Subcutaneous Delivery of Coagulation Factors

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CMO

Catalyst Biosciences

- Essential Medicines for Hemophilia
- Greater Convenience
- Superior Outcomes

Hemophilia Drug Development
Boston, 15 August 2018

CATALYST BIOSCIENCES

Catalyst Biosciences: CBIO

Preventing bleeding with convenient subcutaneous (SQ) dosing

Hemophilia is a large & growing market

- Orphan hematology disease
- FVIIa & FIX products have ~$3.5B in annual sales

Two novel clinical stage SQ product candidates differentiated from IV market leaders

- Simpler, less painful, small dose
- SQ enhances pharmacokinetics
- Potential to maintain continuous protective levels
- Disruptive to all current intravenous products
- Especially well suited for children: 40% of market

FIX: Dalcinonacog alfa - CB 2679d/ISU304

- 22-fold more potent than BeneFIX® in man
- >30% FIX trough levels achieved

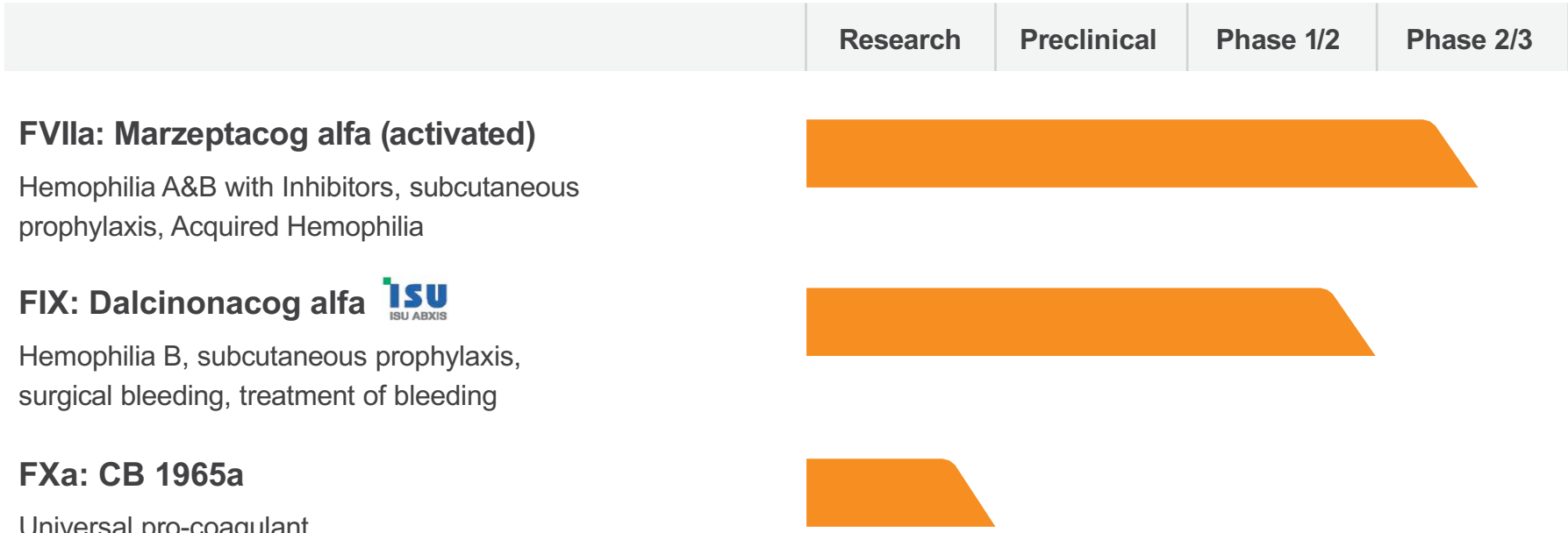
FVIIa: Marzeptacog alfa (activated)

- Phase 1/2 IV study complete
- 9-fold more potent than NovoSeven®
- Phase 2/3 SQ prophylaxis clinical trial enrolling
- PoC demonstrated in P2, significant reduction in ABR with long-term daily SQ prophylaxis
  - A total of 200 exposure days to date
  - Well tolerated
  - No ADAs

CBIO hematology pipeline

~40% of Individuals with hemophilia are children

KOL's, individuals & treaters want a better dosing method & better efficacy



FVIIa: Marzeptacog alfa (activated)

Hemophilia A&B with Inhibitors, subcutaneous prophylaxis, Acquired Hemophilia

FIX: Dalcinonacog alfa ISU ABXIS

Hemophilia B, subcutaneous prophylaxis, surgical bleeding, treatment of bleeding

FXa: CB 1965a

Universal pro-coagulant

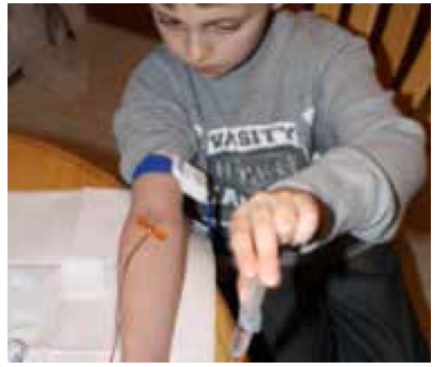
FIX treatable population ~10,000

FVIIa treatable population ~3,200

+ Hemophilia A Inhibitors
+ Hemophilia B Inhibitors
+ Acquired Hemophilia
+ Severe FVII Deficiency

Advantages of subcutaneous prophylaxis

Intravenous infusion



- – Slow infusion through a painful needle stick
- – Requires supervision and skilled insertion of needle into vein
- – Challenging for patient, family, school
- – Activity levels fluctuate, low trough levels

Subcutaneous prophylaxis

- + Subcutaneous injections are easier
- + Home therapy - family or patient
- + Potential for:
  - + Fewer bleeds, reduce joint and muscle damage
  - + Fewer demands on healthcare system
  - + Reduced hospital stays & outpatient visits

Subcutaneous pharmacokinetics

Absorption of subcutaneous injection

- Creation of a depot at the injection site
- Local catabolism at the injection site decreases bioavailability
- Prolongation of observed half-life because of depot returning drug to circulation via Lymphatic and Venous systems
  - Slow subcutis convection and diffusion to Lymphatic and Venous capillaries results in absorption rate-limited PK and prolonged systemic exposure
  - GAG and negative charge barrier
  - SQ absorption of protein is slow with Tmax up to 8 days in humans
  - Large proteins (>20kDa) are mainly transported by Lymphatics
  - Transport in the Lymphatics is unlikely to be the rate-limiting step for the slow absorption after SQ injection

FIX subcutaneous pharmacokinetics

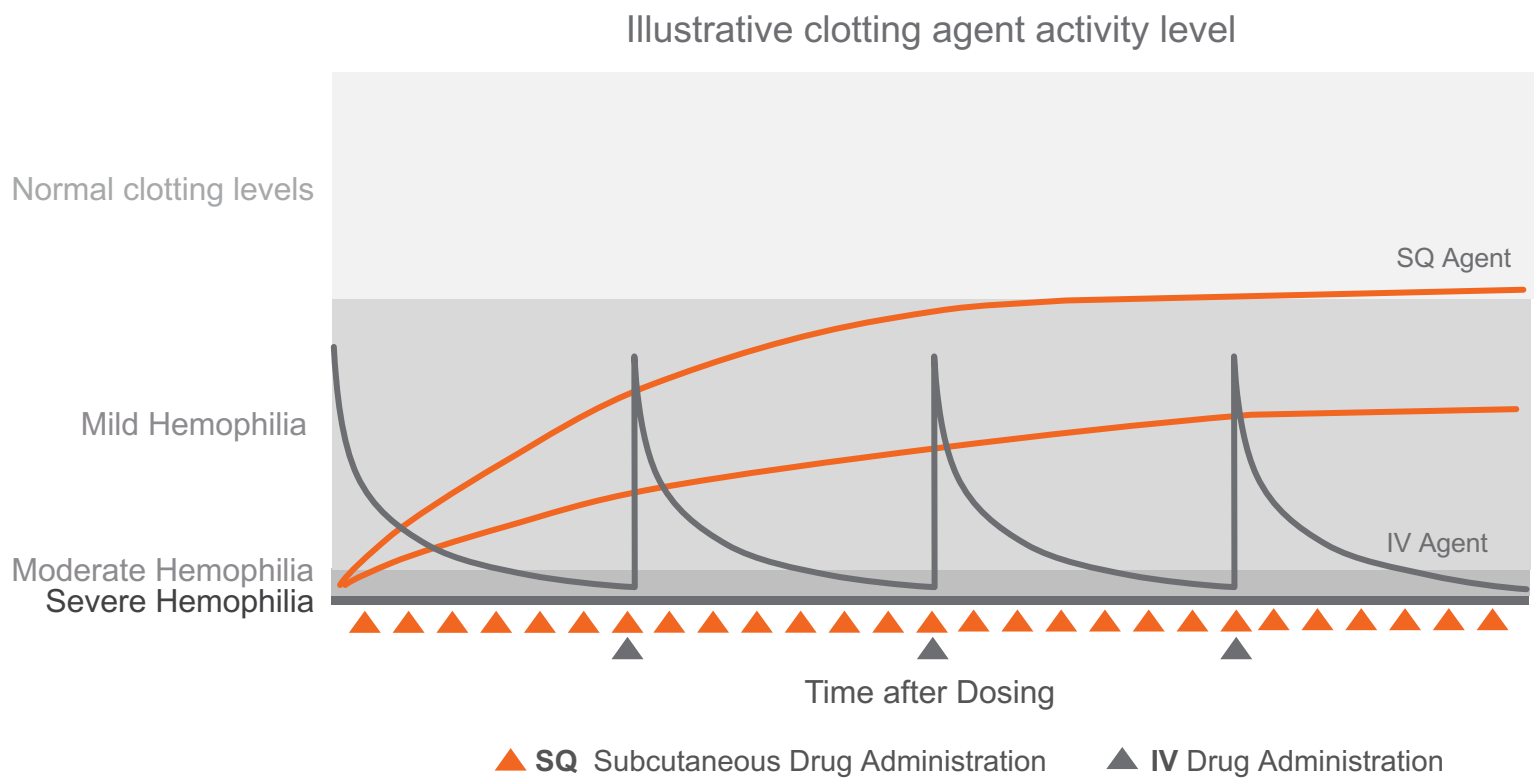
- Extravascular distribution and collagen IV binding further impact factor IX PK
  - Decreases observed bioavailability
  - Later release contributes to prolonged observed half-life

