PHARMACOKINETICS AND PHARMACODYNAMICS OF DAILY SUBCUTANEOUSLY ADMINISTERED CB2679D/ISU304 IN HEMOPHILIA B DOGS

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P075

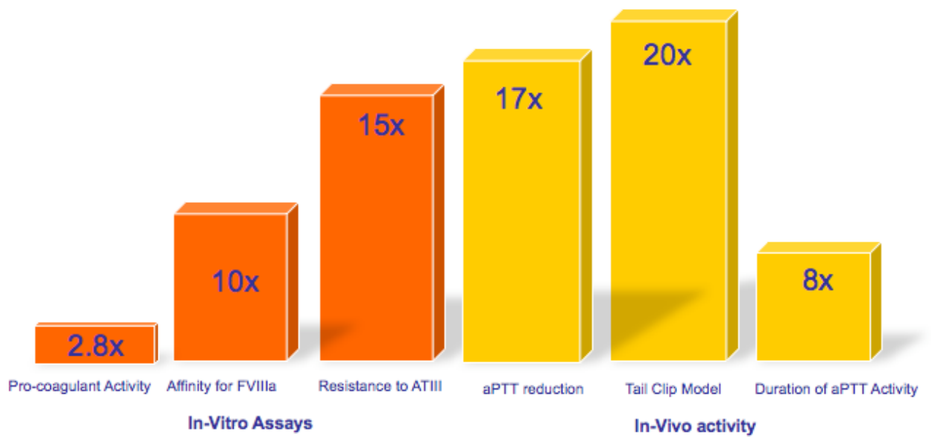
STUDY OBJECTIVES

Determine the pharmacokinetic and pharmacodynamic parameters after subcutaneous administration of a highly potent factor IX (FIX) variant in hemophilia B dogs

INTRODUCTION

- The rapid clearance of FIX necessitates frequent intravenous administrations to achieve effective prophylaxis for patients with hemophilia B
- Subcutaneous administration would be a preferred route of administration but has been limited by low bioavailability and potency of the marketed FIX products
- CB 2679d/ISU304 has enhanced biological properties including resistance to inhibition by ATIII, increased affinity for FVIIIa, and increased catalytic activity compared with wild-type FIX
- The variant has three mutations: R318Y/R338E/T343R that were introduced using rational design

CB 2679D/ISU304 ENHANCED PROPERTIES COMPARED WITH WILD-TYPE FIX



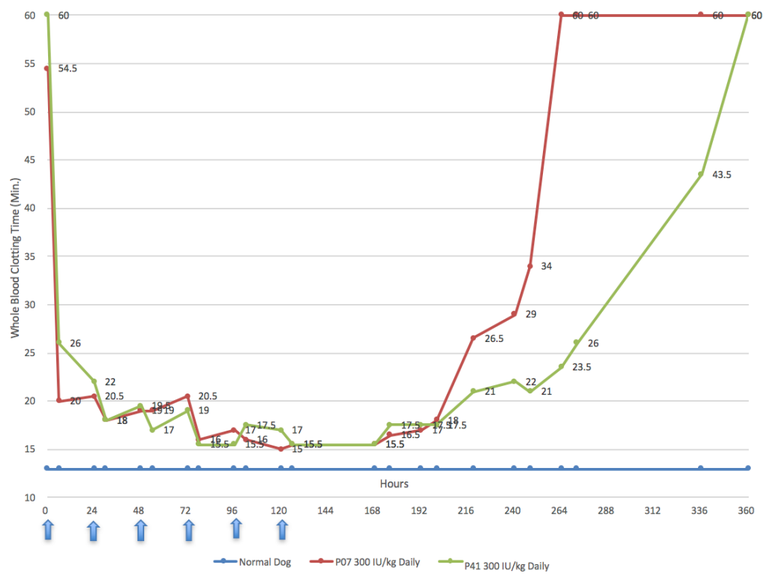
METHODS

- CB 2679d/ISU304 300 IU/kg was injected subcutaneously daily for 6 days in Hemophilia B dogs
- Samples were obtained at 0, 6, 24, 30, 48, 54, 72, 78, 96, 102, 120, 126, 144, 168, 176, 192, 200, 219, 240, 248, 264, 272, 288, 312, 336 and 360 hours
- Whole Blood Clotting Time (WBCT) was measured at each time point
- aPTT was measured at each time point on a STart Hemostasis Analyzer (Diagnostica Stago) using TriniCLOT Automated APTT reagent and 180 second incubation
- FIX antigen was measured using an Asserchrom ELISA Kit
- Hematology, chemistry, d-dimer, prothrombin F1+2, thrombin-antithrombin and fibrinogen were measured

