Dose Selection Of Marzeptacog Alfa (Activated) In Children With Hemophilia: A Population Pharmacokinetic Exposure Matching Strategy

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Conclusions

Population pharmacokinetics simulations support selecting 60 µg/kg as the SQ dose of MarzAA in a clinical trial with pediatric subjects with HA/HB with inhibitors to mimic levels achieved with adults

Key observations

- **The 60 µg/kg SQ dose across all pediatric age groups demonstrated comparable exposure levels to adults**
- **The relationship between MarzAA clearance (CL) and bodyweight (BW) showed a non-linear relationship with higher CL per kilogram of BW at lower BW**
- **A hypothetical doubling of absorption rate resulted in 25-40% increase the area under the curve over 24 hours ($AUC_{0\text{-}24h}$) and 60-80% increase in maximal concentration during the 24 hours (C_{max})**

Objectives

Primary

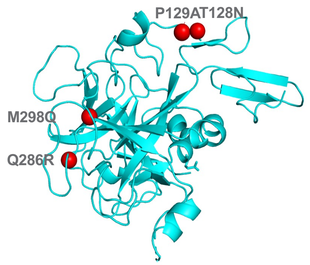
Support the pediatric trial dose selection for SQ MarzAA in children with HA/HB with inhibitors through clinical trial simulations

Secondary

Perform sensitivity analysis in exposure matching to account for a hypothetical increase in absorption in pediatrics relative to adults

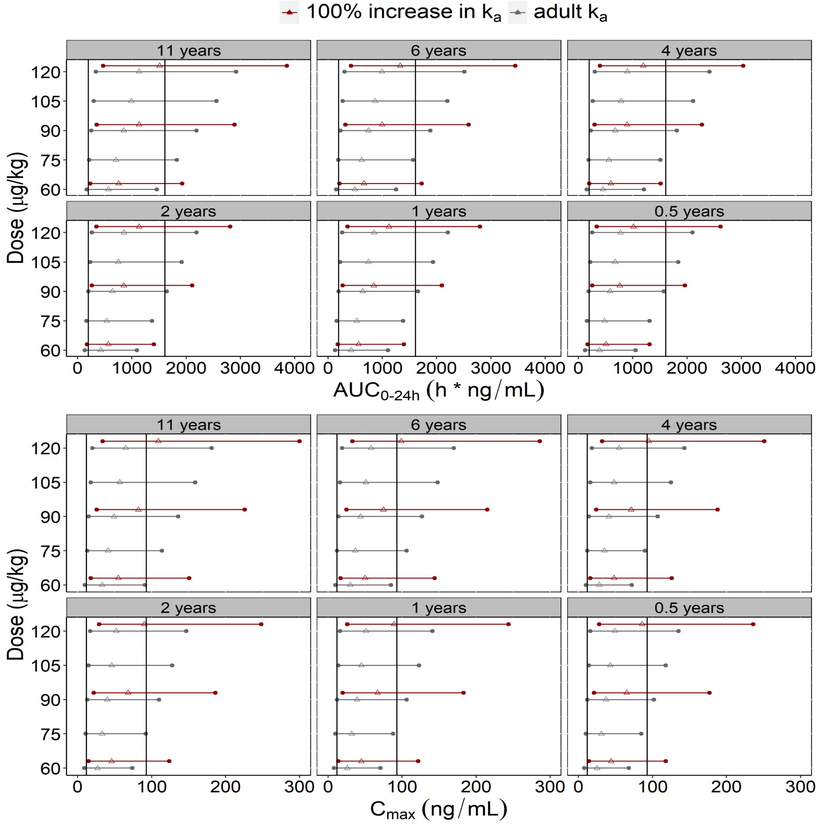
Background

- MarzAA is a novel rFVIIa variant with enhanced potency and bioavailability enabling SQ administration
- Two amino acid substitutions (Q286R and M298Q) in the protease domain increase FX activation in the absence as well as presence of tissue factor
- Two additional substitutions in the EGF2 domain of the light chain (T128N and P129A) create an additional N-linked glycosylation site
- MarzAA has been administered to individuals with hemophilia for a total of ≥625 exposure days without anti-drug antibody formation



