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

P036

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Conclusion

- MarzAA was efficacious when administered subcutaneously (SQ) both after and before injury
- SQ MarzAA can potentially be used on-demand to treat acute bleeding
- These data provide a basis for further clinical investigation of on-demand treatment of a bleed with SQ MarzAA in hemophilia and in FVII deficiency

Objectives

Primary objective

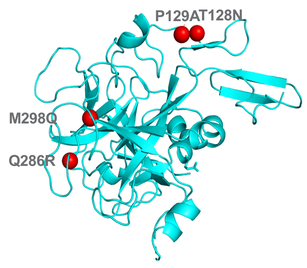
Evaluate the effect SQ MarzAA on-demand, ie, dosed *after* injury in hemophilia A (HA) mice

Secondary objectives

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

Background

- Marzeptacog alfa (activated) (MarzAA) is a novel rFVIIa variant with improved potency 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 (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



Methodology

- Animals: FVIII deficient, HA mice - strain B6;129S4-F8tm1Kaz/J
- Each mouse was initially weighed and briefly anesthetized with isoflurane
- 5 µL blood collected for baseline hemoglobin levels to accurately quantify blood loss
- Test articles MarzAA and NovoSeven RT or saline control were administered at 5 mL/kg at defined timepoints before or after the injury (Figure 1 & 2)
- 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
- License PPL PAF4E3C19 held by Dr. Jill Reckless at RxCelerate Limited and issued by the UK Secretary of State

Study Design

Figure 1
Model as used for dose response experiment with MarzAA administered by SQ injection 15 minutes before injury

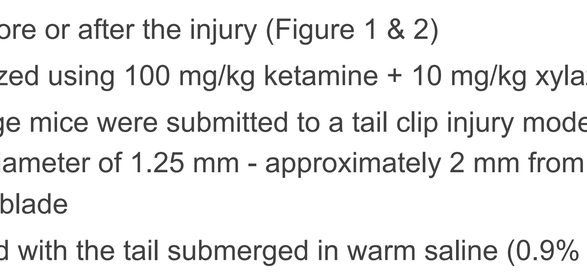
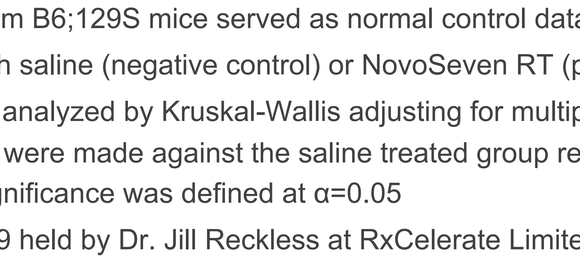


Figure 2
On demand treatment of a bleed experiment with MarzAA administered by SQ injection 1 minute *after* bleeding was initiated



