therapy might be another subset of study patients at greater risk of thrombotic events. Accordingly, we asked the Sponsor to analyze the rate of primary endpoint events during interruptions of double blind treatment of at least 3 days duration, since events in the first 2 days after the last dose of study drug are captured as on treatment events. Note that all on treatment analyses favored rivaroxaban. [Table 72](#) and [Table 73](#) provide information on the number and percentage of patients in the treatment arms with interruptions of treatment of at least 3 days in duration and the primary event rates associated with those interruptions, respectively. The event window for this analysis was from 3 days after the last dose of study drug to 3 days after resumption of double-blind treatment.

Table 72. ROCKET - Interruptions Of Treatment \geq 3 Days In Duration

Safety Population (excluding site 042012)

	Rivaroxaban (N = 7061) n (%)	Warfarin (N = 7082) n (%)	Total (N = 14143) n (%)
Subjects with at least 1 interruption	2307 (32.67)	2668 (37.67)	4975 (35.18)
Duration of interruption			
3-7 days	1361 (58.99)	1689 (63.31)	3050 (61.31)
8-14 days	468 (20.29)	482 (18.07)	950 (19.1)
15-30 days	298 (12.92)	298 (11.17)	596 (11.98)
\geq 31 days	180 (7.8)	199 (7.46)	379 (7.62)
Mean (SD)	12.48 (18.23)	11.7 (18.49)	12.06 (18.38)
Median	6	6	6
Min	3	3	3
Max	215	383	383

Table 73. Adjudicated Primary Endpoint Events During Treatment Interruptions \geq 3 Days

Safety Population (excluding site 042012)

	Rivaroxaban		Warfarin		R vs. W	
Interruption Period Length	N= 2307 n (%)	Event Rate (100 Pt-yr)	N= 2668 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
All	9 (0.39)	9.86	8 (0.30)	8.01	1.26 (0.48,3.25)	0.64
3-7 Days	5 (0.37)	20.36	4 (0.24)	13.31	1.53 (0.41,5.68)	0.529
8-14 Days	1 (0.21)	6.21	2 (0.41)	12.24	0.51 (0.05,5.60)	0.58
15-30 Days	1 (0.34)	5.31	0 (0.00)	0	-	-
\geq31 Days	2 (1.11)	6.28	2 (1.01)	5.75	1.10 (0.15,7.79)	0.926

Time to event analysis with event window ranging from 3 days after last dose to 3 days after resumption of therapy.

About 33% and 38% of patients in the rivaroxaban and warfarin arms, respectively, had interruptions of treatment. About 60% of these in each arm were between 3 and 7 days in duration. The longest such interruption was 383 days. Interruptions in each arm averaged about 12 days, with a median of 6 days.

There were only 17 primary efficacy endpoint events overall that were associated with treatment interruptions, and the rates in the treatment arms did not differ substantially. significantly. For all interruptions regardless of length, the event rates were 9.86 and 8.01 events per 100 patient-years in the rivaroxaban and warfarin arms, respectively, with a hazard ratio of 1.26 (95% CI, 0.48,3.25, p=0.64). Event rates were highest in the shortest subset of interruptions (3-7 days, see [Table 73](#)).

These data do not support an important difference in the risk of thrombotic events in patients during interruptions of therapy with rivaroxaban compared to warfarin. However, like the on-treatment analyses, this analysis could have been biased in favor of rivaroxaban by the overall sub-optimal control of anticoagulation in the warfarin arm.

6.1.10.3.4 J ROCKET

J ROCKET also showed an excess of post treatment primary endpoint events in the rivaroxaban arm. In fact, J ROCKET ended several months before ROCKET and the ROCKET DSMB was aware of the J ROCKET findings, which they believed were due at least in part to suboptimal anticoagulation after discontinuation of study drug, and expressed concern about the possibility of this occurring in ROCKET.

Primary endpoint events on treatment and after discontinuation of study drug in the J ROCKET study are summarized in [Table 74](#). During the on treatment period, up to the last dose + 2 days, there were 11 and 22 primary endpoint events in treated patients in the rivaroxaban and warfarin arms, respectively. The duration of treatment was 71 and 60 weeks in the rivaroxaban and warfarin arms, respectively. In the 4 weeks following the on treatment period, there were 11 and 3 primary endpoint events in the rivaroxaban and warfarin arms, respectively. Thus in the rivaroxaban arms, there were an equal number of events in the two periods, but the on treatment period was nearly 18 x the duration of the post-treatment event window.

All post-treatment primary endpoint events in either arm were strokes. In the rivaroxaban arm, there were 10 patients with ischemic strokes and one with a hemorrhagic stroke. All four patients with strokes in the warfarin arm had ischemic strokes. As in ROCKET, the rate of post-treatment events was higher in each treatment arm in patients who discontinued study drug early compared to those who completed the study, and post treatment rates overall and in the subgroups of patients with early discontinuation of study drug and completers were higher in the rivaroxaban arm than for warfarin. As in ROCKET, the event rates in the warfarin arm were similar in the on treatment period and for completers in the post treatment period.

Table 74. J ROCKET – Summary Of Primary Endpoint Events On Treatment And After Discontinuation Of Study Drug

Safety Population

Event Window	Riva n/N (%)	Event Rate (100 pt-yr) ¹	Warfarin n/N (%)	Event Rate (100 pt-yr) ¹
On-treatment (last dose + 2 days) ²	11 / 639 (1.7)	1.26	22 / 639 (3.4)	2.60
Day 3-30 after last dose – All patients	11 / 628 (1.8)	22.8	3 / 630 (0.5)	6.2
Early Discontinuations	6 / 148 (4.1)	52.8	2 / 162 (1.2)	16.1
Completers	5 / 480 (1.0)	13.6	1 / 468 (0.2)	2.8

¹ On treatment event rates were provided by Sponsor. Post treatment event rates were calculated by FDA assuming no attrition of subjects during the 28 day event window, yielding rates somewhat lower than the actual rates.

² Median duration of treatment was 71 and 69 weeks in the rivaroxaban and warfarin arms, respectively.

6.1.10.3.5 Post discontinuation data from other clinical programs

The sponsor provided information on CV event rates from controlled studies of the use of rivaroxaban for other indications.

In the 4 RECORD studies of DVT prevention, rivaroxaban 10 mg once daily was compared to enoxaparin/VKA in over 12,000 orthopedic surgery patients treated for 12 or 35 days. There was no signal of excess CV events (MI, ischemic stroke, CV death) during treatment. However, for events occurring later than one day after the end of treatment (the end of the event window is not stated), there were 16 (0.26%) CV events in the rivaroxaban arm (N=6097) vs. 10 (0.16%) such events in the comparator arm (N=6195). There were 5 cases of ischemic stroke (0.08%) vs. 1 case (0.02%); 5 cases of MI (0.8%) vs. 4 cases (0.6%), 6 cardiovascular deaths (0.10%) vs. 3 (0.05%), and 1 unexplained death (0.02%) vs. 3 (0.05%).

In the 2 Einstein studies of DVT treatment with rivaroxaban vs. enoxaparin/VKA or other control in over 4500 patients, there was no signal of excess post-treatment events for rivaroxaban.

However, for both DVT prevention (where a potential signal of risk was observed in RECORD studies) and DVT treatment, thrombotic risk is believed to usually abate over weeks to months, which allows treatment to end. Such patients are not anticoagulated for life. However, atrial fibrillation patients for whom anticoagulation is indicated typically require anticoagulation until they achieve demonstrably stable sinus rhythm. If anticoagulation is discontinued before that occurs, the patient will be a high risk for stroke. In addition, there are differences between arterial and venous clots that may be relevant. Thus, negative studies regarding post-treatment thrombotic risk in patients with or at risk for DVT are of little value in predicting risk for AFib patients.

6.1.10.3.6 Laboratory Data Relating to Hypercoagulability

We asked the sponsor for information relating the potential existence of a hypercoagulable state in patients who came off rivaroxaban therapy that may be contributed to the excess number of events those patients. The sponsor indicated that they had not performed such studies. However, they provided the results of an investigation of the effects of rivaroxaban on thrombin-anti-thrombin complex (TAT) and fibrinogen levels in an in vivo model of hypercoagulability in rats. Rivaroxaban was administered to rats IV at doses providing plasma levels of 3-1930 µg/L. This range overlaps both the range of trough levels (12.2-137µg/L) and the C_{max} levels (184-343µg/L) associated with a dose of 20 mg once daily in AFib patients. TAT, a marker of thrombin generation and fibrinogen levels were measured 10 minutes after injection of tissue factor in rats, when maximal increase of TAT was achieved.

Rivaroxaban inhibited the increase of TAT in a dose-dependent manner. Fibrinogen levels remained constant. The lowest dosages examined (0.0009-0.0027 mg/kg; 3-16 µg/L plasma concentration) had no effect on TAT and fibrinogen. However, low doses of the melagatran control were associated with increased levels of TAT and decreased fibrinogen. While this experiment suggests that trough levels of rivaroxaban are not thrombogenic, it does not model complete withdrawal of rivaroxaban after chronic use.

In another experiment, the sponsor studied thrombin activity and prothrombin fragment 1+2 (F1+2) (markers for tissue factor-mediated thrombin formation) in plasma from healthy volunteers in the absence or presence of TM (thrombomodulin) or in protein C-deficient plasma. TM was added to plasma to activate protein C.

Rivaroxaban inhibited thrombin generation in a concentration-dependent manner over the broad concentration range of 8 µg/L - 475 µg/L, covering both the trough (12.2-137µg/L) and C_{max} (184-343µg/L) levels associated with a dosage of 20 mg once daily in AFib patients, in normal plasma in the absence and presence of thrombomodulin and in protein C-deficient plasma. The sponsor suggests that the results indicate that, under

the experimental conditions, rivaroxaban does not affect the negative–feedback reaction of the thrombin-TM/APC (activated protein C) system.

Assay sensitivity was confirmed by the use low concentrations of melagatran and dabigatran, which increased thrombin formation in the presence of TM or in protein C-deficient plasma. However, like the preceding experiment, this does not exclude the possibility that chronic use of rivaroxaban might induce adaptive, pro-coagulant alterations in the clotting system that would be unmasked when rivaroxaban was withdrawn.

6.1.10.3.7 Summary of data

The sponsor's data submitted in response to our request for information on the possibility that rivaroxaban may induce a hypercoagulable state on withdrawal are not conclusive. However, the ROCKET and J ROCKET study data suggest that patients with events were generally at high risk and that anticoagulation was not well managed after withdrawal of study drug, to the extent that data are available. The US data on primary endpoint rates in completing patients during from day 3 to day 30 after the last dose study of study drug are reassuring: 1 event in 546 subjects in the rivaroxaban arm (2.45 events per 100 patient-years) vs. 0 events in 556 subjects in the warfarin arm ($p=0.56$). In the US, more than 90% of subjects were taking VKA at baseline, suggesting that US investigators were comfortable with VKA treatment and understood its necessity in high risk AFib patients. These data suggest that the high rate of events globally in the rivaroxaban arm after completion of study drug could have been related to poor anticoagulation management. However, a rigorous assessment of the coagulation system in patients who have been withdrawn from long-term rivaroxaban therapy has not been performed, and the existence of abnormalities in such patients predisposing them to thrombotic events has not been ruled out. The latter should done prior to approval. In addition, a transition regimen to warfarin upon discontinuation of rivaroxaban has not been clinically validated with respect to bleeding risk or risk for thrombotic events. For more discussion of this last issue, see Section [6.1.10.3.8](#).

6.1.10.3.8 Instructions for the transition from rivaroxaban to warfarin

The sponsor has submitted proposed labeling with an algorithm for transition from rivaroxaban to warfarin. The text of the new instructions follows:

“In patients who are switching from XARELTO to warfarin, warfarin should be given concurrently with XARELTO for two days using standard warfarin dosing. The INR should be measured **only immediately prior** to administration of the XARELTO dose beginning on Day 3 and daily thereafter, until the $\text{INR} \geq 2.0$. XARELTO should be stopped once the $\text{INR} \geq 2.0$.”

These instructions were not used in any atrial fibrillation study.

Notably, the available safety data suggest that there is an unexplained excess of bleeding in rivaroxaban arm patients in the post-discontinuation period that persists to the 30 day safety event cutoff (Sec 7). At 30 days, the rate of bleeding events is continuing to diverge further from the warfarin arm; the curves are not yet parallel. Addition of concomitant rivaroxaban and warfarin therapy to this situation, even if the overlap with is short, may be problematic. It seems prudent to sort this out in a study in atrial fibrillation patients prior to approval. The study should focus on delineating bleeding risk; a study to rigorously delineate thrombotic event risk would be too large, although thrombotic events could be secondary endpoints. An open label trial in patients taking rivaroxaban chronically (perhaps at least 90 days) and then switched to warfarin would be appropriate. The goal would be to rule out a specified rate of major bleeding over the 60 to 90 days after the transition; the bleeding rate to be ruled out is to be determined. Data on thrombotic events would be collected in such a study, but the study may not be adequately powered to rule an unacceptable increase in the rate of such events. However, there are reasons to believe that an increased rate in thrombotic events would be unlikely:

- There was only 1 thrombotic event in > 500 completers in the US in the period from day 3 to day 30 after the last dose study drug in the rivaroxaban arm, compared to 0 for warfarin. In the US, greater than 90% of patients were on VKA at baseline, and the mean TTR during the study was 63%, suggesting that US physicians understand how and when to anticoagulated AFib patients. The low event rate during the post-discontinuation period in US completers is reassuring.
- The sponsor's proposed transition instructions would keep patients on rivaroxaban during warfarin therapy until the INR is 2. The contribution of rivaroxaban to INR at the interdosing interval with once daily dosing is small in most patients during concomitant warfarin use. Thus, if the INR has reached 2, patients will be in or very near the therapeutic range for warfarin treatment. This too is reassuring.

Reviewer conclusions:

- *The sponsor should perform a study to confirm the safety of the proposed transition regimen. The need to confirm the antithrombotic efficacy of the regimen is less pressing.*
- *The study could be part of a study to demonstrate that rivaroxaban is as effective as warfarin when the latter is used skillfully (see Section 1.1). If the warfarin comparator study is not performed, an open label study could be performed in AFib patients taking rivaroxaban for at least 90 days. Patients could be randomized to be transitioned to warfarin using the proposed transition regimen or continued on rivaroxaban. The study could be powered to detect an increase in the rate of major bleeding, the magnitude of which*

could be based on data from other transition regimens (such as ximelagatran, dabigatran or perhaps apixaban if such data are available in time).

6.1.10.4 Data Regarding Adjudication of the Primary Endpoint

The adjudication process by the CEC is described in detail in Section 5.3.1.10. Strokes and TIAs were adjudicated as a group. All investigator-reported strokes and TIAs were adjudicated, as well as “system-generated events”. The latter were not reported as strokes or TIAs by the investigator, but were identified by a computer algorithm that searched for specified diagnostic procedures and results on relevant CRF pages that might suggest the occurrence of the event of interest. A total of 1022 reported or potential stroke/TIA events were adjudicated. Similarly, a total of 101 investigator-reported and system-generated potential systemic embolic events were sent for adjudication.

Counts of these events, broken down by treatment group, are displayed in Table 75. The 5th column displays the total number of CEC events that were ultimately adjudicated by the CEC as strokes and systemic emboli. The next two columns display the number of “discordant” events. The 6th column (Investigator Yes, CEC No) shows the number of events that were reported by the investigator as strokes or systemic emboli but not adjudicated as such by the CEC. The 7th column (Investigator NO, CEC YES) shows, in the case of strokes the number of events that were reported by the investigator as TIAs or were not reported as either strokes or TIAs (i.e., were system generated), and were ultimately adjudicated by the CEC as strokes. In the case of systemic emboli, the 7th column shows the number of events that were system-generated and ultimately adjudicated by the CEC as systemic emboli.

This reviewer (MR) reviewed the adjudication packages of randomly selected patients represented in the 6th and 7th columns, focusing mostly on events in rivaroxaban arm patients represented in the 6th column and warfarin arm patients represented in the 7th column, because they represent the cases where bias of the CEC could influence the results. The number of such reviewed cases is in parentheses in the relevant cell in column 6 or 7. In each case, the final decision of the CEC seemed reasonably supported by the information in the adjudication package, although some of the cases might reasonably have been decided differently.⁸ Decisions regarding the categorization of

8 One case that might have been decided differently is RIVAROXAFLL3001-086031-111471 (rivaroxaban arm), a 55 year old Chinese woman with dilated cardiomyopathy X 8 years (EF = 23%). AFib X 3 years, and a history of prior lower limb thrombectomy 3 years before the event of interest. She was admitted with a 5 day h/o of continuous abdominal pain. She was afebrile with normal BP, and had abdominal tenderness without rebound. There was shifting dullness. Her WBC was 14.5 K, with 90% “N”, presumably neutrophils. Abdominal CT was negative and pelvic US was not informative. An unidentified study (possibly ultrasound) showed plaque in the left internal carotid artery. She could not afford abdominal angiography. She received antibiotics and anticoagulation, and improved over 10 days. She received multiple medical and surgical consults. The consensus diagnosis was mesenteric arterial occlusion. The CEC adjudicated the case as no systemic embolism because of the lack of imaging

stroke type were not systemically reviewed, but in the reviewed stroke cases, the CEC was consistent in declaring stroke cases with no imaging or autopsy results supporting a specific stroke type to be “unknown” stroke. In addition, there was no information in the adjudication packages that would have unblinded the adjudicators regarding treatment assignment. However, there were notations that some patients were on open-label warfarin, but these patients were no longer taking double-blind study drug.

It is noteworthy that of the stroke cases in the 7th column (Inv. NO, CEC YES), representing system-generated cases), there were 12 cases in the rivaroxaban arm vs. 25 in the warfarin arm, despite the fact that there were 39 system-generated cases sent to adjudication of stroke/TIA from each arm. However, no evidence of bias was found in reviewing the cases. All cases reviewed were consistent with the conclusion that adjudication process was fair and competent.

Table 75. ROCKET - Discordance In Adjudication Of The Primary Endpoint

(All Adjudicated Events, Regardless of Treatment Exposure)

					Discordant Events	
	No. Sent to CEC for Adjudication ²	Inv. Reported Events	System-Generated Events ⁴	CEC Adj. Events (YES)	Inv Yes, CEC No (# re-viewed)	Inv No ¹ , CEC Yes (# re-viewed)
STROKES						
Rivaroxaban	500	341 (120) ³	39	296	58 (9)	13 (2)
Warfarin	522	342 (141) ³	39	309	58 (7)	25 (8)
ALL	1022	683 (261) ³	78	605	116 (16)	38 (10)
SYSTEMIC EMBOLI						
Rivaroxaban	49	40	9	20	22 (5)	2 (0)
Warfarin	52	46	6	29	18 (3)	1 (1)
ALL	101	86	15	49	40 (8)	3 (1)

Inv = Investigator; Adj = Adjudicated

1 Investigator did not classify the event as a stroke or systemic embolism

2 All reported strokes and TIAs and system-generated events that might have been strokes or TIAs were grouped for adjudication

3 The first number is the number of reported strokes; the number in parentheses is the number of reported TIAs; all reported strokes and TIAs, as well as system-generated events, were sent for adjudication

4 See text for discussion of system-generated events

confirmation, but the protocol permitted a diagnosis of systemic embolism on clinical grounds. The CEC might have accepted the clinical diagnosis of systemic embolism in this rivaroxaban arm patient, but did not. However, there are many causes of abdominal pain with an elevated white count besides embolism. The decision of the CC seems not unreasonable. I observed nothing in the adjudication package PDF provided to us that might have unblinded the CEC.

Clinical Review: Nhi Beasley, Preston Dunnmon and Martin Rose
Application type: Standard, NDA 22-439
Xarelto (rivaroxaban)

Reviewer comment: There is no evidence that the adjudication process was biased or produced unreasonable results.

7 Review of Safety

Safety Summary

NDA 202439 is submitted for the use of rivaroxaban in the AFib indication. The primary safety concern for this application was the potential for drug-associated bleeding because:

- the dose has been doubled to 20 mg daily from the 10 mg daily dose approved for VTE/PE prevention
- dosing will be chronic as opposed to short term as in the DVT/PE prevention indication, and
- The intended population of AFib patients in which the drug will be used for the prevention of cardiogenic systemic emboli is also at risk for coronary artery disease due to commonality of risk-factors, and thus will likely have a higher incidence of co-therapy with anti-platelet agents, which could increase hemorrhagic risk.

However, excess bleeding as defined by the trial's principal safety endpoint did not occur in ROCKET. There are no additional issues that preclude rivaroxaban's US approval on safety grounds (understanding that ischemic stroke is considered an efficacy outcome in ROCKET). There are no novel safety concerns.

Bleeding Safety – ROCKET Double Blind

Single study approval of rivaroxaban in the US for the prevention of ischemic stroke and systemic embolization in patients with AFib is sought on the basis of the ROCKET trial (39039039AFL3001), which enrolled 14,236 patients into the safety population of subjects who received at least one dose of study medication (7111 rivaroxaban treated, 7125 warfarin-treated patients).

While a second trial, J-ROCKET, was executed simultaneously in Japan with a similar design and endpoints, there were important differences between these two studies, including a lower target INR for Japanese patients \geq age 70 (1.6 – 2.6 versus 2.0 to 3.0 in ROCKET). Furthermore, ROCKET is approximately 11 times larger than J-ROCKET, so integrated results between these two trials are driven by ROCKET. Therefore, this reviewer's analyses of bleeding risk focus primarily on the overall ROCKET population, as well as its US subset.

There were three pre-defined data scopes in which safety data was analyzed:

- 1) LD+2 (on-treatment) – time from randomization to last dose of study drug plus 2 days, and
- 2) LD+30 (to-Follow-up) – time from randomization to either the follow up visit (scheduled for 30 days after last dose \pm a window), or from randomization to

exactly LD+30 days. These two different ways of looking at the follow-up period generally produced similar results.

- 3) Regardless of duration – for ROCKET, included the period of time from randomization until the study was completed and terminated by the sponsor. Death specifically was not adjudicated in J-ROCKET after the 30 day follow up visit. Bleeding was not assessed in either study for this data scope.

To assess bleeding risk, the sponsor defined three categories of bleeding severity based on ISTH nomenclature as follows:

- Major Bleeding
 - A decrease in hemoglobin of 2 g/dL or more, or
 - Transfusion of 2 or more units of packed red blood cells or whole blood, or
 - Critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
 - A fatal outcome
- Non-Major Clinically Relevant Bleeding
 - Overt Bleeding not meeting major criteria but associated with medical intervention, unscheduled physician contact, temporary interruption of drug, or subject discomfort
- Minimal Bleeding
 - All other overt bleeding

This definition of major bleeding was similar to that used in RE-LY. To assess for more severe occurrences of major bleeding, FDA reanalyzed various safety outcomes using the TIMI major bleeding criteria, which was bleeding associated with any of the following:

- $A \geq 5$ g/dL decrease in hemoglobin (each unit of packed red blood cells or whole blood transfused counting as 1g of hemoglobin)
- $A \geq 15\%$ absolute decrease in hematocrit (each unit of packed red blood cells or whole blood transfused counting as 3% points)
- Intracranial location (confirmed by magnetic resonance imaging or computer tomography).

Relevant to all comparative bleeding analyses that follow is the fact that with respect to 100 p-y rates of major bleeding, ICH, and hemorrhagic stroke, the warfarin arm of ROCKET performed very similarly to the warfarin arm of RE-LY, another contemporary warfarin-controlled study. This was true even though the ROCKET design was double-blinded as opposed to open label, the ROCKET population was sicker with a higher

mean CHADS2 score, and the definitions of major bleeding between the two trials, though similarly based on ISTH categories, were not exactly the same (see section 7.3.4, subsection Warfarin Consistency Across ROCKET and RE-LY).

The prospectively defined principal safety outcome of the ROCKET trial was a composite of major and clinically relevant non-major bleeding in the LD+2 data scope. The outcomes for the principal safety endpoint (a composite of major and non-major clinically relevant bleeding), major bleeding as well as its components, non-major clinically relevant bleeding (NMCR bleeding), and minimal bleeding, are summarized for ROCKET per [Table 76](#) as follows:

Table 76. CEC adjudicated bleeding in ROCKET

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p (diff)
	N=7111 n (%)	ER per 100 p-y	N=7125 n (%)	ER per 100 p-y		
Safety Endpoint	1475 (20.74)	14.91	1449 (20.34)	14.52	1.03 (0.96, 1.11)	0.442
Major Bleeding	395 (5.55)	3.60	386 (5.42)	3.45	1.04 (0.90, 1.20)	0.576
Hb drop	305 (4.29)	2.77	254 (3.56)	2.26	1.22 (1.03, 1.44)	0.019
Transfusion	183 (2.57)	1.65	149 (2.09)	1.32	1.25 (1.01, 1.55)	0.044
Critical site	91 (1.28)	0.82	133 (1.87)	1.18	0.69 (0.53, 0.91)	0.007
Death	27 (0.38)	0.24	55 (0.77)	0.48	0.50 (0.31, 0.79)	0.003
Non-major	1185 (16.66)	11.80	1151 (16.15)	11.37	1.04 (0.96, 1.13)	0.345
Minimal	258 (3.63)	2.35	226 (2.17)	2.03	1.16 (0.97, 1.39)	0.102

In ROCKET, there were no statistically significant differences between the two treatment groups with respect to the Principal Safety Endpoint, Major Bleeding, NMCR Bleeding, or Minimal Bleeding. However, considering the various components of Major Bleeding, there were significantly more hemoglobin drops and transfusions of 2 units or more in the rivaroxaban arm, which were offset by a statistically significant decrease in critical site bleeding and bleeding resulting in death. As will be seen, this trend toward more hemoglobin decreases and transfusions with rivaroxaban, but fewer critical organ bleeds and death, occurred on virtually every analysis and sub-analysis of major bleeding that was performed. Parity in both the principal safety endpoint of the trial

(major and NMCR bleeding), as well as major bleeding, was demonstrated throughout the time course of the trial in the on-treatment, safety population (see Figure 39 and Figure 40 in Section 7.3.4).

From the ROCKET on-treatment (LD+2) safety population, intracranial bleeds, a subset of critical organ bleeds, occurred less frequently in rivaroxaban-treated patients, as did most of the sub-categories of ICH, including non-traumatic Intraparenchymal bleeds, as can be seen [Table 77](#). Intraparenchymal bleeds together with intraventricular bleeds together defined hemorrhagic strokes in ROCKET.

Table 77. ROCKET ICH Occurrence (LD+2, safety pop)

	<i>Rivaroxaban</i> <i>N = 7111</i> <i>n (%)</i>	<i>Warfarin</i> <i>N = 7125</i> <i>n (%)</i>
Intracranial hemorrhage	55 (0.77)	84 (1.18)
Intraparenchymal	37 (0.52)	56 (0.79)
Non-traumatic	33 (0.46)	54 (0.76)
Traumatic	4 (0.06)	2 (0.03)
Intraventricular	2 (0.03)	4 (0.06)
Subdural hematoma	12 (0.17)	22 (0.31)
Subarachnoid	4 (0.06)	1 (0.01)
Epidural hematoma	0	1 (0.01)

Rivaroxaban's advantage over warfarin in the LD+2 safety population for ICH and hemorrhagic stroke were both statistically significant (HR= 0.67, p=0.019 and HR=.59, p=0.024 respectively), and the K-M curves continuously separated for these events as the trial progressed (see Figure 47 and [Table 92](#), Section 7.3.4)

Due to the small numbers of events, time to fatal bleeding was assessed for the integrated ROCKET and J-ROCKET datasets. The time to first fatal bleed in the overall integrated safety population favored rivaroxaban regardless of whether a broad definition of bleeding-related death (CEC adjudicated major bleeding event and died of any cause within 30 days) or a narrow definition was employed (CEC adjudicated major bleeding event and died with 30 days, where the primary cause of death was adjudicated as vascular), as can be seen in [Table 78](#) below (source: AFib ISS):

Table 78. Time To First Fatal Bleed (ROCKET To Follow Up Visit)

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p (diff)
Fatal Bleeding	N = 7111 n (%)	Event Rate/ 100 pt-yrs	N = 7125 n (%)	Event Rate/ 100 pt-yrs		
Broad Definition	50 (0.70)	0.42	80 (1.12)	0.67	0.63 (0.44, 0.90)	0.011
Narrow Definition	27 (0.38)	0.23	50 (0.66)	0.42	0.55 (0.34, 0.87)	0.012

By a large margin, the predominant site of on-treatment major bleeding in the safety population for both rivaroxaban and warfarin-treated patients was gastrointestinal (GI-Upper, GI-lower, and Rectal), with a somewhat higher percentage of total major bleeds being GI in etiology for the rivaroxaban-treated group than for the warfarin-treated group (incidence 3.18% vs. 2.02%, respectively). Warfarin-treated patients experienced more major bleeds in the intracranial location.

In the United States, bleeding rates of all categories and almost all sub-categories were higher than for the global trial, in both treatment arms, as seen in [Table 79](#) below:

Table 79 ROCKET CEC Adjudicated Bleeds – US – (LD+2, Safety Pop)

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p (diff)
	N=962 n (%)	ER per 100 p-y	N=964 n (%)	ER per 100 p-y		
Safety Endpoint	322 (33.47)	25.24	275 (28.53)	19.54	1.28 (1.09, 1.50)	0.003
Major Bleeding	123 (12.79)	8.06	87 (9.02)	5.35	1.50 (1.14, 1.98)	0.004
Hb drop	99 (10.29)	6.42	64 (6.64)	3.92	1.64 (1.19, 2.24)	0.002
Transfusion	72 (7.48)	4.62	47 (4.88)	2.87	1.61 (1.12, 2.33)	0.011
Critical site	18 (1.87)	1.13	22 (2.28)	1.33	0.85 (0.46, 1.59)	0.614
Death	6 (0.62)	0.38	10 (1.04)	0.60	0.63 (0.23, 1.72)	0.365
Non-major	237 (24.64)	17.86	211 (21.89)	14.72	1.20 (1.00, 1.45)	0.049
Minimal	48 (4.99)	3.10	42 (4.36)	2.58	1.20 (0.79, 1.81)	0.395

Unlike the global trial, there were more major bleeding events in the US. However, examining the pattern of bleeding within the major bleeding sub-categories reveals the same overall pattern as the global trial: an increased frequency of hemoglobin drops and transfusions is offset by a trend toward fewer critical site bleeds and fatal bleeding. While the overall increase in bleeding in the US may be related to the increased ASA usage in the US versus the global population, and the older age of the US population, other demographic factors that might have been expected to increase exposure were absent (estimated GFR in the US was higher, as was the average weight of the US patients). Furthermore, ASA usage and age were not imbalanced within the US, so did not explain the difference between the warfarin and the rivaroxaban treatment arms within the US. With respect to timing, the K-M curves for major bleeding on warfarin and rivaroxaban begin separating almost immediately and continue to do so until approximately trial day 130, at which point they become parallel with rates in both groups that stay fairly constant, per [Figure 53](#) (Section 7.3.4). North American regional compliance was similar to the global trial, though numerically lower.

To explore this finding further, an analysis of major bleeding by TTR quartile was performed for the US, and then for the global on-treatment safety populations. Unique to the US was a notable decrease in major bleeding rates on warfarin as TTR within the US improved (100 p-y major bleeding rates in the warfarin arm decreased from 7.20 in the worst quartile of warfarin management to 3.61 in the best quartile of warfarin

management), as seen in Table 103, Section 7.3.4. This TTR-based difference in warfarin major bleeding was not present in the global data set, though rivaroxaban major bleeding increased in the global analysis as a function of warfarin TTR, an unexpected finding. Thus, two different mechanisms accounted for the increased bleeding in the 4th TTR quartile globally (an increase in rivaroxaban bleeding rates with higher warfarin TTR) than in the US (a decrease in warfarin bleeding rates with higher warfarin TTR). This suggests the possibility that US major bleeding rate differences as compared to the global trial may have been a chance finding.

Bleeding Safety – ROCKET Posttreatment Transition to Warfarin

In ROCKET, shortly following the early posttreatment transition period in which an elevated stroke rate was noted in rivaroxaban-treated patients relative to warfarin-treated patients, the late transition period demonstrated a statistically significant increase in the occurrence of the principal safety outcome of the trial (major bleeding plus NMCR bleeding) in patients who had taken rivaroxaban during the double-blind phase relative to their warfarin-treated counterparts (113 [1.59%] versus 68 [0.95%]) with a hazard ratio 1.65 (95% CI 1.22 to 2.22; p-value 0.001), as demonstrated in Figure 54 (Section 7.3.4).

During this transition period, there was no difference between the treatment groups in overall major bleeds, with critical organ bleeding and fatal bleeding once again favoring rivaroxaban. This increased bleeding late in transition was driven almost entirely by an increase in NMCR bleeding long after rivaroxaban had washed out, at a time when many patients were being transitioned to VKAs, and a time when there was no protocol-driven control over anticoagulation maintenance. This is unlikely to have been related to rivaroxaban.

Bleeding Safety – Concomitant Aspirin, Thienopyridines, or Both

The PK-PD Outcome study demonstrated an exaggeration of the direct relationship that was demonstrated between PT and Major Bleeding in rivaroxaban-treated patients who had also taking ASA at least 50% of the time during the trial, per table 19 (Section 4.4.3). Aspirin increased the 100 p-y event rate for major bleeding in rivaroxaban-treated patients from 3.02 to 5.82. However, ASA similarly increased the 100 p-y event rate of major bleeding in patients taking warfarin from 3.03 to 4.76.

To explore this phenomenon in more detail, the ROCKET population was examined based on whether patients had taken aspirin at any time during the trial or not. Aspirin usage during ROCKET was common (approximately 2200 patients in both treatment arms). Among patients treated with ASA alone (without thienopyridine co-therapy), all bleeding category rates and almost all major bleeding subcategory rates in both study arms were higher than for patients taking neither ASA or thienopyridines. However, among those taking aspirin, there was no difference in major bleeding between the two

study arms, and once again, critical organ bleeding and fatal bleeding rates favored rivaroxaban.

There were approximately 100 people in each trial arm who took a thienopyridine during the trial without concomitant ASA. In this small group, all bleeding category rates and all major bleeding subcategory rates for both study arms were higher than for patients not taking thienopyridines or ASA. However, among those taking thienopyridines, there were no differences in major bleeding between the two study arms, there were numerically fewer critical organ bleeds in rivaroxaban-treated subjects, and there was only one fatal bleed in each group.

There were 109 rivaroxaban-treated subjects and 143 warfarin-treated subjects who took combination ASA and Thienopyridine therapy during the trial. Among these subjects, all bleeding category rates and all major bleeding subcategory rates for both study arms were higher than for patients not taking either thienopyridines or ASA. However, among those taking ASA and thienopyridines, there were no differences in major bleeding between the two study arms, and once again, there were numerically fewer major bleeds, critical organ bleeds, and fatal bleeds in rivaroxaban-treated patients.

Liver Safety

Extensive review of rivaroxaban's hepatic safety profile, including eDISH analysis of all ALT-TBili elevations from all prior long-term warfarin-controlled studies showed no imbalances of LFT abnormalities between rivaroxaban and its comparators. Case-by-case review of all ROCKET Hy's Law and marked ALT elevations demonstrated alternative causes for all cases.

Post-Market Safety

From the First quarter PSUR, the sponsor is currently considering a change to its Company Core Data Sheet (CCDS) to address six cases of severe pulmonary bleeding, three of which resulted in death. Of these six cases, three were diagnosed with bronchiectasis, one with a lung abscess, one with documented lung cancer, and another with suspected lung cancer who experienced a massive pulmonary hemorrhage 30 minutes before death. This reviewer concurs with a change to the CCDS to address the co-occurrence of bronchiectasis with pulmonary bleeding, and addressing this issue in section 6.4 of the revised label (Postmarketing Experience).

Other occurrences being tracked in the PSUR, but not felt to be drug-associated, are pancreatitis, thrombocytopenia, hypersensitivity, hepatobiliary disorders, skin disorders, and pancytopenia. Of the 1,021 new cases of medically confirmed, serious listed events reported in the first quarter of 2011, 756 were from clinical trials. The majority of these were bleeding events (GI, GU, post-op, hematoma, and anemia).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In the three RECORD series of trials that were the basis for approval for the post-joint replacement DVT/PE prophylaxis indication, Rivaroxaban dosed 10 mg once daily for approximately 12 to 35 days was studied in a total of 9011 patients (4487 Rivaroxaban treated, 4524 enoxaparin-treated patients). In contrast, for the AFib indication which is this subject of this submission, Rivaroxaban dosing was twofold higher (20 mg once daily), dosing was chronic, and the large single study based on which approval is sought, ROCKET (39039039AFL3001), enrolled 14,236 patients into the safety population of subjects who received at least one dose of study medication (7111 rivaroxaban treated, 7125 warfarin-treated patients). Therefore, the ROCKET trial is the focus of the safety analysis for the AFib indication.

While the J-ROCKET study (BAY 59-7939 / 12620) enrolled 1278 patients into the safety population of subjects who received at least one dose of study medication (639 Rivaroxaban treated, 639 warfarin-treated patients), this study employed a different dose of rivaroxaban at 15 mg daily to achieve similar overall exposure in Japanese patients compared to non-Japanese patients. However, there were more important differences:

- A lower INR target was used in J-ROCKET for patients \geq age 70 (1.6 – 2.6 in J-ROCKET versus 2.0 to 3.0 in ROCKET)
- J-ROCKET patients were followed for death only until LD+30 as opposed to ROCKET where all patients were to be followed until the end of the trial for fatal outcomes regardless of the length of that follow up period
- Concomitant anti-platelet therapy was different in the two trials (ROCKET patients could have been on thienopyridine monotherapy on entering the trial, whereas J-ROCKET patients could not)
- There were no US patients in J-ROCKET, and
- The ROCKET study population was approximately 11 times larger than that of J-ROCKET.

Because of these structural differences between ROCKET and J-ROCKET, and because in any integration, ROCKET results will predominate due to its sheer size, J-ROCKET results are considered supportive. Safety analyses for the US sub-population of ROCKET will be considered where appropriate.

7.1.2 Categorization of Adverse Events

Adverse events were coded in ROCKET using MedDRA version 13.0 and in J-ROCKET using MedDRA version 12.1.

There were some differences between the CEC adjudications for ROCKET and J-ROCKET. In ROCKET, all deaths were adjudicated, regardless of exposure, whereas deaths in J-ROCKET were only adjudicated to the follow up visit (approximately LD+30). Bleeding events were adjudicated for both studies only to the follow up visit.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

When data from ROCKET and J-ROCKET were pooled for the purpose of adverse event analyses, adverse events from J-ROCKET were re-coded using MedDRA version 13.0. The sponsor pooled ROCKET and J-ROCKET data for safety analyses in the ISS, though not for efficacy assessments in the ISE.

Given the important differences in the patients and patient management between ROCKET and J-ROCKET, integrated safety was noted, but safety assessments in this review are based predominantly on ROCKET (see Section 7.1.1 for a description of important differences between ROCKET and J-ROCKET).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

ROCKET was a randomized, double-blind, double-dummy, trial that enrolled 14, 236 patients into its safety population. There were 7111 patients randomized to rivaroxaban and 7125 patients randomized to warfarin. The mean / median duration of treatment exposure was 572.23 days / 589 days for the rivaroxaban patients and 579.86 days / 593 days for warfarin patients respectively. The majority of patients received therapy for at least 18 months.

Exposure was adequate for describing safety in the intended population.

The breakdown of rivaroxaban exposure from ROCKET into duration blocks is demonstrated in [Table 80](#) (source: ROCKET FSR):

Table 80. Rivaroxaban Exposure In ROCKET

<i>Rx Duration</i>	<i>Rivaroxaban</i>	<i>Warfarin</i>
> one dose	7111 (100.0)	7125 (100.0)
> 1 month	6800 (95.63)	6854 (96.20)
> 3 months	6477 (91.08)	6551 (91.94)
> 6 months	6089 (85.63)	6222 (87.33)
> 9 months	5800 (81.56)	5888 (82.64)
> 12 months	5558 (78.16)	5624 (78.93)
> 18 months	4001 (56.26)	4074 (57.18)
> 24 months	2512 (35.33)	2571 (36.08)
> 30 months	1057 (14.86)	1062 (14.91)
> 36 months	141 (1.98)	147 (2.06)
> 42 months	1 (0.01)	1 (0.01)
Mean (Days)	572.23	579.86
SD (Days)	294.66	290.08
Min (Days)	1	1
Median (Days)	589	593
Max (Days)	1263	1263

The majority of patients were male (60.32%), white (83.28%), with a mean age of 71 years (range 25 – 97 years). Most patients had received prior VKA therapy (62.42%), and 36.49% had previously taken chronic acetylsalicylate therapy. The population risk factors of prior CVA, TIA, and non-CNS systemic embolism were well balanced between the 2 treatment groups.

7.2.2 Explorations for Dose Response

Only a single dose was explored in ROCKET – 20 mg / day (15 mg / day for patients with moderate renal impairment). Therefore, Dose response relationships could not be assessed. See section 6.1.8 for a discussion of dose selection.

7.2.3 Special Animal and/or In Vitro Testing

No special animal testing and/or in vitro testing performed to support the AFib submission. There was a PK-PD sub-study performed to assess rivaroxaban PK relationships to pharmacodynamic responses with respect to indices of coagulation, including the Prothrombin time (PT), Factor Xa activity (FXa), and Prothrombinase-induced clotting time (PiCT). See Section 4.4.3 thorough discussion of the PK-PD substudy, and the relationship between these PD effects and clinical outcomes with respect to major bleeding.

7.2.4 Routine Clinical Testing

Per the ROCKET protocol, “Subjects returned for visits at Week 1, 2, 4 and then every 4 weeks thereafter for the duration of the double-blind treatment period. After Week 1, all visits during the first year were Full Visits. Clinical laboratory tests (hematology and chemistry) were performed twice during the first year (Week 24 and Week 52); liver-related laboratory testing (ALT, total and direct bilirubin) was performed at Week 2 and then every 4 weeks for the first year. Double-blind treatment visits occurring after 1 year took place every 4 weeks and either a Brief Visit or a Full Visit was performed according to the Time and Events Schedule. A 12-lead ECG and clinical laboratory tests (hematology and chemistry) were performed annually. Unscheduled visits for INR measurement or evaluation of efficacy or safety events occurred at any time during the study.” The ROCKET trial’s schedule of safety procedures is shown in [Table 81](#) below:

Table 81. ROCKET Schedule Of Safety Procedures

Table 4: Schedule of Safety Assessments for ROCKET						
Safety Assessment	Screen	Brief Visits	Full Visits	Discontinuation Visit	EOS Visit	FU Visit
12-lead ECG ^a	X			X	X	
Physical examination	X			X	X	
Vital signs	X			X	X	
INR	X	X	X	X	X	
Hematology and Chemistry ^{a,b}	X			X	X	
Liver-related laboratory tests ^c	X		X	X	X	X ^d
Adverse events ^e	X	X	X	X	X	X

Key: ECG = electrocardiogram; EOS = end of study; FU = follow-up; INR=international normalized ratio;
Screen = screening visit
^a After the first year, ECGs and Hematology and Chemistry were performed annually.
^b Hematology includes hemoglobin, hematocrit, WBC with differential and platelet count. Chemistry includes sodium, potassium, albumin, glucose, BUN, creatinine, amylase and lipase.
^c Includes ALT, AST, bilirubin (total and direct) and alkaline phosphatase at screening. ALT and bilirubin (total and direct) measured at all other visits; AST and alkaline phosphatase done only if ALT>3xULN.
^d For subjects receiving study drug at the EOS visit.
^e Includes bleeding and non bleeding adverse events.

Routine testing was adequate to assess safety in the intended population.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new data submitted. See NDA 022406.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This is discussed in Section 2.4 (important issues with consideration to related drugs).

7.3 Major Safety Results

7.3.1 Deaths

In the integrated data set for both ROCKET and J-ROCKET (LD+2, safety population) all-cause mortality was lower for rivaroxaban than for warfarin, though vascular death was numerically but not statistically higher for rivaroxaban, per Table 82 below (source: ISS Table 1-16):

Table 82. ROCKET + J-ROCKET Death (LD+2, Safety Pop)

Endpoints	----- Rivaroxaban -----		----- Warfarin -----		---- Rivaroxaban vs. Warfarin ----	
	N= 7750 n (%)	Event Rate (100 Pt-yr)	N= 7764 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
All Cause Mortality	217 (2.80)	1.80	257 (3.31)	2.11	0.85 (0.71,1.02)	0.088
Vascular Death	177 (2.28)	1.47	197 (2.54)	1.62	0.91 (0.74,1.11)	0.356
Non-vascular Death	23 (0.30)	0.19	37 (0.48)	0.30	0.63 (0.37,1.06)	0.081
Unknown Death	17 (0.22)	0.14	23 (0.30)	0.19	0.75 (0.40,1.40)	0.364

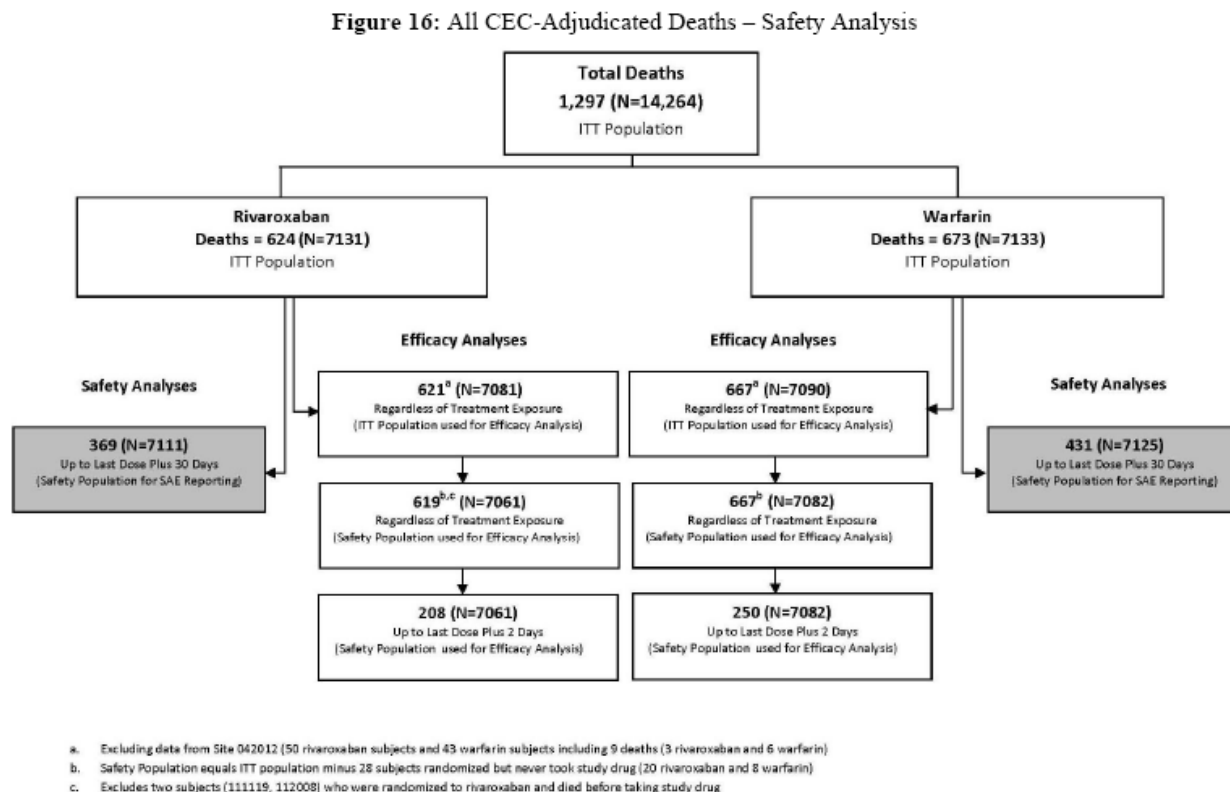
Of note, there were fewer intracranial hemorrhages, non-intracranial hemorrhages, strokes, myocardial infarctions, and episodes of respiratory failure that culminated in fatality in rivaroxaban treated patients than in warfarin treated patients, per Table 83 below (source: ISS Table 1-15):

Table 83. ROCKET + J-ROCKET Causes Of Death (Regardless Of Exp, Safety Pop)

Primary Cause Of Death	Rivaroxaban	Warfarin	Total
Death Cause Sub-Class	(N=7750)	(N=7764)	(N=15514)
	n (%)	n (%)	n (%)
Total no. subjects Who Died	636 (8.21)	685 (8.82)	1321 (8.51)
Vascular	408 (5.26)	433 (5.58)	841 (5.42)
Sudden or Unwitnessed Death	185 (2.39)	188 (2.42)	373 (2.40)
Congestive Heart Failure / Cardiogenic Shock	91 (1.17)	77 (0.99)	168 (1.08)
Intracranial Hemorrhage	31 (0.40)	46 (0.59)	77 (0.50)
Non-Hemorrhagic Stroke	33 (0.43)	40 (0.52)	73 (0.47)
Other Vascular	27 (0.35)	29 (0.37)	56 (0.36)
Myocardial Infarction	18 (0.23)	22 (0.28)	40 (0.26)
Hemorrhage, Not Intracranial	7 (0.09)	15 (0.19)	22 (0.14)
Dysrhythmia	10 (0.13)	7 (0.09)	17 (0.11)
Atherosclerotic Vascular Disease (Excluding Coronary)	2 (0.03)	5 (0.06)	7 (0.05)
Pulmonary Embolism	4 (0.05)	3 (0.04)	7 (0.05)
Directly Related to Revascularization (Cabg or Pci)	0	1 (0.01)	1 (0.01)
Non-Vascular	165 (2.13)	173 (2.23)	338 (2.18)
Malignancy	67 (0.86)	59 (0.76)	126 (0.81)
Infection	29 (0.37)	42 (0.54)	71 (0.46)
Respiratory Failure	20 (0.26)	26 (0.33)	46 (0.30)
Sepsis	23 (0.30)	18 (0.23)	41 (0.26)
Accidental/Trauma	6 (0.08)	13 (0.17)	19 (0.12)
Other Non-Vascular	6 (0.08)	8 (0.10)	14 (0.09)
Renal Failure	9 (0.12)	5 (0.06)	14 (0.09)
Suicide	2 (0.03)	2 (0.03)	4 (0.03)
Liver Failure	3 (0.04)	0	3 (0.02)
Unknown	63 (0.81)	79 (1.02)	142 (0.92)

For the ROCKET trial alone, a summary of all CEC-adjudicated deaths, by data scope and population, is presented in [Figure 35](#) (source: figure 16, ROCKET FSR):

Figure 35. ROCKET All CEC Adjudicated Deaths



Through the ROCKET LD+30 data scope, the incidence of death was lower in the rivaroxaban arm than for the warfarin arm in all major death categories (all-cause, vascular, non-vascular, and unknown), and in almost all death sub-categories, per [Table 84](#) (source: table 49, ROCKET FSR):

Table 84. ROCKET Death Cause And Subclass (LD+30, Safety Pop)

Primary Cause Of Death Death Cause Sub-Class	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Total no. subjects Who Died	369 (5.19)	431 (6.05)	800 (5.62)
Vascular	272 (3.83)	316 (4.44)	588 (4.13)
Sudden or Unwitnessed Death	134 (1.88)	146 (2.05)	280 (1.97)
Congestive Heart Failure / Cardiogenic Shock	50 (0.70)	49 (0.69)	99 (0.70)
Intracranial Hemorrhage	23 (0.32)	37 (0.52)	60 (0.42)
Non-hemorrhagic Stroke	26 (0.37)	27 (0.38)	53 (0.37)
Myocardial Infarction	14 (0.20)	17 (0.24)	31 (0.22)
Other Vascular	11 (0.15)	18 (0.25)	29 (0.20)
Hemorrhage, Not Intracranial	4 (0.06)	11 (0.15)	15 (0.11)
Dysrhythmia	7 (0.10)	5 (0.07)	12 (0.08)
Pulmonary Embolism	2 (0.03)	3 (0.04)	5 (0.04)
Atherosclerotic Vascular Disease (Excluding Coronary)	1 (0.01)	3 (0.04)	4 (0.03)
Non-vascular	72 (1.01)	84 (1.18)	156 (1.10)
Infection	19 (0.27)	27 (0.38)	46 (0.32)
Malignancy	15 (0.21)	16 (0.22)	31 (0.22)
Respiratory Failure	13 (0.18)	15 (0.21)	28 (0.20)
Sepsis	14 (0.20)	10 (0.14)	24 (0.17)
Accidental/trauma	3 (0.04)	7 (0.10)	10 (0.07)
Other Non-vascular	2 (0.03)	4 (0.06)	6 (0.04)
Renal Failure	3 (0.04)	3 (0.04)	6 (0.04)
Suicide	2 (0.03)	2 (0.03)	4 (0.03)
Liver Failure	1 (0.01)	0	1 (0.01)
Unknown	25 (0.35)	31 (0.44)	56 (0.39)

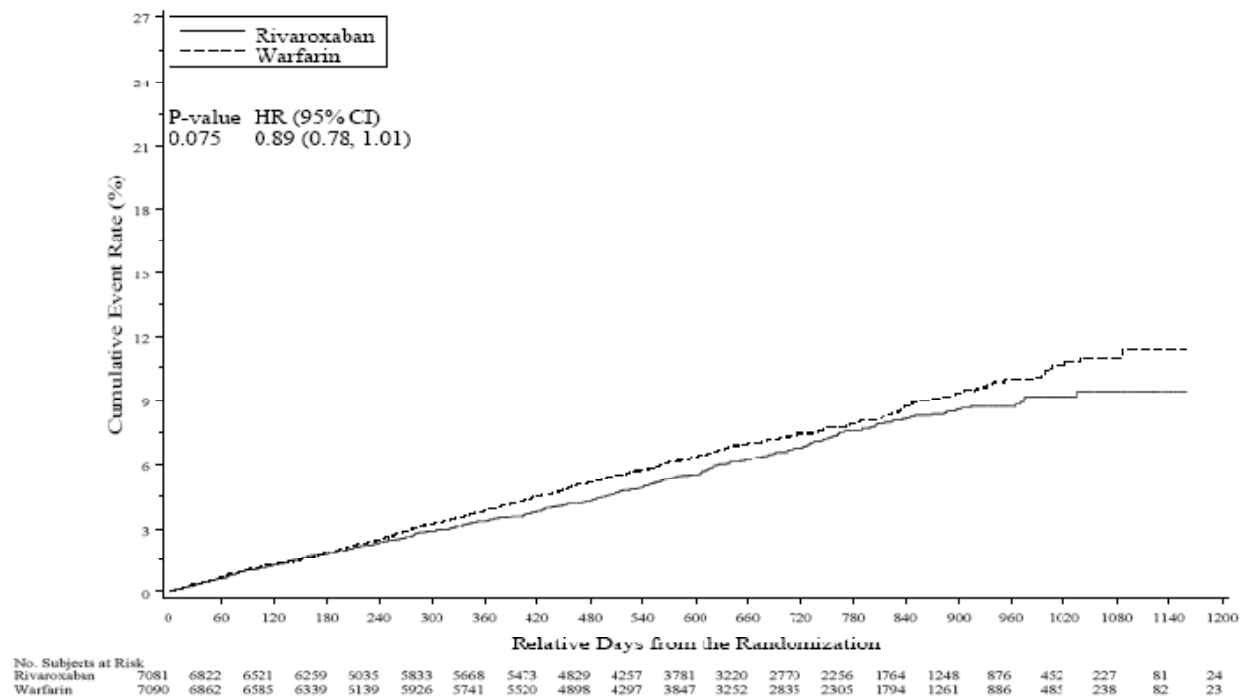
In the safety population, the 15 most common investigator-reported adverse events leading to death based on incidence in the rivaroxaban group are shown in Table 85. Similar to CEC adjudicated deaths, the most common investigator-reported AEs leading to death included sudden death and cardiac failure in both treatment arms.

