Using PBPK Modeling to support an adaptive “First-in-Pediatric” trial design of Sonlicromanol for the treatment of Primary Mitochondrial Disease

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Intro

Effective novel therapies for treating primary mitochondrial diseases (PMD) in children are an unmet need. Sonlicromanol (KH176), a small, orally available molecule developed to treat PMDs, is a CYP3A4 and P-gp substrate [1]. A PBPK model-based approach was used to establish dosing regimens and sampling times for sonlicromanol in children [2,3].

Methods

A PBPK model was developed for sonlicromanol and its metabolite KH176m (Fig. 1). The model was used to extrapolate PK to children (Fig. 3) for establishing the pediatric equivalent dose (PED) and sampling times for the “first-in-pediatric” trial, leveraging knowledge of enzyme ontogeny and child physiology [4]. PBPK model analysis of the PK data of each age group of an adaptive PK study was conducted to support the confirmation of the PED by a data safety and monitoring board (DSMB). Elder age groups were studied before their younger counterparts for continuous model verification and risk mitigation

Results

The PBPK model well-characterized observed PK data of the adaptive study with the model simulations for sonlicromanol and its metabolite KH176m. The model could match individual PK profiles across all studied age ranges. The inferred variability of the population-level PK of sonlicromanol and KH176m within the age groups (PBPK population simulations, Fig. 2) matched the variation in the adult population, confirming the previously defined PEDs and concluding that no adjustment in the initial dose recommendations was required.

