Phase 1 Trial of Single and Multiple Dose Subcutaneously Administered Factor IX Variant ISU304/CB 2679d: Pharmacokinetics, Activity and Safety

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Disclosure for Chur Woo You

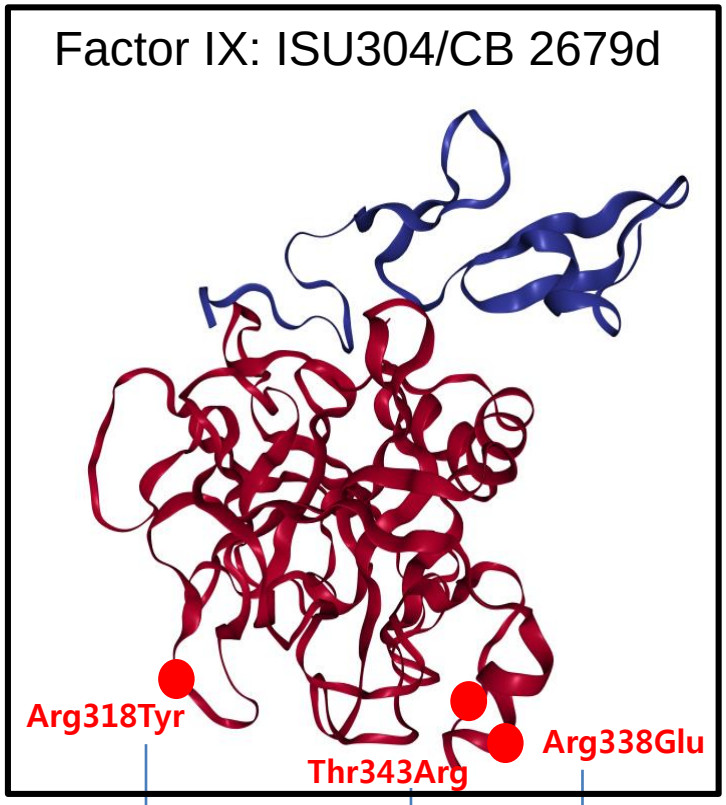
In compliance with COI policy, WFH requires the following disclosures to the session audience:

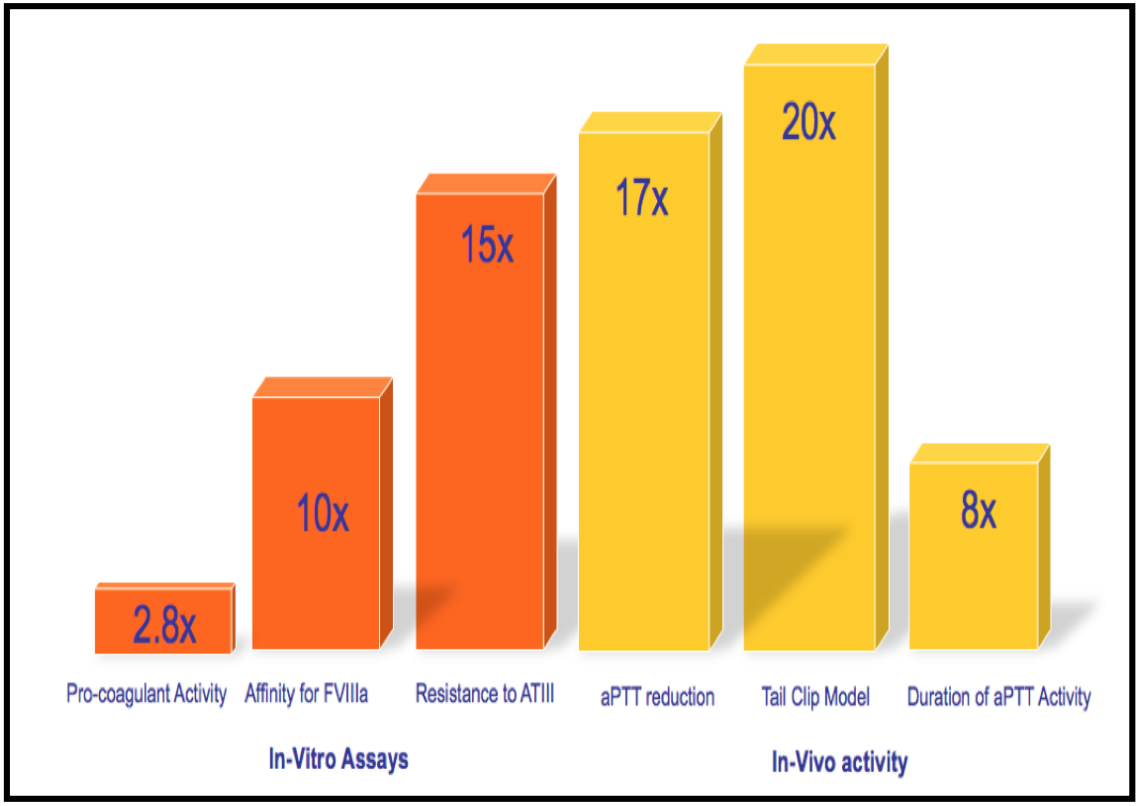
Shareholder	**No relevant conflicts of interest to declare**
Grant / Research Support	**No relevant conflicts of interest to declare**
Consultant	**No relevant conflicts of interest to declare**
Employee	**No relevant conflicts of interest to declare**
Paid Instructor	**No relevant conflicts of interest to declare**
Speaker bureau	**No relevant conflicts of interest to declare**
Other	**No relevant conflicts of interest to declare**

