Relationship between eslicarbazepine exposure and safety endpoints for eslicarbazepine acetate monotherapy

1.312

Toufic Fakhoury,[1] Jay H Harvey,[2] Robert T Wechsler,[3] Julie Passarell,[4] Jill Fiedler-Kelly,[4] Elizabeth Ludwig,[4] David Blum,[5] Soujanya Sunkaraneni[5]

[1]St Joseph Neurological Associates, Kentucky One Health, Lexington, KY, USA; [2]Texas Epilepsy Group, Dallas, TX, USA; [3]Idaho Comprehensive Epilepsy Center, Consultants in Epilepsy and Neurology PPLC, Boise, ID, USA; [4]Cognigen Corporation – a subsidiary of Simulations Plus, Buffalo, NY, USA; [5]Sunovion Pharmaceuticals Inc., Marlborough, MA, USA

INTRODUCTION

- In two Phase III trials (093-045 and -046) of eslicarbazepine acetate (ESL) monotherapy in patients with partial-onset seizures (POS) uncontrolled by 1–2 antiepileptic drugs (AEDs), the incidence of treatment-emergent adverse events (TEAEs) was found to be related to ESL dose.[1,2]
- Also, higher ESL doses led to greater eslicarbazepine exposure.[3]
- In this analysis, pooled data from studies -045 and -046 were used to evaluate the relationship between eslicarbazepine exposure and the time to first onset of TEAEs, and the relationship between exposure and serum sodium levels, during ESL monotherapy.
  - To assess whether monitoring plasma eslicarbazepine concentrations could be useful to physicians when making decisions regarding potential development or worsening of hyponatremia, or when determining the optimal dose of ESL monotherapy.
- ESL is not approved for monotherapy use.

OBJECTIVE

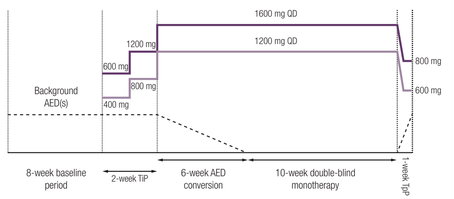
- To develop statistical models describing the relationship between eslicarbazepine exposure and time to first onset of dizziness, headache and nausea, and the relationship between exposure and serum sodium levels, during ESL monotherapy.

METHODS

Study design (studies -045 and -046)

- Data from two Phase III studies (studies -045 and -046) were pooled for this analysis. Both studies were 18-week, double-blind, multicenter, randomized, conversion-to-monotherapy studies which evaluated the efficacy and safety of ESL 1600 mg and 1200 mg once daily (QD) as monotherapy, compared with a historical control (as described by French, et al. 2010[4]).
- Both studies had the same design (**Figure 1**). Following an 8-week baseline period, patients with POS not well controlled by 1–2 AEDs were randomized (2:1) to receive ESL 1600 mg or 1200 mg QD.
  - Patients entered an 18-week, double-blind, treatment period, which consisted of a 2-week titration period, a 6-week AED conversion period (with gradual withdrawal of baseline AEDs), and a 10-week monotherapy period. Patients then had the option to either continue into an open-label extension study or enter a 1-week tapering-off period.
- Major inclusion and exclusion criteria have been previously reported.[1,2]

Figure 1. Study design



AED: antiepileptic drug; QD: once daily; TiP: titration period; TpP: taper period.

Patients

- Patient baseline demographics and characteristics (for the patients whose adverse event [AE] records were used to evaluate the relationship between eslicarbazepine exposure and the time to first onset of TEAEs) are shown in **Table 1**.
  - Median age was 38 years, and the majority of patients were Caucasian.
  - Carbamazepine, valproic acid, and levetiracetam were used by ≥20% of patients.
  - Approximately two-thirds of patients were taking one AED at baseline and ~1/3 were taking two.
- Patient baseline demographics and characteristics (for the patients whose serum sodium level measurements were used to evaluate the relationship between eslicarbazepine exposure and serum sodium levels) were similar to those shown in **Table 1**.
  - Median serum sodium concentration during the baseline period was 140 mEq/L (range: 126–152 mEq/L), and was similar between treatment groups.

Table 1. Baseline demographics and characteristics[a]

Characteristic	Patients (n = 302)
Age, years; median (range)	38.0 (16–68)
Weight, kg; median (range)	79.0 (39–188)
Gender, male; %	50
Race; n (%)	
Caucasian	250 (83)
Black or African American	25 (8)
Asian	5 (2)
American Indian or Alaskan Native	2 (1)
Other	17 (6)
Multiple	3 (1)
Baseline use of carbamazepine; n (%)	78 (26)
Baseline use of levetiracetam; n (%)	73 (24)
Baseline use of valproic acid; n (%)	63 (21)
Number of AEDs at baseline; n (%)	
1	204 (68)
2	98 (33)

[a]For patients included in the analysis of time to first AE.
AE: adverse event; AEDs: antiepileptic drugs.