Redosing within 3 half-lives results in accumulation of plasma levels

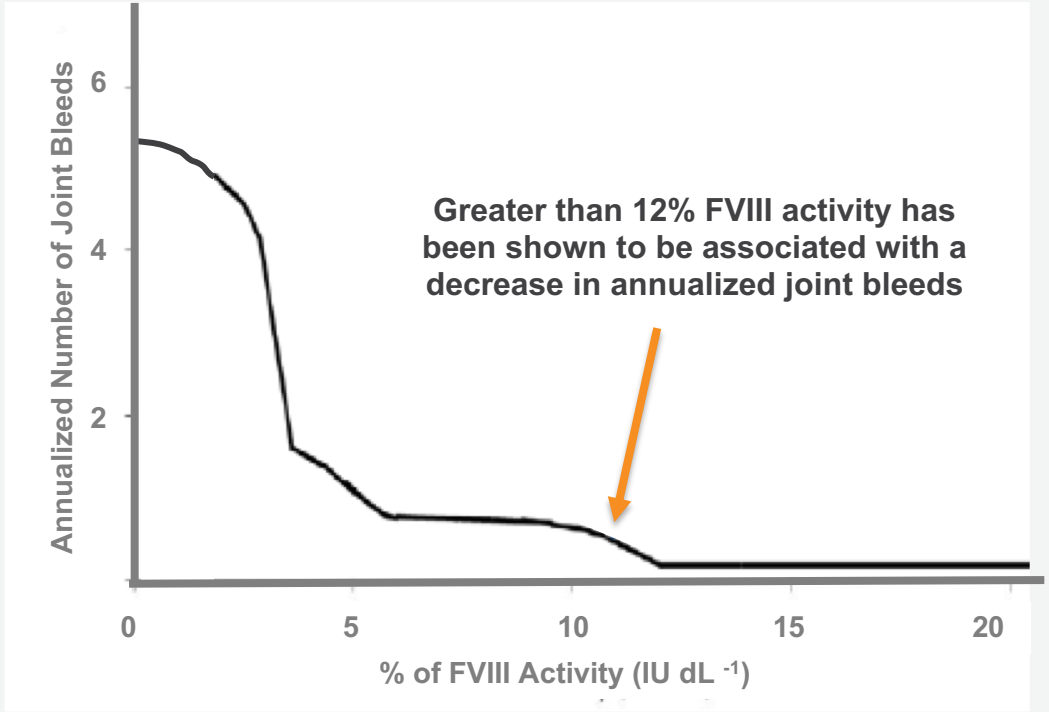
Advantages of subcutaneous prophylaxis

Redosing within 3 half-lives results in accumulation of plasma levels

Time in mild range predicts protection from spontaneous bleeds



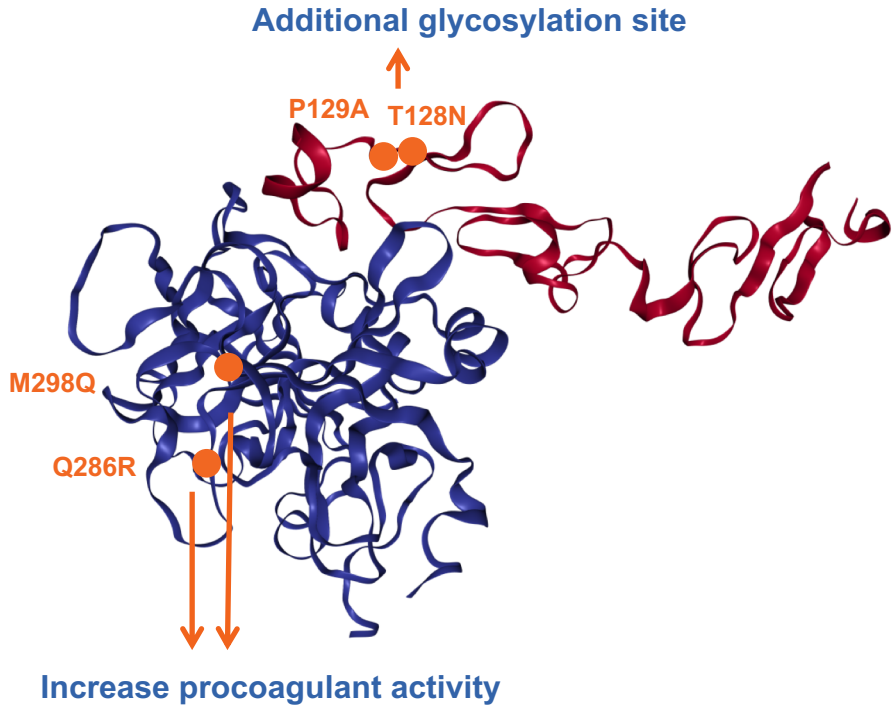
Improving hemophilia outcomes through sustained FIX activity >12%



den Uijl IEM *et al*. Haemophilia. 2011, 17: 849-853; chart adapted from den Uijl, *et al.*, 2011

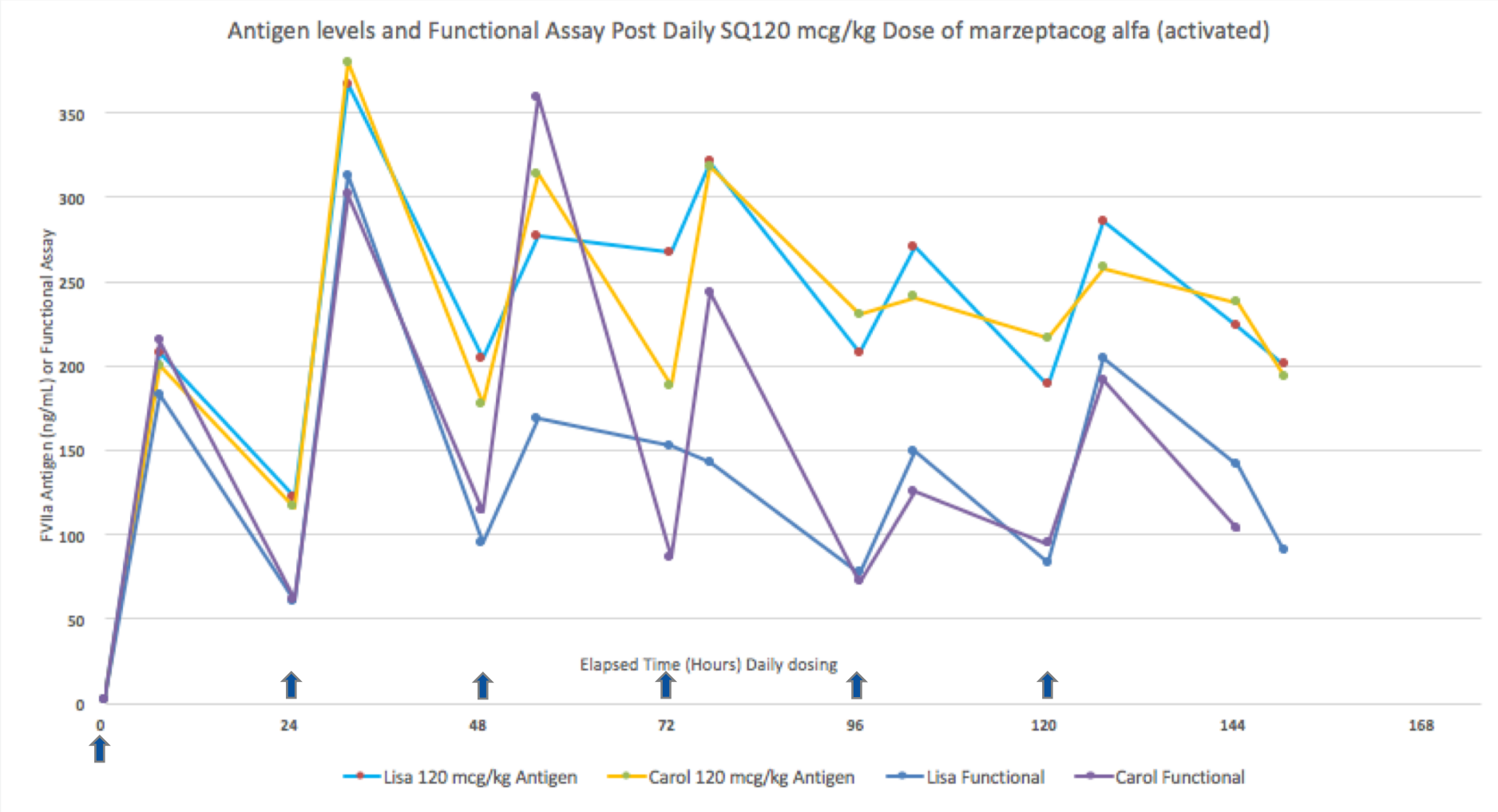
FVIIa engineered variant & intellectual property

