Phase 1/2 Trial of Subcutaneously Administered Factor IX Variant CB 2679d/ISU304: Pharmacokinetics and Activity

Chur Woo You, MD PhD, Ho-Jin Shin, MD, **Howard Levy** MBBCh PhD, Martin Lee, PhD, Seung-Beom Hong, PhD, Jamie Ellen Siegel, MD and June Young Park, MD

87 Session 322. Disorders of Coagulation or Fibrinolysis: Novel Therapies and Clinical Trials in Bleeding Disorders

ASH

9 December 2017

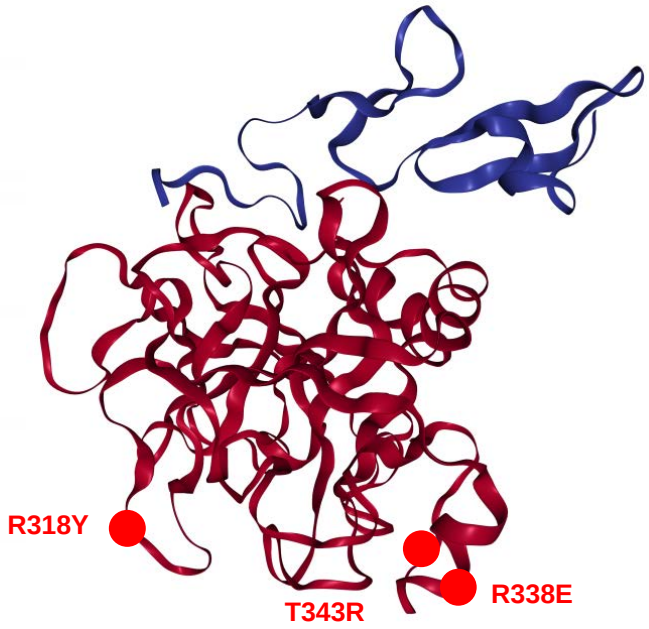
Disclosure

- Employee and Stockholder of Catalyst Biosciences

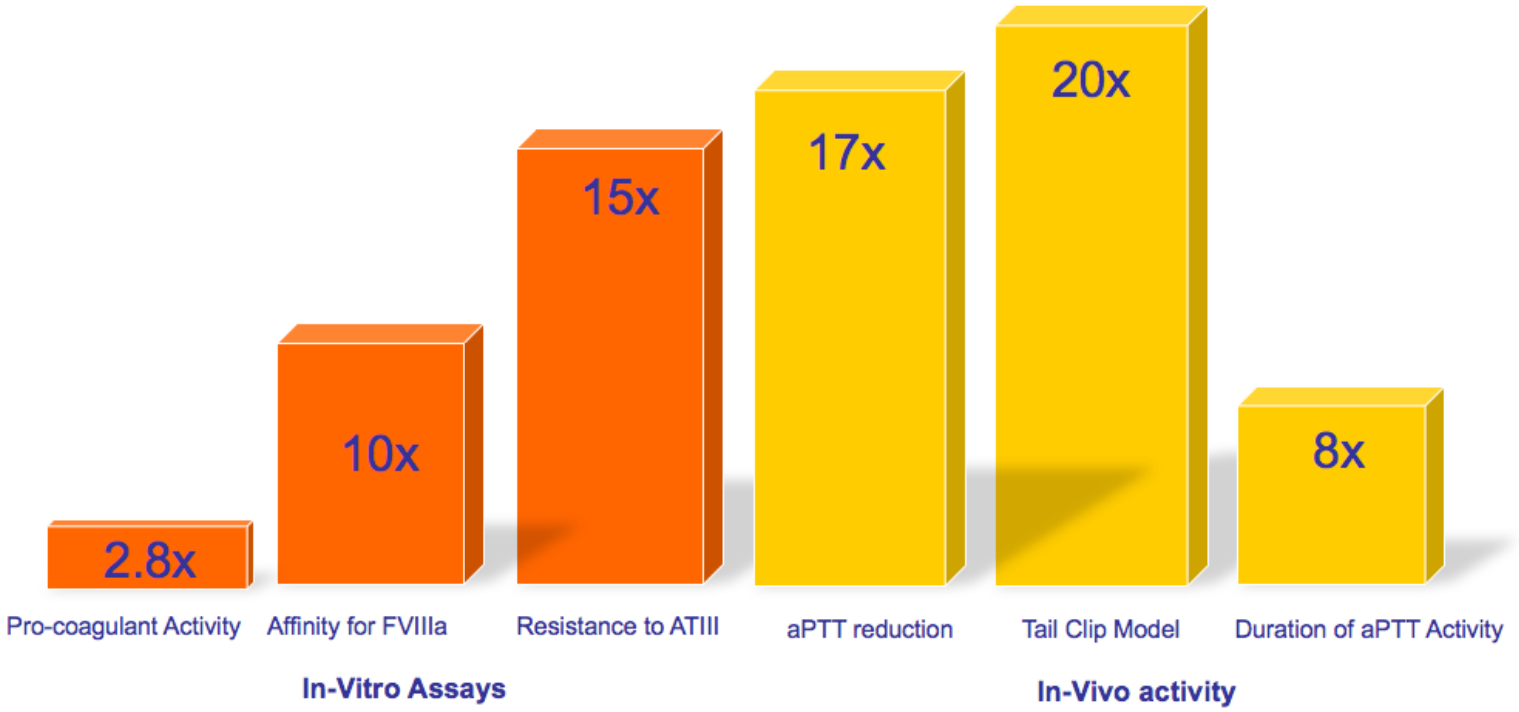
Factor IX Modified with 3 Point Mutations

