1. Introduction

Rivaroxaban is an orally available Factor Xa inhibitor with a proposed indication for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Rivaroxaban (10 mg once daily) is currently approved for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery. It is also being developed for other thrombosis-mediated conditions, including secondary prevention of cardiovascular events after an acute coronary syndrome.

The CMC, pharmacology-toxicology and clinical pharmacology reviewers did not identify any issues that would preclude approval of the proposed doses (20 mg once daily and 15 mg once daily in patients with CrCl 30 to < 50 mL/min) in patients with atrial fibrillation. The clinical and statistical reviewers do not dispute the findings reported by the applicant for any of the critical analyses in the pivotal trial, an international, randomized, double-blind, double-dummy, event-driven, non-inferiority study comparing rivaroxaban to warfarin. The primary endpoint of this trial was a composite endpoint of stroke and systemic embolism and it is recognized that this trial established rivaroxaban’s non-inferiority to warfarin as it was used in the study. At issue, however, is how well the active comparator, warfarin, was managed in the trial and how to interpret the study’s findings in light of warfarin’s management. This has also fueled discussion regarding what the regulatory standard should be for the approval of an anticoagulant in this indication. Other important issues identified by the reviewers include the following:

- strokes occurring in patients transitioned off of rivaroxaban at the end of the study
- data supporting the dose and dosing regimen studied

I did not identify any other major issues in my review of the NDA, hence this memorandum will focus on these same topics.
2. Background

Atrial fibrillation is common (estimates indicate ~ 2.5 million Americans) and embolic events, primarily strokes, are an important complication of this condition. Two agents, warfarin (a vitamin K antagonist) and dabigatran (a direct thrombin inhibitor), are currently approved in the United States for the reduction of stroke and systemic embolism in patients with atrial fibrillation.

Warfarin’s efficacy in preventing ischemic strokes in patients with atrial fibrillation was established via randomized controlled trials conducted almost 20 years ago. Dabigatran (150 mg dose) was approved in October 2010 based on the findings in RE-LY, a non-inferiority study of open-label warfarin administration and blinded administration of two doses of dabigatran (110 and 150 mg). In this trial, dabigatran 150 mg demonstrated statistical superiority to warfarin on the primary endpoint, a composite of stroke and systemic embolism (HR of 0.66; 95% CI 0.53 to 0.82; p<0.003 for superiority). At this dose, favorable effects were seen on both ischemic strokes (the types of strokes prevented by warfarin) and also hemorrhagic strokes (an unintended and adverse effect of anticoagulant therapy). For ischemic strokes, the HR for dabigatran 150 mg vs. warfarin was 0.75 (95% CI 0.58, 0.97); for hemorrhagic strokes it was 0.26 (95% CI 0.14, 0.49). Importantly, these finding were seen in the context of what would be widely accepted as reasonable warfarin management (and perhaps what many would consider “well-administered” warfarin).

There has been some discussion about what, if any, precedent dabigatran has set for the approval of drugs in this therapeutic area in 2011 and beyond. This issue was broached by Drs. Dunnmon and Rose in their Clinical Review and at the Advisory Committee Meeting; it is also addressed in my review.

3. CMC/Device

There are no unresolved CMC issues at this time. Rivaroxaban is currently approved at a 10 mg once daily dose for the DVT prophylaxis indication and Dr. Chu’s review focused on CMC data pertaining to the drug product for the atrial fibrillation indication- a film coated immediate release tablet available in a 15-mg and 20-mg strength. Based on her review, an information request was sent to the applicant (June 12, 2011); according to Dr. Chu, the issues raised in this letter have been adequately addressed by the Applicant. From a biopharmaceutics standpoint (review conducted by Dr. Ghosh), the proposed dissolution method and acceptance criterion are acceptable and the provided dissolution data support the approval of the scale-up from pilot to commercial scale manufacturing at the proposed site.

**Drug substance:** Rivaroxaban is a synthetic small molecule with a molecular weight of 435.89. The drug substance is a non-hygroscopic powder and, based on the BCS classification system, is categorized as a class 2 compound with low solubility and high permeability. It has a single stereogenic center and is synthesized as a single enantiomer. The drug substance is micronized in order to improve bioavailability.
Drug product: According to Dr. Chu’s review, the excipients used in the core tablet formulation are standard compendial excipients. Standard specifications for solid oral dosage forms have been proposed. No new degradation products have been observed in the drug product. Primary stability studies have been performed and based on these studies, an expiration dating period of 36 months is granted for the bottle and blister configuration. The release specifications were deemed to be adequate and the release testing results conform to these specifications.

Facilities review/inspection: Pre-approval inspections for the drug substance, drug product and packaging sites were not felt to be necessary (based on prior inspections) and were not conducted.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved pharmacology/toxicology issues. Dr. Harlow’s review focused on new data/data not previously reviewed for the DVT prophylaxis indication.

General nonclinical pharmacology/toxicology considerations: Rivaroxaban reversibly binds to and inhibits the activity of Factor Xa, a coagulation protease that converts prothrombin to thrombin; thrombin converts fibrinogen to fibrin resulting in formation of a blood clot. The main toxicity seen in animals was related to rivaroxaban’s therapeutic effect/pharmacological activity (e.g. bleeding and prolongation of coagulation parameters). According to Dr. Harlow’s review, a satisfactory safety margin was demonstrated for other observed toxicities.

Carcinogenicity: The Executive Carcinogenicity Assessment Committee concluded that the carcinogenicity studies were adequate and that no clear drug-related neoplasms were seen.

Reproductive toxicology: Fertility, early embryo, embryo-fetal development and pre-/postnatal development studies were felt to be adequate. No increased risk of structural malformations or impairment of fertility was seen. Rivaroxaban crosses the placenta and maternal hemorrhagic complications were seen in rats while increased post-implantation loss occurred in rabbits. Fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) were seen in rabbits and rats at doses corresponding to ~4 and 14 (decrease in fetal body weight) times, respectively, the human exposure of unbound drug at the 20 mg dose (based on AUC comparisons). Rivaroxaban/its metabolites is excreted into the milk of rats.

Juvenile rat studies: Dr. Harlow reviewed two juvenile rat studies. These studies did not reveal any toxicities not previously observed in adult animals, however the toxicokinetic data indicated a 6 to 10-fold higher exposure for rivaroxaban between postnatal days 10 and 15 than on postnatal day 31 or 86.

Other notable issues: In the rat carcinogenicity study, a greater incidence of valvular fibrosis was seen in the hearts of male and female rats treated with rivaroxaban compared with concurrent controls. However, the incidence of valvular fibrosis in these controls was at or below the range seen in two previous carcinogenicity studies conducted by the applicant. Consequently, the difference between treatment arms was attributed to inconsistency of
histopathological sampling of heart valves leading to variability in histopathological diagnosis. Furthermore, in all but one rat, chronic cardiomyopathy, a common age-related finding in the rat, accompanied the valvular findings.

As noted in the Clinical Review, examination of the data from ROCKET did not reveal any clear clinical signal of valvular fibrosis. Admittedly, detecting a signal in the clinical setting would be difficult given the patient population studied and the absence of a prespecified plan to systematically and carefully collect data that could address this issue. Nonetheless, I don’t think that the data, in its totality, suggest valvular toxicity; the primary reviewers appear to have reached a similar conclusion.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical pharmacology review conducted by Drs. Sabarinath and McDowell focused on clinical studies specific to the atrial fibrillation indication and studies not previously reviewed for the DVT indication. Selected PK and PD drug attributes are discussed below, along with the data supporting the proposed dose and dosing regimen; Office of Clinical Pharmacology (OCP) recommendations for transitioning patients from rivaroxaban to warfarin are discussed in Section 12 Risk Benefit Assessment.