Factor VIIa: Marzeptacog alfa (activated)

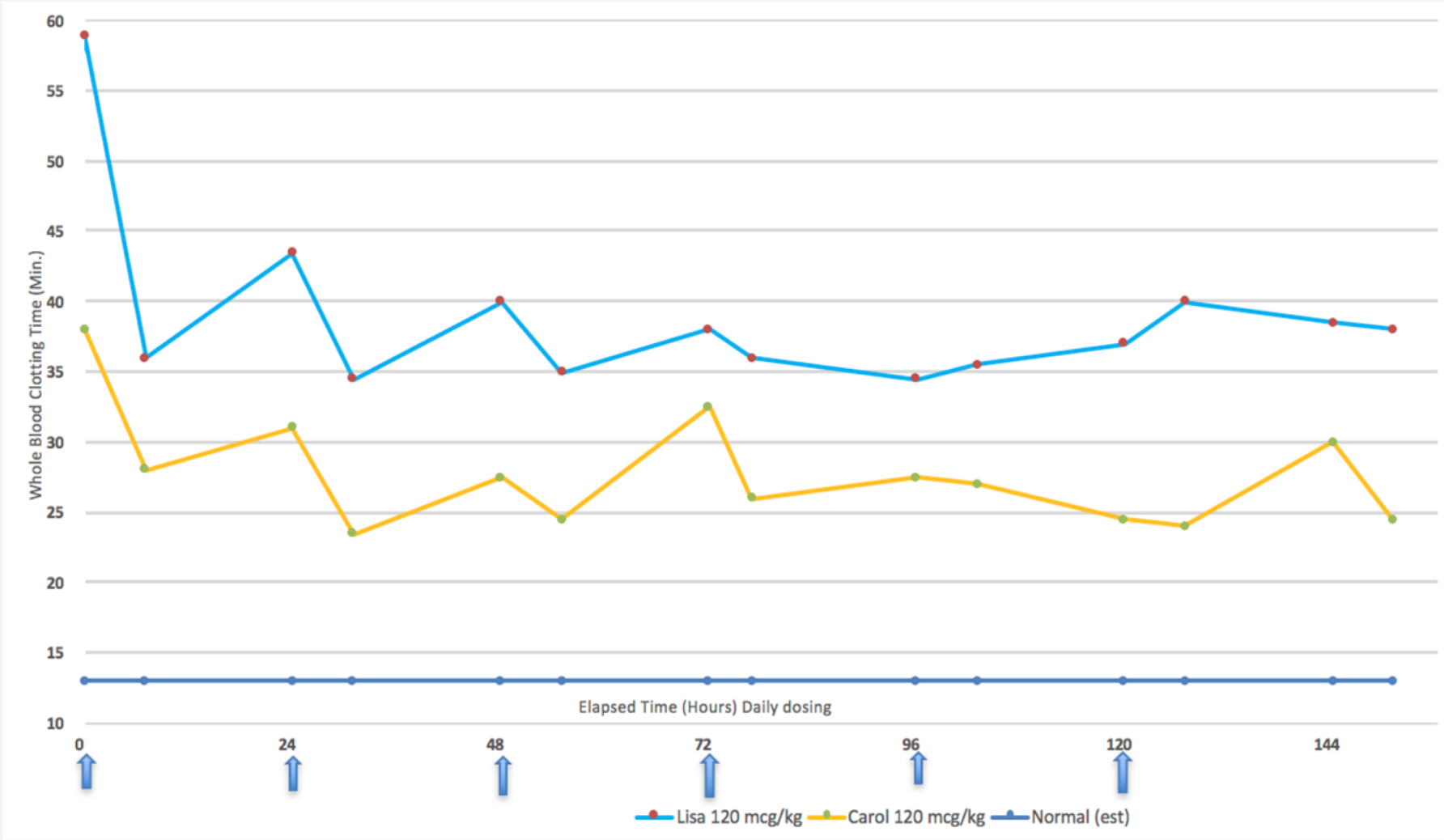


- Phase 1/2 IV study complete
- 9-fold more potent than NovoSeven®
- Phase 2/3 SQ prophylaxis clinical trial enrolling and treating
- Worldwide patents cover MarzAA and related molecules
- Granted and pending through 2029 without extensions
- Orphan Drug Designation in US

MarzAA hemophilia A dogs – Daily 120 µg/kg SQ injections antigen and activity



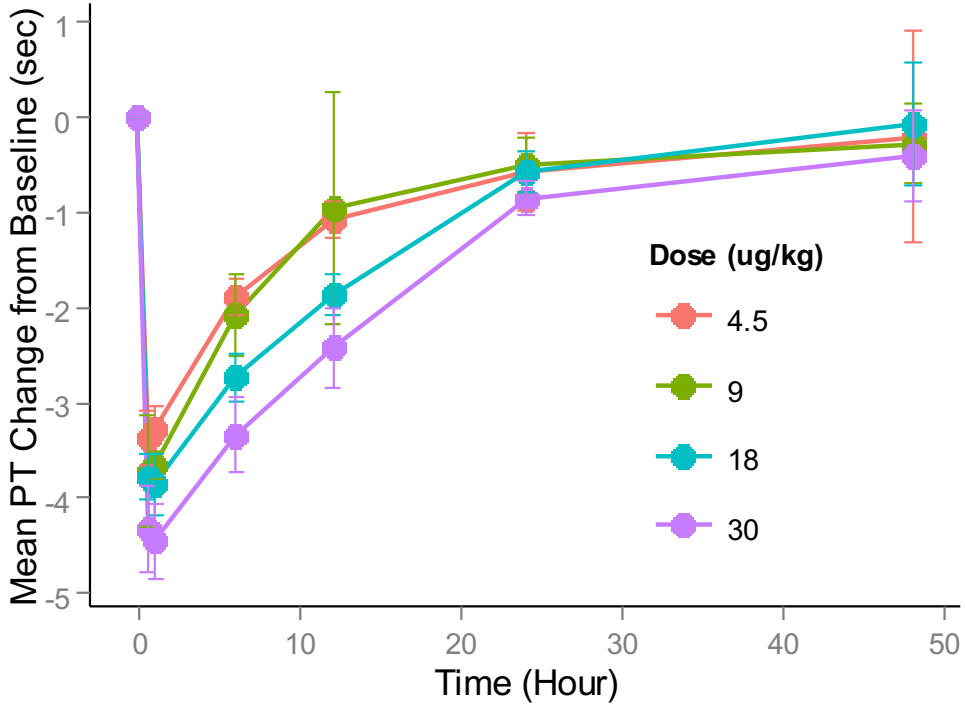
MarzAA Hemophilia A dogs – Daily 120 µg/kg SQ injections whole blood clotting time



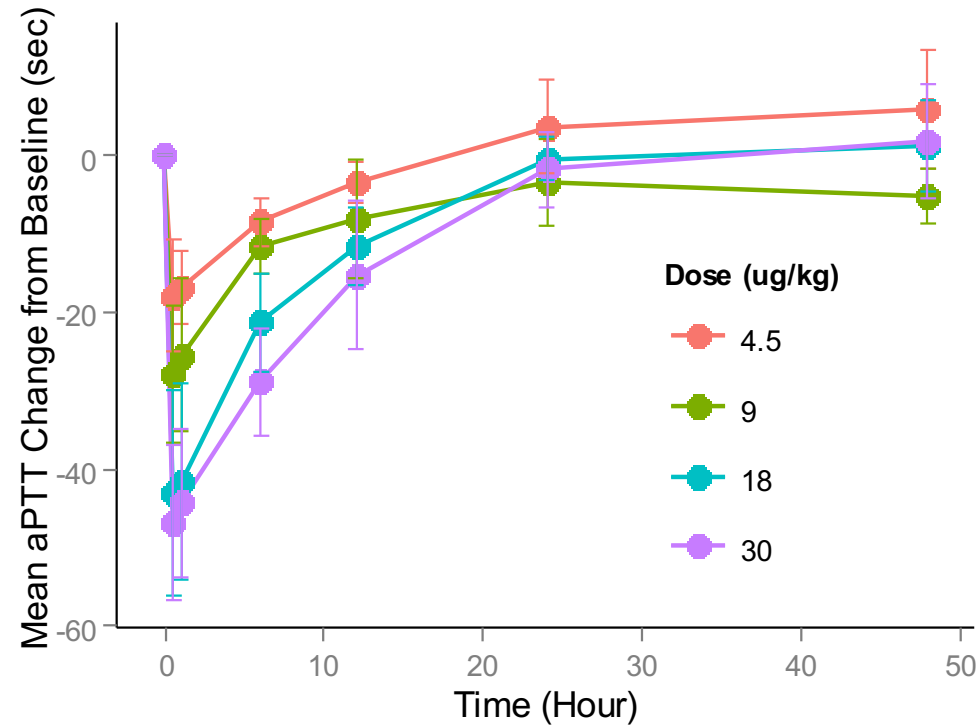
Marzeptacog alfa (activated) – Phase 1 IV

