Fast Onset of Action of Subcutaneously Administered Marzeptacog Alfa (Activated) Supports On-Demand Treatment in Hemophilia A Mice

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Results

- **SQ administration of MarzAA resulted in a dose dependent reduction in bleeding in hemophilia A mice when administered as late as 15 minutes before injury**
- **Full efficacy was achieved as bleeding in the mice treated with the highest dose was comparable to the blood loss observed in normal hemostatically competent mice**
- **The ED_{50} for MarzAA was 387 µg/kg when injury was 15 mins after SC administration**
- **When dosed as a rescue therapy one minute after injury, SQ MarzAA significantly reduced bleeding to 350±46 µL from 635±50 µL (vehicle) p = 0.02**

Conclusions and Perspectives

- **MarzAA was efficacious when administered SQ both after and before injury**
- **These data suggest that SQ MarzAA can be used on-demand to treat acute bleeding**
- **The mouse data provide a basis for further clinical investigation of on-demand treatment of a bleed with SQ MarzAA in hemophilia as well as in FVII deficiency**

Objectives

Primary objective

- Evaluate the effect SQ MarzAA on-demand, *ie*. dosed *after* injury in HA mice

Secondary objectives

- Evaluate the effect SQ MarzAA dosed before injury in HA mice
- Evaluate the dose response of SQ MarzAA in hemophilia A (HA) mice
- Compare the effect of select doses of MarzAA to NovoSeven by SQ and IV in HA mice

Methods

+ Animals: FVIII deficient, HA mice - strain B6;129S4-F8tm1Kaz/J
+ Each mouse was initially weighed and briefly anesthetized with isoflurane for collection of 5 µL blood to assess baseline hemoglobin levels to accurately quantify blood loss after bleeding
+ Test articles MarzAA and NovoSeven RT or saline control were administered at 5 mL/kg at defined timepoints before or after the injury (Fig 1)
+ All mice were anaesthetized using 100 mg/kg ketamine + 10 mg/kg xylazine
+ For the bleeding challenge mice were submitted to a tail clip injury model completely transecting the tail at a diameter of 1.25 mm - approximately 2 mm from the end of the tail - using a sharp razor blade
+ Blood loss was monitored with the tail submerged in warm saline (0.9% isotonic sodium chloride solution heated to 37˚C) for 20 minutes and quantified by hemoglobin content
+ Historic bleeding data from B6;129S mice served as normal control data
+ Controls were dosing with saline (negative control) or NovoSeven RT (positive control)
+ Non-gaussian data were analyzed by Kruskal-Wallis adjusting for multiple comparisons by Dunn's. Comparisons were made against the saline treated group representing the no effect level. Statistical significance was defined at α=0.05

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SQ MarzAA dose response – full normalization

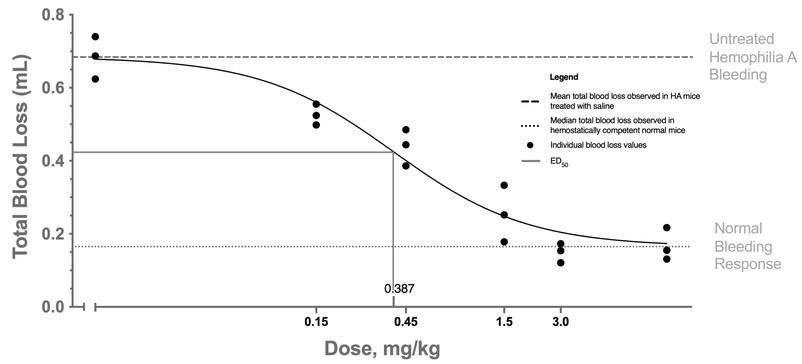


Fig 1. Dose Response of MarzAA dosed SQ 15 minutes before injury. The non-linear curve fit was constrained with a no effect level equal to the mean of the saline treated group and with a max effect level at the level of normal historic controls. The two control groups not labelled with a dose were included on the graph for completeness. The negative control was SQ saline, the positive control was IV MarzAA dosed at 1.5 mg/kg.

