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Evaluating two strategies for the design of pediatric pharmacokinetic studies

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Background: To justify the design of pediatric pharmacokinetic (PK) studies, a common criterion (standard) is that the study should provide 80% power to obtain acceptable precision (95% confidence intervals (CI) of the mean estimates within 60-140%) of interested PK parameters in each sub-group. An alternative method based on the accuracy of dose selection (ADS) was previously proposed, focusing on clinically-relevant aspect. This work aimed to compare ADS with the standard approach including estimated power and sensitivity to different variables, using model-based simulation and re-estimation.

Methods: This work was based on an example where a single-dose pediatric study of anti-tuberculosis drug pretomanid was designed with the aim to select doses for a subsequent long-term study. A population PK model adjusted for children (with allometry and metabolic maturation) was used to perform simulations.

In the base scenario of the simulated single-dose trial, 36 patients <18 years were given different doses according to six weight groups. Limited by the tablet formulation, pretomanid was dosed only in multiples of 5 mg, up to 200 mg (approved dose for adults). To study a scenario with higher PK variation on both approaches, the interindividual variability of clearance (CV%) was doubled in simulation. For the ADS approach, scenarios for the sensitivity of minimal available tablet sizes (from 0.1 to 25 mg) were also studied.

In the ADS approach, an optimal group dose (OGD) was selected for each dosing group using the simulation model to provide exposures closest to the target. Estimated group doses (EGD) were selected in the same way but using the re-estimated model based on data from a simulated trial. The ratio of EGD to OGD for each dosing group would represent the accuracy of selected doses. The standard approach was implemented by computing precisions (95% CIs) of clearance and volume parameters in the same re-estimated model. Each above-mentioned scenario was repeated 500 times. The study power for each dosing group was summarized as the percentage of the 500 ratios (ADS) or 95% CIs (standard) within 60-140%.

Results: Under the base scenario, the ADS approach suggested that with the planned design, almost all the dosing groups could reach the power of 80%, implying that the study was deemed sufficient for selecting the doses accurately at later steps. However, the standard approach showed that only three dosing groups reached around 80% power for clearances, while the lightest weight group was <30% to provide the required precision in clearance, suggesting larger sample size was needed for better parameter precision. Higher variation in clearance lowered the power of obtaining precise parameters (standard), while the study was still sufficiently powered for selecting accurate doses (ADS). For the ADS approach, when the minimal tablet size was large enough, the lightest group reached almost 100% power. Decreasing the minimal tablet size to fine steps did not significantly worsen the power.

Conclusions: The ADS approach may be a good alternative for study power evaluation that allows lower sample size when the study is focused on determining doses using discrete tablet sizes.