Presentation includes discussion of the following off-label use of a drug or medical device: N/A

Factor IX Modified with 3 Point Mutations

- 22-fold potency advantage over wt-FIX allows subcutaneous delivery





ISU304/CB 2679d ENHANCED PROPERTIES COMPARED WITH WILD-TYPE FIX IN HEMOPHILIA B MICE

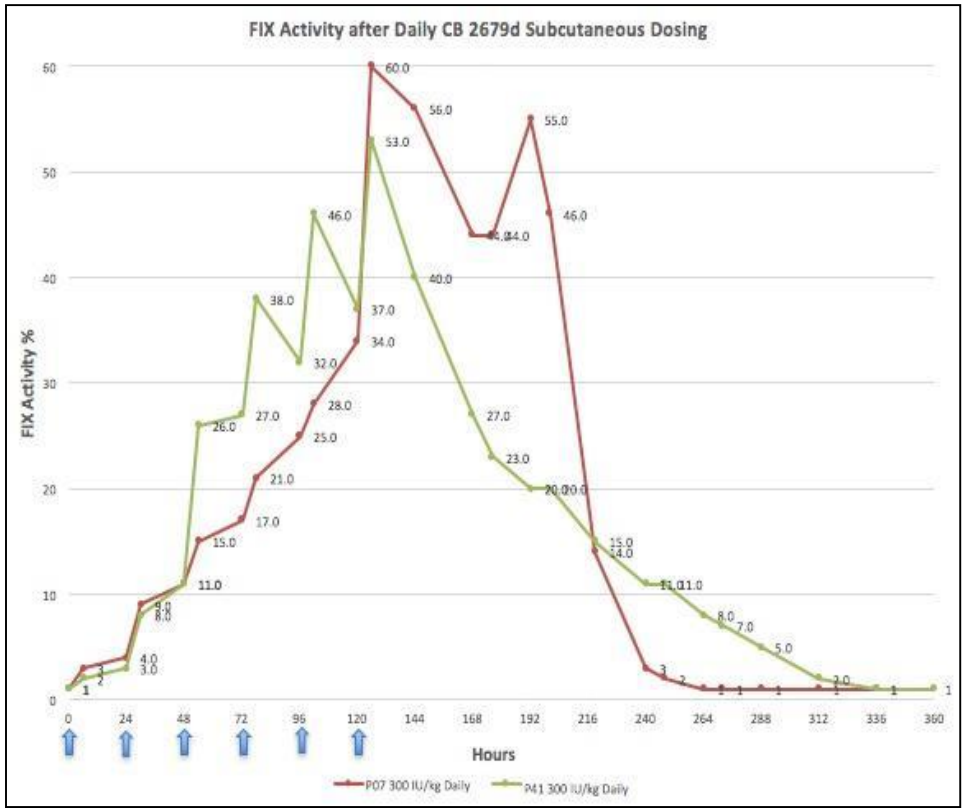
Daily subcutaneous dosing of ISU304 in HB dogs

