Marzeptacog Alfa (Activated) Population pharmacokinetics Simulations for dose selection in Phase 3 trials

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Conclusions

- **A population PK model was developed for clinical trial simulations for subcutaneous (SQ) marzeptacog alfa (activated) (MarzAA) to confirm dosing in Phase 3**
- **The model predicts that target levels for hemostasis may be rapidly achieved and sustained over 24 hours in the upcoming Phase 3 CRIMSON trial using 60 µg/kg dosed SQ once, twice or three times at 3-hour intervals**

Key observations

- **The final PopPK model accurately described the clinical data**
- **The terminal elimination half-life of MarzAA was estimated at 3.2 hours for IV dosing, while the SQ absorption and elimination half-lives were both estimated to be 14 hours indicating flip-flop kinetics**
- **SQ bioavailability was estimated at 26% with inter-individual variability of 54%**
- **Single SQ dosing as well as 2 and 3 doses, e.g. at 0, 3 and 6 hours may be used to achieve and maintain prolonged exposure in the target range**

Objectives

Primary objective

- Characterize the population pharmacokinetics (PopPK) of MarzAA after intravenous (IV) and subcutaneous (SQ) administration to support dose selection for a Phase 3 trial

Secondary objectives

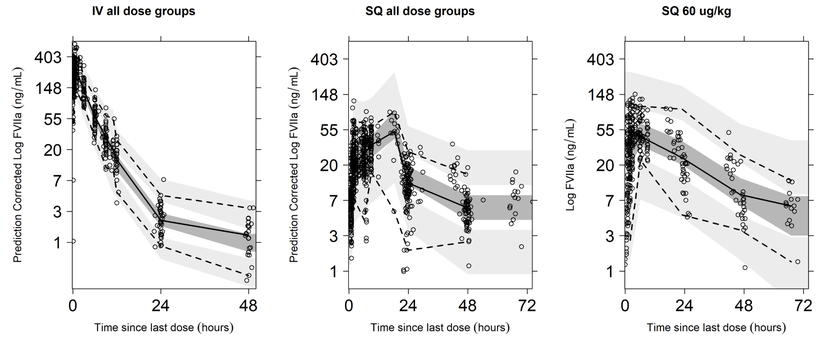
- Conduct trial simulations with varying dose regimens to evaluate the proportion of the population that achieve levels within the target range and estimate the time that these levels are maintained for each regimen

Methodology

+ MarzAA FVIIa clot activity data (STACLOT assay) from the following trials were included
  NCT01439971 - single IV doses at 4.5, 9, 18 or 30 µg/kg (n=25)
  NCT03407651 - single IV doses at 18 ug/kg and repeat SQ doses 30 or 60 µg/kg/day (n=10)
  NCT04072237 - single IV doses at 18 µg/kg and single SQ doses at 30, 45, 60 and 120 µg/kg or repeat SQ doses of 2 and 3 times 60 µg/kg for a total of 120 and 180 µg/kg respectively (n=10)
+ Using nonlinear mixed-effects modeling, data was sequentially modeled evaluating both IV and SQ data, including nonlinearities and allometric scaling
+ The modeling included data from individuals that were dosed on several separate occasions to describe intra-individual variability
+ Model discrimination was based on parameter uncertainty, plausibility and changes in the objective function value (ΔOFV=-3.84, p<0.05, one degree of freedom)
+ To describe inter-patient variability simulations were completed for a population of 1000 random subjects
+ The target range was defined as the level of MarzAA equivalent to 6 to 30 IU/mL wild-type rFVIIa, with the conservative assumption that MarzAA has 5-fold higher potency over rFVIIa