- Rapid clearance of FIX necessitates frequent intravenous administrations to achieve effective prophylaxis
- Subcutaneous administration is the preferred route of administration but has been limited by low bioavailability and potency of the marketed FIX products
- Designed as best-in-class high potency recombinant FIX product
- Orphan Drug Designation in US and EU

Factor IX: CB 2679d/ISU304



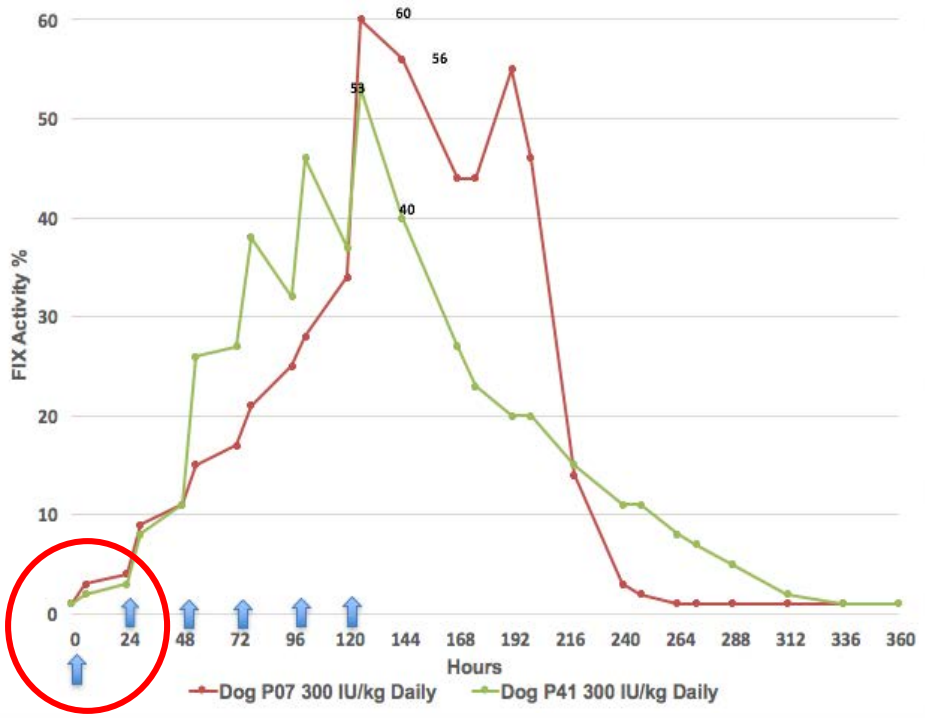
CB 2679d/ISU304 Potency Advantage over wt-FIX



- 20-fold increased potency of CB 2679d over wild-type FIX in tail clip model

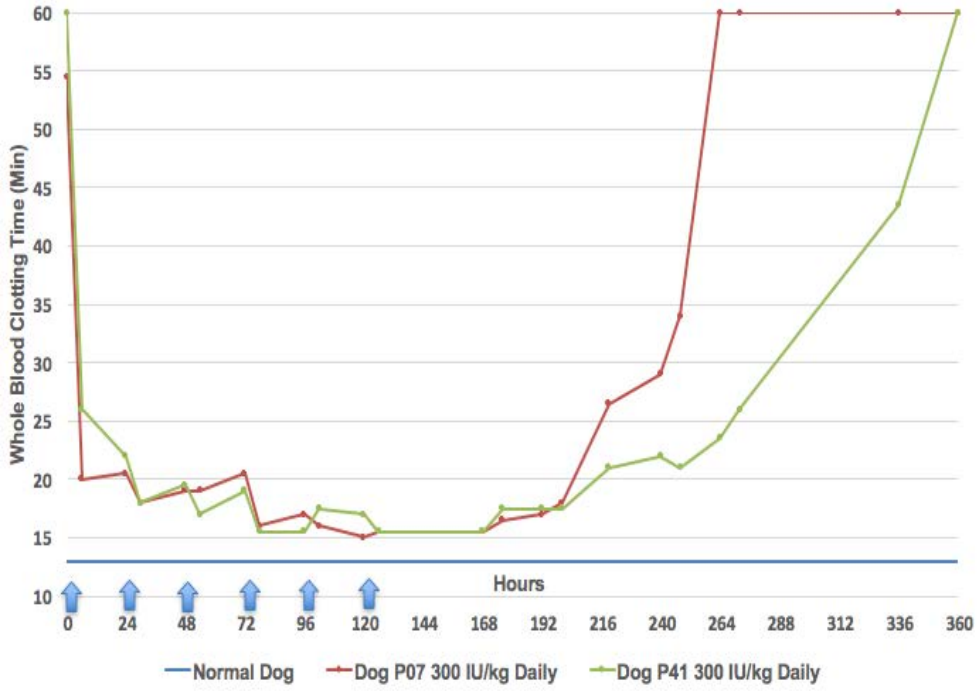
Normalization of FIX Activity and Rapid Whole Blood Clotting Time Correction with Daily SQ Dosing of CB 2679d/ISU304 (300 IU/kg) in Hemophilia B Dogs*