PK of single SC injection

- 22-fold potency advantage
- Half-life 155 hours
- Bioavailability 10.3%

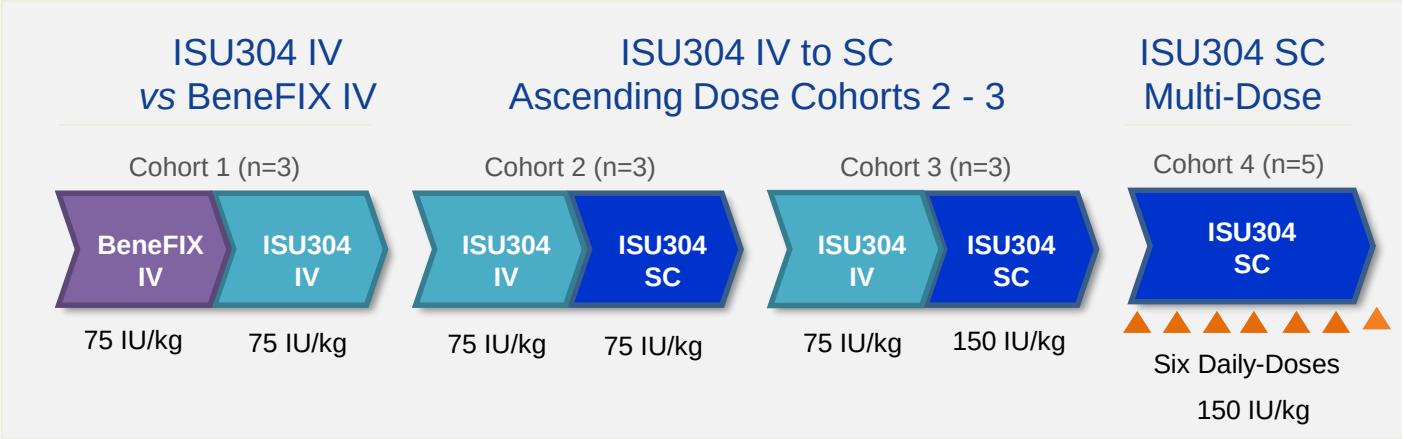
Daily subcutaneous dosing of 300 IU/kg

- Steady state activity sufficient to correct Severe HB to Mild HB after 4 days
- No emergent clinical adverse events or abnormal chemistry lab abnormalities



FIX ACTIVITY AFTER DAILY SUBCUTANEOUS ADMINISTRATION OF ISU304 IN HEMOPHILIA B DOGS

Phase 1 study design

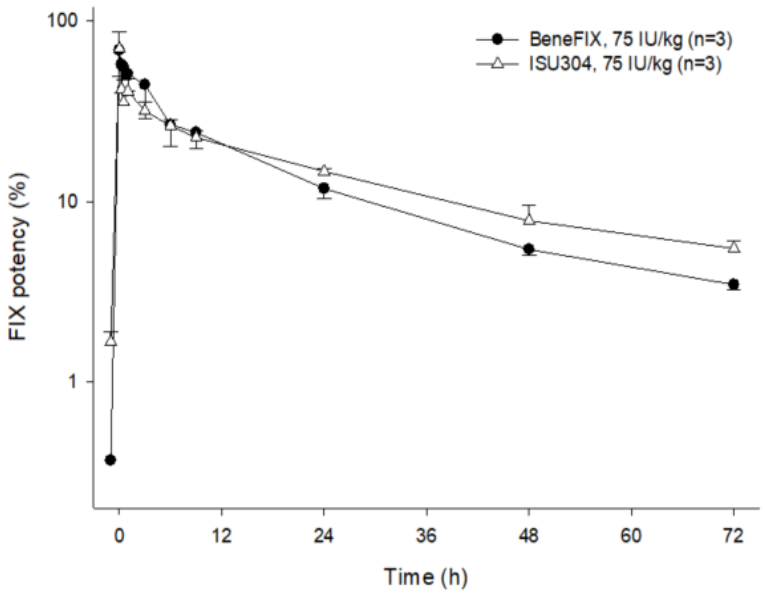


- **12 Korean PTP with SHB over 12 years old**
- **2 Patients participated in Cohort 1 and 4**

