PHARMACOKINETICS AND PHARMACODYNAMICS OF DAILY SUBCUTANEOUSLY ADMINISTERED MARZEPTACOG ALFA (ACTIVATED) IN HEMOPHILIA DOGS

P076

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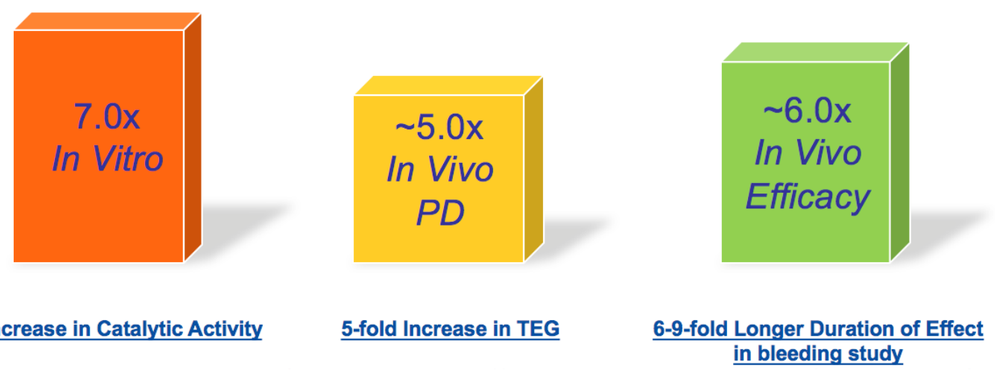
STUDY OBJECTIVES

Determine the pharmacokinetic and pharmacodynamic parameters after subcutaneous administration of a highly potent factor VIIa variant in hemophilia dogs

INTRODUCTION

- The rapid clearance of FVIIa necessitates frequent intravenous administrations to attempt prophylaxis for patients with hemophilia A or B with inhibitors
- Subcutaneous administration would be a preferred route of administration but has been limited by low bioavailability and potency of the marketed FVIIa products
- Marzeptacog alfa (activated) has four mutations that were introduced using rational design and has enhanced biological properties including 7-fold increased catalytic activity, measured by the rate of Factor Xa generation *in vitro*, in the presence and absence of tissue factor, and prolonged duration of effect *in vivo* compared with wild-type rFVIIa
- A human intravenous single-dose escalation study up to 30µg/kg showed a half-life of 3.5 hours and dose-dependent pharmacodynamic effects on prothrombin time, aPTT and thrombin generation and a good safety profile