Assessments and endpoints

- AEs were recorded at each clinic visit.
- Blood samples for serum sodium analysis were collected at all 10 study visits (during screening; Day 0; Weeks 1, 2, 5, 8, 11, 14, and 18; end of study) and processed at a central laboratory.
- The safety endpoints for this analysis included: time to first occurrence of dizziness, headache, and nausea; and changes in serum sodium levels.

Population pharmacokinetic modeling

- The following measures of eslicarbazepine exposure were calculated for each patient, based on a previously developed population pharmacokinetic (PK) model:
  - average concentration (C_{av})
  - area under the concentration–time curve (AUC_{0-24})
  - predicted minimum drug concentration (C_{min})
  - predicted maximum drug concentration (C_{max}).
- The PK model for time to first occurrence of AEs was developed through the following steps:
  1. exploratory data analysis
  2. base structural model development incorporating drug exposure
  3. evaluation of covariate effects
  4. final model refinement
  5. model evaluation.
- The final models for the relationship between eslicarbazepine exposure and time to first AE were validated using simulation-based visual predictive check methodology, to assess concordance between the observed and simulated data.
- An exploratory graphical analysis was performed to assess the relationship between eslicarbazepine exposure and serum sodium levels. No formal model was developed for this endpoint.

RESULTS

Time to first occurrence of dizziness, headache, and nausea AEs

- Predictive models were developed for the three most frequently reported central nervous system AEs, i.e. dizziness, headache, and nausea.

Analysis dataset

- A total of 32,994 AE records relating to 302 patients were used for this analysis.

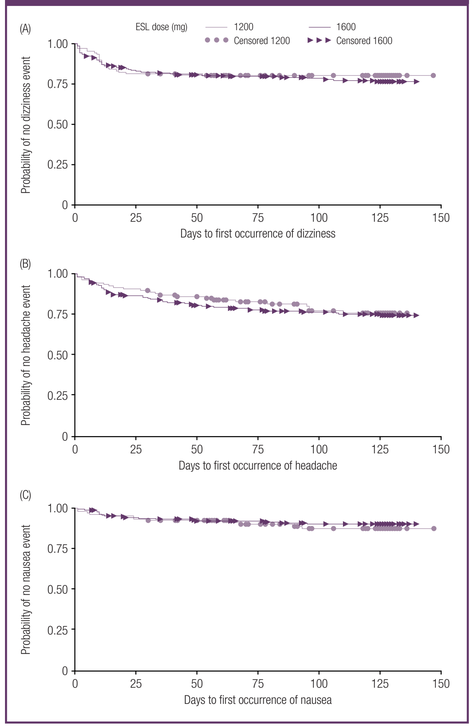
Time to first occurrence of dizziness

- Overall, 65 patients (22%) had an occurrence of dizziness.
- The majority of dizziness AEs occurred towards the beginning of the study (in the first 25 days; **Figure 2A**).
- There was no significant relationship between eslicarbazepine exposure and time to first occurrence of dizziness (**Figure 3**).

Time to first occurrence of headache

- Overall, 70 patients (23%) had an occurrence of headache.
- The Kaplan–Meier plot of time to first occurrence of headache is shown in **Figure 2B**.
- There was no significant relationship between eslicarbazepine exposure and time to first occurrence of headache (**Figure 3**).

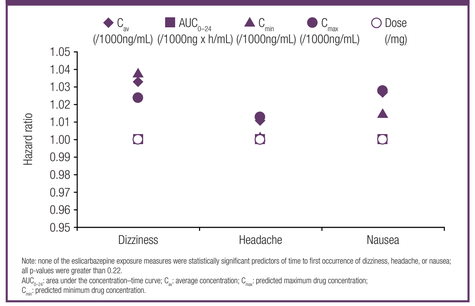
Figure 2. Kaplan–Meier plots of time to first occurrence of (A) dizziness, (B) headache, and (C) nausea



Time to first occurrence of nausea

- Overall, 30 patients (10%) had an occurrence of nausea.
- The Kaplan–Meier plot of time to first occurrence of nausea is shown in **Figure 2C**.
- There was no significant relationship between eslicarbazepine exposure and time to first occurrence of nausea (**Figure 3**).