Increase in FIX Activity After Daily SQ Dosing



*Levy *et al*. ISTH 2017 Res Pract Thromb Haemost (2017), 1 (Suppl. 1), 142

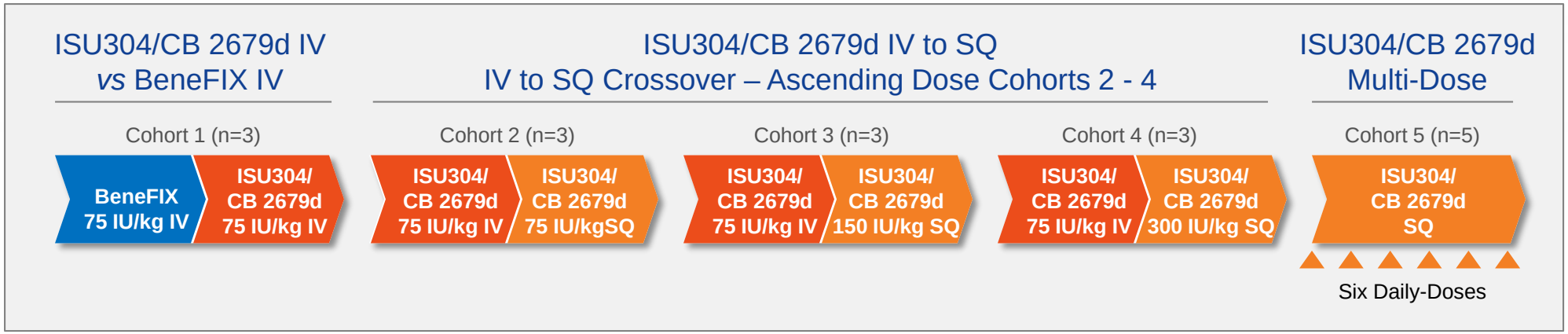
Decrease in Whole Blood Clotting Time After Daily SQ Dose



*Levy *et al*. EAHAD 2017 Haemophilia (2017), 23 (Suppl. 2), 29-140

Design of Ongoing Phase 1/2 Trial

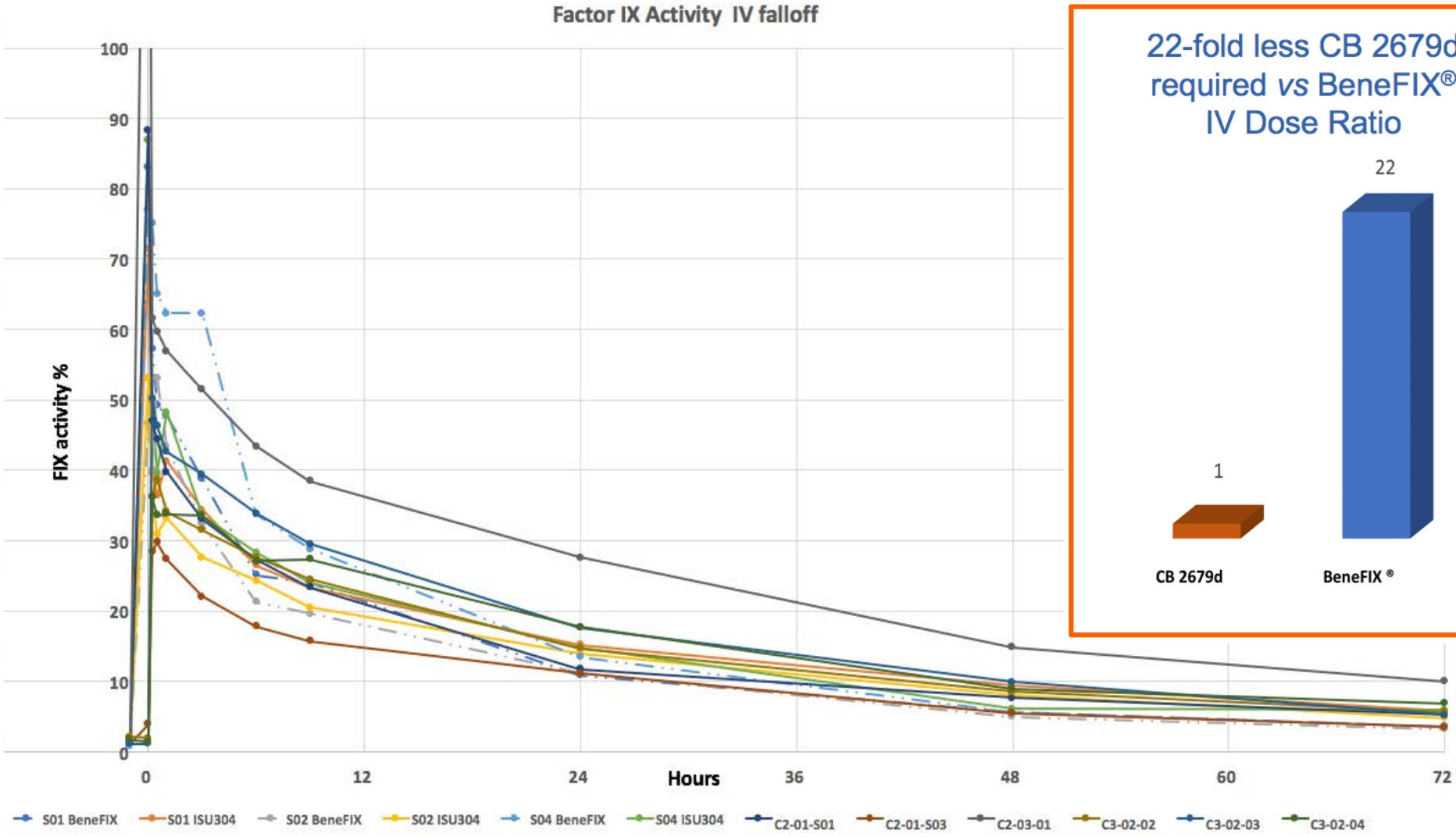
- ISU Abxis is executing the Phase 1/2 trial
- Cohort 3 has been completed