Cohort 1 Results

Parameters	BeneFIX (n=3)	ISU304 (n=3)
	Mean ± SD (Min - Max)	Mean ± SD (Min - Max)
T_{max}† (h)	0.02 [0.02-0.50]	0.02 [0.02-0.02]
C_{max} (%)	71.10 ± 15.87 (53.10 - 83.10)	70.47 ± 16.92 (53.10 - 86.90)
AUC_{last} (h·%)	912.48 ± 154.35 (777.13 - 1080.57)	977.97 ± 69.88 (904.60 - 1043.74)
AUC_{inf} (h·%)	1033.34 ± 149.96 (882.95 - 1182.85)	1214.01 ± 110.98 (1108.50 - 1329.75)
$t_{1/2}$ (h)	**24.12 ± 5.13 (19.69 - 29.75)**	**29.75 ± 4.28 (25.64 - 34.18)**

† Data are presented as median [min - max]



Mean plasma FIX potency-time profiles of BeneFIX or ISU304 after a single intravenous dose of 75 IU/kg

Average BW: 73Kg

Mean ISU 304 injection volume: 0.66 mL

Mean Benefix injection volume : 27.67 mL

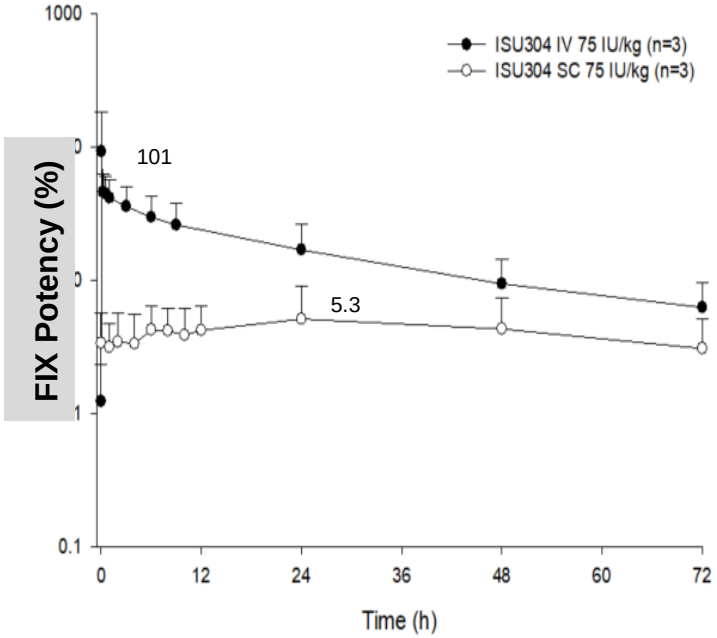
PK Analysis: WinNonlin® 7.0 (Pharsight, A Certara™ Company, Princeton, NJ, USA)

Cohort 2 Results: ISU304 IV: 75 IU/kg; SC: 75 IU/kg

Compared with IV dose, a single SC dose of ISU304 75 IU/Kg demonstrated lower Cmax but longer half-life (>2 fold). The bioavailability for SC dose was 25.9%.

Parameters	ISU304 75 IU/kg IV (n=3)	ISU304 75 IU/kg SC (n=3)
	Mean ± SD (Min - Max)	Mean ± SD (Min - Max)
T_{max}† (h)	0.02 [0.02-0.50]	8.00 [6.00-23.95]
C_{max} (%)	100.80 ± 78.00 (29.80 – 184.30)	**5.30 ± 3.69** (2.60 – 9.50)
AUC_{last} (h·%)	1099.00 ± 541.21 (673.19 – 1708.05)	302.11 ± 206.74 (147.91 – 537.04)
AUC_{inf} (h·%)	1390.37 ± 684.21 (810.52 – 2145.02)	639.55 ± 369.60 (264.00 – 1002.89)
$t_{1/2}$ (h)	32.48 ± 6.66 (27.20 – 39.96)	**80.52 ± 37.93** (57.47 – 124.30)
Bioavailability (%)	NA	**25.9 ± 5.0** (22.0 – 31.4)

† Data are presented as median [min - max]
No baseline adjustment



Mean plasma FIX potency-time profiles of ISU304 after a single intravenous then single subcutaneous dose of 75 IU/kg