Selected PK attributes and their implications for labeling for the atrial fibrillation indication:

- A reduction in bioavailability is seen at higher tablet strengths. Absolute bioavailability of the 20 mg dose is ~66% in the fasted condition; food increases the AUC and Cmax of the 20 mg dose by ~39 and ~76%, respectively. In the pivotal efficacy study, subjects were instructed to take rivaroxaban in the evening with food. OCP is also recommending that rivaroxaban be taken with the evening meal and I think this is sensible. There has been some discussion about whether or not the label should specify administration with the evening meal as opposed to the largest meal of the day. The advantage to specifying the evening meal is that it better ensures regular administration with respect to the last dose of rivaroxaban (i.e., dosing every ~24 hours). As previously noted, it also reflects how rivaroxaban was administered in the pivotal efficacy study and hence is an approach that is supported by the clinical trial data.

- Almost 50% of an oral dose of rivaroxaban undergoes hepatic metabolism, predominately by CYP3A, CYP2J2 and hydrolysis. OCP is recommending that patients with moderate hepatic impairment (Child-Pugh B) receive 10 mg once daily based on a dedicated hepatic impairment study and exposure matching. I have concerns about this recommendation for safety reasons. Bleeding is an important adverse effect of this class of agents and as described later in this review, serious gastrointestinal bleeding was more common in rivaroxaban compared to warfarin treated subjects in the applicant’s phase 3 trial. Abnormalities in coagulation are seen in patients with hepatic impairment and cirrhosis; bleeding is also an important complication of chronic liver disease. Furthermore, at this time there is no established antidote for rivaroxaban’s anticoagulant effect, or proven means to effectively monitor or adjust therapy in individual patients. In the absence of clinical trial data that can speak to the risk of bleeding in patients with moderate hepatic impairment/Child-Pugh B, I do not favor providing dosing recommendations for this population.
Approximately 36% of an oral dose is eliminated renally (by active tubular secretion and glomerular filtration) as unchanged drug. The pivotal trial allowed enrollment of patients with a CrCl ≥30 mL/min; for patients with a CrCl<50 mL/min at enrollment a reduced dose of 15 mg once daily was used. OCP is recommending that patients with a CrCl of 30- 49 mL/min receive 15 mg rivaroxaban once daily. In addition, based on modeling, OCP is recommending that patients with severe renal impairment (CrCl of 15-29) receive 15 mg rivaroxaban once daily.

It may be reasonable to provide a recommendation for dosing in this population, but I have reservations about doing so at this time. From a safety perspective, patients with severe renal impairment are at higher risk of acute kidney injury/acute deteriorations in renal function. Given rivaroxaban’s renal clearance, this could lead to periods of higher exposure and resulting bleeding. For patients who bleed in this setting, there is no established antidote and the clearance of the drug would be prolonged. Efficacy considerations have also influenced my approach to this issue- as discussed later in the review, some uncertainty remains about the magnitude of rivaroxaban’s effect on stroke and systemic embolism relative to warfarin or warfarin used well. Because of safety concerns that are not offset by a clear efficacy advantage, my bias is to err on the side of safety. I also worry that providing recommendations (even with caveats about its source), may signal greater confidence in the data/recommendation than we may have. One approach that has been proposed is to more narrowly define a population of patients with severe renal impairment in whom the use of rivaroxaban would be highly likely to result in net benefit (e.g., patients not likely to have episodes of acute kidney injury/acute deteriorations in renal function). Even if such a population exists, I am not convinced that we will be able to reliably direct prescribers to this subset of patients via language in labeling; I also question if attempts to do so would lead us to such a narrowly defined subset of patients with several renal impairment that the recommendation would become more or less irrelevant.

**PD effects**: Concentration-dependent changes in prothrombin time (PT), factor Xa activity and prothrombinase induced clotting time (PiCT) are seen and the relationship between PT and rivaroxaban plasma concentration is close to linear. The onset and offset of the PD effects track with PK.

**Data supporting the proposed dose/dosing regimen**: The discussion on dose and dosing regimen has been shaped by several observations and also by analyses that were conducted by Drs. Sabarinath and McDowell as part of their Clinical Pharmacology review.

- Rivaroxaban has a relatively short elimination half-life (6 to 8 hours in healthy subjects and 11 to 13 hours in elderly subjects).
- Effects on PD parameters vary greatly over the 24-hour dosing interval and simulations (shown below) suggest that a twice daily dosing regimen of rivaroxaban would have resulted in lower peak to trough ratios than a once daily regimen.
No dose-ranging studies were performed in patients with atrial fibrillation. A single dose/dosing regimen (with adjustment for renal impairment) was studied in the applicant’s pivotal phase 3 study and this was based on the findings in two DVT dose-ranging studies. The lowest total daily dose tested in these studies was 20 mg/day and only a small number of outcome events were seen. Only one study (study 11223) included treatment arms that studied the same total daily dose administered either as a once daily or twice daily regimen. One could argue (as the Applicant has) that the findings from the DVT studies do not show a clear and marked difference between regimens; one could also argue (as the Clinical Reviewers have) that the results of study 11223 suggest that a twice daily regimen might have been preferable.

Data from a phase 2 study in the acute coronary syndrome (ACS) development program indicated that in patients on concomitant aspirin (a medication often used in patients with atrial fibrillation), a total daily dose of rivaroxaban given as a once daily as opposed to a twice daily regimen resulted in a greater incidence of bleeding. Based on this finding, lower doses (2.5 and 5.0 mg) and a twice daily dosing regimen were carried into the phase 3 ACS program.

Analyses performed on data from ROCKET, the sponsor’s phase 3 study in patients with atrial fibrillation, showed a flat relationship between PT and ischemic strokes at the doses studied (with confidence intervals that did not exclude a slope < 1). These analyses (see figures below) also showed that as the PT increased, the probability of a major bleed increased. Similar findings were seen when other pharmacodynamic measures were used (e.g., pre-dose factor Xa activity, PiCT, last observed INR).
Opinions have varied regarding whether or not it was sensible for the applicant to have used the dose/dosing regimen that was used in ROCKET. Opinions have also varied as to what one can and cannot conclude from these data regarding the relative merits of a different dose or dosing regimen from the one studied in ROCKET. This latter issue (whether or not a different dose or dosing regimen might have produced a better balance of safety and efficacy) has perhaps received the most attention and so I will focus on it as well. On the one hand, I do not think that the data as a whole provide a great deal of reassurance about the dose and dosing regimen used in ROCKET. On the other hand, I also do not think one can conclude from these data that a different dose or dosing regimen would have provided a better balance of safety and efficacy. Hence, I think attention should be placed on the experience in ROCKET with the dose that was studied. Clearly, drugs in this therapeutic area provide important clinical benefits and also pose significant risks and so it makes sense that one would want to identify a dose/dosing regimen that does a particularly good job of balancing a drug’s risks and benefits. At the same time, the only way to get a clear understanding of the relative merits of one versus another dose/dosing regimen in this therapeutic area is to study more than one dose/dosing regimen in phase 3 studies. The Division routinely encourages sponsors to study more than one dose/dosing regimen in phase 3 studies but has not required it. Based on the regulations and considering the large size of trials conducted in this therapeutic area, I don’t think the Division can do more than that.

6. Clinical/Statistical- Efficacy

Clinical development program
As previously noted, rivaroxaban is being developed for multiple thrombosis-mediated conditions. No dose-ranging studies were performed in the atrial fibrillation population prior to embarking on phase 3 studies in this population and only one dose (with adjustment for renal impairment) was studied in the pivotal efficacy trial.

In support of the proposed indication, the applicant conducted the ROCKET study, a large (14,000+ subjects), non-inferiority study comparing the efficacy of rivaroxaban to warfarin in
the prevention of stroke and systemic embolism (described further below). The clinical
development program also included a second phase 3 study conducted in Japan (J-
ROCKET). Because of its design, J-ROCKET does not contribute in a meaningful way to an
understanding of rivaroxaban’s effectiveness. J-ROCKET was designed as a safety study
and, with 1280 subjects, was not powered to demonstrate non-inferiority to warfarin. Other
important differences between J-ROCKET and ROCKET (including differences in the target
INR range in warfarin subjects) are discussed in the FDA Clinical Review. Hence, the
discussion that follows focuses on ROCKET.

