Model-informed once-daily dosing strategy for children, adolescents and adults for bedaquiline and delamanid

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Background

- Current dosing schedules for bedaquiline (BDQ) and delamanid (DLM) are complex for tuberculosis treatment in people across all ages
- Simpler once-daily dosing (ODD) is critical to ensure patient-friendly regimens with good adherence, and to enable development of fixed-dose combinations

Aim

- Assess expected drug exposures with novel model-informed ODD regimens for adults
- Compare model-informed ODD strategies for children with current World Health Organization (WHO) recommended dosing

Methods

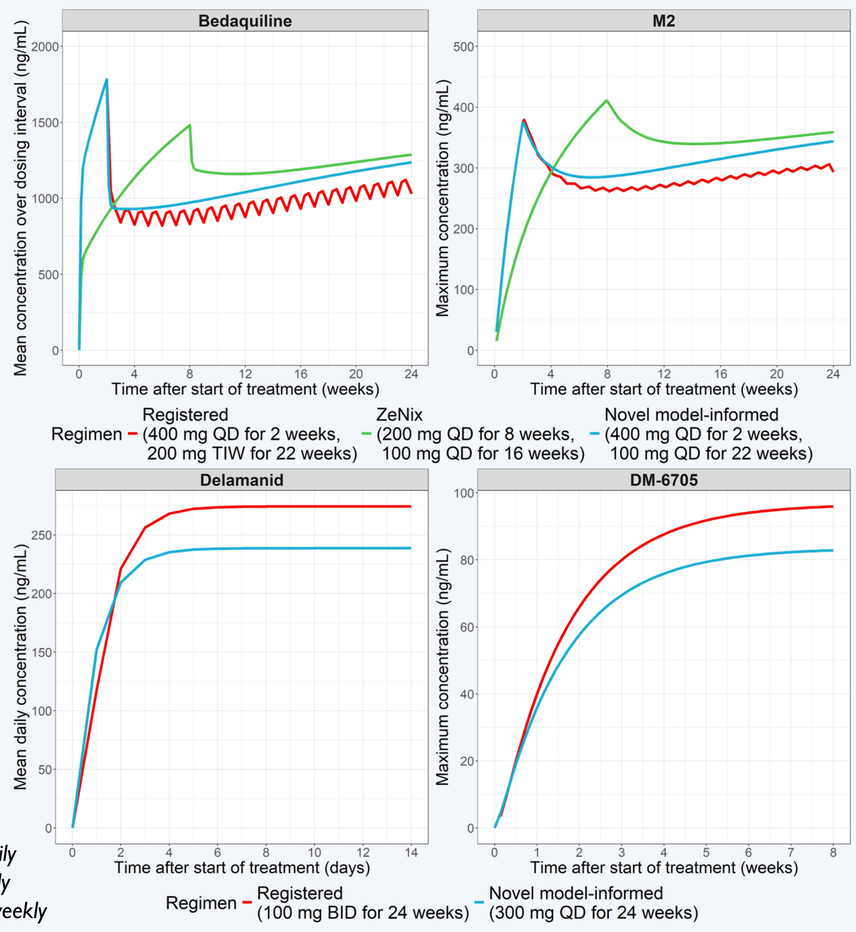
- For PK simulation, published population models were utilized:

	Adults	Children
BDQ and its metabolite M2	Svensson model [1]	Svensson model [1]
DLM and its metabolite DM-6705	Tanneau model [2]	Sasaki model [3]

- A reference adult individual was used to compare full PK profiles under registered, previously proposed ODD in the ZeNix trial and novel model-informed ODD regimens
- A virtual pediatric population (n = 40,000, 0-15 years, 3-<80 kg and 40% of black race) was generated for simulation. Exposures were compared to model-based targets
- Different CYP3A4 ontogeny profiles (Johnson, Salem and Upreti) [4,5,6] were tested