Substantial & dose dependent correction of PT & aPTT at all doses

PT



aPTT



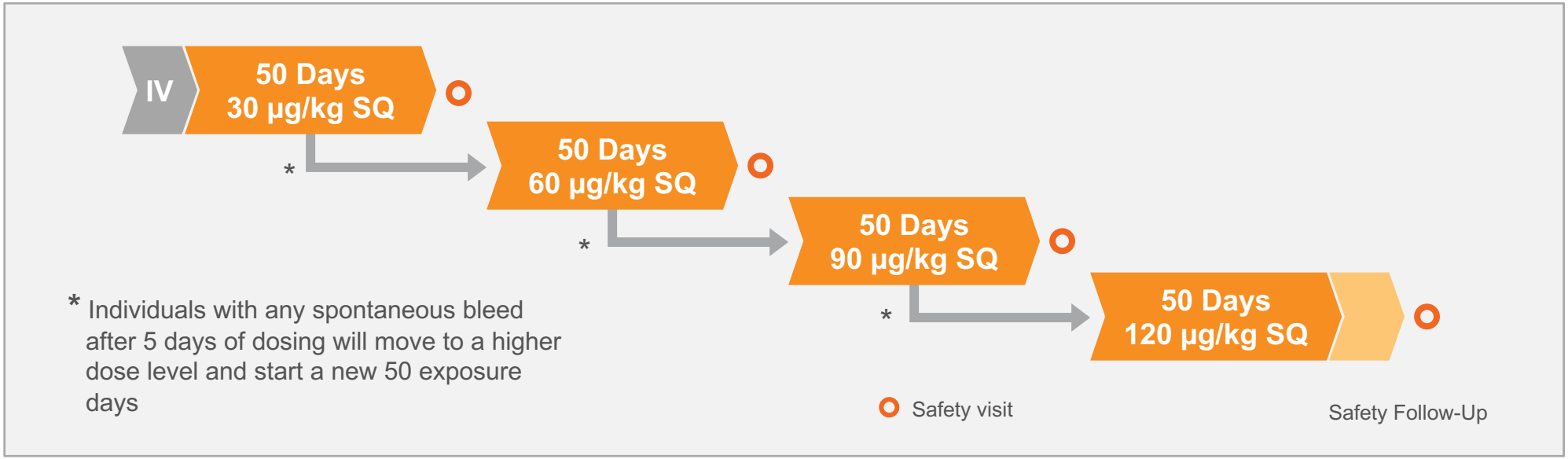
MarzAA Phase 2 part of Phase 2/3 study

Phase 2 SQ multi-dose & dose escalation

- Hemophilia A & B with Inhibitors
- Open label SQ individual dose escalation study, only if a breakthrough bleed occurs
- Up to 12 adult subjects with documented annualized bleeding rate (ABR) >12
- Study enrolling

Phase 2 clinical data

- Interim data presented at ISTH 18 July 2018
- Study end points
  - Safety & tolerability of daily SQ dosing
  - Monitoring of potential inhibitor formation
  - ABR *vs* recorded historical ABR
  - After 50 exposure days with no bleeds, individuals will move to safety follow-up



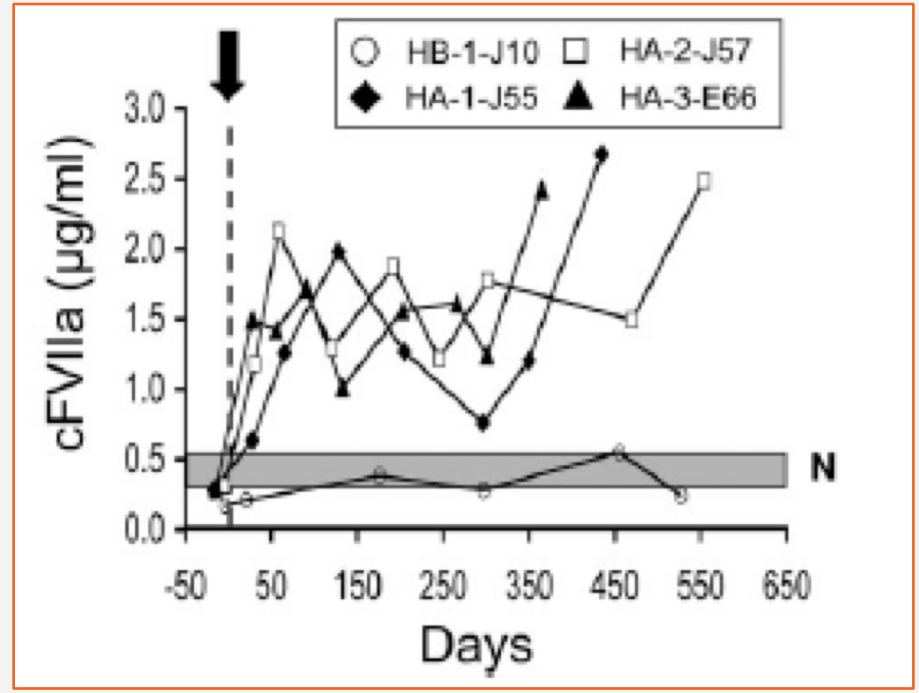
Selection of initial FVIIa dosing level for prophylaxis treatment

rVIIa IV continuous infusion during surgery

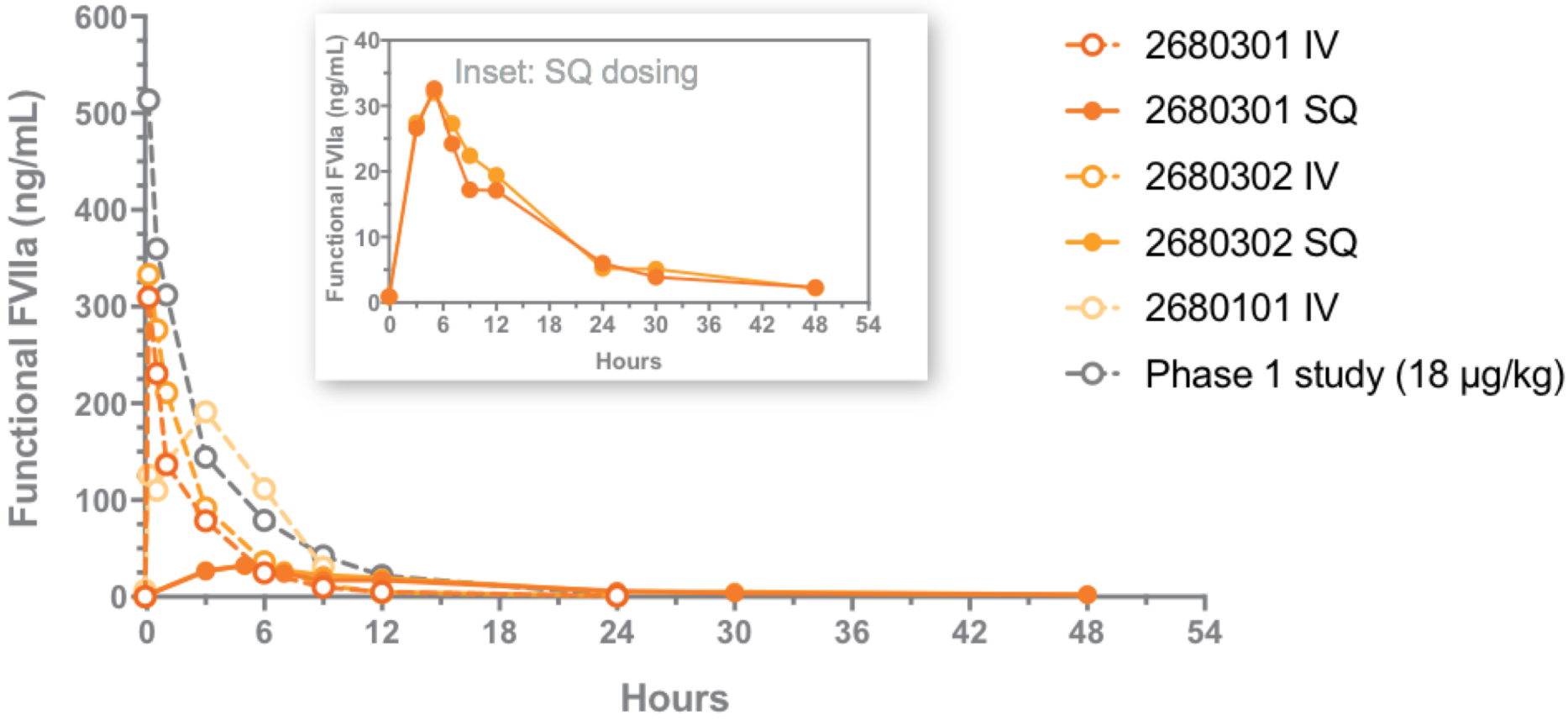
- 10 IU/mL unacceptable bleeding

+ 40 IU/mL “Satisfactory” control 6 patients had breakthrough bleeding (800 ng/mL NovoSeven ~100 ng/mL MarzAA) Ludlam et al 2003

+ Gene therapy in dogs:
  + No bleeding for a year at as low as 250 ng/mL FVIIa
  + *Equivalent to* ***~30 ng/mL MarzAA***