Design of the pivotal efficacy study: ROCKET was an international, randomized, double-
blind, double-dummy, event-driven, non-inferiority study comparing rivaroxaban 20 mg orally
once daily (15 mg once daily in patients with CrCl 30-49 mL/min) to warfarin titrated to target
an INR of 2.5 (range of 2.0 to 3.0).

ROCKET enrolled patients with non-valvular atrial fibrillation and compared to other recent
RCTs in this area, ROCKET targeted a population at higher risk of embolic events (at least
based on current prediction models). Specifically, ROCKET required that patients with non-
valvular atrial fibrillation meet one of the following criteria to qualify for enrollment: (1) a prior
stroke (ischemic or unknown type), transient ischemic attack or systemic embolism OR (2)
two or more of the following factors: age ≥ 75 years, hypertension, diabetes mellitus or heart
failure/left ventricular ejection fraction ≤ 35%.

The study excluded patients who might be at particularly high risk of bleeding by using
hemorrhage risk-related exclusion criteria (see the FDA Clinical Review), though patients on
aspirin ≤ 100 mg monotherapy and thienopyridine monotherapy could be enrolled. As
previously noted, rivaroxaban is renally cleared and patients with a calculated CrCl < 30
mL/min were excluded from the study.

A double dummy technique was used in ROCKET. To address the decrease in bioavailability
of the 20 mg dose, rivaroxaban (or its matching placebo) was to be taken in the evening with
food. Warfarin (or its matching placebo) was to be dose-adjusted based on real INR results
(or sham results in the case of placebo) obtained using a specially designed point-of care INR
device. In attempt to maintain the blind, the protocol also specified that while on study drug,
unblinded INR measurements were not to be performed except in the setting of a medical
emergency. With regard to ensuring the quality of warfarin administration, the protocol
specified only that INR be measured “as clinically indicated but at least every 4 weeks.” No
recommended algorithm for dose adjustment was provided.

The trial was event-driven and was designed to establish the non-inferiority of rivaroxaban to
warfarin in the reduction of stroke and systemic embolism. A non-inferiority margin of 1.46
was used (based on the risk ratio), though the study also had 90% power using the accepted
FDA margin of 1.38. Efficacy endpoints and safety endpoints of interest (i.e. bleeding and
liver findings) were adjudicated by an independent blinded clinical endpoint committee.

An overview of ROCKET’s design is shown below.
Efficacy findings in ROCKET

Analyses in ROCKET were conducted in several populations; a variety of observation periods were also used. In the discussion that follows, the definitions shown below apply.

Populations:
- Intent-to-Treat Population (ITT): all unique participants randomized to treatment (n=14,264)
- Safety Population: all participants in ITT population who received at least 1 dose of study medication (n=14,236)
- Per-protocol Population (PP): all participants in safety population who did not have major protocol violations (n=14,054)

Observation period:
- On-treatment: up to last dose of study drug plus 2 days
- Up to site notification: up to the date of notification that the required number of endpoint events had been met; by definition this analysis excludes events occurring during the transition period at the end of the study
- Up to follow-up visit: up to the post-treatment visit (~30 days after the last dose of study drug)
- Regardless of treatment exposure: all of the above plus data up to the last study contact for prematurely discontinued subjects who were followed by telephone

Primary endpoint: The pre-specified primary analysis for ROCKET was a per protocol on-treatment analysis. Compared to other analyses, this analysis yielded one of the most favorable results- a HR (rivaroxaban vs. warfarin) of 0.79 (95% CI 0.66 to 0.96, p<0.001 for superiority). The results of analyses using other observation periods and populations are shown in the table below. An analysis restricted to the on-treatment period produced similar
findings as the per protocol analysis. In contrast, the upper bound of the 95% CI crosses one in the ITT analysis and an analysis using the ITT population but including events only up to site notification of study termination. In the various sensitivity analyses explored by the statistical reviewer, the upper bound of the 95% CI never exceeded 1.08 and thus in all of the sensitivity analyses that were conducted, the upper bound of the 95% CI remained well below the FDA non-inferiority margin of 1.38.

Table 1. Primary efficacy endpoint findings

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (event rate)</td>
<td>n (event rate)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>While on treatment (up to last dose plus 2 days)</td>
<td>N=7061</td>
<td>N=7082</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>189 (1.70)</td>
<td>243 (2.15)</td>
<td>0.79 (0.65, 0.95)</td>
</tr>
<tr>
<td>Stroke Type</td>
<td>184 (1.65)</td>
<td>221 (1.96)</td>
<td>0.85 (0.70, 1.03)</td>
</tr>
<tr>
<td>Primary Hemorrhagic Stroke</td>
<td>29 (0.26)</td>
<td>50 (0.44)</td>
<td>0.59 (0.37, 0.93)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>149 (1.34)</td>
<td>161 (1.42)</td>
<td>0.94 (0.75, 1.17)</td>
</tr>
<tr>
<td>Unknown Stroke Type</td>
<td>7 (0.06)</td>
<td>11 (0.10)</td>
<td>0.65 (0.25, 1.67)</td>
</tr>
<tr>
<td>Non-CNS Systemic Embolism</td>
<td>5 (0.04)</td>
<td>22 (0.19)</td>
<td>0.23 (0.09, 0.61)</td>
</tr>
<tr>
<td>ITT up to Site Notification</td>
<td>N=7081</td>
<td>N=7090</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>269 (2.12)</td>
<td>306 (2.42)</td>
<td>0.88 (0.74, 1.03)</td>
</tr>
<tr>
<td>Stroke Type</td>
<td>253 (1.99)</td>
<td>281 (2.22)</td>
<td>0.90 (0.76, 1.07)</td>
</tr>
<tr>
<td>Primary Hemorrhagic Stroke</td>
<td>33 (0.26)</td>
<td>57 (0.44)</td>
<td>0.58 (0.38, 0.89)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>206 (1.62)</td>
<td>208 (1.64)</td>
<td>0.99 (0.82, 1.20)</td>
</tr>
<tr>
<td>Unknown Stroke Type</td>
<td>19 (0.15)</td>
<td>18 (0.14)</td>
<td>1.05 (0.55, 2.01)</td>
</tr>
<tr>
<td>Non-CNS Systemic Embolism</td>
<td>20 (0.16)</td>
<td>27 (0.21)</td>
<td>0.74 (0.42, 1.32)</td>
</tr>
<tr>
<td>ITT regardless of treatment exposure</td>
<td>N=7081</td>
<td>N=7090</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>293 (2.20)</td>
<td>320 (2.40)</td>
<td>0.91 (0.78, 1.07)</td>
</tr>
<tr>
<td>Stroke Type</td>
<td>277 (2.07)</td>
<td>295 (2.21)</td>
<td>0.94 (0.80, 1.10)</td>
</tr>
<tr>
<td>Primary Hemorrhagic Stroke</td>
<td>37 (0.27)</td>
<td>57 (0.42)</td>
<td>0.65 (0.43, 0.98)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>226 (1.69)</td>
<td>220 (1.64)</td>
<td>1.03 (0.85, 1.24)</td>
</tr>
<tr>
<td>Unknown Stroke Type</td>
<td>20 (0.15)</td>
<td>20 (0.15)</td>
<td>1.00 (0.54, 1.86)</td>
</tr>
<tr>
<td>Non-CNS Systemic Embolism</td>
<td>20 (0.15)</td>
<td>27 (0.2)</td>
<td>0.74 (0.42, 1.32)</td>
</tr>
</tbody>
</table>

[Source: Applicant, CSR 39039039AFL3001, page 146, Table 31 (on treatment); page 909, Attachment 6.44 (site notification); page 822, Attachment 6.5 (ITT)]

Event rate is per 100 patient-year exposure; analyses exclude site 042012

With regard to the components of the composite, fewer hemorrhagic strokes were seen in subjects randomized to rivaroxaban (see table above). In contrast, ischemic stroke rates were similar in the two treatment arms. Findings for non-CNS systemic embolisms were favorable. The primary endpoint findings were further supported by a numerically smaller number of disabling and fatal strokes in the rivaroxaban arm. For the most part, efficacy findings were consistent across important subgroups; however, the Clinical Review notes a possible treatment by subgroup interaction based on history of stroke/TIA/systemic embolism (HR of 0.92 if prior history and 0.59 if no prior history; treatment by subgroup interaction nominal p=0.04).
In sum, while the finding of superiority was not robust, the finding of non-inferiority to warfarin (as administered in this study) was, even when considering the amount of missing data (see the Clinical Review for one "worst case" scenario that was explored). Nonetheless, the efficacy findings must be interpreted in the context of how well warfarin was managed in this trial and with attention to the particular components of the composite endpoint that are driving the results (i.e., a marked reduction in hemorrhagic strokes on rivaroxaban but no clear advantage on ischemic strokes).

