Author's response to reviews

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

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Author's response to reviews: see over
Dear Dr Shipley

On behalf of my colleagues, I would like to re-submit to *BMC Neurology* this manuscript of original clinical research entitled “Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a historical-control phase III study”.

All the reviewer’s comments of 12 January 2015 have been addressed (please see a point-by-point response to the reviewer’s comments below), and amendments to the manuscript have been made where necessary.

Many thanks for your time to review this re-submission. If you have any further questions, please do not hesitate to contact me using the contact details above. I look forward to hearing from you.

Respectfully,

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Response to reviewer’s comments of 12 January 2015

#1. The limitation of using historical controls. The outline of this limitation (lines 399-412) 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 meta-regression of exit rates on CBZ prevalence will be possible in the historical studies. The current yardstick is thus very liberal. The same comments that are made in line 76-77 on direct equivalence studies thus also hold for this study.

< Response 1. We continued to use the 65.3% threshold in this publication for the following three reasons:
1) CBZ did not statistically significantly affect exit rate in either this study (analysis using a Cox proportional hazards regression model with CBZ as a covariate, showed that CBZ use did not statistically significantly affect exit rate) or in the trials comprising the historical control [French et al 2010]
2) The upper limit of the confidence interval for subjects taking CBZ at baseline was below the 65.3% threshold, therefore any adjustment would not alter the conclusion of the current study
3) Only prospectively defined endpoints are reported in this publication, not post-hoc endpoints. >

#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 participants who met the exit criteria during the active trial period? Were they immediately converted back to their baseline therapy? If so, how was this possible if 2/5 criteria were determined after the trial. How was this risk avoided – having a participant on the trial therapy when it was no longer indicated?

< Response 2. In this study, the investigators did indeed require patients to exit (during the trial) based on the 2 exit criteria relating to doubling of seizure rates. When patients exited the trial (by meeting an exit criterion), they either re-started their previous AEDs or added a new AED, at the investigator’s discretion. Analyses of the 2- and 28-day seizure rates were performed by the study statisticians for computation of the primary endpoint. Some patients could have been reclassified as non-exits by this post-study analysis by the statisticians. This statistical method was recommended by the FDA. However, if the investigator had required a patient to exit due to an incorrect calculation, they would probably have also required the patient to exit based on criterion 5 (general worsening). In fact, the results based on investigator attribution (Table 1 below) were virtually identical to those calculated for the primary
#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)?

< Response 3. At the investigator meeting, investigators were trained on seizure classification and methods for recording seizures in diaries. All subject diagnoses and seizure classifications were reviewed by a central 3rd party (Epilepsy Consortium, NYU Medical Center) and the investigators received feedback on seizure classification, to ensure uniform assessment and recording. Almost all patients (>95%) who exited the study met criteria determined from seizure diaries and less than 5% of exits were based on the investigator’s judgement. Therefore the number of investigators involved in the study would have had no impact on outcomes. In addition, because the primary endpoint was determined principally from patient-completed data, independent review was not appropriate.

The proportion of patients meeting exit criterion 5 (investigator judgement) was consistent with that in the historical control trials (not stated in the manuscript, to conserve word count). >

#4. Difference between exit rate for the ESL dose groups. Lines 253-255. 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 349. 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 352-3 ‘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.

< Response 4. We have amended lines 349-356 of the discussion as suggested, in order to address this point. However, we have not deleted lines 253-255 and 258-260 (in the results section), because testing the difference between doses was an integral part of the prospectively defined primary endpoint: the study protocol stated specifically that if the upper confidence limit of the exit rate for both ESL doses was lower than the 65.3% threshold, then the difference between doses would be tested. We do not believe that we should omit reporting part of the primary endpoint of a trial. We have therefore
amended lines (253-255 and 258-260) to make clear that the study was not powered to detect a difference between doses. >

#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.

< Response 5. The y-axis labels of Figures 4 and 5 have been amended to the following: “Cumulative exit rate at 112 days (Kaplan–Meier estimate) (%; 95% CI)”. Please note that the plotted data is not the raw exit rate, but the Kaplan–Meier estimate at 112 days. >

Table 1 Proportion of subjects reaching each exit criterion (efficacy population)

<table>
<thead>
<tr>
<th>Exit Criterion</th>
<th>Statistic</th>
<th>Efficacy Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. One episode of status epilepticus.</td>
<td>n (%)</td>
<td>0 (0%, 0%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(0%, 0%)</td>
</tr>
<tr>
<td>2. One secondary generalized partial seizure (in subjects who did not have generalized seizures during 6 months prior to screening).</td>
<td>n (%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(0.0%, 3.9%)</td>
</tr>
<tr>
<td>3. A two fold increase in any consecutive 28 day seizure rate compared to the highest consecutive 28 day seizure rate during the 8 week baseline period. (Investigator Assessment)</td>
<td>n (%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(1.2%, 15.2%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(0.0%, 12.8%)</td>
</tr>
<tr>
<td>4. A two fold increase in any consecutive 28 day seizure rate compared to the highest consecutive 28 day seizure rate during the 8 week baseline period. (Sponsor’s Programmatic Assessment)</td>
<td>n (%)</td>
<td>5 (5.0%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(1.6%, 11.3%)</td>
</tr>
<tr>
<td>5. More than one exit event category is counted based on the first occurrence.</td>
<td>n (%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(0.6%, 12.7%)</td>
</tr>
</tbody>
</table>

Note: Subjects reaching more than one exit event category are counted based on the first occurrence. Note: Percentages and exact 95% CIs (based on binomial exact methods) are based on the number of subjects in the Efficacy population. Note: Subjects who withdrew due to a non-exit reason that are reassigned as exits are not included.

Reference