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## STUDY OBJECTIVES

Determine the pharmacokinetic and pharmacodynamic parameters for subcutaneous administration of a highly potent factor IX (FIX) variant in normal minipigs

## INTRODUCTION

- The rapid clearance of FIX necessitates frequent intravenous administrations to achieve effective prophylaxis for patients with hemophilia B (HB)
- Subcutaneous (SC) 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 (17-fold) compared with wild-type FIX
- The variant has three mutations: R318Y/R338E/T343R that were introduced using rational design

## METHODS

- All Minipigs received BeneFIX 0.15 mg/kg or ISU304 0.05 or 0.15 mg/kg IV followed 168 hours later by the same dose SQ
- After IV administration blood was sampled at 0, 0.25, 1, 4, 8, 24, 48, 72, 96 and 144 hours, and after SQ administration at 0, 1, 4, 6, 8, 24, 48, 72, 96, and 144 hours
- Daily SQ injection in minipigs of ISU304 at 0.1 mg/kg (460 IU/kg) for 6 days was sampled at 24, 48, 72, 96, 120, 121, 124, 126, 128 and 144 hours
- FIX antigen was measured using a sandwich ELISA
- Pharmacokinetics of FIX was performed using PKSolver
- Activity was calculated from the known relationship with antigen from our prior work in HB mice where 1 ng/mL of ISU304 corresponded to 0.5794 % FIX activity

## RESULTS

### INTRAVENOUS PHARMACOKINETICS IN NORMAL MINIPIG

Parameter	Unit	Minipig Number					
		#1	#2	#3	#4	#5	#6
Test Article		BeneFIX		ISU304		ISU304	
Dose level	mg/kg	0.15		0.05		0.15	
Dose level	IU/kg	42		230		690	
t1/2	h	12.3	11.7	10.1	11.8	11.0	10.4
Tmax	h	0.25	0.25	0.25	0.25	0.25	0.25
Cmax	ng/ml	1070	1490	368	468	1,517	1548
C0	ng/ml	1,147	1,559	376	526	1,649	1,799
Clast_obs/Cmax		0.017	0.013	0.042	0.044	0.009	0.006
AUC 0-t	ng/ml*h	12,221	15,368	5,019	4,569	16,242	14,037
AUC 0-inf_obs	ng/ml*h	12,542	15,693	5,243	4,920	16,466	14,172
AUC 0-t/0-inf_obs		0.97	0.98	0.96	0.93	0.99	0.99
AUMC 0-inf_obs	ng/ml*h <sup>2</sup>	194,599	227,837	66,323	78,657	221,865	183,819
MRT 0-inf_obs	h	15.5	14.5	12.6	16.0	13.5	13
Vz_obs	ml/kg	212	161	139	173	144	159
Cl_obs	ml/kg/h	12	10	10	10	9	11
Vss_obs	ml/kg	186	139	0.00012	0.00016	0.00012	0.00027

### SUBCUTANEOUS PHARMACOKINETICS IN NORMAL MINIPIG

Parameter	Unit	Minipig Number					
		#1	#2	#3	#4	#5	#6
Test Article		BeneFIX		ISU304		ISU304	
Dose level	mg/kg	0.15		0.05		0.15	
Dose level	IU/kg	42		230		690	
t1/2	h	35.1	30.3	*Missing	21.6	33.0	24.6
Tmax	h	8	8	24	6	6	8
Cmax	ng/ml	79	92	27	66	221	86
Tlag	h	0	0	0	0	0	0
Clast_obs/Cmax		0.185	0.043	0.534	0.278	0.097	0.290
AUC 0-t	ng/ml*h	3,988	3,907	1,014	1,940	6,648	3,053
AUC 0-inf_obs	ng/ml*h	4,721	4,077	Missing	2,510	7,673	3,499
AUC 0-t/0-inf_obs		0.84	0.96	Missing	0.77	0.87	0.87
AUMC 0-inf_obs	ng/ml*h <sup>2</sup>	243,148	184,034	Missing	82,414	348,573	132,249
MRT 0-inf_obs	h	51.5	45.1	Missing	32.8	45.4	37.8
Vz/F_obs	ml/kg	1,607	1,609	Missing	620	932	1,524
Cl/F_obs	ml/kg/h	32	37	Missing	20	20	43
Bioavailability	%	33	25	20	42	40	22



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## Acknowledgements:

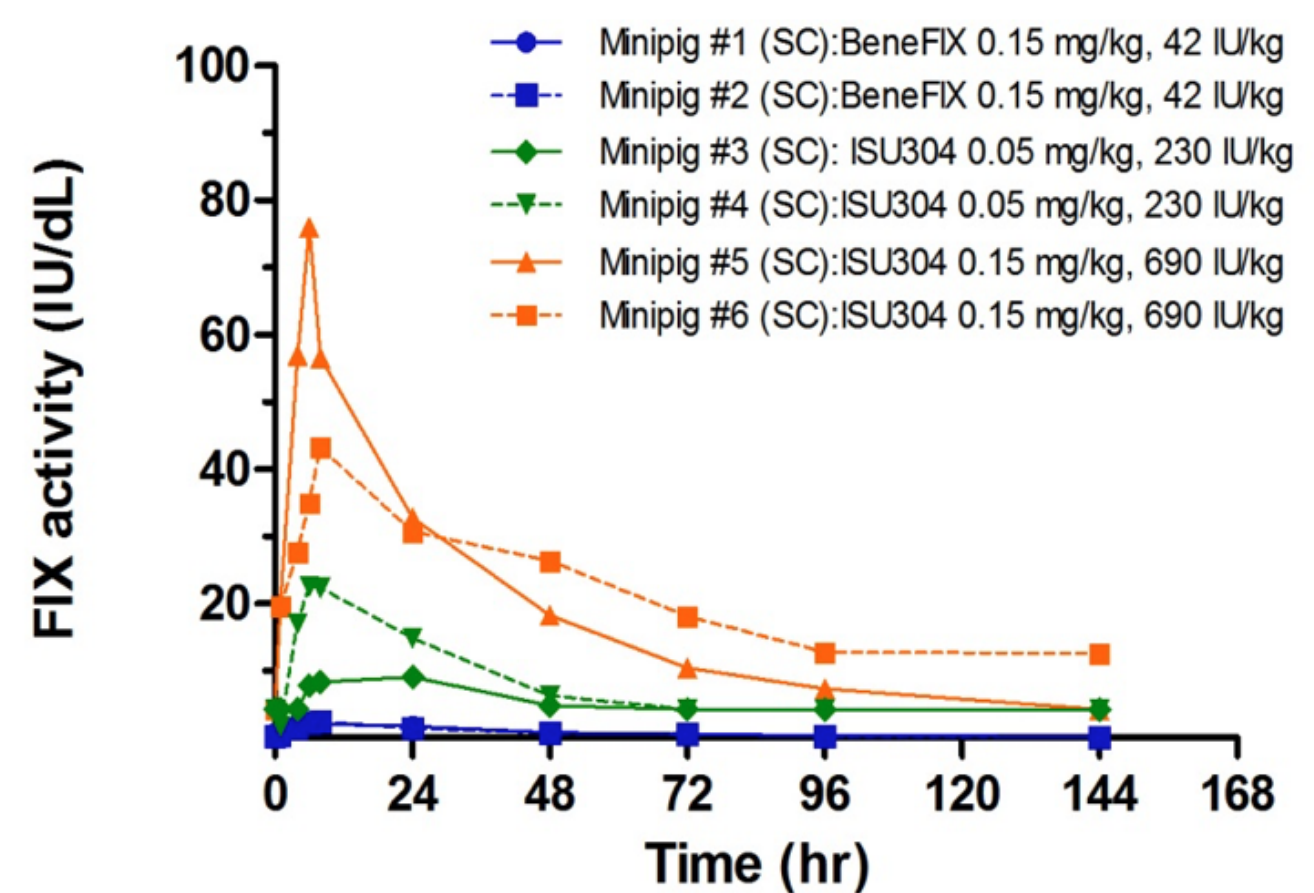
Youngsoo Sohn, Sanghyun Han, Taehee Yim (Process Development ISU Abxis) contributed by producing CB 2679d/ISU304 used in this study

## Disclosures:

Hong: ISU Abxis: Employment. Levy: Catalyst Biosciences: Employment. Jung: ISU Abxis: Employment. Park: ISU Abxis: Employment. Seo: ISU Abxis: Employment