Table 85. ROCKET 15 Most Frequent AEs Leading To Death (Safety Pop)

Dictionary-Derived Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
	n (%)	n (%)
Total no. subjects with adverse events resulting in death	446 (6.27)	512 (7.19)
Sudden death	80 (1.13)	68 (0.95)
Cardiac failure	23 (0.32)	20 (0.28)
Cardiac failure congestive	19 (0.27)	21 (0.29)
Death	19 (0.27)	23 (0.32)
Myocardial infarction	18 (0.25)	22 (0.31)
Ischaemic stroke	15 (0.21)	25 (0.35)
Cardiogenic shock	12 (0.17)	7 (0.10)
Cerebrovascular accident	12 (0.17)	8 (0.11)
Respiratory failure	12 (0.17)	9 (0.13)
Sepsis	12 (0.17)	13 (0.18)
Sudden cardiac death	12 (0.17)	13 (0.18)
Ventricular fibrillation	11 (0.15)	8 (0.11)
Cardiac arrest	9 (0.13)	24 (0.34)
Haemorrhagic stroke	9 (0.13)	9 (0.13)
Pneumonia	8 (0.11)	16 (0.22)

When death is analyzed for the “regardless of exposure” data scope for the ITT population, there was no difference between rivaroxaban and warfarin therapy, as seen in [Figure 36](#) below:

Figure 36. ROCKET All Cause Death (Regardless, ITT)



7.3.2 Nonfatal Serious Adverse Events

Overall, there were fewer serious adverse events in the rivaroxaban arm of ROCKET than in the warfarin arm, with numerically fewer episodes of cardiac failure and cardiac failure congestive, pneumonia, and TIA favoring rivaroxaban, and fewer episodes of syncope, anemia, and GI bleeding favoring warfarin, as can be seen in [Table 86](#) showing the 15 most frequent treatment emergent SAEs (TESAEs) by treatment group:

Table 86. ROCKET Most Common TESAEs

Preferred Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects with treatment- emergent serious adverse events	2489 (35.00)	2598 (36.46)
Cardiac failure	261 (3.67)	292 (4.10)
Cardiac failure congestive	158 (2.22)	193 (2.71)
Atrial fibrillation	145 (2.04)	155 (2.18)
Pneumonia	141 (1.98)	170 (2.39)
Gastrointestinal haemorrhage	80 (1.13)	60 (0.84)
Angina unstable	70 (0.98)	87 (1.22)
Sudden death	67 (0.94)	61 (0.86)
Anaemia	64 (0.90)	27 (0.38)
Chronic obstructive pulmonary disease	55 (0.77)	52 (0.73)
Syncope	54 (0.76)	37 (0.52)
Haematuria	53 (0.75)	42 (0.59)
Upper gastrointestinal haemorrhage	51 (0.72)	31 (0.44)
Transient ischaemic attack	44 (0.62)	67 (0.94)
Cellulitis	38 (0.53)	58 (0.81)
Epistaxis	37 (0.52)	39 (0.55)

7.3.3 Dropouts and/or Discontinuations

In ROCKET, the numbers of patients discontinuing study medication due to an adverse event were similar between the warfarin and rivaroxaban treatment groups in ROCKET, as can be seen in [Table 87](#) below (source ROCKET FSR table 52):

Table 87. AEs Leading To EDSM By PT (Safety Pop)

Dictionary-Derived Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects with post baseline adverse events leading to permanent study medication discontinuation	1118 (15.72)	1082 (15.19)
Sudden death	68 (0.96)	63 (0.88)
Gastrointestinal haemorrhage	47 (0.66)	27 (0.38)
Epistaxis	35 (0.49)	24 (0.34)
Cardiac failure	34 (0.48)	33 (0.46)
Haematuria	33 (0.46)	24 (0.34)
Anaemia	31 (0.44)	12 (0.17)
Cardiac failure congestive	25 (0.35)	25 (0.35)
Upper gastrointestinal haemorrhage	22 (0.31)	13 (0.18)
Renal failure	19 (0.27)	6 (0.08)
Liver function test abnormal	18 (0.25)	13 (0.18)
Gingival bleeding	16 (0.23)	4 (0.06)
Ischaemic stroke	16 (0.23)	21 (0.29)
Melaena	16 (0.23)	6 (0.08)
Myocardial infarction	15 (0.21)	19 (0.27)
Alanine aminotransferase increased	14 (0.20)	7 (0.10)
Rectal haemorrhage	14 (0.20)	11 (0.15)
Transient ischaemic attack	14 (0.20)	13 (0.18)

Mucosal bleeding (GI bleeding, epistaxis, hematuria, and gingival bleeding) resulted in more rivaroxaban withdrawals than warfarin withdrawals. This raised the question as to whether major bleeding events might be happening disproportionately in rivaroxaban-treated patients after study discontinuation, causing a potential underestimation of rivaroxaban's true hemorrhagic risk relative to warfarin. To assess for such a trend, Early Study Medication Discontinuation (ESMD) patients from both study arms were analyzed for bleeding events occurring in the 30 days following their last dose of study medication based on whether they had experienced non-major bleeding in the 30 days prior to ESMD, per [Table 88](#) below:

Table 88. Bleeding In Patients With NMCR Bleed 30d Before ESMD

ROCKET Global Safety On-Treatment Population Bleeding days 1-30 after ESMD, patients with NMCR bleed within 30 days of ESMD		
	Rivaroxaban N=7111 n (%)	Warfarin N=7125 n (%)
Patients with NMCR 30 days before ESMD	130 (1.83)	72 (1.01)
Major Bleeds	11 (8.53)	4 (5.56)
NMCR Bleeds	2 (1.54)	0
Minimal Bleeds	1 (.077)	1 (1.39)

This same analysis was also performed based on whether patients had experienced NMCR bleeding at any time prior to ESMD, with results as follows in [Table 89](#):

Table 89. Bleeding In Patients With NMCR Bleed Any Time Before ESMD

ROCKET Global Safety On-Treatment Population Bleeding days 1-30 after ESMD, patients with NMCR any time before ESMD		
	Rivaroxaban N=7111 n (%)	Warfarin N=7125 n (%)
Patients with NMCR 30 days before ESMD	390 (5.48)	327 (4.59)
Major Bleeds	16 (4.10)	17 (5.20)
NMCR Bleeds	15 (3.85)	8 (2.45)

As seen from [Table 88](#) and [Table 89](#), more patients on Rivaroxaban withdrew early from the study with a history of antecedent NMCR bleeding, but the differences were not large. After ESMD, numerically more rivaroxaban-treated patients experienced bleeding events in the following 30 days, but again, these differences were small. Differences in bleeding tendencies following the 30 day follow up visit could not be assessed because bleeding histories were not collected after the day 30 follow-up visit. Notably, of the patients who dropped out of the study completely (as opposed to simply discontinuing study medication but remaining in the trial), more warfarin-treated patients had experienced a NMCR bleeding event (907 (12.8%) for rivaroxaban, 930 (13.1%) for warfarin). Thus, there is not convincing evidence that posttreatment major bleeding events were underestimated in an important way in the rivaroxaban arm due to differential NMCR bleed-driven dropouts.

In ROCKET, there were a larger number of renal failure episodes leading to withdrawal of rivaroxaban patients in the on-treatment safety population (19 of 7111 for rivaroxaban

versus 6 of 7125 for warfarin). However, there were fewer overall acute renal failure TEAEs in the rivaroxaban treated group than in the warfarin group, per [Table 90](#) (source: table 78 of the ROCKET FSR):

Table 90. ROCKET TE Acute Renal Failure (SMQ, Safety Pop)

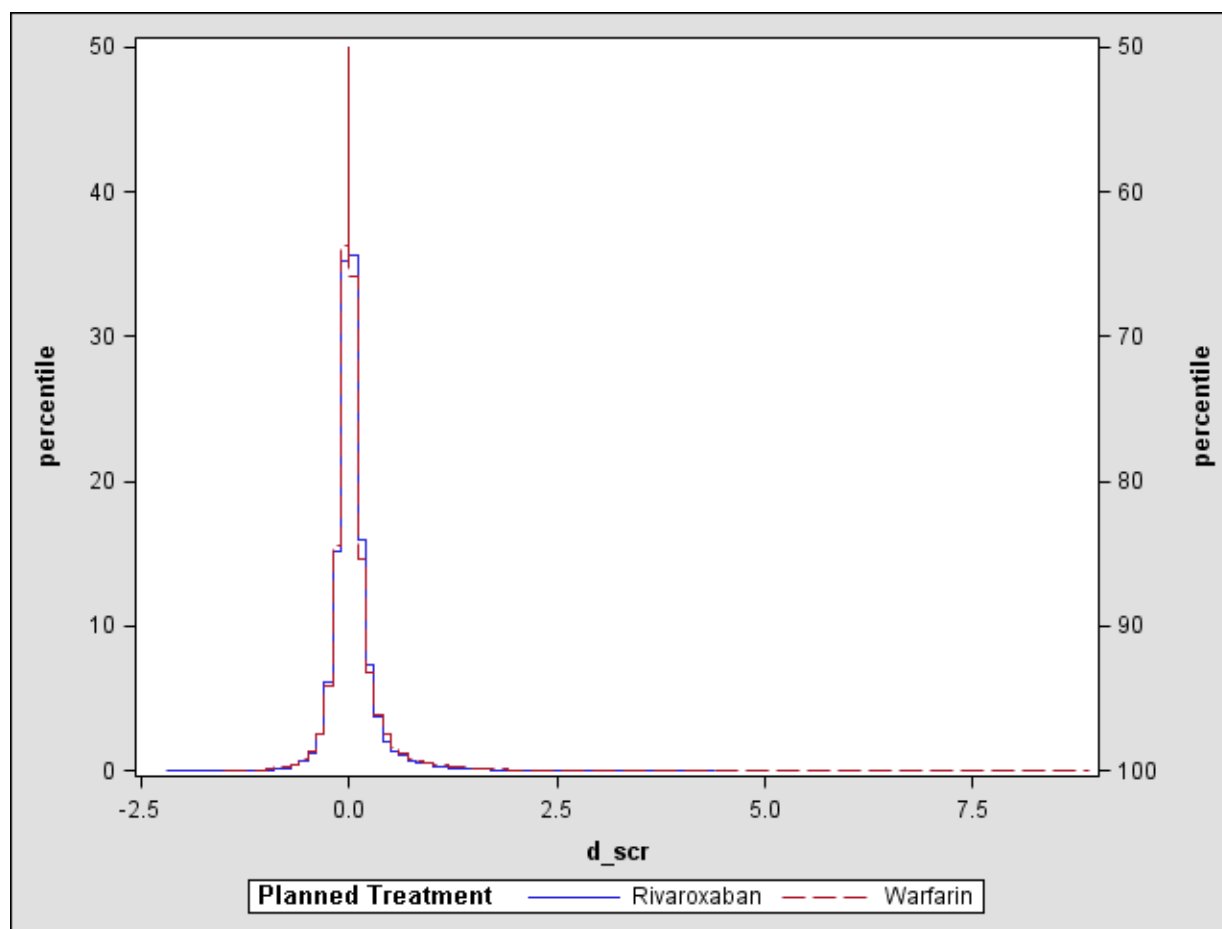
(Study 39039039AFL3001: Safety Analysis Set)		
	Rivaroxaban	Warfarin
Body System Or Organ Class	(N=7111)	(N=7125)
Preferred Term	n (%)	n (%)
Total no. subjects with treatment emergent acute renal failure (SMQ) adverse events	263 (3.70)	282 (3.96)
Renal and Urinary Disorders	176 (2.48)	175 (2.46)
Renal Failure	81 (1.14)	67 (0.94)
Renal Failure Acute	50 (0.70)	61 (0.86)
Renal Impairment	39 (0.55)	41 (0.58)
Proteinuria	6 (0.08)	3 (0.04)
Acute Prerenal Failure	3 (0.04)	5 (0.07)
Azotaemia	2 (0.03)	1 (0.01)
Nephropathy Toxic	1 (0.01)	0
Tubulointerstitial Nephritis	1 (0.01)	0
Albuminuria	0	1 (0.01)
Anuria	0	1 (0.01)
Nephritis	0	1 (0.01)
Oliguria	0	4 (0.06)

In J-ROCKET, discontinuations due to renal failure/impairment favored rivaroxaban, with 2 discontinuations for renal failure in the rivaroxaban group, and 3 discontinuations for renal failure in the warfarin group.

In the integrated data set to LD+30 days, deaths due to renal failure were balanced between rivaroxaban and warfarin treated patients (3 (0.4%) in both arms), and treatment-emergent acute renal failure SMQ adverse events were similar between rivaroxaban and warfarin treated patients (2.49% and 2.37%, respectively).

The most convincing evidence for a lack of nephrotoxicity with rivaroxaban therapy, however, comes from FDA's "Mountain Plot" percent change from baseline analyses of all available serum creatinine values from all patients that were performed on week 24 chemistries, as seen below in [Figure 37](#) (FDA analysis: X-axis serum creatinine change from baseline; Y-Axis, percentile, all creatinine lab values from all patients for whom labs were available at week 24) . This analysis demonstrates very clearly that there are no differences between rivaroxaban-treated patients and warfarin-treated patients with respect to change from baseline in their serum creatinine values at 24 weeks, in either the central tendencies (medians) of the change from baseline, or the shapes of the change in serum creatinine tails of the two curves.

Figure 37. Creatinine Percentile Change From Baseline, Week 24



Of note, the first quarter 2011 PSUR notes that MAH is planning to delete renal failure as a potential risk from the EU RMP.

7.3.4 Significant Adverse Events - Bleeding

Clinical Bleeding - Definitions and Report Triggering

The ROCKET and J-ROCKET trials defined bleeding according to the categories of the international Society of Thrombosis and Hemostasis, as follows:

- Major Bleeding
 - A decrease in hemoglobin of 2 g/dL or more, or
 - Transfusion of 2 or more units of packed red blood cells or whole blood, or

- Critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal
 - A fatal outcome
- Non-Major Clinically Relevant Bleeding (NMCR bleeding)
 - Overt Bleeding not meeting major criteria but associated with medical intervention, unscheduled physician contact, temporary interruption of drug, subject discomfort
- Minimal Bleeding
 - All other overt bleeding

This definition of major bleeding was similar to that used in RE-LY. To assess for more severe occurrences of major bleeding, FDA reanalyzed various safety outcomes using the TIMI major bleeding criteria, which was defined as bleeding associated with any of the following:

- A ≥ 5 g/dL decrease in hemoglobin (each unit of packed red blood cells or whole blood transfused counting as 1g of hemoglobin)
- A $\geq 15\%$ absolute decrease in hematocrit (each unit of packed red blood cells or whole blood transfused will count as 3% points)
- Intracranial location (confirmed by magnetic resonance imaging or computer tomography).

In ROCKET, there were protocol-driven triggers for evaluation by CEC:

- Critical bleeding site
- Medical/surgical intervention
- Unscheduled contact with doctor
- Associated discomfort
- Action taken related to study drug
- Death
- Decreases in hemoglobin (Hb) or transfusion

Clinical Bleeding – Overall (Global) Population Results

The principle safety endpoint in both ROCKET AND J-ROCKET was the composite of all major and NMCR bleeding as adjudicated by the CEC in the on-treatment (LD+2) safety population. CEC adjudicated bleeding results for the ROCKET LD+2 safety population, including the principal safety endpoint is shown in [Table 91](#) below:

Table 91. ROCKET CEC Adjudicated Bleeding (LD+2, Safety Pop)

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p (diff)
	N=7111 n (%)	ER per 100 p-y	N=7125 n (%)	ER per 100 p-y		
Safety Endpoint	1475 (20.74)	14.91	1449 (20.34)	14.52	1.03 (0.96, 1.11)	0.442
Major Bleeding	395 (5.55)	3.60	386 (5.42)	3.45	1.04 (0.90, 1.20)	0.576
Hb drop	305 (4.29)	2.77	254 (3.56)	2.26	1.22 (1.03, 1.44)	0.019
Transfusion	183 (2.57)	1.65	149 (2.09)	1.32	1.25 (1.01, 1.55)	0.044
Critical site	91 (1.28)	0.82	133 (1.87)	1.18	0.69 (0.53, 0.91)	0.007
Death	27 (0.38)	0.24	55 (0.77)	0.48	0.50 (0.31, 0.79)	0.003
Non-major	1185 (16.66)	11.80	1151 (16.15)	11.37	1.04 (0.96, 1.13)	0.345
Minimal	258 (3.63)	2.35	226 (2.17)	2.03	1.16 (0.97, 1.39)	0.102

For the global trial safety population at LD+2, there were numerically more major and non-major bleeds, as well as composite safety endpoint events, in the Rivaroxaban arm of ROCKET vs. the warfarin arm, but these differences were small and did not attain statistical significance. In assessing major bleeding events based on the 4 sub-classes of major bleeding as defined by the ISTH, there were statistically significantly more major bleeds defined as hemoglobin drops and 2 unit blood transfusions, versus statistically significantly fewer critical site bleeds and fatal bleeds. This opposing trend of these sub-classes of major bleeding will be noted throughout virtually every analysis and sub-analysis of ROCKET bleeding data that follow.

To begin at the highest “altitude”, time to first occurrence K-M curves for any bleeding event, the principal safety endpoint, and major bleeds for ROCKET (LD+2, safety population) are displayed in [Figure 38](#), [Figure 39](#), and [Figure 40](#), respectively, showing no differences between the rivaroxaban and warfarin arms for the occurrence of these events:

Figure 38. ROCKET Any Bleeding Events (LD+2, Safety Pop)

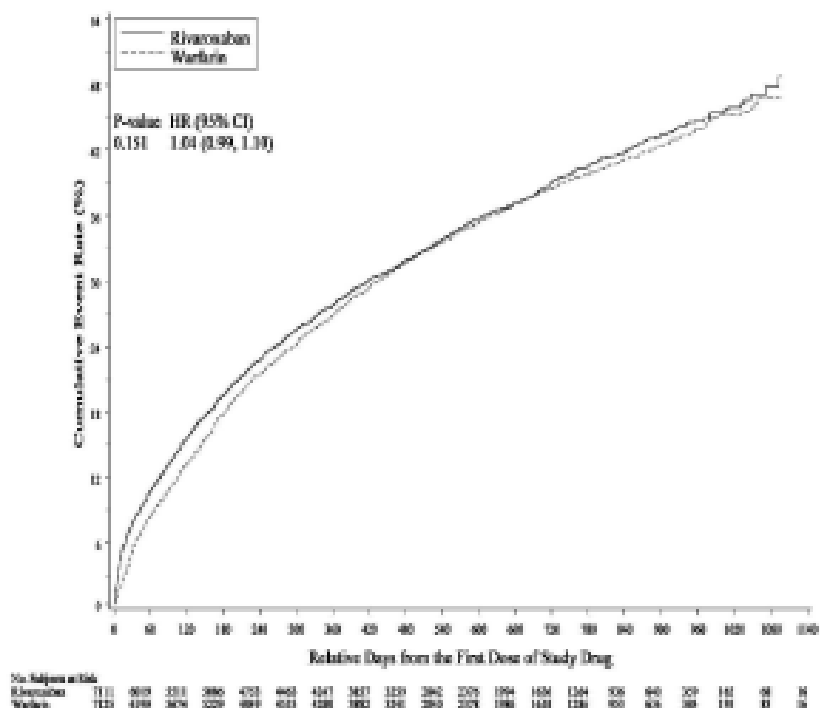


Figure 39. ROCKET Principal Safety Endpoint (LD+2, Safety Pop)

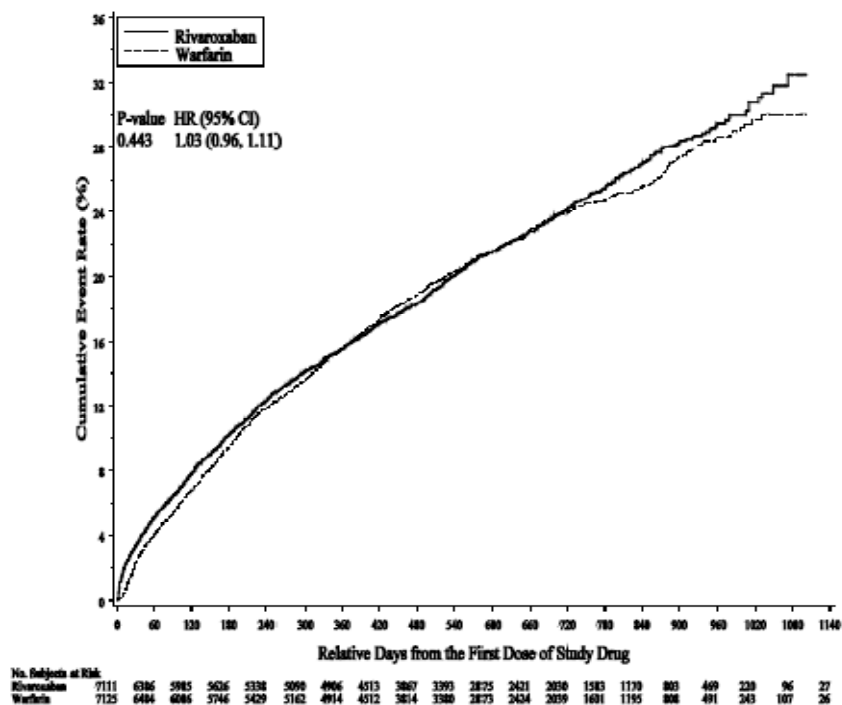
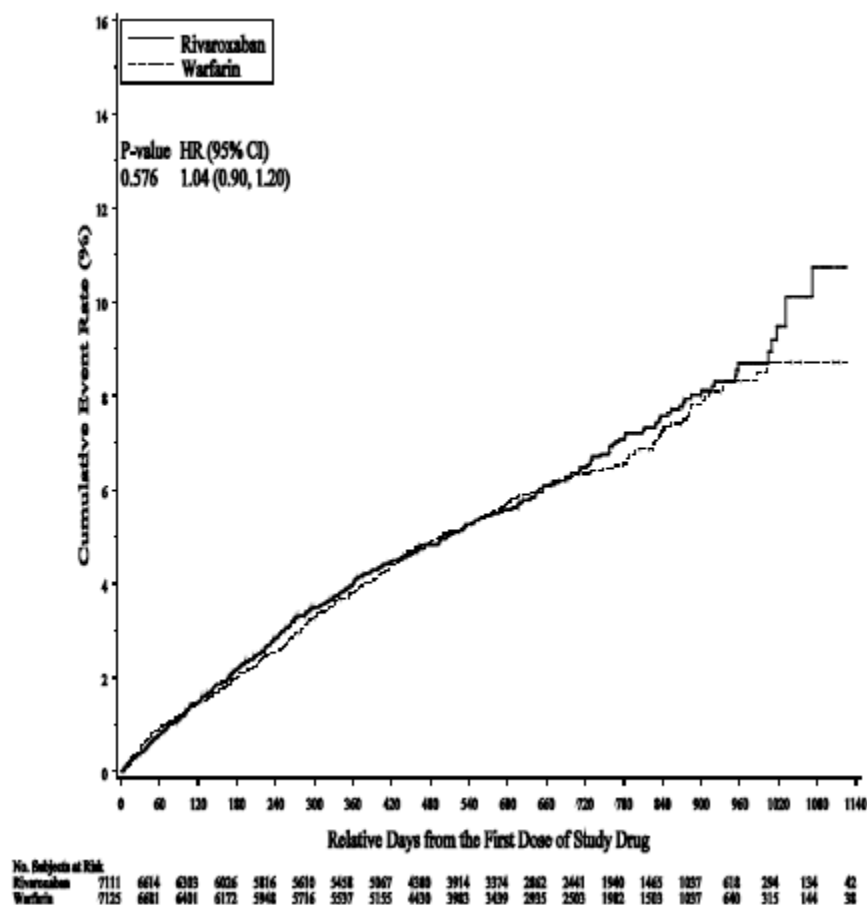
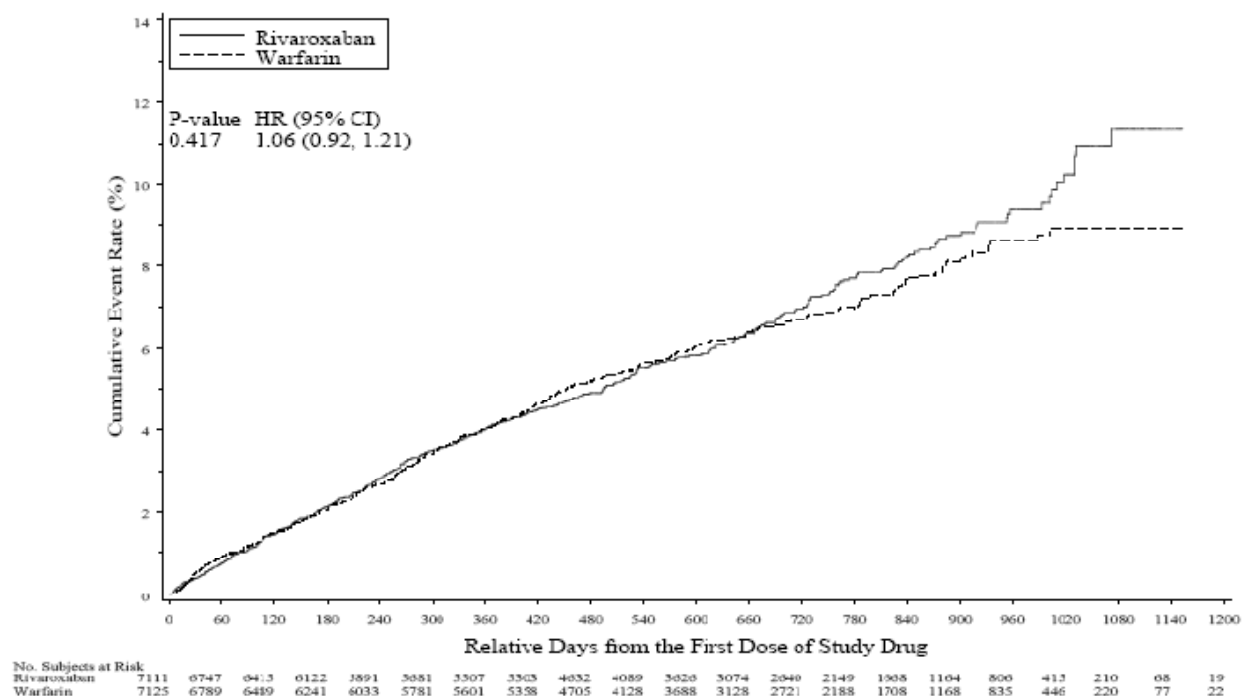


Figure 40. ROCKET Major Bleeds (LD+2, Safety Pop)



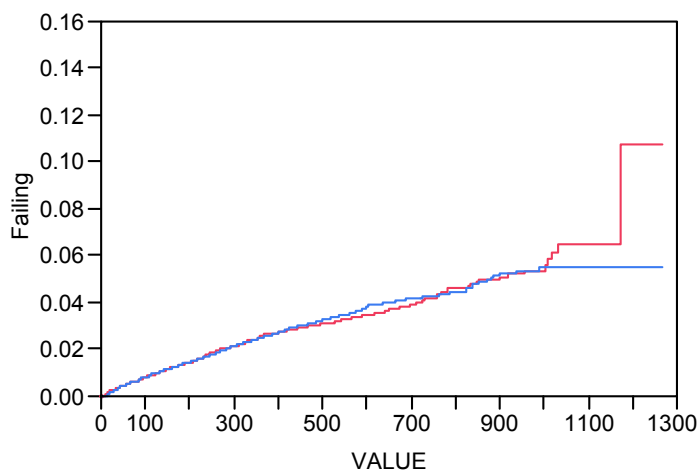
For major bleeding, similar results were demonstrated in K-M curves for the following additional data scopes: LD+2 investigator reported, LD+7, and LD+14. At LD+30, a slight late divergence of the major bleeding curves (approximately day 720) favoring warfarin became more prominent toward the end of the trial, but this occurred at a point where relatively few patients remained in the study, and was not statistically significant, as seen in [Figure 41](#) below:

Figure 41. ROCKET Major Bleeds (LD+30, Safety Pop)



As a cross-check, this reviewer analyzed the integrated ROCKET and J-ROCKET safety data sets for both ISTH and TIMI major bleeding, in an effort to confirm the sponsor's overall results, and to rigorously examine both trials for the most serious bleeding events, including specifically intracranial hemorrhaging. These analyses of the integrated data set confirmed no differences in either ISTH major bleeding or TIMI major bleeding during either the LD+2 or LD+30 data scopes for the global trial populations, as show below in [Figure 42](#), [Figure 43](#), and [Figure 44](#):

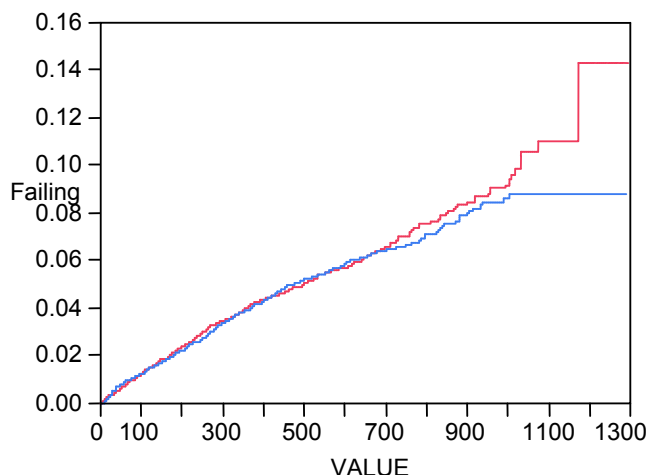
Figure 42. ROCKET + J-ROCKET TIMI Major Bleeds (LD+2, Safety Pop)



Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0024	1	0.9608
Wilcoxon	0.0820	1	0.7746

Group	Number failed	Number censored	Mean	Std Error
Rivaroxaban	246	6865	1133.87	2.64734
Warfarin	251	6874	957.074	1.8722
Combined	497	13739	1134.28	1.82442

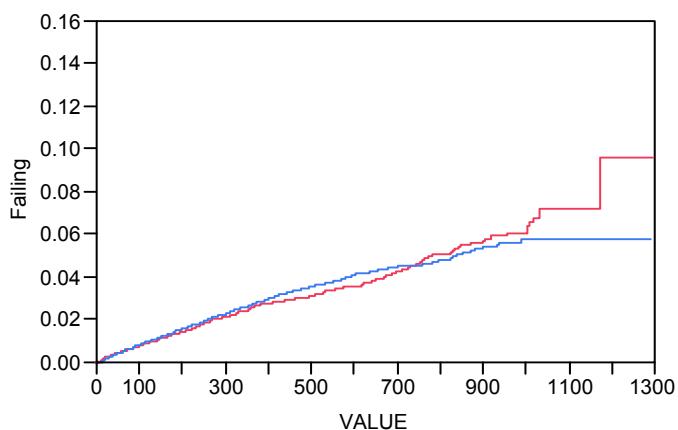
Figure 43. ROCKET + J-ROCKET ISTH Major Bleeds (LD+30, Safety Pop)



Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.9476	1	0.3303
Wilcoxon	0.0605	1	0.8057

Group	Number failed	Number censored	Mean		Std Error
Rivaroxaban	833	13389	1106.89	Biased	2.32833
Warfarin	807	13443	953.807	Biased	1.65903
Combined	1640	26832	1109.28	Biased	1.59098

Figure 44. ROCKET + J-ROCKET TIMI Major Bleeds (LD+30, Safety Pop)

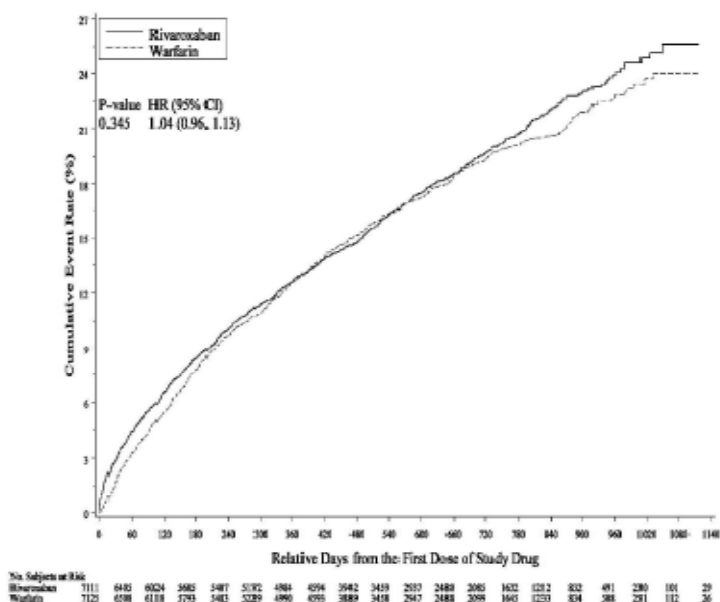


Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.0167	1	0.8972
Wilcoxon	0.4010	1	0.5266

Group	Number failed	Number censored	Mean		Std Error
Rivaroxaban	277	6834	1130.49	Biased	2.65383
Warfarin	278	6847	954.973	Biased	1.90595
Combined	555	13681	1131.33	Biased	1.83002

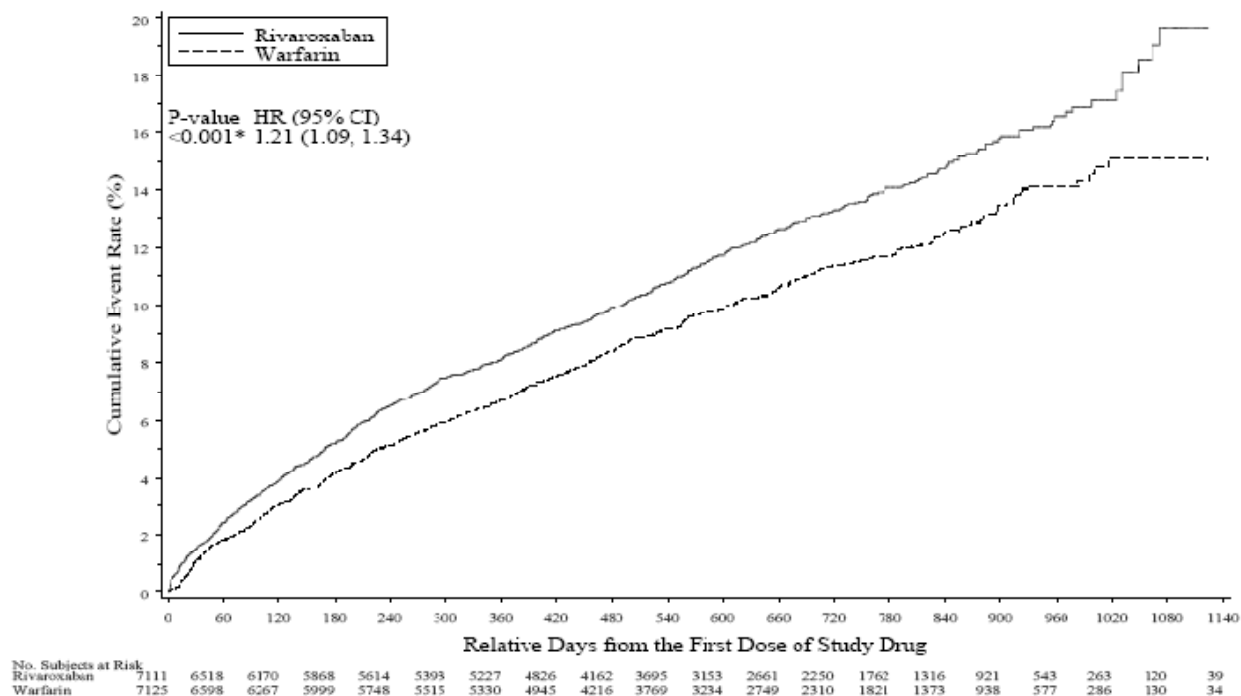
Likewise, for the global ROCKET on-treatment population, K-M analysis demonstrated no significant differences in ISTH NMCR bleeds, as shown in [Figure 45](#) below:

Figure 45. ROCKET Non-Major CR Bleeds (LD+2, Safety Pop)



Of note, while there was concordance between the investigators and the CEC with respect to the adjudication of on-treatment major bleeding, the investigators differed with the CEC adjudications for on-treatment NMCR bleeds, per [Figure 46](#):

Figure 46. ROCKET Investigator NMCR Bleeds (LD+2, Safety Pop)



As would be expected from the advantage demonstrated by rivaroxaban over warfarin for critical site bleeding in the global on-treatment safety population, analyses of intracranial hemorrhaging confirms this effect. Specifically, there were fewer ICH events in rivaroxaban-treated ROCKET patients than in their warfarin-treated counterparts, as well as numerically fewer events in all but one subclass of ICH, as demonstrated in [Table 92](#) below:

Table 92. ROCKET ICH Incidence (LD+2, Safety Pop)

		<i>Rivaroxaban</i> <i>N = 7111</i> <i>n (%)</i>	<i>Warfarin</i> <i>N = 7125</i> <i>n (%)</i>
Intracranial hemorrhage		55 (0.77)	84 (1.18)
Intraparenchymal		37 (0.52)	56 (0.79)
Non-traumatic		33 (0.46)	54 (0.76)
Traumatic		4 (0.06)	2 (0.03)
Intraventricular		2 (0.03)	4 (0.06)
Subdural hematoma		12 (0.17)	22 (0.31)
Subarachnoid		4 (0.06)	1 (0.01)
Epidural hematoma		0	1 (0.01)

ICH incidence results for the LD+30 data scope in the safety population were similar ([Table 93](#)), and time to ICH analysis at LD+30 statistically favored rivaroxaban ([Table 94](#)):

Table 93. ROCKET ICH Incidence (LD+30, Safety Pop)

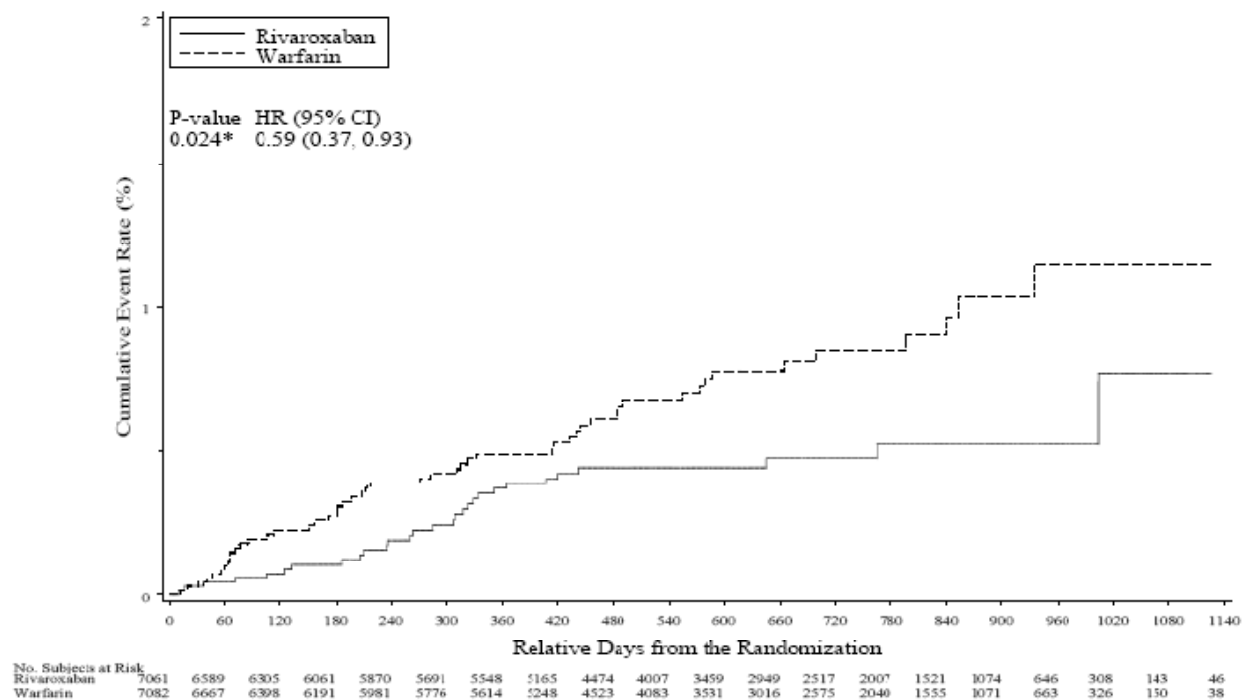
	<i>Rivaroxaban</i> <i>N = 7111</i> <i>n (%)</i>	<i>Warfarin</i> <i>N=7125</i> <i>n (%)</i>
Intracranial hemorrhage	67 (0.94)	102 (1.43)
Intraparenchymal	45 (0.63)	72 (1.01)
Non-traumatic	41 (0.58)	68 (0.95)
Traumatic	4 (0.06)	4 (0.06)
Intraventricular	2 (0.03)	4 (0.06)
Subdural hematoma	16 (0.23)	24 (0.34)
Subarachnoid	4 (0.06)	1 (0.01)
Epidural hematoma	0	1 (0.01)

Table 94. ROCKET Time To ICH (LD+30, Safety Pop)

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p value
	N = 7111 n (%)	Event Rate per 100 pt-yrs	N = 7125 n (%)	Event Rate per 100 pt-yrs		
Intracranial Hemorrhage	67 (0.94)	0.57	102 (1.43)	0.85	0.67 (0.49, 0.91)	0.010
Intra-parenchymal	45 (0.63)	0.38	72 (1.01)	0.60	0.63 (0.44, 0.92)	0.016
Subdural Hematoma	18 (0.25)	0.15	30 (0.42)	0.25	0.61 (0.34, 1.09)	0.097

In ROCKET, hemorrhagic strokes were defined as the composite of non-traumatic intraparenchymal and intraventricular bleeds. Thus, from the data tables above, it is clear that at both follow up data scopes, hemorrhagic strokes were the prominent majority of ICH, and these events were fewer in rivaroxaban-treated patients in the safety population. Accordingly, the K-M analysis for hemorrhagic stroke (LD+2, safety pop), significantly favored rivaroxaban as compared to warfarin, per [Figure 47](#):

Figure 47. ROCKET Hemorrhagic Stroke (LD+2, Safety Pop)



This significant reduction in hemorrhagic stroke was a robust finding that was reproduced in the LD+14 safety, LD+30 safety, and Regardless-ITT analyses, as shown in [Figure 48](#), [Figure 49](#), and [Figure 50](#) respectively:

Figure 48. ROCKET Hemorrhagic Stroke (LD+14, Safety Pop)

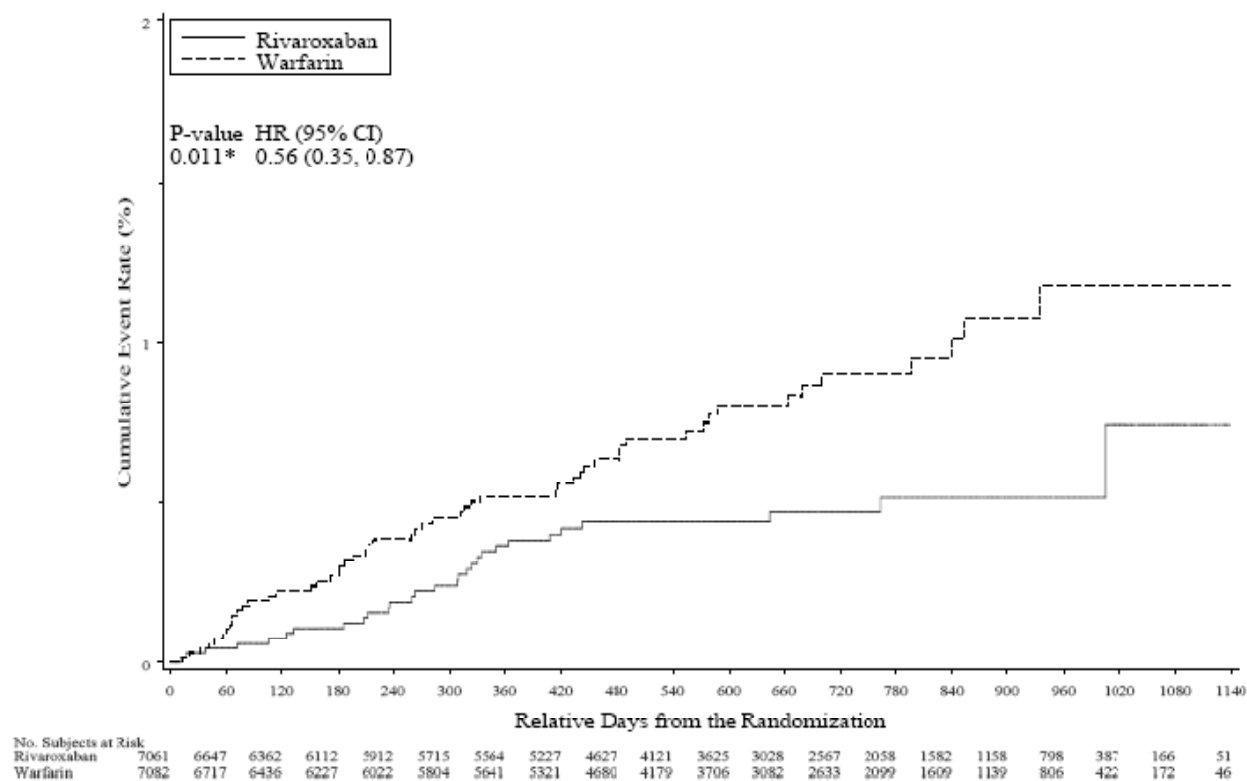


Figure 49. ROCKET Hemorrhagic Stroke (LD+30, Safety Pop)

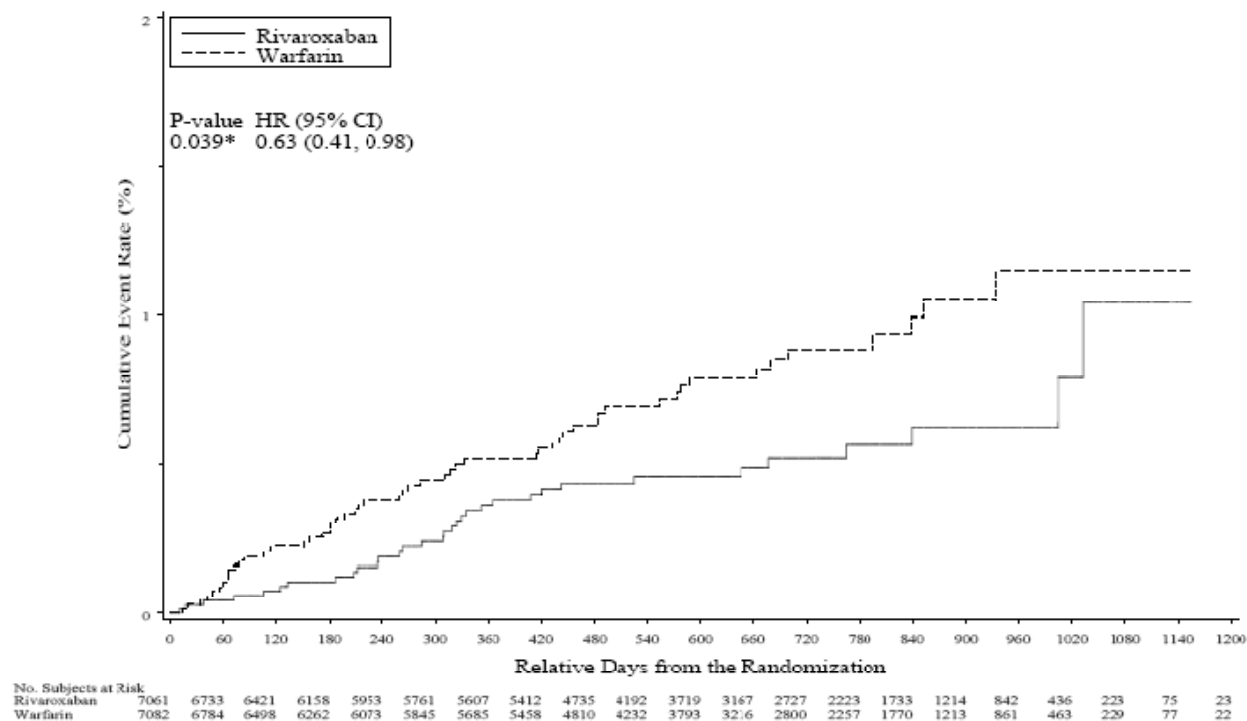
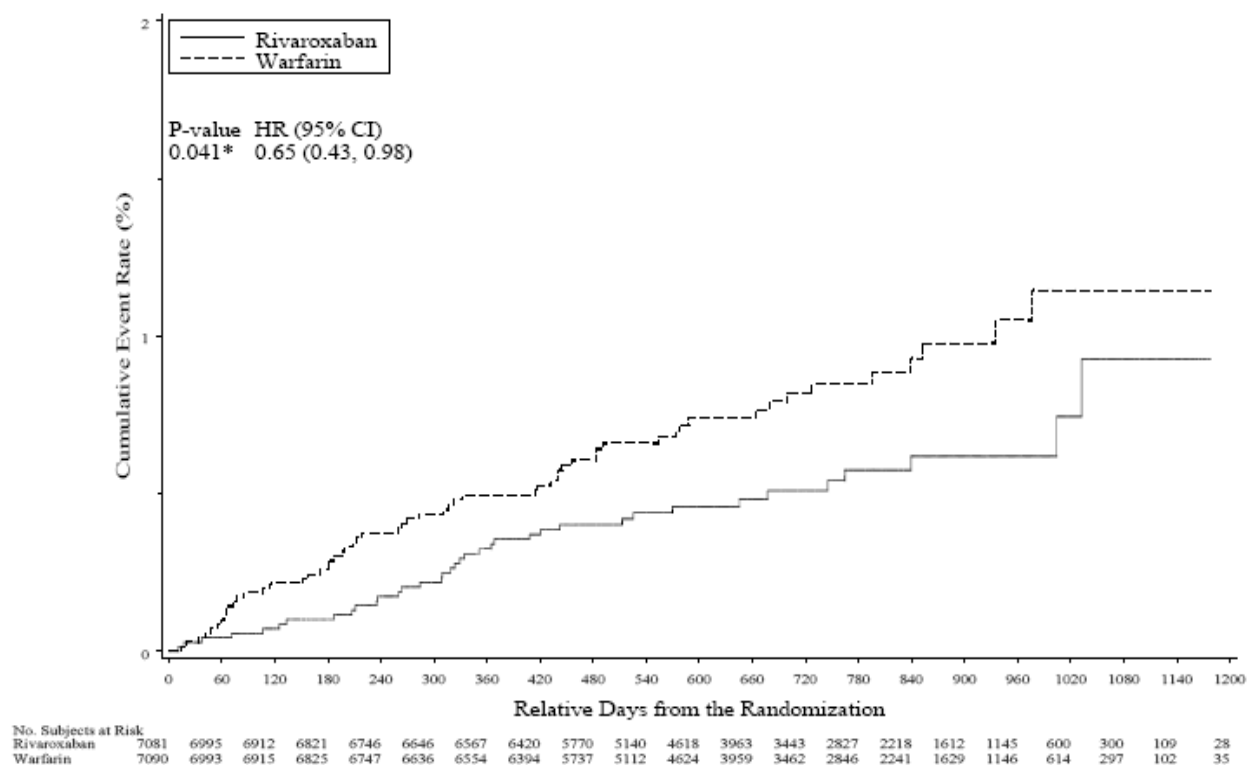


Figure 50. ROCKET Hemorrhagic Stroke (Regardless, ITT)



Likewise, rivaroxaban treatment was associated with statistically fewer fatal bleeding events , as seen in [Table 95](#) below:

Table 95. ROCKET Time To Fatal Bleed (LD+30, Safety Pop)

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p (diff)
Fatal Bleeding	N = 7111 n (%)	Event Rate per 100 pt-yrs	N = 7125 n (%)	Event Rate per 100 pt-yrs		
Broad Definition	50 (0.70)	0.42	80 (1.12)	0.67	0.63 (0.44, 0.90)	0.011
Narrow Definition	27 (0.38)	0.23	50 (0.70)	0.42	0.55 (0.34, 0.87)	0.012

Clinical Bleeding - Warfarin Consistency Across ROCKET and RE-LY

In assessing differential bleeding rates between rivaroxaban and warfarin, it is reassuring that the warfarin arm of ROCKET performed consistently with what was seen from the warfarin arm of RE-LY, utilizing a similar (but not identical) definition of major bleeding as seen in [Table 96](#):

Table 96. Major Bleeding Definitions, ROCKET vs. RE-LY

ROCKET Major Bleeding	RE-LY Major Bleeding
• 2 g/dL Hb drop	• 2 g/dL Hb drop
• 2 unit blood transfusion	• 2 unit blood transfusion
• Critical organ bleed	• Critical organ bleed
• Death	• Death
	• Hypotension requiring pressors
	• Surgical intervention to stop bleeding

In addition to slightly different definitions of major bleeding, cross-trial comparison of warfarin behavior must also be considered in the context of differing trial designs (open label trial with an ITT analysis versus a double-blind and double-dummy trial with on-on-treatment analysis). That being said, comparative results for major bleeding, ICH, and

hemorrhagic stroke events for ROCKET and RE-LY are shown in [Table 97](#), and demonstrate the consistency of the warfarin effect in these bleeding outcomes:

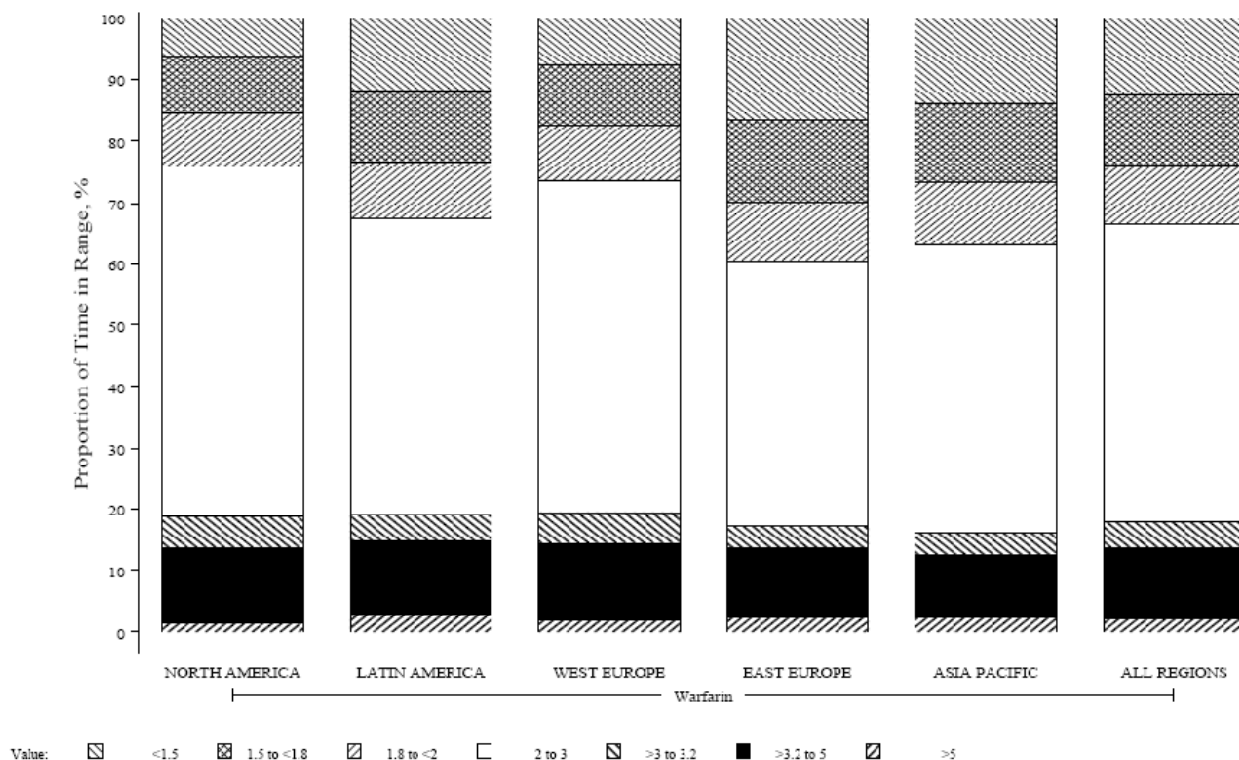
Table 97. ROCKET vs. RE-LY Major Bleeding

	<i>ROCKET W LD+2</i>	<i>ROCKET W LD+30 f/u</i>	<i>RE-LY W Safety</i>	<i>RE-LY W ITT</i>
Number of Subjects	7125	7125	5998	6022
Major Bleeds (100 p-y)	386 (3.45)	421 (3.61)	378 (3.55)	421 (3.57)
ICH (100 p-y)	84 (0.74)	102 (0.85)	82 (0.77)	85 (0.72)
Hemorrhagic CVA (100 p-y)	50 (0.44)	53 (0.45)	40 (0.38)	45 (0.38)
Fatal Bleeding (b) (100) p-y	63 (0.88)	80 (1.12)	31 (0.29)	71 (0.14)

Clinical Bleeding - US Results and TTR analyses

Warfarin management in ROCKET on a global basis was sub-optimal, with a trial average TTR, defined as an INR of 2.0 to 3.0, of 55% (median 58%). This level of TTR is inconsistent with contemporary global phase III warfarin-controlled trial data and it is likewise inconsistent with US practice as demonstrated in ROCKET. Time outside of therapeutic range (INR 2.0 to 3.0) has both low INR and high INR components. A breakdown by-region of time-below, time-in, and time-above the target INR range of 2.0 to 3.0, as shown in [Figure 51](#), demonstrates the heterogeneity of warfarin management in ROCKET (source: ROCKET FSR, Appendix 6.2, page 38,489):

Figure 51. ROCKET Observed INRs (Region Means of Subject Mean INRs)



From [Figure 51](#), it is evident that the time-below therapeutic range was lowest in North America, and highest in Eastern Europe. Yet, as shown in [Table 98](#), Eastern Europe contributed by a large margin the greatest number of patients that were enrolled in ROCKET:

Table 98. ROCKET Enrollment by Region

Region	Treatment Group	Start of Enrollment	Screened	Randomized	ITT	Safety	Per-Protocol
Total	Total	14Dec2006	17232	14269	14264	14236	14054
	Rivaroxaban	14Dec2006		7133	7131	7111	7008
	Warfarin	15Dec2006		7136	7133	7125	7046
North America	Total	14Dec2006	3500	2682	2681	2673	2641
	Rivaroxaban	14Dec2006		1340	1339	1334	1316
	Warfarin	15Dec2006		1342	1342	1339	1325
Latin America	Total	22May2007	2318	1879	1878	1877	1858
	Rivaroxaban	24May2007		940	940	939	922
	Warfarin	22May2007		939	938	938	936
West Europe	Total	05Mar2007	2561	2097	2096	2089	2054
	Rivaroxaban	16Mar2007		1046	1046	1040	1023
	Warfarin	05Mar2007		1051	1050	1049	1031
East Europe	Total	03May2007	6227	5502	5500	5493	5426
	Rivaroxaban	08May2007		2752	2751	2746	2711
	Warfarin	03May2007		2750	2749	2747	2715
Asia Pacific	Total	27Apr2007	2626	2109	2109	2104	2075
	Rivaroxaban	01May2007		1055	1055	1052	1036
	Warfarin	27Apr2007		1054	1054	1052	1039

For patients taking rivaroxaban in the United States, there was statistically significantly more major bleeding and NMCR bleeding ([Table 99](#)).

