

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)
Marriott Inn and Conference Center,
University of Maryland University College (UMUC)
East, Adelphi, Maryland
September 8, 2011

QUESTIONS TO THE COMMITTEE

Cardiovascular and Renal Drugs Advisory Committee Questions: September 8, 2011

The Advisory Committee is asked to opine on the approvability of rivaroxaban, a factor Xa inhibitor, to reduce the risk of stroke and non-central nervous system systemic embolus (SEE) in patients with non-valvular atrial fibrillation.

The support for this claim comes primarily from ROCKET-AF, a double blind study in which 14264 subjects with persistent or paroxysmal atrial fibrillation and additional risk factors for stroke¹ were randomized to warfarin or to one regimen of rivaroxaban. The trial was event-driven, and median exposure was about 19 months. Important results are as follows:

| | Hazard ratio for rivaroxaban vs. warfarin | | |
|---------------|---|--------------------------------|-------------------|
| | Safety population ² | ITT population | |
| | “On treatment” ³ | Up to site notification | To data cutoff |
| Stroke/SEE | 0.79 (0.66, 0.96) | 0.88 (0.78, 1.03) | 0.91 (0.78, 1.07) |
| —Isch stroke | 0.95 (0.76-1.18) | 0.99 (0.82, 1.20) | 1.03 (0.85, 1.24) |
| —Hem stroke | 0.59 (0.37, 0.93) | 0.58 (0.38, 0.89) | 0.65 (0.43, 0.98) |
| —SEE | 0.23 (0.09, 0.61) | 0.74 (0.42, 1.32) | 0.74 (0.42, 1.32) |
| Any mortality | 0.85 (0.70, 1.02) | 0.92 (0.82, 1.03) | 0.93 (0.84, 1.04) |
| —Hemorrhagic | 0.56 (0.41, 0.92) | 0.63 (0.44, 0.90) ⁴ | 0.66 (0.47, 0.92) |
| “Major” hem | 1.04 (0.90, 1.20) | — | — |
| —Intracranial | 0.67 (0.47, 0.93) | — | — |

The FDA review team identified bleeding as the only significant safety issue. However, despite results on the primary end point that appear to show superiority to warfarin in reduction of the risk of stroke and systemic embolus at no evident increase in bleeding risk, several issues warrant discussion.

¹ (a) Prior ischemic stroke, TIA, or systemic embolism, or (b) any two of the following: age >75, hypertension, heart failure or ejection fraction <35%, or diabetes

² Anyone receiving at least one dose of randomized treatment.

³ Up to last dose plus 2 days

⁴ Through the follow-up visit.

QUESTIONS TO THE COMMITTEE (cont.)

The Committee is being asked to consider *how* effective rivaroxaban is, and whether that degree of effectiveness is adequate for approval.

Questions:

- 1) **DISCUSSION:** Please comment on the adequacy of the *design* of ROCKET-AF.
 - a. Was the planned warfarin management strategy reasonable?
 - b. Was it reasonable to test a single regimen of rivaroxaban in ROCKET-AF? Was the specific choice of regimen reasonable, given the short half-life and nonlinear kinetics of rivaroxaban?
 - c. The primary analysis included events that occurred within 2 days of discontinuing study drug. For how many days should end point events that occurred after discontinuation of study drug—during the study or at its end—be counted?
 - d. Are there other aspects of study design that importantly affect interpretation of the study?

- 2) **DISCUSSION:** The interpretation of a non-inferiority study depends upon certain understanding of the effect of the active control. If the active control is used to achieve less than its expected effect, a finding of non-inferiority may not be informative regarding the effectiveness of the study drug. Similarly, a finding of superiority to a suboptimally administered active control cannot be used to support superiority of the study drug. Please comment on the adequacy of the conduct of ROCKET-AF.

QUESTIONS TO THE COMMITTEE (cont.)

One measure of the quality of warfarin management, time in therapeutic range (TTR), was not as good in ROCKET-AF as in many recent randomized, controlled studies.

| Study | Mean TTR |
|------------------|-----------------|
| ACTIVE W | 64% |
| AMADEUS | 64% |
| ARISTOTLE | 62% |
| RE-LY | 64% |
| SPORTIF III | 66% |
| SPORTIF V | 68% |
| <i>ROCKET-AF</i> | 55% |

- a. Was anticoagulation on warfarin in ROCKET-AF good enough so that the warfarin group is an appropriate comparator to show ...
1. ... effectiveness of rivaroxaban?
 2. ... superiority of rivaroxaban to warfarin?
- b. Disposition of subjects in ROCKET-AF is summarized below:

| | Warfarin | Rivaroxaban | |
|--------------------|-----------------|--------------------|------|
| Intent to treat | 7133 | 7131 | 100% |
| Completed on drug | 4657 | 4591 | 65% |
| Completed off drug | 1372 | 1444 | 20% |
| Died ⁵ | 638 | 583 | 9% |
| Withdrew | 458 | 493 | 7% |

⁵ These are deaths as a cause for leaving the study. Deaths by intent to treat were 673 on warfarin and 624 on rivaroxaban.