**Time course of effects:** The primary endpoint analysis used the Cox proportional hazards model with treatment as a factor. One important issue raised by Dr. Lawrence in his statistical review was whether or not the proportional hazards assumption was valid. As shown in the figure below for the PP population using the on-treatment observation period, the KM curves for the primary efficacy endpoint appeared to separate early and there did not seem to be significant widening of this separation over time.

![Figure 3. Kaplan-Meier curves for the Per Protocol population on-treatment analysis](Source: Applicant, CSR 39039039AFL3001, page 133, Figure 9)

According to Dr. Lawrence, based on the log(-log(survival)) curve, the proportional hazard's assumption appeared violated overall for the primary efficacy outcome. As another way of looking at the proportional hazard assumption, he estimated the hazard functions directly by:

1. splitting the time into intervals of 6 months and counting the number of events in each group in each time window and
2. estimating the hazard function on each day and then using local polynomial regression to fit a curve through the estimates for each day. As shown in the figure below, the analysis suggests that the difference between groups is larger at earlier time points. Beyond 6 months, there does not appear to be much of a difference between groups.
Figure 4. Estimated hazards function over time

[Source: FDA Statistical Review, page 17, Figure 5]
The points are from the estimated hazard functions over 6 month time periods; the smooth curves are from the estimated hazard functions for each day. The analysis is based on the PP population and the on-treatment observation period.

An important question is whether these findings are being driven by poor control of the INR/anticoagulation in the warfarin arm in the early months of the study. As shown in the figure below, a significant amount of time was spent below an INR of 2 during this early time period.
Other efficacy endpoints: ROCKET’s protocol also specified secondary efficacy endpoints— the first two (“Major Efficacy Endpoint 1" and “Major Efficacy Endpoint 2") were composite endpoints. Major Secondary Efficacy Endpoint 1 included the primary endpoint and vascular death; Major Secondary Efficacy Endpoint 2 included the primary endpoint, vascular death and myocardial infarction. In the on-treatment analysis, the HR for Major Secondary Efficacy Endpoint 1 was 0.86 (95% CI 0.74 to 0.99) and the HR for the Major Secondary Efficacy Endpoint 2 was 0.85 (95% CI 0.74 to 0.96), reflecting the aforementioned findings for the primary endpoint as well as numerical imbalances in myocardial infarction and vascular death that favored rivaroxaban (see table below).
Table 2. On-treatment hazard ratios for myocardial infarction and vascular death

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rivaroxaban N=7061</th>
<th>Warfarin N=7082</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>101 (1.43)</td>
<td>126 (1.78)</td>
<td>0.81 (0.63,1.06)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>170 (2.41)</td>
<td>193 (2.73)</td>
<td>0.89 (0.73,1.10)</td>
</tr>
</tbody>
</table>

[Source: Applicant, CSR 39039039AFL3001, page 146, Table 31]
Percent given reflects percent of subjects with event

*Adequacy of anticoagulation in the warfarin arm:* Time in therapeutic range has been used to gauge the adequacy of anticoagulation in subjects randomized to warfarin in anticoagulant trials. Relative to other recent controlled trials, the percent of time subjects spent in therapeutic range (defined as an INR of 2-3) was lower in ROCKET. The study’s mean TTR was 55%; the median TTR was 58%. In contrast, in other recent RCTs, TTR has been upwards of 60% (mean TTR range of ~62-73%). Of the time spent out of therapeutic range in ROCKET, the majority was spent below range therapeutic range; over the course of the trial, subjects were below range ~29% of the time.

ROCKET’s low TTR (relative to other trials) appears to have resulted from important differences in the management of warfarin in different regions of the world, high enrollment at non-U.S. sites and ROCKET’s design which largely left the management of warfarin to the discretion of study investigators. In ROCKET, TTR varied widely across the geographic regions. TTR was highest in North America (mean of 64.1%) and lowest in Eastern Europe (49.7%).

There were also significant regional differences in another plausible metric of warfarin management- the time to repeat INR testing following a low INR value. According to the 2003 American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy, when the INR reaches therapeutic range and becomes stable, INR testing can be reduced to intervals as long as 4 weeks. When dose adjustments are need, frequent monitoring should be resumed. Consistent with these recommendations, in North America, the median number of days to the next INR measurement after an INR < 1.5 and < 2 was 8 and 14, respectively. In contrast, in Latin American, Eastern Europe and Asia-Pacific (regions which collectively enrolled ~67% of study patients), the median number of days to the next INR measurement after an INR < 1.5 ranged from 25 days in Latin America to 28 days in Asia-Pacific; the numbers were similar after an INR < 2. Importantly, after this significant delay in testing, the proportion of measurements <2 remained high in these regions (50-55% if the previous measurement had been < 1.5 and 38-45% if the previous measurement had been < 2.0). Such data indicate that the strategy employed in these regions was not effective at keeping patients in the range needed to ensure protection from embolic events.

Another way to explore how well warfarin was administered in ROCKET is to compare the event rate in the warfarin arm of ROCKET with (1) event rates in the warfarin arm of other recent RCTs, (2) event rates in the placebo arm of historical trials, and (3) estimated untreated event rates in a similar population. In ROCKET, the stroke incidence per 100 patient-years was 2.4% in the ITT population including events up to site notification. In the subset with and without a history of stroke/TIA/systemic embolism, the incidence was 2.9% and 1.9%, respectively (though the mean CHADS2 score in the latter group was still high-
2.9). Compared to the stroke rate in the warfarin arm of recent RCTs (1.1 to 2.2), the stroke rate in ROCKET was somewhat higher; however, the population studied in ROCKET was also at greater risk of strokes (based on history of stroke/TIA and mean CHADS2 score). Compared to the placebo arms of the primary prevention and secondary prevention trials, the rate was significantly lower. In the primary prevention studies, the stroke incidence per 100 patient-years in the placebo arm ranged from 3.0% to 7.8% (median 4.8%). In the placebo arm of EAFT, a secondary prevention trial, the rate was 12.3%. It is hard to know to what extent advances in the treatment of conditions common in atrial fibrillation patients might have impacted rates in untreated patients. However, compared to estimated untreated event rates in a similar population (as defined by CHADS2 score), event rates in the warfarin arm of ROCKET were also lower. The mean and median CHADS2 score in ROCKET was 3.5 and 3, respectively. In the ATRIA study, estimated untreated event rates for an ischemic stroke or peripheral embolism was 5.3 (95% CI 4.2 to 6.7) per 100 patient year for a CHADS2 score of 3; in the original CHADS2 validation study, the event rate for an ischemic stroke was 5.9 (95% CI 4.6-7.3).1 2 Hence, when taken as a whole and considering ROCKET’s population, the data indicate that patients randomized to warfarin in ROCKET received a treatment benefit in terms of stroke reduction.

