Individualized dosing with high inter-occasion variability is correctly handled with model-informed precision dosing - using rifampicin as an example

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Background: Rifampicin exhibits complexities in its pharmacokinetics (PK), including high inter-occasion variability (IOV), which is challenging for dose individualization. Model-informed precision dosing (MIPD) can be used to optimize individual doses. In this simulation-based study we investigated the magnitude of IOV in rifampicin PK on an exposure level, the impact of not acknowledging IOV when performing MIPD, and the number of sampling occasions needed to forecast the dose.

Methods: Subjects with drug-susceptible tuberculosis were simulated from a previously developed population PK model. To explore the magnitude of IOV, the $AUC_{0\text{-}24h}$ after 35 mg/kg in the typical individual was simulated for 1000 sampling occasions at steady-state. The impact of ignoring IOV for dose predictions was investigated by comparing the prediction error of a MIPD approach including IOV to an approach ignoring IOV. Furthermore, the number of sampling occasions needed to predict individual doses using a MIPD approach was assessed.

Results: The $AUC_{0\text{-}24h}$ in the typical individual varied substantially between simulated sampling occasions [95% prediction interval (PI): 122.2-331.2 h · mg/L], equivalent to an IOV in $AUC_{0\text{-}24h}$ of 25.8%, compared to an inter-individual variability of 25.4%. The median of the

individual prediction errors using a MIPD approach incorporating IOV was 0% (75% PI: -14.6-0.0%), and the PI for the individual prediction errors was narrower with than without IOV (median: 0%, 75% PI: -14.6-20.0%). The most common target dose in this population was forecasted correctly in 95% of the subjects when IOV was included in MIPD. In subjects where doses were not predicted optimally, a lower dose was predicted compared to the target, which is favorable from a safety perspective. Moreover, the imprecision (relative root mean square error) and bias in predicted doses using MIPD with IOV decreased statistically significant when a second sampling occasion was added (difference in imprecision: -9.1%, bias: -7.7%), but only marginally including a third (difference in imprecision: -0.1%, bias: -0.1%).

Conclusion: In conclusion, a large variability in exposure of rifampicin between occasions was shown. In order to forecast the individual dose correctly, IOV must be acknowledged which can be achieved using a MIPD approach with PK information from at least two sampling occasions.