Table 99. ROCKET CEC Adjudicated Bleeds - US Alone - (LD+2, Safety Pop)

	Rivaroxaban		Warfarin		R vs. W HR (95% CI)	p (diff)
	N=962 n (%)	ER per 100 p-y	N=964 n (%)	ER per 100 p-y		
Safety Endpoint	322 (33.47)	25.24	275 (28.53)	19.54	1.28 (1.09, 1.50)	0.003
Major Bleeding	123 (12.79)	8.06	87 (9.02)	5.35	1.50 (1.14, 1.98)	0.004
Hb drop	99 (10.29)	6.42	64 (6.64)	3.92	1.64 (1.19, 2.24)	0.002
Transfusion	72 (7.48)	4.62	47 (4.88)	2.87	1.61 (1.12, 2.33)	0.011
Critical site	18 (1.87)	1.13	22 (2.28)	1.33	0.85 (0.46, 1.59)	0.614
Death	6 (0.62)	0.38	10 (1.04)	0.60	0.63 (0.23, 1.72)	0.365
Non-major	237 (24.64)	17.86	211 (21.89)	14.72	1.20 (1.00, 1.45)	0.049
Minimal	48 (4.99)	3.10	42 (4.36)	2.58	1.20 (0.79, 1.81)	0.395

However, as in the global population, the excess in major bleeding was driven by hemoglobin drops and transfusions, and offset by a trend to fewer critical site and fatal bleeds that did not reach statistical significance in this relatively small subset analysis. The excess in major bleeding on rivaroxaban was evident at all time points during the on-treatment period for both the principal safety endpoint as well as for major bleeding, as seen in [Figure 52](#) and [Figure 53](#) respectively:

Figure 52. ROCKET K-M Safety Endpoint - US Alone (LD+2, Safety Pop)

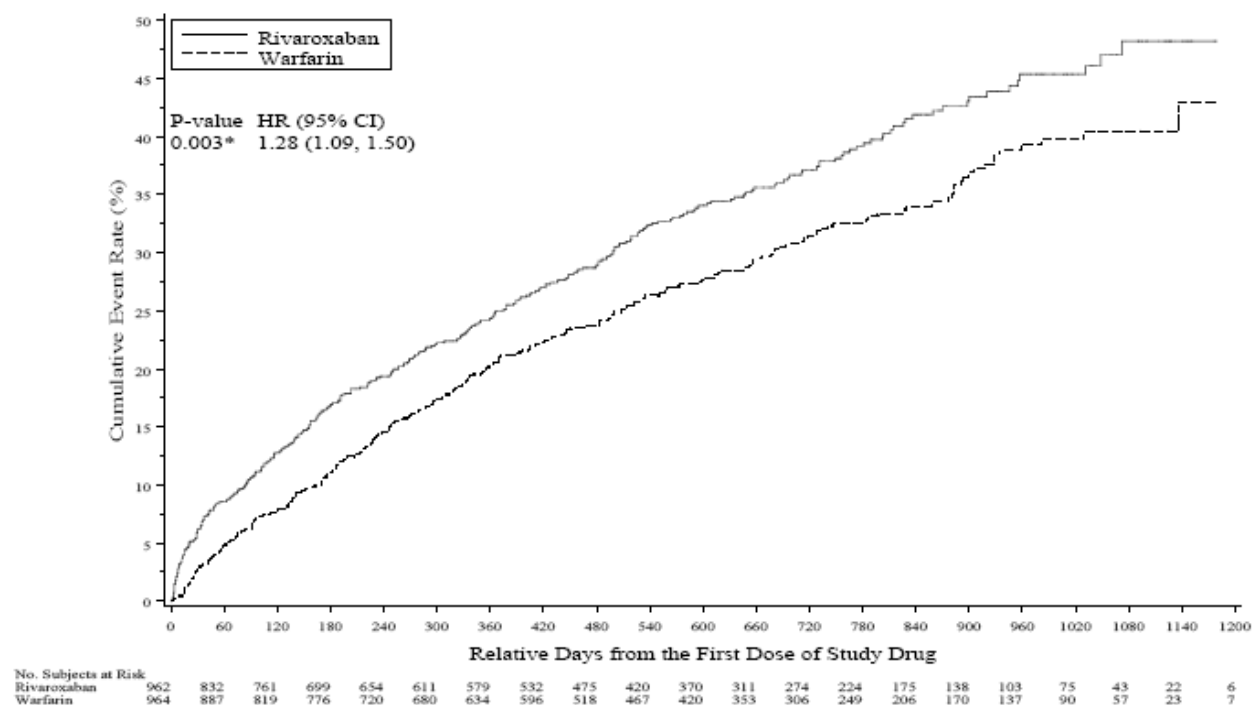
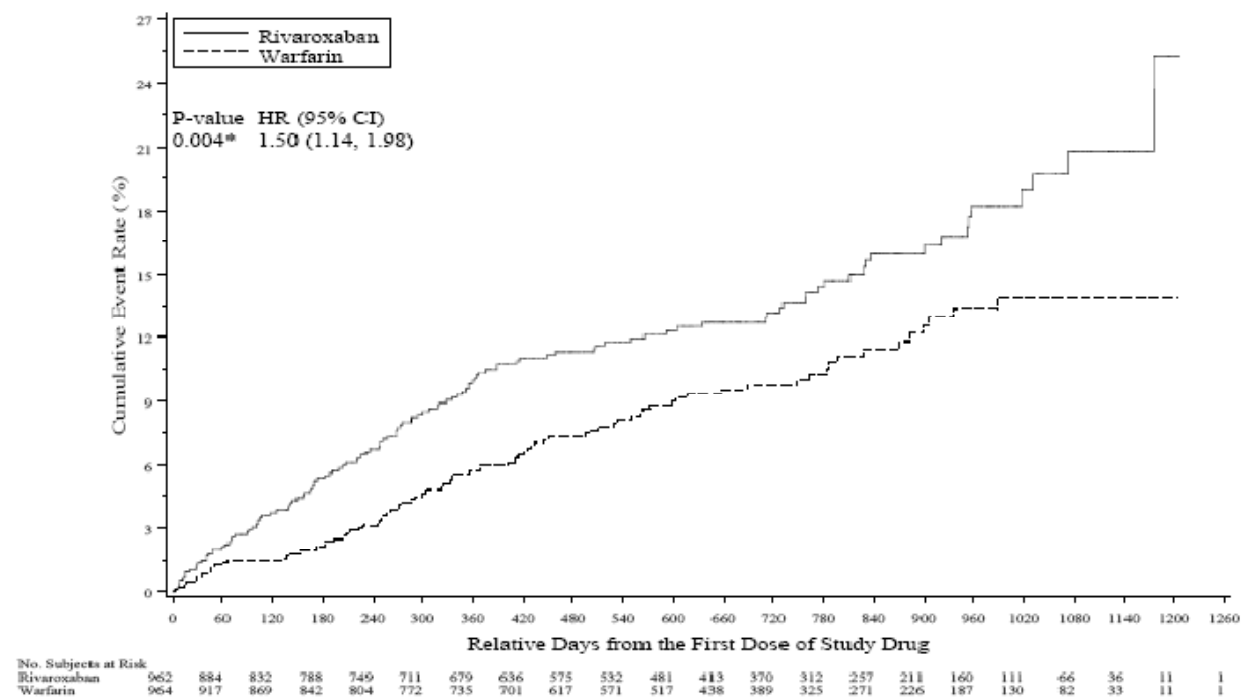


Figure 53. ROCKET K-M Major Bleeds - US Alone (LD+2, Safety Pop)



The finding of excess bleeding for the US population was robust in that it was reproducible across virtually all subgroups. In fact, the point estimate for the hazard ratio of the principle safety endpoint was greater than 1.00 (favoring warfarin) in 101 out of 106 subgroups assessed in forest plots, and many of these demonstrated a lower 95% CI that was also greater than 1.0 favoring warfarin. Concordantly, the percentage of patients in the safety population from the US that discontinued study medication early due to bleeding adverse events was almost twice that percentage from the global population, as well as nearly twice the rate of ESMD for bleeding seen in the US warfarin-treated population, as seen in [Table 100](#):

Table 100. Comparative Completion - ROCKET (Safety Pop)

	US Population		Global Population	
	Rivaroxaban N=962 N (%)	Warfarin N=964 N (%)	Rivaroxaban N=7111 N (%)	Warfarin N=7125 N (%)
Completed Study Med	546 (56.76)	556 (57.68)	4591 (64.56)	4657 (65.36)
ESMD for bleeding	81 (8.42)	43 (4.4)	304 (4.28)	219 (3.07)

Demographically, there was no apparent explanation for this finding, given that the age, weight, and renal function were similar between treatment groups, both within the US, and within the global population, as seen in [Table 101](#):

Table 101. Comparative Demographics - ROCKET US vs. Global (ITT)

	US Population		Global Population	
	Rivaroxaban N=965 N (%)	Warfarin N=966 N (%)	Rivaroxaban N=7131 N (%)	Warfarin N=7133 N (%)
Mean Age	74.10	74.27	71.21	71.18
Mean Weight	93.20	91.45	82.07	81.64
Mean BMI	31.48	31.48	29.06	28.85
Mean CrCl	79.26	76.13	72.97	72.53
Prior VKA	871 (90.26)	880 (91.10)	4443 (62.31)	4461 (62.54)
Chronic ASA use	353 (36.58)	336 (34.78)	2586 (36.26)	2619 (36.72)

Not only were patient factors balanced that might have increased drug exposure (age, weight, and creatinine clearance), the higher weight and concomitantly higher estimated GFRs of US patients compared to their global counterparts should have produced less rivaroxaban-associated bleeding in the US if drug exposure alone was the explanation for this finding.

One final element of exposure that was closely examined was the possibility of differential compliance within the US versus all other geographies in the trial. The ROCKET FSR defines compliance as the number of days on drug minus the number of days that the physician directed that drug be held, divide by the number of days on drug. Using this somewhat unique definition of compliance led to mean compliance rates of 98.54% and 98.57% (ROCKET FSR table 16). FDA requested a recalculation of compliance based on the following definition:

- Numerator = Denominator – (Days of physician-driven interruptions + Total number of days of patient-driven skipped doses)
- Denominator = Last dose date – Randomization date + 1

Based on this definition of compliance, pill-count-based compliance percentages were calculated for the five regions per [Table 102](#):

Table 102. ROCKET Percent Compliance By Region

	Rivaroxaban	Warfarin
North America	94.9	94.7
Asia-Pacific	95.7	95.8
Eastern Europe	96.9	96.6
Latin American	95.4	95.4
Western Europe	95.8	95.6

Thus, the possibility that higher compliance in North America drove higher exposures which in turn drove higher major bleeding rates was not borne out by the compliance data. However, it is noted that North America, while having the very lowest compliance (per [Table 102](#)), also had the very highest regional TTR (per [Figure 51](#)). Likewise, Eastern Europe, with the highest regional contribution to trial enrollment by a substantial margin ([Table 98](#)), demonstrated the very highest regional compliance ([Table 102](#)), but the very lowest regional TTR (per [Figure 51](#)). *This result is counterintuitive to the expected compliance/TTR relationship. Indeed, the sponsor states that, “Time in Therapeutic Range (TTR; i.e., 2.0 to 3.0) can be used as a surrogate for or indirect measure of treatment compliance.” (ROCKET FSR PAGE 122).*

When major bleeding was in fact assessed based on TTR, the United States data demonstrates the expected reduction in major bleeding in subjects on warfarin as warfarin management improves, per [Table 103](#):

Table 103. ROCKET US Major Bleeds By Site TTR Quartile (LD+2, Safety Pop)

TTR Quartile	<u>20 mg Rivaroxaban</u>			<u>Warfarin</u>			<u>20 mg Rivaroxaban vs. warfarin</u>	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR	(95% CI)
Major Bleeding								
0.00 - 57.21	227	26	7.6	239	25	7.200	1.07	(0.62 - 1.85)
57.21 - 64.75	241	29	7.58	228	25	6.430	1.19	(0.70 - 2.03)
64.75 - 70.39	220	34	9.02	247	21	4.700	1.93	(1.12 - 3.33)
70.39 - 100	219	28	7.99	250	16	3.610	2.35	(1.19 - 4.07)
Overall	962	123	8.06	964	87	5.350	1.50	(1.14 - 1.98)

Of note, in all quartiles, overall major bleeding rates are higher with rivaroxaban. In contrast, per [Table 104](#), the global major bleeding analysis by warfarin TTR demonstrated:

- No change in major bleeding rates for warfarin-treated patients based on TTR
- Increased major bleeding in rivaroxaban-treated patients as a function of warfarin TTR, and
- An overall HR of 1.04 for major bleeding (rivaroxaban vs. warfarin).

Table 104. ROCKET Global Major Bleeds By Site TTR Quartile (LL+2, Safety Pop)

TTR Quartile	<u>20 mg Rivaroxaban</u>			<u>Warfarin</u>			<u>20 mg Rivaroxaban vs. warfarin</u>	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR	(95% CI)
Major Bleeding								
0.00 - 46.8	1765	64	2.47	1725	80	3.25	0.76	(0.55 - 1.06)
46.8 - 55.9	1724	88	3.39	1764	96	3.54	0.95	(0.71 - 1.27)
55.9 - 63.9	1709	90	3.25	1787	99	3.43	0.95	(0.72 - 1.27)
63.9 - 100	1690	142	5.15	1803	108	3.50	1.47	(1.14 - 1.89)
Overall	7111	395	3.6	7125	386	3.45	1.04	(0.90 - 1.20)

Note the consistency that the lower 95% CI for major bleeding exceeds 1.00 in the 3rd quartile of the US data, and it does so in the 4th quartile of the global data, which is the US 3rd quartile TTR range equivalent.

Thus, the increased major bleeding rate noted in the US rivaroxaban arm relative to US warfarin-treated patients occurs by a different mechanism (decreased bleeding on

warfarin with improved warfarin TTR) than does the increased risk of bleeding on rivaroxaban in the global rivaroxaban-treated patient group in the 4th quartile of TTR (an increase in rivaroxaban-associated bleeding with improving warfarin management). This suggests the possibility that the US major bleeding rate difference as compared to the global trial may have been a chance finding in a relatively small subset analysis.

TTR analyses for the US and global data to LD+30 days produced similar results.

As was consistently the case over other bleeding analyses, it was notable that in the US, critical organ bleeding and hemorrhagic death were both decreased, and that hemoglobin drops and transfusions drove the overall increase in major bleeding. Also of note, a sub-analysis of US bleeding by dose group (20 mg/day vs. 15 mg/day) was performed to examine the effect that moderate renal insufficiency might exert on bleeding proclivity, in spite of an approximately equivalent systemic drug exposure. In contrast to the overall ROCKET result, the US data suggest that the relative excess risk of the principal safety endpoint as well as major bleeding were amplified in patients with moderate renal insufficiency, though warfarin therapy still carried an excessive risk of critical organ bleeding and fatal bleeding in this population, as can be seen in the following tables (sources Table 61 & 62, ROCKET FSR; Table 61 & 62, Geographically-Based Analyses, FDA IR):

Table 61: Incidence and Event Rate for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) for Subjects Receiving 20mg and 15mg Rivaroxaban Based on the First Assigned Dose and for Subjects Receiving Warfarin With Baseline Creatinine Clearance of <50 and ≥ 50 mL/min (Study 39039039AFL3001: Safety Analysis Set)

Parameter	----- Riva 20 mg -----		----- Riva 15 mg -----		--- Warf (<50 mL/min) ---		--- Warf (≥ 50 mL/min) --	
	N= 5637 n (%)	Evt Rate (100 Pt-yr)	N= 1474 n (%)	Evt Rate (100 Pt-yr)	N= 1476 n (%)	Evt Rate (100 Pt-yr)	N= 5640 n (%)	Evt Rate (100 Pt-yr)
Principal safety endpoint(a)	1145 (20.31)	14.24	330 (22.39)	17.82	342 (23.17)	18.28	1107 (19.63)	13.67
Major	302 (5.36)	3.39	93 (6.31)	4.49	100 (6.78)	4.70	286 (5.07)	3.17
Hemoglobin hematocrit drop	227 (4.03)	2.54	78 (5.29)	3.76	70 (4.74)	3.28	184 (3.26)	2.03
Transfusion	134 (2.38)	1.49	49 (3.32)	2.34	43 (2.91)	2.00	106 (1.88)	1.16
Critical organ bleeding(b)	75 (1.33)	0.83	16 (1.09)	0.76	30 (2.03)	1.39	103 (1.83)	1.13
Death	21 (0.37)	0.23	6 (0.41)	0.28	16 (1.08)	0.74	39 (0.69)	0.43
Non-major clinically relevant	926 (16.43)	11.35	259 (17.57)	13.77	260 (17.62)	13.63	891 (15.80)	10.86
Minimal	200 (3.55)	2.25	58 (3.93)	2.80	44 (2.98)	2.07	182 (3.23)	2.02

Table 62: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC)
While on Treatment (up to Last Dose Plus 2 Days) for Subjects Receiving 15mg Rivaroxaban Based on the First Assigned Dose and for
Subjects Receiving Warfarin With Baseline Creatinine Clearance <50 mL/min
(Study 39039039AFL3001: Safety Analysis Set)

Parameter	----- Riva 15 mg -----		---- Warf (<50 mL/min) ----		Riva 15 mg vs. Warf (<50 mL/min) Hazard Ratio (95% CI)
	N= 1474 n (%)	Evt Rate (100 Pt-yr)	N= 1476 n (%)	Evt Rate (100 Pt-yr)	
Principal safety endpoint(a)	330 (22.39)	17.82	342 (23.17)	18.28	0.98 (0.84,1.14)
Major	93 (6.31)	4.49	100 (6.78)	4.70	0.95 (0.72,1.26)
Hemoglobin hematocrit drop	78 (5.29)	3.76	70 (4.74)	3.28	1.14 (0.83,1.58)
Transfusion	49 (3.32)	2.34	43 (2.91)	2.00	1.17 (0.77,1.76)
Critical organ bleeding(b)	16 (1.09)	0.76	30 (2.03)	1.39	0.55 (0.30,1.00)
Death	6 (0.41)	0.28	16 (1.08)	0.74	0.39 (0.15,0.99)
Non-major clinically relevant	259 (17.57)	13.77	260 (17.62)	13.63	1.01 (0.85,1.20)
Minimal	58 (3.93)	2.80	44 (2.98)	2.07	1.35 (0.91,2.00)

Study 39039039AFL3001-Subjects in US Alone

Output T61DAEBPH725B: Incidence and Event Rate for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC)
While on Treatment (up to Last Dose Plus 2 Days) for Subjects Receiving 20mg and 15mg Rivaroxaban Based on the First Assigned Dose and for Subjects Receiving Warfarin With Baseline Creatinine Clearance of <50 and >=50 mL/min

Analysis Set: Safety

Parameter	----- Riva 20 mg -----		----- Riva 15 mg -----		--- Warf (<50 mL/min) ---		-- Warf (>=50 mL/min) --	
	N= 771 n (%)	Evt Rate (100 pt-yr)	N= 191 n (%)	Evt Rate (100 pt-yr)	N= 208 n (%)	Evt Rate (100 pt-yr)	N= 754 n (%)	Evt Rate (100 pt-yr)
PRINCIPAL SAFETY ENDPOINT(a)	259 (33.59)	24.21	63 (32.98)	30.53	56 (26.92)	20.11	219 (29.05)	19.46
MAJOR	97 (12.58)	7.63	26 (13.61)	10.22	20 (9.62)	6.41	67 (8.89)	5.12
HEMOGLOBIN HEMATOCRIT DROP	76 (9.86)	5.90	23 (12.04)	9.03	13 (6.25)	4.16	51 (6.76)	3.87
TRANSFUSION	55 (7.13)	4.22	17 (8.90)	6.62	9 (4.33)	2.86	38 (5.04)	2.87
CRITICAL ORGAN BLEEDING(b)	16 (2.08)	1.21	2 (1.05)	0.76	7 (3.37)	2.21	15 (1.99)	1.13
DEATH	5 (0.65)	0.37	1 (0.52)	0.38	3 (1.44)	0.95	7 (0.93)	0.52
NON-MAJOR CLINICALLY RELEVANT	196 (25.42)	17.60	41 (21.47)	19.20	40 (19.23)	14.17	171 (22.68)	14.90
MINIMAL	37 (4.80)	2.86	11 (5.76)	4.29	6 (2.88)	1.94	36 (4.77)	2.74

Study 39039039AFL3001-Subjects in US Alone

Output T62DAEBPH726B: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC)
While on Treatment (up to Last Dose Plus 2 Days) for Subjects Receiving 15mg Rivaroxaban Based on the First Assigned Dose and for
Subjects Receiving Warfarin With Baseline Creatinine Clearance <50 mL/min

Analysis Set: Safety

Parameter	----- Riva 15 mg -----		---- Warf (<50 mL/min) ----		Riva 15 mg vs. Warf (<50 mL/min) Hazard Ratio (95% CI)
	N= 191 n (%)	Evt Rate (100 pt-yr)	N= 208 n (%)	Evt Rate (100 pt-yr)	
PRINCIPAL SAFETY ENDPOINT(a)	63 (32.98)	30.53	56 (26.92)	20.11	1.48 (1.03,2.12)
MAJOR	26 (13.61)	10.22	20 (9.62)	6.41	1.56 (0.87,2.79)
HEMOGLOBIN HEMATOCRIT DROP	23 (12.04)	9.03	13 (6.25)	4.16	2.12 (1.07,4.19)
TRANSFUSION	17 (8.90)	6.62	9 (4.33)	2.86	2.25 (1.00,5.05)
CRITICAL ORGAN BLEEDING(b)	2 (1.05)	0.76	7 (3.37)	2.21	0.33 (0.07,1.61)
DEATH	1 (0.52)	0.38	3 (1.44)	0.95	0.40 (0.04,3.81)
NON-MAJOR CLINICALLY RELEVANT	41 (21.47)	19.20	40 (19.23)	14.17	1.33 (0.86,2.06)
MINIMAL	11 (5.76)	4.29	6 (2.88)	1.94	2.24 (0.83,6.07)

In both the overall ROCKET on-treatment group as well as the US on-treatment group, for patients whose GFR was initially > 50 mL/min and then fell on two consecutive measurements to < 50 mL/min, who were assigned initially to 20-mg rivaroxaban and were then maintained on this dose, overall bleeding results with rivaroxaban versus warfarin were similar to the overall US population, though the numbers of events and patients were small.

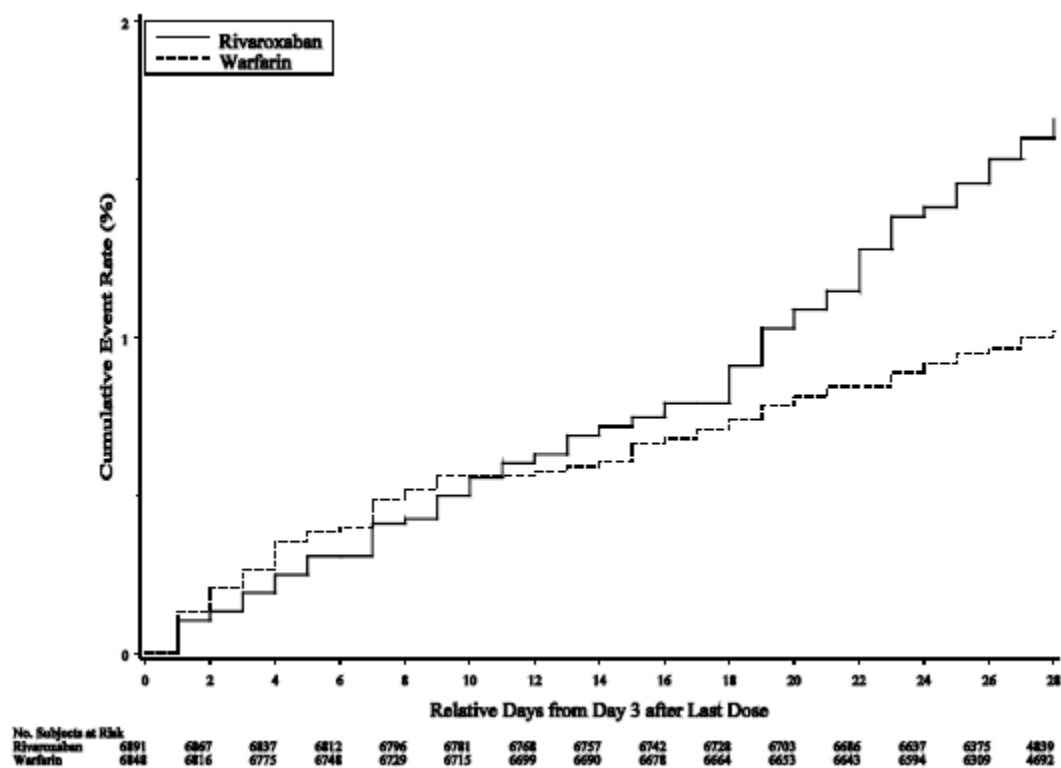
The incidence of intracranial bleeding during the treatment period was numerically lower with rivaroxaban therapy than with warfarin, as was the incidence of fatal bleeding events (1.14% vs. 1.45%, and 0.73% vs. 1.04%, respectively), though the number of people suffering a fatal bleeding event during the treatment period was numerically

higher in the rivaroxaban group (5 vs. 4). Incidence trends for ICH and fatal bleeding through the 30 day follow up period were similar.

Clinical Bleeding – the day 3 – 30 post-dose transition period

Shortly following the early transition period in which an elevated stroke rate was noted after ROCKET patients withdrew from study drug, the late transition period demonstrated a statistically significant increase in the occurrence of the principal safety outcome of the trial, as demonstrated in [Figure 54](#):

Figure 54. ROCKET Principal Safety Endpoint (Post 3-30, Safety Pop)



This finding was driven by an increase in non-major clinically relevant bleeding, as seen in the following table (source attachment 7.35 of the ROCKET FSR):

Rivaroxaban: Clinical Study Report 39035039AFL3001

Attachment 7.35: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC)
(From Day 3 to Day 30 After Last Dose)

Page 1 of 1

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Study 39035039AFL3001

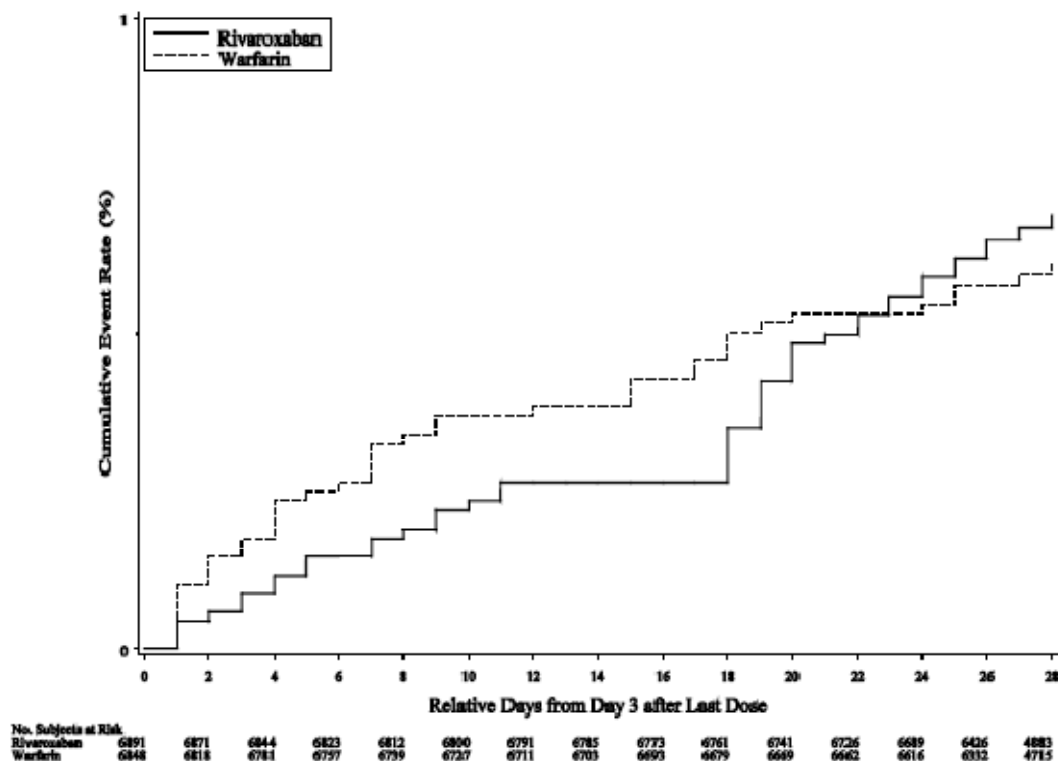
Output DAEPM249: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC) (From Day 3 to Day 30 After Last Dose)

Analysis Set: Safety

Parameter	Rivaroxaban		Warfarin		Hazard Ratio (95% CI)	p-value
	N= 7111 n (%)	Event Rate (100 pt-yr)	N= 7125 n (%)	Event Rate (100 pt-yr)		
PRINCIPAL SAFETY ENDPOINT(s)	113 (1.59)	22.24	68 (0.95)	13.52	1.65 (1.22, 2.22)	0.001*
MAJOR	46 (0.65)	9.02	41 (0.58)	8.14	1.11 (0.73, 1.69)	0.628
NEUROLOGIC HEMATOCRIT DROP	12 (0.17)	4.46	21 (0.29)	4.14	1.56 (0.60, 3.99)	0.374
TRANSFUSION	17 (0.24)	3.33	12 (0.17)	2.38	1.40 (0.67, 2.93)	0.371
CRITICAL ORGAN BLEEDING(b)	13 (0.18)	2.54	20 (0.28)	3.96	0.64 (0.32, 1.29)	0.213
DEATH	6 (0.08)	1.17	4 (0.06)	1.78	0.66 (0.25, 1.86)	0.471
NON-MAJOR CLINICALLY RELEVANT	72 (1.01)	14.13	28 (0.39)	5.55	2.55 (1.65, 3.94)	<0.001*
MINIMAL	8 (0.11)	1.56	12 (0.17)	2.38	0.66 (0.27, 1.61)	0.361

Thus, when major bleeding and NMCR bleeding were disaggregated and analyzed separately with K-M curves, a clearer picture emerged of what was transpiring. Specifically, and somewhat surprisingly, warfarin-treated patients during the early transition (most to open-label warfarin) demonstrated an increase in major bleeding events relative to patients who had received rivaroxaban as study drug then entered the transition, as seen in [Figure 55](#) below:

Figure 55. ROCKET Major Bleeds (Post 3-30, Safety Pop)



Yet by the end of the transition period, the two K-M curves for major bleeding had merged. There were no differences seen in the occurrence of hemorrhagic stroke during the transition interval or from day 3 post-dose until the end of the study, as seen in [Figure 56](#) and [Figure 57](#) below:

Figure 56. ROCKET Hemorrhagic Stroke (Post 3-30, Safety Pop)

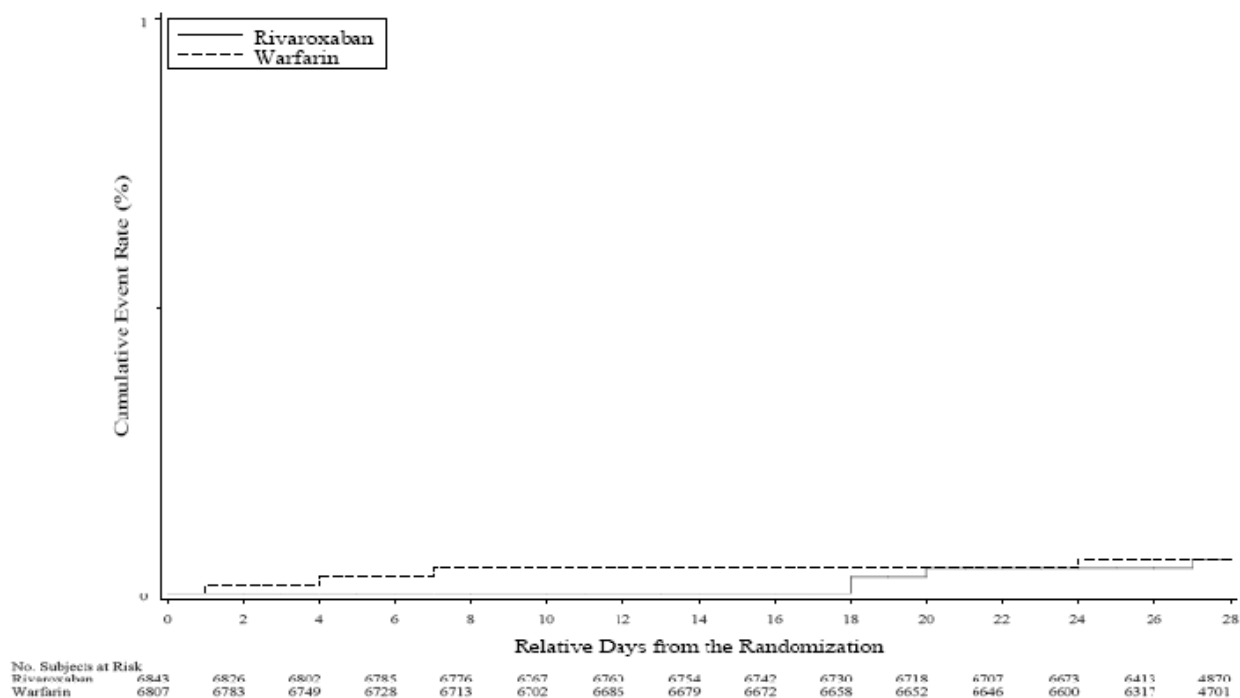
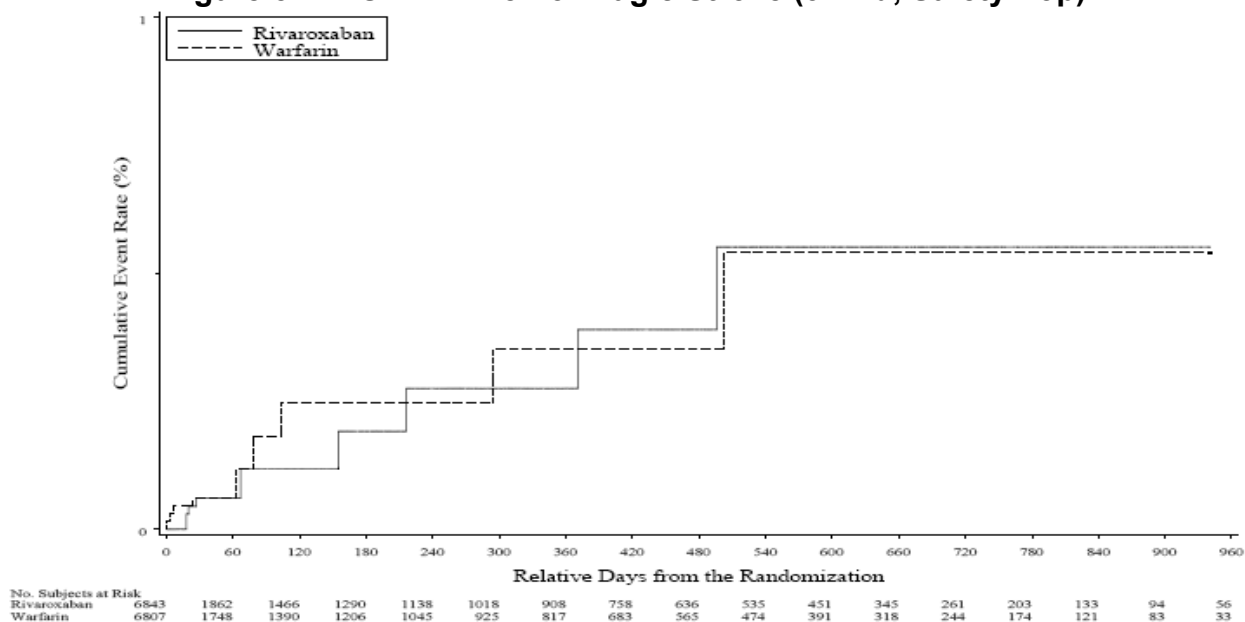
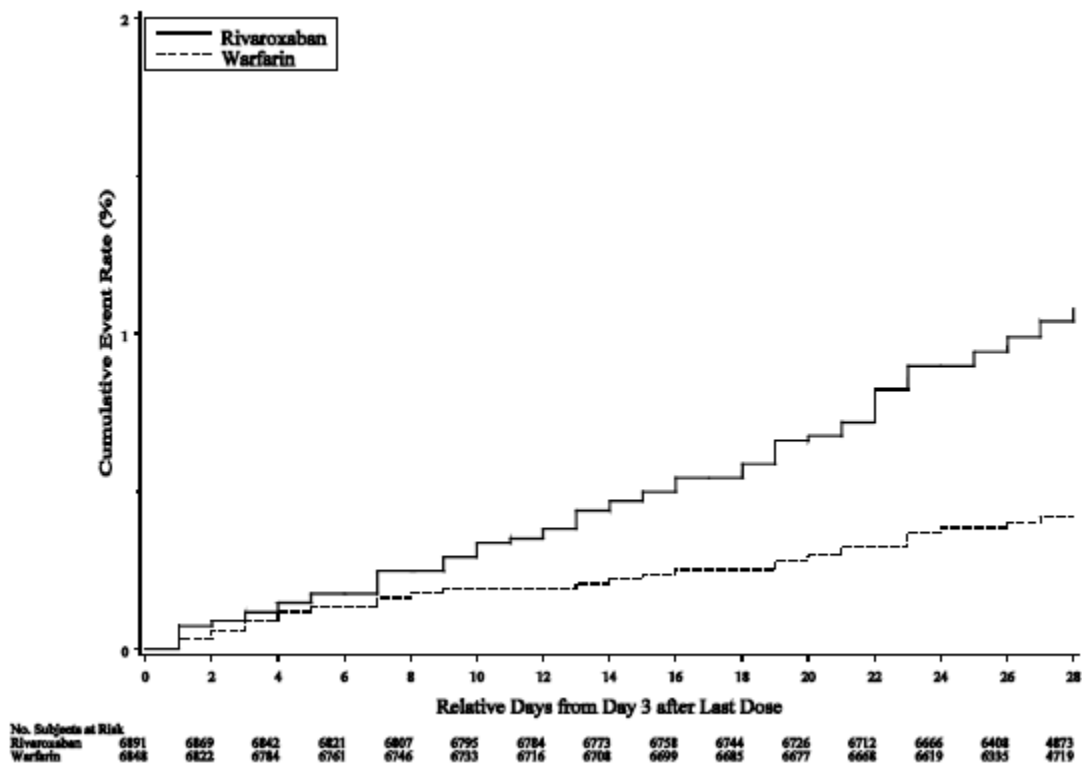


Figure 57. ROCKET Hemorrhagic Stroke (3-End, Safety Pop)



In contrast, NMCR bleeds began to increase impressively at day 8 of the transition period, and these K-M curves continued to separate until the end of the transition period for the overall trial population, as seen in [Figure 58](#) below:

Figure 58. ROCKET ISTH Non-Major CR Bleeds (Post 3-30, Safety Pop)



Similar findings for bleeding during the transition were noted in the US dataset, which demonstrated excess bleeding for patients treated with rivaroxaban during the double-blind phase, driven primarily by CRNM bleeding with numerically fewer major bleeds in that group compared to patients transitioning from blinded warfarin therapy, as seen in the [Figure 59](#) and [Figure 60](#) respectively (source: Geographically-Based Analyses IR):

Figure 59. Time To Non-Major Clinically Relevant Bleeding

US Patients, Safety Population, to Last Dose + 30 days

NDA 202439: Response to FDA IR (Geographically-Based Analyses) of March 2011

Figure F26FAEB180VBOC: Kaplan-Meier Plots of Time From Day 3 After Last Dose to the First Occurrences of Non-Major Clinically Relevant Bleeding Events (Adjudicated by CEC) (up to Last Dose Plus 30 Days)
(Study 39039039AFL3001-Subjects in US Alone: Safety Analysis Set)

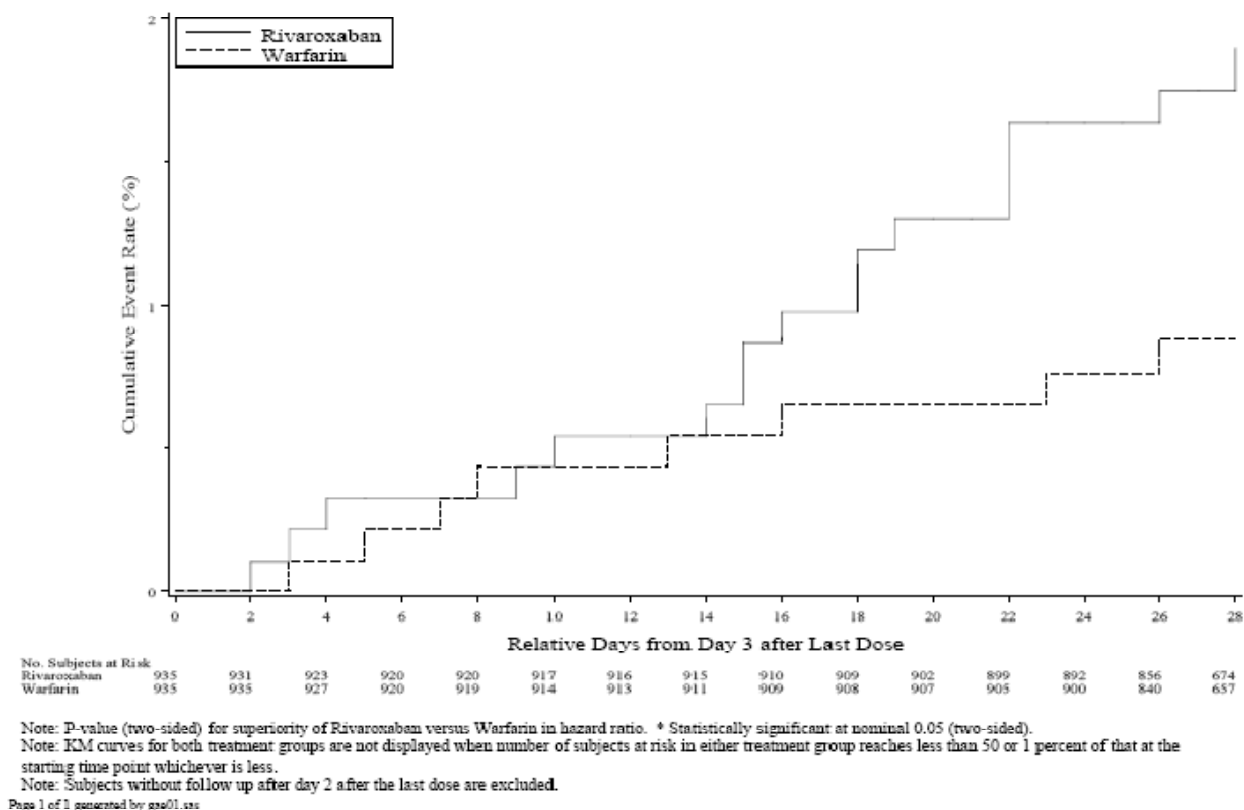
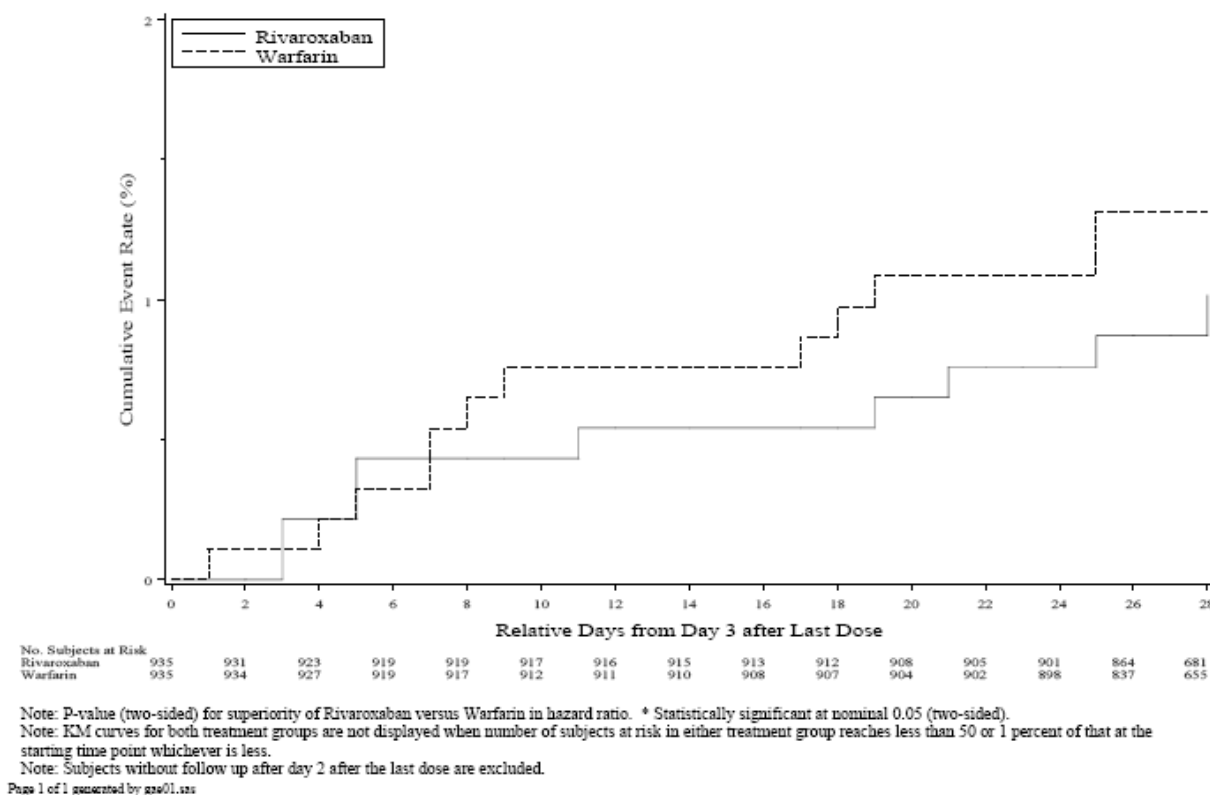


Figure 60. Time To Major Bleeding

US Patients, Safety Population, to Last Dose + 30 days

NDA 202439: Response to FDA IR (Geographically-Based Analyses) of March 2011

Figure F25FAEB170VBOC: Kaplan-Meier Plots of Time From Day 3 After Last Dose to the First Occurrences of Major Bleeding Events (Adjudicated by CEC) (up to Last Dose Plus 30 Days)
(Study 39039039AFL3001-Subjects in US Alone: Safety Analysis Set)



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Bleeding Safety – Concomitant Aspirin

The PK-PD-Outcome analysis from ROCKET demonstrated an exaggeration of the direct relationship that was noted between PT and Major Bleeding in rivaroxaban-treated patients who had also taken ASA at least 50% of the time during the trial, per [Figure 10](#) (Section 4.4.3). Aspirin increased the 100 p-y event rate for major bleeding in rivaroxaban-treated patients from 3.02 to 5.82. However, ASA similarly increased the 100 p-y event rate of major bleeding in patients taking warfarin from 3.03 to 4.76.

To explore this phenomenon in more detail, the ROCKET population was examined based on whether patients had taken aspirin at any time during the trial or not. Aspirin usage during ROCKET was common (approximately 2200 patients in both treatment arms). Among patients treated with ASA alone (without thienopyridine co-therapy), all bleeding category rates and almost all major bleeding subcategory rates in both study arms were higher than for patients taking neither ASA or thienopyridines. However, among those taking aspirin, there was no difference in major bleeding between the two study arms, and once again, critical organ bleeding and fatal bleeding rates favored rivaroxaban.

There were approximately 100 people in each trial arm who took a thienopyridine during the trial without concomitant ASA. In this small group, all bleeding category rates and all major bleeding subcategory rates for both study arms were higher than for patients not taking thienopyridines or ASA. However, among those taking thienopyridines, there were no differences in major bleeding between the two study arms, there were numerically fewer critical organ bleeds in rivaroxaban-treated subjects, and there was only one fatal bleed in each group.

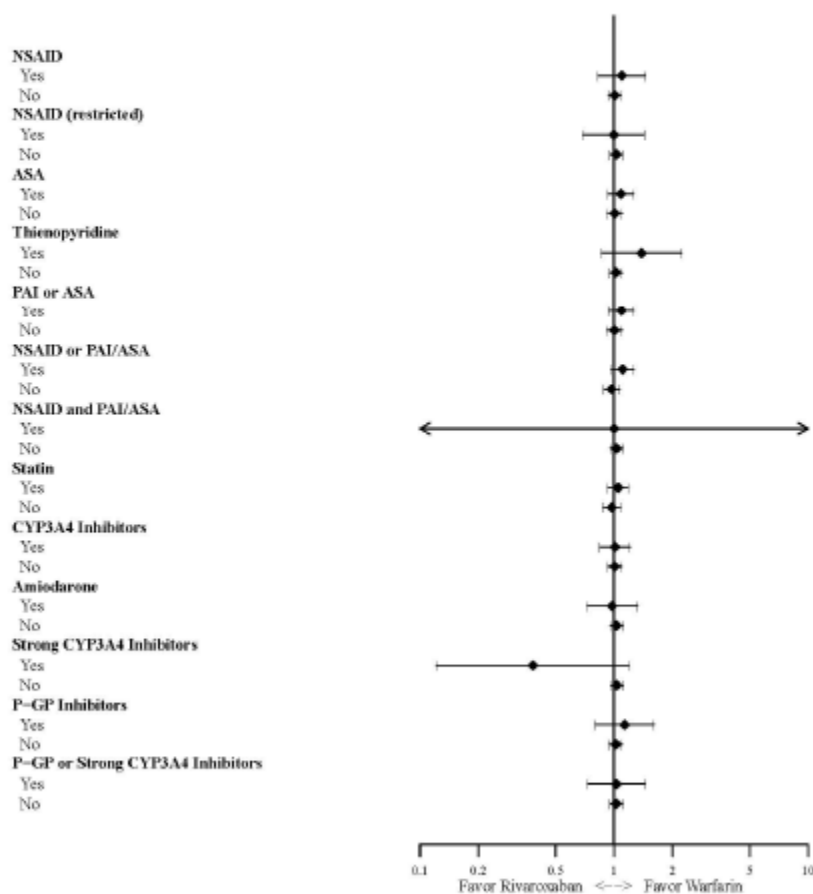
There were 109 rivaroxaban-treated subjects and 143 warfarin-treated subjects who took combination ASA and Thienopyridine therapy during the trial. Among these subjects, all bleeding category rates and all major bleeding subcategory rates for both study arms were higher than for patients taking neither thienopyridines nor ASA. However, among those taking ASA and thienopyridines, there were no differences in major bleeding between the two study arms, and once again, there were numerically fewer major bleeds, critical organ bleeds, and fatal bleeds in rivaroxaban-treated patients.

Concordantly, the sponsor's subgroup analysis corroborates a lack of aspirin or thienopyridine impact on the principal safety endpoint of ROCKET, per [Figure 61](#):

Figure 61. Hazard Ratio For Principal Safety Endpoint By Post-Baseline Concomitant Medications

Rivaroxaban: Clinical Study Report 39039039AFL3001

Figure 23: Plots of the Principal Safety Endpoint (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) by Post-Baseline Concomitant Medications
(Study 39039039AFL3001: Safety Analysis Set)



Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X-axis range.
Page 1 of 1 for figure FAEBPH721

7.3.5 Submission Specific Primary Safety Concerns

Liver:

Hy's law cases are balanced within ROCKET and within the other long-term, active-controlled trials of rivaroxaban (Figure 62 and Figure 63). OSE reviewed and re-adjudicated all significantly abnormal liver laboratory findings from ROCKET and found plausible alternative explanations for all cases. Dr. Senior's final recommendations were:

- No additional labeling warnings or precautions beyond those already included in the current draft language are suggested.
- Rivaroxaban appears relatively safe for long-term as well as short-term use as an anticoagulant agent for reduction of the incidence of DVT and PE in patients having knee or hip replacement procedure, as well as for reduction of ischemic strokes in patients with non-valvular atrial fibrillation.
- Routine monitoring of serum indicators of liver injury during treatment has been found to be inefficient, ineffective, very burdensome, and is neither necessary nor recommended for this drug.

Figure 62 ROCKET - Plot of Transaminase and Bilirubin Elevations

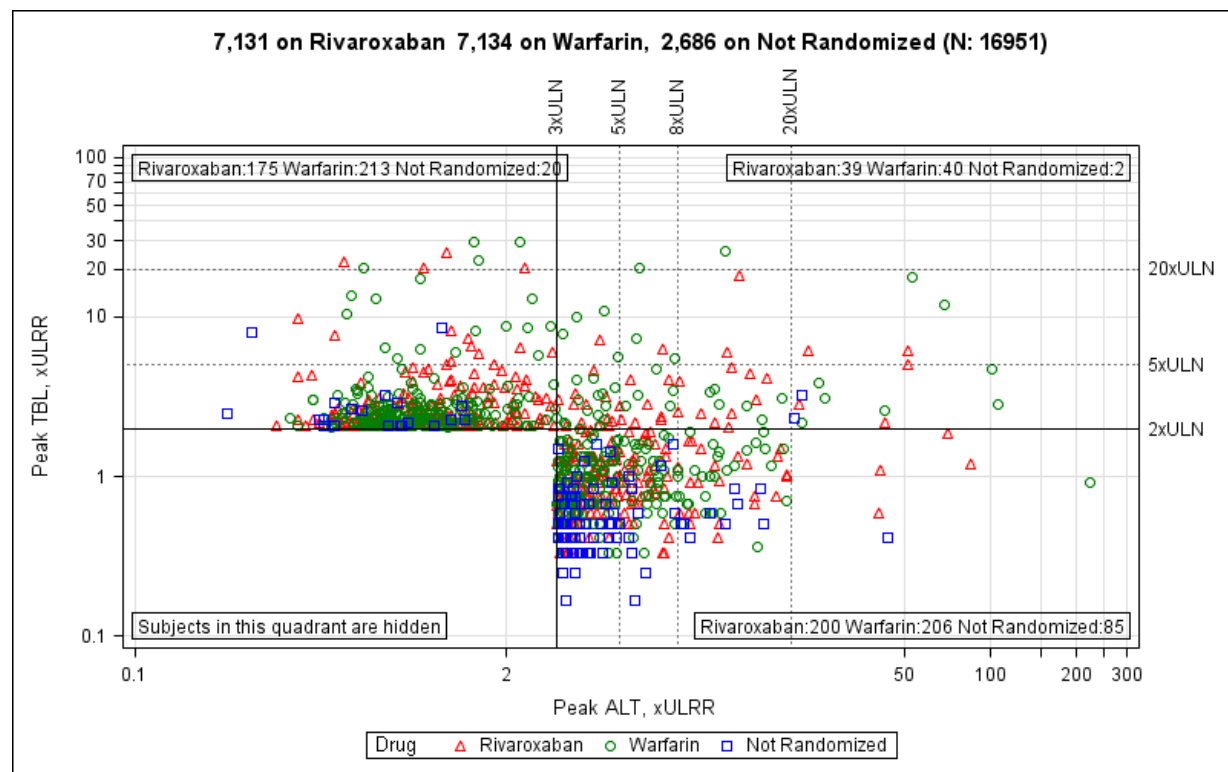
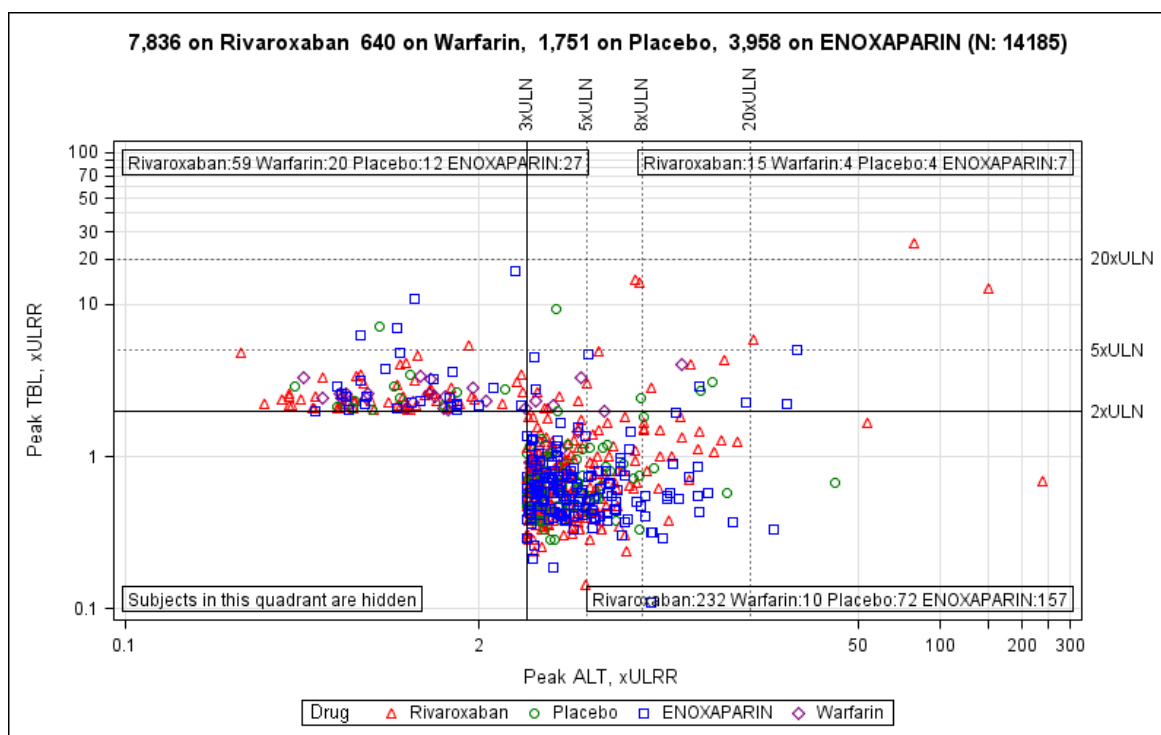


Figure 63. Plots of Transaminase and Bilirubin Elevations in J-ROCKET, EINSTEIN Phase 2, EINSTEIN DVT, EINSTEIN PE, EINSTEIN Extension, ODIXa DVT Phase 2, ATLAS ACS TIMI 46, & MAGELLAN



7.4 Supportive Safety Results

7.4.1 Common Non-Bleeding Adverse Events

There were no substantial differences between the treatment groups for the incidence of post-baseline, treatment emergent, serious non-bleeding adverse events. The percentages of patients experiencing non-bleeding adverse events > 2 days from the termination of rivaroxaban therapy or non-bleeding serious adverse events > 2 days from the termination of rivaroxaban therapy was similar between the two arms, though numerically higher in the rivaroxaban group. Non-bleeding adverse events leading to study drug discontinuation were the same between the two study arms. The 15 most common non-bleeding adverse events are displayed in [Table 105](#):

Table 105. ROCKET – Incidence Of The Most Common TEAEs

Table 46: Incidence of the 15 Most Frequent Non-Bleeding Treatment-Emergent Adverse Events Based on the Rivaroxaban Treatment Group by Preferred Term
(Study 39039039AFL3001: Safety Analysis Set)

Preferred Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects with non-bleeding treatment-emergent adverse events	5479 (77.05)	5525 (77.54)
Oedema peripheral	435 (6.12)	444 (6.23)
Dizziness	433 (6.09)	449 (6.30)
Nasopharyngitis	421 (5.92)	455 (6.39)
Cardiac failure	397 (5.58)	420 (5.89)
Bronchitis	396 (5.57)	417 (5.85)
Dyspnoea	380 (5.34)	394 (5.53)
Diarrhoea	379 (5.33)	397 (5.57)
Cough	343 (4.82)	353 (4.95)
Back pain	338 (4.75)	347 (4.87)
Upper respiratory tract infection	336 (4.73)	325 (4.56)
Headache	324 (4.56)	363 (5.09)
Arthralgia	301 (4.23)	331 (4.65)
Urinary tract infection	293 (4.12)	321 (4.51)
Influenza	273 (3.84)	229 (3.21)
Atrial fibrillation	261 (3.67)	259 (3.64)

7.4.2 Laboratory Findings

There were no substantial differences between the treatment groups in treatment emergent routine laboratory findings over time for either hematology or chemistry in ROCKET.