MarzAA PK IV 18 µg/kg then SQ 30 µg/kg

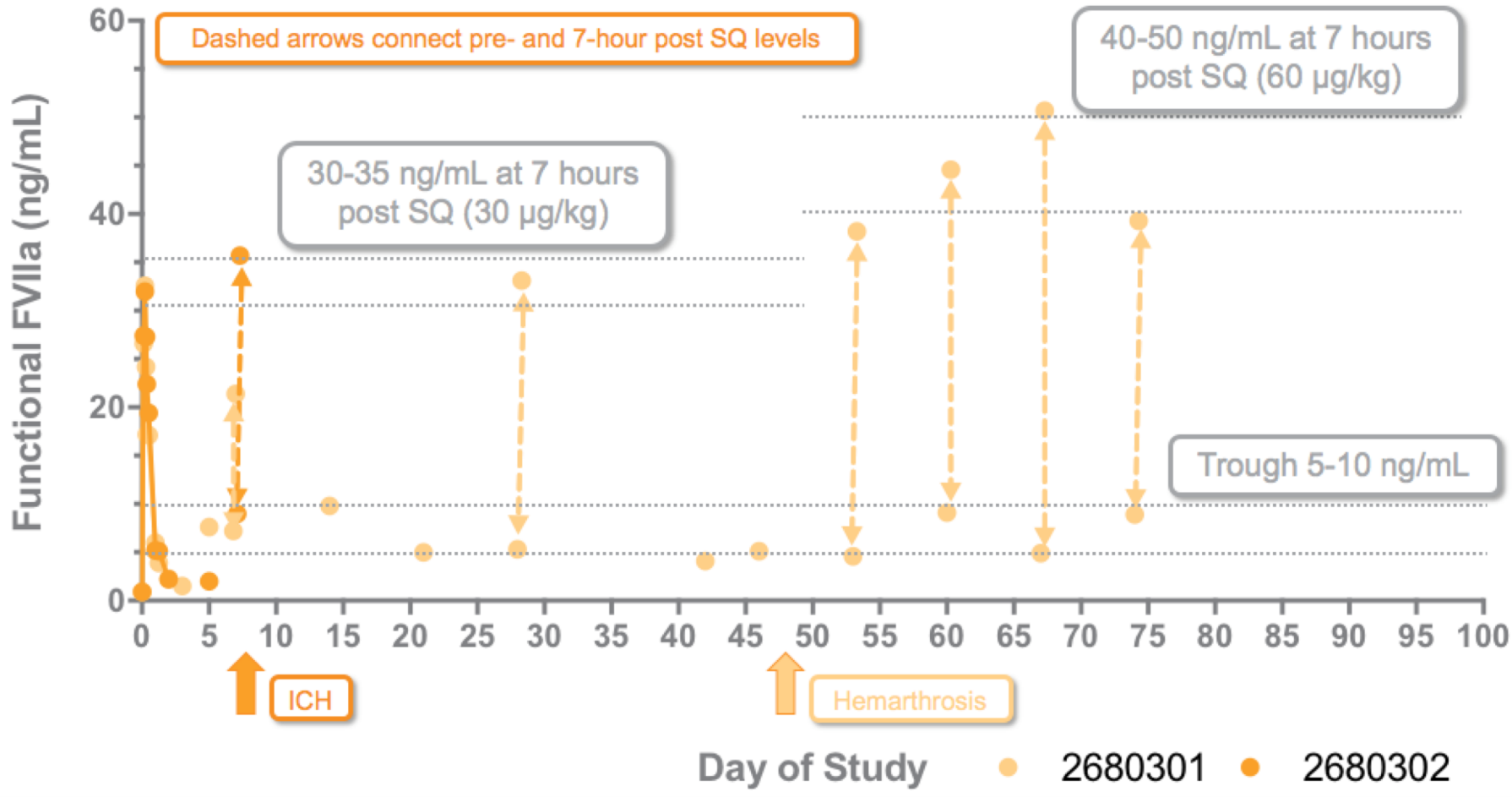


MarzAA PK: IV 18 µg/kg then SQ 30 µg/kg

Subject	Route	Cmax (ng/mL)	Tmax (hr)	Half-life alpha (hr)	Half-life beta (hr)	Mean Residence Time (hr)	$AUC_{0\text{-}inf}$ (ng/mL*hr)	$AUC_{0\text{-}t}$ (ng/mL*hr)	Bioavailability
2680301	IV	309.8	0.08	1.7	3.8	3.1	694	690	37.5%
	SQ	32.6	5	-	9.6	14.8	450	431	
2680302	IV	333.1	0.08	1.6	3.1	2.8	881	879	32.4%
	SQ	32.0	5	-	9.4	14.5	492	475	
2680101	IV	191.5	3	-	4.6	5.2	1212	1054	-
Phase 1*	IV	496.2	0.142	-	3.3	4.96	1557	1557	-

* Phase 1 study used a new drug manufacturer and a different analytic laboratory

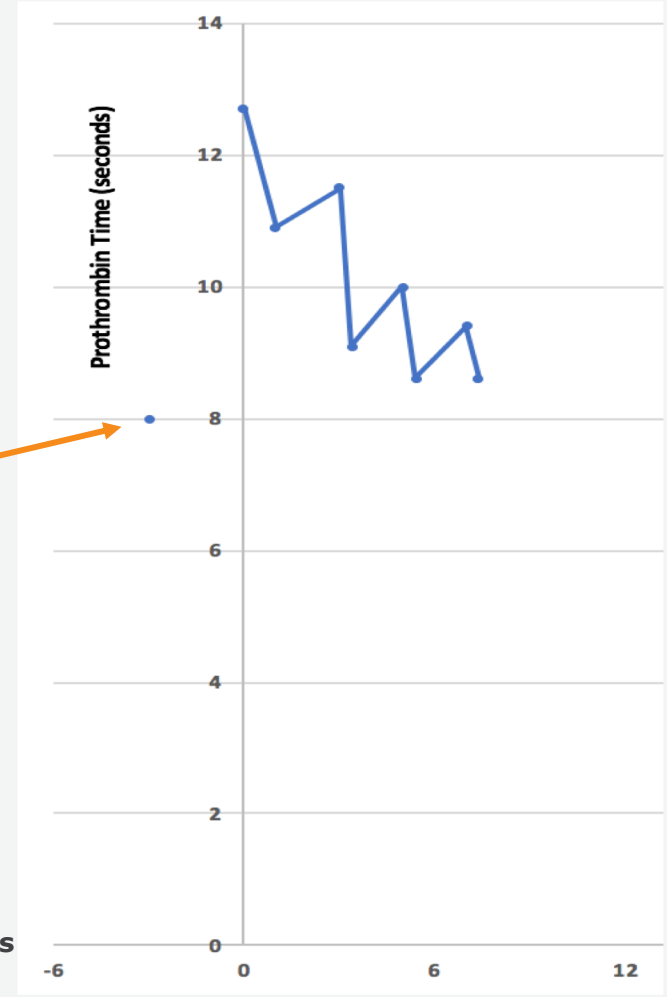
Functional MarzAA daily SQ 30 µg/kg



MarzAA daily SQ 30 µg/kg Prothrombin Time

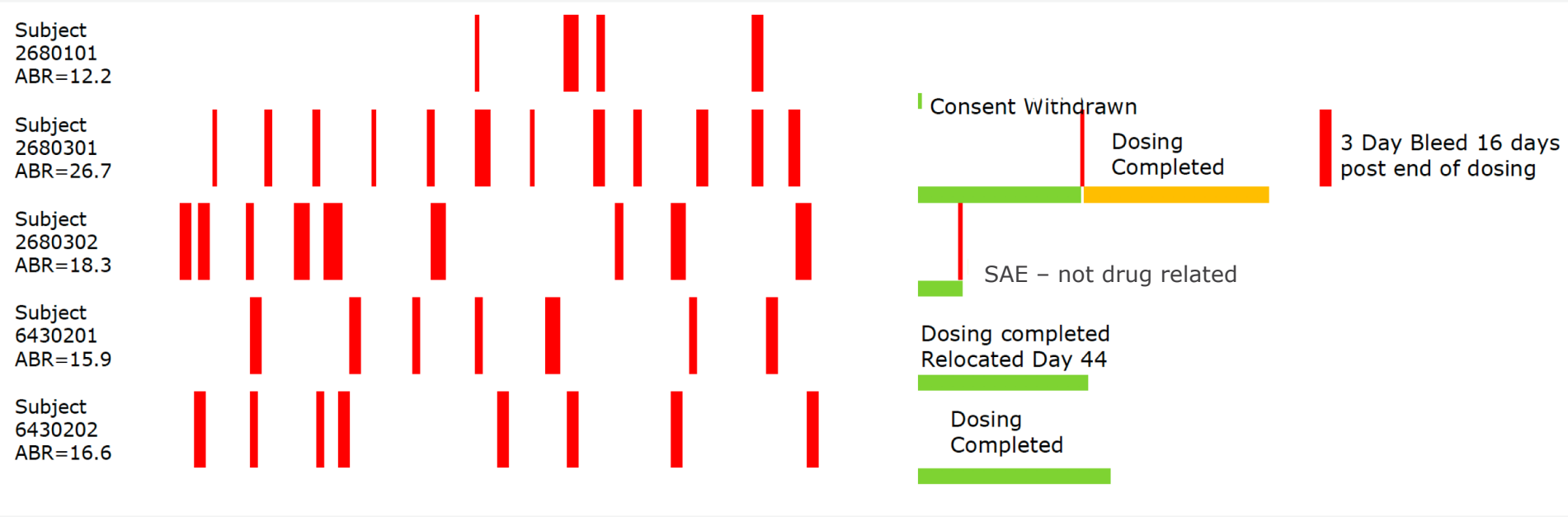
Reference range 9.4-12.5 seconds

IV dose 18 µg/kg



Bleeding History Prior to & During Treatment with MarzAA

MarzAA 30 µg/kg & 60 µg/kg



The width of the red line represents bleed duration: 1, 2 or 3 days
ABR = Annualized Bleed Rate