QUESTIONS TO THE COMMITTEE (cont.)

Please comment on how the disposition data affect your ability to infer ...

- 1.... effectiveness of rivaroxaban?

- 2.... superiority of rivaroxaban to warfarin?
 - c. Was follow-up for end point events adequate in both treatment groups?

 - d. Are there other aspects of study conduct that importantly affect interpretation of the study?

- 3) **DISCUSSION:** Please comment on effectiveness. How does rivaroxaban compare with warfarin ...
 - a. ... as used in ROCKET-AF?

 - b. ... as used in the US?

 - c. ... when it is well managed?

As part of the Clinton administration “Reinventing Government” initiative, FDA published (Federal Register 1995 60(147):39180-1) a policy that said, in part,

“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.”

QUESTIONS TO THE COMMITTEE (cont.)

- 4) **DISCUSSION:** The “as effective” policy explicitly does not apply if the new therapy is studied in a new population. In considering how this exclusion might apply to rivaroxaban, here are some points for comparison of the warfarin arms in RE-LY and ROCKET-AF.

| Baseline | RE-LY | ROCKET | Study | RE-LY ⁶ | ROCKET ⁷ |
|-----------------------------|-------|--------|--------------------------|--------------------|---------------------|
| Age >75 | 40.2 | 37.8 | Stroke/SEE | | |
| VKA naïve | 51.4 | 37.3 | TTR <46.8 | 1.87 | 2.60 |
| Prior stroke, TIA or SEE | 21.4 | 54.6 | 46.8-55.9 | 2.41 | 2.59 |
| | | | 55.9-63.9 | 2.10 | 2.43 |
| | | | >63.9 | 1.49 | 2.06 |
| CHADS2 | | | Major bleed ⁸ | | |
| <2 | 30.9 | 0 | TTR <46.8 | 4.00 | 3.30 |
| 2 | 37.0 | 13.1 | 46.8-55.9 | 3.39 | 3.67 |
| >2 | 32.1 | 86.8 | 55.9-63.9 | 3.80 | 3.66 |
| | | | >63.9 | 3.65 | 3.68 |

Is the population in ROCKET-AF sufficiently distinct from the population in RE-LY that the “as effective” policy does not apply? If so, how?

- 5) **DISCUSSION:** If you conclude that the policy does apply and that rivaroxaban needs to be “as effective as” something, ...
- a. ... what does “as effective” mean operationally?
 - b. ... is it sufficient to be “as effective” as warfarin? If so, is it?

⁶ Data from RE-LY are based on ITT analysis of the quartile cutpoints from ROCKET-AF. The breakdown of RE-LY subjects by ROCKET-AF quartile 5%, 10%, 22%, and 63%.

⁷ Data from ROCKET are based on events observed up to site notification of study closure, roughly equivalent to the ITT analysis of RE-LY.

QUESTIONS TO THE COMMITTEE (cont.)

- c. ... is it necessary to be “as effective” as something else? If so, ...
 - 1. ... do you need a direct comparison to the “something else”?
 - 2. ... is it?

- 6) **DISCUSSION:** Are there adequate instructions for use with regard to ...
 - a. ... what regimen to use in most patients? If not, does this matter?

 - b. ... what dose adjustments are needed in patients at extremes of exposure or risk? If not, does this matter?

 - c. ... transitioning between rivaroxaban and other anticoagulant therapy? If not, does this matter?

 - d. ... actions to take in the event of serious bleeding? If not, does this matter?

- 7) **VOTING:** Should rivaroxaban be approved for the reduction of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation?

- 8) **DISCUSSION:** If you voted to approve rivaroxaban to prevent strokes in patients with atrial fibrillation, does it merit ...
 - a. ... a superiority claim to warfarin?

 - b. ... a claim as an effective alternative to warfarin?

 - c. ... a claim as effective?

 - d. ... a claim for patients failing other anticoagulant therapy? If so, what constitutes failure?

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QUESTIONS TO THE COMMITTEE (cont.)

- 9) **DISCUSSION:** If rivaroxaban were to be approved for stroke prevention in patients with atrial fibrillation, ...
- a. ... are there any constraints you would place on the population in whom it would be indicated?

 - b. ... are there any issues you would want to resolve post-marketing?