Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to <10 years of age
MAIN ISSUES

To bridge the **data** gap of limited or no information using M&S

- data integration
- evidence “synthesis”
Background & Rationale

**Topiramate**

*Adjunct therapy*
- Approved: 2 yrs, 6 yrs, 10 yrs
- Data

*Mono therapy*
- Approved: [bar showing approved years]
- Data
Available Data

- 11 studies
  - 8 adjunct: 2-68 years (12 patients < 6 years)
  - 3 monotherapy: 6-85 years
- PK
  - 1217 patients, 4640 observations
- PD Efficacy endpoint
  - Adjunct therapy
    - % reduction in seizure frequency
    - Responder rate
  - Monotherapy:
    - time to first seizure
M&S Assumptions

Pediatrics vs Adults

- Epilepsies in children:
  - Partial onset seizures (POS) and Lennox-Gastaud syndrome
    - treatment effect can be extrapolated from adults to children
  - Infantile epilepsies are specific to children: most relevant issue +++
    - no possible extrapolation for treatment effect from adults to children
    - no possible extrapolation for PK/PD
      - epilepsy is often refractory and may even be worsened
  - no possible extrapolation for adverse events
  - possible model-based extrapolation for PK
Where are we?

1. Will the drug be used in a special population (ethnic group or rare disease)?
   - Yes
     ② Is the indication the same as in the current label?
       - Yes
         ③ Is the disease process similar to the current indications?
           - Yes
             ④ Is the outcome of therapy likely to be similar in the new population?
               - Yes
                 ⑤ Does efficacy correspond with blood levels in adult?
                   - Yes
                     ⑥ Is the dose-conc. relationship likely to match that of the current indication?
                       - Yes
                         PK & safety data
                         (Efficacy/safety extrapolated from reference population)
                       - No
                         PK & safety data
                         (Efficacy/safety extrapolated from reference population)
                   - No
                     PK & safety data
                     (Efficacy/safety extrapolated from reference population)
                 - No
                   PD
                   PK & safety data
                   (Efficacy/safety extrapolated from reference population)
             - No
               - No
                 Clinical efficacy PK & safety data
   - No
     ① Is the indication the same as in the current label?
       - Yes
         ② Is the indication the same as in the current label?
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                         PK & safety data
                         (Efficacy/safety extrapolated from reference population)
                       - No
                         PK & safety data
                         (Efficacy/safety extrapolated from reference population)
                   - No
                     PK & safety data
                     (Efficacy/safety extrapolated from reference population)
               - No
                 Clinical efficacy PK & safety data
             - No
               - No
                 No clinical development
Factors Determining Treatment Response...

ADME
- Dose
- Formulation
- Compliance
- PK
  - Absorption
  - Distribution
  - Clearance
  - Metabolism
- Biophase
  - RO
  - Distribution to target

Pharmacodynamics
- Biomarkers
  - Expression
  - GT/PH
  - Pathway
  - Disease association

Disease
- Early Clinical
  - Expression
  - Onset
  - Heterogeneity
  - Time-course
- Late Clinical
  - Expression
  - Onset
  - Heterogeneity
  - Time-course

Reference Population
- Target Population
M&S Results (PK)

Two-compartment with 1\textsuperscript{st} –order absorption

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical value (%SE)</th>
<th>Interindividual variability (%SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLSTM (baseline clearance monotherapy) (θ₁)</td>
<td>1.21 (1.2)</td>
<td>27.28 (10.2)</td>
</tr>
<tr>
<td>CLSTA (effect of adjuvant) (θ₂)</td>
<td>0.479 (25.3)</td>
<td></td>
</tr>
<tr>
<td>FCWT (effect of weight) (θ₃)</td>
<td>0.453 (9.0)</td>
<td></td>
</tr>
<tr>
<td>FCAGE (effect of age) (θ₄)</td>
<td>-0.00306 (30.9)</td>
<td></td>
</tr>
<tr>
<td>FCIN (effect of INMD) (θ₅)</td>
<td>1.94 (7.8)</td>
<td></td>
</tr>
<tr>
<td>FCVP (effect of valproate) (θ₆)</td>
<td>0.686 (7.8)</td>
<td></td>
</tr>
<tr>
<td>FCNE (effect of NEMD) (θ₇)</td>
<td>0.635 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Central volume of distribution (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VST (θ₈)</td>
<td>4.61 (33.2)</td>
<td>116.2 (35.0)</td>
</tr>
<tr>
<td>FVWT (effect of weight) (θ₉)</td>
<td>1.14 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Ka (h⁻¹) (θ₁₀)</td>
<td>0.105 (27.0)</td>
<td>22.34 (88.2)</td>
</tr>
<tr>
<td>K23 (h⁻¹) (θ₁₁)</td>
<td>0.577 (16.7)</td>
<td>NE</td>
</tr>
<tr>
<td>K32 (h⁻¹) (θ₁₂)</td>
<td>0.0586 (23.6)</td>
<td>NE</td>
</tr>
<tr>
<td>CCV residual error (%CV)</td>
<td>25.46 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Additive residual error (mg/L)</td>
<td>0.1797 (39.9)</td>
<td></td>
</tr>
</tbody>
</table>