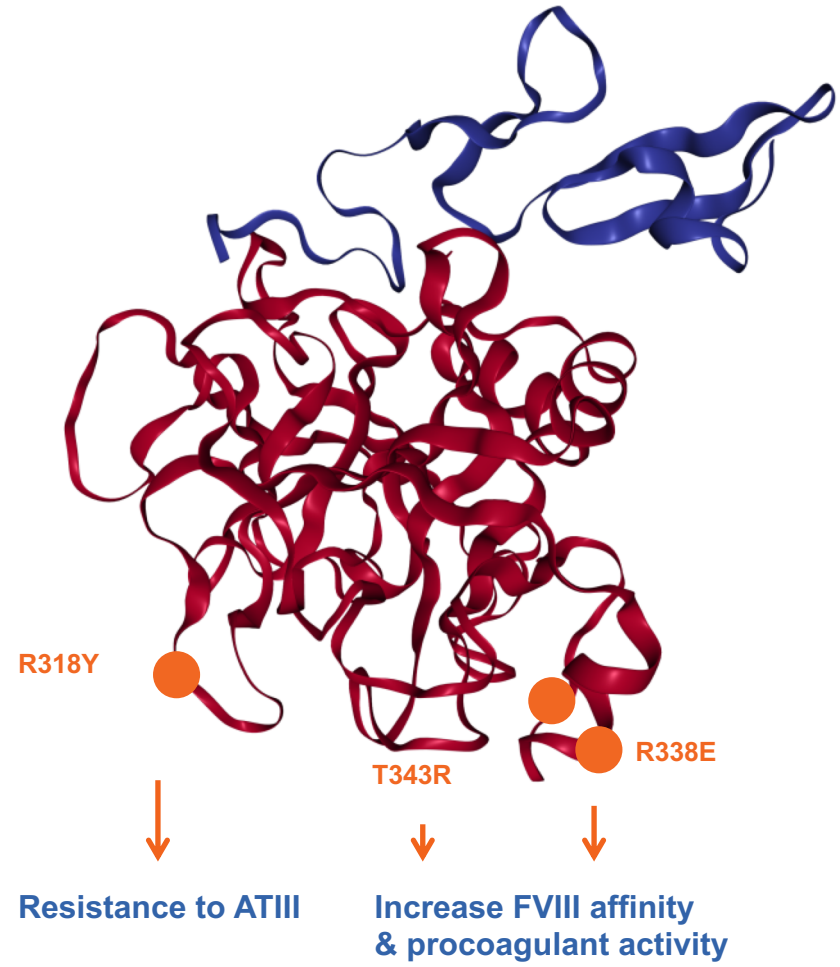
MarzAA program summary

- MarzAA was designed as a best-in-class high potency recombinant Factor VIIa
- 9-fold potency advantage *vs* NovoSeven allows subcutaneous administration
- SQ delivery significantly increases half-life 2.7-fold to 9.5 hours
- Daily SQ dosing of 30 µg/kg appears to be the appropriate initial dose

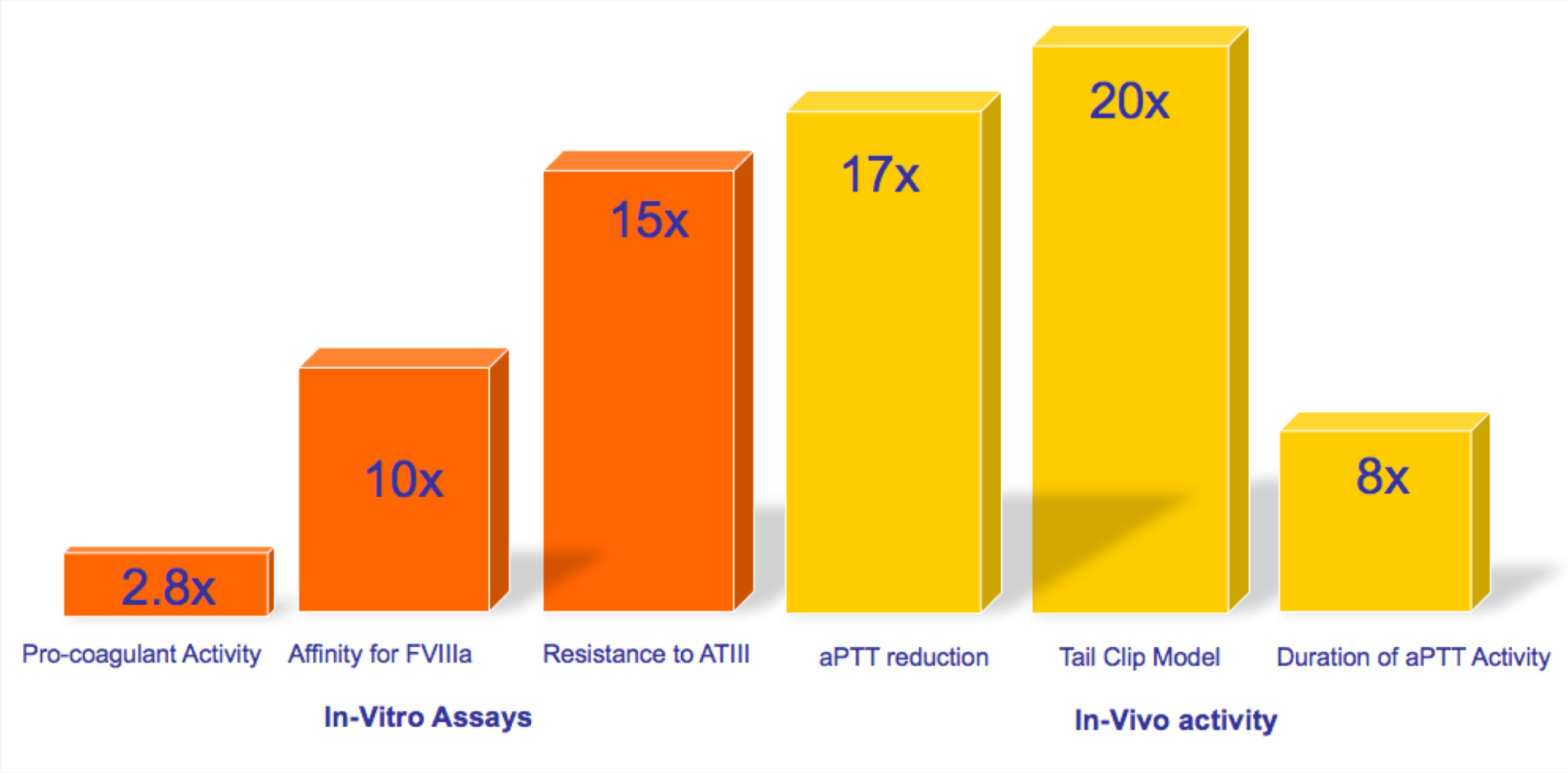
- Daily SQ dosing appears to result in significant bleeding reduction
  - >200 SQ doses administered without injection site reactions
  - No nAbs detected to date

FIX engineered variant & intellectual property

- **FIX: Dalcinonacog alfa [CB 2679d/ISU304]**
- 3 Engineered amino acid substitutions
- 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 - 22-fold more potent than BeneFIX® in man
- WW IP Granted and pending through 2031 without extensions
- Orphan Drug Designation in US & EU