MARZEPTACOG ALFA (ACTIVATED) ENHANCED PROPERTIES COMPARED WITH WILD-TYPE rFVIIa



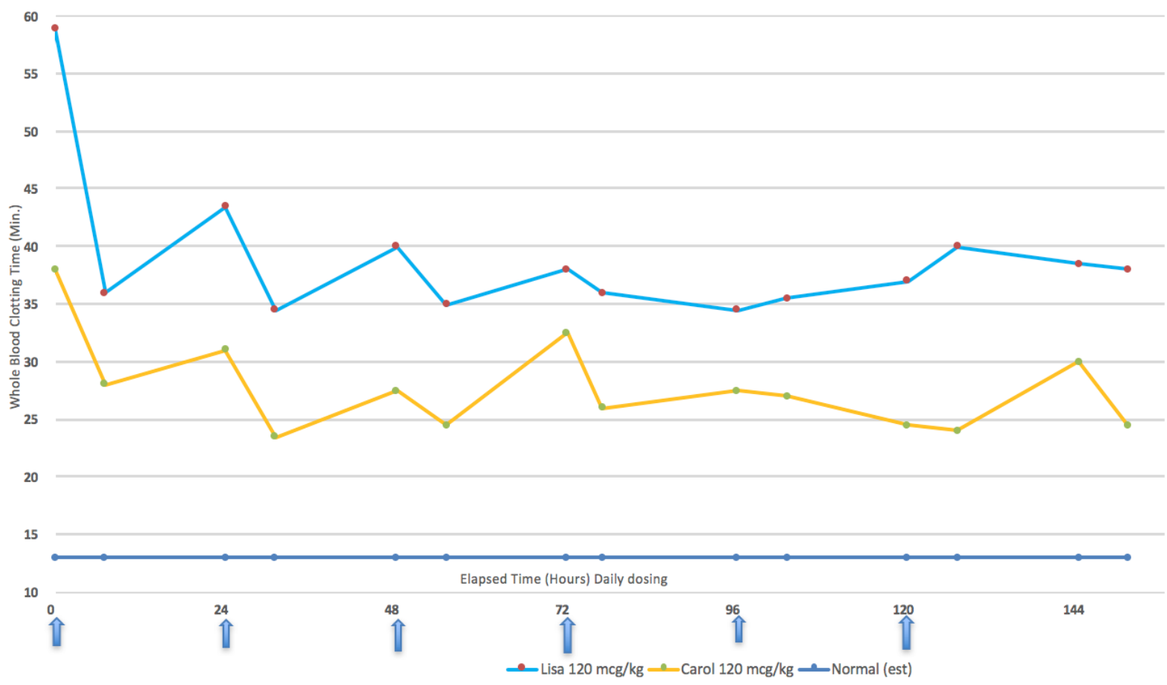
METHODS

- Marzeptacog alfa (activated) 120µg/kg was injected daily subcutaneously for 6 consecutive days in 2 hemophilia A dogs
- Samples were obtained at 0, 7, 24, 31, 48, 55, 72, 77, 96, 103, 120, 127, 144, and 150 hours
- Whole Blood Clotting Time (WBCT), aPTT using TriniCLOT activation and marzeptacog alfa (activated) antigen using Factor VII Antigen ELISA Kit were measured at each time point
- Subcutaneous bioavailability was calculated using previously obtained intravenous pharmacokinetic data in dogs

RESULTS

- WBCT was 60 and 52.5 mins at baseline (normal <13 minutes) and decreased to 36 and 26 mins respectively at 7 hours
- Further decrease in WBCT occurred with daily dosing with minimal difference between daily nadir and peak
- The shortest WBCT was 24 minutes at 127 hours
- WBCT after daily subcutaneous 120 µg/kg were comparable to 50 µg/kg intravenous marzeptacog alfa (activated) or 270 µg/kg intravenous NovoSeven
- aPTT baseline of 60 and 57 seconds reduced to 41 seconds (27-31% reduction)
- Previously reported intravenous doses of 10 or 50 µg/kg marzeptacog alfa (activated) had a Cmax of 145 and 1431 ng/mL and an 18% and 49% shortening of aPTT respectively
- Peak antigen level after subcutaneous dosing was 376 ng/mL and the highest trough was 267 ng/mL
- Activity of FVIIa mirrored antigen concentration
- Subcutaneous bioavailability was 44% and half-life was 50-136 hours
- There were no emergent clinical adverse events or abnormal chemistry lab abnormalities

WHOLE BLOOD CLOTTING TIME AFTER DAILY SUBCUTANEOUS ADMINISTRATION OF 120 µg/kg MARZEPTACOG ALFA (ACTIVATED)



- **Daily subcutaneous injections can correct the whole blood clotting time in hemophilia A dogs**

ANTIGEN LEVELS AND FUNCTIONAL ASSAY AFTER DAILY SUBCUTANEOUS ADMINISTRATION OF 120 µg/kg MARZEPTACOG ALFA (ACTIVATED)

- **Daily subcutaneous dosing resulted in stable trough levels**

SUMMARY

- Marzeptacog alfa (activated) with enhanced biological properties was developed using a rational protein design approach
- Bioavailability of subcutaneous injection of marzeptacog alfa (activated) was 44% and half-life was 50-136 hours and may reflect an effect of continuing adsorption from the injection site
- Daily subcutaneous dosing of marzeptacog alfa (activated) demonstrated the effects of the bioavailability, potency, time to maximal concentration, and half-life by reaching steady-state levels sufficient to correct coagulation abnormality comparable to published data in hemophilia dogs having FVIIa gene therapy that had no spontaneous bleeding for more than 1 year
- The increased potency of marzeptacog alfa (activated) facilitates the initiation of the Phase 2/3 subcutaneous dosing study in individuals with hemophilia B with inhibitors and a target of achieving normal coagulation pharmacodynamics

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Disclosures:
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