SQ MarzAA dose response – full normalization

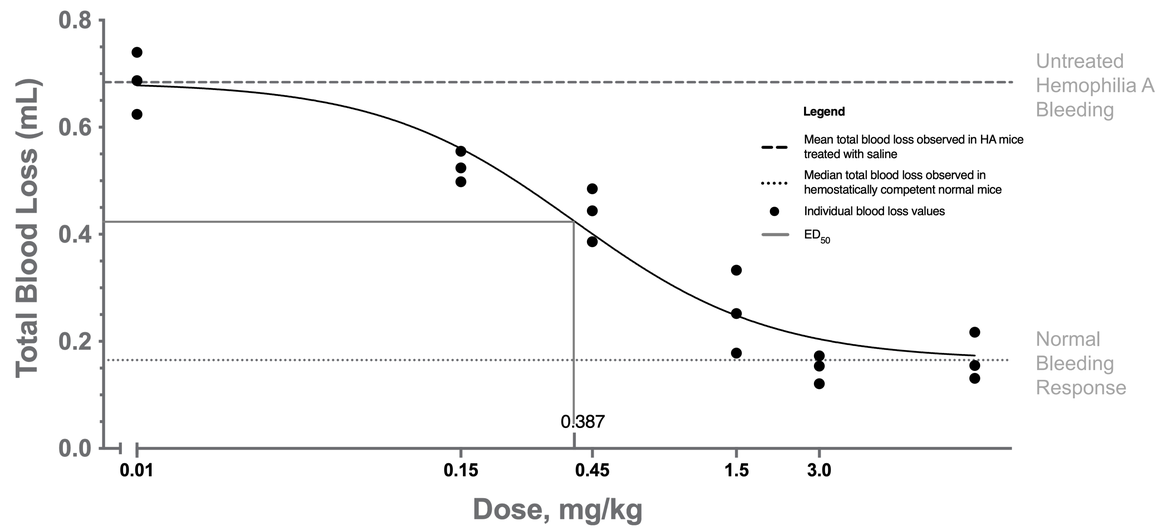


Figure 3 Dose Response of MarzAA dosed SQ 15 minutes before injury. The non-linear curve fit was constrained with a no effect level equal to the mean of the saline treated group and with a max effect level at the level of normal historic controls. The two control groups not labelled with a dose were included on the graph for completeness. The negative control was SQ saline, the positive control was IV MarzAA dosed at 1.5 mg/kg.

IV NovoSeven – select doses for comparison

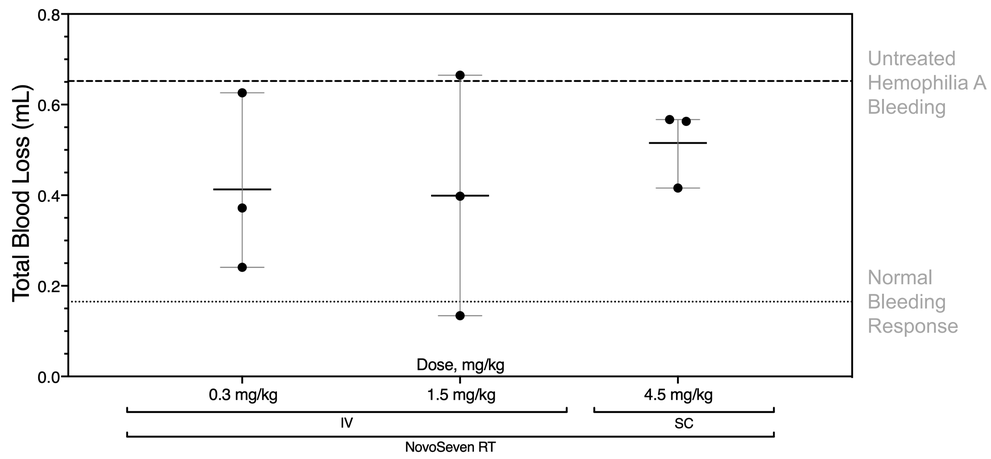


Figure 4 Blood loss after different doses of NovoSeven dosed either IV (0.3 and 1.5 mg/kg) or SC (4.5 mg/kg). NovoSeven was dosed by IV administration 5 minutes prior to injury or by SC administration 15 minutes prior to injury.