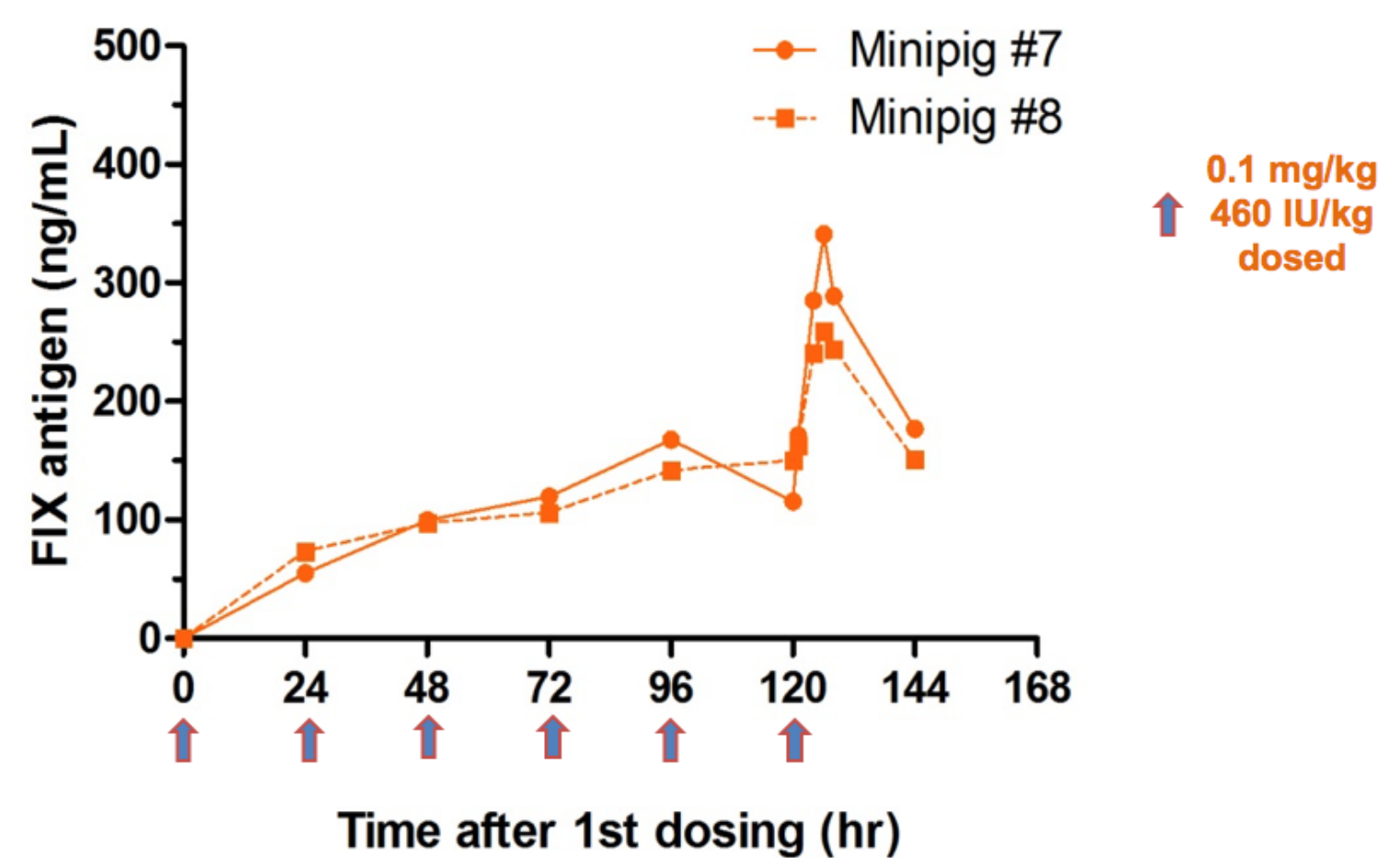
## BLOOD LEVELS OF FIX PREDICTED ACTIVITY AFTER SUBCUTANEOUS CB 2679D/ISU304 ADMINISTRATION IN NORMAL MINIPIG

[CALCULATED FROM ANTIGEN/ACTIVITY RATIO IN HEMOPHILIA B MICE]