7.4.3 Vital Signs

There were no important differences in the mean changes of SBP, DPB, pulse rate, or weight in ROCKET. Vital sign changes in the RECORD studies were similar between rivaroxaban and warfarin over time.

7.4.4 Electrocardiograms (ECGs)

A thorough QT study was performed with the following design elements:

- 27 male and 27 female subjects
- randomized, double-blinded, four-way crossover study with
- single oral doses
 - 15 mg BAY 59-7939
 - 45 mg BAY 59-7939
 - Placebo
 - 400 mg of moxifloxacin

Results were as follows in [Table 106](#) and [Figure 64](#):

Table 106. TQT Study Results

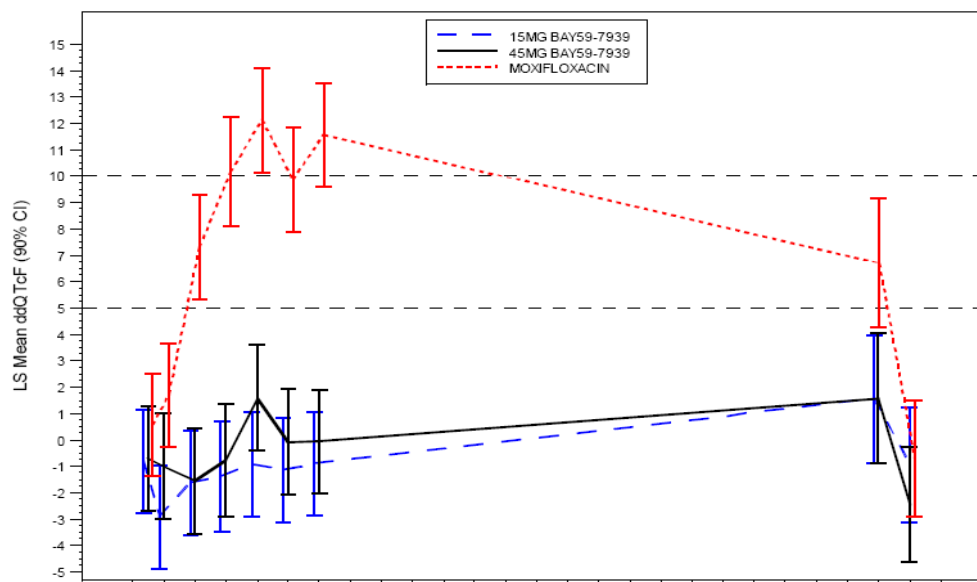
Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BAY 59-7939 (15 mg and 45 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
BAY 59-7939 15 mg	24	1.5	(-0.9, 4.0)
BAY 59-7939 45 mg	24	1.6	(-0.9, 4.0)
Moxifloxacin 400 mg*	4	12.1	(10.2, 14.1)

*Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 9 time points is 9.1 ms.

Figure 64. Time Course Of QT Changes

Figure 4: $\Delta\Delta QTcF$ Time Course



TQT Study Conclusions:

- Largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcF$ for moxifloxacin was greater than 5 ms
- Moxifloxacin profile over time is adequately demonstrated
- Assay sensitivity of the study was established
- Largest upper bounds of the 2-sided 90% CI for the mean difference between BAY 59-7939 (15 mg and 45 mg) and placebo were below 10 ms
- No significant QT prolongation effect of BAY 59-7939 (15 mg and 45 mg).

7.4.5 Special Safety Studies/Clinical Trials

ROCKET and J-ROCKET only. No special safety trials submitted.

7.4.6 Immunogenicity

No new immunogenicity data was submitted with this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

One dose tested on ROCKET.

7.5.2 Time Dependency for Adverse Events

See Section 7.3.4.

7.5.3 Drug-Demographic Interactions

Nursing mothers; discontinue drug or discontinue nursing, per current label.

7.5.4 Drug-Disease Interactions

Renal impairment. Patients with moderate renal dysfunction (creatinine clearance 30 to <50 mL/min) should have dose decreased to 15 mg per day to approximate exposure of patients with normal or minimally depressed renal function. Rivaroxaban was not studied on ROCKET in patients with CrCl < 30 mL/min. Based on simulated pharmacokinetic data, patients with renal impairment receiving XARELTO with P-gp and

weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use since both pathways of rivaroxaban elimination are affected.

Hepatic impairment. Clinical data in patients with moderate hepatic impairment indicate a significant increase in rivaroxaban exposure and pharmacodynamic effects. No clinical data are available for patients with severe hepatic impairment. Rivaroxaban is not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

7.5.5 Drug-Drug Interactions

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure. Per the current label,

In a drug interaction study, co-administration of XARELTO (20 mg single dose with food) with a P-gp and strong CYP3A4 inducer (rifampicin; titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and C_{max} , respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy. Concomitant use of XARELTO with a P-gp and strong CYP3A4 inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) should be avoided.

In drug interaction studies evaluating the concomitant use with combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- *Ketoconazole (P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Ritonavir (P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Clarithromycin (P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in

exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.

- *Erythromycin (P-gp and moderate CYP3A4 inhibitor)*: Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.

Avoid or use XARELTO with caution during concomitant administration of certain combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

As with warfarin, co-administration of rivaroxaban with anti-platelet agents increases the incidence of major bleeding.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There have been no prior concerns identified in the review of NDA 022406 for human carcinogenicity, nor was this a concern raised by the sponsor in the current NDA for the AFib indication. From ROCKET, and from the integrated ROCKET and J-ROCKET data set, the total incidences of neoplasms, along with the incidences of the 10 most frequently occurring neoplastic subtypes from the rivaroxaban arm of ROCKET, are shown in [Table 107](#) below:

Table 107. Neoplasms In ROCKET And J-ROCKET

	ROCKET + J-ROCKET		ROCKET	
	Rivaroxaban N=7750 n (%)	Warfarin N=7764 n (%)	Rivaroxaban N=7111 n (%)	Warfarin N=7125 n (%)
All Neoplasms	373 (4.81)	385 (4.96)	350 (4.92)	361 (5.07)
Basal Cell CA	47 (0.61)	57 (0.73)	47 (0.66)	57 (0.80)
Skin CA	19 (0.25)	18 (0.23)	19 (0.27)	18 (0.25)
Prostate CA	21 (0.27)	20 (0.26)	18 (0.25)	20 (0.28)
Prostatic Adenoma	17 (0.22)	4 (0.05)	17 (0.24)	4 (0.06)
Colon CA	14 (0.18)	14 (0.18)	14 (0.20)	13 (0.18)
Squamous Cell CA (skin)	14 (0.18)	26 (0.33)	14 (0.20)	26 (0.36)
Skin papilloma	13 (0.17)	9 (0.12)	11 (0.15)	5 (0.07)
Breast CA	10 (0.13)	12 (0.15)	10 (0.14)	12 (0.17)
Lung Neoplasm	10 (0.13)	14 (0.18)	10 (0.14)	14 (0.20)
Lung Neo Malignant	10 (0.13)	9 (0.12)	9 (0.13)	8 (0.11)

7.6.2 Human Reproduction and Pregnancy Data

In the sponsor's experience both in clinical trials and spontaneous reports, there have been 13 reported on-rivaroxaban conceptions (3 spontaneous reports, 10 from RCTs). The mean maternal age was 33.2 years for 11 of 13 cases where age was reported. The outcomes of those conceptions are as follows:

- Elective Abortions - 8
- Healthy Live Deliveries - 2
- Spontaneous Abortions - 2
- Congenital Anomaly - 1 (facial dimorphism and renal pelvis dilation)

The numbers are small and so conclusions cannot be drawn. However, 3/5 (60%) of pregnancies that were not electively terminated ended in spontaneous abortion or congenital anomaly. Considering this data, along with animal data, and from input that the hematology received from their maternal-fetal health consultant during the review of NDA 022406, the just-approved label addresses this issue as follows:

XARELTO should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of \geq

10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 11 times the human exposure of unbound drug, based on AUC comparisons at the maximum recommended human dose of 10 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 40 times the human exposure of unbound drug.

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Warnings – pregnancy related hemorrhage in the absence of a reversal agent

Black Box Warning, Spinal/Epidural Hematoma – Spinal hematomas may occur in patients who are anticoagulated and are receiving neuroaxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term paralysis. Factors that increase this risk include the use of indwelling epidural catheters, concomitant use of other drugs that affect hemostasis, traumatic or repeated epidural or spinal punctures, and a history of spinal deformity or spinal surgery.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric patients studies for the AFib indication. Safety and effectiveness in pediatric patients have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

APCC and FVIIa only transiently decreased bleeding time in an animal study.

Per the current label: “Overdose of XARELTO may lead to hemorrhage. A specific antidote of rivaroxaban is not available. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to high plasma protein binding rivaroxaban is not expected to be dialyzable.”

7.7 Additional Submissions / Safety Issues

Pancreatitis:

No excess pancreatitis treatment emergent adverse events (TEAEs) was demonstrated in ROCKET for rivaroxaban relative to the warfarin control, either in the US or Global populations, per [Table 108](#) below (source: table 76 ROCKET FSR, Table 76 Geographically-Based Analyses FDA IR):

Table 108. Pancreatitis In ROCKET

	US Population		Global Population	
	Rivaroxaban N=962 N (%)	Warfarin N=964 N (%)	Rivaroxaban N=7111 N (%)	Warfarin N=7125 N (%)
Pancreatitis	3 (0.31)	3 (0.31)	12 (0.17)	5 (0.07)
Pancreatitis acute	2 (0.21)	2 (0.21)	9 (0.13)	17 (0.24)
Pancreatitis Hemorrhagic	0	0	0	1 (0.01)
Pancreatitis relapsing	0	0	0	1 (0.01)

(b) (4) MAH is planning to delete this potential risk (b) (4)

Respiratory Failure:

Analysis was requested due to approximately 200 cases noted in an SAE narrative from the DVT prevention program where acute respiratory failure had been re-coded to multisystem organ failure. The concern was for hypersensitivity mediated pneumonic process as a consequence of rivaroxaban therapy. In response to an FDA-IR, J&J-Bayer reviewed their entire clinical trial database with a broad set of preferred terms that would pull up cases of respiratory failure, regardless if this was coded initially as a cardiopulmonary failure multisystem organ failure. Exclusive of ROCKET cases, which were assessed separately, a total of 203 cases were retrieved from the clinical trial database. 6 cases from the postmarketing experience were excluded from the analysis. Thus, 198 cases were from identified, 157 of which were from MAGELLaN, which remained blinded at the time of this assessment. However, respiratory failure was a common entry diagnosis for MAGELLaN patients. In total, from unblinded non-ROCKET and non-J-ROCKET clinical trials, 15 cases of respiratory failure were identified with rivaroxaban versus 22 cases reported on comparator agents. This reviewer reviewed the medical history from all 15 of the rivaroxaban-treated cases and agree that all had alternative explanations for their respiratory decompensations.

From the pooled AFib studies, 27 (.35%) cases of respiratory failure were identified from the rivaroxaban-treated patients, and 33 (.42%) in the warfarin group. All but 3 events were reported at SAEs, and the majority (78% in the rivaroxaban treated patients and 61% of the warfarin treated patients) of these events resulted in death. All cases came from ROCKET; there were no cases from J-ROCKET.

Thrombocytopenia:

No excess thrombocytopenia TEAEs were demonstrated in ROCKET for rivaroxaban relative to the warfarin control, either in the US or Global populations, per [Table 109](#) below (sources: ROCKET FSR, FDA-IR Geographically-Based Analyses):

Table 109. Thrombocytopenia In ROCKET

	US Population		Global Population	
	Rivaroxaban N=962 N (%)	Warfarin N=964 N (%)	Rivaroxaban N=7111 N (%)	Warfarin N=7125 N (%)
Thrombocytopenia	8 (0.83)	11 (1.14)	21 (0.18)	34 (0.48)
Platelet count decreased	2 (0.21)	10 (1.04)	13 (0.18)	31 (0.44)

Cases continue to be tracked in the PSUR.

Hypersensitivity:

There was an imbalance in hypersensitivity reactions in ROCKET, driven primarily by the AE PT “circulatory collapse.” One of these subjects experienced circulatory collapse during a pacemaker placement. Four of the five patients completed the study. 2 cases of anaphylaxis occurred, both considered unrelated by the investigator (one case was a confirmed lisinopril allergy and the other had a negative rechallenge). Both of these subjects continued on study drug and completed the study. The hypersensitivity experience from ROCKET is displayed in [Table 110](#) below (source: ROCKET FSR):

Table 110. Hypersensitivity (SMQ) In ROCKET

	Global Population	
	Rivaroxaban N=7111 N (%)	Warfarin N=7125 N (%)
Total	12 (0.17)	6 (0.08)
Toxic Skin Eruption	2 (0.03)	0
Cutaneous Vasculitis	1 (0.01)	0
Erythema Multiforme	1 (0.01)	0
Exfoliative Rash	1 (0.01)	2 (0.03)
Derm Exfoliative	0	1 (0.01)
Derm exfoliative Gen	0	1 (0.01)
S-J Syndrome	0	1 (0.01)
Circulatory Collapse	5 (0.07)	1 (0.01)
Anaphylactic Reaction	1 (0.01)	0
Anaphylactic Shock	1 (0.01)	0

Acute Renal Failure:

No evidence of drug association. See dropouts and discontinuations section 7.3.3.

8 Postmarketing Experience

There is no post marketing experience in the US to date. Relevant postmarketing reports from outside the US that have been noted in the approved label for rivaroxaban for the PE/DVT indication include:

- **Blood and lymphatic system disorders:** agranulocytosis
- **Gastrointestinal disorders:** retroperitoneal hemorrhage
- **Hepatobiliary disorders:** jaundice, cholestasis, cytolytic hepatitis
- **Immune system disorder:** hypersensitivity, anaphylactic reaction, anaphylactic shock
- **Nervous system disorders:** cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis
- **Skin and subcutaneous tissue disorders:** Stevens-Johnson syndrome.

(b) (4) the sponsor is currently considering a change (b) (4) to address six cases of severe pulmonary bleeding, three of which resulted in death (b) (4)

Of these six cases, three were diagnosed with bronchiectasis, one with a lung abscess, one with documented

lung cancer, and another with suspected lung cancer who experienced a massive pulmonary hemorrhage 30 minutes before death.

Other occurrences being tracked, but not felt to be drug-associated, are pancreatitis, thrombocytopenia, hypersensitivity, hepatobiliary disorders, skin disorders, and pancytopenia.

Of the 1,021 new cases of medically confirmed, serious listed events in this (b) (4), 756 were from clinical trials. The majority of these were bleeding events (GI, GU, post-op, hematoma, and anemia).

9 Appendices

9.1 Literature Review/References

See p. 257 for reference list.

9.2 Labeling Recommendations

Not applicable due to recommendation of CR.

9.3 Advisory Committee Meeting

Issues to be addressed at the AC meeting, currently scheduled for September 8, 2011, are those discussed in Section 1 as important to the evaluation of the NDA. These include:

- What is the proper standard to approve additional drugs for the prevention of thrombotic events in patients with non-valvular AFib?
- Whether there is evidence that rivaroxaban has been shown to be as effective as warfarin.
- Thrombotic events occurring after discontinuation of rivaroxaban, and whether sponsor needs to perform a study of its proposed transition regimen from rivaroxaban to warfarin prior to approval or other additional studies.
- Whether the sponsor needs to further dose-finding studies for rivaroxaban for this indication.

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ATTACHMENT 1

List of Trials of Rivaroxaban

Rivaroxaban: MODULE 5.2 Tabular Listing of All Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Bioavailability Studies				
11273 D Kubitza (Germany) Start: 21 Aug 2006 End: 10 Oct 2006	PK, Safety, PD; CO, OL; fasting Absolute bioavailability IV vs tablet, relative bio- availability	13 13M Median 31.5 (21-46) 13W	Single dose 1 mg IV solution, 5 mg tablet oral, 20 mg tablet oral Batch Number: BX01XRD (5 mg), BX0296H (20 mg); BXA116W (IV)	Complete Full Mod 5.3.1.1
Comparative Bioavailability and Bioequivalence Studies				
10924 Heather Ann Wray, MBChB (UK) Start: 05 Aug 2002 End: 26 Feb 2003	PK, Safety, CO, OL; fasting Intestinal absorption site	9 9M Median 30 (24-46) 9W	Single dose 5 mg tablet, crushed tablet granulate, solution; 5 and 10 mg; oral Batch Number: BX0003J	Complete Full Mod 5.3.1.2
10846 Dagmar Kubitza, MD (Germany) Start: 17 May 2002 End: 27 Jun 2002	PK, Safety, PD; CO, OL; high-fat, high- calorie breakfast Food effect study	10 10M Median 33.5 (26-38) 10W	Single dose 5 mg tablet; 10 mg; oral Batch Number: BX003J Formulation: 105	Complete Full Mod 5.3.1.2
10989 Hartmut Dietrich, MD (Germany) Start: 14 Aug 2002 End: 19 Sep 2002	PK, Safety, PD; CO, OL; high- fat, high- calorie breakfast Influence of food; dose strength equivalence	12 12M 33.6 (19-41) 12W	Single dose 5 mg and 20 mg tablets; 20 mg; oral Batch Number: BX0003J (5 mg); BX00040 (20 mg) Formulation: 001	Complete Full Mod 5.3.1.2
11937 M Lcidig (Germany) Start: 18 Oct 2006 End: 28 Nov 2006	PK, Safety, PD; CO, OL; high-fat, high-caloric breakfast Food Effect Study, Phase 3 10 mg tablet formulation	24 24M 43.0 (28-54) 24W	Single dose 10 mg tablet; 10 mg; oral Batch Number: BX01XZH Formulation: 360	Complete Full Mod 5.3.1.2

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Rivaroxaban: MODULE 2.2 Tabular Listing of All Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex: M/F Age (yr), Mean (Range) Race (W/B/Ot)	Treatment Regimen/Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11938 D Kubitzka (Germany) Start: 27 Mar 2007 End: 14 May 2007	PK, Safety, PD, CO, OL; fasting and fed Food effect study, 20 mg tablet formulation	24 24M 32.9 (20-45) 24W	20 mg tablet; 20 mg; oral Batch Number: BX02BW1 Formulation: 371	Complete Full Mod 5.3.1.2
10990 Dagmar Kubitzka, MD (Germany) Start: 18 Feb 2003 End: 17 Apr 2003	PK, Safety, PD, CO, OL; fasting and fed Extended-Release Development:	12 12M Median 29.5 (20-40) 12W	Single dose 25 mg ER prototype; 5 mg tablet; 25 mg; oral Batch Number: BX0003J (5 mg, formulation 105); BX015JE (25 mg, formulation 203)	Complete Full Mod 5.3.1.2
10995 M Leidig (Germany) Start: 14 Mar 2005 End: 20 Apr 2005	PK, Safety, PD, CO, OL; fasting and fed Extended-Release Development:	12 12M 32.8 (29-47) 12W	Single dose 30 mg ER prototype, 10 mg tablet; 30 mg; oral Batch Number: BX01RW9 (30 mg ER, formulation E402); BX01K43 (10 mg ER, formulation 110)	Complete Full Mod 5.3.1.2
10997 Dagmar Kubitzka, MD (Germany) Start: 13 Apr 2005 End: 24 May 2005	PK, Safety, PD, CO, OL; fasting and fed Extended-Release Development:	12 12M 38.1 (26-55) 12W	Single dose 30 mg ER prototype, 10 mg tablet; 30 mg; oral Batch Number: BX01W5R (30 mg ER, formulation E520); BX01CJT (10 mg ER, formulation 110)	Complete Full Mod 5.3.1.2
10998 Dagmar Kubitzka, MD (Germany) Start: 18 May 2005 End: 20 Jun 2005	PK, Safety, PD, CO, OL; fasting and fed Extended-Release Development:	11 11M 37.7 (28-52) 11W	Single dose 30 mg ER prototype, 10 mg tablet; 30 mg; oral Batch Number: BX01UR8 (30 mg, formulation E 431); BX01K43 (10 mg, formulation 110)	Complete Full Mod 5.3.1.2

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LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11032 D Kubitza (Germany) Start: 21 Apr 2006 End: 02 Jun 2006	PK, Safety, PD, CO, OL; fasting and fed Extended- Release Development:	9 9M 31.0 (26-42) 9W	10 mg ER prototype, 10 mg tablet; 10 mg, oral Batch Number: BX0279L (10 mg, ER, E521); BX01XZH (10 mg IR, formulation 360)	Complete Full Mod 5.3.1.2
11125 Dagmar Kubitza, MD (Germany) Start: 26 Feb 2003 End: 14 Apr 2003	PD, PK, safety and tolerability; OL, no control; Fasting and fed ER versus IR	11 healthy subjects 11M Median 35 (23-42) 11W	Single dose 25 mg ER formulation, fasting and fed; 5 x 5 mg IR tablet as a single 25 mg dose, fasting, 25 mg, oral Batch Number: BX0060S (5 mg IR, formulation 105); BX015JD (25 mg ER, formulation E209)	Complete Full Mod 5.3.1.2
11119/ Dagmar Kubitza, MD (Germany) Start: 10 Mar 2003 End: 25 Apr 2003	PK, Safety, PD, CO, OL; fasting and fed Extended- Release Development:	11 11M Median 29 (26-42) 11W	Single dose 25 mg ER prototype; 5 mg tablet; 25 mg, oral Batch Number: BX0060S (5 mg, formulation 105); BX015JC (25 mg, formulation E205)	Complete Full Mod 5.3.1.2
11321 A Halabi (Germany) Start: 21 Apr 2006 End: 18 May 2006	PK, Safety, PD, CO, OL; fasting and fed Extended- Release Development:	12 12M 31.8 (23-41) 12W	10 mg ER prototype, 10 mg tablet; 10 mg, oral Batch Number: BX0268N (10 mg ER, formulation E522); BX01XZ11 (10 mg IR, formulation 360)	Complete Full Mod 5.3.1.2

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Rivaroxaban: MODULE 5.2 Tabular Listing of All Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11322 M Leidig (Germany) Start: 19 Apr 2006 End: 30 May 2006	PK, Safety, PD; CO, OL; fasting and fed Extended- Release Development	12 12M 36.2 (20-44) 12W	20 mg ER prototype, 10 mg tablet; 20 mg; oral Batch Number: BX025X0 (20 mg ER, formulation E523); BX01XZH (10 mg IR, formulation 360)	Complete Full Mod 5.3.1.2
12362 W Timmer (Germany) Start: 01 Jul 2009 End: 14 Aug 2009	PK, safety and tolerability; non-blinded, 3-way CO, non- controlled; fed	24 healthy subjects 24M 35.0 (25-44) 24W	Single dose rivaroxaban tablet 10 mg, 15 mg and 20 mg; oral Batch number: BX02NLL (10 mg; formulation 110), BX02P1K (15 mg; formulation 115) and BX02PIL (20 mg; formulation 120)	Complete Full Mod 5.3.1.2
14588 D Neuenhofer (Germany) Start: 17 Aug 2009 End: 30 Sep 2009	Bioequivalence of 2x5 mg versus 1x10 mg tablet; OL, no control, CO; fasted	28 healthy subjects 28M 31.4 (19-45) 28W	Single dose rivaroxaban 2x5 mg tablet or 1x10 mg tablet; oral Batch number: BXA4BEW (5 mg); BXA1JPJ (10 mg)	Complete Full Mod 5.3.1.2
11585 D Kubitz (Germany) Start: 24 Jun 2008 End: 04 Aug 2008	PK, safety and tolerability of extended release formulation; unblinded, no control, CO; Fed and fasting	12 healthy subjects 12M 39.8 (27-53) 12W	Single dose of rivaroxaban GITS ER 12 mg tablet, fed and fasted; and 10 mg IR tablet; Oral, Batch number: BX02WNJ (ER 12 mg, formulation 529); BX02LFO (IR 10 mg, formulation 110)	Complete Full Mod 5.3.1.2

Clinical Review: Nhi Beasley, Preston Dunnmon and Martin Rose
Application type: Standard, NDA 22-439
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Rivaroxaban: MODULE 5.2 Tabular Listing of All Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number	Principal Investigator (Country)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/D/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
14022	Erich R. Arcus, MD, PhD (Germany) Start: 30 SEP 2009 End: 16 DEC 2009	PK, safety tolerability and PD of oral suspension formulation; OL, CO; fed and fasting	17 healthy subjects w 17M 34.9 (22-45) 17W	Single dose of rivaroxaban suspension 10 mg (fasting) and 20 mg (fed and fasting), 10 mg IR tablet (fasting), Oral: Batch number: BM03601 (1 mg/mL suspension, formulation 001); BX02LFO (10 mg tablet, formulation 360)	Complete Full Mod 5.3.1.2
13371	H. Kobayashi (Japan) Start: 14 Nov 2008 End: 06 Jan 2009	Bioequivalency between 2 formulations of rivaroxaban 15 mg tablets; fasting; randomized, non blinded, 2way CO study	20 20M 28.7 (21-37) 20Ot (Asian)	Single dose rivaroxaban 15 mg, fasting; oral Batch number: BX02J3E (Development No.365); BX02VCS (Development No.367)	Complete Full Mod 5.3.1.2
Healthy Subject Pharmacokinetic and Initial Tolerability Studies					
10342	Dagmar Kubitz, MD (Germany) Start: 30 Jan 2002 End: 10 Feb 2003	Safety, PD, PK, PG, PC, SB; fasting Single dose escalation	103 Parallel Design Part: 93M Median: 33 (19-45) 93W CO Design Part: 10M Median: 34.5 (21-38) 10W	Single dose 1.25 mg and 5 mg tablets, oral solution; 1.25, 5, 10, 15, 20, 30, 40, 60, 80 mg; oral Batch number: BX0068T (1.25 mg tablet, formulation 101), BX003J (5 mg tablet, formulation 105); 533758E (10 mg solution 0.1%, formulation 100); BX00040 (20 mg tablet, formulation 120)	Complete Full Mod 5.3.3.1
10347	Hartmut Dietrich, MD (Germany) Start: 15 Jul 2002 End: 02 Dec 2002	Safety, PD, PK, PG, PC, SB; fed Multiple dose escalation	68 68M 32.5 (20-45) 68W	Multiple dose 5 mg od/bid/tid, 10 mg bid, 20 mg bid, 30 mg bid /5 days; 5 mg tablet, oral Batch number: BX0003J	Complete Full Mod 5.3.3.1

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Rivaroxaban: MODULE 5.2 Tabular Listing of All Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
10991 J Dickson, MD (UK) Start: 10 Mar 2003 End: 25 Mar 2003	Safety, PK; fasting ¹⁴ C mass balance; metabolism & excretion pattern	4 4M Median 40 (30-54) 4W	Single dose 10 mg; solution; oral Batch number: BX004NZ (rivaroxaban); PLS 0451-1-12-A ([¹⁴ C] rivaroxaban)	Complete Full Mod 5.3.3.1
Patient Pharmacokinetic and Initial Tolerability Studies				
RIVAROXHA1001 (IMPACT12980) Venkatesh Nadar, M D (US) Start: 27 Dec 2007 End: 24 Mar 2009	PK, PD and Safety in CHF; OL, AC (in subjects with acute CHF) and DH, PC (in subjects with chronic CHF)	26 19M/7F 5/8 (25-87) 18W/8B	Cohort 1 (acute CHF): Rivaroxaban 10 mg od for 6 days; oral Enoxaparin 40 mg od for 6 days; subcutaneous Cohort 2 (chronic CHF): Rivaroxaban 10 mg od for 6 days; oral Batch number: BX026SP, BX02LF4, BX02LF5 and BX02U3X	Complete Full Mod 5.3.3.2 Synopsis
Intrinsic Factor Pharmacokinetic Studies				
11529 H Dietrich (Germany) Start: 02 Apr 2004 End: 15 Jun 2004	Safety, PD, PK, PG, PC, SB; fed Single dose escalation in the elderly	52 27M/25F 65.6 (60-76) 52W	Single dose 30, 40, 50 mg; 10 mg tablet; oral Batch number: BX01CJT Formulation number: 110	Complete Full Mod 5.3.3.3
11569 M Leidig (Germany) Start: 15 Jun 2004 End: 27 Sep 2004	Safety, PD, PK, PG, PC, SB; fed Comparison young < 45 y vs. subjects > 75 y	34 17M/17F 53.4 (18-83) 34W	Single dose 10 mg; 10 mg tablet; oral Batch number: BX01CJT Formulation number: 110	Complete Full Mod 5.3.3.3

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Clinical Review: Nhi Beasley, Preston Dunnmon and Martin Rose
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Rivaroxaban: MODULE 5.2 Tabular Listing of All Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
10850 Kenneth Lasseter, MD (US) Start: 17 July 2002 End: 05 September 2002	PK, Safety, PD; PG, PC, SB; fasting Age and gender study	48 24M/24F NA (21-80) 2W/2B/44Ot (Hispanic)	Single dose 10 mg; 5 mg tablet; oral Batch number: BX0003J	Complete Full Mod 5.3.3.3
11568 G Golor (Germany) Start: 25 Aug 2004 End: 29 Oct 2004	Safety, PD, PK; PG, PC, SB; fed Subjects of different weight categories (< 50 kg; 70-80 kg; > 120 kg)	48 16M/32F 34.7 (20-54) 48W	Single dose 10 mg; 10 mg tablet; oral Batch number: BX01CJT Formulation number: 110	Complete Full Mod 5.3.3.3
11002 Th Philipp, MD (Germany) Start: 09 Jul 2004 End: 04 May 2005	Safety, PK, PD; PG, OL; fasting Renal Impairment	32 18M/14F 51.8 (36-69) 32W	Single dose 10 mg; 5 mg tablet, oral; Batch number: BX01CG2 Formulation number: 105	Complete Full Mod 5.3.3.3
11003 A Halabi (Germany) Start: 19 Jan 2005 End: 10 Aug 2005	Safety, PK, PD; PG, OL; fasting Hepatic Impairment	32 18M/14F 54.7 (36-68) 32W	Single dose 10 mg; 5 mg tablet, oral; Batch number: BX01CG2 Formulation number: 105	Complete Full Mod 5.3.3.3
12090 Miguel A. Zimny, MD Maria Josefa Gutierrez, MD (US) Start: 6 Jun 2006 End: 19 Oct 2006	Safety, PD, PK; PG, PC, SB; fed Ethnic and racial differences	47 24M/23F 33.5 (18-45) 15W/16B/16Ot	Single dose 10 mg; 10 mg tablet; oral Batch number: BX01K43 (10 mg)	Complete Full Mod 5.3.3.3

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LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11126 T Tanaka (Japan) Start: 23 Jan 2003 End: 10 Apr 2003	Safety, PD, PK; PG, PC, SB; fasting Single dose escalation, Japan	40 40M 22.7 (20-34) 40Ot (Asian)	Single dose 5, 10, 20, 40 mg; 5 mg tablets; oral Batch number: C03005	Complete Full Mod 5.3.3.3
11127 T Tanaka (Japan) Start: 27 Jun 2003 End: 08 Sep 2003	Safety, PD, PK; PG, PC, SB; fed Multiple dose escalation, Japan	30 30M 23.5 (20-29) 30Ot (Asia)	Multiple dose 10 mg bid, 20 mg bid, 30 mg bid/6 days); 5 mg tablets; oral Batch number: BX0060S	Complete Full Mod 5.3.3.3
11325 H Fukase (Japan) Start: 21 Sep 2004 End: 28 Dec 2004	Safety, PD, PK; PG, PC, SB; fed Single dose escalation in the elderly, Japan	64 32M/32F NA (60-79) 64Ot (Asian)	Single dose 10, 20, 30, 40 mg; 10 mg tablet; oral Batch number: BX01J71	Complete Full Mod 5.3.3.3
12026 H Fukase (Japan) Start: 06 Jul 2006 End: 18 Aug 2006	Safety, PD, PK; PG, PC, SB; fed Multiple dose escalation in the elderly, Japan	36 18M/18F NA (65-78) 36Ot (Asian)	Multiple dose 10, 15, 20 mg od /7 days 5 mg tablet; oral Batch number: BX01XRD	Complete Full Mod 5.3.3.3
11608 Yimin Cui, Professor (China) Start: 18 May 2005 End: 19 Jul 2005	Safety, PD, PK; PG, PC, SB; fasting Single dose escalation, China	50 50M 34.7 (30-39) 50Ot (Asian)	Single dose 2.5, 5, 10, 20, 40 mg; oral 1.25 mg and 5 mg tablets; Batch number: BX01CFT (1.25 mg); BX01CG2 (5 mg)	Complete Full Mod 5.3.3.3

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Study Number Principal Investigator (Country)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Start/End Date (day Month year)				
11509 Yimin Cui, Professor (China) Start: 5 Sep 2005 End: 27 Dec 2005	Safety, PD, PK, PG, PC, SB; fed Multiple dose escalation, China	41 41M 34 / (30-39) 41Ot (Asian)	Multiple dose 5 mg bid, 10 mg bid, 20 mg bid, 30 mg bid/6 days > 10 mg and 10 mg tablets, oral Batch number: BX01CG2 (5 mg); BX01K43 (10 mg)	Complete Full Mod 5.3.3.3
11703 Pei Hu, M.D. (China) Start: 11 Oct 2005 End: 28 Mar 2006	Safety, PD, PK, PG, PC, SB; fed Single dose escalation in the elderly, China	79 40M/39W 62.8 (59-74) 79Ot (Asian)	Single dose 5, 10, 20, 30, 40 mg; 5 mg and 10 mg tablets, oral Batch number: BX01CG2 (5 mg); BX01K43 (10 mg)	Complete Full Mod 5.3.3.3
Extrinsic Factor Pharmacokinetic Studies				
11000 Dagmar Kubitz, MD (Germany) Start: 25 Sep 2003 End: 17 Nov 2003	PK, Safety, PD, CO, OL; fasting Interaction with Ranitidine	12 12M 32.1 (25-39) 12W	Single dose Rivaroxaban 30 mg; 5 mg tablet; oral Multiple dose Ranitidine 150 mg bid/4 days; Zantac® 150 mg; oral Batch number: BX0060S (formulation 105)	Complete Full Mod 5.3.3.4
11001 Dagmar Kubitz, MD (Germany) Start: 10 Sep 2003 End: 16 Oct 2003	PK, Safety, PD, CO, OL; fasting Interaction with aluminum hydroxide/magnesium hydroxide	12 12M 33.1 (20-42) 12W	Single dose 30 mg; 5 mg tablet; oral Single dose Maalox® 10 mL; oral Batch number: BX0060S (formulation 105)	Complete Full Mod 5.3.3.4
10993 Dagmar Kubitz, MD (Germany) Start: 26 Mar 2003 End: 19 May 2003	PK, Safety, PD, CO, OL; fasting Interaction with Midazolam	12 12M 28.5 (19-37) 12W	Single dose 20 mg; 20 mg tablet; oral Dormicum® 7.5 mg tablet; oral Batch number: BX00040 (formulation 120)	Complete Full Mod 5.3.3.4

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Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
10999 H Dietrich (Germany) Start: 10 Nov 2003 End: 14 Jan 2004	PK, Safety, PD; CO, OL; fed Interaction with digoxin	20 20M 33.9 (22-45) 20W	Single & multiple dose (9 days) rivaroxaban; 20 mg bid; 20 mg tablet; oral Multiple dose (28 days) digoxin 0.375 mg od Lenoxin® mite; oral Batch number: BX00040 (formulation 120)	Complete Full Mod 5.3.3.4
12359 M Gladis-Villanueva Cristóbal (Germany) Start: 19 Jan 2007 End: 27 Apr 2007	PK, Safety, PD; CO, OL; fed Interaction with Atorvastatin	26 26M 41.9 (24-53) 26W	Single dose rivaroxaban 20 mg; 20 mg tablet; oral Multiple dose (6 days) Atorvastatin 10 mg (Day 1-3) and 20 mg (Day 4-6) od Lipitor®; oral Batch number: BX0296H (formulation 371)	Complete Full Mod 5.3.3.4
10992 Dagmar Kubitz, MD (Germany) Start: 21 Feb 2003 End: 14 May 2003	PK, Safety, PD; CO, OL; fed Interaction with Ketoconazole 200 mg od	12 12M 33.0 (24-41) 12W	Single dose rivaroxaban 10 mg; 2x5 mg tablet; oral Multiple dose (4 days) Ketoconazole 200 mg od; Nizoral® 200 mg; oral Batch number: BX0003J (formulation 105)	Complete Full Mod 5.3.3.4

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Study Number Principal Investigator (Country)	Study Description/Design	Subjects Evaluated Sex: M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Start/End Date (day Month year)	Objectives, Type of Control			
11935	PK, Safety, PD, ST, OL; fed	20	Multiple doses rivaroxaban 10 mg	Complete
M del Mar Gladis-Villanueva (Germany)	Interaction with Ketoconazole 400 mg od	20M 34.2 (22-45)	od/5 days; 10 mg tablet; oral	Full
Start: 20 Mar 2005		20W	Multiple dose ketoconazole 400 mg od/10 days;	Mod 5.3.3.4
End: 26 Apr 2006			Nizoral® 200 mg tablet; oral	
			Batch number: BX01XZH (formulation 360)	
11935	PK, Safety, PD, ST, OL; fed	18	Single dose rivaroxaban 10 mg;	Complete
M del Mar Gladis-Villanueva (Germany)	Interaction with: Ritonavir	18M 33.2 (18-44)	10 mg tablet; oral	Full
Start: 22 Mar 2005		18W	Multiple dose ritonavir 600 mg bid /6 days; Norvir® 100 mg capsule;	Mod 5.3.3.4
End: 04 May 2006			oral	
			Batch number: BX01XZH (formulation 360)	
11365	PK, Safety, PD, CO, OL; fed	16	Single dose rivaroxaban 10 mg;	Complete
M del Mar Gladis-Villanueva (Germany)	Interaction with: Erythromycin	16M 32.0 (20-44)	10 mg tablet;	Full
Start: 16 Mar 2005		16W	Multiple dose erythromycin 500 mg tid /5 days; Erythrocim®	Mod 5.3.3.4
End: 03 May 2006			500 mg tablet; oral	
			Batch number: BX01XZH (formulation 360)	

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Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/OI)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
12612 U Armeier-Brandt (Germany) Start: 19 Dec 2007 End: 7 Feb 2008	PK, Safety, PD, CO, OL, fed Interaction with Clarithromycin	16 16M 37.6 (24-50) 16W	Single dose Rivaroxaban 10 mg; 10 mg tablet; oral; multiple dose Clarithro-mycin 500 mg bid Klacid®/5 days; oral Batch number: BX02CCX (formulation 360)	Complete Full Mod 5.3.3.4
12580 D Kubitza (Germany) Start: 12 Feb 2007 End: 24 Mar 2007	PK, Safety, PD, ST, OL; fed Interaction with Rifampicin	20 20M 35 (20-47) 20W	Single dose Rivaroxaban 20 mg; 20 mg tablet; oral Multiple dose Rifampicin 150-450 (days 1-3) and 600 (days 4-7) mg od Rifa®/7 days; oral Batch number: BX0296H (formulation 371)	Complete Full Mod 5.3.3.4 Amendment Mod 5.3.3.4
10348 Hartmut Dietrich, MD (Germany) Start: 14 Aug 2002 End: 02 Oct 2002	Evaluation of several PD parameters, Safety, PK; OL, CO; fasting Interaction with Enoxaparin	12 12M 23.6 (24-42) 12W	Single dose rivaroxaban 10 mg; 5 mg tablet; oral; Single dose enoxaparin 40 mg ; subcutaneous; Rivaroxaban and enoxaparin alone and combined Batch number: BX0003J	Complete Full Mod 5.3.3.4

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LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11123 Dagmar Kubitzka, MD (Germany) Start: 06 Apr 2004 End: 07 Jun 2004	Evaluation of several PD parameters, Safety, PK, CO, OL; fasting Interaction with Aspirin®	14 14M 34.6 (19-44) 14W	Single dose rivaroxaban 15 mg; 5 mg tablet; Two doses of Aspirin®: 500 mg (Day 1) and 100 mg (Day 2); oral Batch number: BX0060S (formulation 105)	Complete Full Mod 5.3.3.4
11124 Dagmar Kubitzka, MD Start: 26 Apr 2004 End: 13 Aug 2004	Evaluation of several PD parameters, Safety, PK, CO, OL; fasting Interaction with Naproxen	13 13M 32.5 (25-42) 13W	Single dose Rivaroxaban 15 mg; 5 mg tablet; oral 2 doses (500 mg each) of Naproxen; 500 mg Proxen®; oral Batch number: BX01CG2 (formulation 105)	Complete Full Mod 5.3.3.4
11279 Dagmar Kubitzka, MD (Germany) Start: 28 Jun 2004 End: 01 Sep 2004	Evaluation of several PD parameters, Safety, PK; CO, OL; fasting Interaction with Clopidogrel	14 14M 31.4 (19-42) 14W	Single dose Rivaroxaban 15 mg; 5 mg tablet; oral 2 doses of Clopidogrel: 300 mg (Day 1) and 75 mg (Day 2) Plavix® 75 mg tablet; oral Batch number: BX01CG2 (formulation 105)	Complete Full Mod 5.3.3.4

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LISTING OF CLINICAL STUDIES

Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/OI)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11364 D Kubitz (Germany) Start: 02 Sep 2005 End: 05 Dec 2005	Evaluation of several PD parameters, Safety, PK, CO, OL; fasting Interaction with Clopidogrel	27 27M 33.2 (25-44) 27W	Single dose Rivaroxaban 15 mg; 5 mg tablet; oral 2 doses of Clopidogrel: 300 mg (Day 1) and 75 mg (Day 2); Plavix® 75 mg tablet, oral Batch number: BX01CG2 (formulation 105)	Complete Full Mod 5.3.3.4
12089 D Kubitz (Germany) Start: 26 Jan 2006 End: 02 Mar 2006	Evaluation of several PD parameters, Safety, PK, OL, ST; fasting Pilot interaction with Warfarin	7 7M 31.6 (19-41) 7W	Single dose 5 mg; 5 mg tablet; oral 15 mg Coumadin®; oral 10 mg Koralion® prior to discharge; oral Batch number: BX01XRD (formulation 105)	Complete Full Mod 5.3.3.4
RIVAROXAFIL1001 (DDI 15232) Lva Vets, MD (Belgium) Start: 12 Apr 2010 End: 21 May 2010	PK, PD and Safety; OL, CO; in fed state Interaction with omeprazole	22 7M/15F 30.1 (18-43) 22W	Rivaroxaban: single 20 mg dose; oral Omeprazole: multiple 40 mg doses/5 days; oral Batch number: BX02W6H	Complete Full Mod 5.3.3.4 Synopsis
Healthy Subject Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Studies				
11175 G Golor (Germany) Start: 03 May 2004 End: 26 July 2004	QT effects, Safety, PK; DB, CO; positive control, fed Thorough QT Study ¹¹	54 27M/27F 62.4 (51-74) 34W	Single dose rivaroxaban 15, 45 mg; 5 mg tablet; oral; Control: 400 mg moxifloxacin, oral Batch number: BX0060S	Complete Full Mod 5.3.4.1

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Study Number Principal Investigator (Country)	Study Description/Design	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number) Single dose 5 mg tablet; 5, 10 mg; oral Batch number: BX0003J Formulation: 001	Study Status Type of Study Report CTD Location of Report or Publication
Start/End Date (day Month year) 11140 S Harder (Germany) Start: 10 Jan 2003 End: 18 Mar 2003	Objectives, Type of Control Evaluation of several PD parameters, Safety, PK; PG, PC,OL; fasting Thrombin Generation Study	12 12M 30.2 (27-37) 12W		Complete Full Mod 5.3.4.1
11940 M Wolzt (Austria) Start: 19 Jul 2007 End: 15 Jan 2008	Effect of rivaroxaban with and without Aspirin® on thrombus formation in a perfusion chamber at high and low shear rates, safety, tolerability, PD and PK of rivaroxaban compared to Aspirin and clopidogrel co- administration, OT, parallel and CO (treatment A and treatment B)	51 2 / 9 (18-54) 51W	Treatment A: single dose rivaroxaban 5 mg or 10 mg or 20 mg plus Aspirin once daily on 4 consecutive days: 300 mg (-3d), 100 mg (-2d, -1d, 0d); oral Treatment B: single dose rivaroxaban 5 mg or 10 mg or 20 mg; oral Comparator: clopidogrel + Aspirin Batch number: BX01XRD (5 mg, formulation 105); BX01XZH (10 mg, formulation 360); BX0296H (20 mg, formulation 371)	Complete Full Mod 5.3.4.1
10349 II Dietrich, MD (Germany) Start: 11 Nov 2008 End: 10 Nov 2009	PD, safety, tolerability and PK of switching from warfarin to rivaroxaban, single-blind, PC, parallel group	91 healthy subjects 91M 32.4 (18-45) 90W/1B	Treatment A: after reaching a steady state of warfarin rivaroxaban 20 mg od /4 days, oral Treatment B: after reaching a steady state of warfarin, placebo od/4 days, oral Treatment C: no prior warfarin treatment, rivaroxaban 20 mg od /4 days, oral Batch number: BX02J3F (20 mg tablet, formulation 371)	Complete Full Mod 5.3.4.1

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Study Number Principal Investigator (Country)	Study Description/Design Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Efficacy and Safety Controlled Clinical Studies				
ROCKET AF (39039039AFL3001, BAY59-7939/11630) Robert Califf, MD (US) Keith Fox, MD (Scotland) Start: 18 December 2006 End: 7 September 2010	Pivotal efficacy and safety study in AF; DB, active- controlled, event driven, non- inferiority for efficacy and superiority for safety (Phase 3)	14,264 (ITT) 8,604M/5,660W 71.2 (25-97) 11,879W/180B/1,786Asia/419Ot	Rivaroxaban 20 mg od (15 mg for moderate renal impairment) /variable duration; oral Comparator: warfarin Batch number: See CSR Section 3.4	Complete Full Mod 5.3.5.1 Synopsis
J-ROCKET (BAY59-7939/12620) Masatsugu Hori (Japan) Start: 08 Jun 2007 End: 19 Jan 2010	Safety and efficacy study in AF; DB, active-controlled, non-inferiority for safety (Phase 3)	1,778 (safety) 1030M/248F 71.1 (34-90) 1,278Ot (Asian)	Rivaroxaban 15 mg od (10 mg for moderate renal impairment) /variable duration; oral Comparator: warfarin Batch number: BX02E15 and BX02NE0 (10 mg tablet), BX02E90 and BX02VC5 (15 mg tablet)	Complete Full Mod 5.3.5.1
Other Clinical Studies				
39039039ACS2001 (11898) C. Michael Gibson, MD, MS (US) Start: 17 Nov 2006 End: 19 Sep 2008	Safety and efficacy; DB, PC, Dose escalation/dose confirmation In addition to aspirin with or without thienopyridine in subjects with acute coronary syndrome (Phase 2)	3491 subjects with ACS 2695M/796F 57.4 (24-88) 3322W/123/12/Ot	Rivaroxaban 2.5 mg od, bid; 5 mg od, bid; 10 mg od, bid; 15 mg od and 20 mg od. Batch numbers: BX021XB, BX02NG1, BX01XRF, BX02K8A, BX026SP, BX02LF4, BX02K6B, BX026SR, BX02LF6	Complete Full Mod 5.3.5.4 Synopsis

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Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
EINSTEIN DVT (11/02) Dr Harry R. Buller (The Netherlands) Start: 22 Mar 2007 End: 12 Apr 2010	Multi-center, randomized, OL, parallel group, active controlled, event-driven non- inferiority study in patients with confirmed acute symptomatic proximal DVT without symptomatic PE (Phase 3)	3449 (ITT) subjects with DVT 1960M/1489F 56.1 (18-97) 2646W/823/Ot	15 mg bid for 3 weeks, followed by 20 mg od/3, 6 or 12 months (determined by the investigator individually); oral Comparator: Enoxaparin/VKA Batch number: see CSR.	Complete; Full Mod 5.3.5.4
EINSTEIN DVT/PE Extension (11899) Dr Harry R. Buller (The Netherlands) Start: 28 Feb 2007 End: 17 Sep 2009	Multi-center, randomized, double blind, parallel group, placebo-controlled, event- driven study in subjects with confirmed symptomatic DVT or PE who had been treated (Phase 3)	1196 (ITT) subjects with DVT or PE 693M/503F 58.3 (18-96) 923W/29B/Ot	Rivaroxaban 20 mg od/(determined by the investigator individually); oral Comparator: placebo Batch number: BX0295K, BX02J3F, BX02KW3	Complete; Full Mod 5.3.5.4
11223 (MRR-00150) Giacinto Agnelli, Prof (Italy) Start: 24 Mar 2004 End: 05 Oct 2005	Randomized, OT, (partially blinded), multi- center, multi-national, PG, AC Safety, tolerability and efficacy (Phase 2)	613 (randomized); 543 (ITT) 340M/203F 59.0 (19-91) 499W/10B/24Ot	Rivaroxaban tablet: oral/84 days: 10 mg bid 20 mg bid 40mg od 30 mg bid Comparator: VKA/Enoxaparin Batch number: BX01CJT (10 mg), BX01EEF, BX008SR, BX01EGE BX01CJW (20 mg); BX01CJX BX01EGG (30 mg)	Complete; Full Mod 5.3.5.4

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Study Number Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
11528 (MRR-00223) Harry R. Buller, MD (The Netherlands) Start: 24 Dec 2004 End: 07 Dec 2005	Randomized, OL (partially blinded), multi center, multi-national, PG, ACI Safety, tolerability and efficacy (Phase 2)	543 subjects with acute symptomatic proximal DVT (randomized) 542 (safety) 277M/265F 58.0 (18-94) 507W/29B/6Ot	Rivaroxaban tablet: oral/12 weeks: 20 mg od 30 mg od 40 mg od Comparator: VKA/Enoxaparin Batch number: BX01KKE and BX01JSW (20 mg); BX01JT3 (30 mg)	Complete; Full Mod 5.3.5.4
12024 (MRR-00267) Fumihiko Takeda, et al (Japan) Start: 13 Sep 2005 End: 27 Mar 2006	Randomized, OL, active comparator, PG Safety, tolerability and efficacy (Phase 2)	100 subjects with AF (Safety) 80M/20F 68.1 (30-92) 100Ot (Asian)	Rivaroxaban oral/28 days: 2.5 mg bid 5 mg bid 10 mg bid Comparator: Warfarin Batch numbers: BX01CFT (1.25 mg); BX01CG2 (5 mg); BX01CJT (10 mg)	Complete; Full Mod 5.3.5.4
11390 (MRR-00199) M Hori, et al (Japan) Start: 30 Jul 2004 End: 21 Jun 2005	Uncontrolled, OL, group sequential Safety, tolerability and efficacy (Phase 2)	36 subjects with AF (Safety) 34M/2F 59.3 (34-81) 36Ot (Asian)	Rivaroxaban oral/28 days 10 mg bid 20 mg bid 30 mg bid Batch numbers: BX01CJT (10 mg); BX01EGF (20 mg); BX01CIX (30 mg)	Complete; Full Mod 5.3.5.4

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Study Number	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age (yr): Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration Route of Administration Batch Number (Formula Number)	Study Status Type of Study Report CTD Location of Report or Publication
Principal Investigator (Country) Start/End Date (day Month year)				
11365 (MRR 00297) Masatsugu Hori, Professor (Japan) Start: 03 Jul 2006 End: 14 Feb 2007	Randomized, OL, active comparator, PG Safety, tolerability and efficacy (Phase 2)	102 subjects with AF (Safety) 80M/22F NA (45-85) 102Ot (Asian)	Rivaroxaban oral/28 days: 10 mg od 15 mg od 20 mg od Comparator: Warfarin Batch number: BX01XRD (5 mg); BX01XZH (10 mg)	Complete; Full Mod 5.3.5.4

Ongoing, Other Clinical Studies

(b) (4)

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Principal Investigator (Country)		Sex: M/F	Route of Administration	Type of Study Report
Start/End Date	Study Description/Design	Age (yr): Mean (Range)	Batch Number	CTD Location of Report or (b) (4)

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Principal Investigator (Country)		Sex M/F	Route of Administration	Type of Study Report
Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Age (yr): Mean (Range) Race (W/B/Ot)	Batch Number (Formula Number)	CTD Location of Report or Publication
(b) (4)				

ATTACHMENT 2

Modified Rankin Score (Copied from protocol)

“The subject’s global function will be measured using the modified Rankin Scale. Details pertaining to the administration of the scale will be provided by the sponsor.

Score Description:

- | | |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms: able to carry out all usual duties and activities |
| 2 | Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance |
| 3 | Moderate disability: requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability: bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Patient death” |

ATTACHMENT 3

Additional Protocol and Statistical Plan Information

Special Dosing Instructions – Elective Invasive and Emergency Procedures

Elective Invasive Procedures

It was anticipated that subjects enrolled in this clinical study might require invasive procedures. The sites were instructed that the management of oral anticoagulation during these intervals should balance the risk of thrombosis and that of hemorrhage. The protocol indicated that all study patients should be considered as being at intermediate or high risk of thromboembolism; none should be considered as low risk patients. The following table summarizes the complex set of directions provided in the protocol.

Table 111. ROCKET -- Dosing For Subjects Having An Invasive Procedure

Risk of thrombo-embolism	Warfarin or placebo	Rivaroxaban or placebo	Additional instructions
Intermediate (not defined)	Discontinue approximately 4 days prior to the procedure, and get daily INR. When INR ≤ 1.5 , procedure may be performed	Discontinue approximately 2 days prior to procedure	Consider low dose unfractionated heparin (UH) or prophylactic dose LMW heparin (LMWH) starting 2 days prior to the procedure. Resume study drug when hemostasis is secure and patient can tolerate oral meds. When INR is 2.0 to 3.0 for 2 consecutive days, discontinue parenteral anti-coagulation.
High (not defined)	Same as above	Same as above	As above, except full dose UH or LMWH may be given until 8 or 24 hours before the procedure, respectively. Prophylactic dose UH or LMWH should be restarted when hemostasis is secure. Restart study drug and discontinue parenteral anticoagulation as above.

If an emergency procedure was needed, the blind was to be maintained and the investigator was to manage the subject in the same manner as if warfarin therapy was

administered. For some procedures (e.g., urgent percutaneous coronary intervention, no interruption of study drug was anticipated. In the peri-procedural period, INRs were to be performed as necessary using the point-of-care device.

(b) (4)



Clinical Review: Nhi Beasley, Preston Dunnmon and Martin Rose
Application type: Standard, NDA 22-439
Xarelto (rivaroxaban)

(b) (4)



Time and Event Information

(starts on next page)

Table 112. ROCKET -- Study Time And Event Schedule

Treatment Period	Screening Period ^a	Double-Blind Treatment Period ^b					Posttreatment Observation Period	
	Study Day	-30 to 1 ^c	1 ^d	Brief Visits	Full Visits	Early Study Medication Discontinuation Visit ^d	End of Study Visit ^e	Follow-up Visit ^f
Safety/Efficacy Procedures								
Assess efficacy endpoint events			X ^h	X	X	X	X	X
Physical examination	X					X	X	
Vital signs ^o	X					X	X	
12-lead ECG ^p	X					X	X	
International normalized ratio (INR) ^q	X	X ^r	X	X	X	X	X	
Liver function testing ^s	X			X	X	X	X	X ^t
Clinical laboratory tests (hematology, chemistry) ^s	X					X	X	
Pregnancy test ^u	X	X ^h				X	X	
Adverse event assessment	X ^v	X ^h	X	X	X	X	X	X
Sample (retained) for risk markers/proteomics ^w		X ^h			Wk 24 only			
Concomitant therapy	X	X	X	X	X	X	X	X
HCRU ^x			X	X	X	X	X	X
Anti-Clot Treatment Scale (ACTS) ^y				X	X	X		
Treatment Satisfaction Questionnaire for Medication (TSQM) version II ^z					X			
Telephone contact every 12 weeks						X ^d		

PD=pharmacodynamic; PK=pharmacokinetic; ECG=electrocardiogram; HCRU= Health Care Resource Utilization; PT= prothrombin time; FXa= factor Xa; PiCT= Prothrombinase-induced clotting time; LFTs= liver function test; ICU= intensive care unit; CCU= coronary care unit; VKA= Vitamin K antagonist; ACTS= Anti-Clot Treatment Scale; TSQM=Treatment Satisfaction Questionnaire for Medication version II; INR= International normalized ratio

NOTE: Footnotes are provided on the following page

(Note: Table footnotes are omitted in this review.)