Results

Comparable exposure across age groups compared to adults at various doses

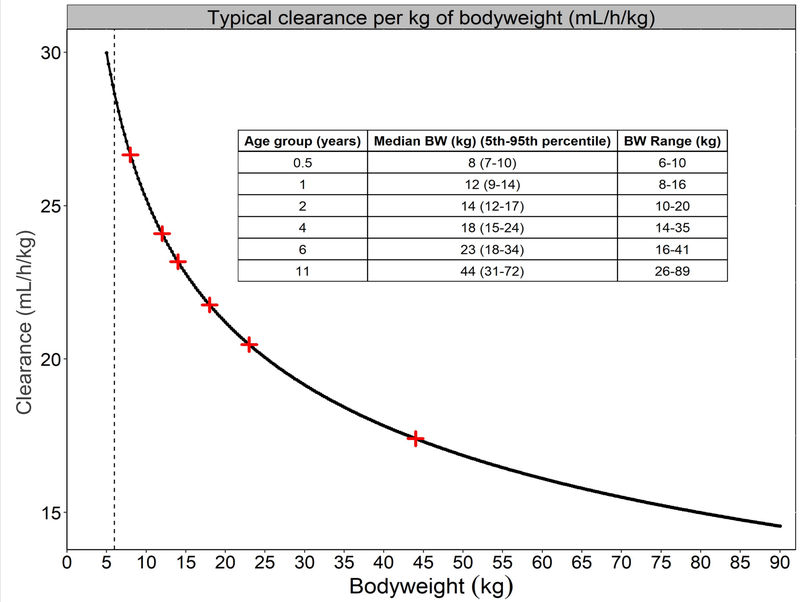


Predictions of $AUC_{0\text{-}24h}$ and C_{max} in the pediatric population for different age groups, dose levels given as a single dose and absorption rates. The triangles and horizontal lines are the median and 95% prediction interval for each dose level. The vertical lines are the 95% prediction interval in adults after 60 µg/kg administered as a single SQ injection. All predictions were based on simulation of 1000 children per age group per dose level.

- The relationship between MarzAA CL and BW was found to be non-linear with higher CL/kg at lower BW, with most of the non-linear trend below 14 kg, corresponding to the median BW in children of 2 years of age as described in The National Health and Nutrition Examination Survey (NHANES) database (https://www.cdc.gov/nchs/nhanes/index.htm).
- Using a single 60 µg/kg dose, the lower bound of the 95% PI of $AUC_{0\text{-}24h}$ in pediatrics was only slightly lower across all pediatric age groups compared to that of adults, and a similar pattern was observed for $C_{max,}$ indicating comparable exposure across pediatric and adult patients.
- A potential increase in absorption would have higher impact on C_{max} compared to $AUC_{0\text{-}24h}$

Results

Nonlinear bodyweight normalized clearance by age group



Age group (years)	Median BW (kg) (5th-95th percentile)	BW Range (kg)
0.5	8 (7-10)	6-10
1	12 (9-14)	8-16
2	14 (12-17)	10-20
4	18 (15-24)	14-35
6	23 (18-34)	16-41
11	44 (31-72)	26-89

Predicted bodyweight-adjusted clearance versus a range of bodyweights (5-90 kg) based on the adult population pharmacokinetic model with allometric scaling. The dashed line is the median bodyweight in children of 0.5 years of age from the NHANES database. The table shows the median and spread statistics of bodyweight for each age group. The red crosses illustrate the median bodyweight in each age group from the NHANES database

Methodology

A previously developed population pharmacokinetic model in adults including allometric scaling was used to predict the dose for the pediatric Phase 3 trial design. Using the model:

- Simulations for 1000 virtual pediatric subjects across several age categories using different doses were assessed to develop rich concentration-time profiles
- The relationship between clearance (CL) and bodyweight (BW) adjusted CL with a range of plausible bodyweight values for adult and pediatric subjects was evaluated
- Median and 95% prediction intervals (PI) of $AUC_{0\text{-}24}$ and C_{max} were derived to identify the dosing regimen that would best match the adult exposure of 60 µg/kg given on-demand.
- As allometric scaling was not included in the model for absorption parameters, the same procedure was repeated for a hypothetical doubling of the absorption rate in pediatrics relative to the adult estimate to study the effect of a potential absorption difference on pediatric dose selection