Methods

- IV PK was sampled at predose, 0, 0.25, 0.5, 1, 3, 6, 9, 24, 48 and 72 hours
- SQ PK was sampled at predose, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours
- A safety follow-up was done 3 weeks after dosing
- FIX antigen and FIX activity, anti-drug antibody to BeneFIX and ISU304 and neutralizing antibody were measured at Haematologic Technologies
- FIX antigen was measured using VisuLize™ Factor IX Antigen KitAG (Affinity Biologicals) and FIX activity was measured using a one-stage clotting assay using ACL TOP 700 and Instrumentation Laboratories reagents
- Calculation of AUC was based on the trapezoidal rule
- Calculation of half-life used Demitasse 2000 which uses an iterative piecewise fitting algorithm based on a robust (M-regression) log-linear model
- All activity data were adjusted for baseline assuming exponential falloff after IV administration and a half-life of 20 hours

Cohort 1, 2 & 3:
IV BeneFIX & IV CB 2679d/ISU304 75 IU/kg



IV BeneFIX vs IV CB 2769d/ISU304 PK 75 IU/kg

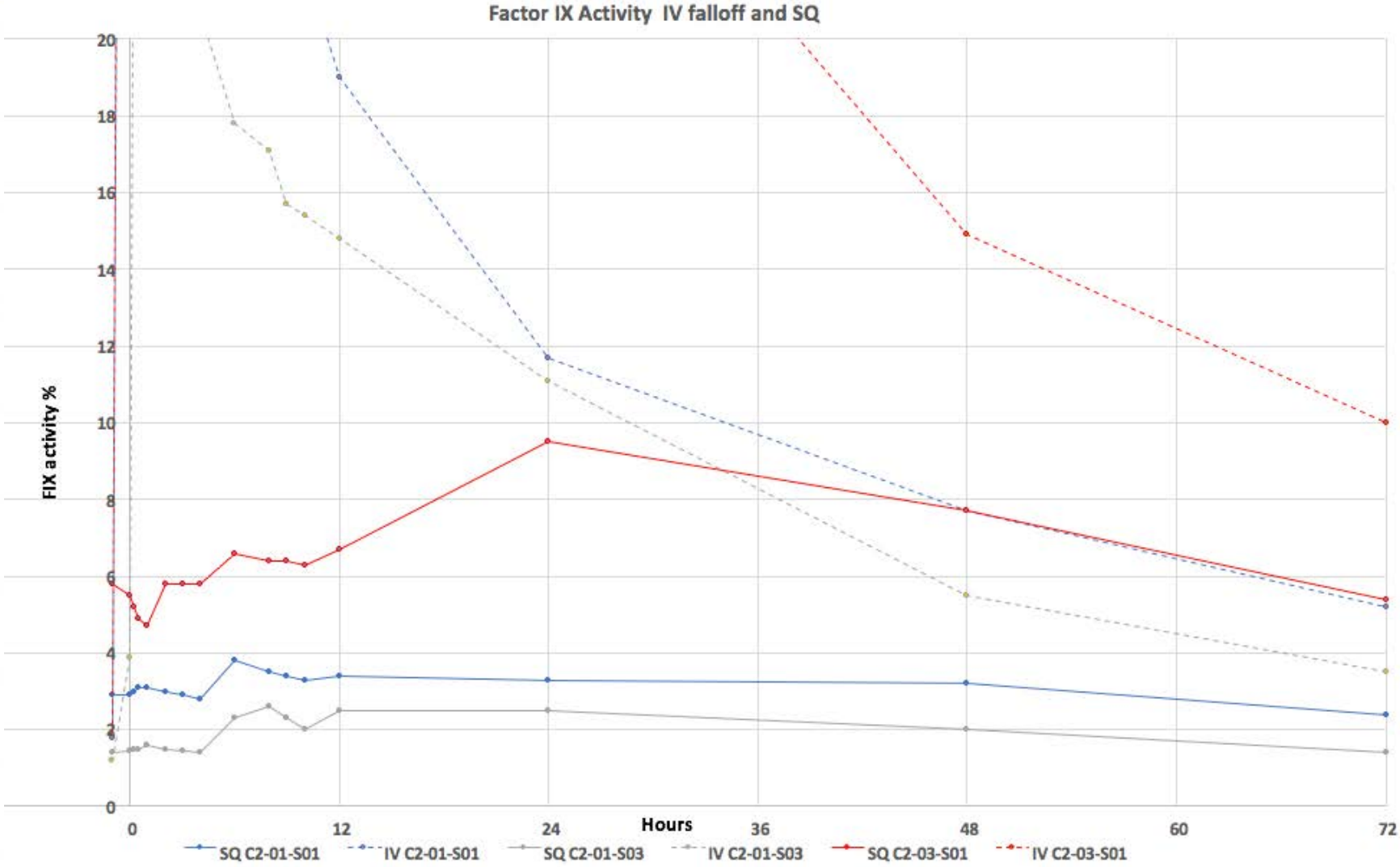
PK profiles after IV administration (mean ± SD)

