

A model-informed learn-confirm approach for balovaptan paediatric dose selection to achieve adult-equivalent drug exposure

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Introduction

- Balovaptan is a vasopressin receptor 1a antagonist initially developed to help improve socialization and communication in autism spectrum disorder (ASD)
- The first study conducted in paediatric participants was a Phase II, randomized, double-blind, 24-week, placebo-controlled study to investigate the efficacy, safety and pharmacokinetics (PK) of balovaptan in children and adolescents with ASD aged 5-17 years (aV1ation [NCT02901431])
- Target for the pediatric dose selection was to achieve an exposure distribution equivalent to the steady-state AUC (AUCss) previously observed at 4 and 10 mg in adults, without exceeding an exposure cap
- Dose- and time-dependent PK observed in adults [3] had adequately been described with an empirical approach in a preliminary PopPK model

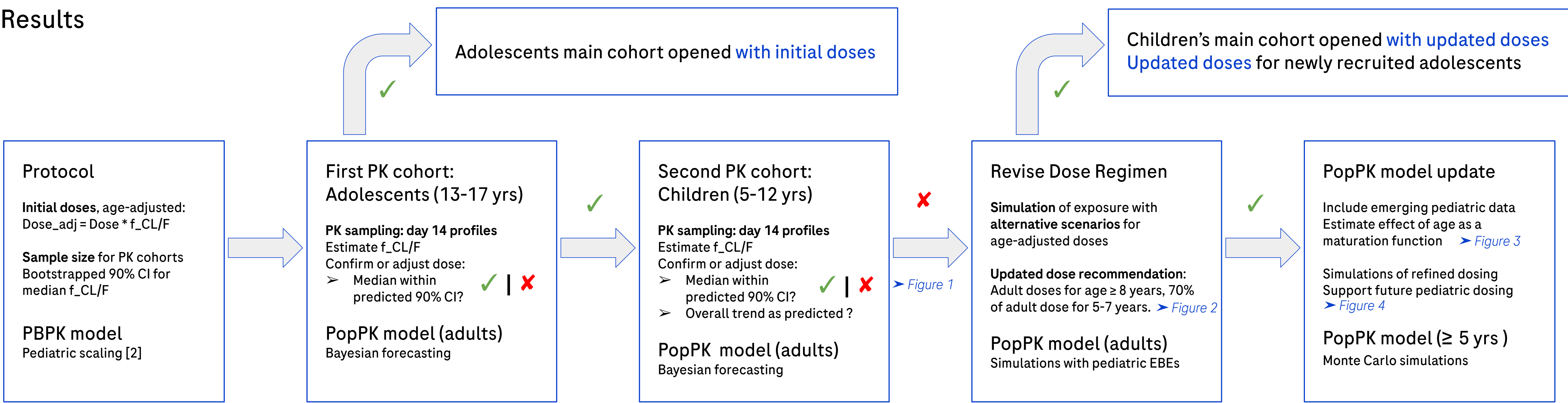
Objectives

- To present the **model-informed learn-confirm approach** used to support the balovaptan **dose selection and confirmation for the pediatric population aged 5 to 17 years**, to achieve a homogenous, adult-equivalent exposure distribution across all ages in the aV1ation study

Methods

- Recruitment to aV1ation was opened stepwise by age, conditioned on dose confirmation:
 - A PK cohort in adolescents (13-17 yrs, N=24, 16 active / 8 placebo), for dose confirmation
 - Full recruitment of adolescents to the main study part at confirmed doses
 - A PK cohort in children (5-12 yrs, N=24, 16 active / 8 placebo), for dose confirmation
 - Full recruitment of children to the main study part at confirmed doses
- Selection of initial doses, equivalent to 4 mg and 10 mg in adults, was guided by the PBPK model-based predictions of pediatric exposure and variability [2]:
 - Four paediatric age/dose bands: two for adolescents (13-14 and 15-17 yrs), and two for children (5-7 and 8-12 yrs)
 - Doses adjusted to the predicted fractions of apparent clearance (CL/F) in pediatrics ($f_{CL/F}$), relative to CL/F in adults
- PK sampling and Bayesian forecasting for dose confirmation per age/dose group
 - Population PK (PopPK) model in adults → obtain empirical Bayes estimates (EBEs) of pediatric individual parameters
 - Compare $f_{CL/F}$ with the PBPK predictions and 90% CI
 - Confirm doses OR use EBEs for simulating updated dosing scenarios
- Update the PopPK model with emerging pediatric PK data in aV1ation
 - Exposure simulations to inform future pediatric dosing

