

**Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee**

September 8, 2011

**Location: UMUC Inn and Conference Center by Marriott, 3501 University Boulevard East,
Adelphi, Maryland, 20783**

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

**These summary minutes for the September 8, 2011 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on
____ October 28, 2011 _____.**

I certify that I attended the September 8, 2011 Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Kristina A. Toliver, Pharm.D.
Designated Federal Officer, CRDAC

/s/
A. Michael Lincoff, M.D.
Acting Committee Chair

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 8, 2011 at the UMUC Inn and Conference Center by Marriott, 3501 University Boulevard East, Adelphi, Maryland, 20783. Prior to the meeting, members and invited consultants were screened and cleared for conflict of interest, and provided copies of the background material from the FDA and the sponsor. The meeting was called to order by A. Michael Lincoff, M.D. (Acting Cardiovascular and Renal Drugs Advisory Committee Chair); the conflict of interest statement was read into the record by Kristina A. Toliver, Pharm.D. (Designated Federal Officer). There were approximately 100 persons in attendance. There were no speakers for the Open Public Hearing session.

Issue: The committee discussed new drug application (NDA) 202439, rivaroxaban tablets, submitted by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. on behalf of Ortho-McNeil-Janssen Pharmaceuticals, for the prevention of stroke and systemic embolism (blood clots other than in the head) in patients with non-valvular atrial fibrillation (abnormally rapid contractions of the atria, the upper chambers of the heart).

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):

Allan Coukell, B.Sc., Pharm. (Consumer Representative), Sanjay Kaul, M.D., Mori Krantz, M.D., F.A.C.C., Darren McGuire, M.D., M.H.Sc., F.A.C.C.

Special Government Employee Consultants (Temporary Voting Members):

Scott Emerson, Ph.D., Thomas Fleming, Ph.D., A. Michael Lincoff, M.D. (Acting Chair), Debra McCall, B.S., M.A.M (Patient Representative), Steven Nissen, M.D., Philip Sager, M.D.

Regular Government Employee Consultants (Temporary Voting Members):

Vasilios Papademetriou, M.D., Andrei Kindzelski, M.D.

Cardiovascular and Renal Drugs Advisory Committee Member (Non-Voting):

Jonathan Fox, M.D., Ph.D., F.A.C.C. (Industry Representative)

Cardiovascular and Renal Drugs Advisory Committee Members Not Attending:

Jonathan Halperin, M.D., Judith Hochman, M.D.,

FDA Participants (Non-Voting):

Robert Temple, M.D., Norman Stockbridge, M.D., Ph.D.

Designated Federal Officer:

Kristina A. Toliver, Pharm.D.

Open Public Hearing Speakers:

None

The agenda was as follows:

| | |
|--|--|
| Call to Order and Opening Remarks Introduction of Committee | A. Michael Lincoff, M.D. Acting Chair, CRDAC |
| Conflict of Interest Statement | Kristina Toliver, Pharm.D. Designated Federal Officer, CRDAC |

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|--|---|
| Opening Remarks | Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products (DCRP), Office of Drug Evaluation (ODE) I, CDER, FDA |
| <u>Sponsor Presentation</u> | <u>Johnson & Johnson Pharmaceutical Research and Development, L.L.C.</u> |
| Introduction | Gary R. Peters, M.D. Vice President, Cardiovascular Development, Johnson & Johnson Pharmaceutical Research & Development |
| Medical Landscape & Study Design | Kenneth W. Mahaffey, M.D. Co-Director, Duke Clinical Research Institute Cardiovascular Research Director, Duke Clinical Research Institute Clinical Endpoint Committee Group |
| Efficacy | Robert M. Califf, M.D. Vice Chancellor Clinical Research, Duke University Medical Center Director, Duke Translational Medicine Institute |
| Safety | Christopher C. Nessel, M.D. Senior Director, Clinical Research Johnson & Johnson Pharmaceutical Research & Development |
| Key Issues, Benefit Risk and Conclusions | Robert M. Califf, M.D. |
| Clarifying Questions for Sponsor Presenters | |
| Break | |
| <u>FDA Presentation</u> | NDA 202439 |
| Dose Selection | Preston Dunnmon, M.D. Clinical Reviewer Division of Cardiovascular and Renal Products |
| Issues Affecting Interpretation of the Efficacy Data | Martin Rose, M.D., J.D. Clinical Reviewer Division of Cardiovascular and Renal Products |
| Clarifying Questions for FDA Presenters | |
| Lunch | |

Open Public Hearing

Questions to the CRDAC and CRDAC Discussion

Break

Questions to the CRDAC and CRDAC Discussion

Adjourn

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 stroke 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 | ITT population | |
| | “On treatment” | 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) | 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.

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?