Group	t-half alpha (hrs)	t-half beta (hrs)	MRT (hrs)	Cmax (mU/mL)	AUC 0-t (mU/mL*hr)	AUC 0-inf (mU/mL*hr)
BeneFIX	5.3 ± 0.8	21.0 ± 1.1	25.1 ± 1.5	70.2 ± 16.0	855 ± 163	933 ± 177
CB 2679d/ ISU304	8.5 ± 4.0	27.0 ± 2.2	35.8 ± 2.5	70.0 ± 46.9	973 ± 274	1148 ± 334
P-value by two-sample t-test*	0.22	0.0014	0.00004	0.995	0.50	0.32

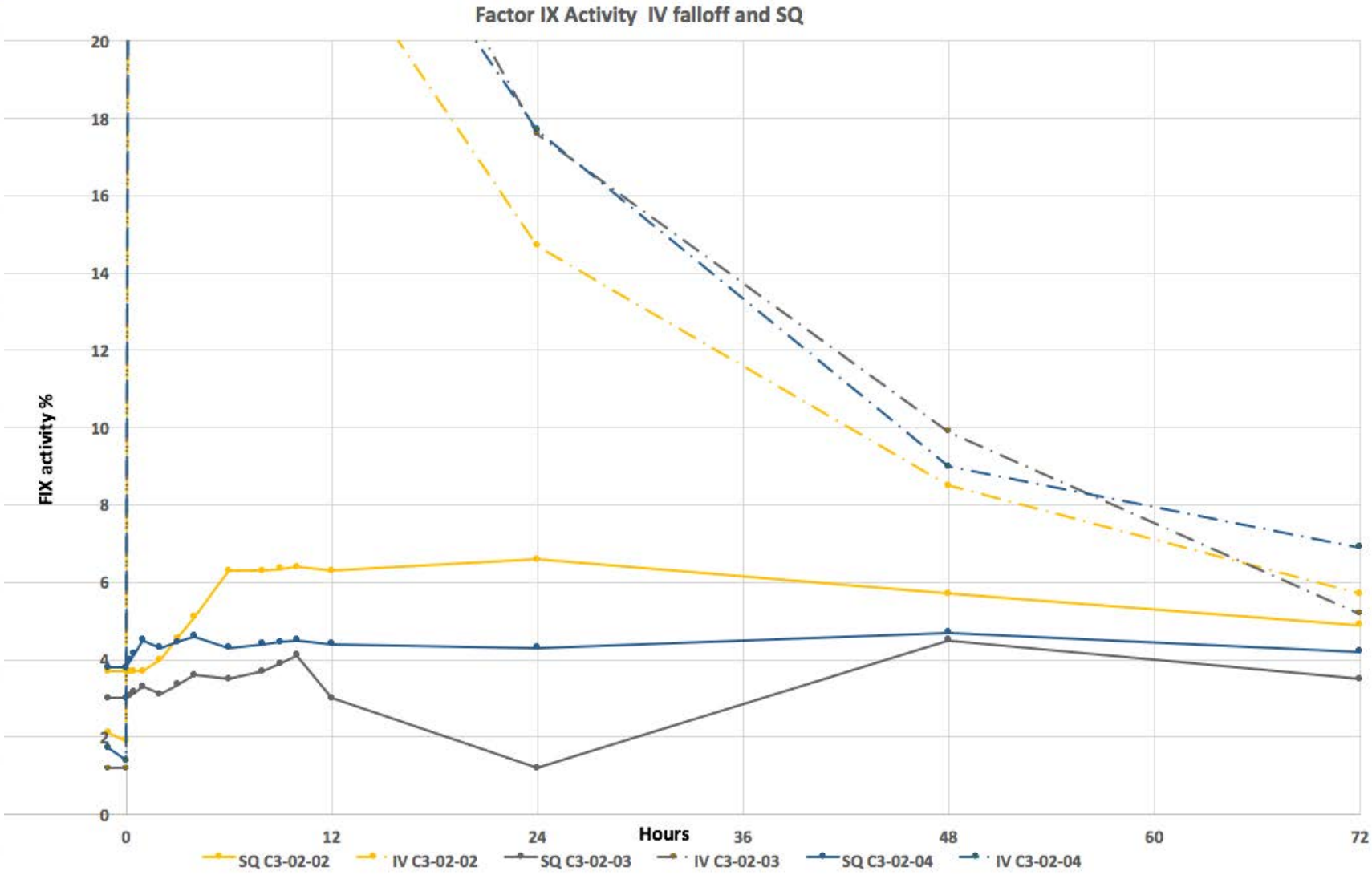
*ignoring the matching from Cohort 1

- IV CB 2679d has a significantly longer half-life and mean residence time than BeneFIX

Cohort 2: 75 IU/kg IV then 75 IU/kg SQ CB 2679d/ISU304



Cohort 3: 75 IU/kg IV then 150 IU/kg SQ CB 2679d/ISU304