Site-level TTR analyses: Several site-level TTR analyses were done as a way to explore the potential impact of warfarin management on the study’s findings. Outcomes were compared after stratifying subjects into quartiles by site-level INR control. Because mean TTR in ROCKET was lower than in other recent RCTs, the TTR cuts defining ROCKET’s quartiles were also lower. Hence, additional TTR cuts were examined (e.g., the TTR cut point defining the upper quartile in RE-LY). Finally, as a way to get around the issue of seemingly arbitrary cut points of site-level TTR, the relationship between outcomes and warfarin management was also explored in a more continuous manner- via excluding sites one by one/sequentially based on their TTR. The results of this latter analysis are shown below; in general, analyses based on various TTR cut points paint a similar picture. As shown in the figure, as the site-level TTR increases above ~65, the point estimate of the HR begins to rise. At higher values of site-level TTR, the point estimate appears to reach/exceed one and then drops down; it does not clearly exceed or consistently stay above the FDA margin of 1.38. As is also shown in the figure, the percent of study subjects at sites with higher values of TTR was small and the 95% CI corresponding to these HR point estimates are very wide reflecting the uncertainty around the point estimate. The upper bound of the 95% CI is also difficult to interpret at higher values of site-level TTR given the small number of subjects/events. The main impression one gets from the site-level TTR analyses is that the amount of data from sites exhibiting what might be considered “good” or “reasonable” warfarin management was limited in ROCKET, making it difficult to assess how rivaroxaban might have performed if warfarin had been managed better.
Patients from U.S. sites: In ROCKET, 1931 patients (13.5%) were randomized from U.S. sites; 2681 patients (18.9%) came from sites in “North America” (subjects designated by the sponsor as coming from “North America” came from sites in the U.S. or Canada). In the U.S., the point estimate for the hazard ratio for the primary endpoint ranged from 0.54 to 0.87 depending upon the population/analysis used; the upper bound of the 95% CI ranged from 1.01 to 1.35 (all less than the FDA margin of 1.38). As noted in the Clinical Review, the U.S. efficacy findings was seen in the setting of a mean and median TTR of 63 and 65 respectively—much higher than that seen in ROCKET overall and more similar to TTRs reported in other recent RCTs. Hence, to some extent, the U.S. findings provide reassurance that rivaroxaban would have performed favorably if warfarin management had been better in ROCKET; nonetheless, caution should be exercised when interpreting the U.S. findings.

- Compared to the study overall, drop out rates and study medication discontinuation rates were also higher in the U.S. Approximately 8.6% of U.S. subject not known to have died discontinued follow up prematurely; ~42.7% of U.S. subjects discontinued study medication.
- If weight is to be given to the U.S. point estimate for efficacy (as an indication of what the trial findings might have looked like if warfarin had been better managed), then perhaps equal emphasis should be given to the bleeding findings as an indication of rivaroxaban’s safety. In the U.S. the incidence of major bleeding was significantly higher in patients randomized to rivaroxaban (HR=1.5; 95% CI of 1.14 to 1.98; nominal p=0.004).

Vitamin K antagonist-naïve and –experienced patients: The mean TTR in patients who were VKA naïve at baseline was much lower than in patients who were on a VKA (~48% vs.~60%, respectively). Hence, analyses in these subpopulations may provide insight on how warfarin management in ROCKET could have influenced the study’s findings. In patients with no prior history of VKA use, the point estimate for the HR for the primary efficacy endpoint was 0.76.
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(95% CI of 0.59, 0.99) and was 0.90 (95% CI of 0.71, 1.15) for major bleeding (analyses based on the ITT population using data up to site notification). In contrast, in patients with prior VKA use, the point estimate for the HR was 0.96 (95% CI of 0.78, 1.2) for the primary efficacy endpoint and was 1.12 (95% CI of 0.94, 1.33) for major bleeding. The upward shift of these point estimates suggests that findings in ROCKET would not have been as favorable if warfarin had been managed better.

7. Safety

Bleeding: The major safety finding was bleeding, an expected adverse event given rivaroxaban’s mechanism of action. In ROCKET, bleeding severity and bleeding site were adjudicated. As shown in the table below, overall rates of adjudicated major bleeding were similar in the two treatment arms of ROCKET. While hemoglobin drops and transfusions occurred at a lower rate on warfarin, critical site and fatal bleeds occurred at a higher rate. The seemingly incongruent findings for the various components reflect different sources/sites of bleeding in the two treatment arms and also the fact that the GI tract, a frequent source of bleeding in patients, was not defined as a “critical site.” Major GI bleeds occurred at a higher incidence in rivaroxaban compared to warfarin treated subjects. ICH (a sub-type of critical site bleeding), occurred at a lower incidence in rivaroxaban compared to warfarin treated subjects. Concomitant use of aspirin increased the risk of bleeding on rivaroxaban, but did so to a similar extent in patients on warfarin.

Table 3. Major Bleeding in ROCKET

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (N=7111)</th>
<th>Warfarin (N=7125)</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>rate</td>
<td>n (%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>395 (5.6)</td>
<td>3.60</td>
<td>386 (5.4)</td>
</tr>
<tr>
<td>Hb drop</td>
<td>305 (4.3)</td>
<td>2.77</td>
<td>254 (3.6)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>183 (2.6)</td>
<td>1.65</td>
<td>149 (2.1)</td>
</tr>
<tr>
<td>Critical site</td>
<td>91 (1.3)</td>
<td>0.82</td>
<td>133 (1.9)</td>
</tr>
<tr>
<td>Death</td>
<td>27 (0.4)</td>
<td>0.24</td>
<td>55 (0.8)</td>
</tr>
</tbody>
</table>

[Source: FDA Clinical Review, page 191, Table 76]
Event rate per 100-patient years

The risk of bleeding on warfarin has been shown to increase when the INR exceeds 3. In ROCKET, the mean percent of time subjects were above the targeted range of 2-3 was ~16%. In comparison, in RE-LY, the mean percent of time subjects were above an INR of 3 was ~13%. Analyses stratifying subjects into quartiles defined by site-level INR control in ROCKET show an increasing risk of major bleeding on rivaroxaban (relative to warfarin) with increasing quartile of site level control. This finding was driven primarily by an increasing rate of events in the rivaroxaban arm at sites with higher TTRs.

1 The ROCKET definition of major bleeding was 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.
Table 4. Site-level TTR analyses for Major Bleeding

<table>
<thead>
<tr>
<th>TTR range defining quartile</th>
<th>Rivaroxaban (N=6888)</th>
<th>Warfarin (N=7079)</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (event rate)</td>
<td>n (event rate)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>&lt;46.8</td>
<td>64 (2.5)</td>
<td>80 (3.3)</td>
<td>0.76 (0.55, 1.06)</td>
</tr>
<tr>
<td>46.8-55.9</td>
<td>68 (3.4)</td>
<td>96 (3.5)</td>
<td>0.95 (0.71, 1.27)</td>
</tr>
<tr>
<td>55.9-63.9</td>
<td>90 (3.3)</td>
<td>99 (3.4)</td>
<td>0.95 (0.72, 1.27)</td>
</tr>
<tr>
<td>63.9-100</td>
<td>142 (5.2)</td>
<td>108 (3.5)</td>
<td>1.47 (1.14, 1.89)</td>
</tr>
</tbody>
</table>

[Source: Reviewer's analysis (applicant's datasets=combine, come03b; reviewer sas file=TTR_equal_size_quartiles] Site-level TTR calculated by determining value for each subject at that site and then taking the mean of those values.

Events following the discontinuation of therapy: In contrast to some other recent RCTs, ROCKET did not specify an algorithm for transitioning subjects from study medication to warfarin at the end of the study, nor did the trial require a period of overlap of study medication with warfarin. In patients who completed the study on rivaroxaban, 22 primary endpoint events (18 ischemic strokes and four hemorrhagic) occurred between days 3-30 following the discontinuation of study medication. In contrast, among patients who completed the study on warfarin, six primary endpoint events (four ischemic strokes and two of unknown stroke type) occurred during this time window. In ROCKET, a similar finding was seen following completion of study medication (10 ischemic strokes and one hemorrhagic stroke in the rivaroxaban arm and four ischemic strokes in the warfarin arm). Two possibilities were strongly considered: a rebound hypercoagulable state or a poorly handled transition from rivaroxaban to warfarin.