Table 113. ROCKET -- PK/PD Data Time And Event Schedule

PHARMACOKINETIC/PHARMACODYNAMIC SAMPLING SCHEDULE

	Day 1	Between Week 2 and the End-of-Study Visit			Week 12 ^a	Week 24 ^a	At Least 1 Month, Preferably at Least 6 to 12 Months, After the First Matched PK/PD Sample ^b	
	Hours Predose	Hours Predose	Hours Postdose ^c				Hours Predose	Hours Postdose 1-3
			1-3	3-16				
PD sampling only (ALL subjects)	X ^d				X	X		
Matched ^e PK & PD blood sampling (select sites and subjects) ^f		X	X	X			X	X ^g

^a PD sampling may be taken as either a predose or postdose sampling for the Weeks 12 and 24. Predose or postdose sampling must be documented.

^b As close to the end-of-study visit as possible.

^c Postdose samples will be taken after supervised study drug administration; study drug is to be administered in the evening.

^d Only subjects enrolled at sites participating in the matched PK/PD substudy will have a baseline PD sample collected. The baseline sample may be drawn either at screening or on Day 1 (before dosing).

^e Matched samples = PD blood samples to determine coagulation characteristics (PT, FXa activity, PiCT) taken at the same time points as PK blood samples.

^f On days of matched PK/PD sample collections, subjects may be confined to the study site.

^g If agreed to by the subject.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology were to be drawn at specified times

and analyzed at the central laboratory. The investigator was to review the laboratory reports and document this review. Screening laboratory samples were to be obtained at least 2 days before planned randomization to allow adequate turnaround time. The following tests were performed:

Hematology

hemoglobin
platelet count

hematocrit
WBC with differential

Serum Chemistry

sodium
blood urea nitrogen (BUN)
glucose
lipase

potassium
creatinine
albumin
amylase

Liver Function Tests (at screening only)

alanine aminotransferase (ALT)
aspartate aminotransferase (AST)

bilirubin, total and direct
alkaline phosphatase

Liver Function Tests (at all other time points)

alanine aminotransferase (ALT) bilirubin, total and direct

aspartate aminotransferase (AST) - *only if ALT was elevated*

alkaline phosphatase - *only if ALT was elevated*

Note: Monitoring of liver function abnormalities is discussed more fully in Section 5.3.1.9.3.

Pregnancy tests

Testing (in women of childbearing potential) was to be performed at screening. Additional serum or urine pregnancy tests may be performed as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy throughout the study.

Serology for hepatitis A, B, C, and if appropriate D and E

Testing was to be performed at baseline only (this sample was to be retained by the central laboratory and was to be analyzed only if the subject develops evidence of hepatic injury during the study)

International Normalized Ratio (INR)

Other safety evaluations

The following safety-related evaluations were to be performed at times specified in the Time and Event Schedule:

- Standard twelve-lead ECGs were recorded.
- Vital Sign evaluation included pulse, blood pressure, height, and body weight. Pulse and blood pressure were to be measured after subjects have been semi-recumbent for 5 minutes.
- A targeted physical examination of the cardiovascular and neurological was performed. Any clinically significant abnormalities persisting at the end of the study were to be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Triggers for CEC Review

The following specific triggers for CEC review were specified for various endpoints:

For stroke/TIA (any one or more of the following):

- Data entered on the stroke/TIA eCRF form
- “Cerebral Angiography” = yes on the Procedures form
- “CT or MRI Imaging of the head” = yes on Procedures 2 form and “No evidence of stroke” was not checked

For non-CNS systemic embolism (any one or more of the following):

- Data entered on non-CNS systemic embolism form
- “Peripheral Angiograph” = yes on the Procedures form
- “Extremity Ultrasound” = yes on the Procedures 2 form and “Diagnostic for arterial embolism” or “Indeterminate for arterial embolism” is checked
- “CT or MRI Imaging of the Chest, Abdomen or Extremity” = yes on the Procedures 2 form and “Diagnostic for arterial embolism” or “Indeterminate for arterial non-CNS arterial embolism” (*sic*) was checked

For MI (any one or more of the following):

- Data entered on MI/UA (unstable angina) form
- “Presence of Significant New Q Wave” is checked on ECG form
- Troponin I, Troponin T, or CK isoenzyme MB (any one or more) are > ULN on Local Cardiac Markers, Core LAB, or coded SAE lab forms (CK > ULN may substitute for CK-MB only if CK-MB was not recorded)
- Point of care Troponin was positive

For major bleeding event/non-major clinically relevant bleeding event (any one or more of the following):

- One of following entries on the Bleed form –
 - One the following was checked: Intra-articular, Intracranial, Intramuscular (with compartment syndrome), Intraocular/retinal, Intraspinal, Pericardial, or Retroperitoneal
 - “Medical or surgical Intervention” = yes
 - “Unscheduled contact with doctor” = yes
 - “Associated discomfort (pain or impairment of daily activities)” = yes
 - “Action taken related to study drug” = “Study drug discontinued and restarted” or “Study drug discontinued permanently”
 - If “Outcome” = “DEATH” OR “Did the event result in Death” = YES “
- One of the following was checked on the Blood Transfusions form –
 - Packed Red Blood Cells- homologous (donor blood)
 - Packed Red Blood Cells- autologous (subject’s own blood)
 - Whole Blood- homologous (donor blood)
 - Whole Blood Cells- autologous (subject’s own blood)
- Specified reductions of hemoglobin from prior values on the Local Lab OR Core Lab or coded SAELAB forms

These criteria were written in a cascading manner so that multiple triggers would not result from the same event.

In addition to the automatic hard triggers described above, a number of other procedures formed a second level of screening to identify endpoints for adjudication. These included, but were not limited to:

- AE pages were analyzed to look for specific preferred terms associated with bleeding events that were not associated with entries on the BLEED form. Such events would trigger queries to the sites instructing them to record the event on the BLEED form, which would trigger the adjudication process. Reports of these AE findings would be prepared on a periodic basis for the CEC.
- Free text in the various laboratory results was analyzed to look for HGB values. Queries would be sent to the sites to recode these as “hemoglobin”. Reports of such occurrences would be prepared periodically for the CEC.
- Analogous procedures were established to find stroke/TIA, systemic emboli, and MI/UA events that were not explicitly coded as such on the relevant forms.

Additional Information Regarding the Statistical Plan

The statistical plan also provided for:

Subgroup Analyses

The homogeneity of treatment effects on the first occurrence of the principal safety endpoint across subgroups was examined (at a 2-sided significance level of 0.05) via a test for the treatment-by-subgroup interaction by adding this term and the subgroup as covariates to the Primary Cox Model, based on on-treatment data from the safety population. Estimates and 2-sided 95% confidence intervals for the hazard ratio (rivaroxaban/warfarin) for each subgroup based on the above model were provided (numerically and graphically). As supplemental information, subgroup analysis of the principal safety endpoint was provided based on all data up to the follow-up visit from the safety population. Lack of a significant interaction implied that the results were consistent across subgroups and that the overall response rates were the most appropriate estimates of treatment effect within each subgroup. If a significant interaction was observed, the results were examined to determine whether the interaction was quantitative or qualitative in nature using the Gail-Simon test. If the interaction was qualitative in nature, clinical explanations of the significant interaction were explored. The effect of multiple testing (that is, false positive) was considered in interpreting the above subgroup analyses.

Bleeding

Based on the safety population, the following additional analyses were performed:

- Analyses of time from the first study medication administration to the first occurrence of each of the following endpoints of bleeding using the Primary Cox Model, as well as summaries of incidences and event rates:
 - Principal safety endpoint
 - Major bleeding
 - Non-major clinically relevant bleeding
 - Minimal bleeding.
- These analyses were based on:
- on-treatment data using therapeutic windows of 2, 7, 14 and 30 days
 - all data up to the Follow-Up visit
 - all data since Day 3 after the last study medication (incidence and event rates only, without Cox model)
- Cumulative event rates over time using the Kaplan-Meier method, and risk differences of rivaroxaban versus warfarin at fixed times (from the first study medication administration):
 - The principal safety endpoint, based on:

- on-treatment data using therapeutic windows of 2, 7, 14 and 30 days
 - all data up to the Follow-Up visit
 - all data since Day 3 after the last study medication administration
- Major and non-major clinically relevant bleeding based on all of the data scopes above for the principal safety endpoint (Kaplan-Meier plots only)
- Analysis of time from the first study drug administration to the first occurrence of the principal safety endpoint using the Primary Cox Model augmented by a variable representing 4 groups of study centers (sites) formed based on the quartiles of the center-averaged proportions of time of INR in the target range (2.0 to 3.0) among warfarin treated subjects. This analysis was based on on-treatment data from the safety population
- Analysis of time from the first study drug administration to the first occurrence of the principal safety endpoint using the Primary Cox Model based on on-treatment data from the safety population, comparing rivaroxaban subjects with the following two subgroups of warfarin subjects, separately:
 - Those whose proportion of time of INR in the target range (2.0 to 3.0) was below or equal to the median
 - Those whose proportion of time of INR in the target range (2.0 to 3.0) was above the median
- Analyses of fatal bleeding using the Primary Cox Model and Kaplan-Meier method based on:
 - on-treatment data (with the 2-day window)
 - all data up to the Follow-Up visit
 - all data regardless of treatment exposure

Both of the following definitions of fatal bleeding were used:

- Broad Definition of Fatal Bleeding: The subject experienced a CEC adjudicated major bleeding event and died of any cause within 30 days (Day 1 was the date of the bleeding event)
- Narrow Definition of Fatal Bleeding: The subject experienced a CEC adjudicated major bleeding event and died within 30 days (Day 1 was the date of the bleeding event). The primary cause of death was to be adjudicated as vascular with subcategories of “Intracranial Hemorrhage” and/or “Hemorrhage, not intracranial.”
- Subgroup analyses of the major and clinically relevant non-major bleeding events based on on-treatment data
- Intracranial hemorrhages by sub-type based on on-treatment data and all data up to the Follow-Up visit

- Incidences of major, non-major clinically relevant and minimal bleeding events based on on-treatment data

If there were indications of imbalance in demographic and baseline characteristics and risk factors, their impact on the first occurrence of the principal safety endpoint was analyzed using the Cox Proportional Hazards model with these factors as covariates

Adverse Events

The reported terms used in the CRFs by investigators to identify adverse events were coded using MedDRA Version 13.0. Treatment emergent adverse events were defined as those adverse events that start between the first study medication administration and the last study medication administration plus 2 days. A summary of the following adverse events were performed by treatment group:

- Post baseline adverse events
- Treatment-emergent adverse events
- Adverse events with onset > 2 days from the stop of study medication
- Serious adverse events
- Post baseline serious adverse events
- Treatment-emergent serious adverse events
- Serious adverse events with onset > 2 days from the stop of study medication
- Adverse events leading to permanent study medication discontinuation
- Adverse events with outcome of death.

In addition, incidences of some of the above adverse events by system organ class and dictionary-derived (preferred) term were provided. These summaries were provided for

- Non-bleeding adverse events
- Bleeding adverse events (based on Hemorrhages Standardized MedDRA Query (SMQ Hemorrhage Terms Excl Laboratory Terms)
- Hepatic disorder adverse events (based on hepatic disorder SMQ, including and excluding the sub-search SMQ liver-related coagulation and bleeding disturbances, and/or liver-related investigations, signs and symptoms)

Subgroup analyses in the adverse event summaries included: Age, Gender, Race, Weight at baseline, BMI at baseline, Region, Prior VKA use, History of prior stroke, TIA and non-CNS systemic embolism, CHADS2 score and groups, Prior chronic ASA use, Screening creatinine clearance level, Congestive heart failure at baseline, Hypertension at baseline, Diabetes at baseline, and Atrial fibrillation type at baseline.

Cumulative event rates of the following are presented using Kaplan-Meier plots (supplemented by p-value and confidence interval for the hazard ratio based on the Cox Proportional Hazards model):

- Time to the first occurrence of treatment-emergent adverse event leading to permanent study medication discontinuation
- Time to the first occurrence of treatment-emergent serious adverse event leading to permanent study medication discontinuation.

Incidences of treatment-emergent adverse events and treatment-emergent serious adverse events (in particular, liver-related treatment-emergent adverse events and treatment-emergent serious adverse events) were compared between the treatment groups based on non-stratified analysis, with 95% confidence intervals for the differences in incidences provided. Other adverse events of special interest included acute pancreatitis, thrombocytopenia, acute renal failure, and hypersensitivity reactions. Standardized MedDRA Queries (SMQ) were used to identify and review cases of interest.

Clinical Laboratory Tests

Descriptive statistics (mean, standard deviation, median, minimum and maximum) were calculated for each laboratory analyte at baseline and at each scheduled time point (according to the protocol) and for changes from baseline. A clinical laboratory test value was considered abnormal if it was outside the reference (normal) range for that laboratory or meeting certain clinical criteria (thresholds).

Incidences of treatment-emergent abnormal laboratory values (including lipase, amylase abnormalities, and calculated creatinine clearance) were summarized by treatment group among subjects who had non-missing baseline laboratory values (that were not abnormal) and non-missing post-baseline on-treatment laboratory values (regardless of normal or abnormal). Incidences of post baseline abnormal laboratory values were summarized by treatment group among subjects who had non-missing post-baseline laboratory values (regardless of normal or abnormal).

The incidences of liver-related parameters were to be compared between the treatment groups based on non-stratified analysis, with 95% confidence intervals for the differences in incidences provided. Kaplan-Meier plots for time to the first occurrence of abnormality (elevation) of liver-related laboratory tests were to be provided.

Concurrent and non-concurrent combined cases of ALT > 3x ULN and Total Bilirubin (TB) > 2 x ULN were to be summarized. ALT > 3 x ULN and TB > 2x ULN were considered to be concurrent if they occur within the same calendar day. ALT>3xULN followed by TB>2xULN within 30 days will be considered non-concurrent. Scatter plots with ALT >3x ULN and total bilirubin >2x ULN thresholds (also known as Evaluation of drug induced serious hepatotoxicity [eDISH] plots) using all available laboratory data obtained at any time during the study, including prior to study drug administration, were utilized to identify all such cases.

For liver safety, summaries of liver-related values and abnormalities as well as HEAC results were provided. Summaries of liver-related adverse events were also provided. Cases meeting the following selection criteria (central and local laboratory values) were assessed by the HEAC: Any ALT >8x ULN, all deaths with ALT >3x ULN within 30 days of death, combined ALT >3x ULN with total bilirubin >2x ULN, and Other (includes certain AE terms selected by clinical; 28 terms from the hepatic disorder SMQ).

For HEAC causality assessment analysis was performed by grouping the number of assessments showing specific patterns (e.g., all 3 probable, 2 or more probable, etc.). The HEAC case selection criteria were grouped into 3 composites:

- Composite criteria #1 (A, B, C, D, E) was any of the 5 criteria,
- Composite criteria #2 (A, B, C) was any of these 3 criteria: concurrent ALT>3x ULN with total bilirubin >2x ULN or non-concurrent ALT>3x ULN with total bilirubin >2x ULN or ALT >8x ULN and
- Composite criteria #3 (A, B) was any of the 2 criteria concurrent ALT>3x ULN with total bilirubin >2x ULN or non-concurrent ALT>3x ULN with total bilirubin >2x ULN).

Absolute differences for causality assessments between the treatment groups were calculated for the 3 composite criteria groupings. Data are also presented descriptively for each of the 5 individual criteria. The same approach was followed for cross classifying causality assessment and alternative etiologies (e.g., all 3 probable causality with all 3 no alternative etiology, etc.). Descriptive summaries are provided for alternative etiologies, type of liver injury, severity of liver injury, liver transplantation and relationship of the liver injury to death as well as for various assessments of inter-rater agreement.

Vital Signs, Physical Examinations and ECG

Descriptive statistics were provided when applicable.

Benefit-Risk Analysis

The net clinical benefit (NCB) analyses were based on:

- On-treatment data from the safety population, and
- All data up to the protocol-specified Follow-Up Visit from the ITT population.

Summaries of event rates, excess numbers of events, and confidence intervals were provided for:

- Time from randomization to the first occurrence of the composite endpoint of death, stroke, MI, major bleeding, and non-CNS systemic embolism

- Time from randomization to the first occurrence of the composite endpoint of death, stroke, MI, major bleeding, non-CNS systemic embolism, and pulmonary embolism
- Time from randomization to the first occurrence of the composite endpoint of vascular death, stroke, MI, major bleeding, and non-CNS systemic embolism
- Time from randomization to the first occurrence of the composite endpoint of vascular death, stroke, MI, major bleeding, non-CNS systemic embolism, and pulmonary embolism.

Statistical plans for further NCB analyses using an unweighted approach and using a weighted approach were finalized prior to the database lock, and the reports from these analyses are to be provided separately from the ROCKET clinical study report.

Unplanned Safety Analyses (after unblinding)

For safety, additional unplanned analyses performed by the sponsor included evaluation of bleeding in relationship to baseline and post-baseline use of concomitant medications of interest. In addition, further evaluations of hypersensitivity reactions and minimal bleeding events were performed.

In order to evaluate the safety in moderate renal impairment, analyses of safety based on baseline CrCl level and rivaroxaban dose were performed on the time to the first occurrence of bleeding events for subjects receiving 15mg rivaroxaban and for subjects receiving warfarin with baseline CrCl <50 ml/min. In addition, analyses were also performed in subjects who had normal renal function or mild renal impairment at baseline and subsequently, developed moderate renal impairment during the treatment period.

Protocol Amendments

The original ROCKET protocol was dated 4 October 2006, and first patient was enrolled 18 December 2006.

Amendment 1 was dated 8 June 2007. In this amendment the following changes to study procedures were made:

- The screening period was lengthened from up to 14 days prior randomization to up to 30 days prior to randomization.
- Modest changes were made to the recommendations for the frequency of unblinded INRs prior to randomization during the transition period to study drug. In addition, the following language was added: **“Investigators are encouraged to randomize subjects before the INR falls below 2.0. Randomization should occur within 36 hours of the last unblinded INR.”**

-
- Criteria for acceptable documentation of atrial fibrillation were changed, but the basic patient population (those with non-valvular atrial fibrillation) was not changed.
 - The definition of prior VKA use (which was a stratification factor) was changed from 2 weeks or longer to 6 weeks or longer.
 - The exclusion for patients with a “prosthetic heart valve” was clarified by adding a parenthetical descriptor: **“(annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted)”**
 - The exclusion for patients with prior “severe, disabling stroke” was changed as follows: “Severe, disabling stroke (modified Rankin score of ~~3~~**4** to 5, inclusive [Attachment 2]) within ~~6~~**3** months or any stroke within ~~30~~**14** days before the randomization visit”
 - Exclusions for concomitant medications conferring bleeding risk were modified.
 - The exclusion concomitant use of strong CYP3A4 inhibitors was clarified by limiting it to systemic formulations only.
 - An exclusion for strong inducers of CYP34 was added
 - The frequency of INR measurements using the point of care device during elective invasive procedures was clarified.
 - The provision on the use of unblinded INRs when transitioning off of blinded study drug was modified as follows: **“To maintain the integrity of the blind, local unblinded INR measurements are discouraged for at least 3 days after the start of open-label VKA therapy. No INR measurements should be done (either with the point of care device or local unblinded) for at least 5 days after the start of open-label VKA. After 53 days VKA ...**
 - A typo in the trigger for additional testing in subjects with LFT abnormalities was corrected as follows: “....concurrent combined ALT >3 x ULN and total bilirubin >2 x ULN with the ratio of direct to total bilirubin ~~>50%...~~” (i.e., > 50% was changed to ≥50%)
 - Collection of an HIV test in the patients qualifying for additional liver testing was qualified to require patient consent and to be “clinically indicated”.
 - The following language was added in the Efficacy section to enhance documentation of stroke: **“Whenever possible, the use of CT scanning or MRI should be employed to assist in the classification of strokes.”**
 - The period that an investigator was barred from publishing individual site data was lengthened from 12 months to 48 months after the “conclusion, abandonment, or termination of the study” in the situation in the event that there has been no multicenter publication and the sponsor had not yet confirmed that there will be no such publication.
 - A sample handling procedure relating to centrifuges was modified.

Amendment 2 was dated 13 February 2009. In this amendment the following changes to study procedures were made:

- A series of changes were made to protocol text to deal with the low enrollment in the planned PK/PD component of the study. The original PK/PD plan was

replaced with a matched PK/PD substudy at selected sites, with the plan to enroll 100 subjects in each arm. A baseline PD sample was added for all subjects at PK/PD sites. Subjects with moderate renal impairment could be enrolled in the substudy.

ATTACHMENT 4

1995 Federal Register Document – Comparative Risk/Benefit

(Starts on next page)

Prevention (CDC), announces the following committee meeting.

Name: NCVHS Executive Subcommittee.
Times and Dates: 9 a.m.-5 p.m., August 29, 1995, 9 a.m.-2 p.m., August 30, 1995.
Place: The Bavarian Inn, Route 1, Shepherdstown, West Virginia 25443.
Status: Open.

Purpose: The purpose of this meeting is for the Executive Subcommittee to review accomplishments, structure, needs and work plans of NCVHS and individual subcommittees.

Contact Person for More Information: Substantive program information as well as summaries of the meeting and a roster of committee members may be obtained from Gail F. Fisher, Ph.D., Executive Secretary, NCVHS, NCHS, CDC, Room 1100, Presidential Building, 6525 Belcrest Road, Hyattsville, Maryland 20782, telephone 301/436-7050.

Dated: July 25, 1995.
Carolyn J. Russell,
Director, Management Analysis and Services Office, Centers for Disease Control and Prevention (CDC).
[FR Doc. 95-18839 Filed 7-31-95; 8:45 am]
BILLING CODE 4185-18-M

Food and Drug Administration

[Docket No. 95N-0185]

Drug Export; Arimidex (Anastrozole) 1 Milligram (mg) Tablet

AGENCY: Food and Drug Administration, HHS.
ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a notice that appeared in the Federal Register of June 29, 1995 (60 FR 33810). The document announced that Zeneca Pharmaceuticals Inc., was requesting conditional approval for export of the human drug Arimidex (Anastrozole) 1 mg tablet to the United Kingdom. The document contained an error in indication for use. This document corrects that error.

FOR FURTHER INFORMATION CONTACT: James E. Hamilton, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301-594-3150.

SUPPLEMENTARY INFORMATION: In FR Doc. 95-15969 appearing on page 33810 in the Federal Register of Thursday, June 29, 1995, the following correction is made:

On page 33810, in the second column, under the heading SUPPLEMENTARY INFORMATION, line 29, the word "colorectal" is corrected to read "breast".

Dated: July 24, 1995.
Betty L. Jones,
Acting Deputy Director, Office of Compliance, Center for Drug Evaluation and Research.
[FR Doc. 95-18747 Filed 7-31-95; 8:45 am]
BILLING CODE 4180-01-F

[Docket No. 95N-0230]

Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices

AGENCY: Food and Drug Administration, HHS.
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its position regarding demonstrations of product effectiveness in new drug applications (NDA's) and premarket approval applications (PMA's). In evaluating NDA's and PMA's, FDA weighs the product's demonstrated effectiveness against its risks and considers other factors such as the seriousness and outcome of the disease being treated and the adequacy of existing treatments. The agency does not require new human drug products or medical devices to be more effective than existing therapies nor does it necessarily require the product to be compared to other products. However, for products intended to treat life-threatening diseases, diseases with irreversible morbidity, and contagious diseases that pose serious health risks to others, it is essential for public health protection that a new therapy be as effective as existing, approved therapies.
DATES: Written comments by October 30, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy (HF-23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2831.

SUPPLEMENTARY INFORMATION: On March 4, 1995, President Clinton announced plans for reforming the Federal regulatory system as part of his "Reinventing Government" initiative. Part of this reform is aimed at reviewing regulatory processes to determine which requirements could be reduced or eliminated without lowering health and safety standards.

Pursuant to the President's "Reinventing Government" initiative, FDA made several recommendations with respect to the regulation of human

drug products and medical devices. One recommendation was the issuance of a public statement clarifying certain aspects of the standards for the effectiveness of human drug products and medical devices.

The Federal Food, Drug, and Cosmetic Act (the act) requires NDA's and PMA's to contain full reports of information demonstrating that the drug or device is safe and effective under conditions of use in the product's proposed labeling. (See sections 505(b) and 515(c) of the act (21 U.S.C. 355(b) and 360e(c)).) The agency must deny approval of a NDA or a PMA if it finds that the application does not demonstrate that the product is safe and effective for the uses indicated in the product's proposed labeling. (See sections 505 (c) and (d) and 515(d) of the act.)

Pharmaceutical and device manufacturers have sometimes claimed that the agency requires new human drug products and especially class III devices (devices for which insufficient information exists to assure that general controls and special controls provide reasonable assurance of safety and effectiveness; in general, these are the higher risk devices) to be more effective for their intended uses than comparable therapies that are already approved for marketing. These firms assert that FDA's requirements for demonstrating effectiveness present unreasonable difficulties in developing new therapies and bringing those new therapies to market.

This notice is intended to address the concerns about a comparative effectiveness standard that have been raised. In evaluating the safety of a new drug or medical device, FDA weighs the product's demonstrated effectiveness against its risks to determine whether the benefits outweigh the risks. This weighing process also takes into account information such as the seriousness and outcome of the disease, the presence and adequacy of existing treatments, and adverse reaction and other safety data.

In evaluating effectiveness, FDA reviews new drug products and devices on their merits. FDA does not require new drug products or devices to be more effective than approved therapies for the same disease or condition. In general, both new drug products and class III devices must be shown to be effective through evidence consisting of clinical investigations that provide a basis on which it can be concluded that the new drug product or class III device will be safe and have the effect that it is represented to have.

For most new drug products and new class III devices intended to treat serious

illness or provide symptomatic relief, a showing of effectiveness is usually based on a clinical trial comparing the product to a placebo. Such a showing does not necessarily involve a comparison to another active treatment or a product that is known to be effective.

In certain circumstances, however, it may be important to consider whether a new product is less effective than available alternative therapies, when less effectiveness could present a danger to the patient or to the public. For example, it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when: (1) The disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or (2) the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted diseases).

It should be noted that new products are often developed for particular subpopulations who either do not respond to or are not able to tolerate an existing approved therapy. FDA will generally approve for use in such a subpopulation a product that is shown to have effectiveness in this group, regardless of whether the product can be shown to be as effective in the broad target population as the alternative therapy. This is because, in effect, there is no available alternative therapy for the subpopulation. For example, a number of patients cannot tolerate a widely used therapy for an acquired immune deficiency syndrome (AIDS)-related pneumonia. FDA approved atovaquone for use in these patients even though the drug had been shown to be less effective than the standard therapy when tested in a broad population.

An additional issue related to product effectiveness concerns the assertion, by some industry officials, that the act not be interpreted as requiring multiple clinical studies when one "pivotal" study could suffice.

FDA believes good science dictates that a showing of effectiveness must be methodologically sound and provide a high level of confidence in the validity of the result. For human drug products, this ordinarily is achieved by independently replicating the result in a second study, to constitute an adequate demonstration of effectiveness for a new product. While a second study may well be needed to replicate results demonstrated in a first study, in some instances, it is possible to replicate results within one large, well-designed, multi-center study. FDA emphasizes

that this approach can be successful only when results are strong. The agency has, in the past, approved new human drug products on the basis of a single, multi-center study. Examples include dornase alfa for the treatment of cystic fibrosis, timolol for treatment of people after a heart attack, and zidovudine for AIDS. A statistically marginal result, even in a very large study, cannot provide convincing evidence without replication.

For medical devices, where the mechanism of action is a result of product design and substantially verified by in vitro performance testing, the agency has routinely relied on single studies evaluated for internal and across-center consistency to provide this high level of confidence in the result.

Dated: July 27, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-18877 Filed 7-31-95; 8:45 am]

BILLING CODE 4180-01-F-M

Statement of Organization, Functions, and Delegations of Authority

Part H, Chapter HF (Food and Drug Administration) of the Statement of Organization, Functions, and Delegations of Authority for the Department of Health and Human Services (35 FR 3685, February 25, 1970, and 56 FR 29484, June 27, 1991, as amended most recently in pertinent part at 58 FR 14214, March 16, 1993) is amended to reflect the following reorganization in the Food and Drug Administration (FDA).

The Office of the Center Director (OCD), Center for Drug Evaluation and Research (CDER) is being reorganized to enhance CDER's responsiveness to its internal and external customers. The Executive Operations Staff is being established to combine project management, executive secretariat, and program management functions. The functions and staff of the Division of Regulatory Affairs are being transferred from the Office of Compliance to OCD as the Regulatory Affairs Staff.

Under section HF-B, Organization:

1. Delete the subparagraph *Office of the Center Director (HFNI)* under the *Center for Drug Evaluation and Research (HFN)*, in its entirety and insert a new subparagraph reading as follows:

Office of the Center Director (HFNI). Promulgates, plans, administers, coordinates, and evaluates overall Center scientific, management, and regulatory programs, plans, and policies.

Provides leadership and direction for all Center activities.

Coordinates and directs the Center management, planning, and evaluation systems to assure optimum utilization of Center manpower, financial resources, and facilities.

Directs Center operations for equal employment activities.

2. Insert a new subparagraph *Executive Operations Staff (HFN11)* under the *Office of the Center Director (HFNI)* reading as follows:

Executive Operations Staff (HFN11). Provides executive secretariat support to the Immediate Office of the Center Director, including coordinating executive and legislative correspondence and activities; managing the preparation and coordination of meetings; and preparing background material, graphics, and other information for meetings, speeches, and presentations.

Provides project management support for Centerwide and Agencywide initiatives to improve the quality and timeliness of regulatory reviews and improve team-based management practices.

Provides management support and advice to senior Center management concerning Center programs, including Center extramural contracts and grants activities.

3. Insert a new subparagraph, *Regulatory Affairs Staff (HFN13)*, under the *Office of the Center Director (HFNI)* reading as follows:

Regulatory Affairs Staff (HFN13). Initiates, develops, and reviews regulations, policies, procedures, and guidelines that affect the drug approval process.

Serves as the Center's focal point on regulatory issues providing advice and assistance on such matters as scope, applicability, and intents of the Food, Drug, and Cosmetic Act and other laws, regulations, and policies.

4. Delete the subparagraph, *Office of Compliance (HFND)*, under the *Center for Drug Evaluation and Research (HFN)* and insert a new subparagraph reading as follows:

Office of Compliance (HFND).

Monitors the quality of marketed drugs through product testing, surveillance, and compliance programs.

Advises the Center Director and other Agency officials on FDA's regulatory responsibilities for drugs.

Develops standards for drug industry practices, including Current Good Manufacturing Practice (CGMP) regulations, and ensures their uniform interpretation.

Directs the Center's bioresearch monitoring program for drug products.

ATTACHMENT 5

Geographic Regions in ROCKET

Each of the 45 countries with sites that enrolled patients were divided was assigned to 1 of 5 regions as follows:

Asia Pacific: Australia, China, Hong Kong, India, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand

Eastern Europe: Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine

Latin America: Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela

North America: Canada, United States

Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, United Kingdom

ATTACHMENT 6

Methods Used to Calculate TTR

Individual TTR methodology

All individual TTR values were calculated using the imputation method of Rosendaal,¹² and excluded values obtained during treatment interruptions of 7 days or more in duration. For additional information, see [Table 114](#).

Center TTR methodology

Sponsor – Center TTR was **not** based on individual TTR values. Instead, it was calculated using the total number of INR values in target range from all warfarin subjects within a center divided by total number of INR values from all warfarin subjects within the center. Neither interruptions of treatment nor values from the first week of treatment were excluded.

FDA – Center TTR was based on individual TTR values. It was calculated as the unweighted mean (or other summary statistic, as relevant) of the individual TTR values (using TTRE, see [Table 114](#) below) of all warfarin arm subjects at the center. Individual TTRE was obtained from the COMEF03B dataset provided the Sponsor. TTRE excludes interruptions of treatment. It was intended to exclude values from the first week of treatment, but it erroneously included those values.

Other aggregate TTR statistics

TTR was calculated for the entire warfarin arm in ROCKET and various subgroups defined by geography or other factors. In each case, the aggregate TTR statistic was calculated by the Sponsor or by FDA as the unweighted mean of the individual TTRs of the members of the relevant group or subgroup. The Sponsor used TTRI excluding the first week of treatment (see [Table 114](#)), and FDA used TTRE from the COMEF03B dataset for these calculations.

Differences in TTR calculated using the various methods

The Sponsor calculated ROCKET global study TTR values using TTRI or TTRE and including or excluding the first week or treatment interruptions. Note that all these methods are based on individual TTR values. All methods produced very similar mean and median TTRs. For the mean, the difference between the lowest TTR (55.12%, for TTRI including the first week of treatment and all interruptions) and highest TTR

(55.75% for TTRE, excluding the first week and all interruptions), was 0.63%. Likewise, the difference between the lowest and highest median TTR calculated using the methods described above was 0.65%.

Table 114. Overall TTR Calculations Using Different Methods in Warfarin-Treated Subjects in the ROCKET AF Study

Method	Data Excluded	Mean TTR (%)	Median TTR (%)
TTRI incl. 1st Week (In Dataset COMEF03B Sent to FDA)	Include first week after first dose and include all interruptions	55.12	57.69
TTRI excl. 1st Week	Exclude first week after first dose and include all interruptions	55.44	57.95
TTRE incl. 1st Week (In Dataset COMEF03B Sent to FDA)	Include first week after first dose and exclude all interruptions	55.43	57.96
TTRE excl. 1st Week	Exclude first week after first dose and all interruptions	55.75	58.34

While methods for calculating aggregate TTR based on the individual TTR of the members of the relevant subgroup yielded relatively similar values, the Sponsor's method for calculating center-based TTR was not based on individual TTR values, and yielded results different from FDA's method, which was based on individual TTR values. The sponsor's method yielded quartile limits that were about 2 – 4% higher than FDA's method, as shown below.

Table 115. Center-based TTR Quartile Upper Limits – Contrast of FDA and Sponsor Results

Safety Population, quartiles with similar numbers of patients

Quartile of Center-based TTR	Upper limit of quartile (%)	
	FDA	Sponsor
1	46.78	50.62
2	55.87	58.54
3	63.91	65.74

Clinical Review: Nhi Beasley, Preston Dunnmon and Martin Rose
Application type: Standard, NDA 22-439
Xarelto (rivaroxaban)

For additional information on quartiles of center-based TTR and a hypothetical example of how differing lengths of follow-up among patients can produce differences between FDA's and the Sponsor's methods of calculating center-based TTR, see the discussion in Sec. [6.1.10.2.2](#).

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/s/

MARTIN ROSE

08/10/2011

PRESTON M DUNNMON

08/10/2011

CLINICAL PHARMACOLOGY REVIEW

NDA	202-439
Submission Date	01/05/2011
Generic Name	Rivaroxaban
Brand Name	XARELTO [®]
Dose & Dosage Form	Once daily, 20 & 15 mg Film Coated Immediate Release Tablets
Indication	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Sponsor	Ortho Mcneil Janssen Pharmaceuticals Inc.
Submission Type	Standard
Reviewers	Sreedharan Nair Sabarinath, PhD Tzu-Yun McDowell, PhD
Pharmacometrics Team Leader	Pravin Jadhav, PhD
Team Leader	Rajanikanth Madabushi, PhD

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1 EXECUTIVE SUMMARY

Ortho Mcneil Janssen Pharmaceuticals Inc. submitted NDA 202-439 for rivaroxaban immediate release tablets for the primary prevention of stroke and systemic embolism in patients with atrial fibrillation (SPAF) on 5th January 2011. Rivaroxaban is a synthetic, competitive and selective oral, direct factor Xa inhibitor. A 10 mg dose strength of rivaroxaban is approved in the US under NDA 022-406 for the prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. This report evaluates the clinical studies relevant to the proposed SPAF indication or the clinical pharmacology studies which were not reviewed under NDA 022-406.

A single pivotal efficacy and safety study (ROCKET-AF) forms the basis for seeking approval in SPAF. ROCKET-AF was a randomized, double-blind, double-dummy study for stroke prevention in subjects with non-valvular atrial fibrillation and at least two other risk factors for stroke such as congestive heart failure (CHF), hypertension, age ≥ 75 years and diabetes or a prior history of stroke, TIA or systemic embolus events. A total of 14,269 patients were randomized to rivaroxaban (20 mg once daily or 15 mg once daily if creatinine clearance was 30-49 ml/min) or to warfarin dose titrated to a target INR of 2 to 3. The primary objective of the study was to demonstrate that the efficacy of rivaroxaban was non-inferior to dose-adjusted warfarin in the studied population. A non-inferiority margin of 1.46 (later changed to 1.38) for the hazard ratio was used to design the study.

The proposed dose strengths for commercial distribution are 20 mg and 15 mg film coated immediate release tablets.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) has reviewed the studies relevant to the proposed indication submitted to NDA 202-439 and used prior OCP reviews on NDA 022-406 for rivaroxaban ([DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo](#)) to derive the following recommendations.

From a clinical pharmacology perspective, the submission is acceptable and can be approved, provided the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

The Office has the following specific recommendations:

- Rivaroxaban should be administered daily at the recommended dose with the evening meal.
- Patients with moderate (creatinine clearance 30-49 ml/min) and severe (creatinine clearance 15-29 ml/min) renal impairment should receive 15 mg rivaroxaban once daily.

- Patients with moderate hepatic impairment (Child-Pugh B) should receive 10 mg rivaroxaban once daily.
- The concurrent use of aspirin is a major risk factor for bleeding. This increase in bleeding risk is similar between rivaroxaban and warfarin. However, concomitant aspirin use does not seem to provide an additional benefit for the stroke prevention. Patients should be advised about the increased bleeding risk with concomitant aspirin use while on rivaroxaban therapy.
- A transition strategy must be employed for switching patients from rivaroxaban to warfarin. A reasonable transition strategy for switching patients from rivaroxaban to warfarin, considering the time course of their PD effects, is concomitant administration of rivaroxaban and warfarin for 2 days or more. The strategy ensures an INR ≥ 2 during the transition period. Rivaroxaban should be stopped once the observed pre-dose INR is ≥ 2 and the INR should be maintained within the target range of 2-3 with warfarin. Since rivaroxaban is recommended to be dosed with the evening meal, for the purpose of monitoring the INR during the transition period, the INR measurement on the next day (ie, after 16 hours post dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured daily during the transition until the INR ≥ 2 .

2 CLINICAL PHARMACOLOGY SUMMARY

2.1 BACKGROUND

Rivaroxaban is an orally active factor Xa inhibitor. Ortho Mcneil Janssen Pharmaceuticals Inc. is seeking approval for rivaroxaban 20 mg and 15 mg tablets for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF). This section summarizes the clinical pharmacology aspects of rivaroxaban ([Reference: OCP review of NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo](#)) and major findings from the studies relevant to the SPAF indication.

2.2 CURRENT SUBMISSION

The current submission (NDA 202-439) for rivaroxaban consists of one pivotal efficacy and safety study (ROCKET-AF, See [Appendix 1](#) for details), a smaller add-on phase III study in Japanese patients (J-ROCKET), and interaction studies with fluconazole and omeprazole ([Appendix 2](#)). All other clinical pharmacology studies reviewed separately under NDA 022-406 were also referenced for this NDA ([NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo](#)). Rivaroxaban 10 mg tablets (NDA 022-406) was approved for the prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

2.3 PHARMACOKINETICS OF RIVAROXABAN

- Absolute bioavailability of 66% in fasted condition for 20 mg dose
- Maximum plasma concentration attained in 2-4 hours
- Food increases AUC and C_{max} of 20 mg dose by ~39 and 76 % respectively
- Almost 50 % of an oral dose undergoes hepatic metabolism
- Metabolism predominantly by CYP3A4 (18%), 2J2 (14%) and hydrolysis (14%)
- No circulating major or active metabolites
- Approximately 36% of oral dose eliminated renally as unchanged drug
- Renal elimination involves active tubular secretion and glomerular filtration
- Approximately 28% of oral dose is excreted in feces
- Substrate for P-gp and BCRP
- Elimination half-life is 6-8 hrs in healthy and 11-13 hrs in elderly subjects

2.4 EXPOSURE-PHARMACODYNAMICS-OUTCOME RELATIONSHIPS

- Concentration dependent changes in pharmacodynamic measures such as prothrombin time (PT), factor Xa activity (FXa) and prothrombinase induced clotting time (PiCT) for rivaroxaban were observed. The PT measurements increased linearly with rivaroxaban concentration. The linear relationship observed in SPAF patients was similar to that observed in healthy subjects.
- The probability of ischemic stroke, a major component of the primary efficacy endpoint, was independent of the PT, measured mostly during 12-24 hours post rivaroxaban dose, over the observed range.
- Major bleeding events increased with an increase in PT, measured mostly during 12-24 hours post rivaroxaban dose, over the observed range.
- As expected, ischemic stroke events with warfarin decreased with an increase in the last observed INR while the risk for major bleeding increased with an increase in the last observed INR.
- The concomitant use of aspirin ($\geq 50\%$ of time) during the double-blind phase significantly increased the risk for major bleeding with rivaroxaban. However, the risk for ischemic stroke was not significantly affected with co-administration of aspirin. A similar increase in bleeding risk with aspirin was found in the warfarin treated patients as well. Patients should be advised about the increased bleeding risk when aspirin and rivaroxaban are co-administered.
- Based on the time-course of the pharmacodynamic effect of rivaroxaban and warfarin, a reasonable transition strategy for switching patients from rivaroxaban to warfarin is concomitant administration of rivaroxaban and warfarin for 2 days or more. The strategy ensures an $\text{INR} \geq 2$ during the transition period. Rivaroxaban should be stopped once the observed pre-dose INR is ≥ 2 and the INR should be maintained within the target range of 2-3 for warfarin. Since rivaroxaban is recommended to be dosed with the evening meal, for the purposes of monitoring INR during the transition, the INR measurement on the next day (i.e, after the 16 hrs post-dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured daily during the transition, until the $\text{INR} \geq 2$.

2.5 INTRINSIC FACTORS

- **Renal impairment:** Exposure to rivaroxaban increased with the severity of renal function impairment as demonstrated in the dedicated renal impairment study ([Study number 11002](#), [OCP review for NDA 022-406](#), [DARTS dates 04/06/2009, 06/03/2011](#) by Dr. Joseph Grillo). The ROCKET-AF study used a 20 mg once daily dose for patients with normal and mild renal impairment. A reduced dose of 15 mg once daily was studied in patients with moderate renal impairment. This dose adjustment provided rivaroxaban exposure in moderate renal impairment comparable to that of normal renal function patients after the 20

mg dose. The efficacy of rivaroxaban compared to warfarin was similar across the renal function categories ([Ref. ROCKET-AF Study report 39039039AFL3001, page 164](#)). The bleeding risk across all three renal function categories was also similar between rivaroxaban and warfarin ([Ref. ROCKET-AF Study report for 39039039AFL3001, page 209](#)). Since the increases in exposure and PT (as AUC-PT) in moderate and severe renal impairment are comparable, it is reasonable to use the same reduced dose of 15 mg once daily in severe renal impairment.

- **Hepatic impairment:** Rivaroxaban exposure did not change significantly in subjects with mild hepatic impairment (Child-Pugh A). Exposure to rivaroxaban increased by approximately 2-fold in subjects with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal hepatic function ([Study number 11003, OCP review for NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo](#)). The PD effects were also increased with the moderate hepatic impairment. No information is available on patients with severe hepatic impairment (Child-Pugh C). No dose adjustments are required for mild (Child-Pugh A) hepatic impairment. A reduced dose of 10 mg should be used in moderate hepatic impairment (Child-Pugh B) so as to have similar exposure as of 20 mg dose in healthy subjects. Avoid the use of rivaroxaban in patients with severe (Child-Pugh C) hepatic impairment and any hepatic disease associated with coagulopathy.

3 QUESTION BASED REVIEW

3.1 BACKGROUND

Ortho Mcneil Janssen Pharmaceuticals Inc. is seeking approval for rivaroxaban for the prevention of stroke and systemic embolism in patients with atrial fibrillation (SPAF). Rivaroxaban as 10 mg immediate release tablets was approved in the US under NDA 022-406 for the prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. A detailed review of clinical pharmacology aspects of rivaroxaban was conducted under NDA 022-406. This modified question based review (QBR) for the current NDA 202-439 will address the issues relevant to the proposed SPAF indication. Please refer to the OCP reviews under NDA 022-406 ([DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo](#)) for clinical pharmacology aspects of rivaroxaban.

Briefly, rivaroxaban is an orally active, competitive and selective, direct factor Xa inhibitor. Activation of factor Xa by intrinsic or extrinsic pathways plays a central role in blood coagulation cascade. The current submission has a single pivotal efficacy and safety study (ROCKET-AF) and an add-on phase III study in Japanese patients (J-ROCKET).

ROCKET-AF was a randomized, multi-center, double-blind, double-dummy, parallel group, active-controlled, event-driven Phase III study with a total of 14,269 patients randomized to rivaroxaban (20 mg once daily or 15 mg once daily if creatinine clearance is 30-49 ml/min) or dose adjusted warfarin for an INR target of 2-3 in patients with non-valvular atrial fibrillation with at least two of the risk factors such as congestive heart failure (CHF), hypertension, age ≥ 75 years and diabetes or a prior history of stroke, TIA or systemic embolus events. Both rivaroxaban and warfarin treatment arms were well balanced in terms of baseline characteristics and had about 37-38% vitamin K antagonist naïve patients in the safety population. Aspirin use during the double blind phase was limited to ≤ 100 mg. The primary efficacy end point was a composite of stroke or non-CNS systemic embolism and the study was designed to demonstrate that the efficacy of rivaroxaban was non-inferior to adjusted-dose warfarin in the studied population. A non-inferiority margin of 1.46 (later changed to 1.38) for hazard ratio was used in designing the study. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

The add-on phase III study, J-ROCKET was designed to evaluate the safety of rivaroxaban in Japanese patients with non-valvular atrial fibrillation and used 15 mg once daily dose (10 mg if creatinine clearance was 30-49 mL/min) compared with dose adjusted warfarin (as per Japanese guidelines for INR maintenance). A reduced rivaroxaban dose of 15 mg was selected to match exposures in Japanese patients to that obtained with a 20 mg dose in other populations. A total of 1,280 patients were randomized to either warfarin or rivaroxaban treatment groups. The rate of the primary safety endpoint, composite of adjudicated major and non-major clinically relevant

bleeding events, was 18.04/100 pt-yrs for rivaroxaban and 16.42/100 pt-yrs for warfarin in the safety, on treatment analysis [HR: 1.11 (0.87-1.42)]. Non-inferiority of rivaroxaban to warfarin was demonstrated for the primary safety endpoint with a pre-specified margin of 2. Rivaroxaban group also had numerically lower event rates for the primary efficacy endpoints, the composite of adjudicated stroke and non-CNS systemic embolism, compared with warfarin in the per-protocol, on treatment population (Event rate: 1.26 vs. 2.61/100 pt-yrs respectively).

The following review questions were identified for the current clinical pharmacology review:

3.2 Is the proposed dose and dosing regimen justified?

The dose selection in ROCKET-AF study was based on the results from two DVT studies (Study Number 11223 ODIXa-DVT and 11528 Einstein-DVT) and the sponsor concluded that a 20 mg once daily dose has desired safety and efficacy profile for studies supporting the SPAF indication. However, the difference between the once daily and twice daily regimens for the same total daily dose was not studied within a single study and the cross-study comparisons were inconclusive. Further, a recently concluded TIMI-ACS 46, a dose selection study conducted in patients with acute coronary syndrome (ACS) covering a total daily dose range of 5 mg to 20 mg, as once or twice daily regimen, showed numerical advantage for safety and efficacy for the twice daily regimen. So the sponsor selected a twice daily regimen for their on-going phase III ACS program based the results from TIMI-ACS 46. The pharmacokinetic and pharmacodynamic characteristics suggest that a twice daily regimen might offer lower peak to trough ratio in PT levels within a dosing interval compared to the once daily regimen (see [Figure 1](#)). The clinical benefit of the difference in the peak to trough ratio and higher trough PT levels after twice daily regimen cannot be derived from the existing data.

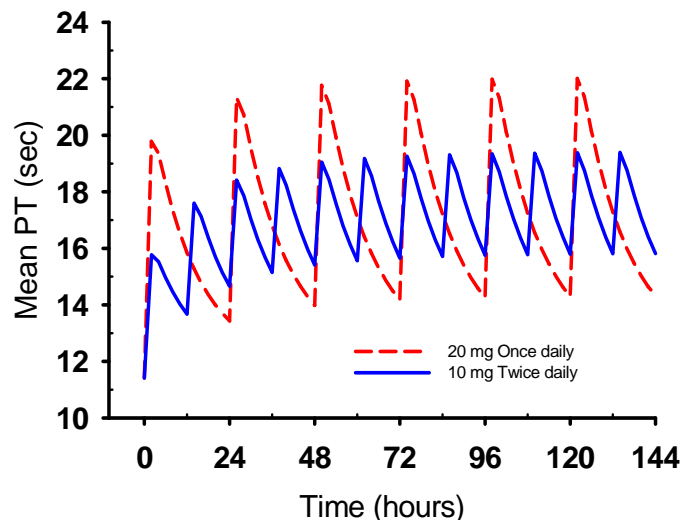


Figure 1 Simulated PT-time course for the PK-PD subset in ROCKET-AF for a total daily dose of 20 mg rivaroxaban, given as once daily (red-dashed line) or as twice daily (blue-solid line). The simulations were based on rivaroxaban PK model and rivaroxaban PK-PT relationship presented in [Figure 2](#).

There are no meaningful dose-ranging studies in the target population of patients with atrial fibrillation. Hence it is not clear whether the 20 mg once daily dose selected in ROCKET-AF is optimal for the SPAF indication. Nevertheless, the results from the ROCKET-AF study showed rivaroxaban 20 mg once daily to be non-inferior to dose-adjusted warfarin (See [Table 1](#)).

Table 1 Top-line efficacy and safety analysis results from ROCKET-AF

Endpoint	Rivaroxaban		Warfarin		Rivaroxaban Vs. Warfarin	
	n/N	Event rate (100 pt-yr)	n/N	Event rate (100 pt-yr)	HR (95 % CI)	p value
Primary efficacy endpoint*	188/6958	1.71	241/7004	2.16	0.79 (0.66-0.96)	<0.001
Principal safety endpoint**	1475/7111	14.91	1449/7125	14.52	1.03 (0.96-1.11)	0.44

*Non-inferiority on primary efficacy endpoint based on treatment data from the per-protocol population

** Superiority on principle safety endpoint on treatment data from the safety population

3.1 Is there a relationship between rivaroxaban concentration and pharmacodynamic (PD) measures such as prothrombin time (PT), factor Xa activity (FXa) and prothrombinase induced clotting time (PiCT)?

In the ROCKET-AF study, matching pharmacokinetic-pharmacodynamic (PK-PD) samples were collected from a subset of about 161 patients (See [Appendix 1](#) for details). The sponsor did not collect PK in all subjects; however, the PD samples were collected during the visits at weeks 12 and 24 from all eligible patients. Most of these PD measurements (~78%) were made during 12-24 hours after the rivaroxaban dose. These PD measures included the PT, FXa and PiCT and were described by the term pre-dose PD in subsequent sections.

Factor Xa activity, PT ([Figure 2](#)) and PiCT were found to be dependent on rivaroxaban concentration in the patients with the matching PK-PD samples. This is in agreement with observations from the dedicated rivaroxaban PK and PD studies in healthy volunteers ([NDA 022-406](#), [DARRTS dates 04/06/2009, 06/03/2011](#) by [Dr. Joseph Grillo](#)). Based on this observation, the PD measures (such as, PT) can be used as surrogates for PK measurements in the PD-Outcome analyses.

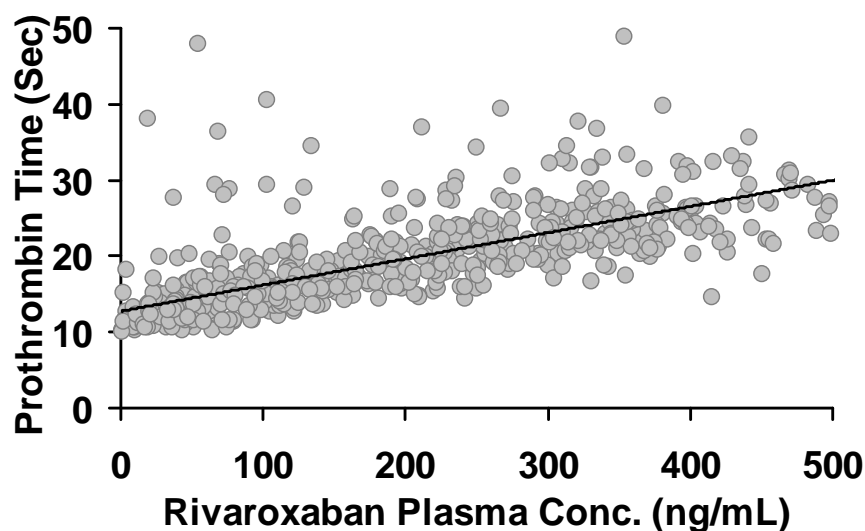


Figure 2 Prothrombin time increases linearly with rivaroxaban concentration. Data from the PK-PD subset of ROCKET-AF is shown. Solid curve is the trend line.

3.2 What are the characteristics of the PD-outcome relationship for efficacy?

The probability of ischemic stroke, a major component of the primary efficacy endpoint, was independent of the pre-dose PT measures over the observed range for rivaroxaban (Figure 3).

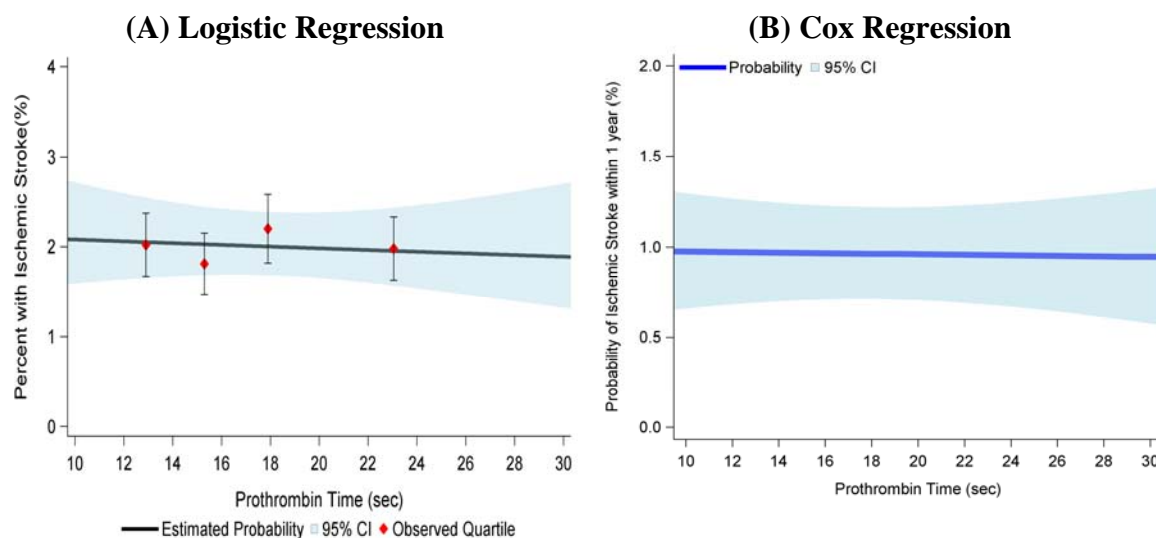


Figure 3 Ischemic stroke events are independent of pre-dose PT over the observed range (per-protocol, on treatment analysis set). Probability of ischemic stroke by pre-dose PT with rivaroxaban shown in (A) linear logistic regression model and (B) Cox regression model with a plot indicating probability of an event within 1 year. The PT measurements made either at week 12 or week 24, whichever was closer to the reported ischemic stroke event was used for the analysis. Majority of the PT measurements were made during 12-24 hours after the previous dose and is referred to as pre-dose PT.

3.3 What are the characteristics of the PD-outcome relationship for safety?

The probability for major bleeding event, the primary safety endpoint as defined as clinically overt bleeding associated with a decrease in hemoglobin ≥ 2 g/dl, or a transfusion of ≥ 2 units of packed red blood cells or whole blood, or bleeding at critical sites, or a fatal outcome, increased with an increase in pre-dose PT as shown in [Figure 4](#). See [Appendix 1](#) for details on PD-Outcome analysis.

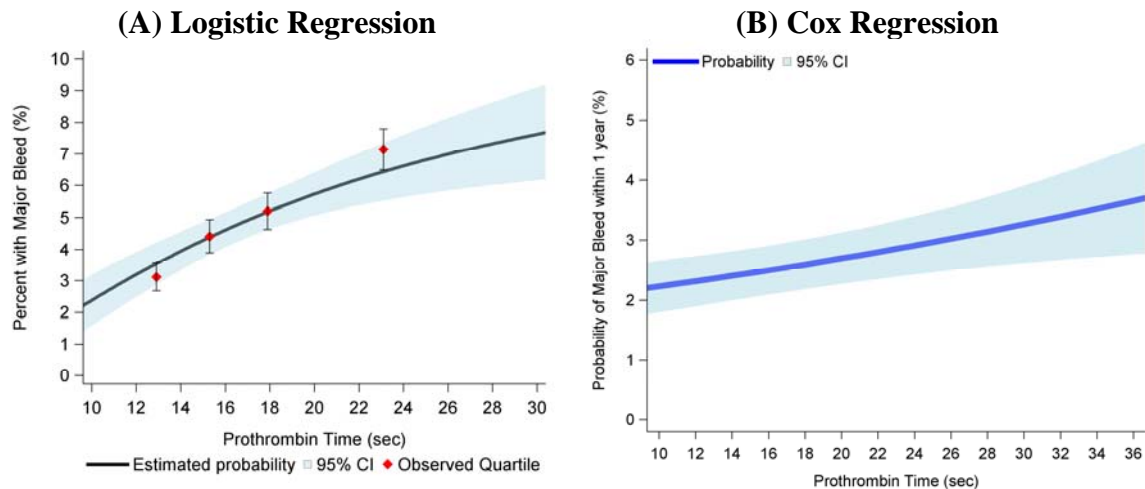


Figure 4 Major bleeding events increased with an increase in pre-dose PT over the observed range (per-protocol, on treatment analysis set). Probability of major bleeding by pre-dose PT with rivaroxaban shown in (A) logistic regression model (E_{\max}) and (B) Cox regression model with a plot indicating probability of an event within 1 year. The PT measurements made either at week 12 or week 24, whichever was closer to the reported major bleeding event was used for the analysis. Majority of the PT measurements were made during 12-24 hours after the previous dose and is referred to as pre-dose PT.