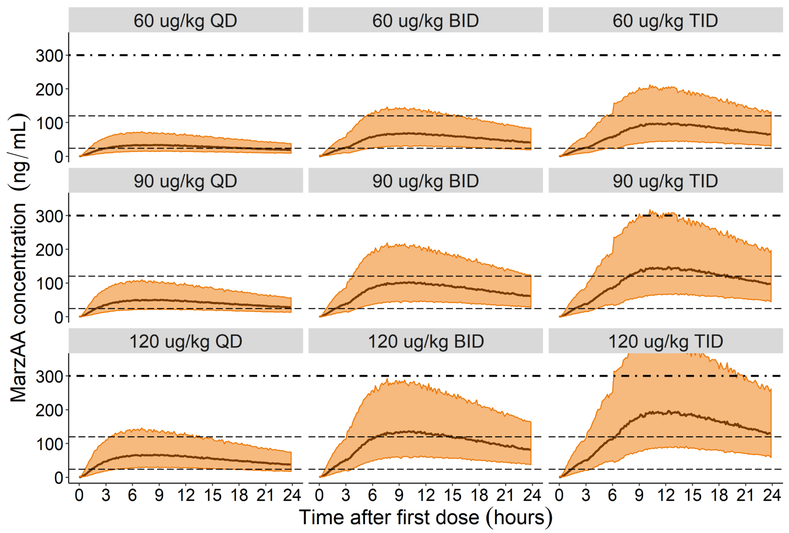
Results

PopPK model accurately describes the clinical data



Prediction corrected visual predictive checks (pcVPC) and visual predictive check (VPC) for log (anti-logged values on the y axis labels) FVIIa concentrations of all dose groups following (a) all dose groups of IV (b) all dose groups of SQ and (c) 60 ug/kg SQ administered MarzAA, respectively. Open circles represent prediction-corrected, i.e. scaled, observations in (a) and (b) and observed concentrations for (c). The solid and dashed lines are the median, 2.5th, and 97.5th percentiles of the observed data, respectively. The shaded areas (top to bottom) are the 95% confidence intervals of the 97.5th (grey), median (dark grey), and 2.5th (grey) percentiles of the simulated data.

Clinical trial simulations using three different dose regimens



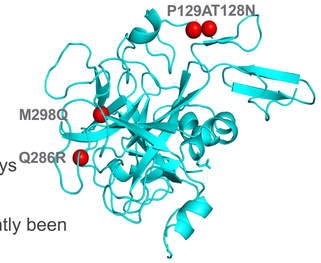
MarzAA concentration after different SQ administered regimens. The black solid line illustrate the median and the shaded area is the 80% prediction interval based on 1000 virtual subjects. The dashed lines illustrate the target concentration window and the long-dashed line illustrates 1/10th of the peak rFVIIa plasma concentration observed after a single IV dose of NovoSeven at 270 µg/kg.

Secondary PK parameters for the intended clinical dose

Regimen	Median $Cmax_{0\text{-}24h}$	Median $Cmin_{0\text{-}24h}$	Median $AUC_{0\text{-}24h}$	Median $Tmax_{0\text{-}24h}$
60 µg/kg x 1 dose at time 0 hours	34.2 ng/mL	19.2 ng/mL	616 h*ng/mL	8.6 hrs
60 µg/kg x 2 doses at 0 and 3 hours	68.9 ng/mL	40.3 ng/mL	1209 h*ng/mL	10.1 hrs
60 µg/kg x 3 doses at 0, 3, and 6 hours	98.8 ng/mL	66.3 ng/mL	1667 h*ng/mL	12.3 hrs

Background

+ MarzAA is a novel rFVIIa variant with improved potency and bioavailability enabling SQ administration
+ Two amino acid substitutions (Q286R and M298Q) in the protease domain and 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 more than 625 exposure days without anti-drug antibody formation
+ A Phase 1 dose escalation trial, MAA-102 has recently been completed and included in the PopPK model



Results

Percentage of population above target levels after 1 to 3 doses of 60 µg/kg

Dose and Regimen	Above target after 1 hr	Above target after 3 hrs	Above target after 6 hrs	Above target after 9 hrs	Above target after 12 hrs	Above target after 24 hrs	Above target after 36 hrs	Above target after 48 hrs
60 µg/kg 1 dose	9.4 %	50 %	69 %	71 %	68 %	35 %	6.3 %	0.9 %
60 µg/kg 2 doses 3 hours apart	10 %	56 %	90 %	95 %	96 %	83 %	45 %	14 %
60 µg/kg 3 doses 3 hours apart	11 %	55 %	91 %	98 %	99 %	96 %	75 %	35 %

Median time required to achieve target levels

Dose	Median
60 µg/kg	2.2 hours
90 µg/kg	1.7 hours
120 µg/kg	1.4 hours

Note: Preclinical data indicate that MarzAA may exhibit hemostatic effect significantly before full target concentrations are reached

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