RESULTS

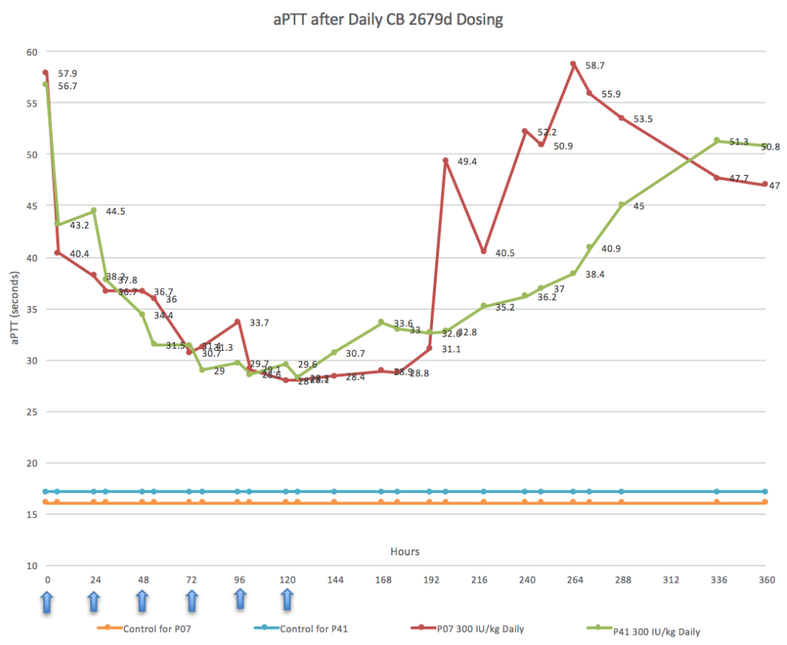
- WBCT was >60 minutes at baseline (normal <13 minutes) and decreased to 20 and 26 minutes at 6 hours
- Progressive decrease in WBCT occurred to a nadir of 15 and 15.5 minutes at 120 and 78 hours respectively
- WBCT remained <18 minutes through 200 hours, 80 hours after the last subcutaneous injection
- aPTT decrease mirrored the reduction in WBCT
- Daily subcutaneous dosing of CB 2679d/ISU304 after 6 doses had peak FIX antigen of 2.9% and 2.7% corresponding to calculated activity of 78% and 84% at 192 and 126 hours respectively
- The subcutaneous Tmax occurred at 6 hours Bioavailability of subcutaneous CB 2679d/ISU304 was 10.3%
- The subcutaneous half-life based on a single-phase was 155 hours compared with an intravenous alpha phase half-life of 28 hours and a beta phase value of 59 hours
- There were no emergent clinical adverse events or abnormal chemistry lab abnormalities

WHOLE BLOOD CLOTTING TIME AFTER DAILY SUBCUTANEOUS CB 2679D/ISU304 ADMINISTRATION IN HEMOPHILIA B DOGS



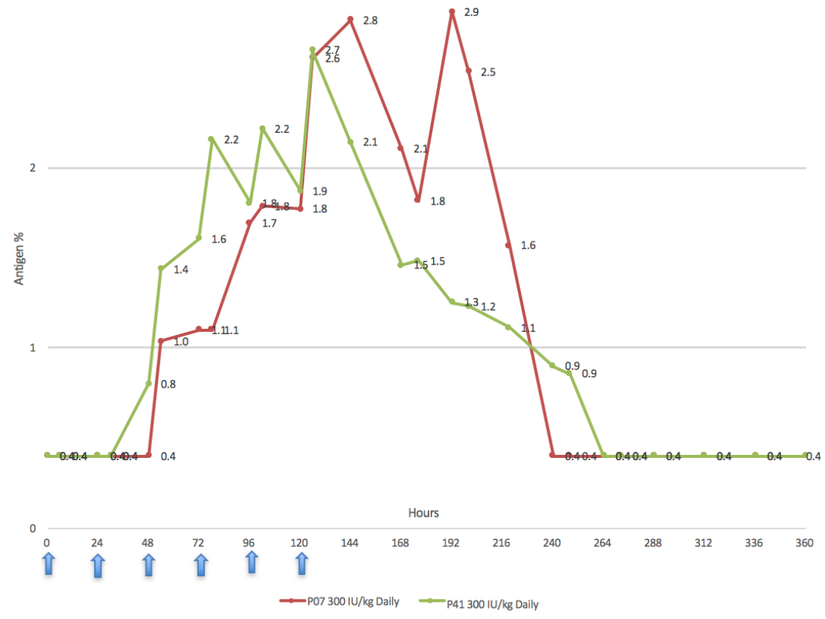
- **Daily subcutaneous injections can normalize whole blood clotting time in hemophilia B dogs**

aPTT AFTER DAILY SUBCUTANEOUS CB 2679D/ISU304 ADMINISTRATION IN HEMOPHILIA B DOGS



- **Daily subcutaneous injections can correct the prolonged aPTT in hemophilia B dogs**

BLOOD LEVELS OF FIX ANTIGEN AFTER DAILYSUBCUTANEOUS ADMINISTRATION OF CB 2679D/ISU304 IN HEMOPHILIA B DOGS



- **Daily subcutaneous dosing resulted in a progressive increase in FIX antigen levels**

SUMMARY

- CB 2679d/ISU304 with enhanced biological properties was developed using a rational protein design approach and has increased resistance to inhibition by ATIII, increased affinity for FVIIIa, and increased catalytic activity compared to wild-type FIX
- There was a progressive increase in plasma Factor IX antigen with daily subcutaneous injection of CB 2679d/ISU304
- Bioavailability of subcutaneous injection of CB 2679d/ISU304 was 10.3% in Hemophilia B dogs
- Daily subcutaneous dosing of CB 2679d/ISU304 demonstrated the effects of the bioavailability, potency, time to maximal concentration, and half-life by reaching a steady-state activity sufficient to correct severe hemophilia to normal in hemophilia B dogs, after 4 days
- The increased potency of CB 2679d/ISU304 facilitates the initiation of the Phase 1/2 subcutaneous dosing study in individuals with hemophilia B with the target of achieving normal FIX activity trough levels

Disclosures:

H. Levy Employee of: CATALYST BIOSCIENCES, T. Nichols Grant/Research support from: CATALYST BIOSCIENCES, E. Merricks: None Declared, R. Raymer: None Declared, A. Hetherington Employee of: CATALYST BIOSCIENCES

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