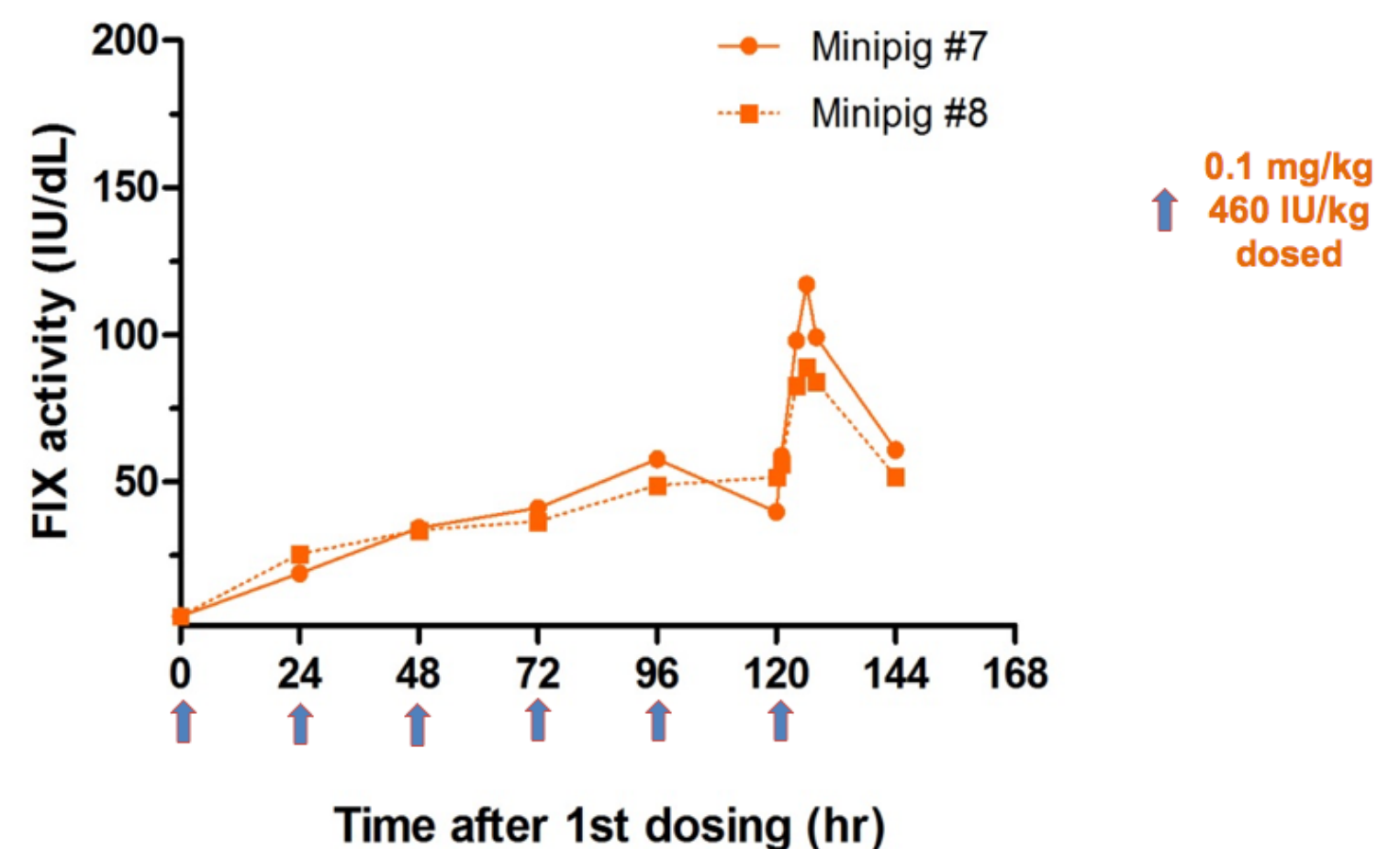
- Dose dependent increase in calculated activity levels

## BLOOD LEVELS OF FIX ANTIGEN AFTER DAILY SUBCUTANEOUS ADMINISTRATION OF CB 2679D/ISU304 IN MINIPIG



- Daily subcutaneous dosing achieved steady-state levels after 6 doses

## BLOOD LEVELS OF PREDICTED FIX ACTIVITY AFTER DAILY SUBCUTANEOUS ADMINISTRATION OF CB 2679D/ISU304 IN MINIPIG



- Daily subcutaneous dosing achieved steady-state levels after 6 doses

## SUMMARY

- There was a dose-dependent increase in plasma Factor IX antigen with subcutaneous injection of CB 2679d/ISU304
- The pharmacokinetic profile of CB 2679d/ISU304 was similar to BeneFIX when dosed using the same mass.
- CB 2679d/ISU304 has approximately 17-times greater potency and therefore can achieve higher activity at an equal mass dosing level
- Bioavailability of subcutaneous injection of CB 2679d/ISU304 in normal minipig was 20-42%
- Daily subcutaneous dosing of CB 2679d/ISU304 demonstrated the effects of the bioavailability, time to maximal concentration, and half-life by reaching a steady-state activity sufficient to correct severe hemophilia to normal, after four 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