3.4 What is the PD-outcome relationship for warfarin in ROCKET-AF study?

The risk for both safety (major bleeding) and efficacy (ischemic stroke) endpoints for warfarin in ROCKET-AF were dependent on the last observed INR ([Figure 5](#)), consistent with the expected warfarin INR-Outcome relationship. For patients who had no events on treatment, their last observed INR before or on the censored date was selected for this analysis. See [Appendix 1](#) for details on PD-Outcome analysis.

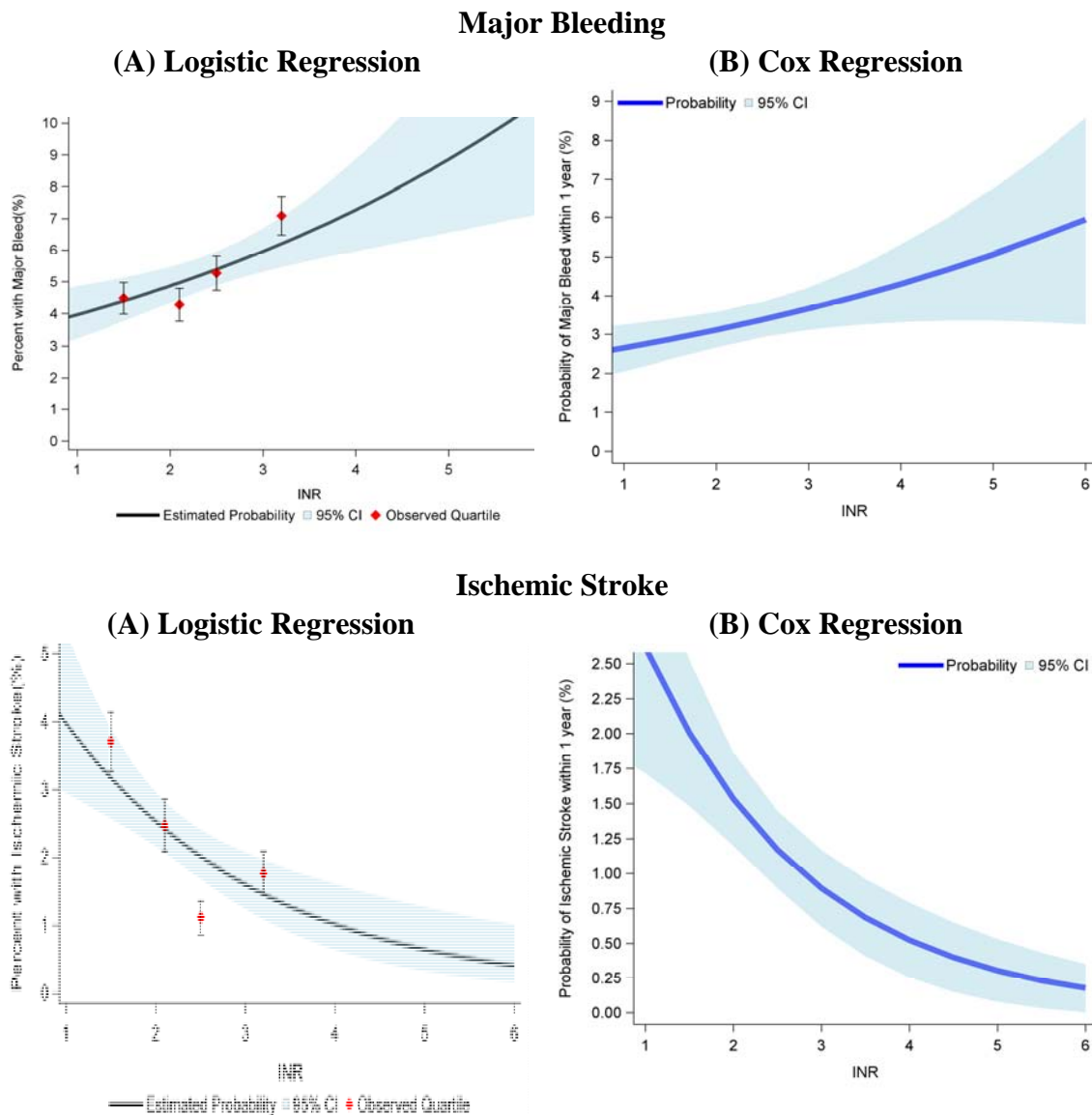


Figure 5 Probability of major bleeding and ischemic stroke by the last observed INR (before or at an event) for warfarin (per-protocol, on treatment analysis set). (A) Linear logistic regression model and (B) Cox regression model with a plot indicating probability of an event within 1 year.

3.5 Does concomitant aspirin use affect the safety and efficacy of rivaroxaban and warfarin?

The concomitant use of aspirin during the double blind phase ($\geq 50\%$ of time) significantly increased the risk for major bleeding with rivaroxaban (Figure 6 & Table 2). The pre-dose PT-major bleeding relationship for rivaroxaban was steeper among the aspirin users. However, concomitant aspirin use seemed not to have a significant effect on the efficacy outcome (ischemic stroke). These observations were consistent with various levels of aspirin use (Yes/No, $\geq 25\%$, 50%, 75% or 90% during the double blind

phase). The concomitant aspirin use with warfarin in ROCKET-AF also had similar results as described in [Figure 6](#) and [Table 2](#) (See [Appendix 1](#) for details). Patients should be made aware that concomitant aspirin use with rivaroxaban will increase the risk for bleeding.

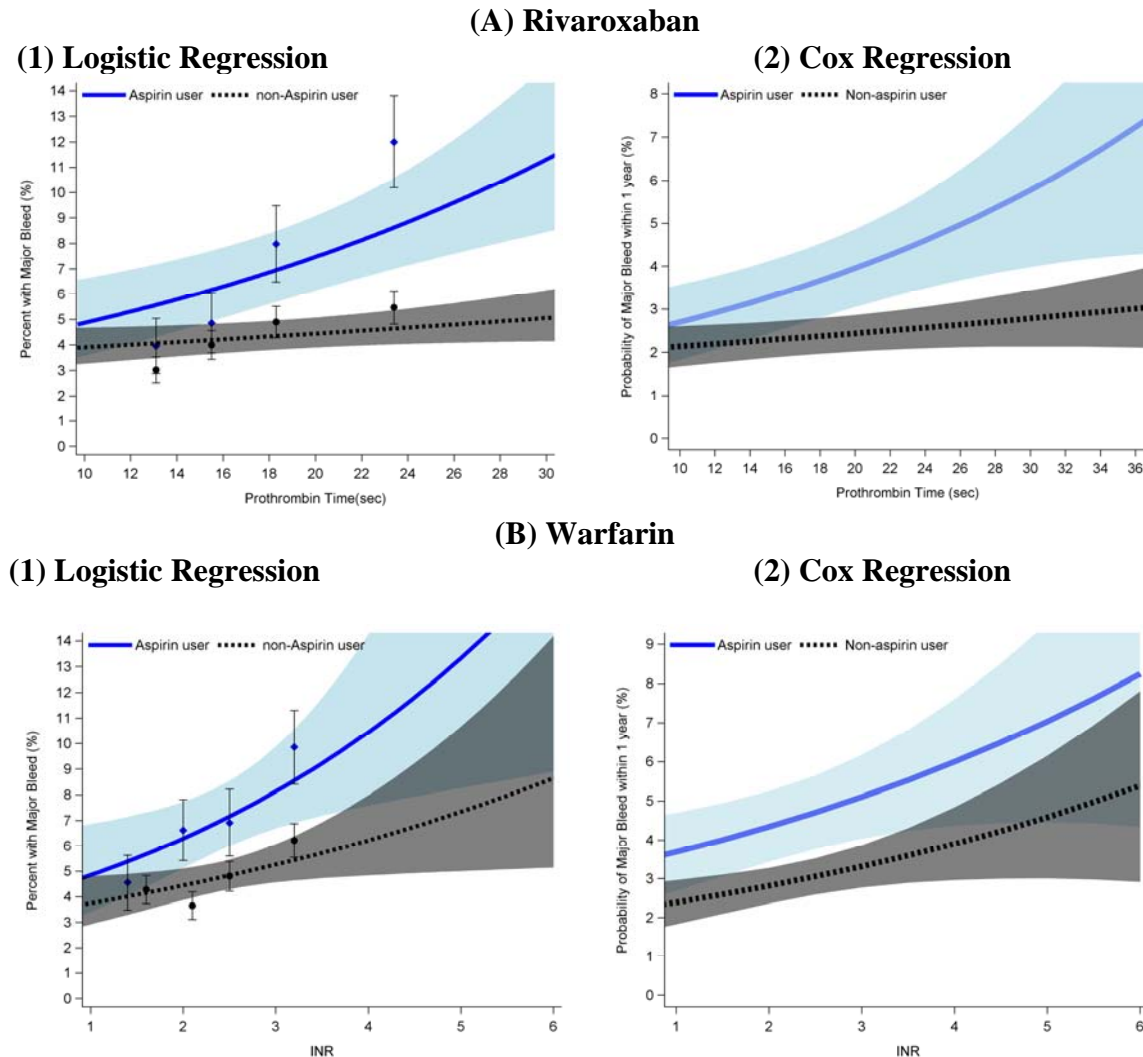


Figure 6 Relationship between probability for major bleeding and PD with or without the concomitant aspirin use during the double blind phase ($\geq 50\%$ of time) in ROCKET-AF for (A) rivaroxaban and (B) warfarin. (1) Linear logistic regression model and (2) Cox regression model with a plot indicating probability of an event within 1 year (per-protocol, on treatment analysis set).

Table 2 Concomitant aspirin use during the double blind phase ($\geq 50\%$ of time) increased event rate for bleeding for both (A) rivaroxaban and (B) warfarin, but did not change event rate for ischemic stroke significantly (per-protocol, on treatment analysis set).

(A) Rivaroxaban (N=7008)				
Endpoint	Aspirin user (N=1577)		Non-Aspirin user (N=5431)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	40 (2.5)	1.69	150 (2.8)	1.73
Ischemic stroke	31 (2.0)	1.31	119 (2.2)	1.38
Primary safety endpoint	407 (25.8)	19.9	1050 (19.3)	13.6
Major bleeding	135 (8.6)	5.82	257 (4.7)	3.02

(B) Warfarin (N=7046)				
Endpoint	Aspirin user (N=1664)		Non-Aspirin user (N=5382)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	57 (3.4)	2.26	185 (3.4)	2.13
Ischemic stroke	37 (2.2)	1.47	124 (2.3)	1.43
Primary safety endpoint	399 (24.0)	18.4	1034 (19.2)	13.4
Major bleeding	118 (7.1)	4.76	260 (68.8)	3.03

3.6 Is there a need for dose adjustments in patients with renal and hepatic impairment?

Renal and hepatic impairment increased the exposures to rivaroxaban relative to normal subjects ([Figure 7](#)). The increase in PT (as AUC-PT) in subjects with moderate and severe renal impairment was more than the observed increase in exposures. In subjects with Child-Pugh B hepatic impairment approximately 2-fold increase in exposure and PT were observed ([NDA 022-406](#), [DARRTS dates 04/06/2009, 06/03/2011](#) by [Dr. Joseph Grillo](#)).

In ROCKET-AF study a reduced dose of 15 mg was used in patients with moderate renal impairment to achieve exposures similar to that observed in normal subjects receiving the 20 mg dose. The event rates (100 pt-yr) for critical organ bleeding, defined as intracranial, intraspinal, intraocular, perichardial, intra-articular, intramuscular with compartment symptom or retroperitoneal bleeding, were comparable (0.76 vs 0.83) between patients with moderate renal impairment (receiving 15 mg dose) and patients with mild renal impairment or patients with normal renal function (receiving 20 mg dose). The efficacy of rivaroxaban compared to warfarin also was similar across the renal function categories ([Ref. ROCKET-AF Study report 39039039AFL3001, page 164](#)). The bleeding risk across all three renal function categories was also similar between rivaroxaban and warfarin ([Ref. ROCKET-AF Study report for 39039039AFL3001, page](#)

209). Therefore, we recommend a reduced dose of 15 mg once daily in patients with moderate renal impairment, as studied in ROCKET-AF study.

Since the increase in exposure observed in moderate and severe renal impairment are comparable (1.5 vs 1.6 fold increase relative to normal) and have similar effect on PD measurements (AUC-PT), a 15 mg dose should be suitable for severe renal impairment as well.

Moderate hepatic impairment results in 2.3 fold increase in rivaroxaban exposure and a 2.1 fold increase in AUC-PT. Therefore, we recommend a dose of 10 mg once daily in patients with moderate hepatic function (Child-Pugh B) to match rivaroxaban exposures to those observed in normal subjects with the 20 mg dose.

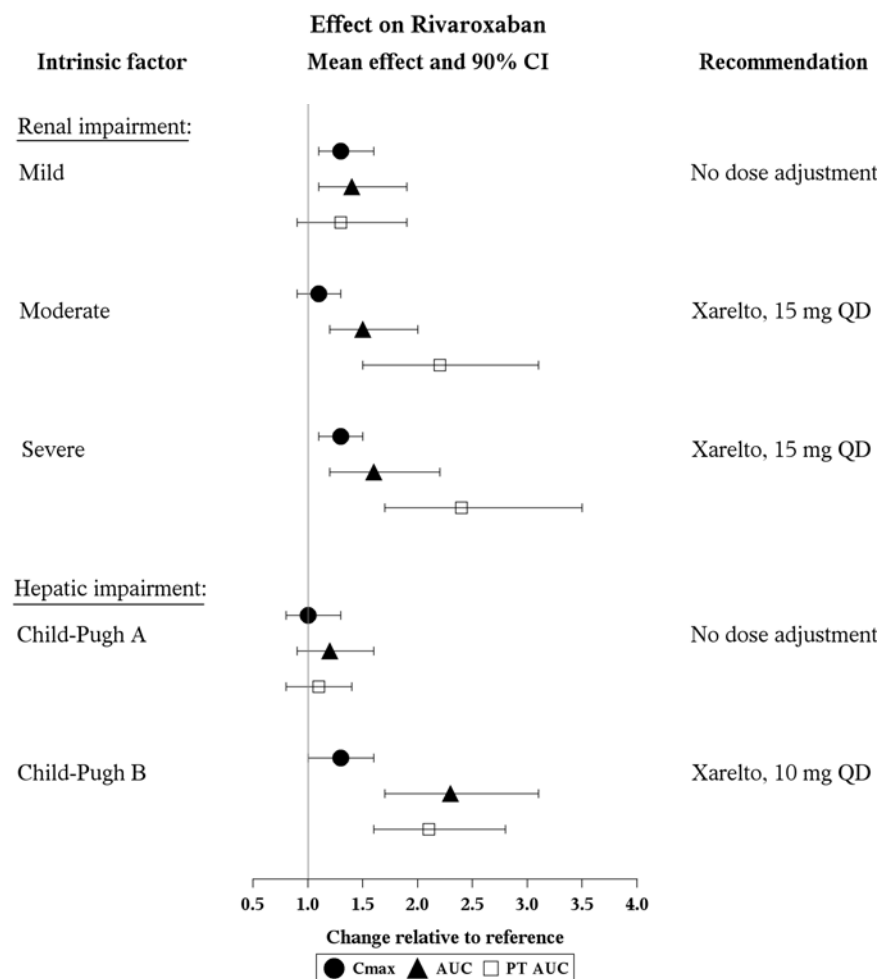


Figure 7 Effect of renal and hepatic impairment on the PK (as AUC and C_{max}) and PD (as AUC-PT) of rivaroxaban. Data from dedicated renal and hepatic impairment study with 10 mg rivaroxaban dose is shown. The X-axis represents changes in PK and PD relative to subjects with normal renal/hepatic function. Creatinine clearance 50-79 ml/min=Mild, 30-49 ml/min=Moderate, 15-29 ml/min=Severe for renal impairment. Dose recommendations made on the basis of exposure matching.

3.9 What is the impact of food on rivaroxaban exposure?

Rivaroxaban at 20 mg dose has significant food effect (Food increases exposure by ~ 39%). In ROCKET-AF study, patients took rivaroxaban with the evening meal as it minimizes the chance for variability in exposure. Therefore, rivaroxaban should be administered daily with the evening meal for the proposed indication.

3.10 What is a safe strategy to transition patients from rivaroxaban to warfarin?

In the ROCKET-AF, after the pre-specified number of adjudicated clinical events was accrued (N=405), sites were notified to close out ongoing subjects. Subjects then had an End of Study (EOS) visit as soon as possible but within approximately 30 days, and a post-treatment observation period with a follow-up visit approximately 30 days (\pm 5 days) after the EOS visit. At the EOS visit, subjects were transitioned from study drug to open-label VKA or other appropriate therapy as determined by the investigator. Importantly, the end-of-study transition from blinded study drug to open-label warfarin (or other VKA or antithrombotic therapy) was to be done without breaking the study blind. Hence, investigators were asked not to measure INR values for at least 3 days after last dose to preserve study blinding. After 3 days, VKA dosing was managed at the discretion of the treating physician using local unblinded INR measurements. Most of the patients who completed study drug treatment were transitioned to open-label warfarin within approximately 1-2 days after the last dose of the study drug in the double-blind phase. Exploratory analysis of the data in the post-treatment phase showed a significant rise in ischemic stroke events in patients who were on rivaroxaban compared to those on warfarin. From day 3 to day 30 after the last dose of study medication, 18/4587 (0.39%) ischemic stroke events occurred among completers in rivaroxaban compared to 4/4652 (0.09%) events in warfarin treated patients.

Similar results were seen with the add-on phase III study J-ROCKET as well. From day 3 to day 30 after the J-ROCKET study, there were more primary efficacy endpoint events in rivaroxaban patients than in warfarin treated patients (11 vs. 4 primary efficacy endpoint events in the ITT population) [[Ref. Study number 12620, J-ROCKET study report, Pages 97-100](#)].

Two potential hypotheses can be laid out to explain this increased event rates for ischemic stroke: 1) potential hypercoagulability (rebound blood coagulation after the withdrawal of an anticoagulant) due to the cessation of rivaroxaban treatment and 2) shorter half-life of rivaroxaban's effects (approximately 12 hours) in comparison to time required to reach therapeutic effect with warfarin that may lead to longer sub-optimal INR levels during transition. It is likely that there was a potential inadequate anticoagulation during the transition from rivaroxaban to warfarin therapy due to the absence of an appropriate bridging strategy.

To explore which of these hypotheses are more likely, a comparison of the incidence of ischemic strokes in the first 30 days following randomization in warfarin naïve patients treated with warfarin (8/2634, ie 0.30 %) and the last ~30 days following completion of

study in patients treated with rivaroxaban during the double-blind phase (18/4587, ie 0.39 %) was made. Since the incidence rates were different initially and comparable at the end of the 30 day period for the two groups (0.30 vs. 0.39%) it may be assumed that the hypercoagulability due to the cessation of rivaroxaban treatment is less likely (See [Figure 8](#)). It is more likely that an optimal transition strategy was not implemented following the completion of ROCKET-AF study.

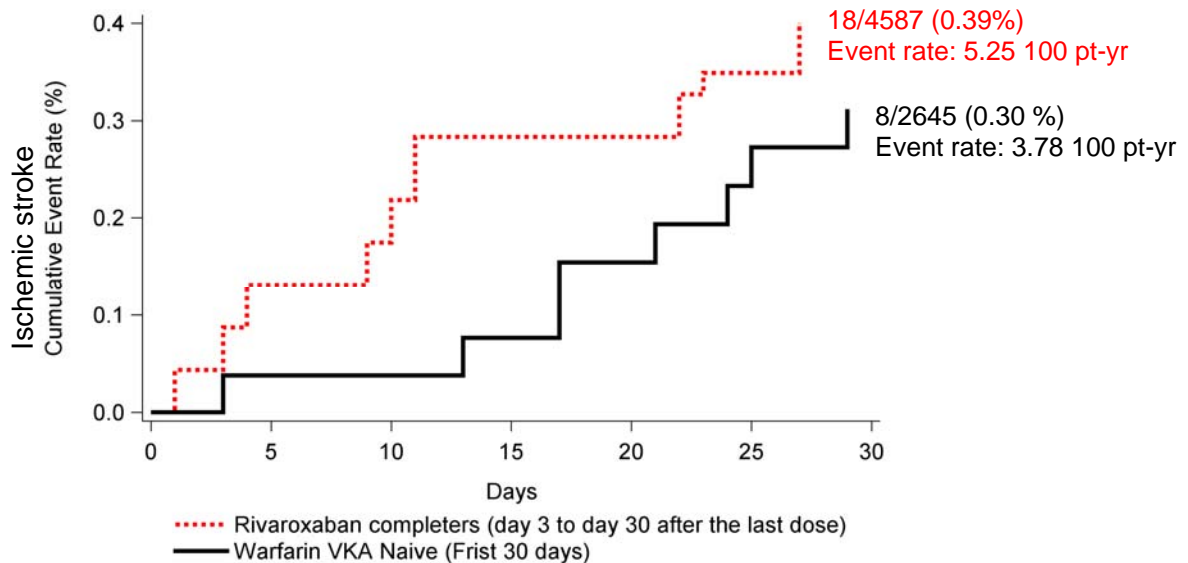


Figure 8 Kaplan-Meier curves for ischemic stroke events for patients who were on rivaroxaban and completed treatment during day 3 to day 30 after the last study medication (red dotted line) and VKA naïve patients on warfarin during the first 30 days of ROCKET-AF study (black solid line).

Given the inadequate strategy in ROCKET studies, a reasonable transition strategy for switching patients from rivaroxaban to warfarin can be derived based on the time-course of the effects of rivaroxaban and warfarin. A concomitant administration of rivaroxaban and warfarin for 2 days or more can be a useful strategy (See [Figure 8](#)). The strategy ensures an $\text{INR} \geq 2$ during the transition period is reached sooner. Rivaroxaban should be stopped once the observed pre-dose INR is ≥ 2 and the INR should be maintained within the target range of 2-3 for warfarin. Since rivaroxaban is recommended to be dosed with the evening meal, for the purpose of monitoring INR during the transition, the INR measurement on the next day (ie, after 16 hours post-dose) can serve as the pre-dose INR for the decision to stop rivaroxaban. The INR should be measured on the daily during transition until the $\text{INR} \geq 2$.

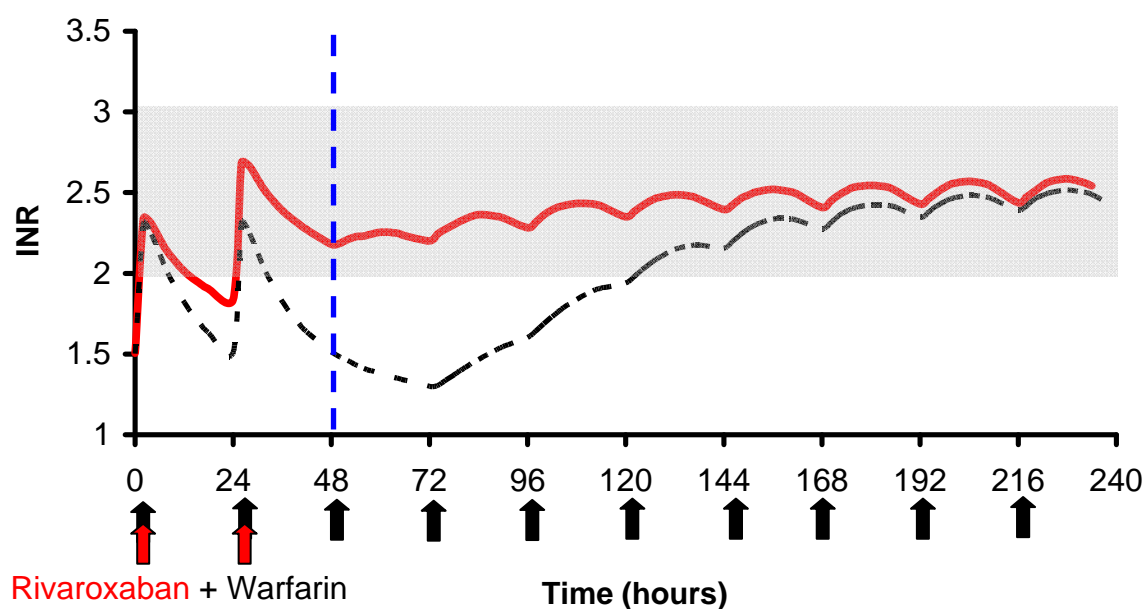


Figure 9 Time-course of INR for two transition strategies. The proposed strategy is represented by red solid-line as INR profile in an average patient after two days of concomitant rivaroxaban and warfarin (rivaroxaban and warfarin dosing indicated as red and black block arrows respectively). The strategy that may have been used in ROCKET-AF study is black dashed-line representing the INR profile in an average patient when open-label warfarin regimen was started with a gap of 24 hours after the last rivaroxaban dosing day (warfarin dose started at 72 hours in the plot). Target INR range of 2 to 3 is marked with the grey-shaded band. The vertical blue dashed line indicates the end of rivaroxaban treatment for both strategies.

APPENDIX 1 – ROCKET-AF ANALYSIS

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4 BACKGROUND

ROCKET-AF was a randomized, multi-center, double-blind, double-dummy, parallel group, active-controlled, event-driven Phase III study with a total of 14,269 subjects randomized to rivaroxaban (20 mg once daily or 15 mg once daily if creatinine clearance was 30-49 ml/min) or dose-adjusted warfarin for an INR target of 2-3 in subjects with non-valvular atrial fibrillation with at least two of the risk factors such as congestive heart failure (CHF), hypertension, age ≥ 75 years and diabetes or a prior history of stroke, TIA or systemic embolus events. Both rivaroxaban and warfarin treatment arms were well balanced in terms of baseline characteristics and had about 37-38% vitamin K antagonist naïve subjects in the safety population. Aspirin use during the double blind phase was limited to ≤ 100 mg. The primary endpoint was a composite of stroke or non-CNS systemic embolism and the study was designed to demonstrate that the efficacy of rivaroxaban was non-inferior to adjusted dose warfarin in the studied population. A non-inferiority margin of 1.46 (later changed to 1.38) for the hazard ratio was used in designing the study. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events. A brief schematic of the study design is presented in [Figure 1](#) below:

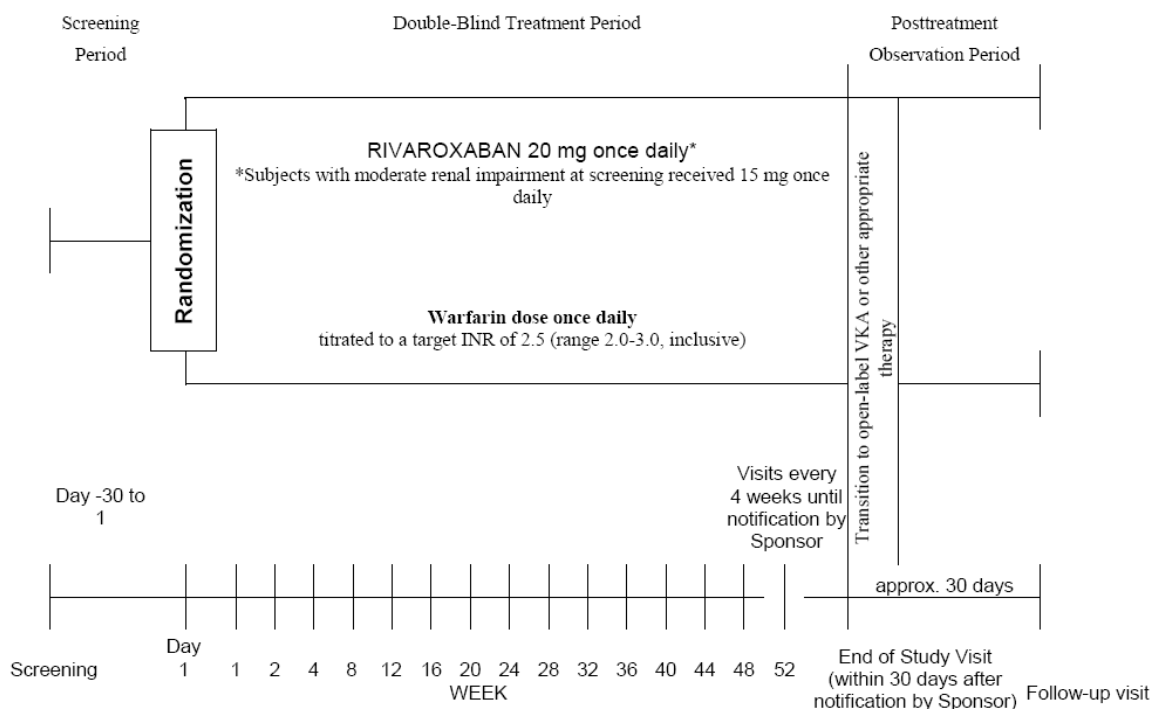


Figure 1 Flow diagram for ROCKET-AF study design. Source: Sponsor's submission Page 40, Figure 1: [\cdsesub1\EVSPROD\NDA202439\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\afib\5351-stud-rep-contr\39039039afl3001](#)

The dose selection in ROCKET-AF was based on the results from two DVT studies (Study Number 11223 ODIXa-DVT and 11528 Einstein-DVT) and the sponsors

concluded that a 20 mg once daily dose has desired safety and efficacy profile for investigation in subsequent studies. However, the once daily and twice daily regimens were not studied within a single study or in the target population and the dose-response relationships in the DVT studies were shallow over the studied dose-range and not adequately powered to explore the effects of different dosing regimen. Moreover, the recently concluded TIMI-ACS 46 study, a dose selection study conducted in subjects with acute coronary syndrome (ACS) covering a total daily dose range of 5 mg to 20 mg as once or twice daily regimen, showed a numerical advantage for safety and efficacy for the twice daily regimen. (Ref. Clinical study report ATLAS ACS TIMI 46, Page 99 and 137). The sponsor selected a twice daily regimen for their phase III ACS program based on the results from TIMI-ACS 46. The pharmacokinetic and pharmacodynamic characteristics of rivaroxaban suggest that a twice daily regimen might offer lower peak to trough ratio in prothrombin time (PT) within a dosing interval compared to the once daily regimen (See Figure 2). The clinical benefit of the difference in the peak to trough ratio and higher trough PT levels after a twice daily regimen cannot be derived from the existing data.

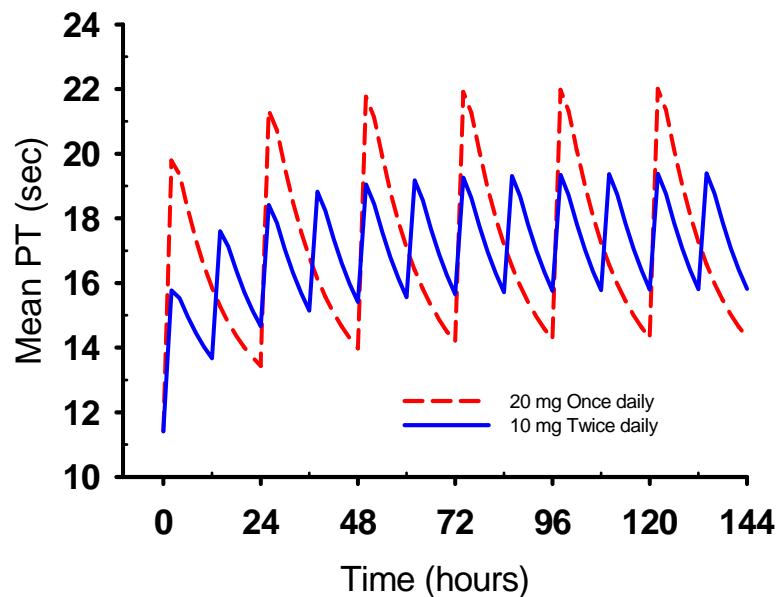


Figure 2 Simulated PT-time course for the PK-PD subset in ROCKET-AF for a total daily dose of 20 mg rivaroxaban, given as once daily (red-broken line) or as twice daily (blue-solid line). The simulations were based on rivaroxaban PK model and rivaroxaban PK-PT relationship presented in Figure 3.

There are no meaningful dose-ranging studies in the target population of subjects with atrial fibrillation. Hence it is not clear whether the 20 mg once daily dose selected in ROCKET-AF is optimal for the proposed indication. Nevertheless, the results from the ROCKET-AF study showed rivaroxaban 20 mg once daily to be non-inferior to dose-adjusted warfarin (Table 1).

Table 1 Top-line efficacy and safety analysis results from ROCKET-AF

Endpoint	Rivaroxaban		Warfarin		Rivaroxaban Vs. Warfarin	
	n/N	Event rate (100 pt-yr)	n/N	Event rate (100 pt-yr)	HR (95 % CI)	p value
Primary efficacy endpoint*	188/6958	1.71	241/7004	2.16	0.79 (0.66-0.96)	<0.001
Principal safety endpoint**	1475/7111	14.91	1449/7125	14.52	1.03 (0.96-1.11)	0.44

*Test for non-inferiority on primary efficacy endpoint based on treatment data from the per-protocol population

**Test for superiority on principle safety endpoint on treatment data from the safety population

A total of 786 time-matched pharmacokinetic-pharmacodynamic (PK-PD) samples were collected from a subset of 161 subjects (2% of per-protocol analysis set) and PD samples were collected during week 12 and 24 visits from all eligible subjects. The PD measures included prothrombin time (PT), factor Xa activity (FXa) and prothrombinase induced clotting time (PiCT). INR values from point-of-care Hemosense INRatio[®] Device and PT-INR derived directly from the measured PT were also provided by the sponsor. See Table 2 for PK-PD sampling schedule followed in ROCKET-AF study.

Table 2 PK-PD sampling schedule in ROCKET-AF. Source: Sponsor's submission Page 61, Table 5: \\cdsesub1\EVSPROD\NDA202439\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\afib\5351-stud-rep-contr\39039039af13001

	Day 1	Between Week 2 and the End-of-Study Visit		Week 12 ^a	Week 24 ^a	At Least 1 Month, Preferably at Least 6 to 12 Months, After the First Matched PK/PD Sample ^b	
	Hours Predose	Hours Predose	Hours Postdose ^c			Hours Predose	Hours Postdose 1-3
			1-3 3-16				
PD sampling only (ALL subjects)	X ^d			X	X		
Matched ^e PK & PD blood sampling (select sites and subjects) ^f		X	X X			X	X ^g

PD=pharmacodynamic; PK=pharmacokinetic; PT= prothrombin time; FXa= factor Xa; PiCT= Prothrombinase-induced clotting time;

^a PD sampling was to be taken as either a predose or postdose sampling for the Weeks 12 and 24. Predose or postdose sampling had to be documented.

^b As close to the end-of-study visit as possible.

^c Postdose samples were taken after supervised study drug administration; study drug was to be administered in the evening.

^d Only subjects enrolled at sites participating in the matched PK/PD substudy had a baseline PD sample collected. The baseline sample was to be drawn either at screening or on Day 1 (before dosing).

^e Matched samples = PD blood samples to determine coagulation characteristics (PT, FXa activity, PiCT) taken at the same time points as PK blood samples.

^f On days of matched PK/PD sample collections, subjects may have been confined to the study site.

^g If agreed to by the subject.

All the PD measurements were found to be dependent on rivaroxaban concentration (Figure 3) in subjects with the matching PK and PD samples. This is in agreement with observations from other PK and PD studies for rivaroxaban (Ref. OCP Review, NDA 022-406, DARRTS dates 04/06/2009, 06/03/2011 by Dr. Joseph Grillo).

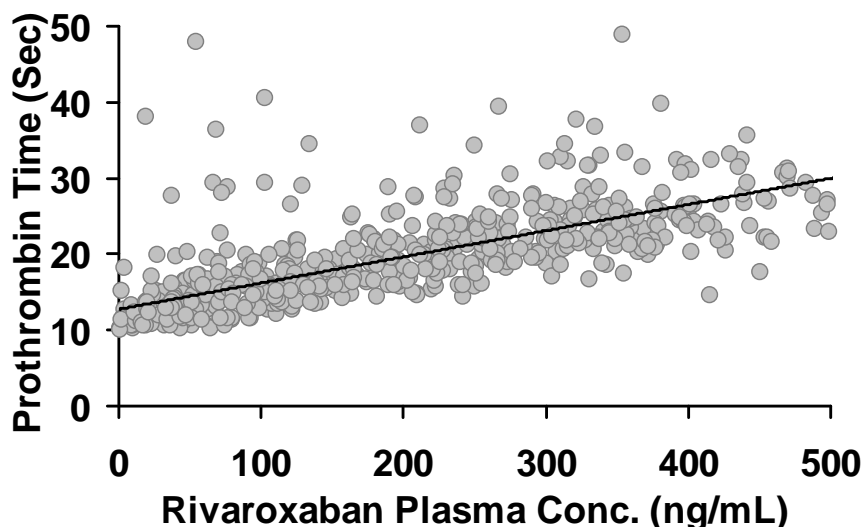


Figure 3 Prothrombin time increases linearly with rivaroxaban concentration. Time matched plasma concentrations of rivaroxaban and PT measures available from the PK-PD subset (161 subjects) of ROCKET-AF are shown. Solid black curve is the trend line.

Therefore, PT measurement, measured at week 12 or week 24 whichever is closer to an event (efficacy/safety), was used as a surrogate for PK. The PD-Outcome analyses were conducted for rivaroxaban using PT as the primary PD measure and the last observed INR value closer to an event was used for similar analyses in the warfarin group.

4.1 PHARMACOMETRIC ANALYSIS

4.1.1 INTRODUCTION

Independent analyses were conducted to explore the relationship between the PD measurements and efficacy as well as safety outcomes in the ROCKET-AF study. All available PD measures (PT, FXa, PiCT, PT-INR and last observed INR) were used in the analyses with a focus on the PT-Outcome relationships. The focus on PT as a surrogate was because PT could be converted to INR for comparison with warfarin. A comparative analysis was performed in the warfarin treatment arm using the last observed INR before or on the date of the endpoint of interest (INR is the most widely used PD marker for warfarin).

These analyses were conducted to address the following review questions:

- What are the characteristics of the PD-Outcome relationship of rivaroxaban for safety?

- What are the characteristics of the PD-Outcome relationship of rivaroxaban for efficacy?
- What is the PD-Outcome relationship for warfarin in ROCKET-AF study?
- Does concomitant aspirin use affect the safety and efficacy of rivaroxaban and warfarin?

4.1.2 OBJECTIVES

The primary objectives included:

1. Evaluate the relationship between the PT measurements at weeks 12 or 24 (closest to the event) and probability of ischemic stroke for rivaroxaban
2. Evaluate the relationship between the PT measurements at weeks 12 or 24 (closest to the event) and probability of major bleeding for rivaroxaban
3. Evaluate the relationship between the last observed INR and probability of ischemic stroke for warfarin
4. Evaluate the relationship between the last observed INR and probability of major bleeding for warfarin

Other objectives included:

1. Relationship between other PD markers and efficacy outcomes for rivaroxaban
2. Relationship between other PD markers and safety outcomes for rivaroxaban

4.1.3 PD-EFFICACY ANALYSIS

4.1.3.1 Data and Methods

All the analyses presented here were done on the per-protocol dataset provided by the sponsor. The PD samples were collected at week 12 and week 24 in almost all subjects in ROCKET-AF (sponsor's dataset: adpd.xpt). To examine any PD-efficacy relationship, a PD measurement that is collected closer and prior to the event of interest was used (last observed PD before an event). For example, if a subject had an efficacy event after week 24, PD measurement at week 24, if available, was used in the analysis. To approximate an on-treatment analysis, the time period from randomization to the last dose of study medication plus 2 days were chosen. If an outcome event did not occur during this timeframe, time was censored at the last dose of study medication plus 2 days. Only time to the first event was considered in the analysis (sponsor's dataset: adtteef3.xpt).

4.1.3.2 Logistic Regression

To examine the relationship between PD and efficacy outcome, subjects were binned into quartiles based on their PD measurements. The observed probability for an efficacy event in each quartile (number of event/ number of subjects in a quartile) was calculated and plotted against the median value of PD measurements for each quartile.

A logistic regression was used to predict the probability of an efficacy event as (1) a linear or (2) an E_{\max} function of a PD measurement.

$$\text{Linear} \quad \text{logit}(\pi) = \ln(\pi/1-\pi) = \text{logit } P_0 + \beta_1 \cdot \text{PD} \quad (1)$$

$$\text{E(max)} \quad \text{logit}(\pi) = \text{logit } P_0 + \text{logit } P_{\max} \cdot (\text{PD})/(\beta_{50} + \text{PD}) \quad (2)$$

where π is the probability of an event; β_1 is the additive effect on the log of the odds for a unit change in PD; P_0 is the probability of event at PD=0; $\text{logit } P_{\max}$ is the additive effect on the log of the odds related to PD (*i.e.* very high value of PD); β_{50} is the value of PD that produces 50% of $\text{logit } P_{\max}$. Equation 2 is a nonlinear function relating probability of an event and PD.

A logistic regression model with a better fit was chosen for plotting. An overlay-plot with observed probability in each quartile of PD as well as a predicted probability from the regression model was used to display the relationship between a PD measurement and an efficacy outcome.

4.1.3.3 Time to Event Analysis

Time to first occurrence of ischemic stroke was modeled with a Cox proportional hazard (PH) model:

$$\lambda(t | X) = \lambda_0(t) \exp(\beta' X)$$

This expression gives the hazard at time t for an individual with a linear function of covariates, where β' is coefficient vector for a set of fixed covariates X .

To identify potential covariates in a model, a bivariate analysis of the association between each covariates (dataset: adsl.xpt) and survival time was performed. Potential covariates tested included age, sex, race, body weight, baseline creatinine clearance, prior stroke/TIA/systemic embolism, baseline CHADS2 score, diabetes mellitus, hypertension, myocardial infarction, prior VKA and PPI use and aspirin use during double blind period.

All covariates that were close to be significant in the bivariate analysis ($p < 0.20$) and other covariates that were judged to be of clinical importance (*e.g.* age) were selected in the final model fitting. The reduced model was then fitted and a covariate was considered to be significant at p value $< .05$. Once a reasonable “main effect” model was selected, biologically plausible interaction terms were tested and significant interaction terms ($p < .05$) were retained to derive the final model. Further, an alternative method using the stepwise selection, which consists of forward selection ($p < .05$) followed by backward elimination steps ($p > .05$), was employed to verify the covariate selection in the final model. The proportional hazard assumption was checked by plotting the weighted Schoenfeld residuals against the log survival time. All the analyses and plots were conducted and generated in SAS 9.2.

4.1.3.4 Prothrombin Time-Ischemic Stroke Relationship for Rivaroxaban

A subset of rivaroxaban per-protocol analysis set [$n = 6193/7008$ (88%)], which included all subjects with a PT measurement closer to an ischemic stroke event, was used in this analysis. The majority of PD samples (~78%) were collected during 12-24 hours post-dose representing trough levels of PD (referred to as pre-dose PD in subsequent sections). The distribution of sampling time for PT measurements is presented in [Figure 4](#).

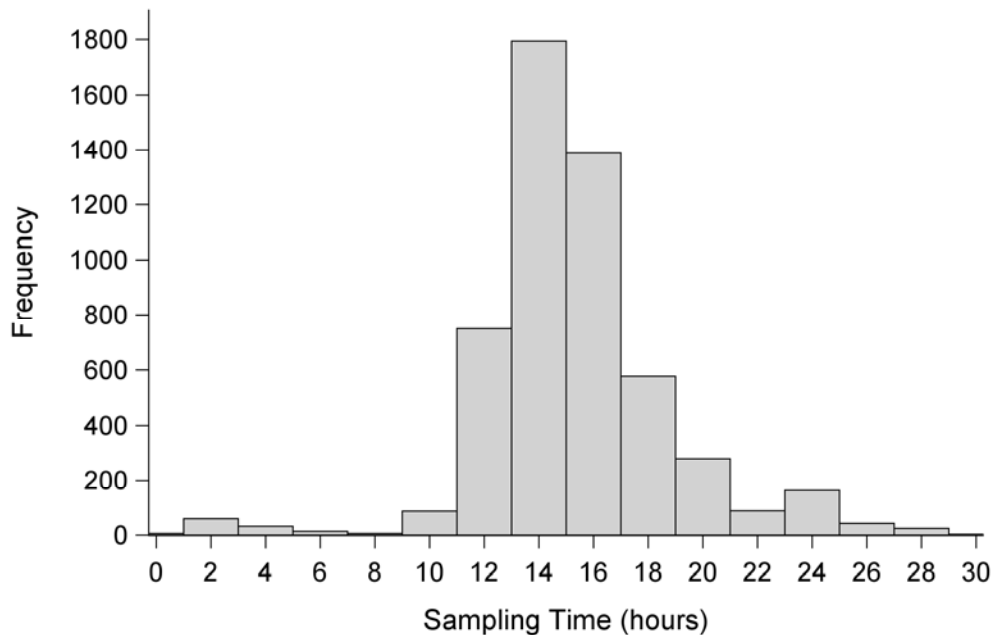


Figure 4 Distribution of PT sampling times in PT-Ischemic stroke subset ($n = 6193$). Majority of the PT samples were collected during the 12-24 hrs post dose window.

A total of 124 ischemic stroke events were included in this subset [83% of ischemic strokes ($n = 150$) in the per-protocol population]. The observed and predicted probability (un-adjusted association) of ischemic stroke by pre-dose PT is shown in [Figure 5](#). This analysis shows that there is no pre-dose PT dependent decrease in ischemic stroke over the range of 10-30 seconds. A sensitivity analyses that included subjects with PT measured between 12-24 hours and 12-15 hours after the dose (limit the subset with trough level of PD) were conducted and showed consistent results as demonstrated in [Figure 5](#).

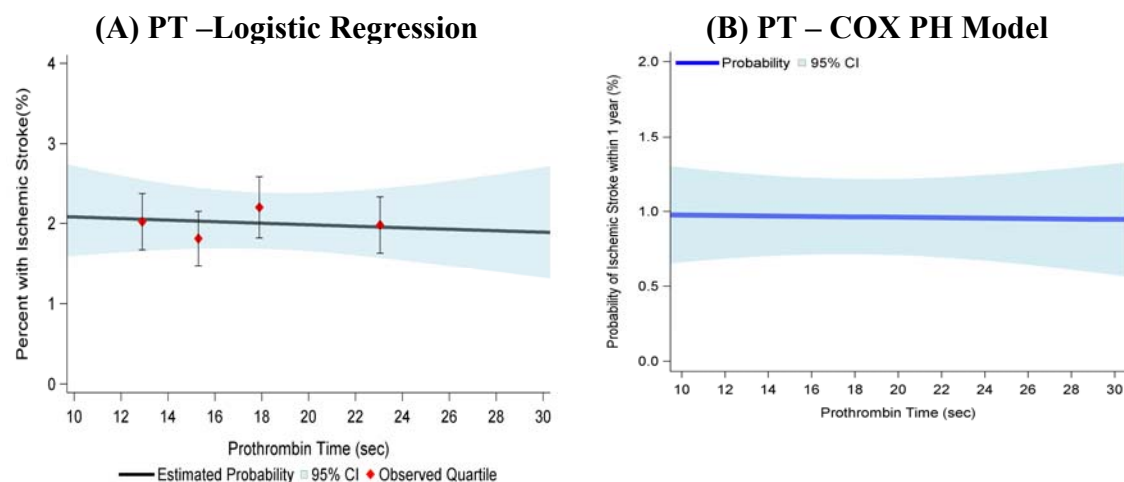


Figure 5 Probability of ischemic stroke as a function of PT and for rivaroxaban. **(A)** Logistic regression. The solid line represents the predicted probability from an unadjusted linear logistic regression. The points represent the observed probability at the median pre-dose PT and the error bar represents standard error for a given quartile. **(B)** Cox PH model. The blue line represents probability of ischemic stroke within 1 year by pre-dose PT for rivaroxaban in ROCKET-AF from the Cox PH model. The shaded regions represent the 95% confidence interval in both plots.

A Cox PH model was used to examine the relationship between pre-dose PT and time to the first ischemic stroke while controlling for potential covariates. Baseline body weight and prior stroke/TIA/embolism were identified as significant risk factors. After adjusting for the covariates, the pre-dose PT remained unassociated with the probability of ischemic stroke but was included in the model for the illustration purpose. [Table 3](#) shows the parameter estimates from the final Cox PH model. The mean predicted probability for ischemic stroke within one year according to PT was calculated from the model and illustrated in [Figure 5](#). The results demonstrated the lack of association between PT and ischemic stroke in ROCKET-AF.

Table 3 Parameter estimates of the final pre-dose PT-ischemic stroke model[†]

Parameter	Estimate (SE)	Hazard Ratio* (95% CI)	P value
Baseline body weight (kg)	-0.01 (0.006)	0.89 (0.80-0.99)	0.04
Prior stroke/TIA/non-CNS Systemic Embolism (Yes vs. No)	0.71 (0.20)	2.11 (1.42-3.14)	0.0005
Pre-dose PT (sec)	-0.001 (0.01)	0.99 (0.77-1.26)	0.92

[†]The region was used as a stratification variable for model fitting to account for different baseline risk across regions

* Hazard ratio for continuous predictors was calculated for 10 units increase for baseline body weight and PT.

4.1.3.5 Other PD measures-Ischemic Stroke Relationship for Rivaroxaban

Further analyses with different PD measurements (Pre-dose Factor Xa activity, PiCT, PT-INR and last observed INR from the point-of-care device) and ischemic stroke events were performed for rivaroxaban ([Figure 6](#)).

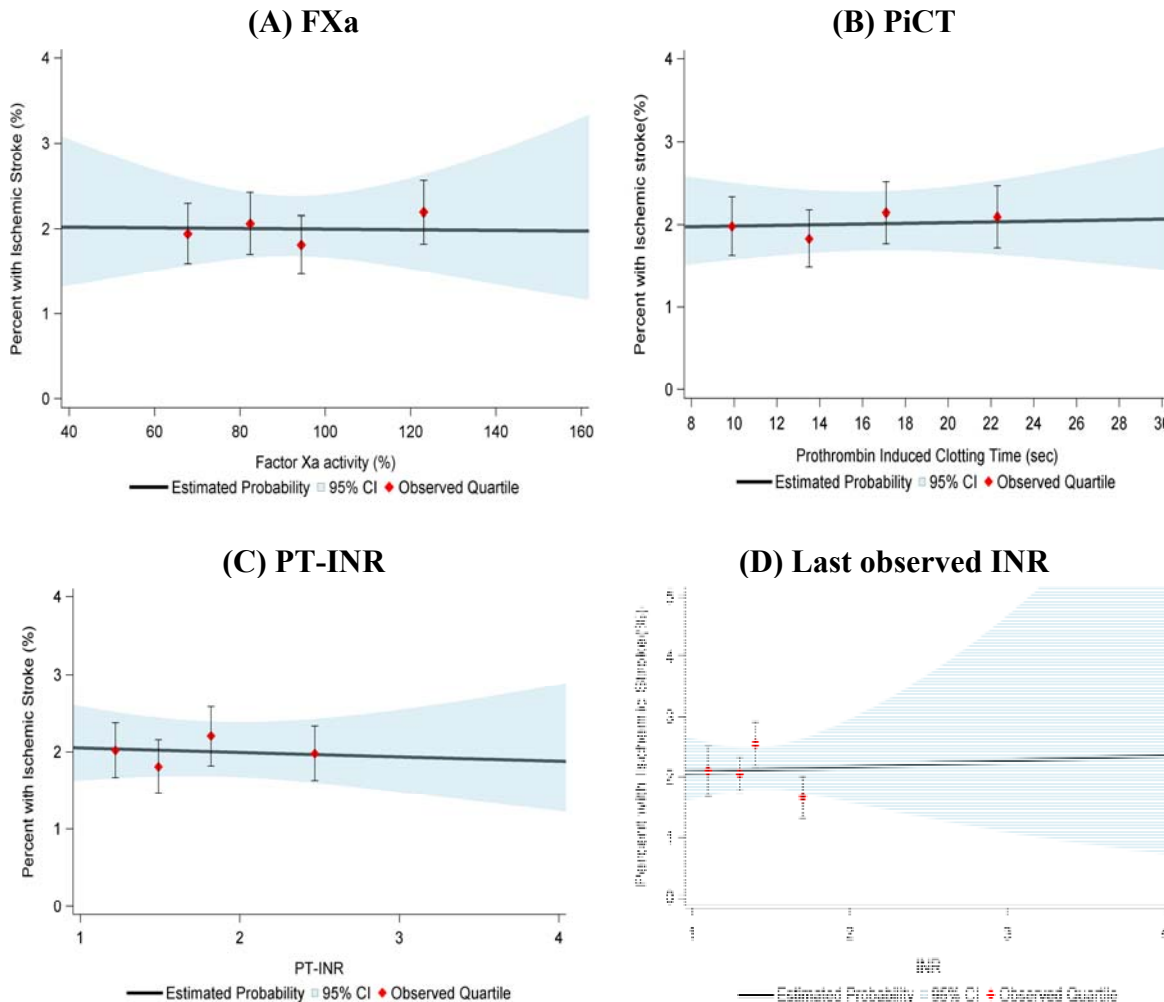


Figure 6 Probability of ischemic stroke as a function of (A) pre-dose Factor Xa activity and (B) Pre-dose PiCT (C) Pre-dose PT-INR and (D) Last observed INR from the point-of-care device for rivaroxaban. The solid line represents predicted probability from an unadjusted linear logistic regression and the shaded region represents the 95% confidence interval. The red points represent the observed probability at the median pre-dose PD and the error bars represent standard errors for a given quartile.

In addition to ischemic stroke, primary efficacy endpoint defined as a composite of stroke and non-CNS systemic embolism was also used to examine the PD-Efficacy relationship. In the per-protocol analysis set (N = 7008), there were total of 190 primary efficacy endpoint events and the results were in agreement with PD-ischemic stroke relationships.

Overall, the results demonstrated the lack of association between any PD measurements used and efficacy endpoints for rivaroxaban. These observations were consistent with the findings from the PT-ischemic stroke analysis (see Section above).

4.1.3.6 Last observed INR-Ischemic Stroke Relationship for Warfarin

The dataset used for this analysis included all warfarin treated subjects in the per-protocol analysis set for whom there were available INR and ischemic stroke information. The last observed INR was defined as the last measured INR value prior to or on the date of ischemic stroke event (censored date if no event). In the ROCKET-AF study, the INRs were measured using a point-of-care device at the study centers for warfarin and an INR of greater than 6 were truncated to 6.1. To avoid the bias associated due to truncation of INR, the analysis excluded patients with INR greater than 6.0 (i.e., $n = 82$; 3 ischemic stroke events excluded). A total of 6,878 subjects with 156 ischemic stroke events were included in the final dataset (ischemic stroke events was 161/7046 in per-protocol warfarin analysis set). [Figure 7](#) illustrates the observed and predicted probability with ischemic stroke by the last observed INR. The results showed that the probability of ischemic stroke reduction was dependent on the last observed INR for warfarin with the smallest observed probability for stroke ranged between INR of 2 and 3 (target INR range).

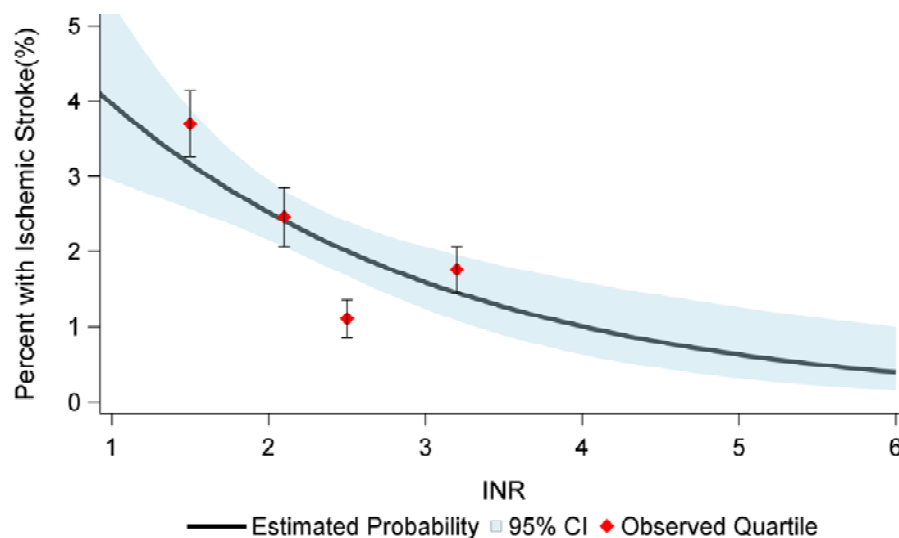


Figure 7 Probability of ischemic stroke as a function of the last observed INR (from point-of-care device) for warfarin. The solid line represents predicted probability from an unadjusted linear logistic regression and the shaded region represents the 95% confidence interval. The red points represent the observed probability at the median INR and the error bars represent standard error for a given quartile.

The Cox PH model was employed to examine the association between the last observed INR and ischemic stroke, while controlling for covariates. The analyses identified baseline body weight, CHADS2 score, and congestive heart failure (CHF) in addition to

the last observed INR as independent predictors of ischemic stroke. Table 4 shows the parameter estimates from the final Cox PH model.

Table 4 Parameter estimates of the final INR-ischemic stroke model in warfarin[†]

Parameter	Estimate (SE)	Hazard Ratio* (95% CI)	P value
Last observed INR	-0.54 (0.13)	0.58 (0.46-0.75)	<0.0001
Baseline body weight (kg)	-0.02 (0.005)	0.82 (0.74-0.91)	0.0002
Baseline CHADS2 score	0.33 (0.09)	1.39 (1.06-2.13)	0.0001
Baseline CHF (Yes vs. No)	0.40 (0.18)	0.67 (0.47-0.94)	0.02

[†] The region was used as a stratification variable for model fitting to account for different baseline risk across regions

* Hazard ratio was calculated for 1 unit increase for last observed INR and baseline CHADS2 score, and 10 units increase in baseline body weight

The mean predicted probability for ischemic stroke within one year as per the last observed INR was calculated from the model (Figure 8). Unlike the findings from pre-dose PT-ischemic stroke analysis for rivaroxaban, the probability of having ischemic stroke within a year for warfarin was dependent on the last observed INR. The results from the logistic regression and Cox PH analyses were consistent.