Results



The age-dependent decrease in CL/F appeared weaker than predicted

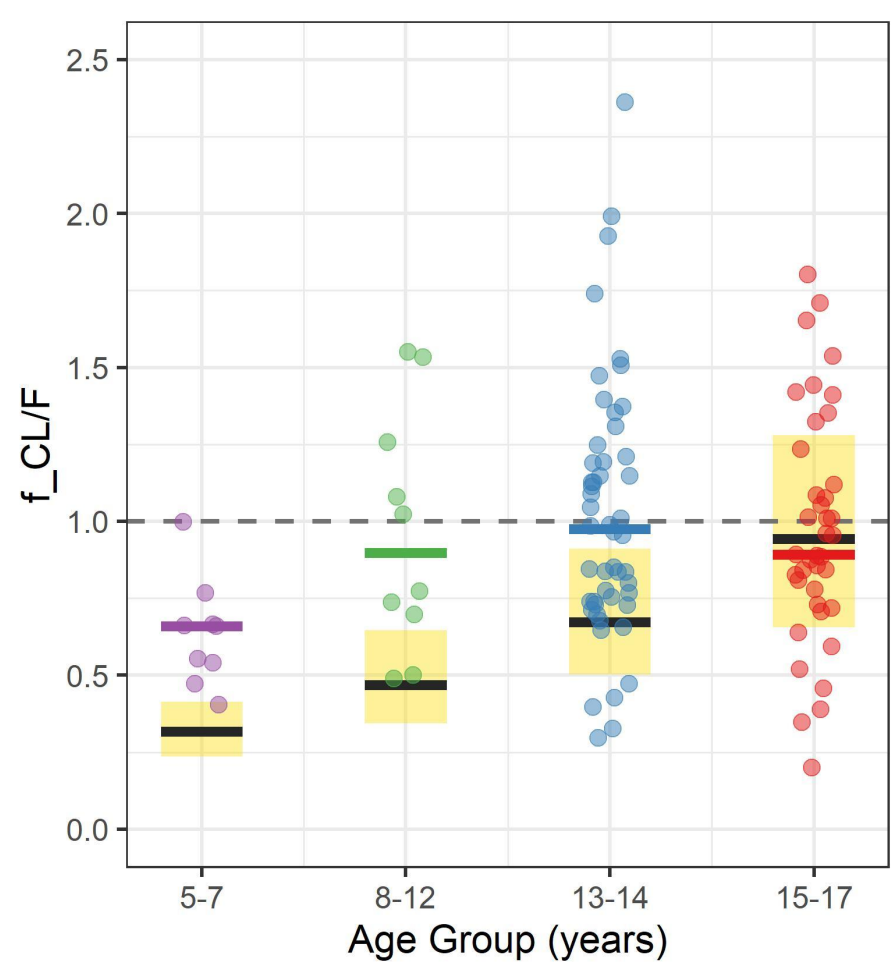


Figure 1: Fraction of CL/F ($f_{CL/F}$) in pediatric subjects in aV1ation, at the time of final dose confirmation. Observed medians for ages <15 years were above the 90% CI for the PBPK predicted medians. Colored lines: observed medians; black lines with yellow areas: predicted medians with 90% CI; symbols: individual values.

Age group (years)	Predicted Median (90% CI)	Observed Median	N
5-7	0.32 (0.24 - 0.41)	0.66	9
8-12	0.47 (0.34 - 0.65)	0.9	10
13-14	0.67 (0.50 - 0.91)	0.98	50
15-17	0.94 (0.66 - 1.28)	0.89	39

An updated dosing algorithm with a reduced number of age/dose bands was proposed, that predicted exposure at target for all age groups, and was confirmed at subsequent PK reviews.

