**Pharmacokinetic/Pharmacodynamic Analysis of Extended-Release Once-Daily SPN-804 (Oxtellar XR™) in Adults with Epilepsy: Correlation of MHD Concentrations and Seizure Reduction**

**Background**

Discontinue AEDs (ECG) is almost completely converted to 10-methyl derivative (MHD), the active metabolite primarily responsible for the drug’s antiseizure activity. An alternate explanation (ER) formulation, fits require twice-daily dosing due to the rapid absorption and extensive first-pass metabolism by CYP3A4. The results have been consistent with the conclusions reached previously on this topic. OXC and MHD increased with weight; production of MHD from OXC was larger when the administered dose was smaller; and compartment model; PK of MHD followed a one-compartment model with MHD produced by a first-order process from the central MHD model was used to estimate MHD Cmin for 166 patients receiving SPN-804 treatment (PROSPER population). PK/PD (Emax) Model

**Methods**

**PROSPER Study**

- Multicenter, multinational, randomized, double-blind, parallel-group study
- Randomization: 1:1 (1200 mg QD, 2400 mg QD: SPN-804 EDI) to blinded dose sequence
- No washout period before baseline seizure frequency

**PK/Safety**

- All patients with refractory partial-onset seizures: A randomized controlled trial.

**PK/PD Modeling**

For this concentration-response analysis, percent change from baseline 28-day seizure frequency (PCH) was plotted against MHD Cmin for each patient in the population subgroup (Fig. 1).

**Population PK Model**

The primary and structural population pharmacokinetic (PK) model (OXC model) and MHD was derived from a nonlinear mixed-effects population PK model fitting 28 days of OXC and MHD concentrations using a maximum likelihood estimation strategy. PK model was used to estimate MHD Cmin for 166 patients receiving SPN-804 treatment (PROSPER population). PK/PD (Emax) Model

Sensitivity analyses were performed to examine the concentration-response relationship above and below critical values of Cmin and PCH. At all Cmin critical values between 10 and 18 mg/L (transitional regions, Fig. 3), the concentration-response (r) was significant (P < 0.05), and number of patients above/below critical PCH was significantly larger for concentrations above the critical r than concentrations below, demonstrating that MHD Cmin values as low as 10 mg/L significantly improves clinical improvement.

**Key Observations**

- PK/PD analysis, 1200 mg SPN-804 was shown to be an efficacious dose in the concentration-response analysis. Most patients receiving SPN-804 1200 mg/day achieved MHD concentrations associated with a significant clinical effect.

**Conclusions**

- Following OXC administration and absorption, OXC is almost completely converted to the MHD active metabolite. As a population PK model was used to estimate MHD Cmin, 180 patients receiving SPN-804 treatment (PROSPER population). PK/PD (Emax) Model

**Figure 1. Plot of Individual MHD Concentration vs. Assigned Dose**

- No washout period before baseline seizure frequency

- All patients with refractory partial-onset seizures: A randomized controlled trial.

**Figure 2. Median % Seizure Reduction in PROSPER Study Population Stratified by MHD Concentration vs. Assigned Dose**

- No washout period before baseline seizure frequency

- All patients with refractory partial-onset seizures: A randomized controlled trial.