SAFETY AND EFFICACY OF FACTOR VIIA-CTP, A NOVEL LONG-ACTING COAGULATION FACTOR PROPOSING AN IMPROVED PROPHYLACTIC AND ON DEMAND TREATMENT OF HEMOPHILIC PATIENTS IN PREPARATION FOR FIRST IN HUMAN STUDY.

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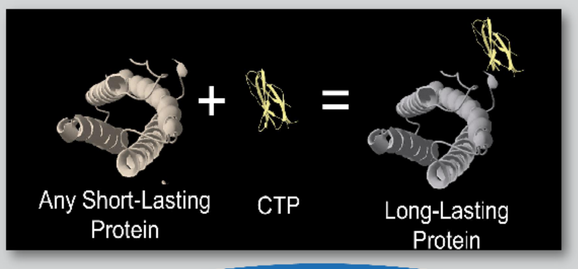
Introduction

PROLOR Biotech is a clinical stage public company developing biobetter long acting versions of existing therapeutic proteins utilizing a technology termed CTP. The technology involves fusion of the C terminus peptide of hCG to one or both ends of the target protein.

The aim of this work was to asses the safety, PK and PD of FVIIa-CTP following administration to rats and monkeys as part of toxicological studies and in preparation to the upcoming FIH clinical study in haemophilc patients .



Methods

FVII-CTP was expressed in CHO cells, purified and activated utilizing a CTP specific purification process. GMP batch was used in the toxicological studies assessed in male rats and monkeys supported by toxicokinetic analysis confirming proper margins above the initial clinical dose in the FIH study.

Summary of completed toxicological studies

Study	Species	Route of Admin.	Frequency of Admin.	Dose/ Compliance	End Points	Study Status
Acute Toxicokinetic	Male Rat	IV	Single dose	0, 1,3,9, 21 mg/kg **Non-GLP**	Clinical observation, bodyweight, food consumption, PK-PD, Clinical pathology (Hematology, Coagulation, Clinical Chemistry), thrombus formation.	Completed
Acute Toxicokinetic	Male Cyn Monkey	IV	Single dose	0,1,3,9 mg/kg **Non-GLP**	Clinical condition, bodyweight, food consumption, PK-PD. Clinical pathology (Hematology, Coagulation, Clinical Chemistry)	Completed
Acute Toxicokinetic GLP study	Male Rat	IV	Single dose	0,1,3,9 mg/kg **GLP**	Clinical condition, bodyweight, food consumption, blood chemistry, expanded coagulation panel, TK, organ weight, histology, pathology, intravascular coagulation, thrombus formation.	Completed
Acute Toxicokinetic GLP study	Male Cyn Monkey	IV	Single dose	0,1,7.5,15mg/kg **GLP**	Clinical condition, bodyweight, food consumption, blood chemistry, TK, organ weight, histology, pathology, intravascular coagulation, thrombus formation.	Completed

Conclusions

Pharmacokinetics Advantages:

- Enhanced Recovery (2X)
- Superior half life (4x)
- Improved exposure (AUC 3-4x)
- Comparable in –vitro clotting activity as commercial product

Safety Assessment Summary:

All the findings noted in the toxicological studies, are consistent with and anticipated based on the mechanism of action of this drug.

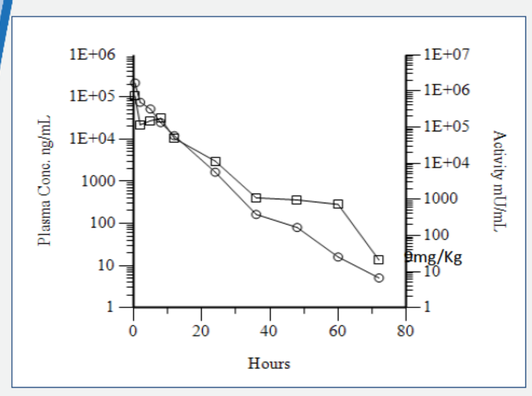
There were no new or unique findings associated with MOD-5014 that have not also been seen for commercial rhFVII or other coagulation factor drugs.