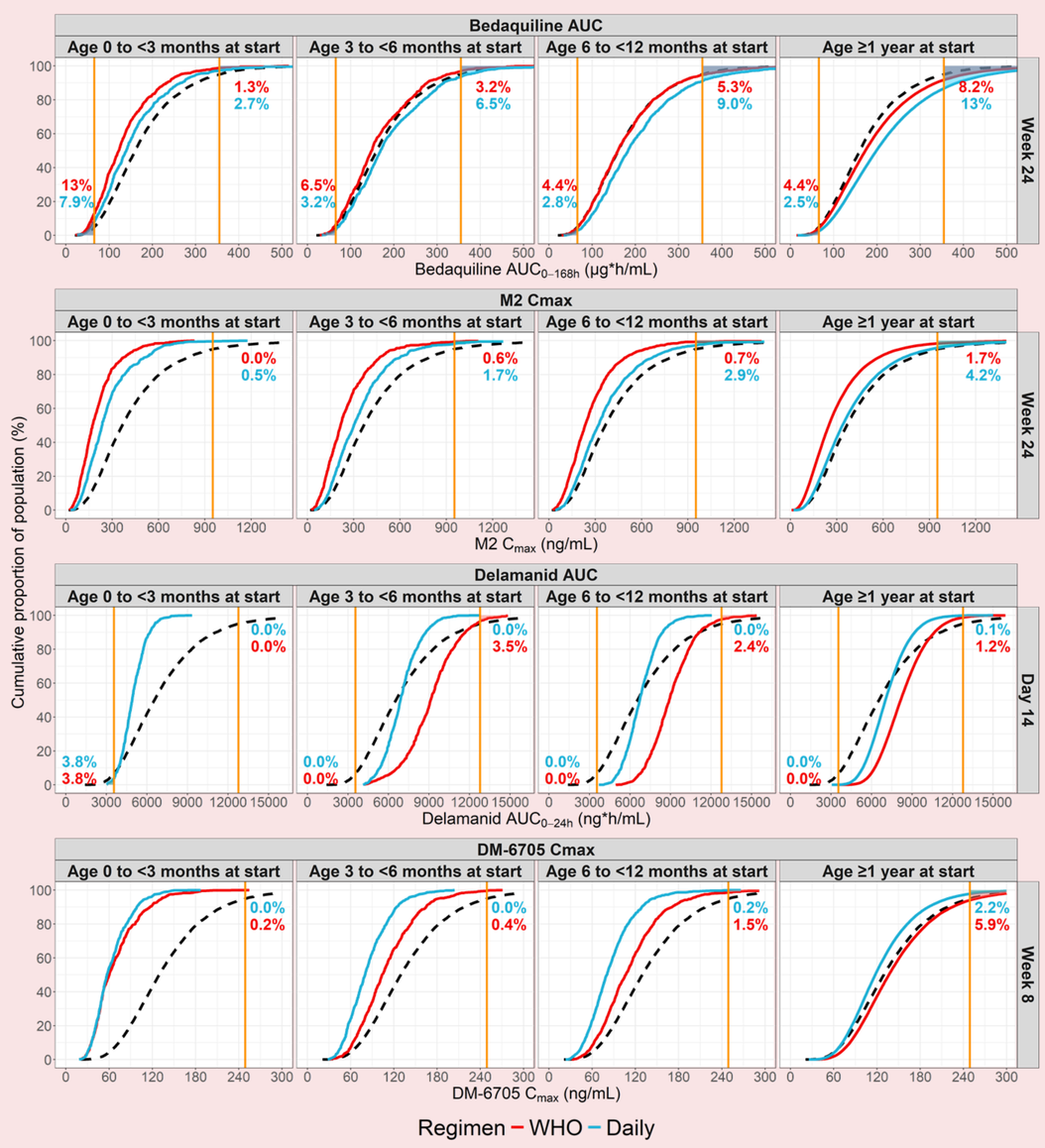
Results

- **In adults**, compared to the registered dosing, novel model-informed ODD yielded:
  1. 14% higher exposures of BDQ and M2 at the end of treatment (24 weeks)
  2. 13% lower exposures of DLM and DM-6705 at steady-state



