Modelling and simulation to support clinical development of eslicarbazepine acetate in partial-onset epilepsy

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INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily (QD) and enteric-coated drug (ECD) approved by the FDA in April 2015 for the treatment of partial onset seizures (POS) as add-on therapy. ESL is approved by the European Medicines Agency as add-on therapy for POS in adults.
- A model-based drug development paradigm was employed for eslicarbazepine acetate (ECD) and relationships between eslicarbazepine acetate and efficacy and safety outcomes, and to inform dose selection.

OBJECTIVE

- To evaluate the PK of eslicarbazepine acetate and assess the exposure–response relationships for drug safety and efficacy.

METHODS

Development of population PK models for eslicarbazepine during ESL adjunctive therapy and monotherapy

- Population PK models for eslicarbazepine (daily administration of ESL) were developed using conditional data from 11 Phase III clinical trials, and three Phase IIb adjunctive therapy studies (NCT-02033 301, 302 - 304, and a separate safety study from Phase IIb monotherapy studies (NCT-01484-116).
- A previously developed structure PK model was initially applied, and then refined using an expanded model to describe individual variability, two additive plus proportional errors were used to account for differences in baseline residual variability between Phase II and Phase IIb

Development of PK/pharmacodynamic (PD) models to describe the relationship between eslicarbazepine exposure and ESL efficacy/safety outcomes

- The following measures of eslicarbazepine exposure were calculated for each individual using the population PK model for ESL: minimum eslicarbazepine plasma concentration (Cmin), area under the plasma concentration-time curve (AVG), apparent volume of distribution (V/F).

- For ESL adjunctive therapy, relationships between eslicarbazepine exposure and the following outcomes were evaluated using non-linear mixed-effects modeling: logic regression or Prognosis regressions: standard deviations of exposure (SD)

- Probability of success (PS)
- Probability of severe/treatment emergent adverse events (sAEs)

- For ESL monotherapy, PK/PD models were developed to describe the relationship between eslicarbazepine exposure and the following safety and efficacy outcomes, using logistic regression or survival analysis:

- Time to study exit (TtSE)
- Time to third or sixth seizure during the 10-week ESL monotherapy period and the 10-week ESL adjunctive therapy period; respectively.
- Probability of seizure freedom during the 10-week ESL monotherapy period and the last 6-week ESL period.

- Time to first occurrence of sAEs.

- The relationship between eslicarbazepine exposure and seizure and adverse event levels was analyzed:

- The influence of selected covariates (including concomitant AEDs) on eslicarbazepine PK/PD models was examined.

- Simulated-based model cutoff or appropriate alternatives were performed.

- The overall process for developing the predictive model is shown in Figure 5

ESL monotherapy: relationship between eslicarbazepine exposure and efficacy outcomes

- Higher eslicarbazepine Cmin and AUC were associated with fewer seizures during the 10-week ESL monotherapy period, respectively.
- Other significant predictors of response to ESL monotherapy included lower baseline serum sodium and a lower baseline Cmin.

ESL monotherapy: relationship between eslicarbazepine exposure and safety outcomes

- Significant safety relationships were identified between eslicarbazepine exposure and adverse events (AEs) occurring during the 10-week ESL monotherapy period, using non-linear mixed-effects modeling.


RESULTS

Population PK models

- The population PK model for ESL during ESL treatment (both adjunctive therapy and monotherapy) was described by a non-compartmental model with first-order absorption/elimination

- Eslicarbazepine clearance (CL/F), distribution volume (V/F), and absorption rate constant (ka) were found to be similar between ESL adjunctive therapy and monotherapy.

- Development of PK/pharmacodynamic (PD) models to describe the relationship between eslicarbazepine exposure and ESL efficacy/safety outcomes.

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REFERENCES

- The results of the exposure response analyses support a potential for clinical development in the treatment of POS, with exposure–response relationships observed for the following outcomes:

- The exposure response relationships are not supported for the following outcomes:

- The population AUC analyses indicate that ESL dose should be increased by 50% when used with phenobarbital, phenytoin, and primidone.

- ESL dose adjustment may be warranted during treatment with concomitant carbamazepine, based on efficacy and tolerability.

- ESL dose adjustments may be required for other AEDs when used with ESL.

ACKNOWLEDGMENTS

- Development of the population PK model for ESL during ESL adjunctive therapy and ESL monotherapy was conducted using the population PK model described above.

- Development of the population PD model for ESL during ESL adjunctive therapy and ESL monotherapy was conducted using the population PD model described above.