Analyses looking at events in the day 3-30 time window in patients who prematurely discontinued study medication showed a high but similar event rate in the two treatment arms, arguing against a significant hypercoagulable state following the discontinuation of rivaroxaban. As described in the Clinical Review, available data suggest poor INR control in this period. The observed excess in hemorrhagic strokes in the rivaroxaban arm during this timeframe could also be viewed as an indicator of a poorly handled transition (assuming these hemorrhagic events were not in fact hemorrhagic conversions of ischemic strokes). Finally, the event rates seen in the rivaroxaban arm at ROCKET’s end (annualized event rate of 6.4% for any stroke and 5.3% for an ischemic stroke) was not inconsistent with projected event rates in untreated populations with similar characteristics.\(^1\)\(^2\)

To further address this finding, the Division of Hematology Products (DHP) was consulted regarding how one might determine if rivaroxaban was causing a rebound hypercoagulable state. DHP did not feel that further preclinical studies could help resolve this issue and also recognized that a large trial of long duration with clinical endpoints such as those used in ROCKET was not likely to be feasible. The consult advised that a period of overlap of rivaroxaban and warfarin be used in patients transitioning from rivaroxaban to warfarin (see Section 12 Risk Benefit Assessment). Finally, DHP proposed that “the sponsor design a small short duration clinical study with appropriate correlative endpoints”. The consult did not specify what “appropriate correlative endpoints” might be, however, in a follow up discussion and email, Dr. Ryan clarified that based on the submitted data, she did not think it was possible for her Division to define these endpoints and that the sponsor should propose a study after careful review of the cases, consideration of possible mechanisms for a hypercoagulable state and discussion with thought leaders in this area.
CDTL comment: While it may be reasonable to discuss DHP’s recommendations with the applicant, I do not think that a postmarketing study is needed to address this issue. I agree that one cannot exclude a possible rebound hypercoagulable state as a cause for the excess of events seen in rivaroxaban-treated patients at the end of ROCKET and J-ROCKET. At the same time and for the reasons described above, I think that the available data suggest that the finding likely reflects a poor handling of the transition to warfarin. Moreover, even if the observed events are because of a rebound hypercoagulable state, the absolute incidence of such events and risk difference (rivaroxaban minus warfarin) was low in ROCKET. In the rivaroxaban arm, 0.48% of subjects experienced a stroke in the transition period compared to 0.13% in the warfarin arm— a difference in absolute incidence of 0.35%. Hence, even if rivaroxaban causes a rebound hypercoagulable state, such an effect, in aggregate, does not appear to be marked.

Other pertinent safety findings in ROCKET are described below:

Deaths: In the study overall, there was a numerical imbalance in deaths, with fewer events seen in the rivaroxaban compared to warfarin-treatment arms. Of the fatalities reported in ROCKET, only a minority occurred while on treatment (up to last dose plus 2 days). In the U.S., there was no difference (numerical or statistical) in deaths between the two treatment arms.

Table 5. Mortality findings in ROCKET

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>While on treatment (up to last dose plus 2 days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=7061</td>
<td>N=7082</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>208 (2.95)</td>
<td>250 (3.53)</td>
<td>0.85 (0.70,1.02)</td>
</tr>
<tr>
<td>Vascular</td>
<td>170 (2.41)</td>
<td>193 (2.73)</td>
<td>0.89 (0.73,1.10)</td>
</tr>
<tr>
<td>Non-vascular</td>
<td>21 (0.30)</td>
<td>34 (0.48)</td>
<td>0.63 (0.36,1.08)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (0.24)</td>
<td>23 (0.32)</td>
<td>0.75 (0.40,1.41)</td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=7081</td>
<td>N=7090</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>621 (8.77)</td>
<td>667 (9.41)</td>
<td>0.93 (0.84,1.04)</td>
</tr>
<tr>
<td>Vascular</td>
<td>398 (5.62)</td>
<td>421 (5.94)</td>
<td>0.95 (0.82,1.08)</td>
</tr>
<tr>
<td>Non-vascular</td>
<td>160 (2.26)</td>
<td>167 (2.36)</td>
<td>0.96 (0.77,1.19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>63 (0.89)</td>
<td>79 (1.11)</td>
<td>0.80 (0.57,1.11)</td>
</tr>
</tbody>
</table>

[Applicant: CSR 39039039AFL3001, page 146, Table 31 (on treatment), page 822, Attachment 6.5 (ITT)]

Percent given reflects percent of subjects with event

SAEs and discontinuations due to AEs: Serious adverse events occurred at a similar incidence in the two treatment arms; analyses of SAE data did not suggest any important toxicities other than bleeding. Study medication discontinuations due to bleeding events were more common on rivaroxaban (4.3% of subjects) compared to warfarin (3.1% of subjects). This discrepancy between treatment arms was particularly true in the U.S. where 81 subjects (8.4%) randomized to rivaroxaban versus 43 subjects (4.5%) randomized to warfarin.
discontinued study medication early because of a bleeding event (see table 41, Clinical Review). In contrast, study medication discontinuations for non-bleeding adverse events were similar in the two treatment arms.

General AEs and results of laboratory tests: Treatment emergent adverse events were common and occurred at a similar incidence in both treatment arms (~81% of subjects). Analyses of AE data did not suggest any important toxicities other than bleeding. No additional safety concerns were raised by the results of laboratory tests.

Other findings in the development program or post-marketing experience:
- Data pertaining to possible liver effects were extensively reviewed; no signal concerning for liver toxicity was seen.
- Rivaroxaban is marketed outside the U.S. for the prevention of venous thromboembolism following elective hip or knee replacement surgery. Dr. Dunnmon’s review of the foreign post-marketing safety experience did not raise any additional concerns.

8. Advisory Committee Meeting
The Advisory Committee Meeting held on September 8, 2011 focused on the major issues raised by the reviewers (see Introduction). I have attempted to incorporate or address issues raised at the Advisory Committee Meeting in various places in this review.

9. Pediatrics
The Applicant has submitted a full waiver request citing the small number of pediatric patients with non-valvular atrial fibrillation as well as other important differences in the etiology and management of atrial fibrillation in pediatric and adult populations. Based on the reported prevalence in the pediatric population, I agree that a pediatric waiver should be granted (i.e., necessary studies are impossible or highly impractical because the number of such patients is so small). A full waiver was also granted to dabigatran for the same indication. The PeRC has yet to issue a final recommendation.

10. Other Relevant Regulatory Issues
Seven clinical investigator sites and the sponsor were inspected. At one foreign site (site 040012 in Romania), the investigator indicated that the INR was intentionally maintained below the protocol-specified level due to concerns regarding bleeding; the investigator at this site reported targeting an INR between 1.5 and 2.0. There were no primary endpoint events in the warfarin arm at this site. This finding/issue is further discussed under Risk Benefit Assessment. Some minor and/or infrequent regulatory violations were also documented but were not felt to have a significant impact on data integrity or subject safety. Based on the inspection findings, Drs. Thompson and Purohit-Sheth have concluded that the study appears to have been conducted adequately at these sites and that the data generated by these sites may be used in support of the indication.

11. Labeling
The label should capture the uncertainty about rivaroxaban’s effectiveness relative to warfarin/warfarin used well. The Clinical Reviewers have proposed an Important Limitations of Use statement to address this issue and I think such an approach makes sense. Some have also proposed approving rivaroxaban as a “second line” therapy (e.g., for use in patients unable to maintain an INR in the therapeutic range on warfarin or in patients who cannot tolerate other therapies for reasons unrelated to bleeding). I don’t favor pursuing this approach. One problem is that rivaroxaban was never directly tested against any agent other
than warfarin; it is hard to draw conclusions about comparative effectiveness in this setting.

Another problem, and one that relates to its use as a “second line” agent to warfarin, is that
patients who do poorly on warfarin (as manifested by the inability to maintain an INR in
therapeutic range) may or may be good candidates for rivaroxaban. If the issue is poor
compliance, such patients may not do well on a drug with a short half-life which may be less
forgiving with regard to missed doses.

