Reviewer’s report

Title: Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a historical-control phase III study

Version: 1 Date: 12 January 2015

Reviewer: Carl J Lombard

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Comments to the authors.

1. The limitation of using historical controls. The outline of this limitation (lines 392-404) is now much clearer. The ideal would be to adjust the historical yardstick (65.3%) to one that takes account of the CBZ prevalence in the current study setting. I am not sure if a this meta-regression of exit rates on CBZ prevalence will be possible in the historical studies. The current yardstick is thus very liberal. The same comment that are made in line 76 on direct equivalence studies thus also hold for this study.

2. The determination of the endpoints now has more information. This description raises more questions. The primary endpoint could be any one of five criteria. Two of these were calculated after the data collection by the statisticians. What happened to participant who met the exit criteria during the active trial period? Where they immediately converted back to their baseline therapy. If so how was this possible if 2/5 criteria where determined after the trial. How was this risk avoided – having a participant on the trial therapy when it was no longer indicated?

3. The primary endpoint was determined by numerous investigators (n=41 sites). What was in place to ensure that the trial endpoint would have good reliability as measurement? What is the reliability in the measurements that they performed for the endpoint. The question on the independent review of the endpoints was not answered. Is there any relationship between the low exit rates and the reliability of the investigator determinations( and or completeness of diaries)?

4. Difference between exit rate for the ESL dose groups. Line 253-254. Since this sample size was not based on the ESL group comparison this sentence can be dropped. This was the comparison that I mention in my previous review #6a. The sequential testing for the trial is fine but the direct comparison between the arms is the problem. This direct comparison is reflected in the first sentence of the discussion which is problematic. The primary analysis result should be the first discussion point. Suggestion – line 347. The primary efficacy endpoint ( the proportion of patients who exited the study on meeting at least one exit criterion, e.g. due to poor seizure control) was <16% in both ESL dose groups and the formal study inference confirmed that the exit rate for ESL monotherapy (both dose levels) was significantly lower than that for the historical control. Thus, the efficacy......
The wording line 348 ‘was similar between ESL groups’ is the problem in the first sentence. This sentence is based on the non-significance of the difference between the exit rate. Having a simple descriptive bit in the first sentence solves the problem.

5. The Y-labels that have been added to Figures 4 and 5 are problematic. The description of the Y-axis can only be a description of the scale of the variable. Cumulative exit rate at 112 days would be more correct in both instances.

**Statistical review:** Yes, and I have assessed the statistics in my report.