CB 2769d – ISU304-001 PK: SQ *vs* IV has 3.6-fold Increase in Half-life

Cohort 2 & 3: PK activity profiles after IV and SQ CB 2679d/ISU304 administration

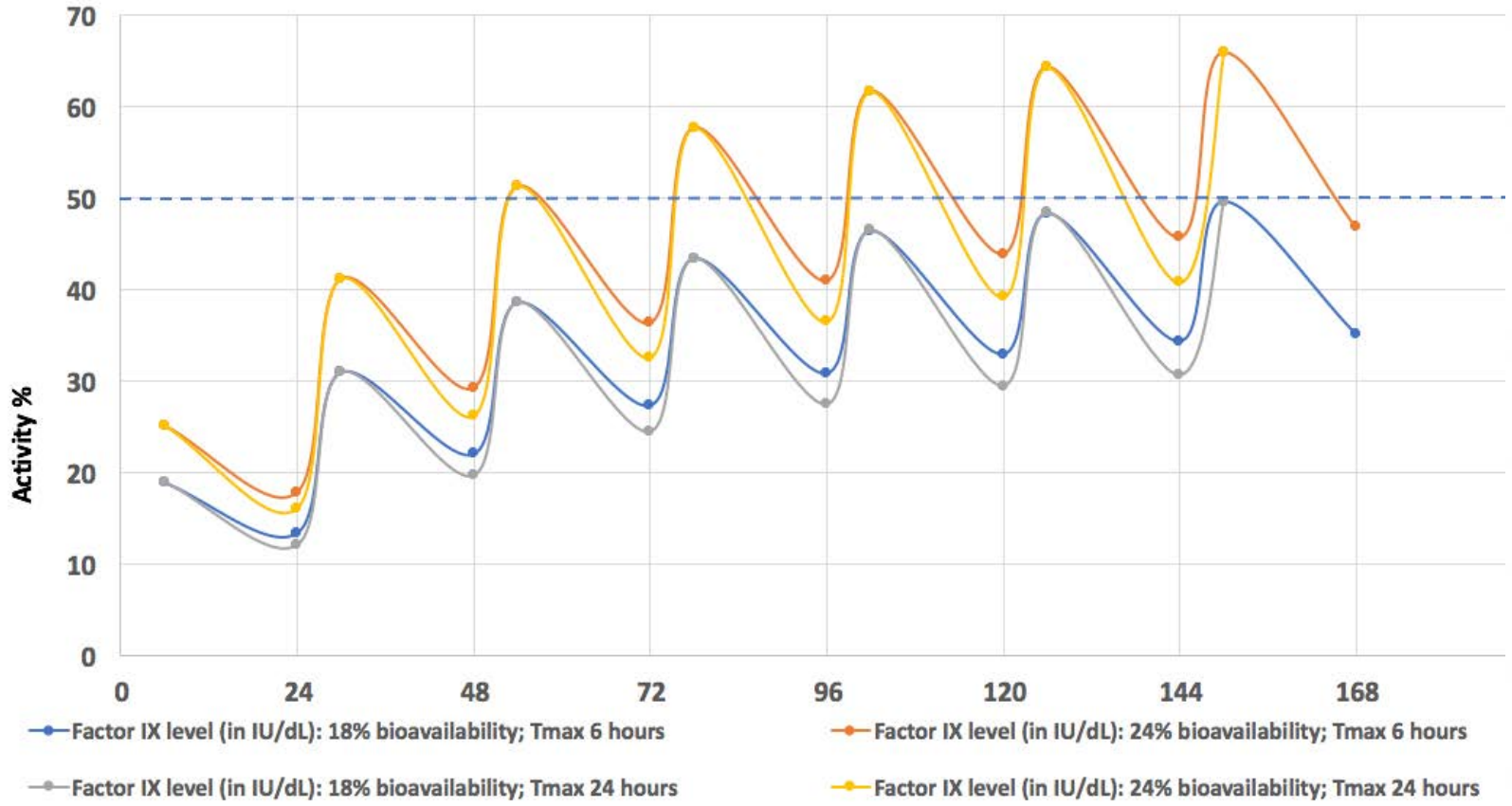
Route		t-half alpha (hrs)	t-half beta (hrs)	Tmax	AUC 0-t (mU/mL*hr)	Bioavailability
IV	Mean ± SD	9.4 ± 4.4	27.0 ± 2.2	16.7 ±11.3 mins	1026 ± 330	
	Median [25%-75%]	9.4 [6.4-13.2]	27.6 [26.4-29.2]	15 mins [5-30]	945 [780-1265]	
SQ	Mean	3.4 (n=1)	242.2 ± 365.5	29.0 ± 16.3 hrs	306 ± 148	19.8 ± 5.2%
	Median [25%-75%]		98.7 [60.0-369.4]	24 hrs [19.5-48]	352 [138-410]	18.5% [15.4-24.7%]