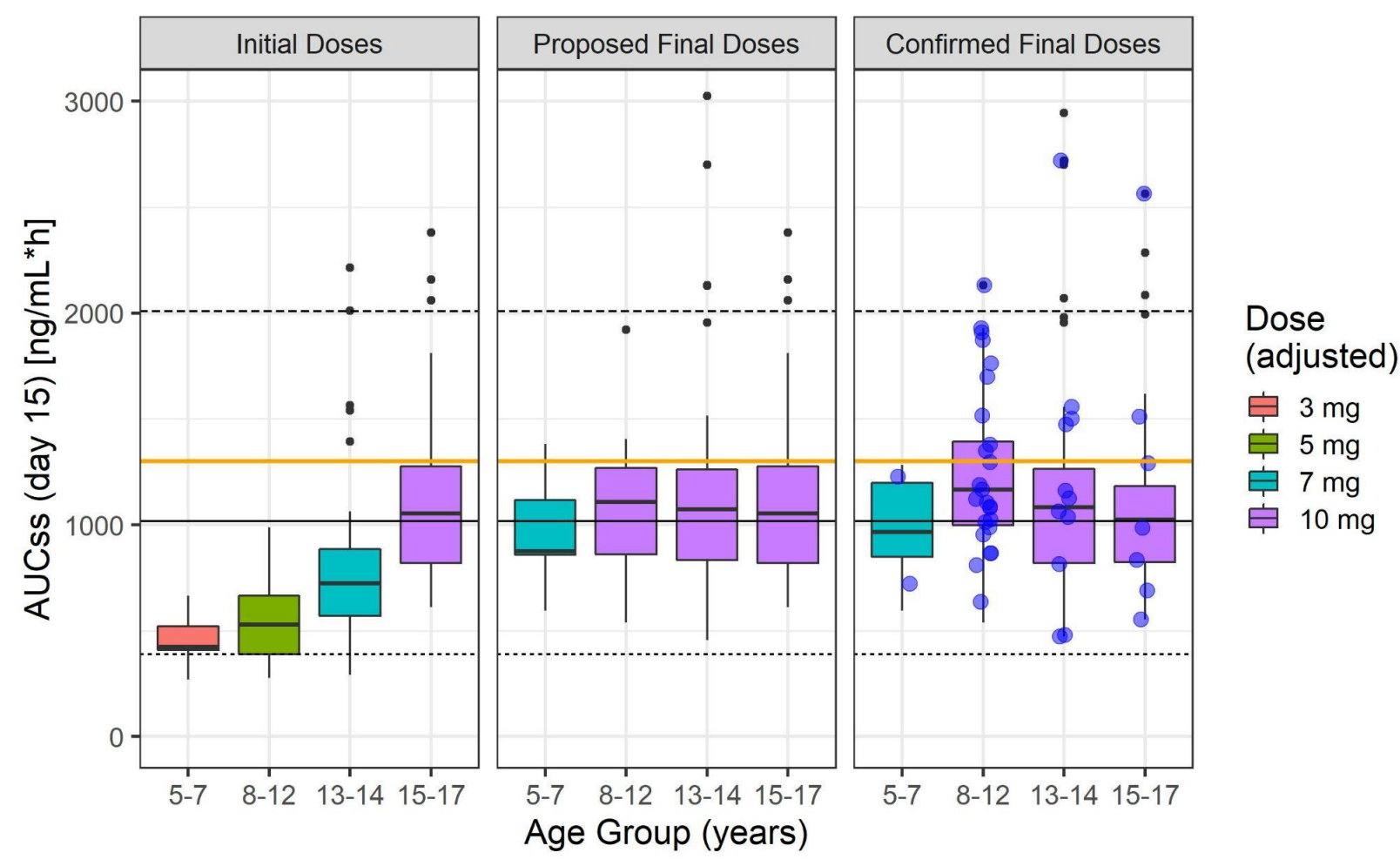


Figure 2: Predicted AUCss in the pediatric population in aV1ation, for the initial and proposed final doses, assuming all participants would receive the 10 mg-equivalent dose. The predictions were derived from simulated PK profiles on day 14, using the adult PopPK model with EBEs for the pediatric individual parameters. Left panel: Exposure for initial doses demonstrate the effect of over-corrected doses, based on the initially predicted age-effect on CL/F, resulting in AUCss below target at younger age. Middle panel: With the proposed final doses for aV1ation, the predicted exposure was distributed around the targeted adult exposure, and below the pre-specified exposure cap for all age groups. Right panel: Emerging new data at subsequent PK reviews (highlighted with blue symbols) confirmed target exposure with final doses. Black lines: Median (solid) and 5th (dotted) and 95th (dashed) quantiles of observed AUCss in adults [1]; yellow line: exposure cap for median exposure. [One value > 4000 ng/mL·h in older adolescents 15-17 yrs is not shown.]

The updated PopPK model incorporates the age effect on CL/F as a continuous relationship, allowing for simulations to inform decisions for future pediatric dosing

