Quantitative Analysis to Support Full Extrapolation of Efficacy in Children for Partial Onset Seizures in Adjunctive Setting: FDA-PEACE Initiative

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Evidence to Support “Full Extrapolation” of Efficacy
Disease Similarity Between Adults & Children

• PEACE/DNP provided the clinical expertise to describe:
  
  – the *pathophysiology* of partial onset seizures (POS)

• After excluding children under age 4 and those with POS associated with epileptic encephalopathies such as Lennox-Gastaut, the pathophysiology of POS is similar in children (≥ 4 year old) and adults.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Population</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
<td>≥ 2 year</td>
<td>Blocks voltage dependent Na channels, increase K conductance and modulate high voltage activated Ca channels</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>≥ 1 month</td>
<td>Acts by binding to SV2A protein. Inhibits voltage sensitive Na channels, stabilize neuronal membranes and modulates presynaptic release of excitatory neurotransmitter</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>≥ 2 year</td>
<td>Inhibits voltage sensitive Na channels, stabilizes neuronal membranes and modulates presynaptic release of excitatory neurotransmitter. Blocks voltage dependent Na channels, augments GABA activity, antagonizes AMPA/Kainate subtype of glutamate receptor, inhibits carbonic anhydrase enzyme.</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>≥ 2 year</td>
<td>Blocks voltage dependent Na channels, augments GABA activity, antagonizes AMPA/Kainate subtype of glutamate receptor, inhibits carbonic anhydrase enzyme. Not known; binds with α2δ subunit of voltage activated calcium channel but therapeutic effects of binding are unknown.</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>≥ 3 years</td>
<td>Noncompetitive antagonist of AMPA glutamate receptor.</td>
</tr>
<tr>
<td>Perampanel (Fycompa)</td>
<td>≥12 year</td>
<td>Noncompetitive antagonist of AMPA glutamate receptor.</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>≥12 year</td>
<td>Not known, enhances the activity of GABA as an inhibitory neurotransmitter.</td>
</tr>
<tr>
<td>Vigabatrin (Sabril)</td>
<td>≥10 year</td>
<td>Not known, increases levels of GABA in CNS.</td>
</tr>
</tbody>
</table>
Trial Design and Primary Endpoint in Approval of AEDs in Adjunctive Setting

- **Baseline Phase**: 8-12 weeks, 1-3 Concomitant AEDs
- **Titration Phase**: 2-6 weeks
- **Double Blind (DB) Phase**: 3X mg
  - 2X mg
  - X mg
- **Placebo (PB)**
- **Maintenance Phase**: 12-24 weeks
- **Primary Endpoint**: Median %CFB in Seizure Frequency/28 days in the DB Phase
- **CFB**: Change from baseline

Plasma samples are collected in the maintenance phase
Evidence to Support “Full Extrapolation” of Efficacy
Observed Efficacy of Approved AEDs in Adults & Children from Registration Trials

<table>
<thead>
<tr>
<th>AED</th>
<th>Adult Dose</th>
<th>Children Dose</th>
<th>Placebo Corrected Median % CFB in Seizure Frequency/28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine</td>
<td>1200 mg/day</td>
<td>2400 mg/day</td>
<td>-32.6, -42.3, -25.4</td>
</tr>
<tr>
<td>Children: 3-17 years of age</td>
<td>30 to 46 mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perampanel</td>
<td>4 mg/day</td>
<td>8 mg/day</td>
<td>-13.1, -22.7, -14.9</td>
</tr>
<tr>
<td>Children: 12 years and above</td>
<td>12 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>3000 mg/day</td>
<td>3000 mg/day</td>
<td>-32.7, -30.3, -28.0</td>
</tr>
<tr>
<td>Children: 4-16 years of age</td>
<td>60 mg/kg/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Labels for oxcarbazepine, perampanel and levetiracetam

M-CERSI-FDA WORKSHOP: QUANTITATIVE ASSESSMENT OF ASSUMPTIONS TO SUPPORT EXTRAPOLATION OF EFFICACY IN PEDIATRICS, 06/01/2016
Observed Efficacy of Approved AEDs in Adults & Children from Registration Trials

