A Tale of Two Subcutaneous Engineered Coagulation Factors

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CATALYST BIOSCIENCES

The Catalyst Biosciences subcutaneous solution

Nasdaq: CBIO

Our highly potent candidates:

+ Quick & simple SQ injection
+ Self-administered
+ Ideal for pediatric patients
+ Achieve higher & more stable factor levels
+ Continuously at protective levels

Subcutaneous pharmacokinetics are complex

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 may be slow with Tmax up to 8 days in humans
  - Large proteins (>20 kDa) are mainly transported by Lymphatics
  - Transport in the Lymphatics is unlikely to be the rate-limiting step for the slow absorption after SQ injection

Subcutaneous pharmacokinetics are complex

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
+ Competition for binding sites with CRIM positive FIX

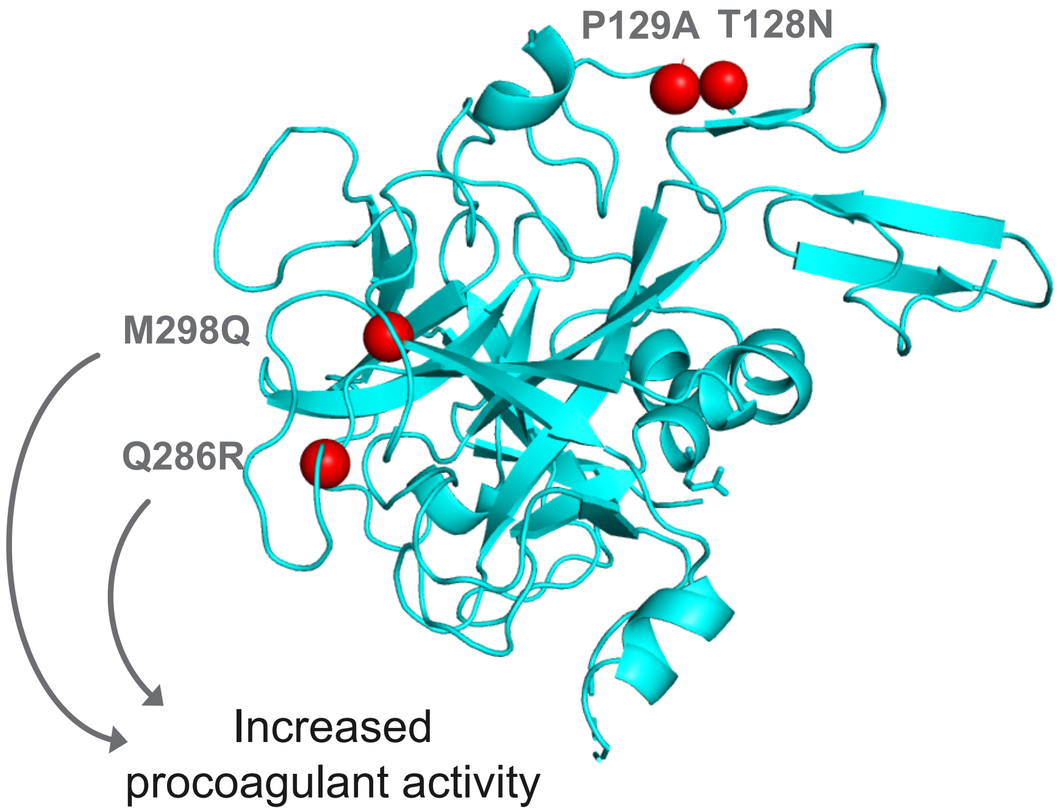
FVIIa subcutaneous pharmacokinetics

+ Rapid absorption from compared with FIX

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

Marzeptacog alfa (activated): MarzAA rFVIIa

SQ prophylaxis and SQ treatment of a bleed are clear unmet needs in hemophilia and other bleeding disorders



- Four engineered amino acid substitutions within the FVIIa protein
- 9-fold more potent catalytic activity than NovoSeven RT
- **Allows subcutaneous dosing**
- Half-life prolonged when using subcutaneous dosing

Orphan Drug Designation in the US and EU

Subcutaneous Prophylaxis: Hemophilia A or B with inhibitors

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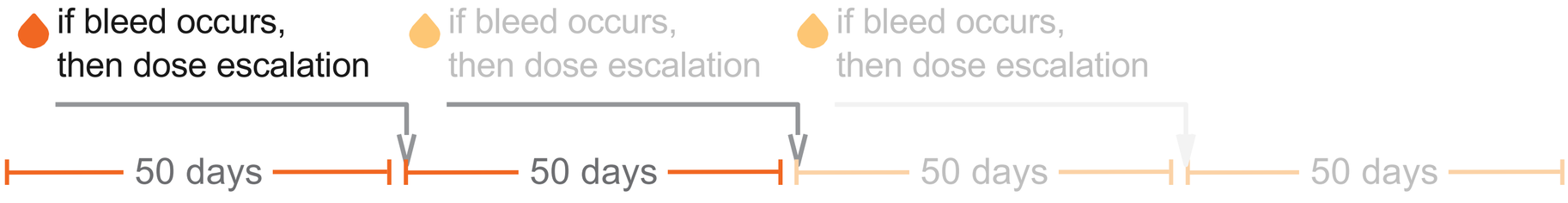
MarzAA phase 2/3 SQ clinical trial MAA-201 design

