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

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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 FVIII 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 anesthetized 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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