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Phase-3 dose selection of marzeptacog alfa (activated) in children enabled by model-informed drug development techniques

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Conclusion

The model supports using SC MarzAA at 60 µg/kg in a Phase 3 pediatric trial in HA/HB with inhibitors. The results suggest that the Phase 3 pediatric PK data should be analyzed as a pooled analysis with previously collected adult data or using priors.

Introduction

- Marzeptacog alfa (activated) (MarzAA), a novel engineered recombinant activated Factor VII is in clinical development for subcutaneous (SC) administration for episodic treatment of bleeding in individuals with hemophilia A (HA) or B (HB) with inhibitors and other inherited bleeding disorders
- This work aimed to support the pediatric Phase 3 trial dose selection for SC MarzAA in pediatrics with HA/HB with inhibitors through simulations investigating:
 - Exposure-matching strategy to support dose selection
 - Probability of trial success (PTS)
 - Trial design power to estimate clearance (CL) and volume of distribution (V)

Methods

- A developed population pharmacokinetic (popPK) model for MarzAA in adults including allometric scaling was used to simulate pharmacokinetic (PK) profiles following varying single SC doses in age groups (0.5, 1, 2, 4, 6, 11 years, n=1000 per group)
- The 95% prediction interval (PI) of AUC_{0-24h} and $C_{max(0-24h)}$ per age group and dose level were compared to the adult PI after a single 60 µg/kg SC dose
- Given that MarzAA PK exhibits absorption-limited elimination and that the rate of absorption in children has been shown in the literature [1, 2] to be higher relative to adults for some therapeutic proteins, a hypothetical increase (2x) of rate of absorption following single SC doses of 60, 90 and 120 µg/kg were simulated for each of the different age groups.
- PTS was evaluated by simulating PK profiles for 24 new pediatric subjects between 0 and 11 years of age in 1000 clinical trials following a single SC dose of 60 µg/kg. Each subjects AUC_{0-24h} and $C_{max(0-24h)}$ was compared with the adult PI (AUC_{0-24h} ; 196-1611 h*ng/mL, $C_{max(0-24h)}$; 12-93 ng/mL) resulting from the same dose. A given trial was considered successful if >80% of the subjects were predicted to be within the adult PI for AUC_{0-24h} or $C_{max(0-24h)}$. PTS was the number of successful trials divided by total number of trials
- The study power to estimate clearance (CL) and volume of distribution (V) with sufficient certainty for a Phase 3 trial in pediatrics given a stand-alone analysis were performed using stochastic simulations and estimations (SSE) [3]

Results

- The AUC_{0-24h} and $C_{max(0-24h)}$ PI were similar to the matching adult PI for the lowest dose of 60 µg/kg for most age groups
- Assuming a doubling of the absorption rate constant in the children compared to the adults favorably shifted the 2.5th percentile in all age groups for the 60 µg/kg dose to better match the adult PI for both AUC_{0-24h} and $C_{max(0-24h)}$
- The PTS following a single dose of 60 µg/kg in all age groups were 93% and 91% based on AUC_{0-24h} and $C_{max(0-24h)}$, respectively. The distribution of AUC_{0-24h} and $C_{max(0-24h)}$ in simulated individuals from all trials is shown in Figure 1
- The power for estimating CL and V with sufficient certainty for a proposed design (n=24 children) was 74% and 6%, respectively, indicating that a stand-alone analysis of the phase-3 pediatric data might be of limited value. Doubling the sample size did not substantially alter this result

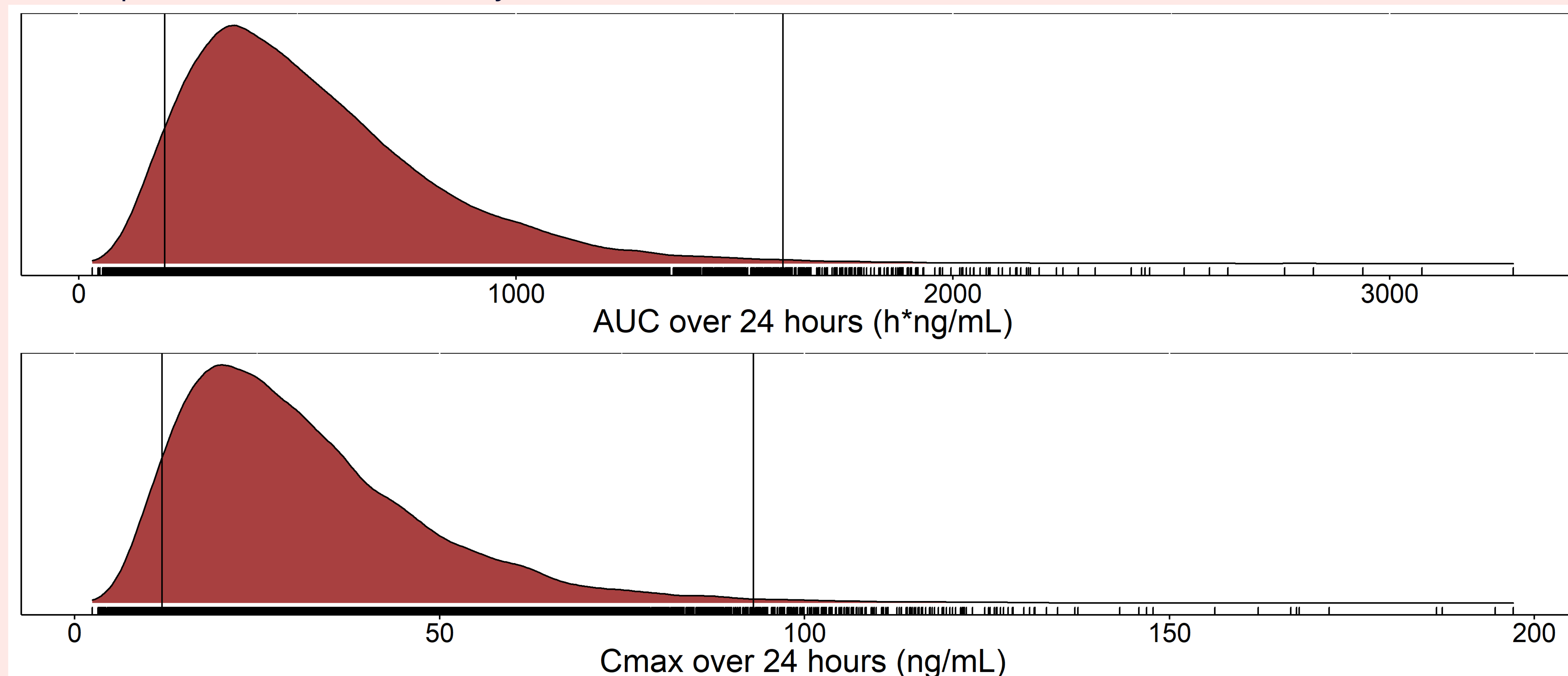


Figure 1. Distribution of AUC_{0-24h} and $C_{max(0-24h)}$ after a single 60 µg/kg dose from 1000 clinical trials with 24 pediatric subjects in each trial. The vertical black lines illustrate the 95% PI from adults given the same dose.

References

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