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FVIIa-CTP, a Long Acting FVIIa, Comprehensive Pharmacokinetics and Pharmacodynamics and Bioavailability Evaluation Following Intravenous (IV) Administration to Hemophilic Animal Models

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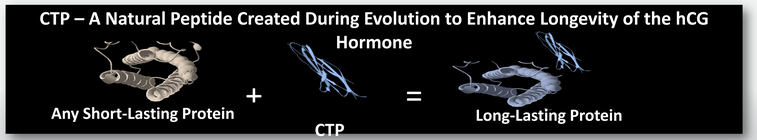
Introduction

OPKO Biologics is a clinical stage public company developing bio better long acting versions of existing therapeutic proteins utilizing a technology termed CTP.



The technology involves fusion of the C terminus peptide of hCG to the target protein. The technology was clinically validated and proven as a safe and efficient way for increasing the half-life of several therapeutic proteins while maintaining their biological activity.

The aim of this study was to comprehensively characterize intravenous and subcutaneous administration of FVIIa-CTP utilizing the most relevant in vivo preclinical models.

Methods

FVII-CTP was expressed in CHO cells, purified and activated utilizing a CTP specific purification process. FVIIa-CTP was assessed in hemophilia A dogs, transient FVII-/- rats and hemophilia A mice.

Summary of pre-clinical studies in hemophilic animal models

Species	Route.	Frequency of Admin.	Dose	End Points
Hemophilia A dogs	IV	Single dose	50, 200, 400, 600 µg/kg	Clinical observation (drug tolerability) ,PK-PD analysis, Thromboelastography (TEG), PT & aPTT
Transient FVII-/- Male Rats	IV	Single dose	1000µg/ml	TVT (Tail vein transduction) , PT & aPTT
Hemophilia A mice	IV	Single dose	28.4mg/ml	Tail cut, TVT, PD analysis

Conclusions

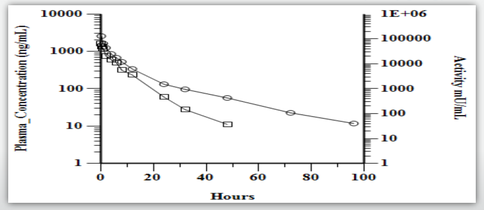
- ✓ Superior PK-PD compared to NovoSeven® published data.
- ✓ Attachment of CTP Increased exposure as reflected by AUC and elevated half-life.
- ✓ Improved bioavailability, translated to a marked in vivo hemostatic effect
- ✓ Profound improvement in clotting parameters

FVIIa-CTP can potentially provide a novel approach for IV and SC prophylactic treatment for hemophilic patients, both pediatric and adults, with the major benefit of significant improvement in quality of life when injected subcutaneously.

Hemophilia A Dogs

MOD-5014 Comparative PK-PD Analysis

Combined representative PK-PD Profile (200µg/kg)



MOD-5014 PK and PD Parameters Following IV Bolus Injection

	AUC PK-(hr*ng/mL) PD-(hr*mU/mL)	CL (mL/hr/kg)	T1/2 (hr)
PK	15000	13.5	19.3
PD	172000	18.2	4.72

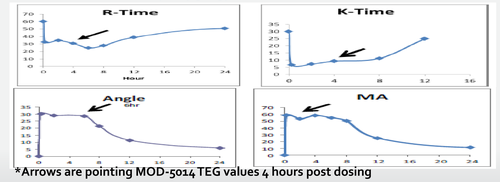
NovoSeven® (270µg/kg) Knudsen *et al.* 2011

	Cl (mL/hr/kg)	T1/2 (hr)
PK	24.5	3
PD	46.1	1.8

TEG

Individual Representative data (1/4)

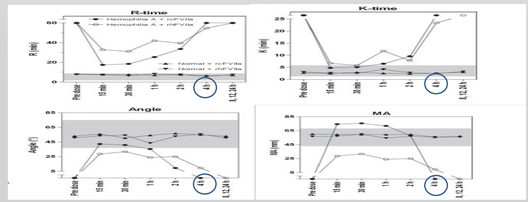
MOD-5014 (200µg/kg) Provides Extended TEG Effect



*Arrows are pointing MOD-5014 TEG values 4 hours post dosing

NovoSeven® (270µg/kg) TEG Profile

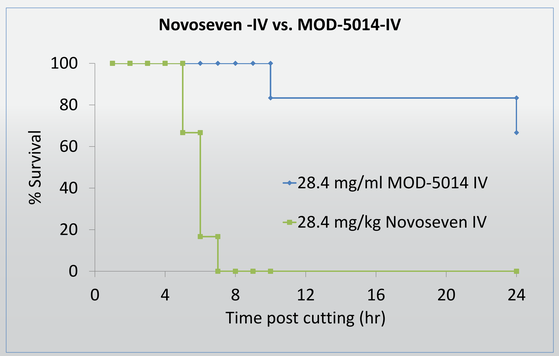
Knudsen et al. 2011



Hemophilia A Mice & Transient FVII-/- Rats

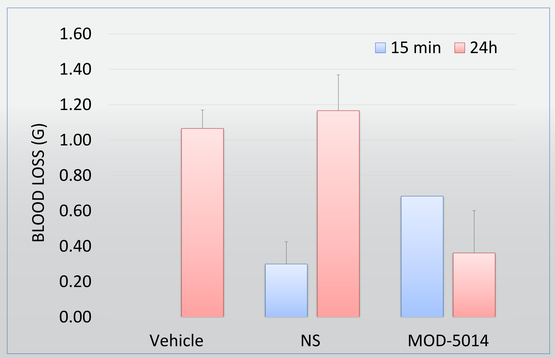
Tail Cut Survival Study in FVIII-/- Mice

MOD-5014 and rFVIIa were administered 24hr prior to bleeding induction. Survival was measured during the first 24 hr post bleeding induction



TVT Study in Warfarin Treated Rats

MOD-5014 and rFVIIa were administered IV 15 min and 24hr prior to TVT. Blood loss was measured during the first 30min post TVT



MOD-5014 Provides Superior, Long Term Hemostatic Protection Compared to NovoSeven® as reflected by reduced duration and intensity of bleeding and improved survival rate

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Novel therapeutic agents
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