

# PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) STUDY IN THE ESTABLISHED STATUS EPILEPTICUS TREATMENT TRIAL

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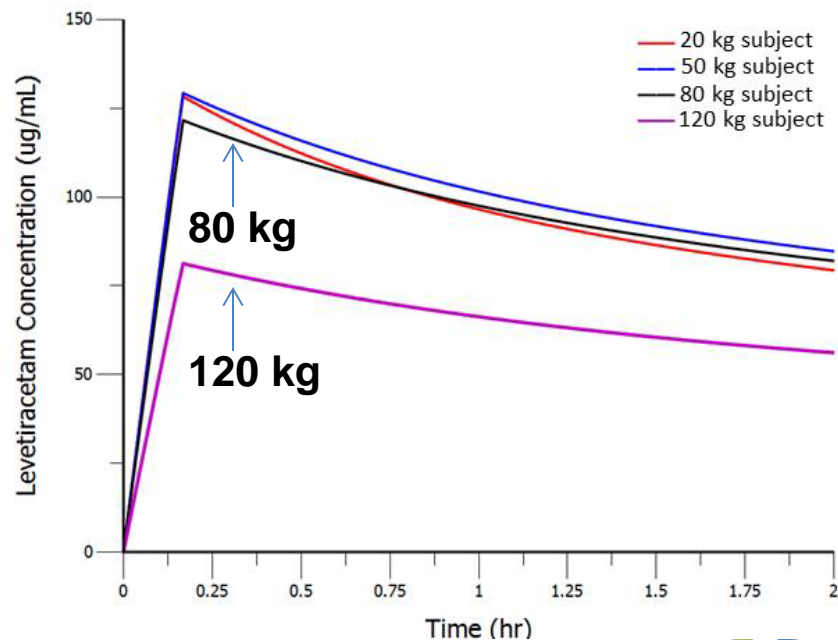
# Key Personnel

Personnel	Institution	Role
<b>James Cloyd, PharmD</b>	<b>UMN</b>	<b>Pharmacology core PI, study oversight</b>
<b>Lisa Coles, MS, PhD</b>	<b>UMN</b>	<b>Study coordination, pharmacometric analysis</b>
<b>Usha Mishra, MS</b>	<b>UMN</b>	<b>Sample analysis</b>
<b>Vijay Ivaturi, PhD</b>	<b>Maryland</b>	<b>Pharmacometric analysis</b>
<b>Jordan Elm, PhD</b>	<b>MUSC</b>	<b>Statistical support</b>

# Rationale

- Drug dosing for ESETT will be made on a mg/kg basis up to 75kg.
- We expect differences in early drug concentrations given the known variability in volume of distribution and protein binding.

- Estimates of distribution volume have a variability of ~20-40%
- Capping mg/kg dose at 75 kg will result in lower drug concentrations in larger patients



**Levetiracetam concentration-time profiles simulations for 10-minute infusion (Dose= 60 mg/kg if weight < 75 kg; 4500 mg if weight ≥ 75 kg)**

# Importance of PK Study

Measurements of drug concentrations serve as both a quality control measure and as a metric to explore the relationship between drug exposure and clinical response and contribution of variables such as body weight.

- 1) confirm the drug measured in plasma is the same as that indicated on label
- 2) provide insight into reasons for treatment success and failure
- 3) provide a basis for revised dosing recommendations

# Study Objectives

- **Confirm that the drug measured in plasma was the same as that indicated on label.**
- **Relate observed drug concentrations with primary clinical outcome measure.**
- **Evaluate the effect of covariates on the relationship between drug conc. and response.**
- **Secondary: Relate drug exposure with key secondary outcome measures (time to termination of clinical seizures).**

# Study Population/Design

## Population

- Same as ESETT

## Inclusion Criteria

- All subjects randomized to receive treatment under the ESETT protocol will be eligible for the PK component of the study.
- Able to provide at 1 mL blood sample

## Design

- A single blood collection PK study

# Study Procedures

- **Blood sample (1-5mL) will be collected either as a venipuncture or from an indwelling catheter NOT used for drug infusion from each subject between 30 and 60 min after start of infusion.**
  - **Record time of blood collection on CRF**
- **Blood samples will be placed on ice immediately and plasma separated via centrifugation within 2 hrs of the blood collection and stored at -20 ° C or lower until shipment.**
- **Plasma will be shipped on dry ice to the Center for Orphan Drug Research (CODR) and stored at -80° C until analysis.**

# Plasma Sample Analysis

- Samples will be analyzed for drug concentration at CODR using validated HPLC-MS methods.
  - Unbound and total phenytoin (PHT)
  - Unbound and total valproate (VPA)
  - Total levetiracetam (LEV)
- PHT, VPA, and LEV will be measured simultaneously.
- Acquired new HPLC/MS/MS which will be used for this study.





# Data Analysis at ESETT Completion

- **Examine the relation of drug concentration to the probability of seizure abortion (at 60 minutes) using logistic regression model.**
- **Examine the relation of drug concentration and secondary endpoints using appropriate tests (for example, time to seizure cessation using Cox Proportional Hazards Ratio).**
- **Literature-based population pharmacokinetic models for these drugs will be used as priors to fit the plasma concentrations. This will allow us to estimate PK parameters that can be used to derive exposure metrics such as partial AUC, time above certain concentration etc. to relate this to clinical outcomes.**
- **Several variables will be tested such as weight, BMI, age, gender, etc., for their effects on the concentration-response.**

# Anticipated Results

- **Determine whether concentrations effect response.**
  - **Do concentrations help explain drug failure?**
- **If yes, determine what variables effect this relationship.**
  - **Do those over 75 kg have lower concentrations and more failures?**
- **Recommend dosing guidelines.**