# Dose Selection For Subcutaneous Marzeptacog Alfa (Activated) In Subjects With Factor VII Deficiency Using Population Pharmacometric Clinical Trial Simulations

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## Conclusions

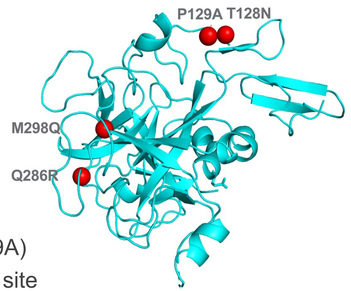
**The clinical trial simulations indicates that hemostasis may be achieved with the proposed doses and that sufficient exposure levels may be sustained in a significant proportion of subjects for 24 hours, even after a single SQ dose of 20 µg/kg or higher**

## Key observations

- **Most subjects are expected to achieve target levels within 3 hours after a single SQ dose of MarzAA at 20 µg/kg**
- **Higher doses shorten the time needed to reach the target level**
- **A vast majority of subjects are expected to sustain above target levels to prevent re-bleeding following a SQ dose of ≥20 µg/kg**
- **Following a single dose of 20 µg/kg, even the lower end of the 80% prediction is above 2 ng/mL, indicating that most subjects reach $C_{max}$ above the target level**
- **A lower SQ dose of 10 µg/kg MarzAA does not achieve target levels in a significant proportion of the population**

## 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

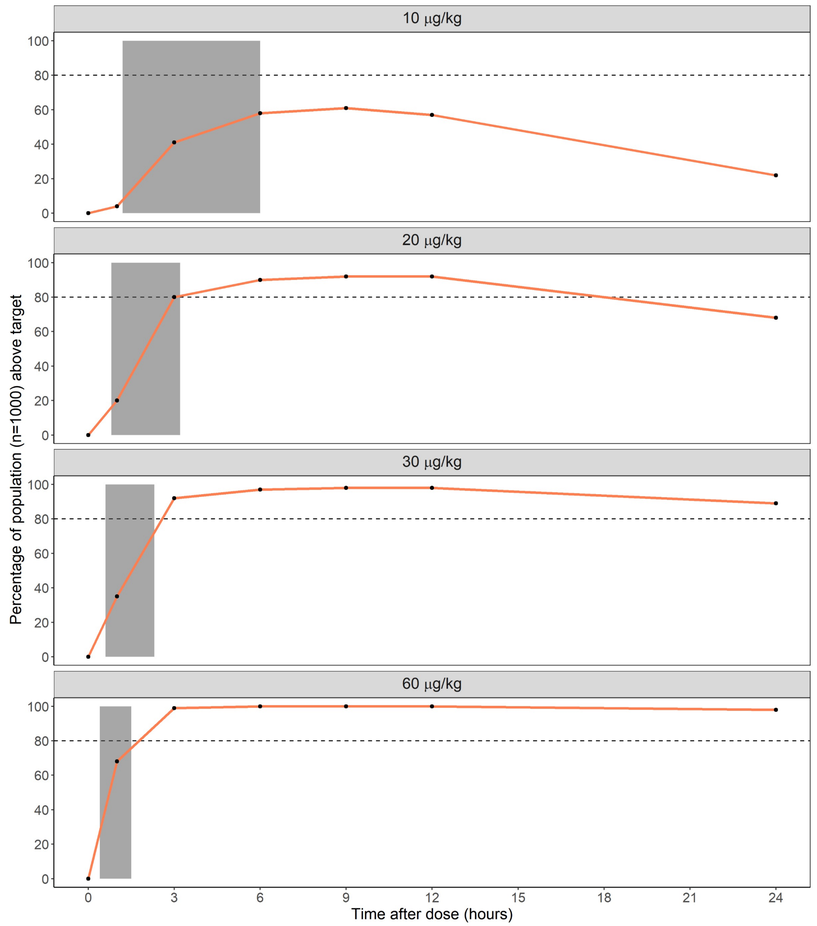



## Objective

To conduct clinical trial simulations using a previously developed population PK model in a large population (n=1000) following different doses to support dose selection for SQ MarzAA in a Phase 1/2 trial in FVIID subjects

## Results

Percentage of the population above target levels at various timepoints following different doses




Percentage of the population (n=1000) above target (2 ng/mL) at different timepoints following a single dose of 10, 20, 30 or 60 µg/kg of SQ MarzAA. The orange line illustrate the percentage of the population above target at selected timepoints and the gray shaded area shows the expected time to target (80% prediction interval) for the different dose levels. The dashed horizontal line marks 80% of the population being above the target.

Secondary PK parameters for the intended clinical dose

| Regimen | Median $Cmax_{0\text{-}24h}$ | Median $Cmin_{0\text{-}24h}$ | Median $AUC_{0\text{-}24h}$ |
|---|---|---|---|
| 10 µg/kg | 2.4 ng/mL | 1.3 ng/mL | 43.8 h*ng/mL |
| 20 µg/kg | 4.8 ng/mL | 2.6 ng/mL | 87.5 h*ng/mL |
| 30 µg/kg | 7.3 ng/mL | 4.0 ng/mL | 131.3 h*ng/mL |
| 60 µg/kg | 14.5 ng/mL | 7.9 ng/mL | 262.5 h*ng/mL |

## Results

- A single dose of 10, 20, 30 or 60 µg/kg resulted in median $C_{max}$ (and 80% prediction intervals (PI)) of 2.4 (1.2-4.8), 4.8 (2.4-9.7), 7.3 (3.7-14.5) or 14.5 (7.3-29.0) ng/mL, respectively
- The median and 80% PI of time-to-target following a single dose of 10, 20, 30 or 60 µg/kg are provided below

| Dose | Median (80% PI) |
|---|---|
| 10 µg/kg | 2.5 (1.2-6.0) |
| 20 µg/kg | 1.5 (0.8-3.2) hours |
| 30 µg/kg | 1.2 (0.6-2.3) hours |
| 60 µg/kg | 0.8 (0.4-1.5) hours |

- A single dose of 10 µg/kg did not reach desirable exposure levels
- A single dose of 20 µg/kg resulted in 80%, 90% and 68% of the population being above target at 3, 6, and 24 hours post dosing, respectively
- Doses of 30 or 60 µg/kg expanded the percentage of population above target to 89% and 98% at 24 hours post dosing, respectively

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

## Methodology

A previously developed population pharmacokinetic (popPK) model in adults was used and modified to better reflect the expected PK profile in FVIID subjects:

- The model estimated adult value of baseline FVIIa was adjusted to reflect baseline levels in severe FVIID subjects, ie., set to 0
- In accordance with the literature, FVIIa recovery was assumed to be lower in FVIID subjects and set to 43.5% relative to that observed in hemophilia A patients
- MarzAA was assumed to be at least 5-fold more potent than wild-type FVIIa
- Rich concentration-time profiles were simulated in a large population following different single doses (10, 20, 30, 60 µg/kg)
- The following exposure metrics were derived:
  - Percentage of the population above target (2 ng/mL) at different time points (0, 1, 3, 6, 9, 12, 24 hours after dose) within the first day were derived
  - Median and 80% prediction interval (PI) of the time to reach target levels
  - Median and 80% PI of $Cmax_{0\text{-}24h}$ ,$Cmin_{0\text{-}24h}$ and $AUC_{0\text{-}24h}$