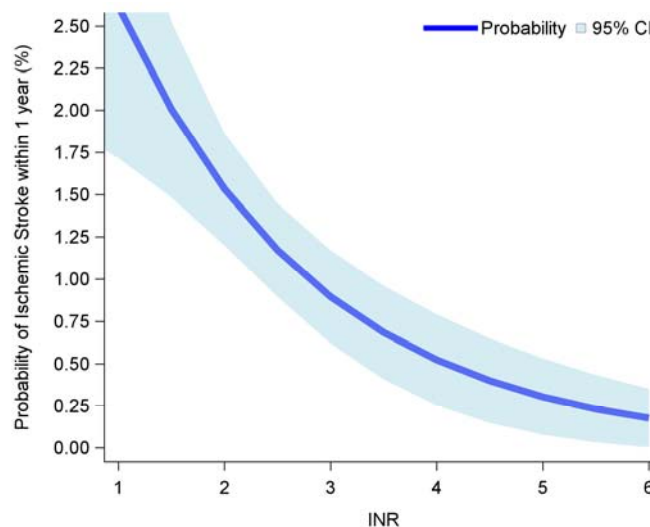


Figure 8 Probability of ischemic stroke within 1 year as a function of the last observed INR for warfarin in ROCKET-AF. The shaded region represents the 95% confidence interval.

4.1.4 PD-SAFETY ANALYSIS

4.1.4.1 Data and methods

PD samples were collected at weeks 12 and 24 in all subjects in ROCKET-AF (dataset: adpd.xpt). To examine the PD-safety relationship, a PD measurement that was collected closer and prior to the target event (major bleeding, TIMI Major bleeding or PLOT bleeding for respective analyses) was used (i.e. the last observed PD measurement before an event). For example, if a subject had a safety event occurred after week 24, PD measurements at week 24, if available, were used in the analysis. To approximate an on-treatment analysis, the time period from the first dose to the last dose of study medication plus 2 days were chosen. If an outcome event did not occur during this timeframe, time was censored at the last dose of the study medication plus 2 days. Only time to the first event was considered (dataset: adttepb.xpt).

4.1.4.2 Logistic Regression

To examine the relationship between PD and safety outcome, subjects were binned into quartiles based on their PD measurements. The observed probability for a safety event in each quartile (number of event/ number of subjects in a quartile) was calculated and plotted against the median value of PD measurements for each quartile.

A logistic regression was used to predict the probability of a safety event as (1) a linear or (2) an E_{\max} function of a PD measurement.

$$\text{Linear} \quad \text{logit}(\pi) = \ln(\pi/1-\pi) = \text{logit } P_0 + \beta_1 \cdot \text{PD} \quad (1)$$

$$\text{E(max)} \quad \text{logit}(\pi) = \text{logit } P_0 + \text{logit } P_{\max} \cdot (\text{PD})/(\beta_{50} + \text{PD}) \quad (2)$$

where π is the probability of an event; β_1 is the additive effect on the log of the odds for a unit change in PD; P_0 is the probability of event at PD=0; $\text{logit } P_{\max}$ is the additive effect on the log of the odds related to PD (i.e. very high value of PD); β_{50} is the value of PD that produces 50% of $\text{logit } P_{\max}$. Equation 2 is a nonlinear function relating probability of an event and PD.

A logistic regression model with a better fit was chosen for plotting. An overlay-plot with observed probability in each quartile of PD as well as a predicted probability from the regression model was used to display the relationship between a PD measurement and a safety outcome.

4.1.4.3 Time to Event Analysis

Pre-dose PT and major bleeding were chosen as the primary PD marker and safety endpoint respectively for the model building. Major bleeding was chosen as a primary endpoint because it was defined in the protocol and provided a sufficient number of “serious” bleeding events for the analysis. Major bleeding event was defined as clinically overt bleeding associated with a decrease in hemoglobin $\geq 2\text{g/dl}$, or a transfusion of ≥ 2 units of packed red blood cells or whole blood, or bleeding at a critical site, or a fatal outcome. Other definitions of serious bleeding events were also explored and documented in the later sections.

Time to first occurrence of bleeding was modeled with a Cox proportional hazard (PH) model:

$$\lambda(t | X) = \lambda_0(t) \exp(\beta' X)$$

This expression gives the hazard at time t for an individual with a linear function of covariates, where β' is coefficient vector for a set of fixed covariates X . To identify the potential covariates in the model, bivariate analysis of the association between covariates (dataset: adsl.xpt) and survival time was performed.

Several potential covariates such as age, sex, race, body weight, baseline creatinine clearance, prior stroke/TIA/Embolic, baseline CHADS2 score, diabetes mellitus, hypertension, myocardial infarction, prior VKA and PPI use and aspirin use during double blind period were tested. Aspirin use was defined as $\geq 50\%$ use during double blind treatment period. Sensitivity analyses using different definitions of aspirin use (any, ≥ 10 , 25, 75, or 90% use) were also tested.

All covariates that were close to be significant in the bivariate analysis ($p < 0.20$) and other covariates that were judged to be of clinical importance (i.e. age) were selected. A reduced model was then fitted and a covariate was considered to be significant at p value $< .05$. Once a reasonable “main effect” model was selected, biologically plausible interaction terms were tested and significant interaction terms ($p < .05$) were retained to derive the final model. Further, an alternative method using the stepwise selection, which consists of forward selection ($p < .05$) followed by backward elimination steps ($p > .05$), was employed to verify the covariate selection in the final model. PH assumption was checked by plotting the weighted Schoenfeld residuals against log survival time. All the analyses and plots were conducted and generated in SAS 9.2.

Upon the request of the medical reviewers some of the exploratory analyses were stratified by region (US and Rest of the world).

4.1.4.4 Prothrombin Time-Major Bleeding Relationship for Rivaroxaban

A subset of rivaroxaban per-protocol analysis set [$n = 6172/7008$ (88%)], including all subjects with an available PT measurement prior to the first major bleeding event, was used in this analysis. There were 306/392 (78% of total events) major bleeding events included in this subset. [Table 5](#) shows the incidence and event rate (per 100 subject years) for the first major bleeding event according to the quartiles of pre-dose PT.

Table 5 Incidence and event rate for the first major bleeding (Adjudicated by CEC) while on treatment (up to last dose plus 2 days) according to pre-dose PT

PT Quartiles	Rivaroxaban (PT-Major bleeding subset) N=6172	
	Incidence n (%)	Event Rate (100 pt-yrs)
Q1 (<14.2 sec)	49/1573 (3.12)	1.88
Q2 (14.2-<16.6 sec)	68/1543 (4.41)	2.54
Q3 (16.6-<19.8 sec)	78/1501 (5.20)	2.95
Q3 (≥19.8 sec)	111/1555 (7.14)	4.29

An increasing bleeding rate was observed in U.S. compared to the rest of the world for rivaroxaban. However, the sample size is relatively small in the U.S. to derive any meaningful conclusions (Table 6). Both incidence and event rate (per 100 subject-years) increased with pre-dose PT quartile.

Table 6 Incidence and event rate for the first major bleeding (Adjudicated by CEC) while on treatment (up to last dose plus 2 days) according to PT: US vs. Rest of the world

PT Quartiles	Rivaroxaban (PT-Major bleeding subset) N=6172			
	US (N = 819)		Other countries (N =5353)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<14.2 sec)	8/108 (7.4)	4.39	41/1465 (2.8)	1.69
Q2 (14.2-<16.6 sec)	15/172 (8.7)	4.38	53/1371 (3.9)	2.27
Q3 (16.6-<19.8 sec)	27/228 (11.8)	6.70	51/1273 (4.0)	2.27
Q4 (≥19.8 sec)	43/311 (13.8)	8.11	68/1244 (5.5)	3.30

Since rivaroxaban showed increased bleeding event rates across PT quartiles in the US compared to rest of the world, we looked into the bleeding event rates for warfarin across the last observed INR values (See Table 7). The major bleeding event rates were higher in the US than rest of the world for both rivaroxaban and warfarin.

Table 7 Incidence and event rate for the first major bleeding (Adjudicated by CEC) while on treatment (up to last dose plus 2 days) according to last observed INR for Warfarin: US vs. Rest of the world

INR Quartiles	Warfarin (INR-Major bleeding subset) N=6877			
	US (N = 946)		Other countries (N =5931)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<1.8)	11/162 (6.8)	4.13	70/1646 (4.3)	2.98
Q2 (1.8-<2.2)	17/215 (7.9)	4.56	50/1349 (3.7)	2.24
Q3 (2.2-<2.7)	24/293 (8.2)	4.62	67/1435 (4.7)	2.83
Q3 (≥ 2.8)	32/276 (11.6)	7.10	94/1501 (6.3)	3.89

The observed and predicted probability with major bleeding by pre-dose PT (unadjusted association) is shown in Figure 9. This analysis showed that risk of major bleeding increased with pre-dose PT. In our dataset, majority of the PD samples (~78%) were collected during 12-24 hours post-dose, which represents through PTs. Sensitivity analyses only including subjects with PT measured between 12-24 hours and 12-15 hours showed consistent results as demonstrated here.

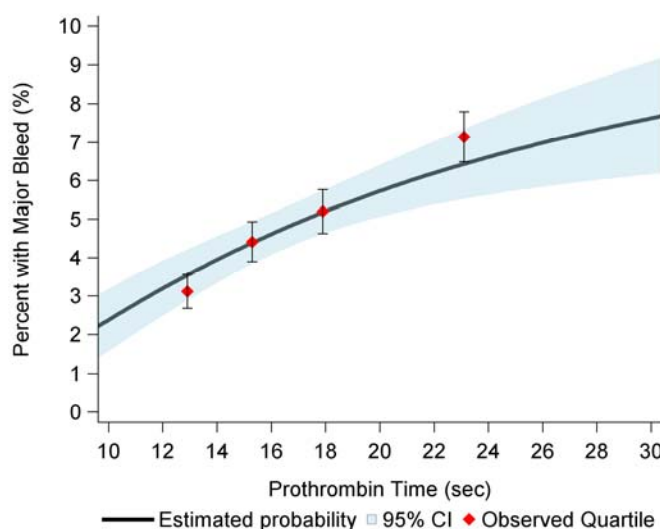


Figure 9 Probability of major bleeding as a function of pre-dose PT for rivaroxaban. The solid line represents the predicted probability from an E_{\max} logistic regression and the shaded region represents the 95% confidence interval. The point represents the observed probability at the median value of pre-dose PT for a given quartile and error bars represent standard errors.

Further analysis of the pre-dose PT-major bleeding relationship demonstrated that the effect of PT on the risk for major bleeding was found to be modified by the aspirin use during the double blind phase (Figure 10). There are 1308/6172 (21%) subjects who had

concomitant use of aspirin with rivaroxaban during treatment period. Aspirin use was defined as $\geq 50\%$ use during double blind treatment period.

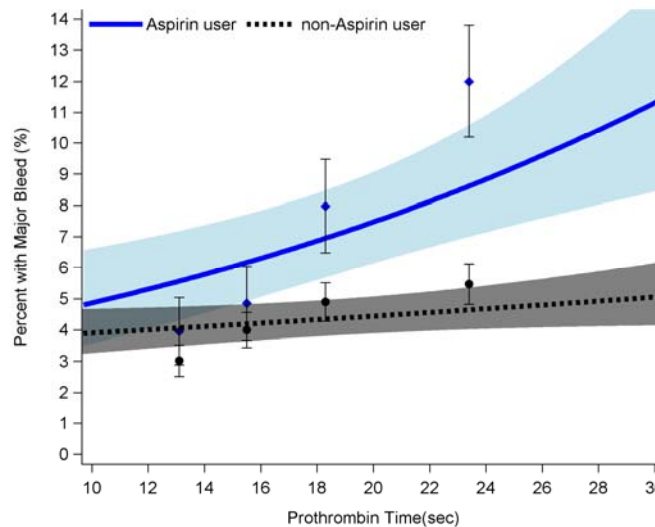


Figure 10 Predicted and observed probability of major bleeding as a function of pre-dose PT and Aspirin use (50 % use during double blind phase) for rivaroxaban in ROCKET-AF. The solid line represents the predicted probability from a linear logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median PT of a given quartile.

Sensitivity analyses using different definitions of aspirin use (any, ≥ 10 , 25, 75, or 90% use) showed similar results (See Figure 11). Subjects who used aspirin during rivaroxaban treatment had an increased risk of major bleeding compared to those who did not use aspirin. The pre-dose PT-major bleeding relationship was steeper among Aspirin users. These findings were observed in both U.S. and the rest of the world with the bleeding event rates increasing with PT quartiles among aspirin users (Table 8).

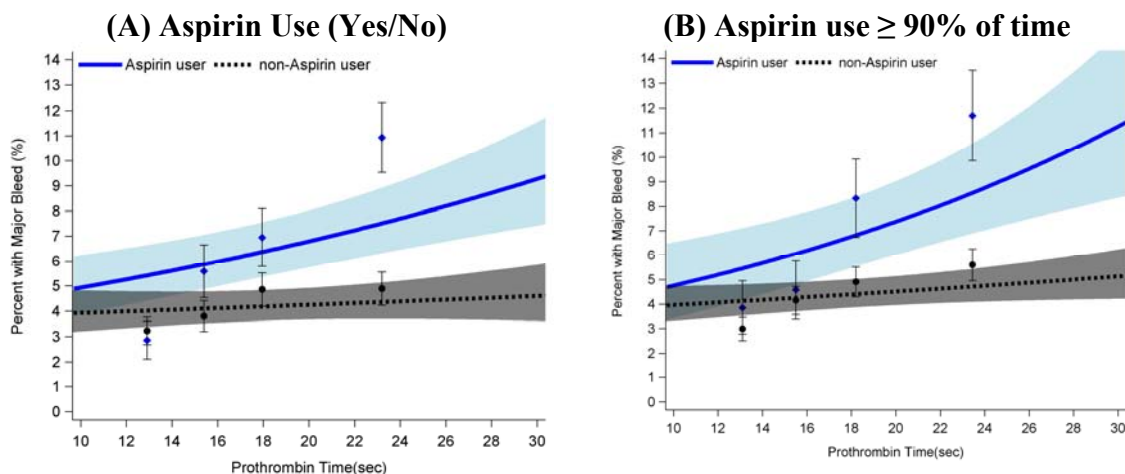


Figure 11 Sensitivity analysis for different levels of aspirin use during double blind phase: Predicted and observed probability of major bleeding as a function of pre-dose PT and Aspirin use (A) defined as Yes/No use and (B) $\geq 90\%$ of time during double blind

phase for rivaroxaban in ROCKET-AF. The solid line represents the predicted probability from a linear logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median PT of a given quartile

Table 8 Incidence and event rate for the first major bleeding (Adjudicated by CEC) on treatment (up to last dose plus 2 days) according to PT and aspirin user in (A) US and (B) other countries

PT Quartiles	(A) US (N = 819)			
	Aspirin user (N =286)		Non-aspirin user (N = 533)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<14.2 sec)	5/41 (12.2)	7.22	3/67 (4.5)	2.66
Q2 (14.2-<16.6 sec)	6/61 (9.8)	5.00	9/111 (8.1)	4.05
Q3 (16.6-<19.8 sec)	7/72(9.7)	5.39	20/156 (12.8)	7.32
Q4 (≥19.8 sec)	26/112 (23.2)	14.37	17/199 (8.5)	4.86
PT Quartiles	(B) Other Countries (N = 5353)			
	Aspirin user (N =1022)		Non-aspirin user (N = 4331)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Q1 (<14.2 sec)	7/269 (2.6)	1.60	34/1196 (2.8)	1.71
Q2 (14.2-<16.6 sec)	9/259 (3.5)	2.01	44/1112 (4.0)	2.34
Q3 (16.6-<19.8 sec)	15/242(6.2)	3.52	36/1031 (3.5)	1.98
Q4 (≥19.8 sec)	19/252(7.5)	4.89	49/992 (4.9)	2.93

A Cox PH model was used to examine the relationship between PT and time to the first major bleeding event while controlling for potential covariates. Age, baseline body weight, baseline proton pump inhibitor use, and PT by aspirin use interaction were identified as significant risk factors. [Table 9](#) shows the parameter estimates and hazard ratios from the final Cox PH model. The parameter of PT by aspirin use interaction was of marginal significance (p=0.06) but was included in the final model. Similar results were obtained when sensitivity analyses were conducted for different definition for Aspirin use (any, ≥10, 25, 75, or 90% use). After adjusting the covariates, there is increased risk of major bleeding with increased PT and the magnitude of that is larger among subjects who had concomitant use of aspirin with rivaroxaban (for 10 sec increased in PT, there is 47% increase in the risk of major bleeding among the aspirin users compared to 14% increase in non-aspirin users). The mean predicted probability of major bleeding within one year according to PT and aspirin use was calculated from the model and illustrated in [Figure 12](#).

Table 9 Parameter Estimates and Hazard Ratio from Cox-Proportional Hazard model for the association between PT and major bleeding[†]

Parameter	Estimate (SE)	P value
Age (years)	0.04 (0.01)	<0.0001
Baseline body weight (kg)	0.008 (0.003)	0.02
PPI use at baseline	0.36 (0.15)	0.01
PT (sec)	0.04 (0.01)	0.8
Aspirin use(> 50%) during double blind phase	-0.09 (0.30)	0.76
PT*Aspirin use (>50% use)	0.03 (0.01)	0.06
Parameter	Hazard ratio (95 % CI)	
Age (10 year increase)	1.50 (1.28-1.75)	
Baseline body weight (10 kg increase)	1.04 (1.02-1.06)	
PPI use at baseline (Yes or No)	1.44 (1.08-1.92)	
Aspirin user (10 sec increase in PT)	1.47 (1.18-1.85)	
Non-Aspirin user (10 sec increase in PT)	1.14 (0.98-1.32)	

[†] The region was used as a stratification variable for model fitting to account for different baseline risk across regions

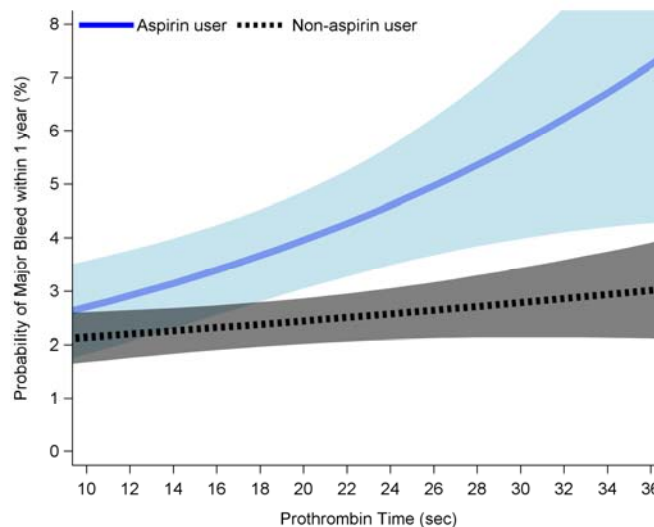


Figure 12 Probability of major bleeding within 1 year as a function of pre-dose PT and aspirin use for rivaroxaban in ROCKET-AF. The shaded region represents the 95% confidence interval.

4.1.3.5 Other PD measures-Bleeding Relationship for Rivaroxaban

Analyses with different pairs of PD measurements (Pre-dose FXa, PiCT, PT-INR and last observed INR from point-of-care device) and safety endpoints were performed for rivaroxaban (Figure 13, Figure 13). In addition to major bleeding event, TIMI major

bleeding and potential life/organ threatening major bleeding event (PLOT) were also used for the analysis (dataset:adtteepb.xpt).

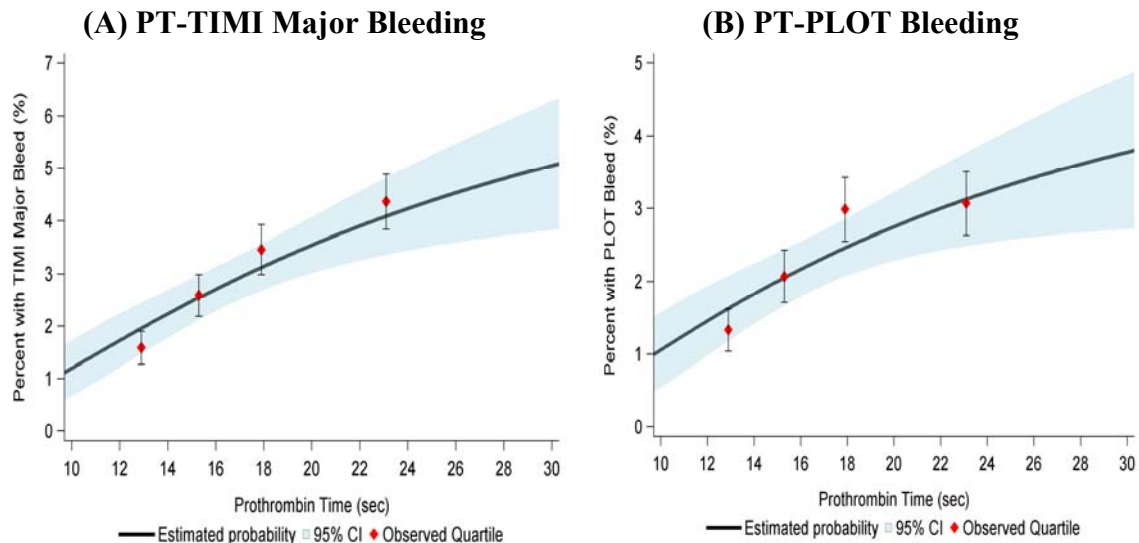
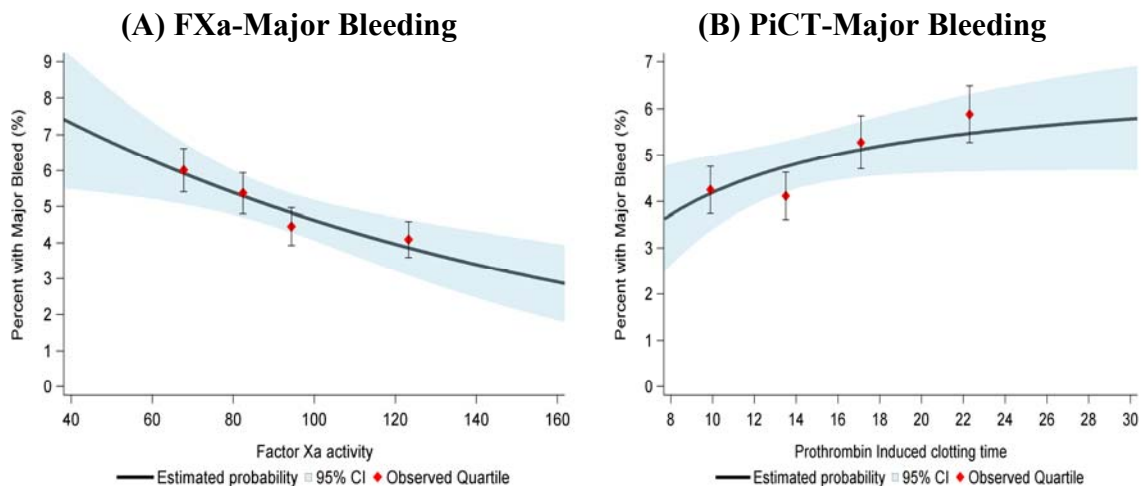


Figure 13 Probability of (A) TIMI major bleeding and (B) PLOT major bleeding as a function of pre-dose PT for rivaroxaban. The solid line represents the predicted probability from a E_{max} logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median value of pre-dose PT and error bar represents standard error for a given quartile.



(C) PT-INR

(D) Last observed INR

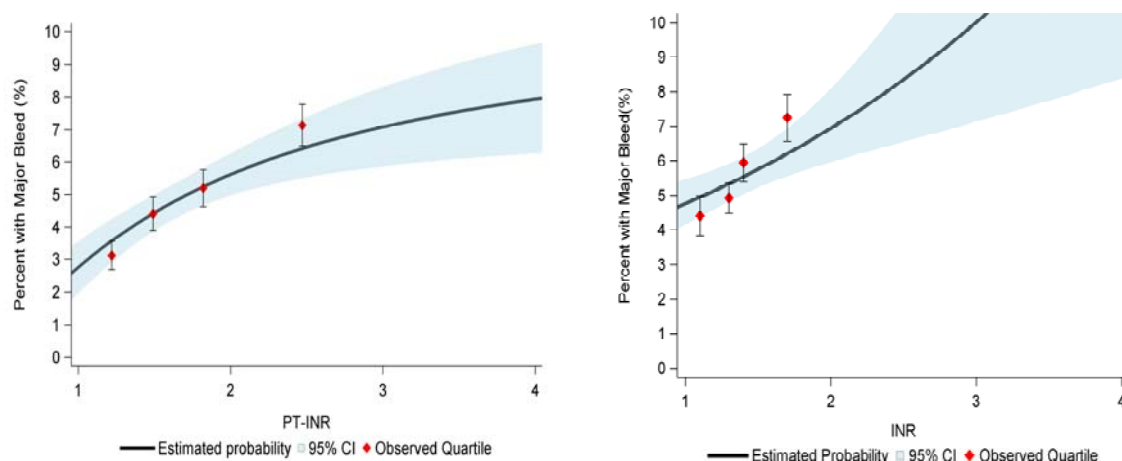


Figure 14 Probability of major bleeding as a function of (A) pre-dose FXa activity (B) pre-dose PiCT for rivaroxaban (C) PT-INR and (D) Last observed INR from the point of care device for rivaroxaban. The solid line represents the predicted probability from an E_{\max} logistic regression and the shaded region represents the 95% confidence interval. The point represents observed probability at the median PD activity and error bar represents standard error for a given quartile.

Overall, all the results demonstrated that the risk of bleeding was associated with all pre-dose PD measurements for rivaroxaban. The results were consistent with the findings from our primary analysis of pre-dose PT-major bleeding relationship.

4.1.3.6 Last observed INR-Bleeding Relationship for Warfarin

The dataset used for this analysis comprised of all warfarin subjects in the per-protocol analysis set for whom there were available INR and major bleeding information. The last observed INR was defined as the last measured INR value prior to or on the date of first major bleeding event (censored date if no event). In the ROCKET-AF study, the INRs were measured using a point of care device at the study centers and an INR of greater than 6 was truncated to 6.1. To examine a fair relationship between continuous INR and major bleeding, those whose last observed INR equaling to 6.1 were excluded ($n = 82$, 10 major bleeding events excluded). A total of 6,877 subjects with 365 major bleeding events were included in the final dataset (378/7046 major bleeding events in the per-protocol analysis set). [Figure 15](#) illustrates the observed and predicted probability of major bleeding by the last observed INR. The result showed that major bleeding increased with the increase in the last observed INR for warfarin.

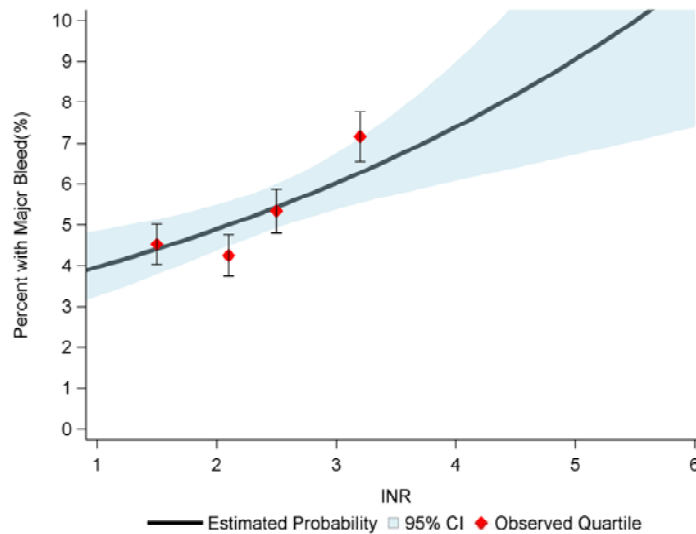


Figure 15 Probability of major bleeding as a function of the last observed INR for warfarin. The solid line represents the predicted probability from a linear logistic regression and the shaded region represents the 95% confidence interval. The red points represent the observed probability at the median value of INR and error bars represent standard errors for a given quartile.

The potential interaction between aspirin use ($\geq 50\%$ use) and the last observed INR for major bleeding risk was also explored. There were 1613/6877 (23%) subjects who had concomitant use of aspirin with warfarin during treatment period. Aspirin use was defined as $\geq 50\%$ use during double blind treatment period. The combined effect of aspirin and INR on the major bleeding on warfarin seems more like an additive effect instead of an interaction effect (changes of slope) observed for rivaroxaban (Figure 16).

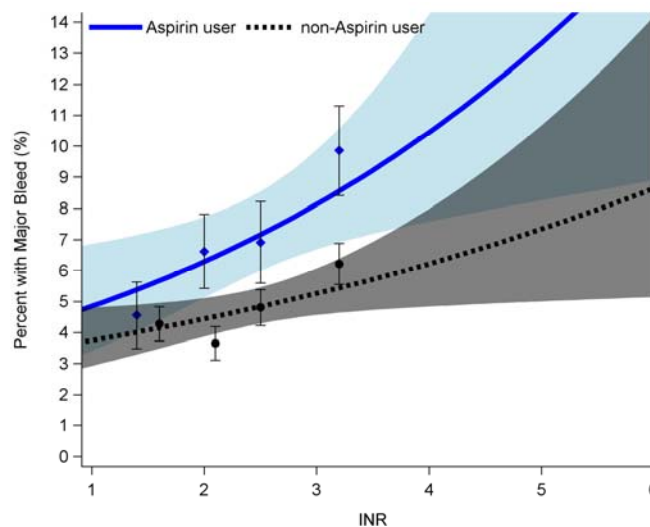


Figure 16 Predicted and observed probability of major bleeding as a function of the last observed INR and Aspirin use for warfarin in ROCKET-AF. The solid line represents the predicted probability from an unadjusted linear logistic regression and the shaded region

represents the 95% confidence interval. The point represents observed probability at the median INR and the error bar is the standard error for a given quartile.

A Cox PH model was used to examine the relationship between INR and time to the first major bleeding event while controlling for potential covariates. Sex, baseline creatinine clearance, baseline proton pump inhibitor use, diabetes mellitus and age by aspirin use interaction were identified as significant risk factors. Interaction between INR and aspirin use was not significant ($p = 0.32$). [Table 10](#) shows the parameter estimates from the final Cox PH model. The mean predicted probability of major bleeding within one year according to the last observed INR and aspirin use was calculated from the model and illustrated in [Figure 17](#).

Table 10 Parameter estimates from the Cox-Proportional Hazard model for the association between last observed INR and major bleeding for warfarin[†]

Parameter	Estimate (SE)	Hazard Ratio (95% CI) [*]	P value
Age (years)	0.02 (0.008)	1.20 (1.03-1.40)	0.02
Sex (female)	-0.27 (0.11)	0.77 (0.61-0.96)	0.02
Baseline creatinine clearance	-0.008 (0.003)	0.93 (0.88-0.98)	0.004
Diabetes mellitus (Yes vs. No)	0.27 (0.11)	1.32 (1.07-1.62)	0.01
Last observed INR	0.15 (0.07)	1.16 (1.02-1.32)	0.02
Aspirin use during double blind phase (Yes vs. No)	0.39 (0.11)	1.48 (1.18-1.85)	0.02

[†] The region was used as a stratification variable for model fitting to account for different baseline risk across regions

^{*} Hazard ratio was calculated for 1 unit increase for last observed INR, and 10 units increase in age and baseline creatinine clearance

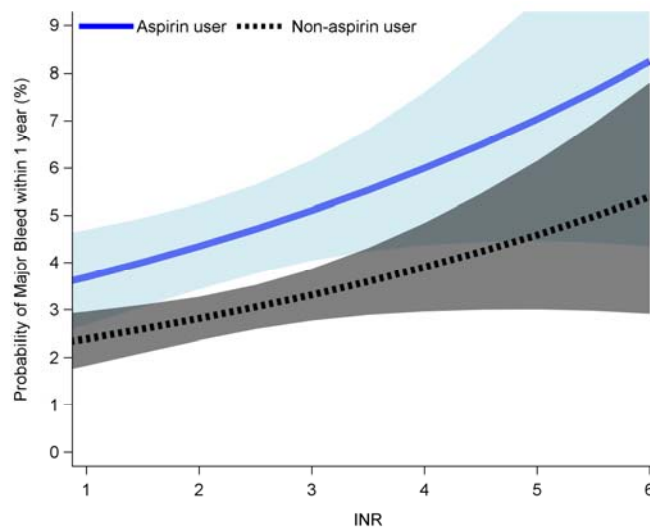


Figure 17 Probability of major bleeding within 1 year as a function of the last observed INR and aspirin use for warfarin in ROCKET-AF study. The shaded region represents the 95% confidence interval.

4.1.5 Impact of concomitant aspirin use - Comparison of Rivaroxaban and Warfarin

The results from the PD-safety analyses showed that concomitant aspirin use during the double blind phase increases the risk of major bleeding in both rivaroxaban and warfarin treatment groups (See Figure 19). The use of aspirin seemed to modify the effect of pre-dose PT on the risk of major bleeding for rivaroxaban. That is, the risk of major bleeding significantly increased with PT among aspirin users but had a shallow relationship among non-aspirin user. However, the concomitant use of aspirin seemed not to affect the risk for ischemic stroke in both rivaroxaban and warfarin groups (aspirin use was not included in the final Cox PH models) (See Figure 19). These results might be partially due to insufficient power to identify risk factors for ischemic stroke. Although the risk of ischemic stroke is not statistically significant between aspirin users or non-aspirin users in rivaroxaban, a decreasing trend in risk reduction with increased PT was observed among aspirin users. There seemed to be no difference in ischemic stroke risk reduction between aspirin users and non-aspirin users in warfarin.

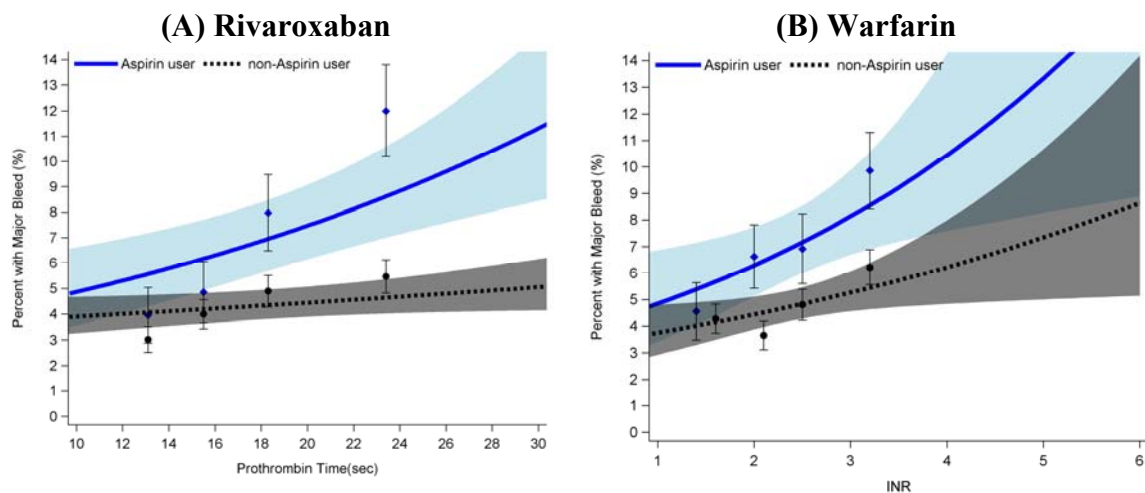


Figure 18 Predicted and observed probability of major bleeding by (A) Pre-dose PT and Aspirin use for rivaroxaban and (B) Last observed INR and Aspirin use from ROCKET-AF. Aspirin use is defined as $\geq 50\%$ use during double blind period.

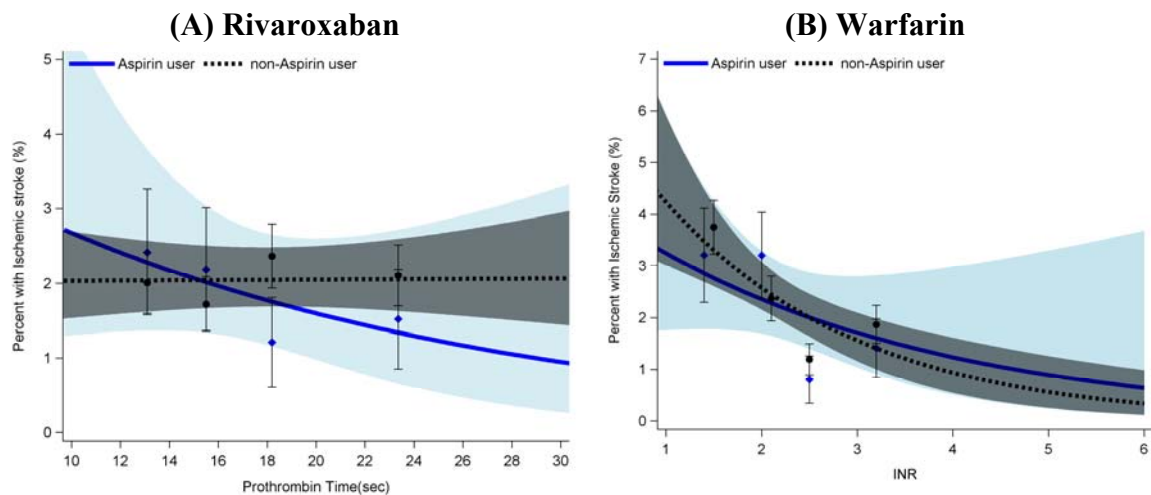


Figure 19 Predicted and observed probability of ischemic stroke by **(A)** Pre-dose PT and Aspirin use for rivaroxaban and **(B)** Last observed INR and Aspirin use from ROCKET-AF. Aspirin use is defined as $\geq 50\%$ use during double blind period.

The analyses comparing the risk of major bleeding and ischemic stroke between aspirin and non-aspirin users are potentially confounded by the unobserved factors that govern the use of aspirin. It might be more reasonable to compare aspirin users and non-aspirin users between treatment arms with regards to risk of having efficacy and safety endpoints. In addition, it is important to know whether or not concomitant use of aspirin with rivaroxaban is associated with exceeding risk in major bleeding compared to that with warfarin.

Table 11 shows the incidence and event rate for efficacy and safety endpoints by treatment groups and aspirin use ($\geq 50\%$ use during double blind) in per-protocol analysis set. Between aspirin users treated with rivaroxaban and warfarin, the event rate for all the efficacy endpoints is numerically in favor of rivaroxaban, especially primary efficacy endpoint and hemorrhagic stroke. On the other hand, the event rate for major bleeding event is numerically in favor of warfarin. Specifically, the higher event rate of major bleeding in rivaroxaban is primary driven by the two components: hemoglobin drop ≥ 2 g/dl and transfusion ≥ 2 units. The aspirin users in rivaroxaban had significantly reduced risk of occurrence of major bleeding event in critical organ compared to those in warfarin (HR: 0.42, 95% CI: 0.24-0.76). Non-aspirin users between treatment groups have similar results across efficacy and safety endpoints.

Table 11 Incidence and event rate for efficacy and safety endpoints by treatment group, (A) Rivaroxaban and (B) warfarin, and aspirin use during double period.

Endpoint	(A) Rivaroxaban (N=7008)			
	Aspirin user (N=1577)		Non-Aspirin user (N=5431)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	40 (2.5)	1.69	150 (2.8)	1.73
Ischemic Stroke	31 (2.0)	1.31	119 (2.2)	1.38
Hemorrhagic Stroke	6 (0.38)	0.25	23 (0.42)	0.27
Primary Safety Endpoint	407 (25.8)	19.9	1050 (19.3)	13.6
Major Bleeding	135 (8.6)	5.82	257 (4.7)	3.02
Hemoglobin drop	118 (7.5)	5.07	184 (3.4)	2.15
Transfusion	79 (5.0)	3.37	102 (1.9)	1.19
Critical Organ Bleeding	16 (1.0)	0.67	75 (1.4)	0.87
Death	7 (0.4)	0.29	20 (0.4)	0.23

Endpoint	(B) Warfarin (N=7046)			
	Aspirin user (N=1664)		Non-Aspirin user (N=5382)	
	n (%)	Event rate (100 pt-yr)	n (%)	Event rate (100 pt-yr)
Primary efficacy endpoint	57 (3.4)	2.26	185 (3.4)	2.13
Ischemic Stroke	37 (2.2)	1.47	124 (2.3)	1.43
Hemorrhagic Stroke	15 (0.9)	0.60	34 (0.6)	0.39
Primary Safety Endpoint	399 (24.0)	18.4	1034 (19.2)	13.4
Major Bleeding	118 (7.1)	4.76	260 (4.8)	3.03
Hemoglobin drop	76 (4.6)	3.05	172 (3.2)	2.0
Transfusion	50 (3.0)	2.0	96 (1.8)	1.11
Critical Organ Bleeding	40 (2.4)	1.59	90 (1.7)	1.04
Death	15 (0.9)	0.60	40 (0.7)	0.50

4.1.6 Impact of concomitant aspirin use –Analysis for Warfarin in RE-LY

To further explore the effects of concomitant use of aspirin with anticoagulants on efficacy and safety outcomes, we also conducted similar analysis using data from the control arm of the RE-LY study submitted in support of dabigatran (NDA 022-512) approval. The dataset used for this analysis comprised of all warfarin subjects for whom there were available INR and outcome information. The last observed INR was defined as the last measured INR value prior to or on the date of targeted event (censored date if no event). A total of 6011 subjects with 133 ischemic stroke events and 249 TIMI major bleeding events (central adjusted event) were included in the dataset. To conduct the exploratory analysis, subjects were first stratified by the aspirin use during the double period (Yes/No) and then divided into 4 quartiles within each stratum based on INR value. The observed probability of an outcome event in each quartile (number of event/ number of subjects in a quartile) by aspirin use was calculated. A logistic regression was used to predict the probability of an event as a function of the last observed INR. An overlay plot with an observed probability at the median INR for each quartile as well as

the predicted probability from the regression model by the aspirin use was created to visually display the relationship (Figure 20).

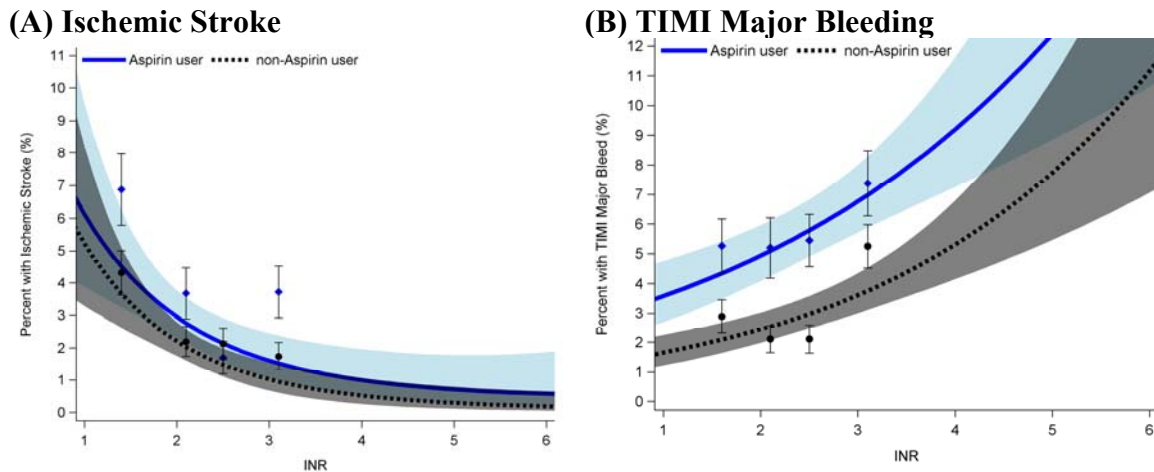


Figure 20 Predicted and observed probability of (A) ischemic stroke and (B) TIMI Major Bleeding by last observed INR and Aspirin use for warfarin in RE-LY study.

The exploratory analysis showed that the aspirin use did not seem to affect risk of ischemic stroke, while demonstrating an additive effect on the risk of TIMI major bleeding for warfarin arm in the RE-LY study. These results were in agreement with our findings for warfarin in the ROCKET-AF study.

4.1.7 SUMMARY

- A twice daily regimen for rivaroxaban provided lower peak to trough ratio in PK and PD for the same total daily dose. However, the clinical impact on safety and efficacy can not be assessed from the available information.
- There was no relationship between pre-dose PT (a surrogate for PK measurement; measured at steady state trough) and primary efficacy outcomes, including ischemic stroke, for rivaroxaban.
- The risk for bleeding with rivaroxaban increased with an increase in PT (mostly measured at steady state trough).
- Stroke reduction and the risk for bleeding were dependent on the last observed INR for warfarin in the ROCKET-AF study. The results were in agreement with the established PD-outcome relationship for warfarin.
- Concomitant aspirin use during the double blind phase significantly increased the risk for major bleeding with rivaroxaban. The risk is particularly higher in those with higher steady state trough PT. This increased risk is mainly driven by major bleeding components including hemoglobin drop ≥ 2 g/dl and transfusion ≥ 2 units.

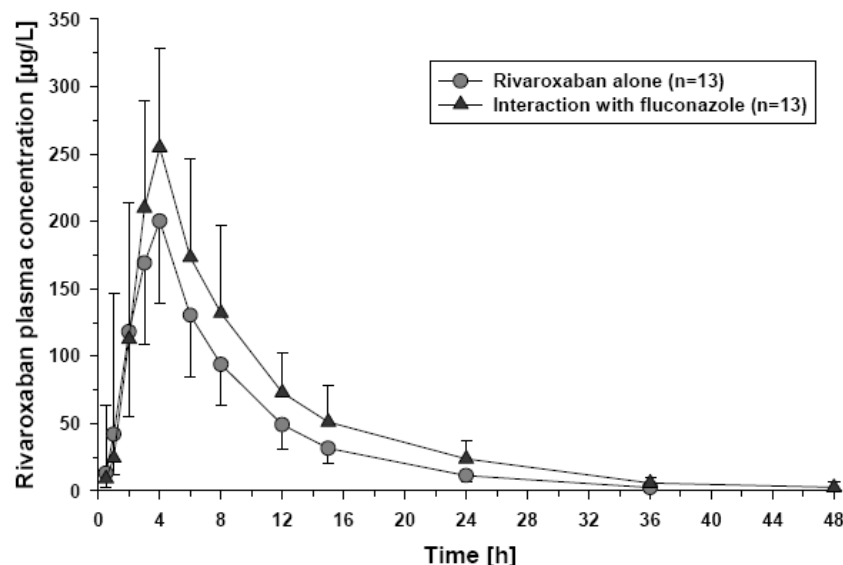
- Concomitant aspirin use with warfarin also increased the risk of major bleeding in the ROCKET-AF. Warfarin treated subjects in RE-LY study also had increased bleeding risk with concomitant aspirin administration.
- The risk of major bleeding among aspirin users in rivaroxaban compared to that of warfarin is similar.

4.2 TABULAR LISTING OF ANALYSIS SCRIPTS

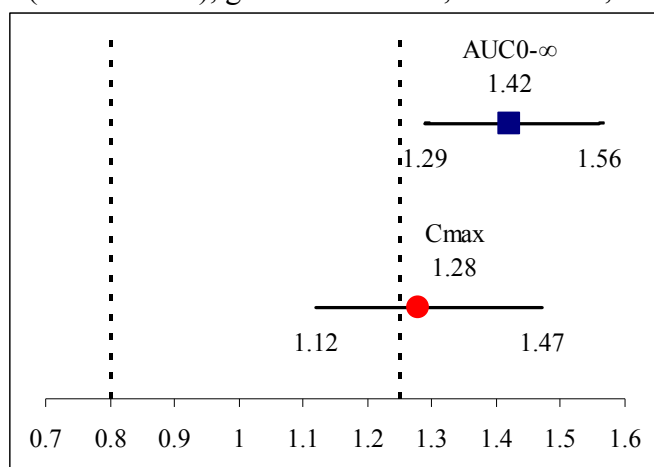
File name	Description	Location in\\cdsbas\pharmacometrics\
PD_outcome_macro.sas INR_outcome_macro.sas	Exploratory analysis on PD-outcome & INR-outcome relationship	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Macro
PT_major.sas	Cox PH model for PT-Major Bleeding	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Bleed
PT_stroke.sas	Cox PH model for PT-Ischemic stroke	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Stroke
INR_major.sas.	Cox PH model for INR-Major Bleeding	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Bleed
INR_stroke.sas	Cox PH model for INR-Ischemic stroke	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\Stroke
INR_outcome_rely	Exploratory analysis on Aspirin use in RE-LY	Reviews\Ongoing PM Reviews\Rivaroxaban_NDA202439\ER Analysis\RELY

5.1 DRUG-DRUG INTERACTION WITH FLUCONAZOLE

Study # 012606		EDR Link: \\cdsesub1\EVSPROD\NDA202439\0048\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\12606-fluconazole-ddi		
Title	Randomized, open label, 2-fold cross-over study to investigate the influence of multiple doses of 400 mg fluconazole on safety, tolerability, and pharmacokinetics of a single oral dose of 20 mg rivaroxaban in healthy male subjects			
Study Design: Multiple-Dose Fluconazole/Single-Dose Rivaroxaban Randomized Open-Label Cross-Over Healthy Vonuteers				
Rationale: Rivaroxaban is metabolized via the CYP3A4/5 and 2J2 enzyme systems. It is also a substrate for Pgp and BCRP for its active renal secretion. In vitro data indicate that the antimycotic fluconazole, reported as a potent inhibitor for CYP2C9 (rivaroxaban is not metabolized via CYP2C9), but only a moderate CYP3A4 inhibitor, inhibited rivaroxaban oxidative metabolism in vitro much less than ketoconazole. This study was to explore the clinical impact and the maximal degree of a potential interaction between fluconazole 400 mg once-daily under steady state conditions on a single dose of 20 mg rivaroxaban.				
Treatment A: 20 mg rivaroxaban single dose on day 0 Treatment B: 400 mg Fluconazole once daily (on days -4 to 1), and 20 mg rivaroxaban single dose (on day 0) 10 days wash out period				
Sampling Times (for rivaroxaban treatment A/B): 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 15 hr (Day 0), 12 hr(Day 1), 0 hr (Days 2, 3 & 4)				
Analytical Method:				
	Analyte	Rivaroxaban	Rivaroxaban	Fluconazole
	Method	HPLC-MS/MS	HPLC-UV	HPLC-MS/MS
	Matrix	Plasma	Urine	Plasma
	Range	0.5 ug/L-500 ug/L	0.1 mg/L-20 mg/L	0.1 mg/mL-100 mg/mL
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.				
Study Population :				
	Randomized/Completed		13	
	Age [Median (range)] years		36 (20-45)	
	Male/Female		Male (100%)	
	Race (Caucasian/Black/Asian/Hispanic)		Caucasians (100%)	
Results				



Rivaroxaban plasma concentrations following oral administration of 20 mg alone (Treatment A) and following 20 mg rivaroxaban added to an on going Fluconazole 400 mg once daily treatment (Treatment B), geometric means, linear scale, N=13



Mean and 90% CI for AUC and Cmax ratio of rivaroxaban with fluconazole/alone

Safety

- Was there any death or serious adverse events? No

Conclusion

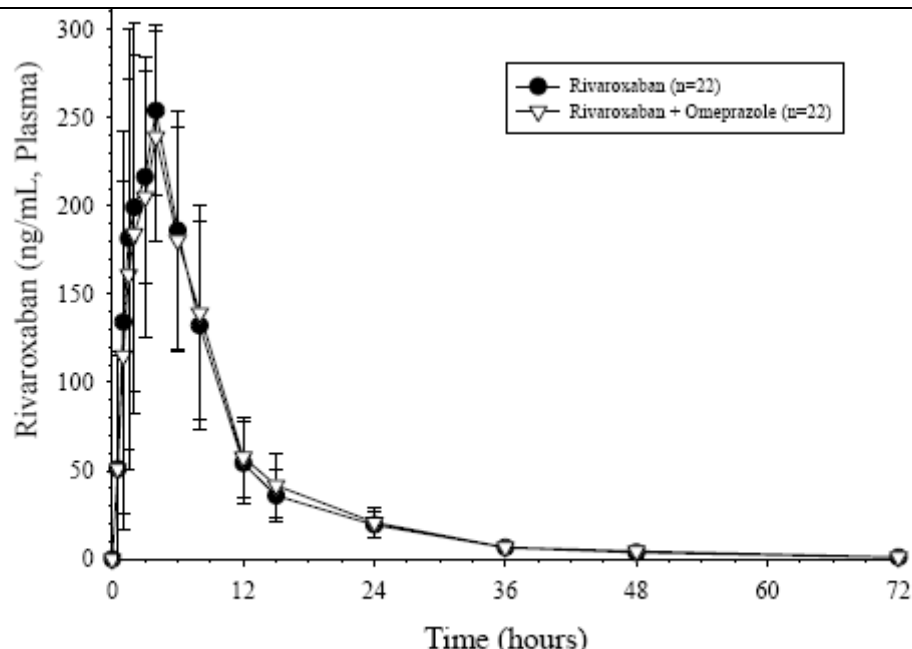
- Fluconazole is a moderate CYP3A4 inhibitor and can also inhibit BCRP
- Rivaroxaban AUC and Cmax had 1.42 and 1.28 fold increase respectively on co-administration with Fluconazole

Comments

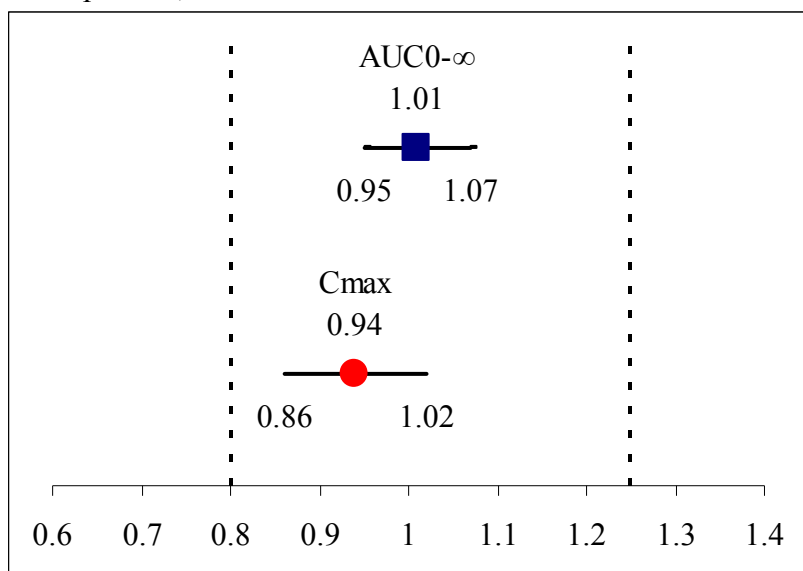
No dose adjustments are warranted for rivaroxaban on co-administration with fluconazole similar to other scenarios such as mild renal impairment which are associated with similar increase in exposure.

5.2 DRUG-DRUG INTERACTION WITH OMEPRAZOLE

Study # 15232		EDR Link: \\cdsesub1\EVSPROD\NDA202439\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\rivarox-afl-1001													
Title	Open-Label, 2-Way Crossover Study in Healthy Subjects to Determine the Effect of Multiple Doses of Omeprazole on the Pharmacokinetics, Pharmacodynamics, and Safety of a Single Dose of Rivaroxaban														
Study Design: Multiple-Dose Omeprazole/Single-Dose Rivaroxaban Randomized Open-Label Cross-Over Healthy Vonuteers															
Rationale: Omeprazole is a proton pump inhibitor, which suppresses gastric acid secretion by inhibition of the H+/K+ adenosine triphosphatase, thereby increasing intragastric pH. Due to omeprazole’s different mechanism of action than ranitidine and Maalox, and because proton pump inhibitors are commonly prescribed to patients with atrial fibrillation and acute coronary syndromes, it was considered important to assess whether or not the use of proton pump inhibitors had the potential to alter the PK of rivaroxaban when co-administered.															
Treatments: Treatment A: single oral 20 mg dose of rivaroxaban administered in the fed state following a standardized breakfast on Day 1 Treatment B: omeprazole 40 mg administered orally once-daily for 5 consecutive days in the fasted state (Day -4 to Day 1) and a single oral dose of 20 mg rivaroxaban, administered in the fed state following a standardized breakfast between 1.5 hours to 2 hours after the fifth omeprazole dose on Day 1. 10 days wash out period <ul style="list-style-type: none">Sampling Times (for rivaroxaban) 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, and 72 hours post rivaroxaban administration in each treatment period															
Analytical Method <table><tr><td>Analyte</td><td>Rivaroxaban</td><td>Omeprazole</td></tr><tr><td>Method</td><td>HPLC-MS/MS</td><td>HPLC-MS/MS</td></tr><tr><td>Matrix</td><td>Plasma</td><td>Plasma</td></tr><tr><td>Range</td><td>0.5 ug/L-500 ug/L</td><td>1.0-1000 ng/mL</td></tr></table>				Analyte	Rivaroxaban	Omeprazole	Method	HPLC-MS/MS	HPLC-MS/MS	Matrix	Plasma	Plasma	Range	0.5 ug/L-500 ug/L	1.0-1000 ng/mL
Analyte	Rivaroxaban	Omeprazole													
Method	HPLC-MS/MS	HPLC-MS/MS													
Matrix	Plasma	Plasma													
Range	0.5 ug/L-500 ug/L	1.0-1000 ng/mL													
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.															
Study Population : <table><tr><td>Randomized/Completed</td><td>22</td></tr><tr><td>Age [Median (range)] years</td><td>30.5 (18-43)</td></tr><tr><td>Male/Female</td><td>7/15</td></tr><tr><td>Race (Caucasian/Black/Asian/Hispanic)</td><td>Caucasians (100%)</td></tr></table>				Randomized/Completed	22	Age [Median (range)] years	30.5 (18-43)	Male/Female	7/15	Race (Caucasian/Black/Asian/Hispanic)	Caucasians (100%)				
Randomized/Completed	22														
Age [Median (range)] years	30.5 (18-43)														
Male/Female	7/15														
Race (Caucasian/Black/Asian/Hispanic)	Caucasians (100%)														
Results															



Mean (SD) plasma concentration-Time profiles following administration of rivaroxaban alone and with omeprazole, N=22



Mean and 90% CI for AUC and Cmax ratio of rivaroxaban with omeprazole/alone

Safety

- Was there any death or serious adverse events? No

Conclusion

No clinically meaningful interaction was observed when rivaroxaban was co-administered with omeprazole. The 90% CIs of the ratios of the geometric means for rivaroxaban C_{max} and AUCs were contained within the bioequivalence criteria of 80% to 125%.