Nasdaq: CBIO

MarzAA IV
18 µg/kg
PK 24 hours

MarzAA SQ
30 µg/kg
PK 48 hours



Daily MarzAA SQ
30 µg/kg

Daily MarzAA SQ
60 µg/kg

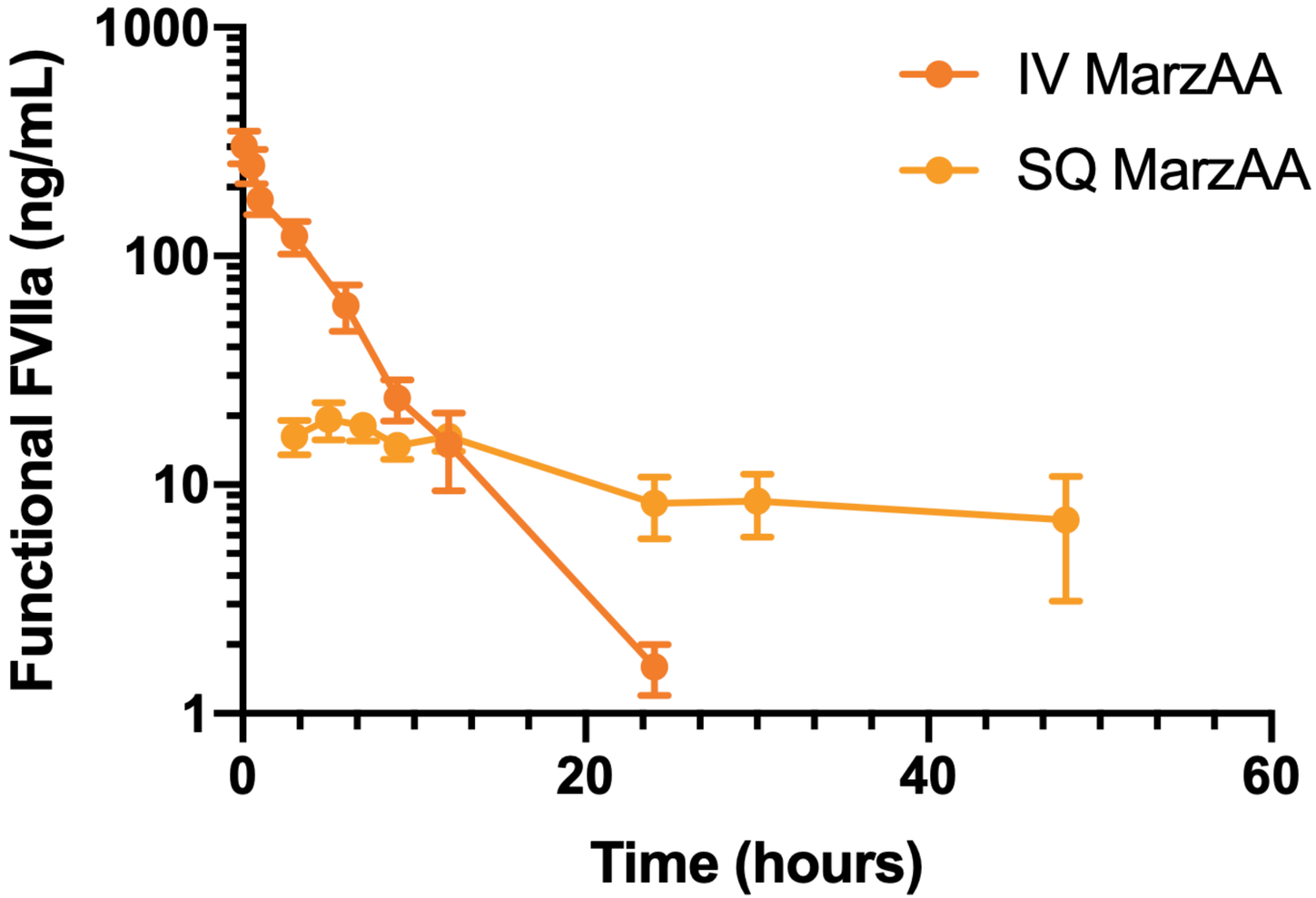
Daily MarzAA SQ
90 µg/kg

Daily MarzAA SQ
120 µg/kg

Endpoint achieved if ABR decreases from ≥12 to ≤6

+ Patients with documented annual bleeding rate (ABR) >12
+ Open label SQ study with individual dose escalation if needed in Hemophilia A or B with inhibitors
+ Primary endpoint: reduction in annualized bleed rate **at final dose level**
+ Secondary endpoints: safety and tolerability, inhibitor formation

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



+ IV half-life of 3.65 hours
+ SQ half-life of 17 hours
+ **Stable levels after SQ dosing for 48 hours without high peak after IV dosing**

MarzAA SQ PK demonstrates prolonged half-life

SQ half-life increased to 17.0 hours from an IV half-life of 3.65 hours

Route	Half-life alpha (hr)	Half-life beta (hr)	Mean Residence Time (hr)	Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng/mL*hr)	AUC_{0-inf} (ng/mL*hr)	Bioavailability
IV Mean ± SEM	1.47 ± 0.29	3.65 ± 0.23	4.05 ± 0.39	375 ± 54	0.5 ± 0.4	1076 ± 97	1102 ± 101	27 ± 6%
SQ Mean ± SEM		**17.0 ± 3.1**	25.8 ± 4.5	24 ± 4.5	7 ± 0.8	473 ± 132	609 ± 190	

MarzAA: Robust reduction in annualized bleed rate (ABR)

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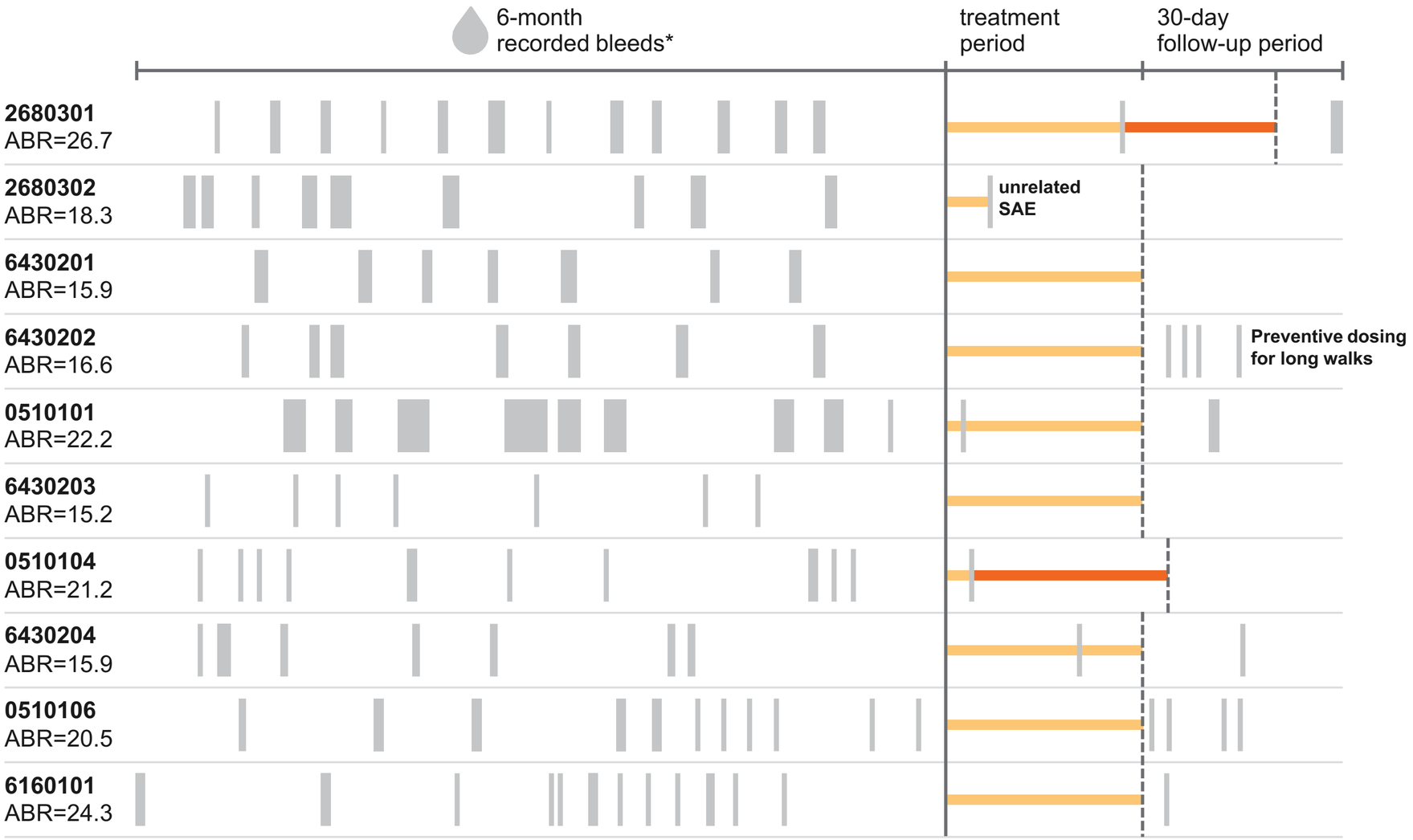