%SE – percent standard error, NE, not evaluated.
M&S Results (PK/PD, adjunct-therapy)

- % change in seizure frequency

\[ Y_{\text{obs},i} = \beta_0 + \beta_1 C_{\text{MIN},i} + \beta_2 [\log(B_i) - \log(B)] + \beta_3 C_{\text{MIN},i} [\log(B_i) - \log(B)] + \varepsilon_{Y,i} \]

where,

\[ Y = \log \left( \frac{100(S - B)}{B} + 110 \right) \]

- responder rate

\[ P_{\text{RESP}} = g \left\{ p_0 + \frac{E_{\text{MAX}} \cdot C_{\text{MIN}}}{E_{\text{C50}} + C_{\text{MIN}}} + p_{\text{PED}} \cdot \text{PED} \right\} \]

where,

\[ g\{x\} = \frac{e^x}{1 + e^x} \]
M&S Results (PK/PD, monotherapy)

\[
\log(\lambda_i) = \lambda_0 + \lambda_t \cdot t + \lambda_{\text{CMIN}} \cdot C_{\text{MIN},i} + \lambda_{\text{BS3-10}} \cdot \text{BS}_{3-10,i} + \lambda_{\text{BS10}} \cdot \text{BS}_{10,i}
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate ± SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_0$</td>
<td>$-3.130 \pm 0.0919$</td>
<td>–</td>
</tr>
<tr>
<td>$\lambda_t$</td>
<td>$-0.051 \pm 0.0036$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\lambda_{\text{CMIN}}$</td>
<td>$-0.112 \pm 0.0151$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\lambda_{\text{BS3-10}}$</td>
<td>$1.048 \pm 0.1046$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$\lambda_{\text{BS&gt;10}}$</td>
<td>$2.411 \pm 0.1356$</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

SE, standard error; $\lambda_0$, hazard (the instantaneous risk of a first seizure after randomization to occur); $\lambda_t$, parameter describing the relationship between log (hazard) and t; $\lambda_{\text{CMIN}}$, parameter describing the relationship between log (hazard) and $C_{\text{MIN}}$; $\lambda_{\text{BS3-10}}$, parameter describing the relationship between log (hazard) and $\text{BS}_{3-10,i}$; $\lambda_{\text{BS>10}}$, parameter describing the relationship between log (hazard) and $\text{BS}_{>10,i}$. 
M&S Results (Dose-Response, monotherapy)
Conclusions

- Absence of evidence of an effect of age is ONLY VALID for POS and Lennox-Gastaut syndrome

- Otherwise MAJOR EFFECT OF AGE
  - other types of epilepsies ... the most relevant to consider specifically
    - symptoms are different (epilepsy syndromes) and are severe
    - refractory epilepsies
    - poor cognitive prognosis

- need for a specific approach to infantile and juvenile epilepsies resistant to usual first and second line anti-epileptic treatment: 2 step approach:
  - add-on observational approach: identification of candidate syndrome(s)
  - add-on comparative trial vs placebo in the identified syndromes

- Avoid oversimplification in extrapolation for PK while ignoring the maturational differences in younger age-groups (below 2 years of age): model-based modelling approach rather than allometric approach

- FDA decision tree is not fully adequate in the most specific aspects of paediatric drug development due to oversimplification