SQ MarzAA is efficacious On-demand

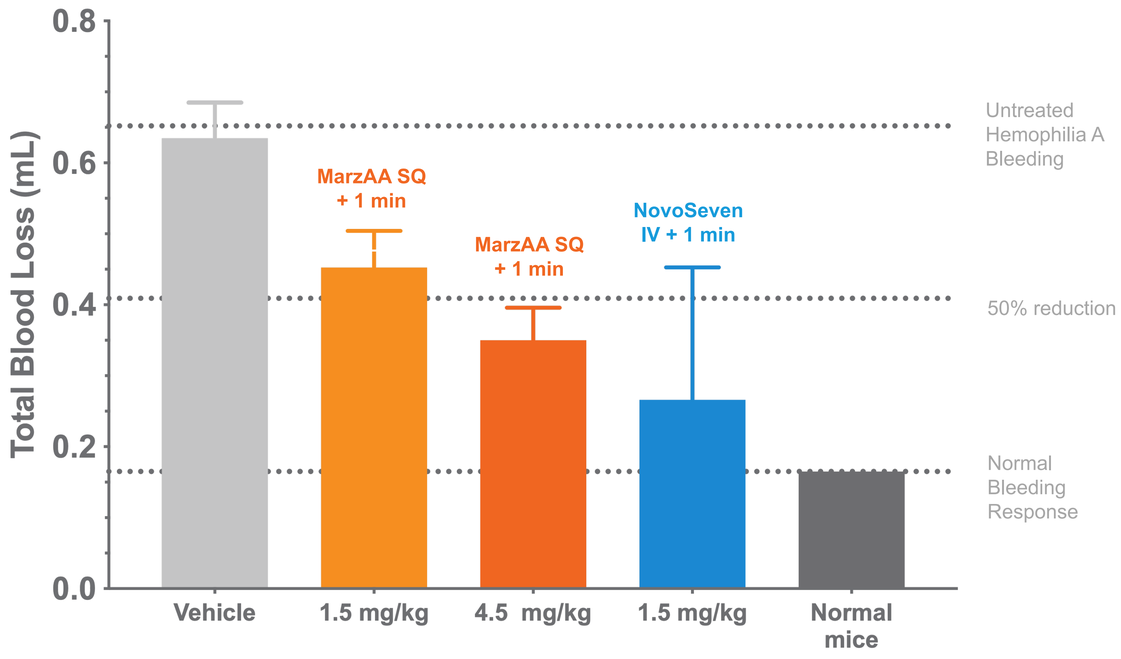


Figure 5 On-Demand Effect of MarzAA administered SQ and NovoSeven RT administered IV one minute after bleeding started. n = 3 mice/group.

SQ MarzAA on-demand used to treat ongoing bleed

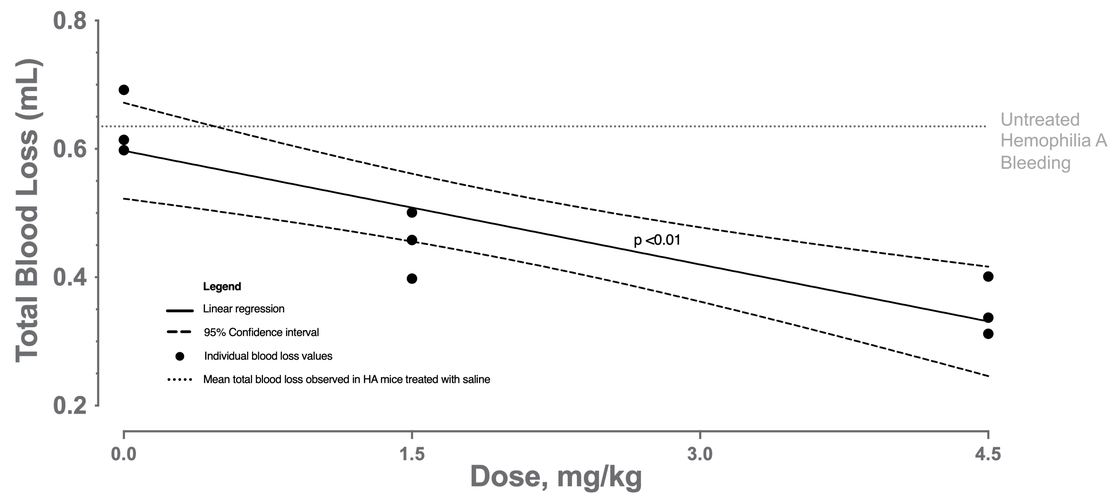


Figure 6 Dose Response of MarzAA Administered SC One minute After Injury. Solid dots represent blood loss for individual mice. Solid line represents the linear regression line. Dashed line represents the 95%CI for the linear regression.

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