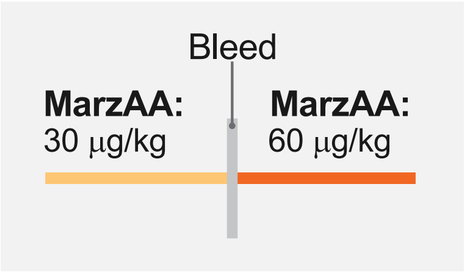

*The width of each grey bar represents bleed duration: 1 to 9 days

Significant reduction in Proportion of Days with Bleeding (PDB)

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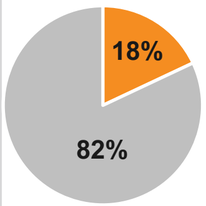
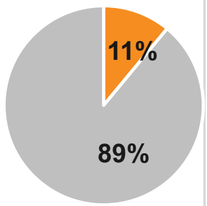
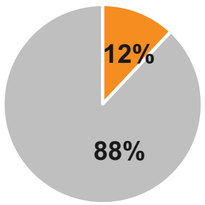
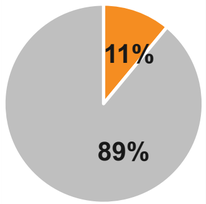
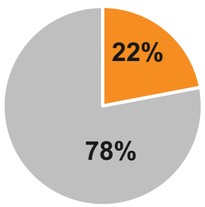
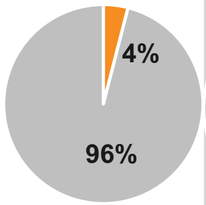
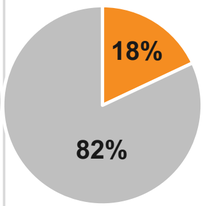
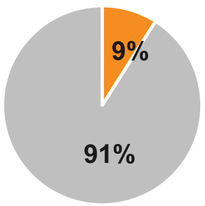
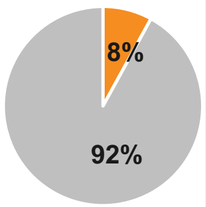
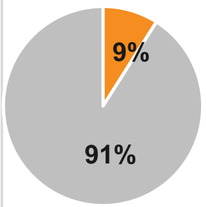
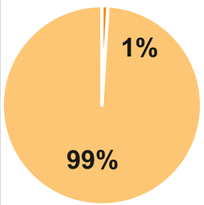
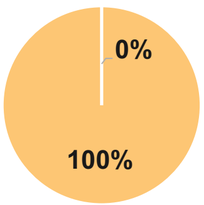
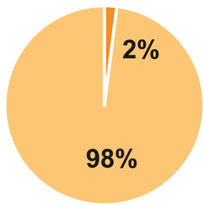
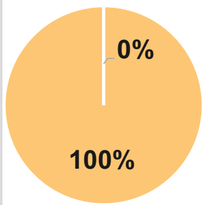
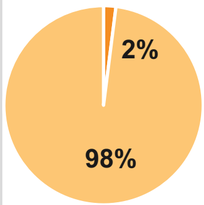
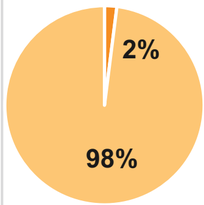
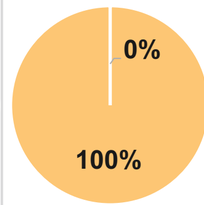
Median Proportion of Days with Bleeding reduced to zero

Subject	2680301	2680302	6430201	6430202	0510101	6430203	0510104	6430204	0510106	6160101
Pre-treatment										
On-treatment		Unrelated SAE								

Orange denotes the Proportion of Days with Bleeding during period of observation

+ Average **pre-treatment** proportion of days of bleeding was **12.3%** (SD 5.8%) [median = 11.0%]
+ Average **on-treatment** proportion was reduced to **0.8%** (SD 0.9%) [median 0%]
+ Analysis of these pairwise differences by Wilcoxon signed-rank test has p=0.009 for 93.8% reduction