- 98.7 hour SQ CB 2679d half-life is similar to IV agents dosed biweekly or weekly:
  - Alprolix 86.52 hours
  - Idelvion 104-118 hours
  - Rebinyn/Refixia 114.9 hours

ISU-304-001 Safety

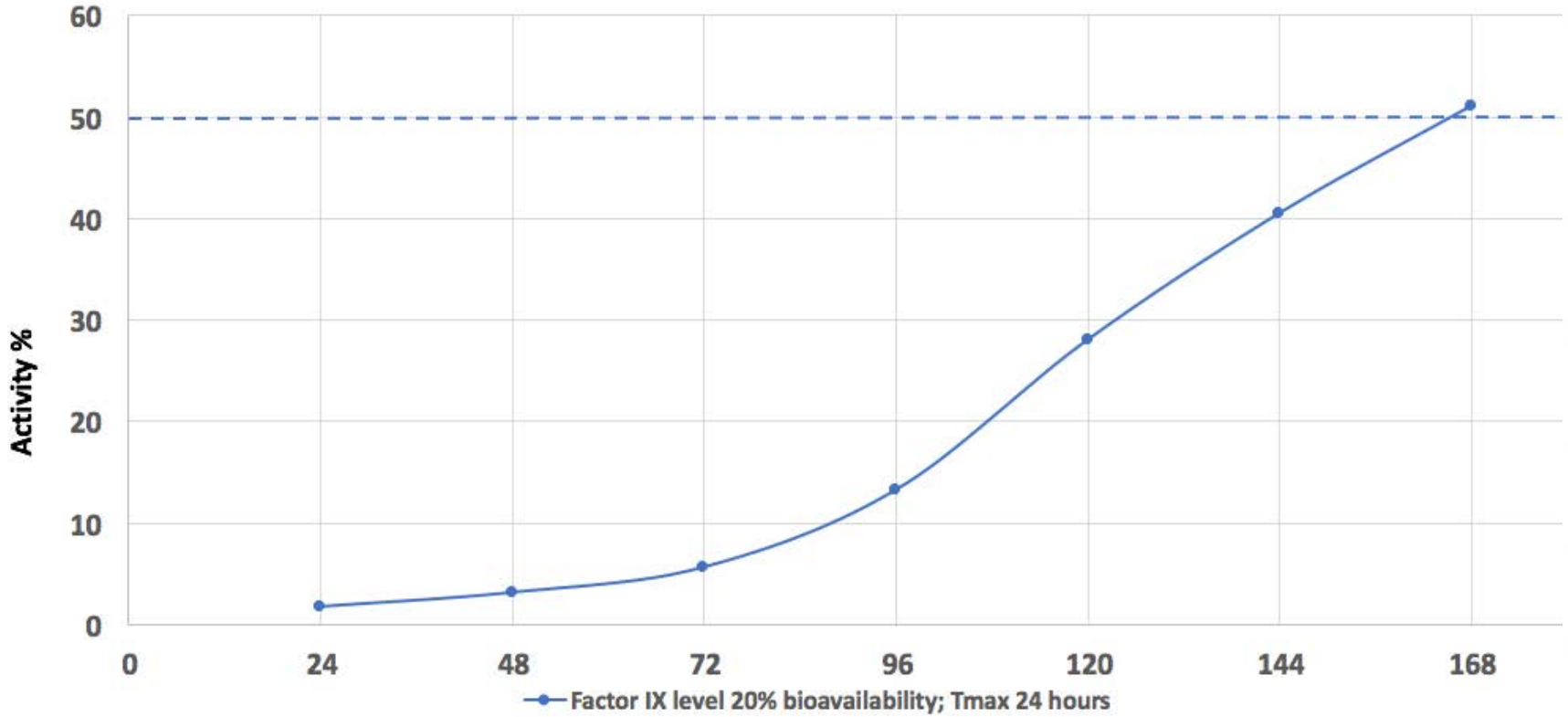
- One subject had a mild general reaction within 1 hour of injection
  - Fatigue/Boredom
  - Headache
  - Dizziness
- Transient mild AEs were reported in cohorts 2 and 3 and all resolved without sequelae:
  - Itching
  - Tenderness
  - Erythema
  - Solidification
  - Injection site discomfort
  - General ache [moderate severity]

Modeling of Daily 75 IU/kg SQ $t_{1/2}$ = 36 hours



- Modeling demonstrates that CB 2679d could achieve **stable** FIX minimum levels in the high mild hemophilia or normal range >50%