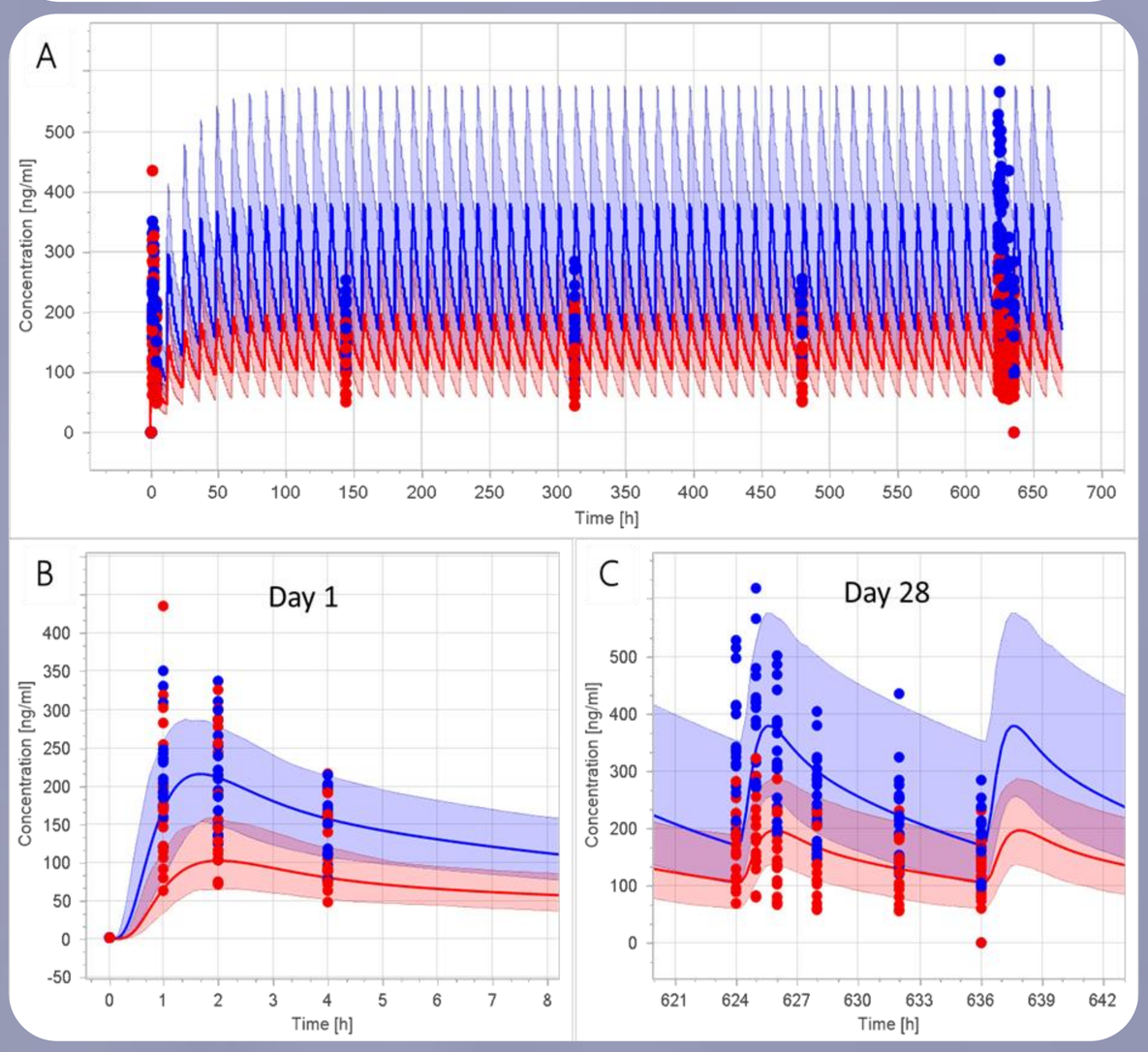

Figure 1: Prediction of PK in adults with b.i.d. dosing of 100 mg over 28 days. Blue curve, shaded areas = geometric mean and 5-95%ile and and data points = observed concentrations of sonlicromanol; red represents the metabolite KH176m.

Conclusion

The study confirmed the utility of PBPK modeling & simulation in establishing dosing regimens and sampling times for “first-in-pediatric” trials. It further highlighted the utility of the modeling approach to mitigate risks for children in an adaptive trial design by enabling informed decision-making of a DSMB.

Confirming the utility of **PBPK for optimization** and **adaptation** of “first-in-**pediatric**” trials