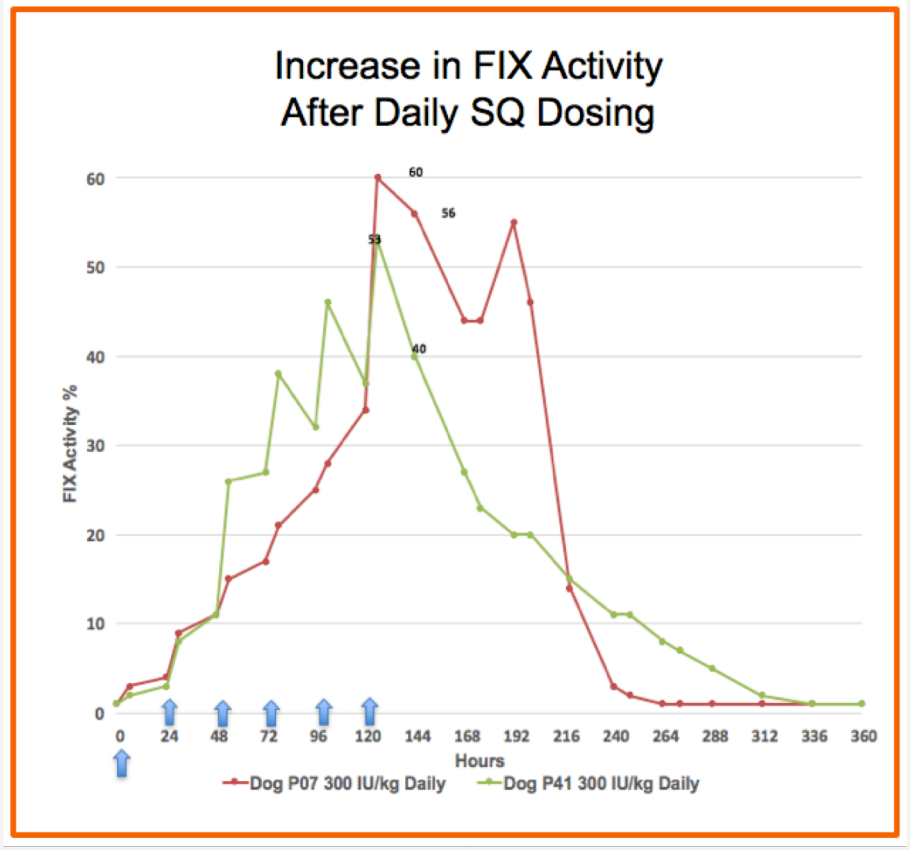


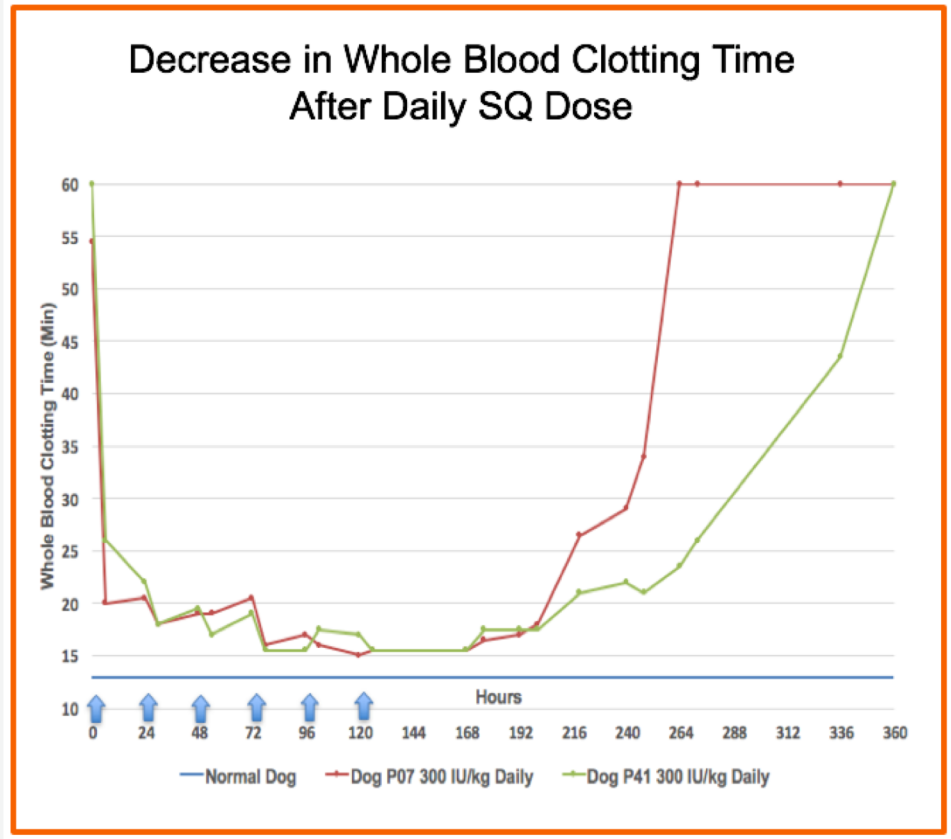
Dalcinonacog alfa Potency Advantage over wt-FIX



+ 20-fold increased potency of Dalcinonacog alfa over wild-type FIX in tail clip model

Normalization of FIX activity and WBCT with daily SQ Dalcinonacog alfa (300 IU/kg) in hemophilia B Dogs*





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

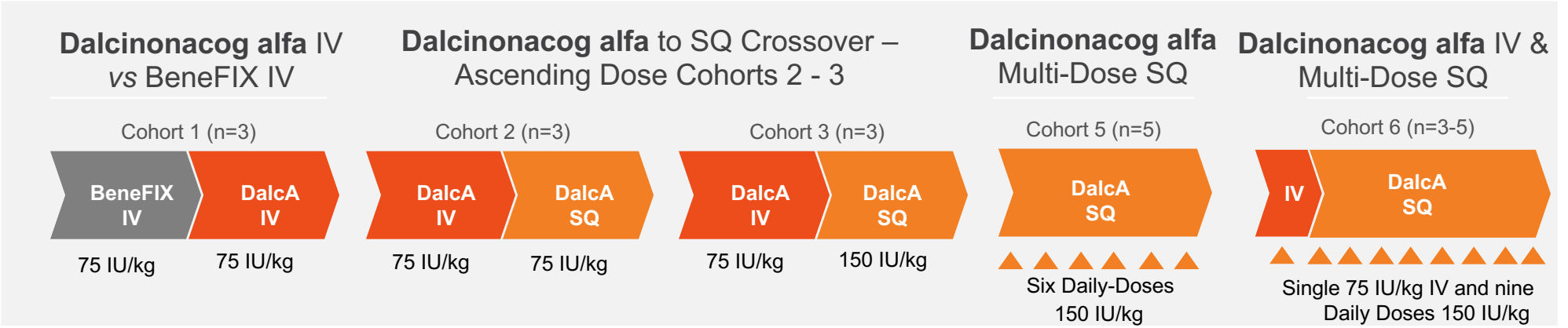
*Levy *et al*. EAHAD 2017 Haemophilia (2017), 23 (Suppl. 2), 29-140

Factor IX program: Dalcinonacog alfa

Nasdaq: CBIO

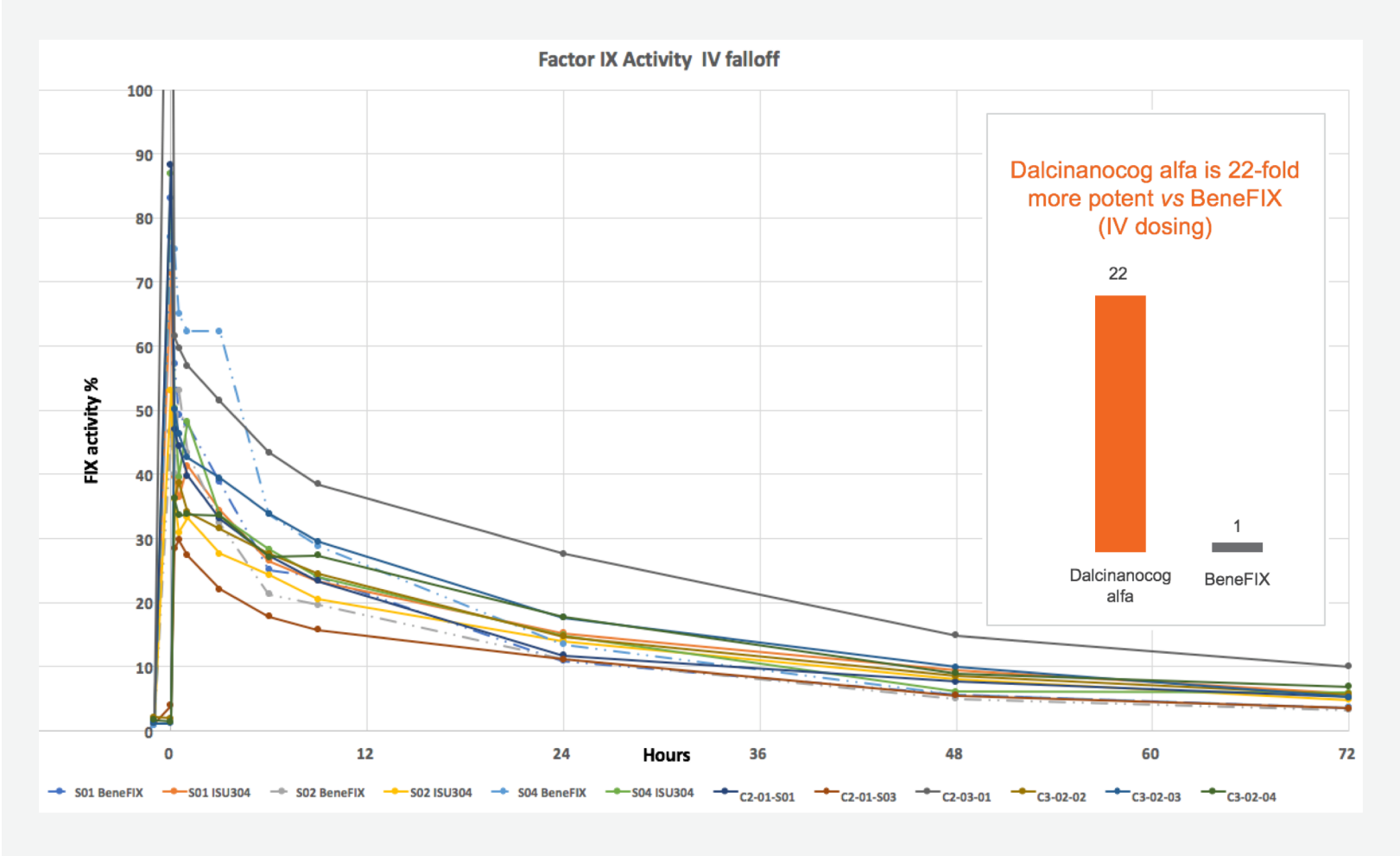
Phase 1/2 open label IV to SQ cross-over design

+ N = 11-14
+ Ascending dose Cohorts followed by Multi-dose SQ Cohorts
+ Cohorts 1-3 & 5 completed
+ **6 daily SQ doses corrects severe hemophilia to mild hemophilia with six daily doses**[1]
+ Well tolerated
+ Cohort 6, 2 subjects enrolled



[1]**You, Levy *et al*. EAHAD 2018**

Cohort 1, 2 & 3: IV BeneFIX & IV Dalcinonacog alfa 75 IU/kg



IV BeneFIX *vs* IV Dalcinonacog alfa PK 75 IU/kg

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
Dalcinonacog alfa	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
Mean ± SD

IV Dalcinonacog alfa has a significantly longer half-life and mean residence time than BeneFIX