Other important issues that should be addressed in labeling include the following:

- events seen in the post-treatment period; emphasis should be placed on the risk of
  embolic events if rivaroxaban is stopped and adequate anticoagulation is not provided by
  another agent; a boxed warning should be considered
- transitioning from rivaroxaban to warfarin; emphasis should be placed on the findings in
  the clinical trial setting in which no provisions were made for a period of overlap with
  warfarin; how much or what the label should say about a particular strategy for
  transitioning merits further internal discussion
- the need to take rivaroxaban with the evening meal
- the bleeding risk (findings in the U.S. should be included)
- rivaroxaban’s effect on PD parameters during the inter-dosing interval
- what is and is not known about the ability of various interventions to reverse bleeding in
  patients

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Assuming agreement can be reached on labeling, I recommend approval. The reasons for my
decision are described below in the Risk Benefit Assessment.

Risk Benefit Assessment

Warfarin’s effectiveness in the reduction of ischemic stroke in patients with atrial fibrillation
was established over a decade ago. In these trials, five primary and one secondary
prevention, the use of warfarin led to a substantial reduction in ischemic strokes. Indeed,
because of this important benefit, placebo-controlled trials cannot be conducted for the
purpose of establishing the effectiveness of new therapies in reducing the risk of stroke in
patients with atrial fibrillation. In light of this constraint, rivaroxaban’s effectiveness was
evaluated in an active-controlled study and, as in other development programs in this area,
the pivotal study was designed as a non-inferiority trial.

ROCKET, the single phase 3 study that was conducted in support of the proposed indication,
was an international, randomized, double-blind, double-dummy, event-driven, non-inferiority
study comparing rivaroxaban to warfarin. The primary endpoint was a composite endpoint
that included stroke (hemorrhagic, ischemic and unspecified) and systemic embolism. In the
prespecified analysis (a per protocol on-treatment analysis), the HR for the primary endpoint
was 0.79 (95% CI 0.66 to 0.96, p<0.001 for superiority), favoring rivaroxaban. However, the
finding of superiority was not seen in the ITT analysis or in an analysis that included events
up to site notification (thereby excluding events that occurred following the discontinuation
of study medication at the end of the trial). In contrast, all of the sensitivity analyses that were
explored showed non-inferiority (based on the FDA accepted margin of 1.38) to warfarin as
used in the trial. As to the break down of events, fewer hemorrhagic strokes (an unintended
and adverse effect of anticoagulant therapy) were seen in subjects randomized to
rivaroxaban. In contrast, ischemic stroke (the benefit of anticoagulant therapy) occurred at a
similar rate in the two treatment arms.
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**Quality of warfarin administration and potential impact on efficacy findings:** An issue that weighs heavily on the regulatory decision for rivaroxaban is the adequacy of anticoagulation in the warfarin treatment arm of ROCKET. Time in therapeutic range (defined as an INR of 2-3) is commonly used to gauge the adequacy of anticoagulation in subjects randomized to warfarin in anticoagulant trials. In ROCKET, mean time in therapeutic range (TTR) was ~55%; in contrast, recent RCTs of novel anticoagulants for atrial fibrillation have reported mean TTRs upwards of 60% (range ~62-73).

It is impossible to know what ROCKET’s results would have looked like if warfarin had been managed better. Some analyses (including estimates of the hazard function over time, some site-based TTR analyses and findings in VKA-naïve vs. –experienced patients) suggest that the findings for rivaroxaban might not have been as favorable. Admittedly, these analyses have limitations- they are based on subgroups, small numbers of events and/or seemingly arbitrary thresholds of TTR. Unfortunately, such an approach is forced in studies in which the adequacy of anticoagulation in the warfarin control arm is uncertain. Moreover, beyond what these analyses suggest, as in any trial using an active comparator, one could reasonably expect the study’s findings to be influenced by how well the active comparator was used.

**Regulatory standard for approval:** The Clinical Reviewers have recommended a complete response; one reason given is that the data from ROCKET are not adequate to determine whether rivaroxaban is as effective as warfarin when warfarin is used *skillfully.* The Clinical Reviewers argue that in order for atrial fibrillation 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 warfarin is used *skillfully.* They contend that such a requirement stems from an FDA policy that states that it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing if the disease to be treated is life-threatening or capable of causing irreversible morbidity.

A key issue of course, is what is meant by the term *as effective* as alternatives. As some have noted, the only real way to show that a drug is *as effective* as an alternative is to show the new drug’s superiority to that alternative. The Clinical Reviewers have not taken the position that non-inferiority studies should not be done in this therapeutic area. Instead, their focus has been on the meaning of the term “as effective” as it relates to the management of the active comparator warfarin and the achieved TTR in non-inferiority studies.

Clearly, robustly showing non-inferiority to warfarin (or any active comparator) when used particularly well or *skillfully* provides convincing evidence of a new drug’s efficacy. That this should be an absolute criterion for approval is not as obvious. While published reports indicate that there are centers in the U.S. that administer warfarin *skillfully* (as defined by the reviewers), the published literature also suggests that a significant number of patients/centers in the U.S. do not achieve this level of INR control.³ ⁴ One could also argue that with only two drugs approved in this indication (both with advantages and disadvantages), there is still unmet need for highly effective therapies in this disease area; even for therapies that haven’t definitively established robust non-inferiority to *skillfully* used warfarin.

Another consideration is whether or not one should be using the mean time in therapeutic range defined as an INR of 2-3 (and seemingly arbitrary cut points in the mean value) to define the skillful use of warfarin. Assessments of mean TTR are certainly a very reasonable way to look at warfarin management in a trial. However, to assess warfarin management in a trial using the mean (or median) value of TTR alone places a great deal of weight on a single
metric. Moreover, this emphasis may overstep what is actually known about the ability of this tool to accurately measure the quality of warfarin administration in a trial and/or identify important differences in management between studies.

It is unclear how well rivaroxaban compares to well-administered warfarin; at the same time there are strong indicators that rivaroxaban is reasonably effective. Rivaroxaban was robustly non-inferior to warfarin as used in ROCKET and event rate data from the placebo arm of historical trials indicate that, in ROCKET, warfarin was administered in a way that provided some (and perhaps even significant) benefit to patients; comparisons with estimated event rates in untreated populations also suggest as much. The fact that the various analyses exploring the potential impact of the quality of warfarin administration produced the results they did (and not worse) is also somewhat reassuring. While in some of these analyses, hazard ratio point estimates shifted upward and approached or sometimes exceeded one, the point estimates generally didn't jump very high. Moreover, in the U.S., where INR control was better, the results were still favorable. Considering the data in their totality and keeping in mind that the skillful use of warfarin is not always realized in clinical practice, I think the applicant has satisfied the regulatory requirement for effectiveness. Any uncertainty about rivaroxaban’s effectiveness relative to warfarin or skillfully managed warfarin can be and should be reflected in labeling.

**Bleeding:** Overall, the incidence of major bleeds was similar in the two treatment arms of ROCKET, though types and sites of major bleeding differed somewhat between the two drugs. Whereas hemoglobin drops and transfusions occurred at a higher incidence on rivaroxaban, critical site and fatal bleeds occurred at a higher incidence on warfarin. Major GI bleeds was more common on rivaroxaban and intracranial hemorrhages were more common on warfarin.

Like the efficacy findings, the bleeding findings must be viewed in the context of how well warfarin was administered. Bleeding risk increases when INR exceeds the therapeutic range and in ROCKET, patients were above therapeutic range on average (mean) 16% of the time. Site-level TTR analyses suggested that the findings for bleeding (relative to warfarin) might not have been as favorable if warfarin had been administered better. Analyses stratifying patients by baseline vitamin K antagonist use also suggest this. The Clinical Reviewer questions the significance of the site-level TTR analyses because the increase in risk on rivaroxaban (relative to warfarin) resulted from changes in bleeding rates in the rivaroxaban arm (as opposed to decreasing rates of bleeding on warfarin at higher quartiles of TTR). While I think that this perhaps points to some limitations in our understanding of TTR analyses, I don't think it should be a reason to dismiss the finding.

