

Memo to File:

Addendum to Efficacy review for ranolazine:

Subsequent to the filing of the efficacy review of ranolazine, the sponsor submitted responses to additional questions posed in the review. In the opinion of the medical reviewer, these responses do not alter the reviewer conclusions.

The following additional information was sent by the sponsor:

1. CVT 3033: the sponsor was asked to supply the Interim Analysis Procedure:

An Interim Analysis Procedure was received by the medical reviewer. The purpose of the Interim Assessment was to re-evaluate sample size using the standard deviation of the change from baseline in ETT duration from the first half of the study population without unblinding the study with respect to treatment assignment. According to this procedure, the sponsor will remain blinded to any treatment-specific outcome and associated information.

The medical reviewer found this document to be satisfactory.

- 2. The sponsor was asked to explain why the first period analysis in RAN 1514 did not show statistical significance for peak or trough.** In a fax received 8/28/03, the sponsor responded that the first-period-only analysis has low power relative to the primary analysis. In addition, RAN 1514 showed high variability of the between-patient comparisons (evident in the width of the confidence intervals for the treatment differences). By contrast, the power of the primary analysis using all of the crossover periods and within-patient comparisons allows for detection of the statistically significant treatment effects at peak in that analysis. The sponsor also claimed that the first-period-only analysis can be useful for a crossover study in which there is evidence of a carryover effect; according to the sponsor, they have no evidence of a carryover effect in this or any other ranolazine study.

The sponsor also reviewed Table 1 (controlled clinical trials) from the Integrated Summary of Efficacy. The sponsor offered the following comments/corrections to the reviewer's table (received by the reviewer on 8/29/03): 1. RAN 054 contained 144, not 137, randomized; 2. RAN 072 was a single-dose study and therefore, the ranolazine IR single doses (not bid) were 10, 60, 120 and 240 mg; 3. Parallel group studies CVT 3033, RAN 1513 and RAN 2240 were multiple dose; 4. RAN 020 included, as primary endpoints, angina frequency, nitroglycerin consumption, time to exercise-induced angina, total treadmill time, HR/BP/RPP/ workload at end of exercise; 5. RAN 054 included, as primary endpoints, angina frequency, nitroglycerin consumption, total exercise time plus time to exercise-induced angina at peak and trough. 6. RAN 1490 included, as primary endpoint, exercise duration at peak and trough.

The medical reviewer concurs with points #1-3 and notes that RAN 020 did not contain a primary endpoint that was explicitly prespecified in the protocol. According to the sponsor, RAN 054 contained multiple endpoints (as can be seen above). However, from the Statistical Report of RAN 054, the primary efficacy variable of interest was peak total exercise time.

Please note (as the sponsor also noted) that studies RAN 054, RAN 020, RAN 1490 and RAN 015 did not contribute to evaluation of efficacy.

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Medical Reviewer