Marzeptacog alfa (activated) Phase 2: Clinical efficacy

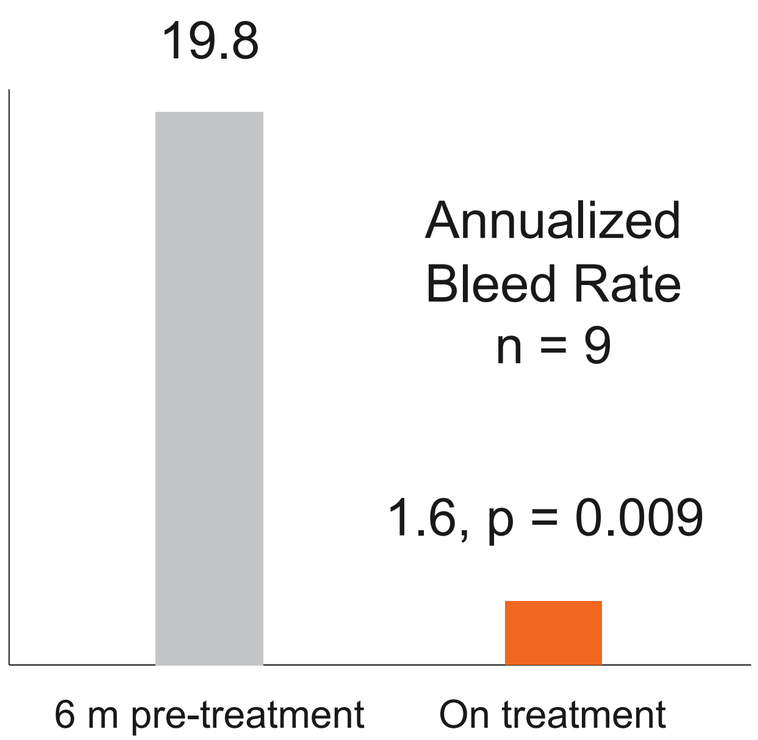
Nasdaq: CBIO

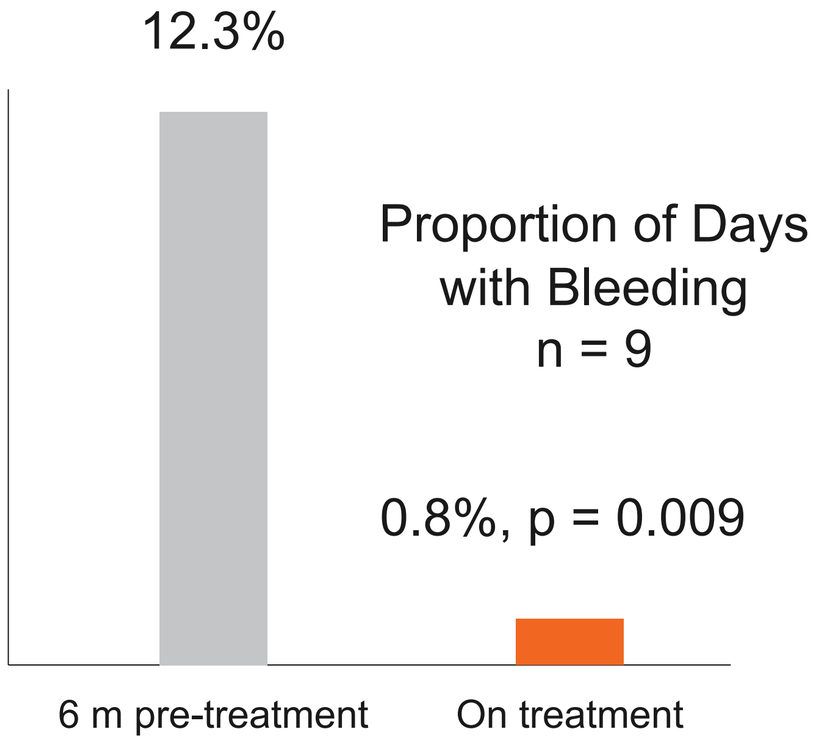
7 of 9 subjects had no bleeding (spontaneous or traumatic) at final dose level

Greater than 90% reduction in all bleeding; Median ABR zero; Median bleeding days zero

Mean Annualized Bleeding Rates (ABR) significantly reduced from 19.8 to 1.6

Mean Proportion of Days with Bleeding (PDB) significantly reduced from 12.3% to 0.8%





MAA-201 safety

Safe & well tolerated

No anti-drug antibodies were detected

- One fatal unrelated SAE: intracerebral hemorrhage due to untreated hypertension
- 517 SQ injections were administered
  - 6 injection site reactions in 2 subjects
    - 1 moderate swelling that resolved without sequelae in one subject
    - 2 mild and 3 moderate redness that resolved without sequelae in the other subject and did not occur with subsequent SQ injections

The Potential for Subcutaneous Treatment of a Bleed

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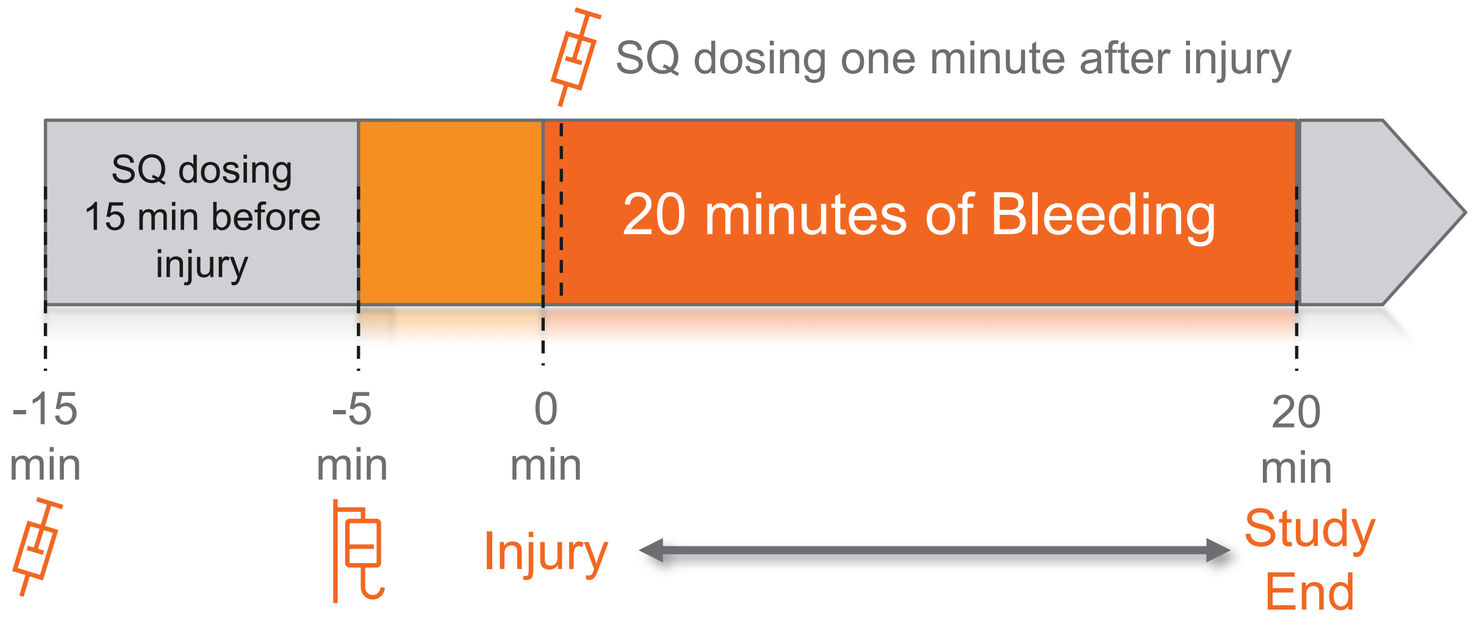
Preclinical evaluation of bleeding in hemophilia mice