Placebo Corrected Median % CFB in Seizure Frequency/28 days

**Topiramate**
- Children: 2-16 years of age
  - 400 mg/day: -39.6%
  - 400 mg/day: -35.9%
  - 6 mg/kg/day: -22.6%

**Lamotrigine**
- Children: 2-16 years of age
  - 500 mg/day: -28.0%
  - 15 mg/kg/day (max = 750 mg): -29.0%

**Gabapentin**
- Adults: 12 years and above
- Children: 3-12 years of age
  - 1200 mg/day: -16.7%
  - 1200 mg/day: -14.0%
  - 1200 mg/day: -16.6%
  - 1800 mg/day: -25.9%
  - 25-35 mg/kg/day: -10.7%

Source: Labels for topiramate, lamotrigine and gabapentin

M-CERSI-FDA WORKSHOP: QUANTITATIVE ASSESSMENT OF ASSUMPTIONS TO SUPPORT EXTRAPOLATION OF EFFICACY IN PEDIATRICS, 06/01/2016
Evidence to Support “Full Extrapolation” of Efficacy
Concentration Metric Utilized for Comparing Exposures in Adults and Children

- Cmin: trough concentration at steady state
- Cavg: average concentration at steady state
- Same metric utilized between adults and children for a given drug
Concentrations at Approved Doses in Adults & Children

*Doses in the boxes denote highest recommended maintenance doses*
Evidence to Support “Full Extrapolation” of Efficacy
Methodology

a) Graphical Analysis

b) Model Based Analysis
Drug A
Exposure-Response in Adults & Children

Mean % CFB in Seizure Frequency/28 days vs Concentration

Log (% CFB in Seizure Frequency/28 days) vs Concentration

Adults
Children
Drug B
Exposure-Response in Adults & Children

Mean % CFB in Seizure Frequency/28 days

Concentration

% CFB in Seizure Frequency/28 days

Doses

Concentration

Adults

Children
Drug G
Exposure-Response in Adults & Children

![Graph showing predicted seizure rate during maintenance phase vs. normalized dose for Drug G](image)

- **Normalized Dose (mg)**
- **Predicted seizure rate during maintenance phase**

- **Red** line: Adults
- **Black** line: Children

**M-CERSI-FDA WORKSHOP: QUANTITATIVE ASSESSMENT OF ASSUMPTIONS TO SUPPORT EXTRAPOLATION OF EFFICACY IN PEDIATRICS, 06/01/2016**
Evidence Gathered from AEDs Approved Between 1960-1980

**Carbamazepine**
- Generally acceptable therapeutic range of total carbamazepine in plasma (i.e. 4-12 µg/mL) is the same in adult and children

**Phenytoin**
- Dose in pediatrics was selected such that it produces plasma concentration within the generally accepted therapeutic target of 10-20 µg/mL, which is same for adults

**Valproic acid**
- Approved in ≥ 10 years age, same dose and the same target therapeutic plasma concentration range (50 -100 µg/mL) are recommended.

Source: Labels for carbamazepine, phenytoin and valproic acid
Quantitative Assessment of Response, Exposures and Exposure-Response Supports “Full Extrapolation” of Efficacy
Required information to Support an Indication for the Treatment of POS in Patients ≥ 4 years

- Approved indication for the treatment of POS in adults.

- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and children (4 years of age and older) populations.

- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.
Acknowledgements

- **FDA:**
  - OCP:
    - Angela Men
    - Atul Bhattaram
    - Mehul Mehta
    - Ramana Uppoor
    - Michael Bewernitz
    - Vikram Sinha*
    - Kevin Krudys
    - Joo Yeon Lee
  - DNP:
    - Billy Dunn
    - Eric Bastings
    - Norman Hershkowitz
    - Philip Sheridan
    - Cathleen Michaloski
- **UMD:**
  - Tao Liu (ORISE Fellow)
  - Joga Gobburu
- **PEACE:**
  - Jack Pellock
  - Neil D’Cruz
  - Jackie French
- **Epilepsy Foundation:**
  - Angela Ostrom
- **Sponsors for providing data**
- **FDA review teams**

*Currently at Merck*