**Events occurring during the transition off of rivaroxaban:** The only other important safety issue identified was a higher incidence of strokes in rivaroxaban (compared to warfarin treated subjects) following study medication discontinuation at the end of ROCKET, a finding also seen in J-ROCKET. As discussed in the body of this memorandum, available data suggest that this finding may reflect poor handling of the transition to warfarin as opposed to a rebound hypercoagulable state.

The transition from rivaroxaban to warfarin at ROCKET’s end was left to the discretion of investigators- no recommended algorithm was provided. Moreover, no provisions were made for a period of overlap with warfarin, despite rivaroxaban’s short half-life and the fact that warfarin’s anticoagulant effect can be delayed for several days. The Applicant has proposed language in labeling indicating that a period of overlap is needed when transitioning from
rivaroxaban to warfarin. Specifically, the applicant has proposed that: (1) warfarin be given concurrently with rivaroxaban for at least two days, (2) INR be measured immediately prior to the administration of rivaroxaban dose beginning on day 3 and daily thereafter until the INR ≥ 2, and (3) rivaroxaban be stopped when the INR ≥ 2. The clinical pharmacology reviewers have endorsed this approach with a slight variation- they recommend that for the purposes of monitoring INR during the transition, an INR measurement taken at least 16 hours post-dose can serve as the basis for the decision to stop rivaroxaban. The Hematology consult recommends a further variation- using the patient's baseline INR on rivaroxaban and not simply an INR between 2 to 3 to decide when to discontinue rivaroxaban. In contrast, the clinical reviewers recommended a complete response, arguing that that the Applicant’s proposed instructions for transitioning have not been evaluated or shown to be safe in terms of bleeding risk or embolic risk in a clinical study. They recommend that such a study be done prior to approval and as the basis for this recommendation, they cite 21 CFR 314.125(b)(4): “insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling”.

There is no regulatory precedent (thus far and based on an n of one- dabigatran) for requiring a development program to test in patients with atrial fibrillation the effectiveness of a transition strategy for achieving a therapeutic INR on warfarin (much less its effects on bleeding and/or thrombotic events during the transition). Recommendations for dabigatran were based on clinical pharmacology attributes of the drug as well as advice given to investigators at the end of the study. The situation here, however, is perhaps somewhat different from the situation we previously faced:

1) There are data from the rivaroxaban program showing a problem in the transition period.
2) There is some uncertainty regarding the nature of rivaroxaban’s benefit. As a consequence, tolerance for risks should be low(er).
3) There are marketed alternatives with more robustly established efficacy and so it is hard to argue that rivaroxaban’s approval can’t or shouldn’t be delayed pending the collection of further data addressing the effectiveness of a given transition strategy should such data be deemed critical for writing labeling.
4) Given the need to administer rivaroxaban with the evening meal and its inconstant effects on INR over the 24 hour inter-dosing interval, it is not clear that implementing what the Applicant has proposed (or any other strategy that have been discussed internally) will necessarily prove to be an acceptable method of transitioning patients in clinical practice.

One issue that has come up during internal discussions is how often patients will need to be transitioned from rivaroxaban to warfarin in clinical practice. It is hard to predict but it seems likely that this will occur (e.g., because a patient wants to switch, their doctor thinks they should switch, because of insurance issues, etc). Another more fundamental question has also been raised- why for this therapy (or for any other therapy that is intended to be used chronically) one needs to be able to write labeling that describes how to transition to an alternative chronic therapy? The present case perhaps takes this question to an extreme: (1) the need to know how to transition from rivaroxaban to one particular, albeit commonly used, chronic therapy (warfarin) and (2) the need to know how to transition directly (i.e., without first placing the patient on a parenteral agent with a fast onset, an approach that is recommended by guidelines when initiating warfarin in patients in whom a rapid effect is required 5).

From a regulatory standpoint, it does not seem sensible to make it a requirement that applicants conduct clinical studies testing how to transition from their particular chronic...
therapy to another/all other marketed chronic therapies. Even if one wanted to make that recommendation here, arguing that this case is unique, it is still not clear such an action would be supported by the regulations and specifically 21 CFR 314.125(b)(4). Though the relative risk of a stroke during the transition period in ROCKET was high in the rivaroxaban compared to warfarin treatment arm (HR of 3.7, 95% CI of 1.5 to 9.2), the absolute incidence was low during the transition and hence the absolute difference in risk (rivaroxaban rate minus warfarin rate) was not marked. In the rivaroxaban arm, 0.48% of subjects experienced a stroke in the transition period compared to 0.13% in the warfarin arm- a difference in absolute incidence of 0.35%. Furthermore, even if these off-treatment events are included in the primary endpoint analysis, the point estimate for the HR remains favorable (0.91) and the upper bound of the 95% CI (1.07) remains well below the FDA non-inferiority margin of 1.38.

For certain, revisions are needed to the Applicant’s proposed label to ensure that this particular safety issue is adequately addressed and that the labeling requirements specified in 21 CFR 201.56 and 201.57 are met. Toward this end, I think the label should indicate that patients with atrial fibrillation who stop rivaroxaban are at immediate risk of strokes/embolic events; this should perhaps be communicated in a boxed warning. It should also indicate that to mitigate this risk adequate anticoagulation would need to be provided by an alternative agent should rivaroxaban be stopped. With regard to transitioning from rivaroxaban to warfarin, the label should describe the experience in the clinical trial setting in which no provisions were made for a period of overlap with warfarin. At this time, it is not clear to me how much or what the label should say about a particular strategy for transitioning (e.g., the strategy proposed by the sponsor, the one proposed by DHP, the use of a parenteral agent to bridge therapies or some other approach). It is an important labeling issue that will need to be considered (and is being considered by the primary review team) as we move forward.

Other issues: As previously noted, the relatively low TTR in ROCKET appears to have resulted in part from important differences in the management of warfarin in different regions of the world and ROCKET’s design which largely left the management of warfarin to the discretion of study investigators. A question that was raised by a member of the Advisory Committee was whether or not trials should be designed to mirror “real-life” practices. This was then carried a step further when a member asked if this also meant that international studies should reflect practices in these countries.

“Pragmatic” global trials (i.e., studies that allow warfarin management to reflect local practices) may provide information about the relative merits of a study drug on a global level. They may or may not, however, produce findings that have any relevance for U.S. patients. If global studies are to support approval in the U.S., they should provide information that speaks to the risks and benefits of novel therapeutic agents within the context of U.S. standards of care. If this necessitates that protocols incorporate measures to ensure this goal is met (e.g., recommended dosing or monitoring algorithms), then, in my view, this should be done.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
A communication plan should address events seen in the post-treatment period (with emphasis on the risk of embolic events if rivaroxaban is stopped and adequate anticoagulation is not provided by another agent) and bleeding risk. It should possibly also address the need to administer rivaroxaban with the evening meal.

2 As described under Other Relevant Regulatory Issues, at one of the foreign sites that was inspected, the investigator reported that he had intentionally maintained the INR between 1.5 and 2.0 so as to minimize the risk of bleeding in subjects on warfarin.
Recommendation for other Postmarketing Requirements and Commitments

Bleeding is an important toxicity of anticoagulants and at this time, there is no established antidote for rivaroxaban. GI bleeding was more common on rivaroxaban and in the U.S., rates of major bleeding were high. A postmarketing study is needed to address methods for reversing rivaroxaban’s anticoagulant activity and hence ensure that rivaroxaban’s risks do not exceed its benefits. Options that should be explored include: (1) preclinical studies (there would need to be confidence that findings from such studies could be easily translated into humans), (2) an enhanced pharmacovigilance plan (this could be linked to the pre-existing postmarketing requirement under NDA 022406), or (3) a clinical study testing the effects of a promising agent/intervention on bleeding in patients experiencing a clinically significant bleed or in patients who require urgent invasive or surgical procedures.

Recommended Comments to Applicant
None at this time.

Reference List


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/s/

ALIZA M THOMPSON
10/06/2011