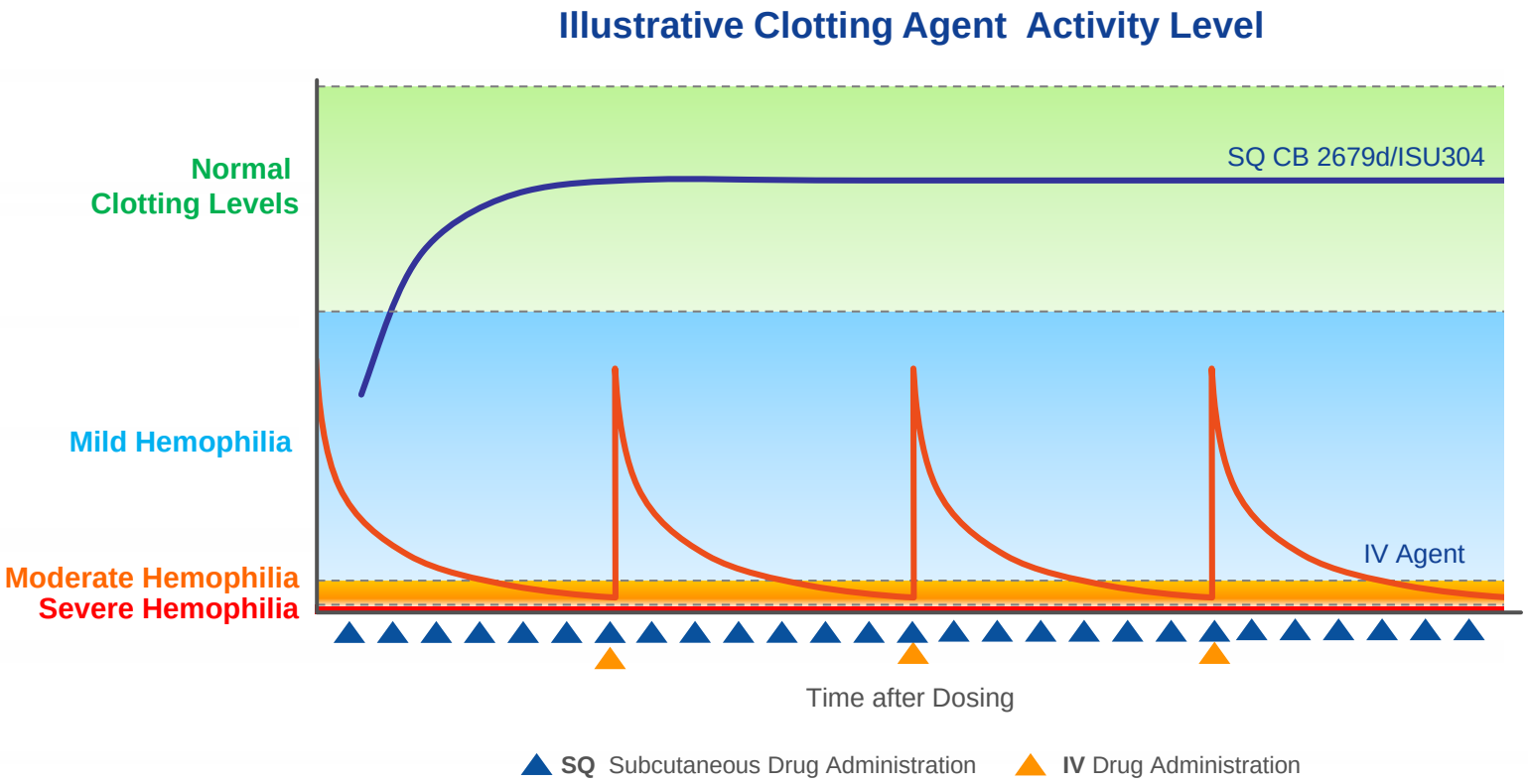
Modeling of Daily 60 IU/kg SQ $t_{1/2}$ = 100 hours



- Normal FIX activity levels of >50% are reached after 7 daily doses of CB 2679d
- No difference between peak and minimum levels when Tmax is 24 hours
- Lower doses of CB 2679d will maintain levels above 50% at all times
- Less frequent dosing is also a possibility

Modeling Predicts Subcutaneous Administration may be a Superior Prophylaxis Regimen Compared with IV Agents

Time in Mild to Normal Levels Predicts Protection from Spontaneous Bleeds



CB 2679d/ISU304 Program Conclusions

- CB 2679d is designed as best-in-class high potency recombinant Factor IX product
- 22-fold potency advantage allows subcutaneous administration
- Normal trough factor IX blood levels achieved after 6 daily subcutaneous doses in hemophilia B dogs
- Phase 1/2 subcutaneous trial is ongoing
  - Cohort 3 (150 IU/kg SQ) has been completed
  - Multi-dose SQ data anticipated Q1 2018
- IV CB 2679d has a longer half-life of 27 hours than 21 hours of wt-FIX
- SQ delivery significantly increases half-life 3.6-fold to 98.7 hours
- SQ dosing may provide superior prophylaxis to IV extended half-life agents
- Orphan drug designations have been granted in US and EU