ESETT ANCILLARY PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) STUDY

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Rationale

- Substantial variability in drug concentrations following administration of AED loading doses
- ESETT protocol uses a mg/kg basis for dosing capped at 75 kg
- Variability in early drug concentrations can be high
- Unknown if drug concentrations correlate with efficacy in acute management of SE
Simulations Show Wide Variability in Drug Exposure Following IV Dosing

Distributions of PHT, LEV, and VPA concentrations over 60 min (pAUC) simulated for 100 patients

Does variability predict response?
Specific Aim

Relate drug exposure [concentration or partial area under the concentration-time curve (pAUC)] from time 0-60 min) with seizure cessation and the key secondary outcomes.

- **Hypothesis 1:** Patients with higher drug exposures (pAUC based on unbound or total plasma concentrations of FOS, LEV, and VPA) will more likely respond.

- **Hypothesis 2:** Patients with higher drug exposures will have a higher incidence of serious adverse effects commonly associated with the study drugs.

- **Hypothesis 3:** The relationship between drug exposure and response will differ by gender, age, and weight or BMI.
Study Overview

Population - Same as ESETT

Inclusion Criteria
• All subjects randomized under the ESETT protocol.
• Able to provide blood sample(s)

Procedures
• Two blood sample collected within specified time ranges
• VPA (total and unbound), PHT (total and unbound) and LEV (total) concentrations measured
• Statistical and pharmacometric analysis
PK/PD Sample Collection Timetable

- Two blood samples (minimum 2-3 mL/sample)
  - 20-50 min and 60-120 min

**Graphical Timetable**

- **Enrollment/Randomization**
  - 00:00
  -observe without infusion

- **Study Drug Infusion**
  - 00:10

- **Blood Collection**
  - 00:20
  - 00:50
  - 00:60
  - 02:00
Study Procedures

• **Record time of blood collection on CRF**
• **Sample centrifuged to separate plasma within 2 hr of the blood collection**
  • Plasma aliquoted into labeled cryovial
Study Procedures

• Blood samples stored at \( \leq -20^\circ\) C until shipment
  • Samples may be stored and batched
• Plasma shipped to the Center for Orphan Drug Research (CODR)
• Shipping kits will be provided
  • labeled cryovials, extra labels, cold packs, and shipping material including pre-paid labels
Plasma Sample Analysis

- Samples will be analyzed for drug concentration at CODR using a validated, highly sensitive, specific assay (chromatographic mass spectrometry assay).
  - Unbound and total phenytoin (PHT)
  - Unbound and total valproic acid (VPA)
  - Total levetiracetam (LEV)
Data Analysis at ESETT Completion

- Use pharmacokinetic models to estimate drug concentration-time profiles and partial area under the curve (pAUC)
- Examine the relation of drug concentration or pAUC to the probability of seizure cessation (at 60 minutes)
- Examine the relation of drug concentration or AUC to secondary endpoints
- Test the effect of variables such as weight, BMI, age, gender, on the drug exposure-response relationship
Outcomes

• Characterization of the exposure-response relationships.
• Provide guidance on how best to use FOS, LEV, and VPA for treatment of SE in children, adults, and elderly.
• Guide selection of optimal dose for future clinical trials.
## Key Personnel

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<thead>
<tr>
<th>Personnel</th>
<th>Institution</th>
<th>Role</th>
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