MOD-5014 demonstrates excellent safety profile, providing adequate exposure margins above the proposed administered clinical doses in the FIH study

Toxicokinetic Analysis

SD Rats

Combined representative PK-PD Profile



MOD-5014 Pharmacokinetic Parameters Based on Plasma Concentration Following IV Bolus Injection Estimated by Non-compartmental Analysis

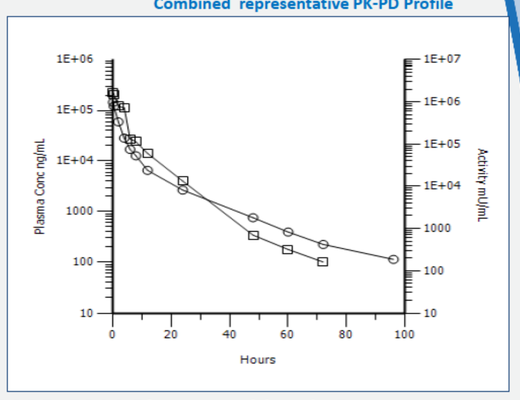
Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC0-t (hr*ng/mL)	T1/2 (hr)
1	10,700	0.50	72,200	7.8
3	24,700	0.50	154,000	15.8
9	102,000	0.50	529,000	7.9
21	190,000	0.50	1,110,000	7.5

MOD-5014 Pharmacodynamics Parameters Based on Plasma Concentration Following IV Bolus Injection Estimated by Non-compartmental Analysis

Dose (mg/kg)	Cmax (mu/mL)	Tmax (hr)	AUC0-t (hr*mu/mL)	t1/2 (hr)
1	155,000	0.50	825,000	5.3
3	606,000	0.50	2,200,000	6.7
9	1,660,000	0.50	5,330,000	5.17
21	3,200,000	0.50	13,400,000	5.8

Cyn. Monkeys

Combined representative PK-PD Profile



MOD-5014 Pharmacokinetic Parameters Based on Plasma Concentration Following IV Bolus Injection Estimated by Non-compartmental Analysis

Dose (mg/kg)	Cmax (ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	$T_{1/2}$ (hr)
1	14300	48800	29.0
3	41200	150000	29.5
9	153000	536000	15.3

MOD-5014 Pharmacodynamics Parameters Based on Plasma Concentration Following IV Bolus Injection Estimated by Non-compartmental Analysis

Dose (mg/kg)	(U/kg)	Cmax (mU/mL)	$AUC_{0-\infty}$ (hr*mu/mL)	$t_{1/2}$ (hr)
1	21,600	158000	471000	5.6
3	64,800	383000	1360000	5.9
9	194,400	1900000	5750000	8.98

Toxicological Studies Results

Rats:

Food consumption, clinical pathology, gross pathology, organ weights and histopathology were monitored and evaluate for all animals. Toxicokinetic and pharmacodynamic assessments were also conducted on the test article. All animals were in good clinical condition. The only detailed clinical observation observed within the main study animals that was considered test article-related was noted in one 9 mg/kg animal with purple or red discoloration of the tail . Reversible, test article-related changes in clinical pathology were observed in the main study animals which included mild reductions in prothrombin time in all test article groups. There were no test article-related macroscopic findings or organ weight changes in the main study animals at the terminal or recovery necropsies

Monkeys:

Food consumption, clinical pathology, gross pathology, organ weights and histopathology were monitored and evaluate for all animals. All animals were in good clinical condition ,administration of a single dose of MOD-5014 intravenously to male cynomolgus monkeys produced decreases in prothrombin time and anti-thrombin III, and an increase in D-dimer at doses of 7.5 and 15 mg/kg. These changes were indicative of a prothrombotic state, which is consistent with the intended mechanism of action of the drug. There were no new or unique findings associated with MOD-5014 that have not also been seen for rhFVIIa or other coagulation factor drugs .