Dalcinonacog alfa PK

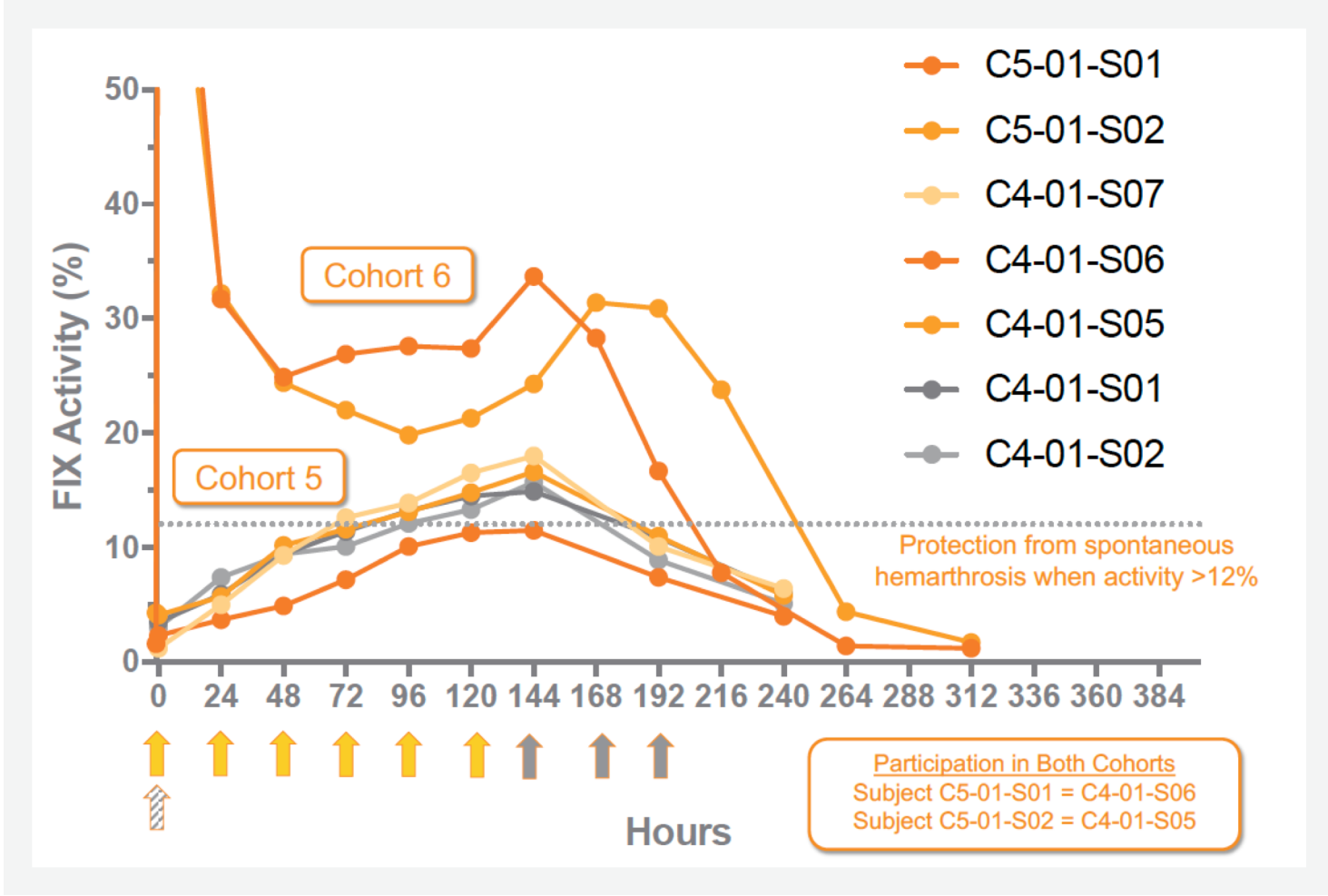
Route		t-half alpha (hrs)	t-half beta (hrs)	Tmax	AUC 0-t (mU/mL*hr)	Bioavailability
IV	Mean ± SD	9.4 ± 4.4	27.0 ± 2.2	16.7 ±11.3 mins	1026 ± 330	
	Median [25%-75%]	9.4 [6.4-13.2]	27.6 [26.4-29.2]	15 mins [5-30]	945 [780-1265]	
SQ	Mean ± SD	3.4 (n=1)	242.2 ± 365.5	29.0 ± 16.3 hrs	306 ± 148	19.8 ± 5.2%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

Cohort 2 & 3: PK activity profiles after IV and SQ Dalcinonocog alfa administration

SQ *vs* IV has 3.6-fold increase in half-life

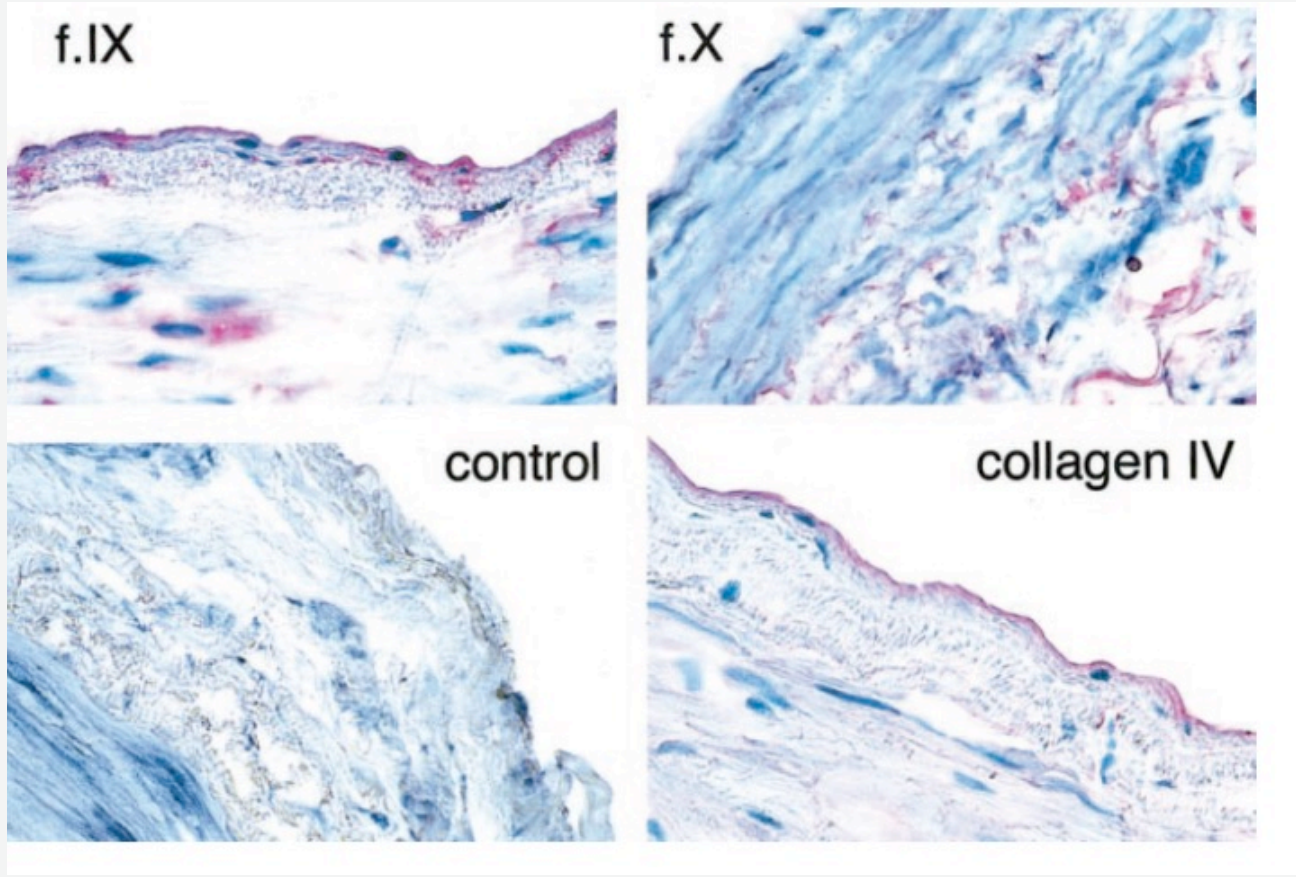
Cohort 5 & 6 FIX activity results

Collagen IV saturation may result in greater bioavailability and higher activity levels



Evidence for extravascular FIX binding to collagen IV

Red Staining shows FIX and Collagen IV



Gui et al, *Blood* 2002;100:153-158

Dalcinonacog alfa phase 1/2 safety

Mild injection site adverse events that resolved without sequelae were reported

- Pain
- Erythema
- Redness
- Tenderness
- Solidification
- Itching

One cohort 5 subject reported AEs of pain, erythema, redness as moderately severe for the first 2 injections and mild for 4 subsequent injections

Inhibitory antibodies, one transient, to Dalcinonacog alfa but not FIX were detected in 2 cousins, who were both in cohort 5 and cohort 6

Dalcinonacog alfa program summary

- Dalcinonacog alfa was designed as a best-in-class high potency recombinant Factor IX
- 22-fold potency advantage *vs* BeneFIX allows subcutaneous administration
- SQ delivery significantly increases half-life 2.3-fold to 63.2 hours
- Daily SQ dosing of 150 IU/kg for 6 days resulted in median 15.7% FIX
- Daily SQ dosing of 150 IU/kg for 9 days following an IV loading dose resulted in median >30% FIX
  - nAbs detected, one transient
  - Does not cross react with wt FIX
  - Analysis ongoing
- Decreased dosing frequency is feasible once target activity level achieved
- Phase 2b study will explore longer-term dosing

Subcutaneous factor delivery

Disruptive approach for factor delivery

Subcutaneous Prophylactic dosing designed to be less painful and much more convenient, especially for children

Stable & high clotting activity could dramatically reduce spontaneous bleeding and improve quality of life

FIX: Dalcinonacog alfa

Confirmed 22-fold potency advantage *vs* BeneFIX

>30% activity levels seen in multiple dose cohorts with daily dosing

- nAb cause under investigation

Potential to maintain FIX activity in the mild hemophilia range with less frequent dosing to be explored in Phase 2b

FVIIa: Marzeptacog alfa (activated)

Phase 2 of a Phase 2/3 program enrolling

No ADA or nAb observed to date

Interim Phase 2 Data presented at ISTH

PoC for reduction in ABR demonstrated

Thank you

CATALYST BIOSCIENCES