Some members thought the planned warfarin management strategy was not reasonable. There was not a standardized algorithm for warfarin maintenance dose adjustment, which other studies have utilized with subsequent higher TTR.. A protocol how to manage out of range INRs may have overcome

mediocre time in therapeutic range TTR. Other members thought the strategy was reasonable as the intent was to reflect the way heparin is actually used in the real world setting and not to provide an artificial warfarin dosing strategy.

Please see transcript for detailed discussion.

- 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?

Some members thought it was reasonable to test a single once-daily regimen of rivaroxaban as the pharmacokinetic data did not show large differences between once-daily and twice-daily dosing and there did not seem to be large difference in the available clinical trial data. Once-daily dosing was also thought to be beneficial from a patient compliance standpoint. Other members thought that studying twice-daily dosing would have been beneficial. There were concerns that not having twice-daily dosing could lead to increased risk of bleeding or reduced efficacy. Additionally, since rivaroxaban has a shorter half-life than dabigatran, which is dosed twice daily, rivaroxaban should have been studied twice-daily. Members questioned why the study couldn't prove superiority over warfarin, considering the warfarin therapy was not optimal.

Please see transcript for detailed discussion.

- 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?

Some members said they were not able to say how many days to count as ITT has to consider events that occur after stopping the drug may be related to the study drug. Some felt that the 2 days used in the trial was reasonable, given the pharmacokinetics of the drug, and that events occurring after 2 days reflect inadequate bridging but not the effect of the drug therapy. Others felt that it is best for ITT duration to follow-up to a target number of events or until everyone is followed for a certain number of months from randomization. Many members believed that two days following study drug discontinuation was too short.. Some members thought it would be best to follow-up 7 – 14 days in order to rule out rebound hypercoagulability. Some members thought follow-up should be conducted for 30 days from on-treatment, as this seemed to capture where events were happening off study drug and that 30 days is commonly used in clinical trials.

Please see transcript for detailed discussion.

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

Members identified many aspects that included TTR percentages, handling of transition off of the study drug, missing data, and double counting of safety events toward efficacy. Members expressed concerns about the exclusion of patients scheduled for cardioversion, since that is often used in the real world. Additionally, members would like to have known how rivaroxaban performed against dabigatran. Furthermore, there was concern among some members that efficacy should only be reflected in ischemic events but others disagreed, as what is important to the patient is having a stroke. The Agency stated that distinguishing between the two different types of strokes may help to determine if different doses are better for the different types of strokes.

Please see transcript for detailed discussion.

- 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

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?

Questions 2.a.1 and 2.a.2 were discussed together. Members were concerned whether or not warfarin was being used as well in ROCKET as it was in other contemporary trials. However, other members stated that it is difficult to keep INR in a fixed range and that it depends on what population you select for the clinical trial and what resources you have for the study. Some members preferred to have seen the TTR higher; however other members thought the TTR in ROCKET was reflective of clinical practice. Members stated that superiority by ITT analysis was not established and it is difficult to understand TTR in determining non-inferiority against warfarin. It was also stated that quartile analysis of three major trials showed no relationship between TTR and relative treatment effect of new anticoagulant vs. warfarin. Some members stated that rivaroxaban is superior to placebo, even with poor TTR, however it is clearly not superior to warfarin.

Please see transcript for detailed discussion.

- 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 | 638 | 583 | 9% |
| Withdrew | 458 | 493 | 7% |

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?

Questions 2.b.1-2, 2c, and 2d were discussed together. Members stated that the ITT analysis did not establish superiority before considering irregularities with TTR. It was also stated that interpretation of non-inferiority is complicated by high levels of missing data due to discontinuation, withdrawal of consent, follow-up of only two days, and high event rates with endpoints such as death. Members appreciated the sensitivity analysis showing that with worst-case scenario, the non-inferiority bound was met. However, it was stated that the ITT comparison was more fragile, and no sensitivity analysis was conducted for that.

Please see transcript for detailed discussion.

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?

Questions 3a, 3b, and 3c were discussed together. Members stated that it may be difficult to compare the effectiveness of rivaroxaban vs. warfarin when it is well managed because the TTR and truncation at plus day 2. Other members stated rivaroxaban is non-inferior to warfarin with regard to efficacy. However, it was pointed out that rivaroxaban failed to show superiority on the primary safety endpoint of major bleeding. Members were concerned about creeping non-inferiority when looking at the TTR in ROCKET and wondered where the line will be drawn. It was stated that some committee members had asked to look at upper bound confidence intervals in subgroups, but that clinical trials can not be powered for statistical significance in subgroups and that the confidence interval criteria in these cases were not meaningful.

Please see transcript for detailed discussion.

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 | ROCKET |
|-----------------------------|-------|--------|--|------------------------------|------------------------------|
| Age >75 | 40.2 | 37.8 | Stroke/SEE TTR <46.8 46.8-55.9 55.9-63.9 >63.9 | 1.87 2.41 2.10 1.49 | 2.60 2.59 2.43 2.06 |
| VKA naïve | 51.4 | 37.3 | | | |
| Prior stroke, TIA or SEE | 21.4 | 54.6 | | | |
| | | | | | |
| CHADS2 | | | Major bleed ¹ | | |
| <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?