Acute injury model with SQ dosing *after* the injury



Acute injury model with SQ dosing *prior* to injury

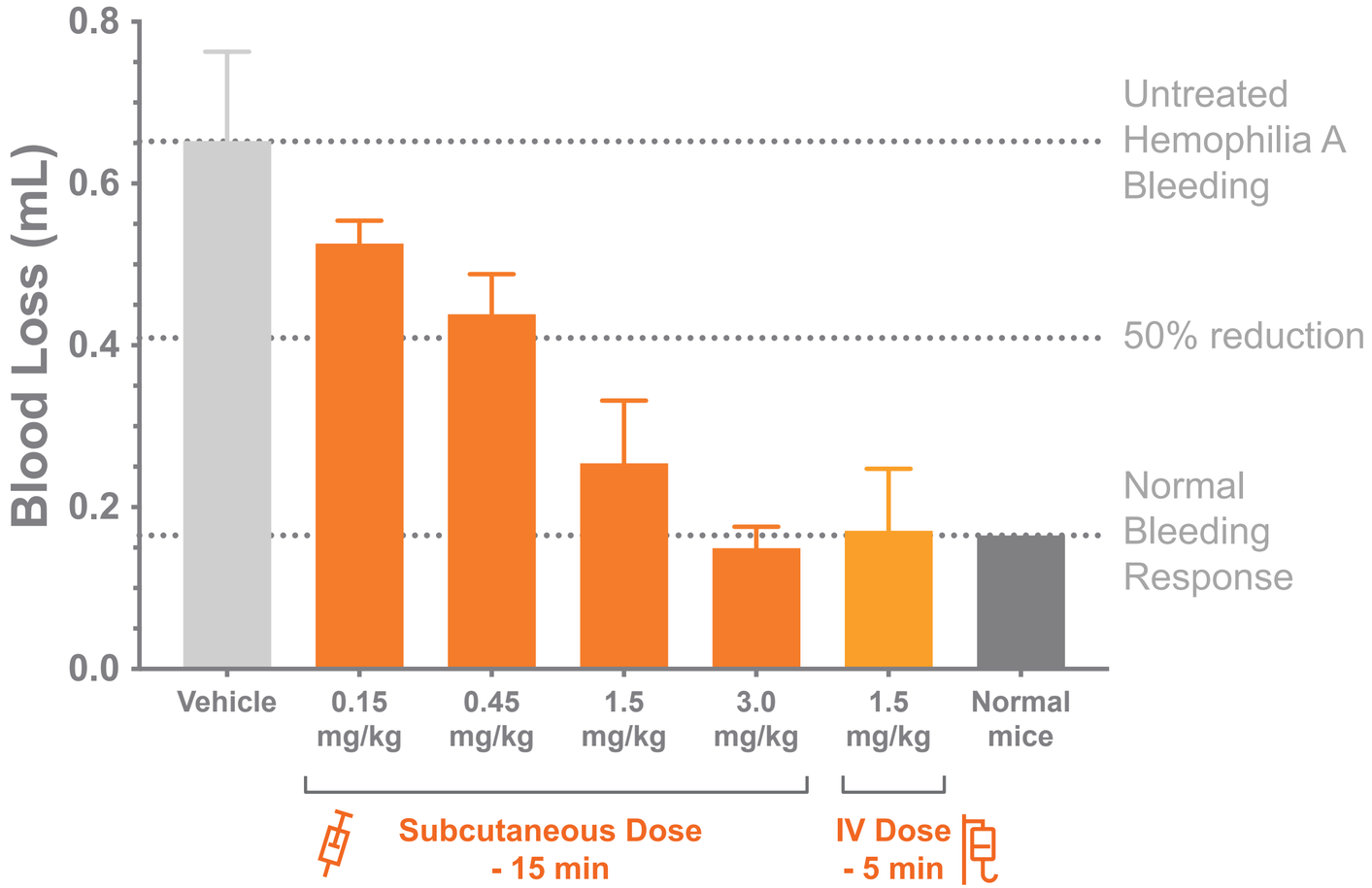
Preclinical hemophilia A mouse model

+ **Standardized** bleeding models are used to evaluate efficacy of hemostatic agents
+ Represents a **traumatic** injury
+ The **standard acute injury model** is IV treatment of the agent 5 min prior to injury to the tail that induces bleeding
+ **Two approaches** to evaluate SQ MarzAA in a hemophilia A mouse model
  + **SQ treatment *prior* to injury**
  + **SQ treatment *after* injury**

Fast onset of action for SQ MarzAA in Hemophilia A mice

Nasdaq: CBIO

Acute mouse injury model with dosing *prior* to injury



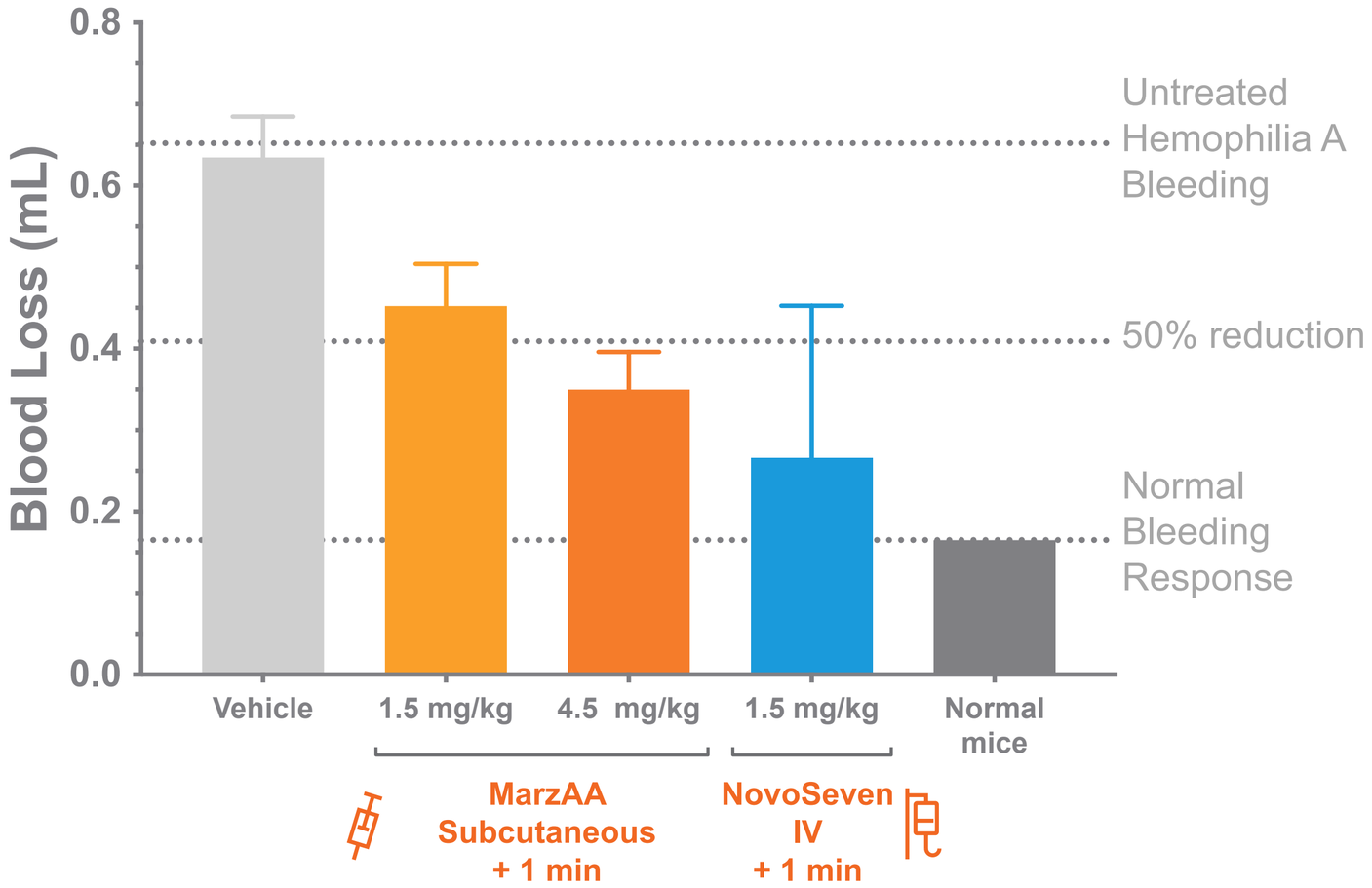
SQ MarzAA normalizes bleeding

+ **SQ treatment** of MarzAA 15 min prior to injury normalizes bleeding
+ Normalization of bleeding demonstrated at comparable SQ and IV doses
+ Clear **dose dependent** effect
+ **Fast onset of action**
+ These doses translate to the **range of doses** (μg/kg) being explored in clinical trials