Mean BW: 64Kg

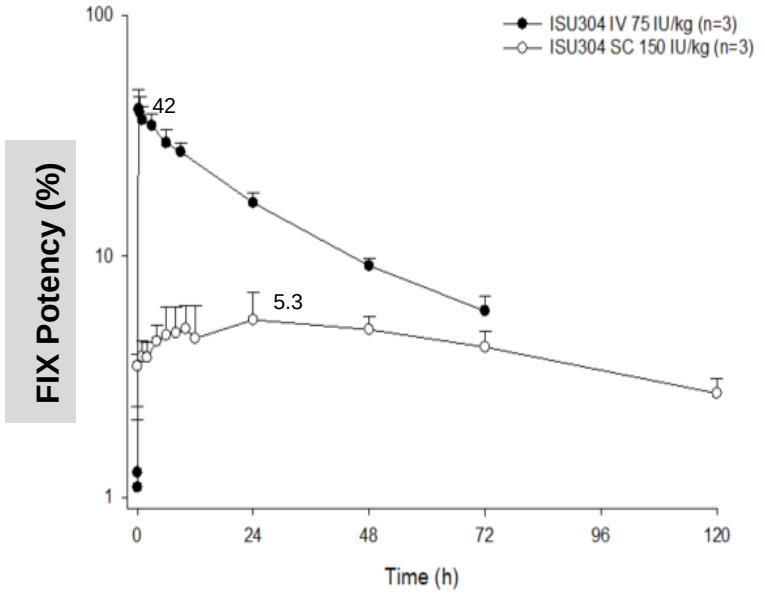
Mean ISU 304 injection volume: 0.56 mL

Cohort 3 Results: ISU304, IV: 75 IU/kg; SC: 150 IU/kg

A single SC dose of ISU304 150 IU/Kg demonstrated lower Cmax but longer half-life (>2 fold) compared with IV dose. The mean bioavailability was 23.5%, similar to the bioavailability of the Cohort 2 (25.9%)

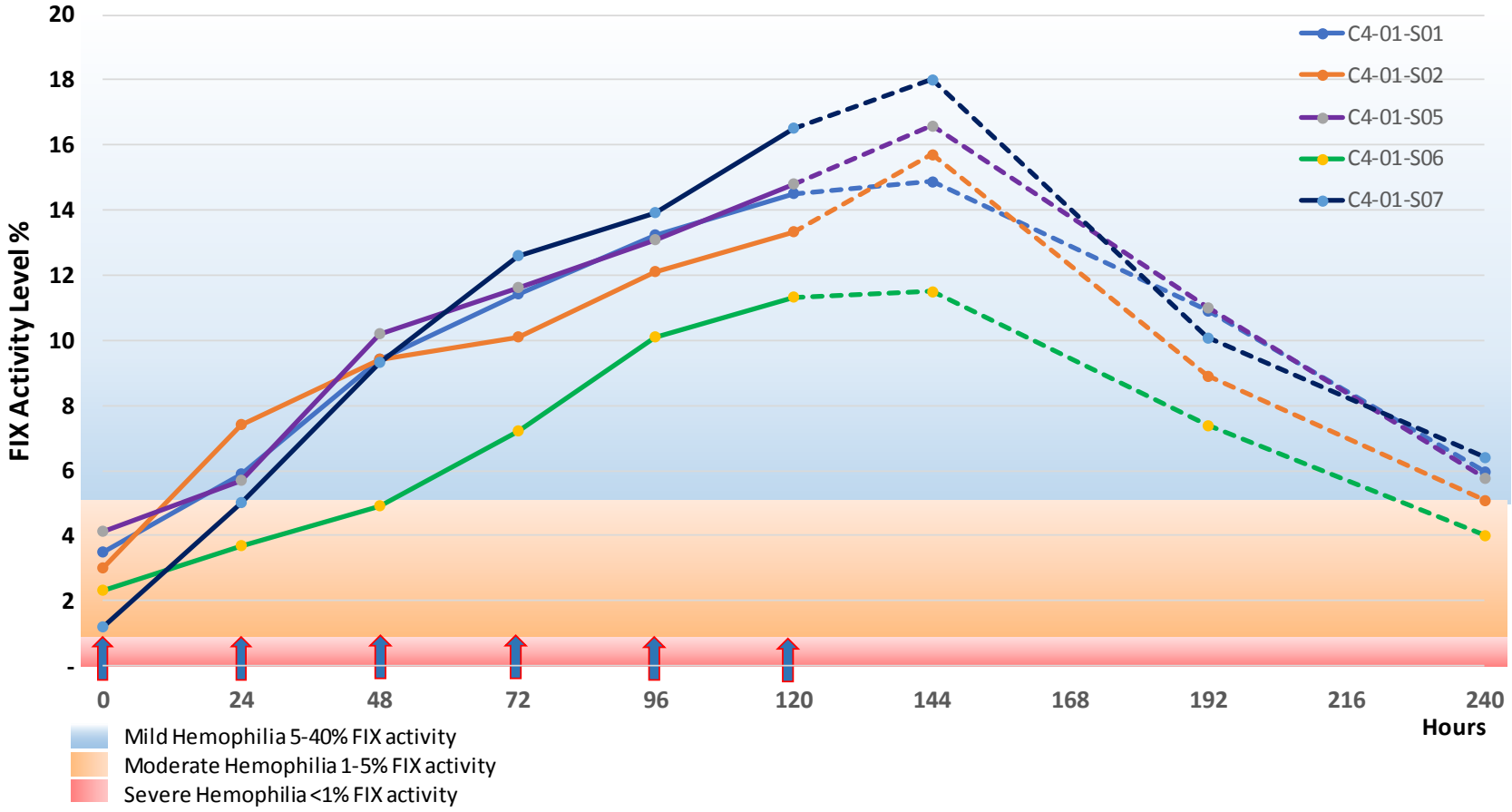
Parameters	ISU304 75 IU/kg IV (n=3)	ISU304 150 IU/kg SC (n=3)
	Mean ± SD (Min - Max)	Mean ± SD (Min - Max)
T_{max}† (h)	0. 27 [0.27-0.52]	47.9 [23.97-47.92]
C_{max} (%)	41.7 ± 7.47 (36.20 – 50.20)	**5.27 ± 1.16** (4.50 – 6.60)
AUC_{last} (h·%)	1073.47 ± 109.87 (953.96 – 1170.11)	495.80 ± 88.22 (409.01 – 585.39)
AUC_{inf} (h·%)	1334.69 ± 79.32 (1243.37 – 1386.51)	837.50 ± 182.01 (657.74 – 1021.68)
$t_{1/2}$ (h)	30.52 ± 4.17 (27.20 – 35.19)	**85.59 ± 28.82** (63.58 – 118.21)
Bioavailability (%)	NA	**23.5 ± 6.7** (17.5 – 30.7)