*BID: twice daily
*QD: once daily
*TIW: thrice weekly

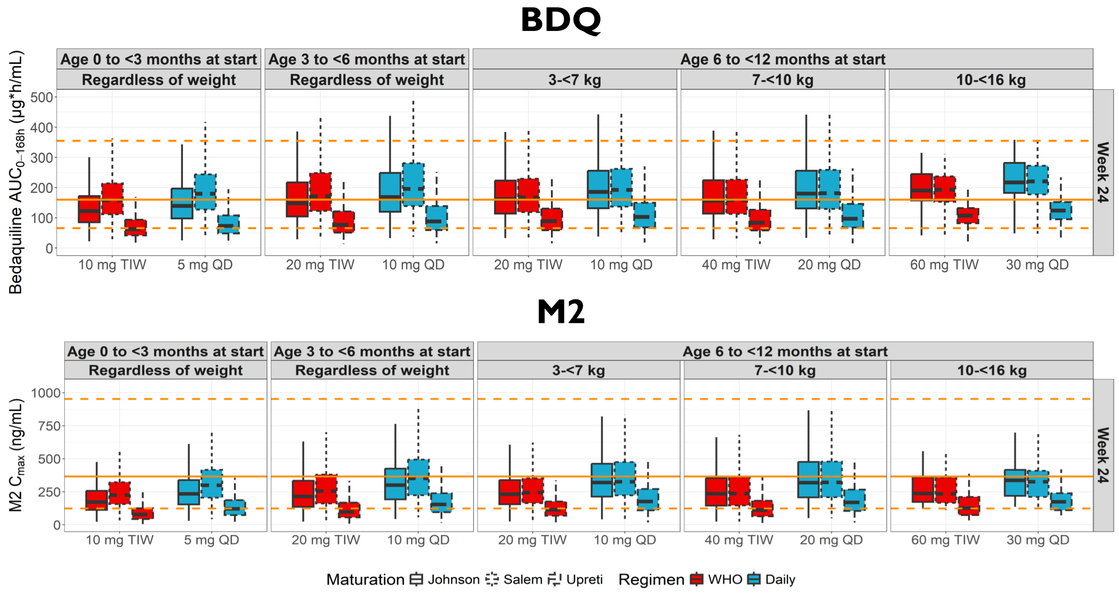
- **In children**, compared to the WHO-recommended dosing, proposed ODD showed: < 5% differences in the cumulative proportions of children of exposures of BDQ and M2 at 24 weeks, DLM and DM-6705 at steady-state



