

Determination of the Individual Pharmacokinetic Exposure Parameter Uncertainty to Support Pediatric EXPOSURE-RESPONSE Trial Design

Daniel Kaschek¹, Benjamin Guiastrennec¹, Henning Schmidt¹, Rajendra Pratap Singh²

¹IntiQuan GmbH, Basel, Switzerland; ²TEVA Pharmaceuticals, West Chester, PA, USA.

Background

- A pediatric exposure-response trial with sparse sampling of the PK concentrations (2 samples per patients) was considered. Due to the sampling limitations, the exposure metric estimates were highly uncertain.
- However, accurate information about individual exposure metrics was required for the evaluation of the drug's safety and efficacy profile.

Rich sampling

C_{max} , C_{avg} , and C_{min} well defined

Pediatric trial

C_{max} , C_{avg} , and C_{min} uncertain

C_{max} : maximal concentration, C_{min} : minimal (trough) concentration, C_{avg} : average concentration

How pediatric exposure metrics were determined

- The HV and pediatric **datasets were combined**
- The **Pop PK model** developed on HV data **was applied** (The PK data of pediatric patients was adequately characterized by the healthy volunteer model)

Dose normalized VPC

Data: pediatric patients

Model: healthy volunteers + covariates

- All parameters (population and individual) were re-estimated (HV) or estimated for the first time (pediatric patients) from the combined data
- Individual **exposure metrics** of pediatric patients **were determined** based on simulation with estimated individual PK model parameters

How precision and accuracy of exposure metrics were assessed

Simulation of new data

Step 1: Simulate the **original study design** with **new individual parameters**

- Number, amount, and time points of doses
- Consider individual patient covariates
- Number and time points of observations
- Consider inter-individual variability

Step 2: Estimate **population and individual** parameters from new data

- Joint estimation using healthy volunteer data + new patient data realization

Step 3: Compare underlying **"true"** and recovered **"estimated"** parameters

Repeat N times (number of trials)

Estimation of model parameters

Statistics

What we could learn from 1 trial

Example: C_{max} in Trial 1

ID = 139

Distribution of estimated C_{max} (all patients) in Trial 1

Distribution of true C_{max} (all patients) in Trial 1

1

Histograms of true and estimated C_{max} overlap.

The estimated absolute difference between the log-means is $< \log(1.25)^*$

The C_{max} distribution was well-characterized by the estimated C_{max} .

2

Histogram of $\log \frac{C_{max\_estimated}}{C_{max\_true}}$ is quite narrow.

~73% of individuals were within the range of $\pm \log(1.25)^*$, and thus well-characterized

Mean squared distance between individual estimated and true C_{max}

Individual C_{max} values had an estimation error of ~22%.

* The threshold of $\log(1.25)$ was motivated by the criterion used in the assessment of bioequivalence of two drugs.

What we could learn from repeated trial simulation

1 Single trial **successful** if $[\delta_-, \delta_+] \subseteq [-\log(1.25), \log(1.25)]$ → Count number of successful trials

Group effect δ

Confidence interval of δ

not well-characterized (= trial not successful)

well-characterized (= successful trial)

δ : Estimated difference of the means of the histograms

$\delta_{\pm}$: Lower and upper bounds of the 68%/90%/95% confidence interval of δ

$\pm \log(1.25)^*$: Thresholds assumed for adequate characterization

Success rate of obtaining well-characterized population PK endpoints

Summarized over 100 trials. Assessment used populations with 139 subjects.

Percentage of trials

Yes No

Well-characterized

Confidence level of the group effect (true vs. estimated): 68% (blue), 90% (orange), 95% (red)

2 Count the number of individuals per trial for which the estimated parameter was close to the true value ($\log\text{-ratio} < \log(1.25)^*$)

In this trial: 73%

$\pm \log(1.25)$

Summarize over all trials by histogram

Application: Tourette syndrome Austedo study (Poster [3])

C_{max} and C_{avg} at steady state well characterized

PK exposure distributions well-characterized in **100%** of the simulated trials

Individual exposure values well-characterized for **>70%** of the patients

C_{min} at steady state underestimated

PK exposure distribution systematically underestimated (**>80%** of the trials)

Individual exposure values well-characterized in **~50%** of the patients

References

[1] Jankovic & Kurlan 2011, Tourette syndrome: evolving concepts. *Mov Disord* 2011;26(6):1149.

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[3] Guiastrennec *et al.* 2021, Population pharmacokinetic analysis of deutetabenazine (AUSTEDO®) in children and adolescents with Tourette syndrome. www.page-meeting.org/?abstract=9814

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