SQ MarzAA reduces bleeding when dosed *After* the Injury

Nasdaq: CBIO

Acute mouse injury model with dosing *after* the injury

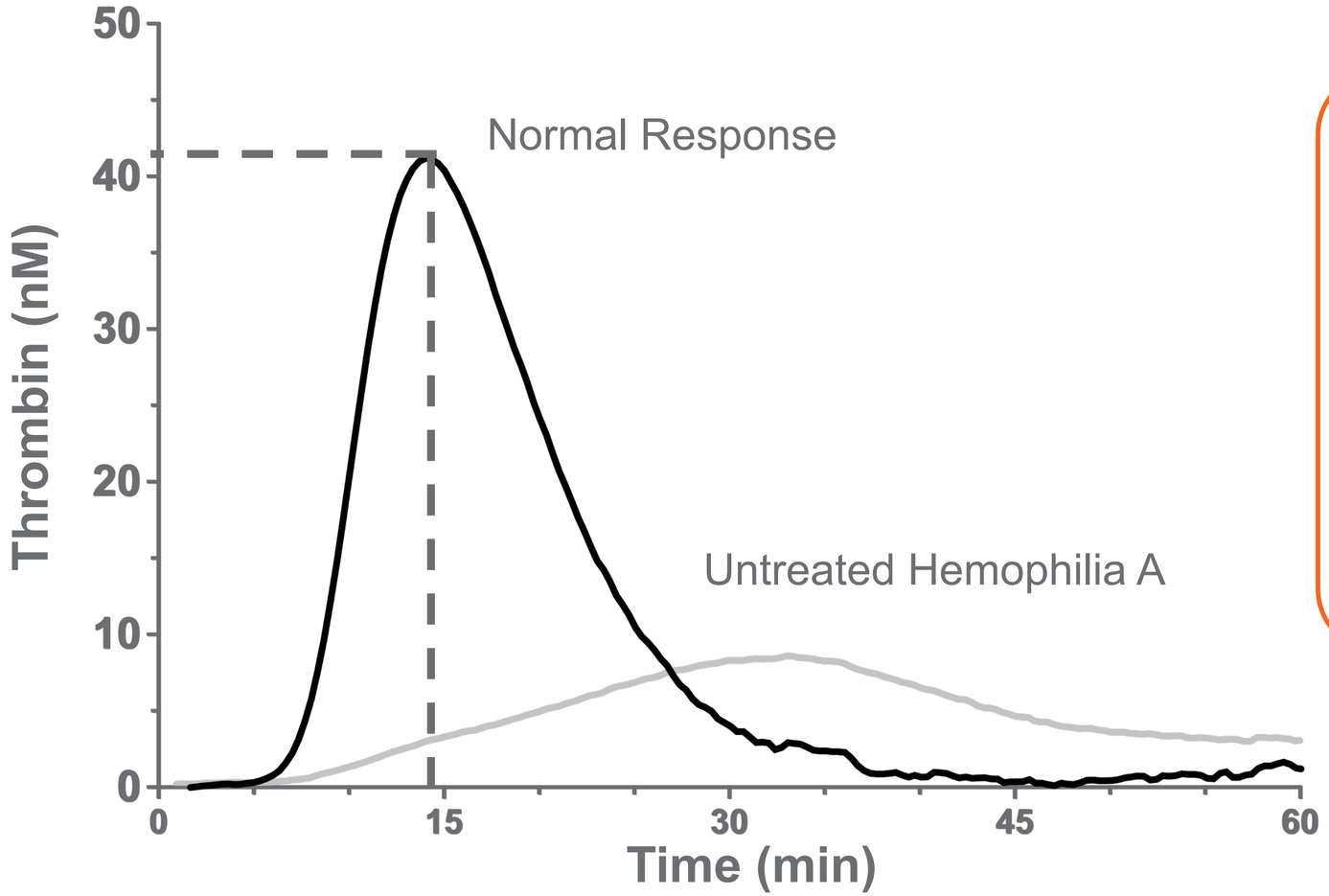


Reduced bleeding *After* Injury

+ Hemophilic mice bleed **considerably more** than normal mice
+ **SQ treatment** of MarzAA one min after traumatic bleeding has started significantly **reduces blood loss** and **stops the bleed**
+ The effect is **dose dependent**
+ Reduction in blood loss **is similar to IV NovoSeven**

