PHARMACOKINETICS AND PHARMACODYNAMICS OF DAILY SUBCUTANEOUS ADMINISTERED MARZEPACOG ALFA (ACTIVATED) IN HEMOPHILIA DOGS

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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

WHOLE BLOOD CLOTTING TIME AFTER DAILY SUBCUTANEOUS ADMINISTRATION OF 125 µg/kg MARZEPACOG 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 MARZEPACOG ALFA (ACTIVATED)

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

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 287 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

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 Cloting 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

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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