† Data are presented as median [min - max]
No baseline adjustment



Mean plasma FIX potency-time profiles of ISU304 after a single intravenous of 75 IU/kg then a single subcutaneous dose of 150 IU/kg
Average BW: 74Kg
Average ISU 304 injection volume: 1.24 mL

Cohort 4 Factor IX Activity: 150 IU/Kg/day SC for 6 consecutive days



Cohort 4 Results

Parameters	ISU304 150 IU/kg SC (n=5) Mean ± SD (Min - Max)
T_{max}† (h)	23.92 (23.83-23.92)
C_{max} (%)	15.34 ± 2.44 (11.5 – 18)
AUC_{last} (h·%)	1300.7 ± 189.66 (989.86 – 1462.84)
AUC_{T} (h·%)	352.38 ± 51.57 (273.61 – 414.06)
AUC_{inf} (h·%)	1815.8 ± 288.14 (1353.56 – 2059.56)
$t_{1/2}$ (h)	65.11 ± 4.3 (61.05 – 72.37)
† Data are presented as median [min - max]	

Safety Data: Cohort 1- 4

- Local & General effects reported within 1 hour from the IP administration
  - One subject experienced Fatigue, Headache, Dizziness
- Other adverse events of injection sites:
  - Erythema: 6 subjects
  - Pain: 5 subjects
  - Redness: 3 subjects
- All AEs were mild to moderate injection site adverse events that resolved without sequelae
- Transient elevated D-dimer level only after SC injection in cohort 2-4 without any changes of TAT, F1-2, likely caused by local effect due to SC injection
- 3 anti-furin antibodies and no neutralizing inhibitors

ISU304 cohort 1- 4 conclusions/perspectives

- **Similar PK to Benefix**
- **22-fold potency advantage** allows subcutaneous administration
- **Daily SQ dosing of 150 IU/kg for 6 days resulted in mean 15.34 ± 2.44% FIX activity**, far over the lowest level of MH, and it could be maintained when daily dosing continue
- **SC dosing of ISU304 may provide superior prophylaxis** to IV extended half-life agents, because easily injected and high trough level of mild HB could be achieved
- **Once FIX activity stabilization achieved, lower dose or decreased frequency required** for pragmatic use in prophylaxis, which will be reflected in upcoming Phase 2 study
- **Additional possible advantages** over other developing SC drugs.

  - Monitoring is easy and it would control of bleeds with same drug

Thank You