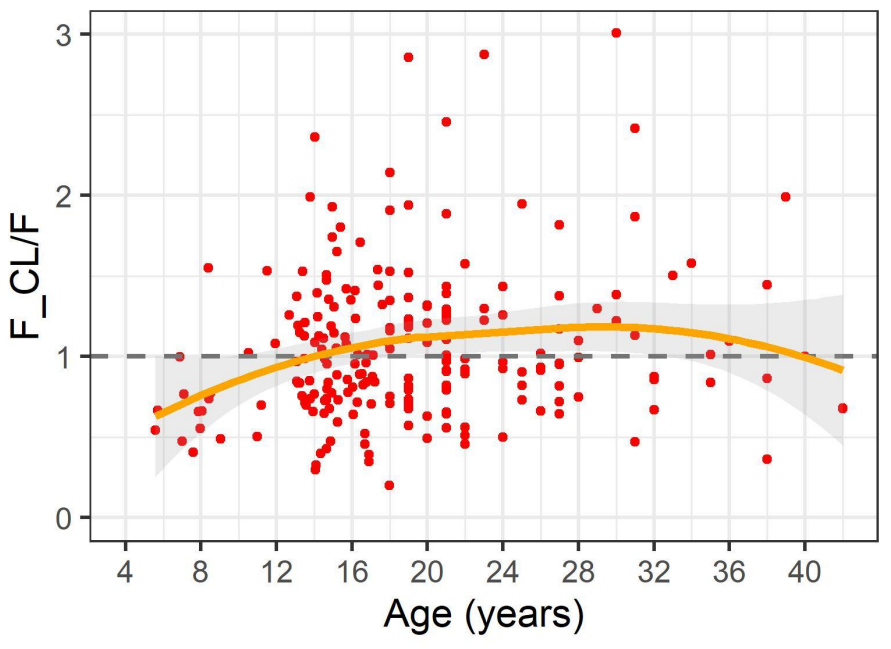


Figure 3: Estimated $f_{CL/F}$ from cumulative PK data emerging from the main cohorts in adolescents and children in aV1ation, combined with data from the adult Phase 2 study [1]. With PK data from younger children available, the overall age trend for CL/F could be estimated in an updated PopPK model (manuscript in preparation). Symbols: individual estimates, line and shaded area: loess smooth with 95% CI. [One value > 4 not shown]

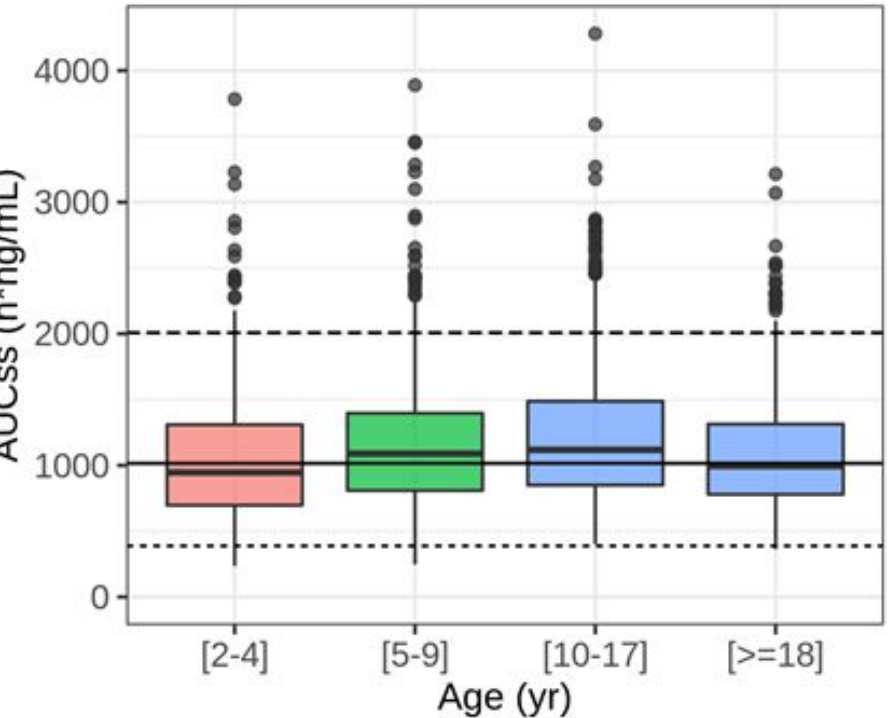


Figure 4: Simulated AUCss distribution for a population including pediatric and adult subjects with ASD aged ≥ 2 years, using the updated PopPK model. Dose/age groups have been slightly updated based on the model estimated age effect on CL/F. Black lines: Median (solid) and 5th (dotted) and 95th (dashed) quantiles of observed AUCss in adults [1].

Conclusions

- A model-informed learn-confirm approach successfully supported the selection and confirmation of paediatric age-adjusted doses for balovaptan.
- The mismatch between PBPK model-predicted and observed age effect on CL/F was unexpected and possibly due to unexplained dose- and time-dependent PK behavior.
- Although the study design, with narrow initial age/dose bands and staggered, age-based inclusion from older to younger participants, appeared complex and sensitive to slow recruitment, it generated informative data for adequate dose confirmation during the study, and for subsequent characterization of pediatric PK in an updated PopPK model.

References

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- Schaedeli Stark F et al. PAGE 24 (2015) Abstr 3553 [www.page-meeting.org/?abstract=3553]
- Derks et al. Expert Opin Investig Drugs 30:893-901, 2021. DOI:10.1080/13543784.2021.1948009