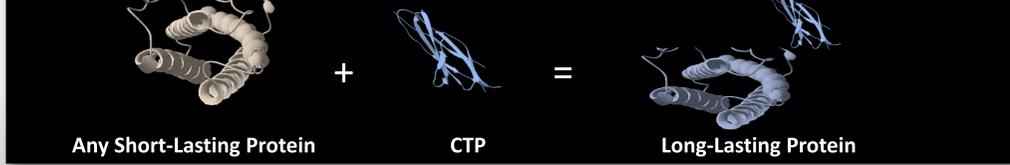


Introduction

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

CTP – A Natural Peptide Created During Evolution to Enhance Longevity of the hCG Hormone



The technology involves fusion of the C terminus peptide of hCG to one or both ends of 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. MOD-5014 is a long-acting form of recombinant Factor VIIa (rFVIIa).

The aim of this work was to comprehensively assess the feasibility of subcutaneous administration of MOD-5014 (FVIIa-CTP) utilizing the most relevant in-vivo preclinical models in preparation for First in Human Study

Methods

FVII-CTP was expressed in CHO cells, purified and activated utilizing a CTP specific purification process. Following single SC administration to FVIII^{-/-} mice MOD-5014 was extensively characterized and compared to NovoSeven[®] by evaluating the following :

- Pharmacodynamics (PD) using STAclot assay
- Long term hemostatic effect-following bleeding challenge (tail clip, tail vein transduction (TVT)) as compared to commercial rFVIIa in FVIII^{-/-} mice.
- PT and aPTT in warfarin treated rats

Conclusions

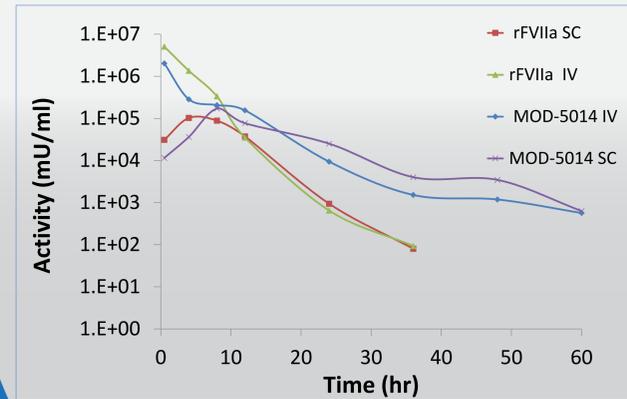
- ✓ Attachments of CTP to FVIIa led to a pronounced enhanced PK-PD, increased exposure as reflected by AUC, elevated half-life and improved recovery following SC administration.
- ✓ FVIIa-CTP injected SC resulted in an improved bioavailability translated to marked in vivo hemostatic effect

Our data suggest that CTP fused FVIIa can potentially provide a novel approach for prophylactic treatment of hemophilic patients with the major benefit of significant improvement in quality of life.

PK-PD in FVIII^{-/-} Mice

PK-PD profile following SC or IV administration of MOD-5014 and rFVIIa to FVIII^{-/-} mice

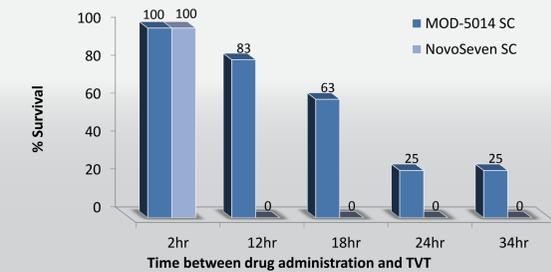
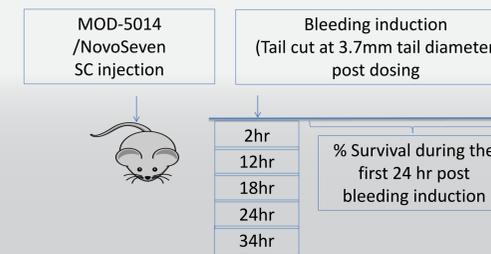
MOD-5014 demonstrated a long term exposure as reflected by clotting activity that was significantly superior in compare with rFVIIa and consistent with MOD-5014 prolonged half life.



Parameter	MOD-5014		rFVIIa	
	IV	SC	IV	SC
t _{1/2} (hr)	5.7	6.8	2.2	2.7
Tmax (hr)	0.5	8	0.5	4
MRT (hr)	4	13.4	2.1	7.4
Bioavailability	23%		6%	

Survival study in FVIII^{-/-} Mice

MOD-5014 Provides Superior, Long Term Hemostatic Protection Compared to NovoSeven[®]



Transient FVII^{-/-} Rats

PT profile following SC administration in transient FVII^{-/-} rats

MOD-5014 Demonstrates Extended and Improved PT Profile Compared to NovoSeven[®] In Warfarin Induced Bleeding Model (SD Rats)