Comments

Omeprazole can be co-administered with rivaroxaban without significant changes to rivaroxaban exposure. No dose adjustments are required.

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/s/

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Concur with reviewers' findings and interpretation



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 202,439/N000

Drug Name: Xarelto (rivaroxaban 20 mg IR tablets)

Indication(s): Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Applicant: Ortho-McNeil-Janssen Pharmaceuticals

Date(s): Received date: Jan 5, 2011
PDUFA date: Nov 5, 2011

Review Priority: Standard

Biometrics Division: Division of Biometrics 1

Statistical Reviewer: John Lawrence, Ph.D.

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Medical Division: Cardiovascular and Renal Products

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Keywords:

active control/non-inferiority, Cox regression, benefit-risk, logrank test, survival analysis

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1. EXECUTIVE SUMMARY

Rivaroxaban was non-inferior to warfarin, as warfarin was used in the study, on the primary endpoint. When analyzing the data up to 2 days after last dose, the confidence interval for the hazard ratio is entirely below 1 (point estimate = 0.79, 95% CI = (0.66, 0.96)). There is a question about whether warfarin was used optimally in the study (the median TTR across sites was 59). For superiority, the ITT analysis is preferred. In the ITT analysis, the confidence interval does not exclude 1 (point estimate = 0.91, 95% CI = (0.77, 1.08)). Rivaroxaban was not superior on all-cause mortality by either the on-treatment or ITT analysis.

2. INTRODUCTION

This is a statistical review for NDA 202439/N000 investigating the efficacy of rivaroxaban as a prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

2.1 Overview

According to the sponsor, rivaroxaban (BAY 59-7939) is a potent and highly selective direct Factor Xa (FXa) inhibitor. Rivaroxaban is currently being co-developed for the prevention and treatment of multiple thrombosis-mediated conditions through a joint collaboration between Bayer Schering Pharma (Bayer) and Johnson & Johnson Pharmaceutical Research and Development, LLC (J&JPRD). Rivaroxaban (10 mg tablet) is currently marketed as Xarelto in over 100 countries worldwide for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

In this submission, the sponsor is seeking approval for rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). According to the sponsor, atrial fibrillation is the most common cardiac arrhythmia of clinical significance and is an important independent risk factor for stroke. It is estimated that AF is currently affecting 6 millions patients in Europe and approximately 2.3 millions in the United States and this patient population is growing rapidly.

Vitamin K antagonists and warfarin in particular have been established as the most effective therapy for the prevention of cardioembolic events in patients with AF. However, the management of warfarin therapy can be challenging. A warfarin dose is generally adjusted to maintain an International Normalized Ratio (INR) between 2.0 and 3.0, inclusive. As an INR increases above this range, the risk of hemorrhagic complications also increases. As an INR decreases below this range, the risk of embolic complications increases. Maintaining INR within the target range is often difficult, requiring frequent monitoring and lab works. Thus, there is an unmet medical need for oral anticoagulants that can be given at fixed doses without the need for laboratory monitoring, that are as effective as warfarin in reducing the risk of stroke and systemic embolism.

The efficacy and safety of rivaroxaban as a prevention of stroke and systemic embolism in patients with non-valvular AF have been studied in two studies. They are listed below.

Table 1. List of all studies included in analysis

Study	Phase	Treatment Period	# of Subjects per Arm	Study Population
ROCKET-AF	Phase 3	Estimated to be 14 – 32 months depending upon reaching the target number of events	~7130 subjects	Non-valvular AF patients
J-ROCKET	Phase 3	Estimated to be 31 months depending upon reach the target number of events	640 subjects	Non-valvular AF patients

Both studies were randomized, double-blind, double-dummy, prospective, multicenter, parallel-group, warfarin-comparator, non-inferiority studies. ROCKET-AF was the pivotal study while J-ROCKET was supposed to be supportive. J-ROCKET was designed primarily to evaluate the safety of rivaroxaban in Japanese patients. It was not supposed to be a stand alone pivotal trial for the U.S. registration. There was no efficacy hypothesis tested in J-ROCKET. The primary safety hypothesis in J-ROCKET was to test whether rivaroxaban was non-inferior to warfarin for major and non-major clinically relevant bleeding.

This review will focus on the efficacy evaluation of ROCKET-AF.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: <\\Cdsub1\evsprod\NDA202439\0000\m5\datasets>. Data for the pivotal study (ROCKET-AF) were submitted in SDTM format and associated SAS programs were also provided for the pivotal study (ROCKET-AF).

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No statistical issues with the data or analysis quality. The data files were in SAS transport format. Some of the files were larger than recommended by the FDA guidance document (50 megabytes).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study ROCKET-AF (also known as JNJ39039039 AFL3001)

ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-center study. Forty-five (45) countries participated in this study and each country was assigned to 1 of 5 regions as follows:

- **Asia Pacific:** Australia, China, Hong Kong, India, Korea, Malaysia, *New Zealand*, Philippines, Singapore, Taiwan, Thailand
- **East Europe:** Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine
- **Latin America:** Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela
- **North America:** Canada, United States
- **West Europe:** Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, *South Africa*, Spain, Sweden, Switzerland, United Kingdom

The study consisted of three periods: a screening period, a double-blind treatment period, and a post treatment observation period (about 30 days in duration). The duration of the double-blind period depended of the time needed to reach 290 primary efficacy endpoint events. The investigated dose was rivaroxaban 20 mg once daily given orally. In patients with creatinine clearance between 30 and 49 mL/min, the dose was decreased to 15 mg once daily. The active control was warfarin with the dose adjusted to the target INR of 2.5 (range between 2 and 3).

The primary efficacy variable was the composite of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation. The primary objective of the study was to show rivaroxaban is non-inferior to warfarin with the non-inferiority margin of 1.46 (The Agency has recommended a non-inferiority of 1.38). If non-inferiority would be achieved, superiority would be tested.

There were two major secondary efficacy variables: 1) the composite of stroke, non-CNS systemic embolism, and vascular death in subjects with non-valvular atrial fibrillation and 2) the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death in subjects with non-valvular atrial fibrillation. In addition, all-cause mortality was also examined. The diagram of multiple testing procedure is as follows:

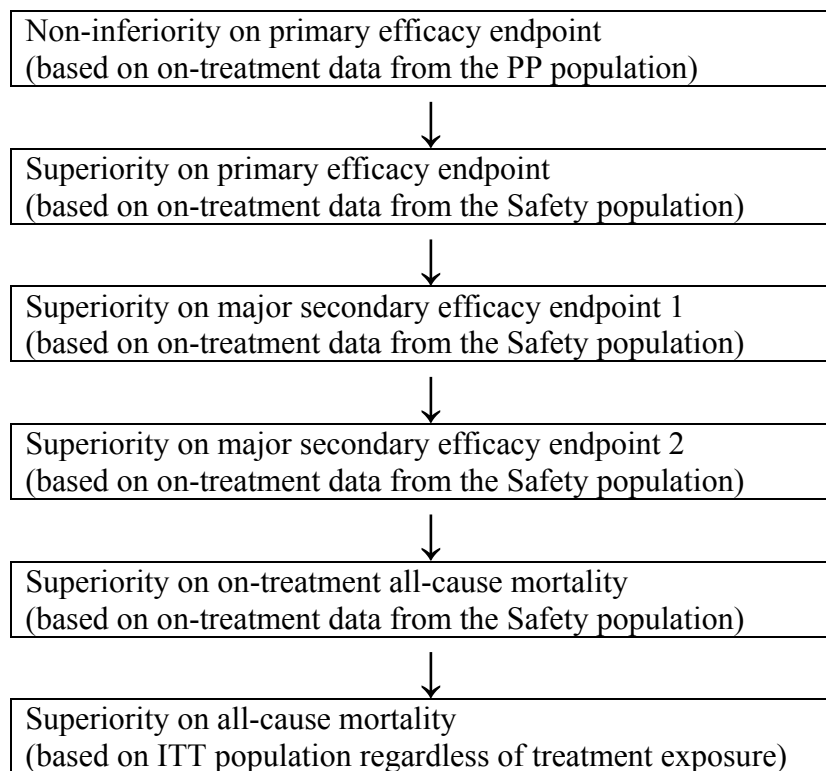


Figure 1. ROCKET-AF: Diagram of multiple testing procedure

The statistical analysis plan (SAP) was originated on Nov 27, 2007, with amendment 1 on June 30, 2009, and amendment 2 on Oct 1, 2010. In the SAP, several analysis sets were stipulated. They are:

- The intent-to-treat (ITT) population which consists of all randomized unique subjects.
- The safety population which consists of all ITT subjects who take at least one dose of study medication after randomization during the double-blind treatment period.
- The per-protocol (PP) population which consists of all ITT subjects excluding those who have specific pre-defined major protocol deviations that occur by the time of enrollment into the study or during the trial.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Study ROCKET-AF

A total of 14,264 subjects were randomized to either rivaroxaban (7,131 subjects) or warfarin (7,133 subjects). This disposition of subjects is summarized in Table 2.

Table 2. ROCKET-AF: Disposition of subjects

	Rivaroxaban (N =7111) n (%)	Warfarin (N =7125) n (%)	Total (N =14236) n (%)
Completed study medication	4591 (64.56)	4657 (65.36)	9248 (64.96)
Early study medication discontinuation	2520 (35.44)	1468 (34.64)	4988 (35.04)
Adverse event	993 (13.96)	919 (12.90)	1912 (13.43)
- Bleeding	304 (4.28)	219 (3.07)	523 (3.67)
- Non-bleeding	689 (9.69)	699 (9.81)	1388 (9.75)
- Missing/Incomplete data	0	1 (0.01)	1 (0.01)
Non-compliant with study medication	134 (1.88)	164 (2.30)	298 (2.90)
Consent withdrawn	671 (9.44)	673 (9.45)	1344 (9.44)
Investigator decision, not protocol-related	191 (2.69)	178 (2.50)	369 (2.59)
Lost to follow-up	6 (0.08)	8 (0.11)	14 (0.10)
Protocol violation	142 (2.00)	124 (1.74)	266 (1.87)
Clinical efficacy endpoint reached	300 (4.22)	332 (4.66)	632 (4.44)
Study terminated by sponsor	82 (1.15)	69 (0.97)	151 (1.06)
Missing/incomplete data	1 (0.01)	1 (0.01)	2 (0.01)

(Source: Clinical Study Report 39039039AFL3001, Table 7, Page 108)

Table 3 summarizes the baseline demographics information of the ITT population. Approximately 60% of the subjects were male. The majority of the patients were white (approximately 83%). Asians accounted for about 13% of the patients. The average age was about 71 years with approximately 45% of the subjects over the age of 75 years. The distribution of the demographics appeared balanced between the two arms.

Table 3. ROCKET-AF: Demographics and Baseline Characteristics (ITT analysis set)

	Rivaroxaban (N = 7131)	Warfarin (N = 7133)	Total (N = 14264)
Sex, n (%)			
Female	2830 (39.69)	2830 (39.67)	5660 (39.68)
Male	4301 (60.31)	4303 (60.33)	8604 (60.32)
Race, n (%)			
White	5922 (83.05)	5957 (83.51)	11879 (83.28)
Black	94 (1.32)	86 (1.21)	180 (1.26)
Asian	897 (12.58)	889 (12.46)	1786 (12.52)
Others	218 (3.06)	201 (2.82)	419 (2.94)
Age			
18 - < 65	1651 (23.15)	1643 (23.03)	3294 (23.09)
65 - < 75	2360 (33.09)	2381 (33.38)	4741 (33.24)
≥ 75	3120 (43.75)	3109 (43.59)	6229 (44.83)
Mean (SD)	71.21 (9.46)	71.18 (9.39)	71.19 (9.42)
Median (Q1, Q3)	73 (65, 78)	73 (65, 78)	73 (65, 78)
Min, Max	25, 97	28, 95	25, 97
Baseline weight (kg)			
N	7129	7132	14261
Mean (SD)	82.07 (19.13)	81.64 (18.92)	81.85 (19.04)
Median (Q1, Q3)	80 (69, 92.6)	80 (69, 92)	80 (69, 92)
Min, Max	36, 209	30, 227	30, 227
Baseline height (cm)			
N	7126	7129	14255
Mean (SD)	167.67 (10.01)	167.73 (10.22)	167.70 (10.12)
Median (Q1, Q3)	168 (160, 175)	168 (160, 175)	168 (160, 175)
Min, Max	120, 207	62.6, 209.6	62.6, 209.6
Baseline BMI (kg/m ²)			
N	7126	7129	14255
Mean (SD)	29.06 (5.70)	28.95 (7.24)	29.00 (6.51)
Median (Q1, Q3)	28.31 (25.15, 32.05)	28.07 (25.06, 31.83)	28.17 (25.10, 31.98)
Min, Max	15.23, 65.17	13.91, 403.19	13.91, 403.19

(Source: Clinical Study Report 39039039AFL3001, Table 8, Pages 109-110)

Table 4 summarizes selected baseline disease characteristics of the ITT population. Two-third of the patients have used vitamin K antagonist previously. The majority of the patients had hypertension at baseline. The majority of the patients had persistent AF type (lasting greater than 7 days at any time). Slightly more than half of the patients had prior stroke, transient ischemic attack, TIA, or non-CNS systemic embolism.

Table 4. ROCKET-AF: Selected Baseline Disease Characteristics (ITT analysis set)

	Rivaroxaban (N = 7131)	Warfarin (N = 7133)	Total (N = 14264)
Congestive heart failure			
No	2663 (37.4%)	2691 (37.7%)	5354 (37.5%)
Yes	4467 (62.7%)	4441 (62.3%)	8908 (62.5%)
Prior VKA used			
No	2688 (37.7%)	2672 (37.5%)	5360 (37.6%)
Yes	4443 (62.31%)	4461 (62.5%)	8904 (62.4%)
Prior Stroke/EM/TIA			
No	3215 (45.1%)	3238 (45.4%)	6453 (45.2%)
Yes	3916 (54.9%)	3895 (54.6%)	7811 (54.8%)
Prior MI			
No	5949 (83.4%)	5847 (82.0%)	11796 (82.7%)
Yes	1182 (16.6%)	1286 (18.0%)	2468 (17.3%)
CHADS2			
1	1 (0.01%)	2 (0.03%)	3 (0.02%)
2	925 (13.0%)	934 (13.1%)	1859 (13.0%)
3	3058 (42.9%)	3158 (44.3%)	6216 (43.6%)
4	2092 (29.3%)	1999 (28.0%)	4091 (28.7%)
5	932 (13.1%)	881 (12.4%)	1813 (12.7%)
6	123 (1.7%)	159 (2.2%)	282 (2.0%)
Hypertension			
No	695 (9.8%)	659 (9.2%)	1354 (9.5%)
Yes	6436 (90.3%)	6474 (90.8%)	12910 (90.5%)
AF type			
Newly diagnosed/onset	100 (1.4%)	102 (1.4%)	202 (1.4%)
Paroxysmal	1245 (17.5%)	1269 (17.8%)	2514 (17.6%)
Persistent	5786 (81.1%)	5762 (80.8%)	11548 (81.0%)

(Source: Clinical Study Report 39039039AFL3001, Tables 8-9, Pages 109-112)

3.2.3 Statistical Methodologies

3.2.3.1 Study ROCKET-AF

The primary efficacy variable is the time from randomization to the first occurrence of the composite of stroke and non-CNS systemic embolism based on the Clinical Endpoint Committee (CEC) adjudication. The primary analysis set is the per-protocol set which consists of all randomized subjects excluding those who have specific pre-defined major protocol deviations that occur by the time of enrollment into the study or during the trial. The analysis window is from the randomization up to the last dose + 2 days. The primary analysis is the Cox proportional hazards model with treatment as a factor. The objective of the primary analysis is to show that rivaroxaban is non-inferior to warfarin. Non-inferiority is achieved when the upper limit of the 2-sided 95% confidence interval of the hazard ratio (rivaroxaban/warfarin) is less than the margin 1.46. It

is noted that the Agency has recommended the margin of 1.38 on several occasions (e.g., Feb 11, 2008 letter to the sponsor).

If non-inferiority is achieved, then the superiority of rivaroxaban over warfarin on the time from randomization to the first occurrence of the composite of stroke and non-CNS systemic embolism would be tested. The analysis model is the Cox proportional hazards model with treatment as a factor. If the upper limit of the 2-sided 95% confidence interval is below 1, then superiority of rivaroxaban over warfarin on the primary efficacy variable is declared.

A number of secondary endpoints were also planned to be tested. The first major secondary endpoint is the time from randomization to the first event of the composite of stroke, non-CNS systemic embolism, and vascular death.

The second major secondary endpoint is the time from randomization to the first event of the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.

3.2.4 Results and Conclusions

3.2.4.1 Study ROCKET-AF: Sponsor's results

The sponsor's overall results on the efficacy evaluation are summarized in Figure 2 and in Table 5. Rivaroxaban was statistically significant to warfarin on the primary efficacy measure (the composite of stroke and non-CNS systemic embolism). Rivaroxaban was statistically significant to warfarin on the first major secondary efficacy measure (the composite of stroke, non-CNS systemic embolism, and vascular death) and on the second major secondary efficacy measure (the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death).

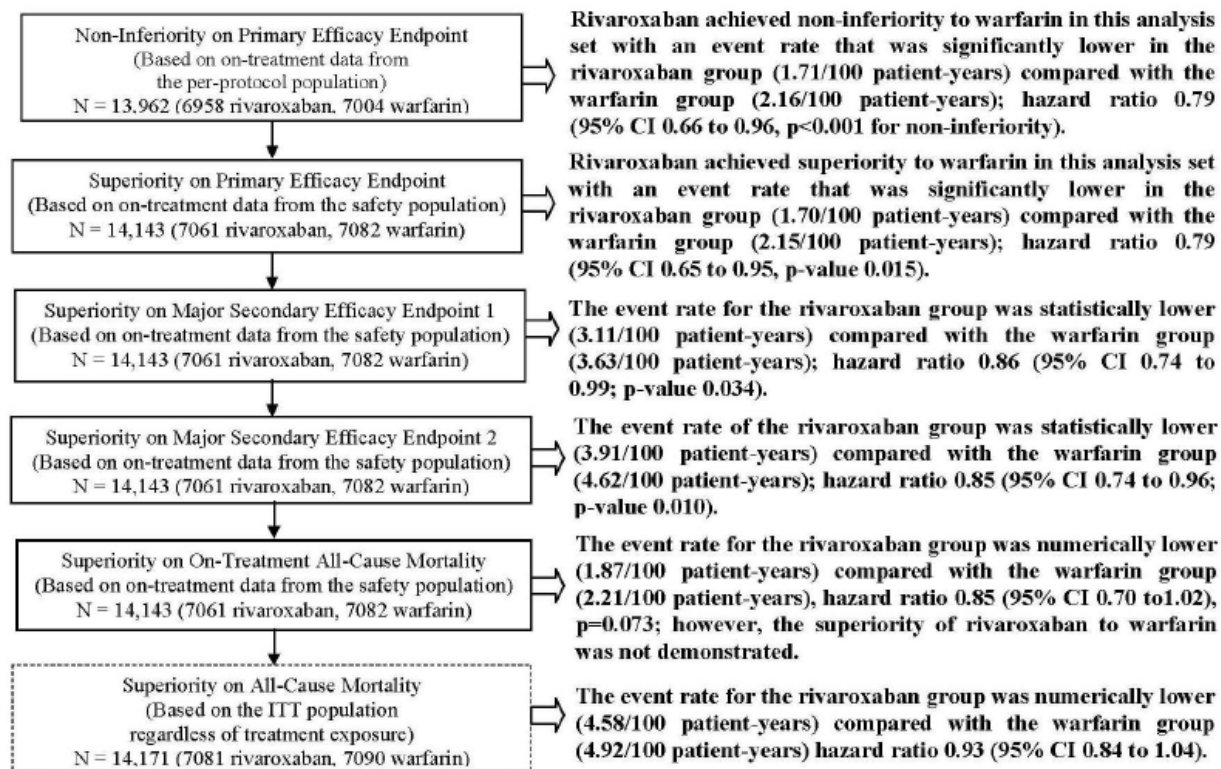


Figure 2. ROCKET-AF: Sponsor's results on prespecified hierarchy of multiple testing procedure for efficacy

(Source: Clinical Study Report 39039039AFL3001, Figure 8, Page 131)

Table 5. ROCKET-AF: Sponsor's efficacy results

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)	P-value
Per protocol – Non-inferiority				
Composite of stroke and non-CNS systemic embolism	241/7004 (3.4%)	188/6958 (2.7%)	0.79 (0.66, 0.96)	<0.001
Safety/on-treatment – Superiority				
- Composite of stroke and non-CNS systemic embolism	243/7082 (3.5%)	189/7061 (2.7%)	0.79 (0.65, 0.96)	0.014
- Composite of stroke, non-CNS embolism, and vascular death	410/7082 (5.8%)	346/7061 (4.9%)	0.86 (0.74, 0.99)	0.033
- Composite of stroke, non-CNS embolism, MI, and vascular death	519/7082 (7.3%)	433/7061 (6.1%)	0.85 (0.74, 0.96)	0.010
- All cause mortality	250/7082 (3.5%)	208/7061 (2.9%)	0.85 (0.70, 1.02)	0.072
ITT/regardless of treatment exposure – Superiority				
- All cause mortality	667/7090 (9.4%)	621/7081 (8.8%)	0.93 (0.84, 1.04)	0.204

(Source: Clinical Study Report: Study ROCKET-AF; Table 25, page 132)

The sponsor performed several sensitivity analyses assessing the robustness of the results.

Kaplan-Meier Curve: Figure 3 captures the Kaplan-Meier curves for the two treatment groups based on the per-protocol analysis set excluding site 042012. The curves showed a separation between the treatment groups from after about one month to the end of the study.

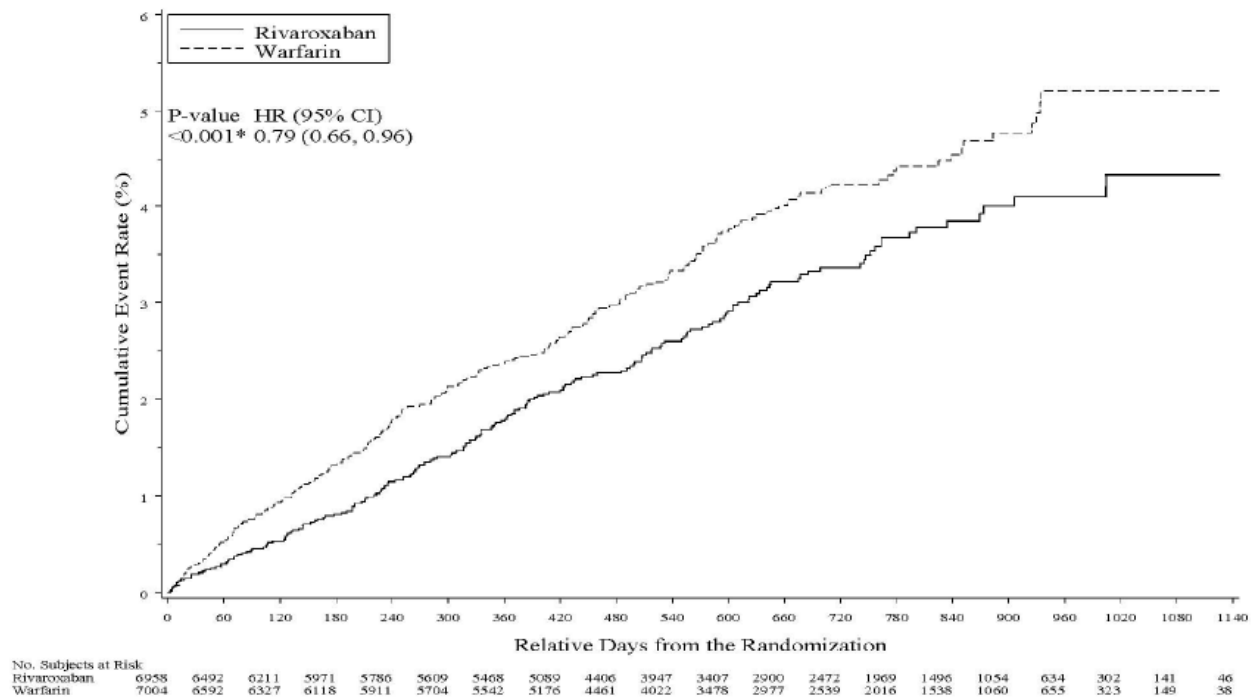


Figure 3. ROCKET-AF: Kaplan-Meier curves for the time from randomization to the first occurrence of the primary efficacy endpoint (adjudicated by CEC) while on treatment (up to last dose + 2 days)
(Source: Clinical Study Report: Study ROCKET-AF; Figure 9, page 133)

3.2.4.2 Study ROCKET-AF: Reviewer’s results

Table 6 summarizes various sensitivity analyses for the primary efficacy endpoint for various analysis sets and various censoring dates. The largest upper bound of the 95% confidence interval was 1.08, far below the 1.38 non-inferiority margin.

Table 6. ROCKET-AF: Reviewer's non-inferiority sensitivity analyses on the composite of stroke and non-CNS systemic embolism

Analysis set	Epoch	Censor at	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)	P-value [#]
Per-protocol ¹ (out.hypo11)	Randomization to first primary efficacy endpoint	last dose + 2 days	241/7004 (3.4%)	188/6958 (2.7%)	0.79 (0.66, 0.96)	0.018
Per-protocol ² (out.hypo12)	Randomization to first primary efficacy endpoint	last dose + 2 days	242/7046 (3.4%)	190/7008 (2.7%)	0.80 (0.66, 0.97)	0.020
ITT ¹ (out.hypo13)	Randomization to first primary efficacy endpoint	last dose + 2 days	243/7090 (3.4%)	189/7081 (2.7%)	0.79 (0.65, 0.95)	0.014
ITT ² (out.hypo15)	Randomization to first primary efficacy endpoint	last dose + 2 days	244/7133 (3.4%)	191/7131 (2.7%)	0.79 (0.66, 0.96)	0.017
Per-protocol ¹ (out.hypo16)	Randomization to first primary efficacy endpoint	last dose + 7 days	253/7004 (3.6%)	219/6958 (3.1%)	0.88 (0.74, 1.06)	0.170
ITT ¹ (out.hypo17)	Randomization to first primary efficacy endpoint	last dose + 7 days	255/7090 (3.6%)	220/7081 (3.1%)	0.88 (0.73, 1.05)	0.147
Per-protocol ¹ (out.hypo18)	Randomization to first primary efficacy endpoint	last dose + 14 days	269/7004 (3.8%)	233/6958 (3.3%)	0.88 (0.74, 1.05)	0.158
ITT ¹ (out.hypo19)	Randomization to first primary efficacy endpoint	last dose + 14 days	271/7090 (3.8%)	235/7081 (3.3%)	0.88 (0.74, 1.05)	0.149
Per-protocol ¹ (out.hypo110)	Randomization to first primary efficacy endpoint	last dose + 30 days	279/7004 (4.0%)	247/6958 (3.5%)	0.90 (0.76, 1.07)	0.229
ITT ¹ (out.hypo111)	Randomization to first primary efficacy endpoint	last dose + 30 days	281/7090 (4.0%)	251/7081 (3.%)	0.91 (0.76, 1.07)	0.251
Per-protocol ¹ (out.hypo117)	From randomization up to follow-up visit	Follow-up visit	283/7004 (4.0%)	252/6958 (3.6%)	0.90 (0.76, 1.07)	0.244
ITT ¹ (out.hypo114)	From randomization up to follow-up visit	Follow-up visit	285/7090 (4.0%)	257/7081 (3.6%)	0.91 (0.77, 1.08)	0.285
Per-protocol ¹ (out.hypo118)	From randomization up to the notification of site date	Site notification	303/7004 (4.3%)	263/6958 (3.8%)	0.87 (0.74, 1.03)	0.101
ITT ¹ (out.hypo115)	From randomization up to the notification of site date	Site notification	306/7090 (4.3%)	269/7081 (3.8%)	0.88 (0.74, 1.03)	0.116
Per-protocol ¹ (out.hypo119)	From randomization up to reference end date**	Reference end date	317/7004 (4.5%)	285/6958 (4.1%)	0.90 (0.77, 1.06)	0.205
ITT ¹ (out.hypo116)	From randomization up to reference end date**	Reference end date	320/7090 (4.5%)	293/7081 (4.1%)	0.91 (0.78, 1.07)	0.263

(Source (in order of analyses): Clinical Study Report: Study ROCKET-AF;

Table 26 (page 136),

Attachment 6.1 (page 818),

[Reviewer's results,](#)

[Reviewer's results,](#)

Table 28 (page140),

[Reviewer's results,](#)

Table 28 (page 140),

[Reviewer's results,](#)

[Reviewer's results,](#)

Table 28 (page 140),

[Reviewer's results,](#)

[Reviewer's results,](#)

Table 28 (page 140),

[Reviewer's results,](#)

Table 28 (page 140))

Table 28 (page 140))

¹ Excluding site 042012 due to non-compliance

² Including site 042012

** Reference end date is the last date of all study-related visits (scheduled and unscheduled)

Log-rank p-value for H₀: HR = 1 (superior)

Proportional hazard assumption: The Cox model relies on the proportional hazard assumption. To examine this assumption, a $\log(-\log(\text{survival}))$ curve was produced. Figure 4 plots the $\log(-\log(\text{survival}(\text{month})))$ versus $\log(\text{month})$. The proportional hazard assumption would be reasonable in the case where the two curves are parallel. Figure 4 suggests that the two lines were not parallel. They appear to be farthest apart around month 6 ($\log 6 \approx 1.8$) and then seem to get closer together for later time points. The proportional hazard assumption appeared violated over all. Thus, the hazard ratio seen in Table 4 can be interpreted as an average of the hazard ratios across time. Despite the possible violation of the proportional hazard assumption, p-values from the likelihood ratio test ($p = 0.018$), the score test ($p = 0.018$), and the Wald test ($p = 0.018$) were consistent with the log-rank test p-value ($p = 0.018$).

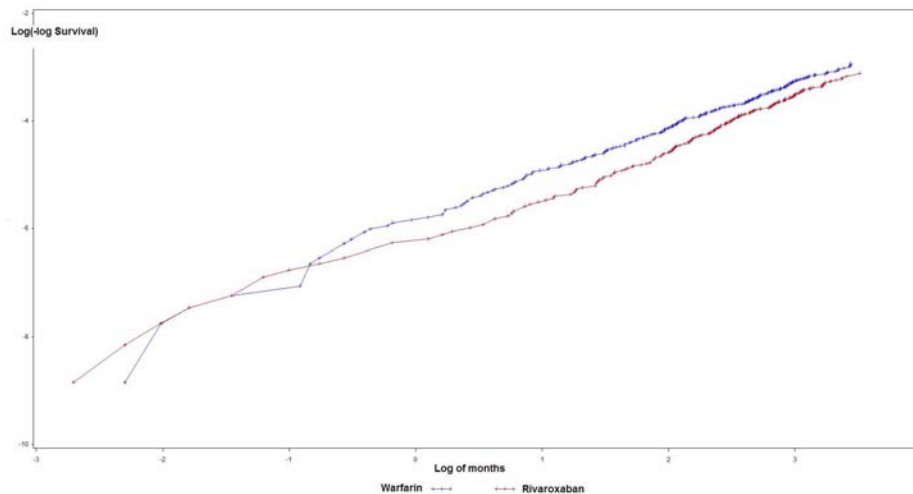


Figure 4. ROCKET-AF: Log(-Log(Survival)) curve for the primary efficacy endpoint

Another way of looking at the proportional hazards assumption is to estimate the hazard functions directly. I split the time into intervals of 6 months. The last time interval is larger than 6 months and includes all events after month 24. I counted the number of events in each group in each time window and the number of patient years of exposure in that time window. The estimated hazard function for each time period within each treatment arm is $\{\# \text{ events}\} / \{\# \text{ patient years of exposure}\}$. Events are counted up to last study dose plus day 2 as in the primary analysis. Similarly, I estimated the hazard function on each day (similar to above, but time period is one day). I then used locally polynomial regression to fit a curve through those estimates for each day. It weights each day according to the amount of information and then combines the information from nearby days to get a better estimate of the hazard function each day. The points in Figure 5 are the points from the estimated hazard functions over 6 month time periods. The smooth curves are

from the estimated hazard functions for each day. The figure suggests that the risk goes down over time (in both groups) and that there is a larger difference between groups in the hazard functions in the earlier time points.

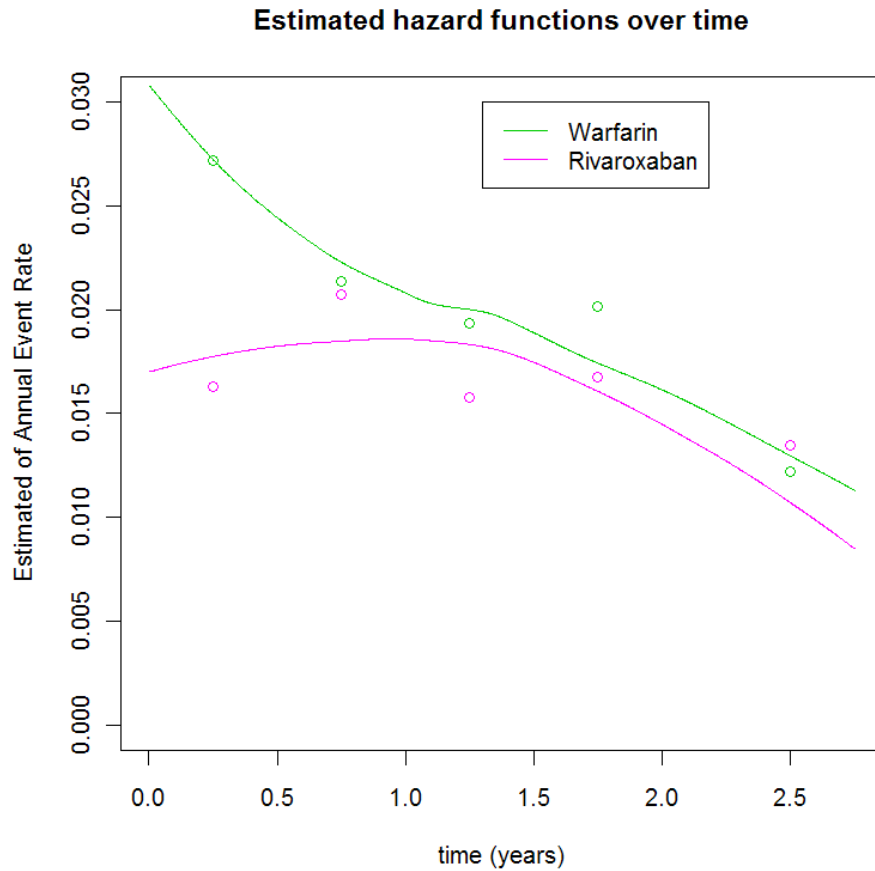


Figure 5. Estimated hazard functions for the primary efficacy endpoint

Distribution of time to censoring: The distribution of the time to censoring for the primary efficacy endpoint appeared balanced between warfarin and rivaroxaban, as shown in Table 7.

Table 7. ROCKET-AF: Distribution of time to censoring for the primary efficacy endpoint (safety sample, excluding site 042012)

	Warfarin N = 7082	Rivaroxaban N = 7061
Primary events	243	189
Max	1265	1265
99 th %tile	1117	1120
95 th	1015	1011
90 th	957	956
75 th	814	813
50 th	612	598
Mean	592.3	582.3
25 th	421	409.5
10 th	141	113
5 th	51	37
1 st	9	7
Min	0	2

(Source: Reviewer's results)

Time in Therapeutic Range The efficacy of warfarin is highly dependent on the time in therapeutic range (TTR). For each subject in the warfarin arm, the TTR is defined as the proportion of time the INR is between 2 and 3 (excluding time periods where the subject was not taking warfarin). For each site, the site level TTR is the average of the TTR for the subjects in that site. Figure 6 shows the distribution of TTR on the subject level and on the site level. The median TTR for all subjects was 58 and the median TTR for all sites was 59.

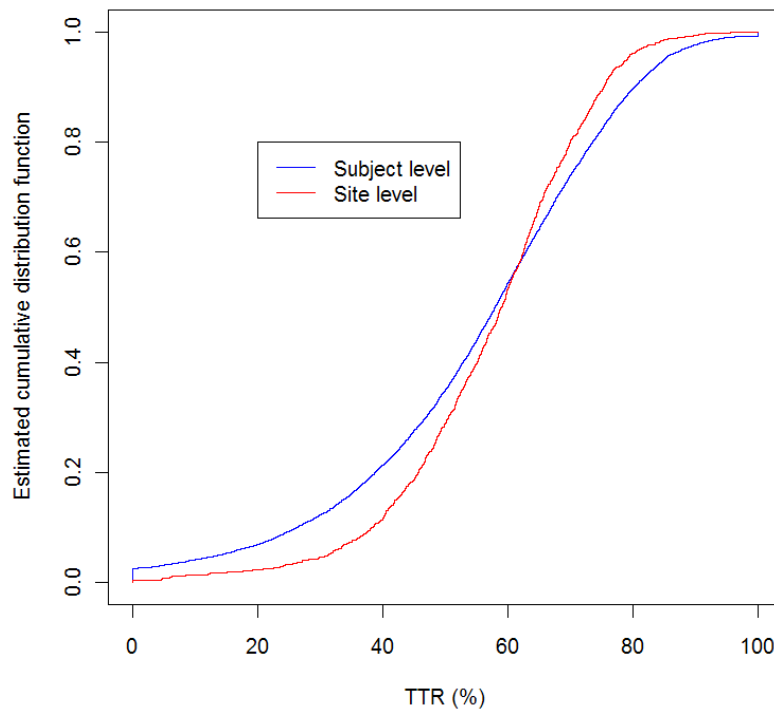


Figure 6. Distribution of TTR across subjects and sites

Figure 7 shows the estimated hazard ratio for sites with TTR above different cutoff values. The x-axis shows what percent of the total subjects are excluded (from sites with TTR lower than the cutoff value). The upper and lower curves are the upper and lower bound of the pointwise 95% confidence intervals. The curves start using all the data, which is the same point estimate and confidence interval as for the primary endpoint, i.e. 0.79 and (0.66, 0.96). The curves at the far right side of the figure are based on a small amount of data (less than 20% of the subjects), but the curves appear to show the point estimate is closer to 1, and in some cases larger than 1 when including sites with high TTR (e.g. greater than 70%).

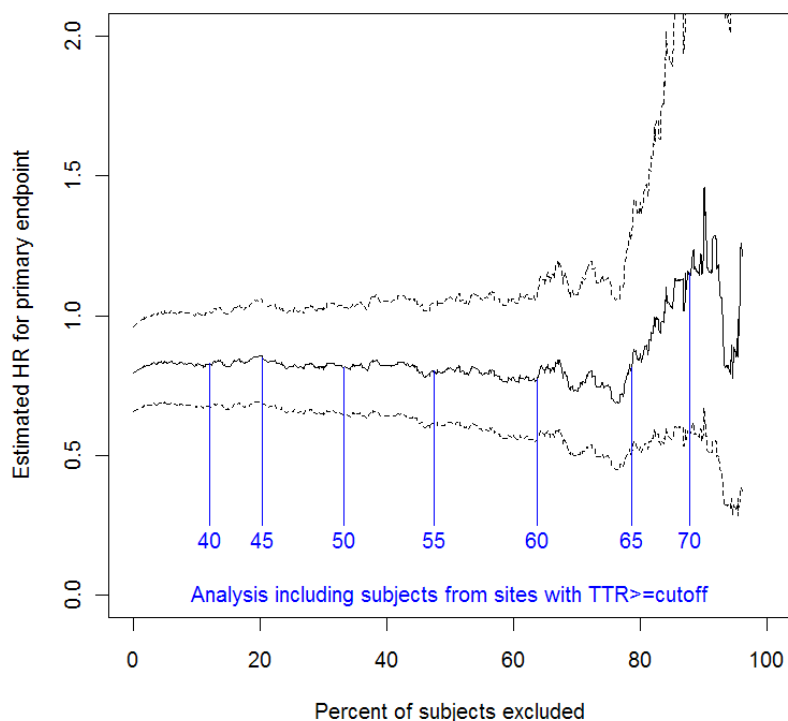


Figure 7. Estimated hazard ratio for primary endpoint among sites with TTR above different cutoff levels.

3.3 Evaluation of Safety

A safety evaluation was not performed. Please refer to the clinical review for the safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study ROCKET-AF

4.1.1.1 Gender

Male patients in this study accounted for about 60% of the sample. Table 8 summarizes efficacy results by sex for the primary and key secondary efficacy measures. It appears that the efficacy was consistent for both sexes.

Table 8. ROCKET-AF: Reviewer's efficacy results by sex

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
Male			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	135/4236 (3.2%)	102/4201 (2.4%)	0.78 (0.61, 1.01)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	136/4283 (3.2%)	103/4270 (2.4%)	0.78 (0.60, 1.01)
- Composite of stroke, non-CNS embolism, and vascular death	265/4283 (6.2%)	221/4270 (5.2%)	0.86 (0.72, 1.03)
- Composite of stroke, non-CNS embolism, MI, and vascular death	341/4283 (8.0%)	282/4270 (6.6%)	0.85 (0.73, 1.00)
Female			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	106/2768 (3.8%)	86/2757 (3.1%)	0.80 (0.60, 1.07)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	107/2799 (3.8%)	86/2791 (3.1%)	0.80 (0.60, 1.06)
- Composite of stroke, non-CNS embolism, and vascular death	145/2799 (5.2%)	125/2791 (4.5%)	0.85 (0.67, 1.08)
- Composite of stroke, non-CNS embolism, MI, and vascular death	178/2799 (6.4%)	151/2791 (5.4%)	0.84 (0.68, 1.04)

(Source: FDA analysis)

4.1.1.2 Race

White patients accounted for about 83% of the sample. For this analysis, race is dichotomized into white versus non-white (other races). Table 9 summarizes the efficacy results by race. Numerical improvements were observed in both white and non-white patients.

Table 9. ROCKET-AF: Reviewer's efficacy results by race

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
White			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	192/5846 (3.3%)	151/5772 (2.6%)	0.81 (0.65, 1.00)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	194/5909 (3.3%)	151/5856 (2.6%)	0.80 (0.64, 0.99)
- Composite of stroke, non-CNS embolism, and vascular death	335/5909 (5.7%)	274/5856 (4.7%)	0.84 (0.71, 0.98)
- Composite of stroke, non-CNS embolism, MI, and vascular death	429/5909 (7.3%)	344/5856 (5.9%)	0.82 (0.71, 0.94)
Others			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	49/1158 (4.2%)	37/1186 (3.1%)	0.73 (0.48, 1.12)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	49/1173 (4.2%)	38/1205 (3.2%)	0.75 (0.49, 1.15)
- Composite of stroke, non-CNS embolism, and vascular death	75/1173 (6.4%)	72/1205 (6.0%)	0.93 (0.67, 1.29)
- Composite of stroke, non-CNS embolism, MI, and vascular death	90/1173 (7.7%)	89/1205 (7.4%)	0.96 (0.72, 1.29)

(Source: FDA analysis)

4.1.1.3 Age

Age was grouped into less than 65 years, 65 to 75 years, and greater than 76 years. Table 10 summarizes the efficacy results by age. It appears that rivaroxaban was not efficacious against warfarin for patients < 65 years of age.

Table 10. ROCKET-AF: Reviewer's efficacy results by age

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
Age < 65 years			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	41/1614 (2.5%)	43/1617 (2.7%)	1.06 (0.69, 1.63)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	42/1636 (2.6%)	43/1642 (2.6%)	1.04 (0.68, 1.58)
- Composite of stroke, non-CNS embolism, and vascular death	81/1636 (5.0%)	75/1642 (4.6%)	0.94 (0.68, 1.28)
- Composite of stroke, non-CNS embolism, MI, and vascular death	99/1636 (6.1%)	91/1642 (5.5%)	0.93 (0.70, 1.24)
Age in [65 – 75] years			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	98/2742 (3.6%)	76/2729 (2.8%)	0.79 (0.58, 1.06)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	98/2768 (3.5%)	77/2767 (2.8%)	0.79 (0.59, 1.07)
- Composite of stroke, non-CNS embolism, and vascular death	161/2768 (5.8%)	140/2767 (5.1%)	0.88 (0.70, 1.10)
- Composite of stroke, non-CNS embolism, MI, and vascular death	199/2768 (7.2%)	173/2767 (6.3%)	0.88 (0.71, 1.07)
Age > 76 years			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	102/2648 (3.9%)	69/2612 (2.6%)	0.69 (0.51, 0.93)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	103/2678 (3.8%)	69/2652 (2.6%)	0.68 (0.50, 0.92)
- Composite of stroke, non-CNS embolism, and vascular death	168/2678 (6.3%)	131/2652 (4.9%)	0.79 (0.63, 0.99)
- Composite of stroke, non-CNS embolism, MI, and vascular death	221/2678 (8.3%)	169/2652 (6.4%)	0.78 (0.63, 0.95)

(Source: FDA analysis)

4.1.1.4 Geographical Region

Table 11 summarizes the efficacy by U.S. versus non-U.S. Greater treatment effects were observed in U.S. patients versus non-U.S. patients.

Table 11. ROCKET-AF: Reviewer's efficacy results by U.S. versus non-U.S.

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
United States (U.S.) sites			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	29/956 (3.0%)	15/950 (1.6%)	0.54 (0.29, 1.01)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	29/964 (3.0%)	15/962 (1.6%)	0.54 (0.29, 1.01)
- Composite of stroke, non-CNS embolism, and vascular death	46/964 (4.8%)	30/962 (3.1%)	0.68 (0.43, 1.08)
- Composite of stroke, non-CNS embolism, MI, and vascular death	70/964 (7.3%)	50/962 (5.2%)	0.74 (0.51, 1.06)
Non-U.S. sites			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	212/6048 (3.5%)	173/6008 (2.9%)	0.83 (0.68, 1.01)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	214/6118 (3.5%)	174/6099 (2.9%)	0.82 (0.67, 1.00)
- Composite of stroke, non-CNS embolism, and vascular death	364/6118 (5.9%)	316/6099 (5.2%)	0.88 (0.75, 1.02)
- Composite of stroke, non-CNS embolism, MI, and vascular death	449/6118 (7.3%)	383/6099 (6.3%)	0.86 (0.75, 0.99)

(Source: FDA analysis)

Figure 8 presents the primary efficacy and principal safety measures by region and country. The primary efficacy measure is the composite of CEC-adjudicated stroke and non-CNS embolism. The principal safety measure is the composite of all CEC-adjudicated major and non-major clinically relevant bleeding events. In the figure, the average percentage of INR in [2-3] range as well as the average percentages of INR higher and lower than the [2-3] range are also presented for warfarin patients. The averages are over all patients in a particular group. The overall time in therapeutic range was 48.6% and for U.S. patients was 56%. The efficacy hazard ratio for the U.S. patients was 0.54 and the principal safety hazard ratio was 1.28.

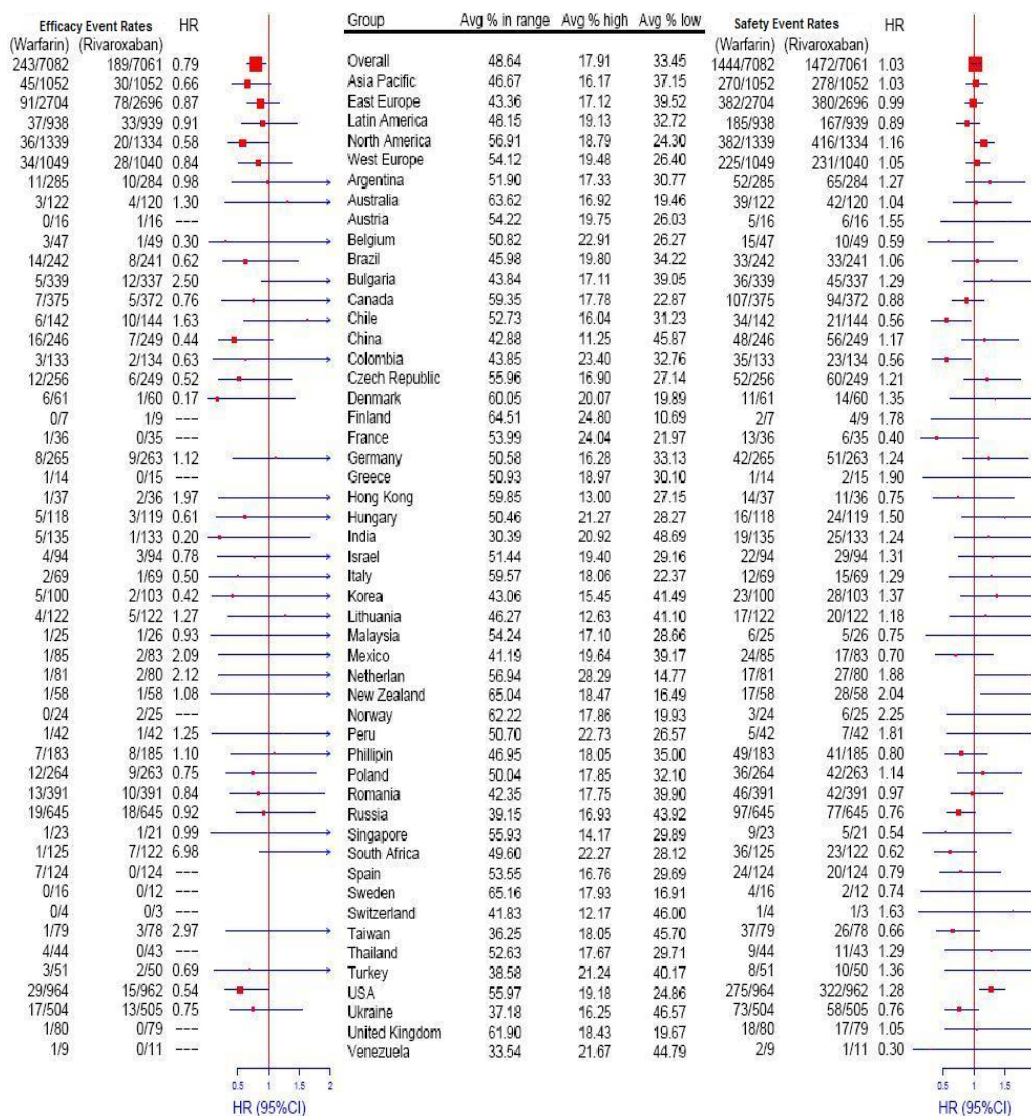


Figure 8. ROCKET-AF: Efficacy and Safety Results by regions/countries

* Efficacy is based on the primary efficacy endpoint (composite of strokes and non-CNS embolism, CEC-adjudicated), from randomization to the first primary efficacy endpoint (or last dose + 2 days) in the safety analysis set (excluding site 042012)

* Safety is based on the principal safety endpoint (composite of all major and non-major clinically relevant bleeding events, CEC-adjudicated), from first dose to first occurrence of principal safety endpoint (or last dose + 2 days), in the safety analysis set (excluding site 042012).

* Avg % in range, Avg % high, and Avg % low are the average percentages of INR in, higher, and lower than [2-3] INR range for patients in warfarin arm.

4.2 Other Special/Subgroup Populations

4.2.1 Study ROCKET-AF

4.2.1.1 Baseline CHADS2 score

Table 12. ROCKET-AF: Reviewer's efficacy results by baseline CHADS2 score

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
CHADS2 in (0, 1, 2)			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	24/924 (2.6%)	20/900 (2.2%)	0.89 (0.49, 1.62)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	24/933 (2.6%)	21/923 (2.3%)	0.92 (0.51, 1.65)
- Composite of stroke, non-CNS embolism, and vascular death			
- Composite of stroke, non-CNS embolism, MI, and vascular death			
CHADS2 in (3, 4)			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	174/5060 (3.4%)	127/5030 (2.5%)	0.74 (0.59, 0.93)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	175/5119 (3.4%)	127/5098 (2.5%)	0.73 (0.58, 0.92)
- Composite of stroke, non-CNS embolism, and vascular death			
- Composite of stroke, non-CNS embolism, MI, and vascular death			
CHADS2 in (5, 6)			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	43/1020 (4.2%)	41/1028 (4.0%)	0.96 (0.63, 1.48)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	44/1030 (4.3%)	41/1040 (3.9%)	0.94 (0.61, 1.44)
- Composite of stroke, non-CNS embolism, and vascular death			
- Composite of stroke, non-CNS embolism, MI, and vascular death			

(Source: FDA analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

One of the issues in any active control study with a non-inferiority design is whether the active control was used correctly. If it was not used correctly, the constancy assumption may be in doubt. It need not have been used optimally, but at a minimum should be used in a way comparably to how it was used in the historical studies used as the basis of the non-inferiority margin. In this case, the historical studies (comparing warfarin to placebo) are fairly old and it is difficult to say whether warfarin was used in this study as well as it was in those studies. Other issues that might affect the constancy assumption include the populations studied and the background therapy. It is difficult to compare those factors in the current study to the historical studies. Some statistical analyses can help with looking into these issues, but ultimately it is up to the clinical reviewers to decide.

Another important issue for active control noninferiority studies is the definition of the analysis population. Some would say that for the noninferiority analysis, the on-treatment or per-protocol population may be the more important analysis, but others would say the ITT is still important. If there were big difference in results for the two, it would be necessary to look into the reasons for that. However, there was not a big difference in this application as far as testing noninferiority is concerned. For testing superiority, the ITT analysis is preferred.

5.2 Conclusions and Recommendations

Rivaroxaban was non-inferior to warfarin, as warfarin was used in the study, on the primary endpoint. When analyzing the data up to 2 days after last dose, the confidence interval for the hazard ratio is entirely below 1 (point estimate = 0.79, 95% CI = (0.66, 0.96)). There is a question about whether warfarin was used optimally in the study (the median TTR across sites was 59). For superiority, the ITT analysis is preferred. In the ITT analysis, the confidence interval does not exclude 1 (point estimate = 0.91, 95% CI = (0.77, 1.08)). Rivaroxaban was not superior on all-cause mortality by either the on-treatment or ITT analysis.

CHECK LIST

Number of Pivotal Studies: 1.

Trial Specification

Specify for each trial: ROCKET-AF

Protocol Number (s): 39039039AFL3001

Protocol Title (optional): A prospective, randomized, double-blind, double-dummy, parallel-group, multicenter, event-driven, non-inferiority study comparing the efficacy and safety of once daily oral rivaroxaban (BAY 59-7939) with adjusted-dose oral warfarin for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation.

Phase: 3

Control: Active Control

Blinding: Double-Blind

Number of Centers: 1172

Region(s) (Country): 45 countries

- Asia Pacific: Australia, China, Hong Kong, India, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand
- East Europe: Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine
- Latin America: Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela
- North America: Canada, United States
- West Europe: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, United Kingdom

Duration: Event-driven trial, initiated on Dec 18, 2006 and completed on Sept 7, 2010

Treatment Arms: Rivaroxaban

Treatment Schedule: 20 mg orally once daily or warfarin (orally once daily, titrated to the INR of 2.5 [range 2.0 to 3.0, inclusive])

Randomization: Yes

Ratio: 1:1

Method of Randomization: stratification

If stratified, then the Stratification Factors: country, prior VKA use, and history of prior stroke, TIA, or non-CNS systemic embolism

Primary Endpoint: Time from randomization to the first occurrence of stroke or non-CNS systemic embolism

Primary Analysis Population: Per-protocol

Statistical Design: Non-Inferiority/Superiority

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data?

Margin = 1.38

%Retained = 50%

Adaptive Design: No
Primary Statistical Methodology: Cox proportional hazard model
Interim Analysis: Yes (mainly for futility consideration)

If yes:

No. of Times: 1 (at midpoint)
Method: Cox model
 α Adjustment: Yes
 α Spending Function: Haybittle-Peto
DSMB: Yes

Sample Size: 405 primary efficacy events (14,000 randomized patients)

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes/No

Statistic = log-rank

Power= 95%

Δ = to rule out the non-inferiority margin of 1.46

α = 0.05

- Was there an Alternative Analysis in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation: Several sensitivity analyses are planned
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the Covariates pre-specified in the protocol? No.
- Did the Applicant perform Sensitivity Analyses? Yes.
- How were the Missing Data handled? Subjects were censored when lost to followup or 2 days after last study dose administered. Censoring was assumed non-informative in the log-rank test.
- Was there a Multiplicity involved? Yes
If yes,
Multiple Arms (Yes/No)? No.
Multiple Endpoints (Yes/No)? Yes.
Which method was used to control for type I error? Endpoints were tested sequentially in a pre-specified order.
- Multiple Secondary Endpoints: Are they being included in the label? If yes, method to control for type I error: Yes. Sequential testing.
Were Subgroup Analyses Performed (Yes/No)? Yes.
- Were there any Discrepancies between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes.

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/s/

JOHN P LAWRENCE
07/28/2011

HSIEN MING J J HUNG
07/28/2011
concur