Thrombogenicity risk can be evaluated *in vitro*

The thrombin generation assay is an effective model of coagulation



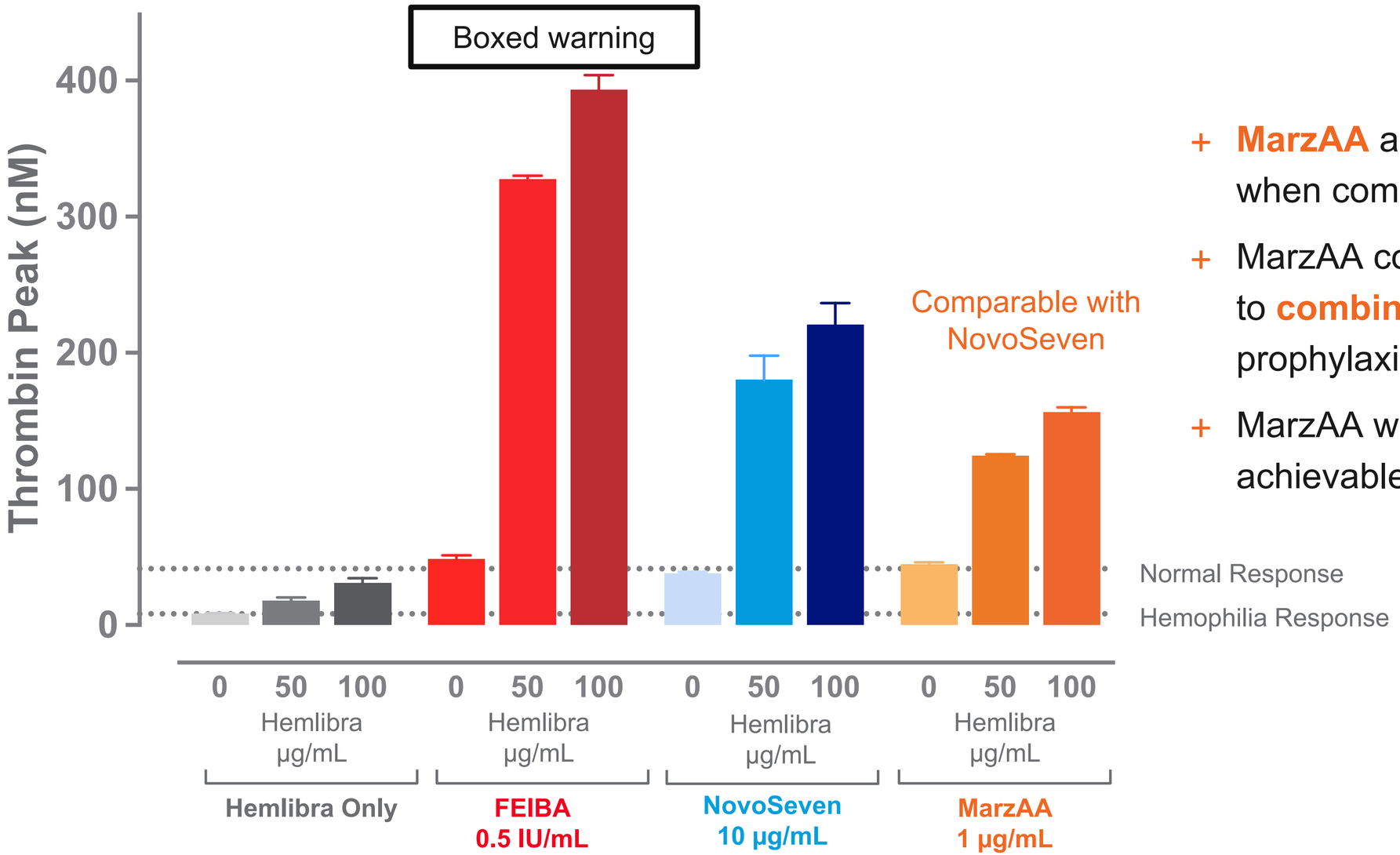
Thrombin Generation Assay

- ✓ Standard assay
- ✓ Highly accepted
- ✓ Representative of *in vivo* coagulation

Potential to treat break through bleeds in patients on Hemlibra

Nasdaq: CBIO

MarzAA has a preferred coagulation profile that is similar to NovoSeven



+ **MarzAA** and **NovoSeven** behave similarly when combined **with Hemlibra**
+ MarzAA could allow hemophilia A patients to **combine two SQ therapies** - "sports prophylaxis" or treat breakthrough bleeds
+ MarzAA works well at plasma levels achievable with SQ dosing

Data supports SQ MarzAA for treatment of a bleed

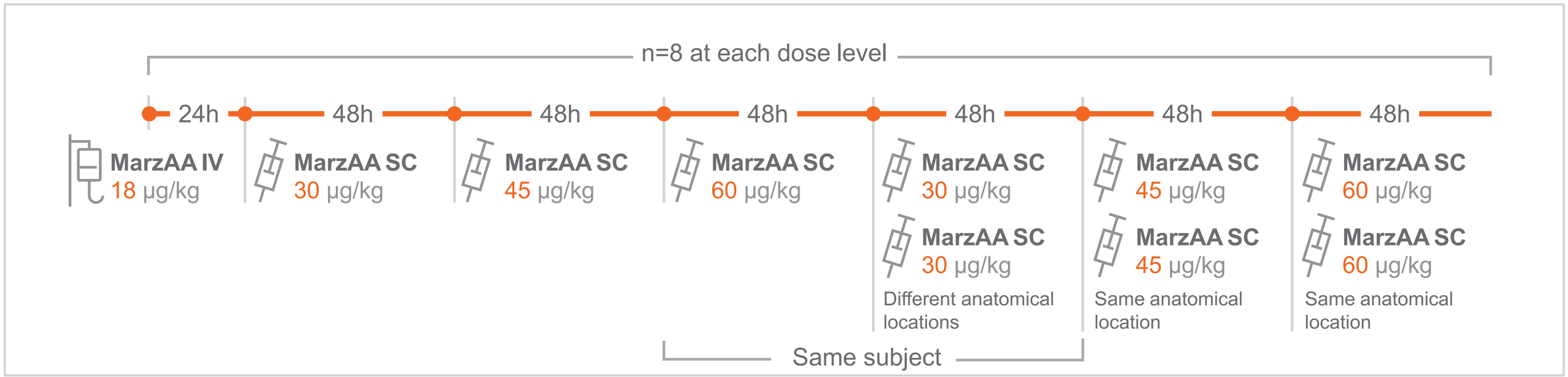
SQ MarzAA rapidly reaches therapeutic concentrations in humans

SQ MarzAA reduces bleeding *before* and *after* an injury in preclinical models

Thrombin generation for MarzAA + Hemlibra is similar to NovoSeven + Hemlibra *in vitro*

MAA-102 Study Design

IPK assessment of intravenous (IV) and subcutaneous (SC) MarzAA



Primary:

+ Evaluate the pharmacokinetics (PK) of ascending subcutaneous (SC) doses of MarzAA

Secondary:

+ Determine if PK behaves in a dose proportional manner
+ Determine whether a split injection provides the same PK as a single injection
+ Determine the pharmacodynamics (PD) of SC MarzAA
+ Evaluate the safety of SC MarzAA

Marzeptacog alfa (activated) program

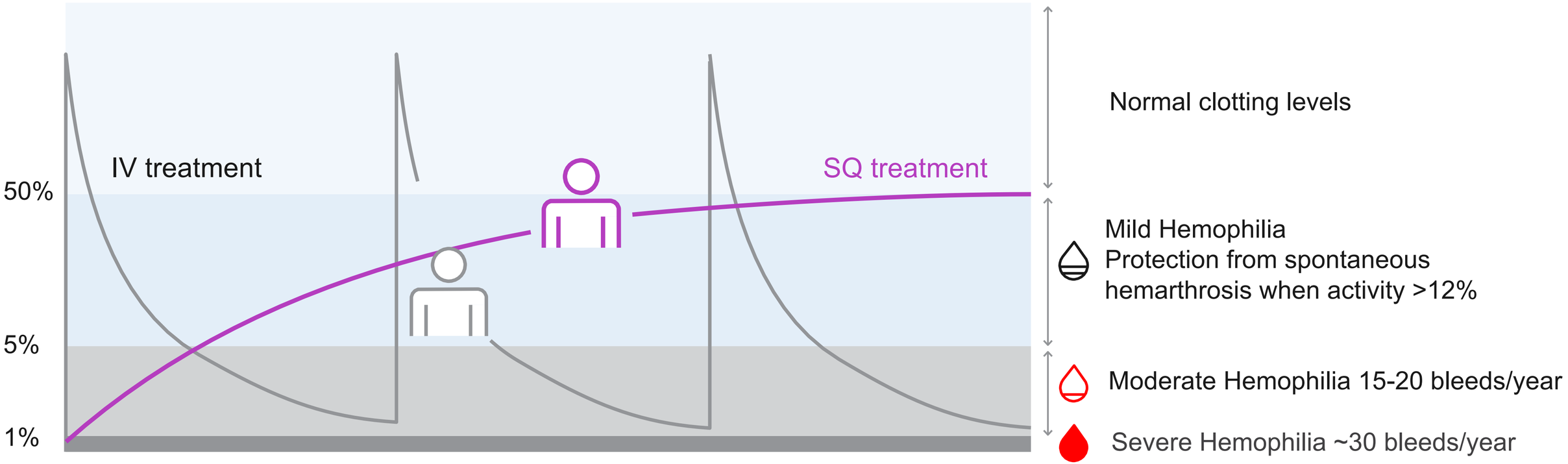
Moving forward in clinical development to address key unmet needs

- Robust SQ prophylaxis clinical efficacy demonstrated
- Safe and well tolerated
- No anti-drug antibodies detected
- Pivotal trial guidance obtained from EMA & MHRA
- PK study initiated to assess range of clinical doses
- Exploring the use of SQ MarzAA in treatment of a bleed
- Preparing for End of Phase 2 meeting 4Q 2019
- Moving forward with Phase 3 study planning

