**Results**

**Objective**

To develop statistical models describing the relationship between eslicarbazepine exposure and selected efficacy outcome measures (standardized seizure frequency [SSF], probability of response [PR], and weekly seizure frequency over time) in patients with POS.

**Methods**

Study design

- The design of the three randomized trials included in this analysis has been reported previously.
- Each trial included an 8-week baseline period and a 14-week double-blind period (2 weeks titration; 12 weeks maintenance).
- ESL doses: 400 mg (Studies 301 and 302 only), 800 mg, and 1200 mg QD.
- All baseline, 48.6% of patients were receiving concomitant carbamazepine.
- SSF during the baseline period showed a high level of variability (from 0 to 412 seizures per 28 days).

Relationship between exposure and measures of efficacy

**Predictive model for standardized seizure frequency**

- The model predicted a decrease in SSF with ESL dose (ESL 400 mg, 5.4 seizures/28 days; ESL 800 mg, 4.8 seizures/28 days; ESL 1200 mg, 4.3 seizures/28 days; ESL 300 mg, 5.0 seizures/28 days).

- The reduction in SSF with ESL (maximum pharmacologic effect \( E_{\text{max}} \); see Figure 1) was predicted to be less in patients who were taking carbamazepine at baseline, and in those from Western Europe (WE).

**Predictive model for weekly seizure frequency**

- A lower PR was predicted for patients from WE than for non-WE patients (see Figure 2).
- For the WE group, predicted PR was 0.12 for ESL 400 mg, 0.23 for ESL 800 mg, and 0.26 for ESL 1200 mg.
- For the non-WE group, predicted PR was 0.21 for placebo, 0.30 for ESL 400 mg, 0.35 for ESL 800 mg, and 0.40 for ESL 1200 mg.

**Predictive model for probability of response**

- ESL led to dose-related improvements in most efficacy outcomes, with an effective dose range of 800–1200 mg QD.
- ESL dose-related improvements in most efficacy outcomes, with an effective dose range of 800–1200 mg QD.
- The model predicted a decrease in SSF with increasing ESL dose (ESL 400 mg, 5.4 seizures/28 days; ESL 800 mg, 4.8 seizures/28 days; ESL 1200 mg, 4.3 seizures/28 days; ESL 300 mg, 5.0 seizures/28 days).

**Key inclusion criteria**

- Age ≥18 years (Study 301 or 302) or ≥16 years (Studies 301 and 302)
- History of simple or complex partial seizures, and secondarily generalized seizures
- ESL during baseline, with no seizure-free period >21 consecutive days (Studies 301 and 302) or >14 days in baseline, with no seizure-free period >28 consecutive days (Study 304)

**Key exclusion criteria**

- Concomitant use of
  - Oxcarbazepine use
  - Felbamate use (Studies 301 and 302; allowed if stable in Study 304).

**Clinical trial endpoints**

- Placebo ESL 400 mg, ESL 800 mg, ESL 1200 mg QD.

**CONCLUSIONS**

- The predictive model developed for standardized seizure frequency (SSF) agreed closely with that developed for probability of response (PR).
- Both models predicted a better outcome with higher eslicarbazepine exposure \( C_{\text{av}}\text{-}\text{ss} \) and a worse outcome in patients from WE.
- The SSF model predicted a worse outcome for patients who were taking carbamazepine at baseline.

- The predicted relationship between exposure and SSF was similar to the observed relationship: only slight improvements in seizure control are expected at higher concentrations of eslicarbazepine.

**References**