SQ MarzAA is efficacious On-demand

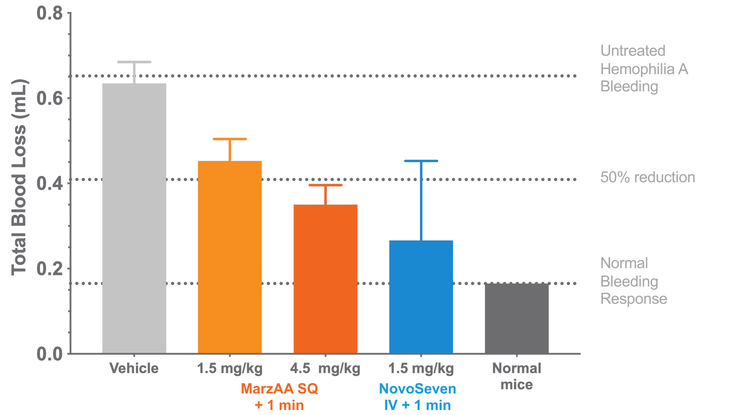


Fig 2. On-Demand Effect of MarzAA administered SQ and NovoSeven RT administered IV one minute after bleeding started. n = 3 mice/group.

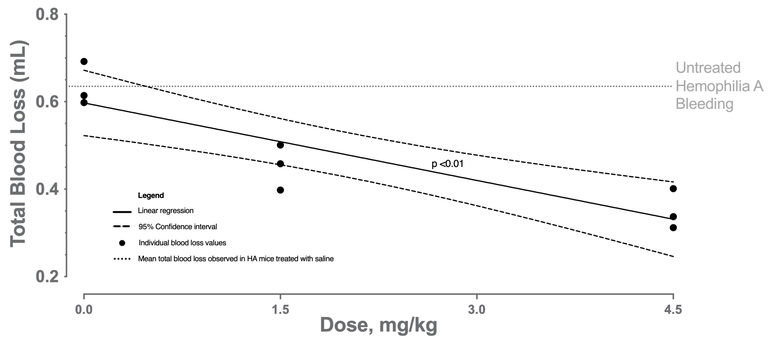
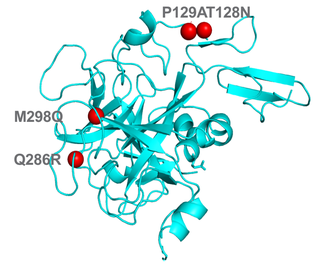


Fig 3. Dose Response of MarzAA Administered SC One minute After Injury. Solid dots represent blood loss for individual mice. Solid line represents the linear regression line. Dashed line represents the 95%CI for the linear regression.

Background

+ Marzeptacog alfa (activated) (MarzAA) is a novel rFVIIa variant with improved potency enabling subcutaneous (SQ) administration
+ MarzAA is currently in clinical development by Catalyst Biosciences
+ 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 humans for more than 500 exposure days without anti-drug-antibody formation



Study Design – Dose response

Acute injury model with SQ dosing *before* injury

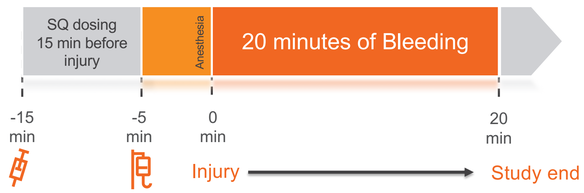


Fig 4. Study Design. Dose Response - MarzAA administered by SQ injection 15 minutes before injury.

Study Design – On-demand treatment

Acute injury model with SQ dosing *after* the injury

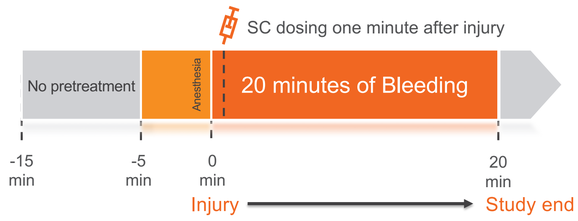


Fig 5. Study Design. Dose Response - MarzAA was administered by SQ injection 1 minute *after* bleeding was initiated.

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