Some members stated that the ROCKET patient population was a sicker patient population than in the RELY trial. However, other members felt there was substantial overlap between the patient populations of both trials. Some members felt that if the indication is the same as for the therapy in the other trial, the “as effective” policy applies. Some members did not feel that the question was appropriate with regard to the policy because a new population and new therapy is not a concern when doing a non-inferiority assessment because the new therapies were not available in the historical trials

- 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?
 - 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?

Questions 5a, 5b, and 5c 1-2 were discussed together. Members stated that “as effective” means ruling out non-inferiority. It was stated that rivaroxaban would be sufficient to be non-inferior to warfarin unless other agents had unequivocally been established to be superior and to become the new standard of care (in which case, rivaroxaban would need to be as effective as the best of those other therapies. Members were uncomfortable saying that rivaroxaban is non-inferior to an inferior product). However, most felt that dabigatran has not achieved status as standard of care superior to warfarin. With the differences in population between ROCKET and RELY, it is difficult to compare the relative treatment effects of rivaroxaban and dabigatran vs. warfarin. It is not clear how dabigatran would compare against warfarin in a sicker population, but rivaroxaban is at least non-inferior to warfarin in a sicker population. However there was concern that a drug such as dabigatran that is superior in a less sick population may not be proven to be superior in a sicker population. Members thought it was beneficial to have competitive therapies and that rivaroxaban would be better than clopidigrel or clopidigrel with aspirin.

Please see transcript for detailed discussion.

- 6) **DISCUSSION:** Are there adequate instructions for use with regard to ...
- ... what regimen to use in most patients? If not, does this matter?
 - ... what dose adjustments are needed in patients at extremes of exposure or risk? If not, does this matter?
 - ... transitioning between rivaroxaban and other anticoagulant therapy? If not, does this matter?
 - ... actions to take in the event of serious bleeding? If not, does this matter?

Questions 6a through 6d were discussed together. The committee was concerned that there was no data on how to address discontinuation and/or transitioning between rivaroxaban and other anticoagulant therapies. The blinded design of ROCKET made it difficult to address discontinuation. It was stated that it is not known how to bridge most anticoagulant therapies, but physicians will do what they feel is best. Members thought that a properly performed clinical trial examining INR's, which would not need to be large, would be informative to address the medical needs of discontinuation of rivaroxaban and provide needed information to healthcare providers.

Please see transcript for detailed discussion.

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

Yes: 9 No: 2 Abstain: 1

The members who voted yes felt that rivaroxaban was non-inferior to warfarin. Many members felt it was beneficial to have an additional option for oral anticoagulation. The members were pleased with the patient population used in ROCKET. There was concern about the once-daily dosing being used as a marketing ploy and about the lack of data informing the transition to warfarin..

The members who voted no were worried that based on the half-life of the drug, it should be administered twice daily. There were also concerns regarding the TTR and the lack of a dosing scheme for warfarin in ROCKET. The members felt the lack of a plan for bridging was an approvability issue and that rivaroxaban may be a step back instead of a step forward when thinking about dabigatran.

The member who abstained felt that rivaroxaban was superior to placebo, but felt it could not be concluded that it is superior to warfarin, and that it may be possible to justify non-inferiority to warfarin. There was concern regarding TTR levels, events occurring at transition, deaths two days post study drug, and missing data.

Please see transcript for detailed discussion.

- 8) **DISCUSSION:** If you voted to approve rivaroxaban to prevent strokes in patients with atrial fibrillation, does it merit ...
- ... a superiority claim to warfarin?
 - ... a claim as an effective alternative to warfarin?
 - ... a claim as effective?
 - ... a claim for patients failing other anticoagulant therapy? If so, what constitutes failure?

Questions 8a through 8d were discussed together. The committee felt that rivaroxaban was not superior to warfarin. Most, although not all members, felt that rivaroxaban met criteria as an effective alternative to warfarin. Members felt it was effective vs. placebo and some viewed it as effective. Rivaroxaban was considered to merit a claim for patients failing other anticoagulant therapies. Failure of other

anticoagulant therapies was defined as issues such as difficulty using warfarin, inability to maintain appropriate INR, warfarin-induced skin necrosis or gastrointestinal upset with dabigatran.

Please see transcript for detailed discussion.

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?

Questions 9a and 9b were discussed together. Members preferred constraints on the indicated population for patients with end stage renal disease, end stage liver disease, those well-controlled on warfarin without reasons to switch, and those with low body weight. Members also preferred for studies to be conducted to exclude hypercoaguability and to test different bridging regimens. Many members wanted the bridging studies to be conducted premarketing.

Please see transcript for detailed discussion.

Meeting adjourned at approximately 5:00 p.m.