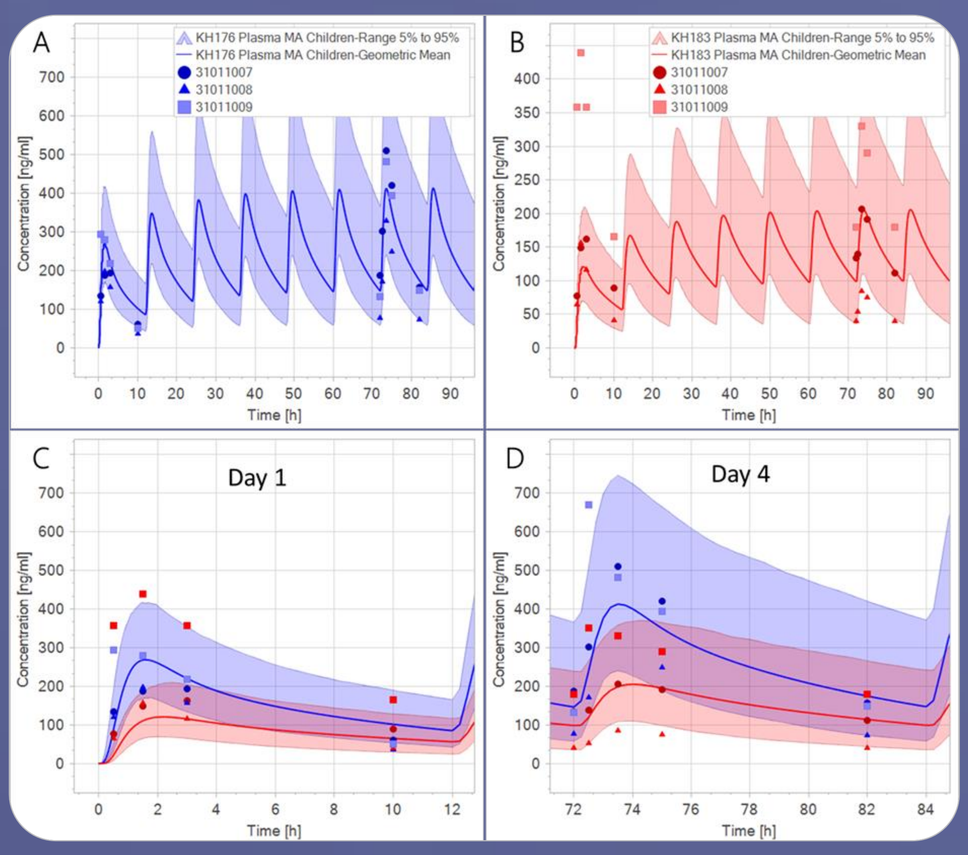

Figure 2: Prediction of PK with b.i.d. dosing of 55 mg over 4 days in middle-aged children (Age 6-12). The blue curve, shaded areas, and data points represent geometric mean and 5-95%ile and observed concentrations of sonlicromanol (KH176); red represents plasma concentrations of the metabolite KH176m (KH183).

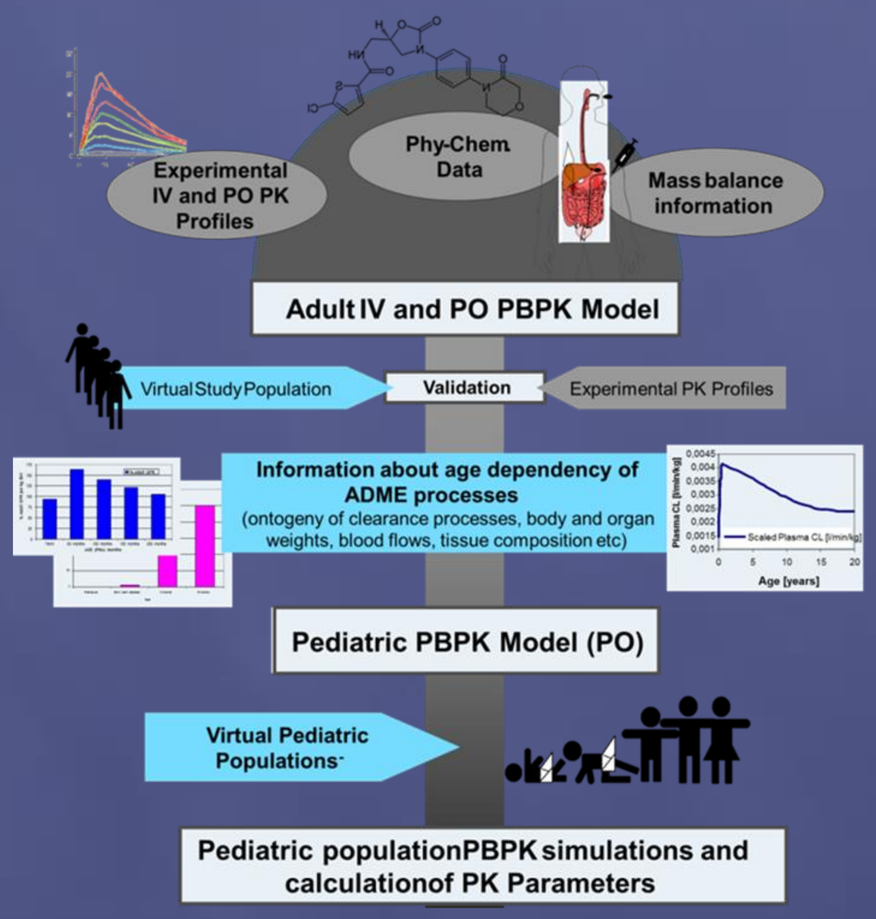

Figure 3: Modeling & simulation workflow in PBPK-based pediatric evaluations [4] (Figure is courtesy of www.open-systems-pharmacology.org)

References

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Presented at PAGE 2023, A Coruna, Spain; Abstract #10660

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