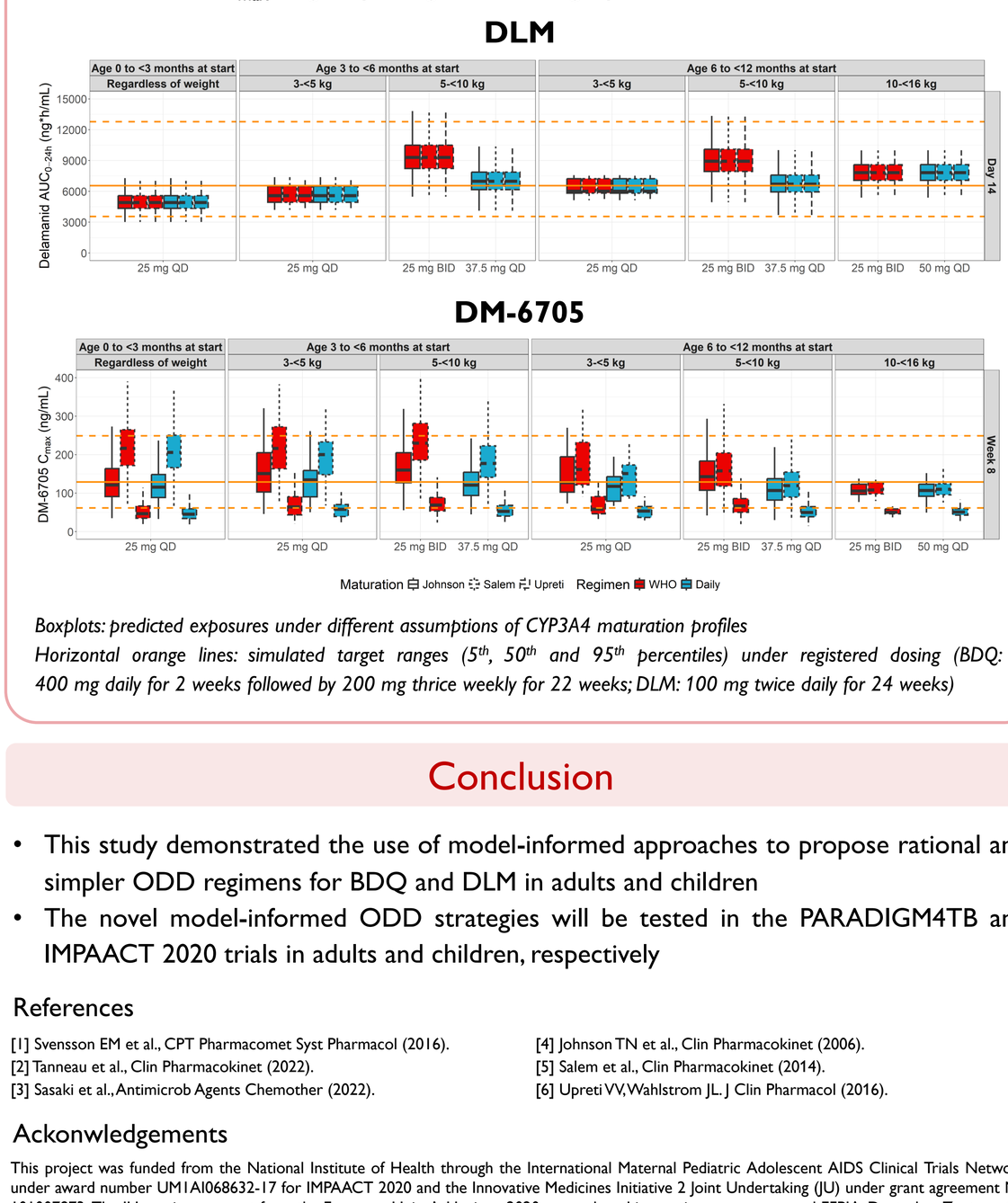
Solid curves: pediatric population; Dashed curves: adult population under registered dosing (BDQ: 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks; DLM: 100 mg twice daily for 24 weeks)
Vertical orange lines: simulated targets (5th and 95th percentiles for BDQ and DLM, 95th percentile for metabolites)
Shaded areas and correspondent numbers in percentages: % of population under or above target exposure ranges

Simulation with different CYP3A4 ontogeny profiles in children < 1 year

- >90% fell within BDQ and M2 target ranges by using Johnson and Salem ontogenies
- 34% were below the lower limit of BDQ $AUC_{0\text{-}168}$ target by using Upreti ontogeny



- No difference in DLM exposures (small contribution of CYP3A4 in metabolism)
- 26% (aged <3 months) and 15% (aged 3-<6 months) were above the upper limit of DM-6705 C_{max} target by using Salem ontogeny



Boxplots: predicted exposures under different assumptions of CYP3A4 maturation profiles
Horizontal orange lines: simulated target ranges (5th, 50th and 95th percentiles) under registered dosing (BDQ: 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks; DLM: 100 mg twice daily for 24 weeks)

Conclusion

- This study demonstrated the use of model-informed approaches to propose rational and simpler ODD regimens for BDQ and DLM in adults and children
- The novel model-informed ODD strategies will be tested in the PARADIGM4TB and IMPAACT 2020 trials in adults and children, respectively

References

[1] Svensson EM et al., CPT Pharmacomet Syst Pharmacol (2016).
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Ackonwledgements

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