Figure 3. Relationship between predicted eslicarbazepine exposure and time to first occurrence of dizziness, headache and nausea



Note: none of the eslicarbazepine exposure measures were statistically significant predictors of time to first occurrence of dizziness, headache, or nausea; all p-values were greater than 0.22.
AUC_{0-24}: area under the concentration–time curve; C_{av}: average concentration; C_{max}: predicted maximum drug concentration; C_{min}: predicted minimum drug concentration.

Relationship between eslicarbazepine exposure and serum sodium

Analysis dataset

- A total of 2265 measurements of serum sodium from 299 patients were used for this analysis.

Analysis

- In most patients, there was no notable trend in serum sodium levels throughout the duration of the study.
  - A total of 23 patients (7.7%) had a reduction in serum sodium level >10 mEq/L, versus baseline; 16 (8.3%) with ESL 1600 mg and seven (6.5%) with ESL 1200 mg.
- Similar changes in serum sodium levels were observed in both ESL dose groups.
- Linear regression model analysis showed a shallow negative relationship between serum sodium levels and eslicarbazepine exposure; serum sodium levels tended to decrease slightly with higher ESL exposures (**Figure 4**).
  - Notably, serum sodium concentrations were highly variable, and some individuals had large reductions in serum sodium concentration at moderate levels of exposure.
- At the highest eslicarbazepine C_{max} values, linear regression predicted a <3 mEq/L decrease in serum sodium concentration from baseline.

CONCLUSIONS

- Eslicarbazepine exposure was not a statistically significant predictor of time to first occurrence of dizziness, headache, or nausea.
  - This may be because these AEs tended to occur soon after initiation of ESL, including during the first 2 weeks of the study (the titration period) when ESL dose and eslicarbazepine exposure would have been low.
  - It is also possible that these AEs were related to the AEDs that were being used before the conversion-to-ESL monotherapy, as they occur with other commonly used AEDs. This may also explain why events occurred primarily during the titration and monotherapy conversion periods.
- With increasing eslicarbazepine exposure, serum sodium levels appeared to decrease slightly.
  - The predicted reduction in serum sodium level does not appear to be clinically significant, even at the highest exposures. However, individual patients may have significantly low sodium levels, regardless of exposure.
  - Although hyponatremia occurred in 15 patients taking ESL as monotherapy, this analysis suggests that eslicarbazepine exposure is not a predictor of this TEAE.
- There was no significant relationship between eslicarbazepine exposure and hyponatremia, or first occurrence of selected AEs (dizziness, headache, or nausea). Therefore, monitoring plasma eslicarbazepine concentrations does not appear to be useful for making decisions regarding hyponatremia, or for determining the optimal dose of ESL monotherapy.

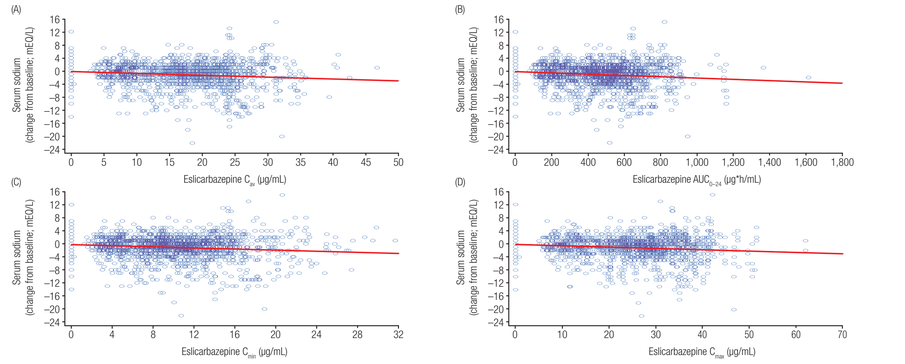
REFERENCES

1. Sperling MR, et al. Epilepsy Curr 2014;14(Suppl. 1):431–2.
2. Pazdera L, et al. Epilepsy Curr 2014;14(Suppl. 1):108.
3. Falcão A, et al. CNS Drugs 2012;26:79–91.
4. French JA, et al. Epilepsia 2010;51:1936–43.

ACKNOWLEDGMENTS

Medical writing support was provided by Mallory Gough of FireKite, part of the KnowledgePoint360 Group, an Ashfield company, and was funded by Sunovion Pharmaceuticals Inc.

Figure 4. Relationship between eslicarbazepine exposure measures and change in serum sodium concentration from baseline:* (A) C_{av} (B) AUC_{0-24} (C) C_{min} and (D) C_{max}



*The linear regression (solid red line) overlays the scatter plot of change in serum sodium concentration.
AUC_{0-24}: area under the concentration–time curve; C_{av}: average concentration; C_{max}: predicted maximum drug concentration; C_{min}: predicted minimum drug concentration.