The new standard in hemophilia B prophylaxis

Nasdaq: CBIO

Patients in high mild range are protected from spontaneous bleeds



- Our concept of prophylactic treatment is to keep severe & moderate hemophilia patients in the high mild range
- Subcutaneous factor treatments build up over time, offering long-term stability in clotting levels

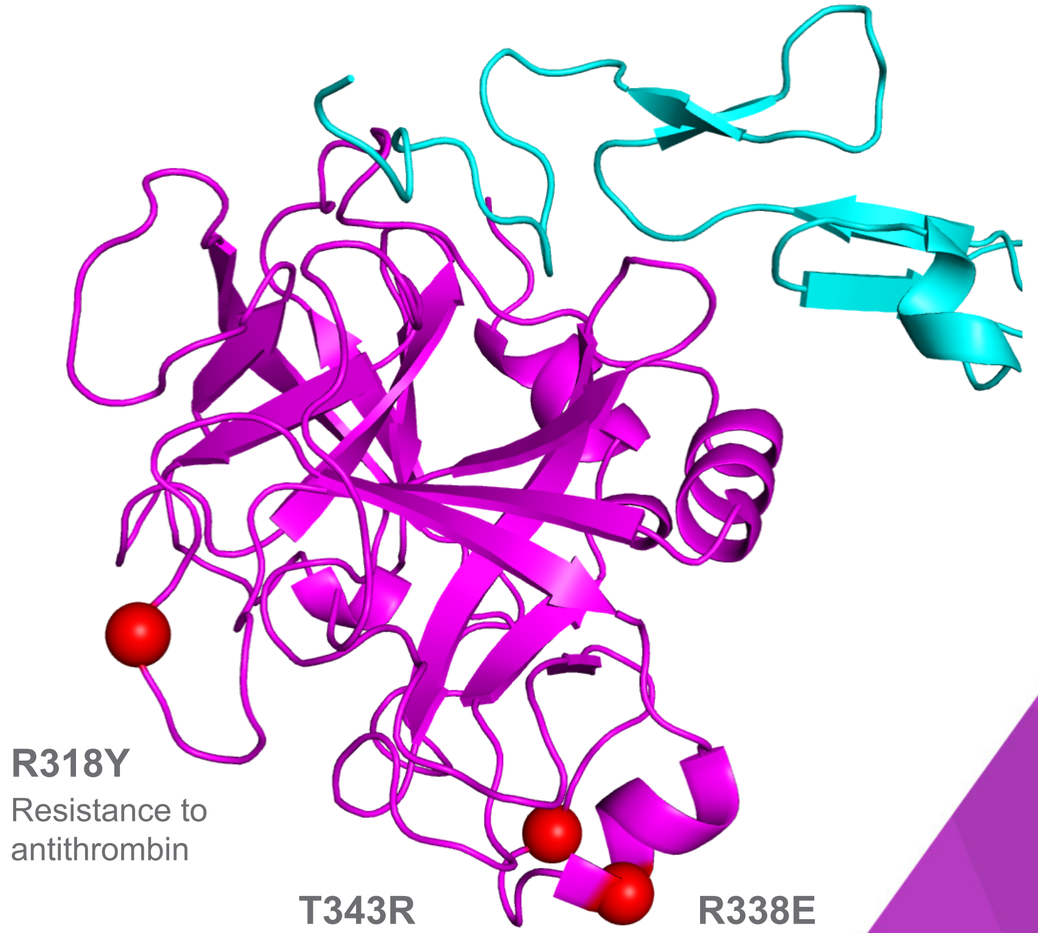
Dalcinonacog alfa – DalcA

Novel clinical stage SQ FIX product candidate differentiated from IV market leaders

Phase 1/2 completed

+ 22-fold more potent than BeneFIX in man
+ **Allows subcutaneous dosing**
+ Half-life prolonged when using subcutaneous dosing
+ Maintains continuous protective FIX activity levels of 12 – 30%
+ Disruptive to all intravenous products

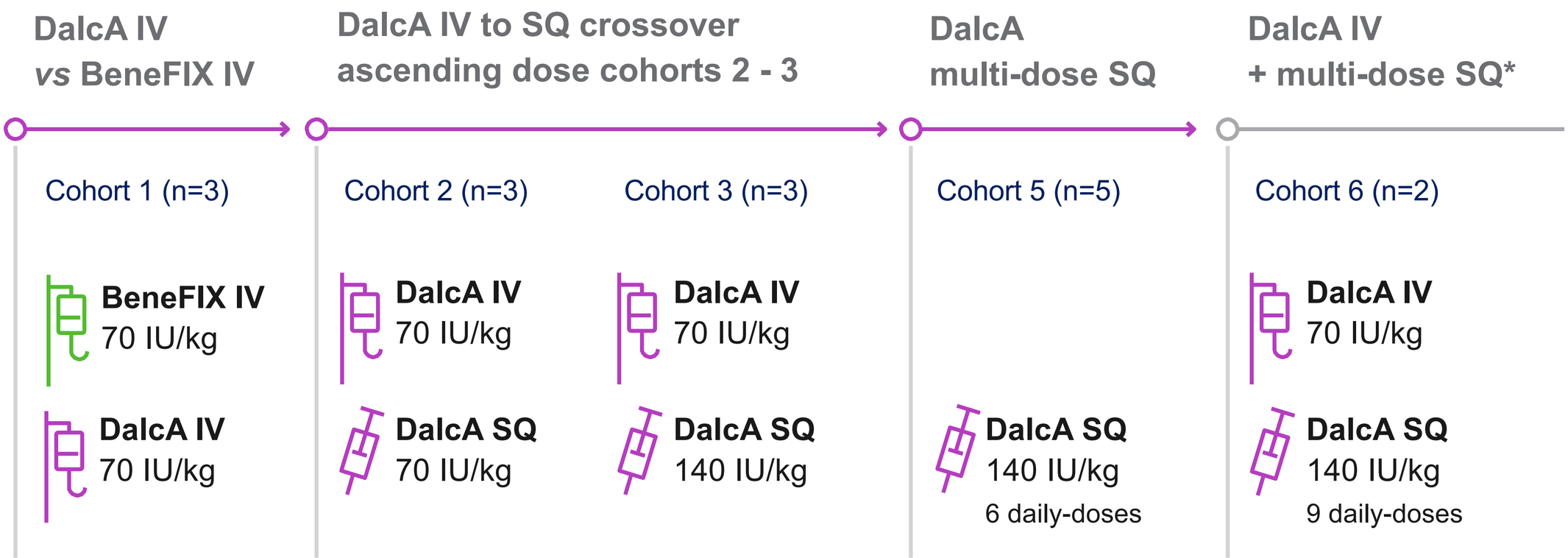
Orphan Drug Designation in US & EU



Dalcinonacog phase 1/2 open label design

Nasdaq: CBIO

Hemophilia B FIX



*First SQ dose 30 min post-IV

SQ DalcA PK increases half-life by 3.6 fold over IV

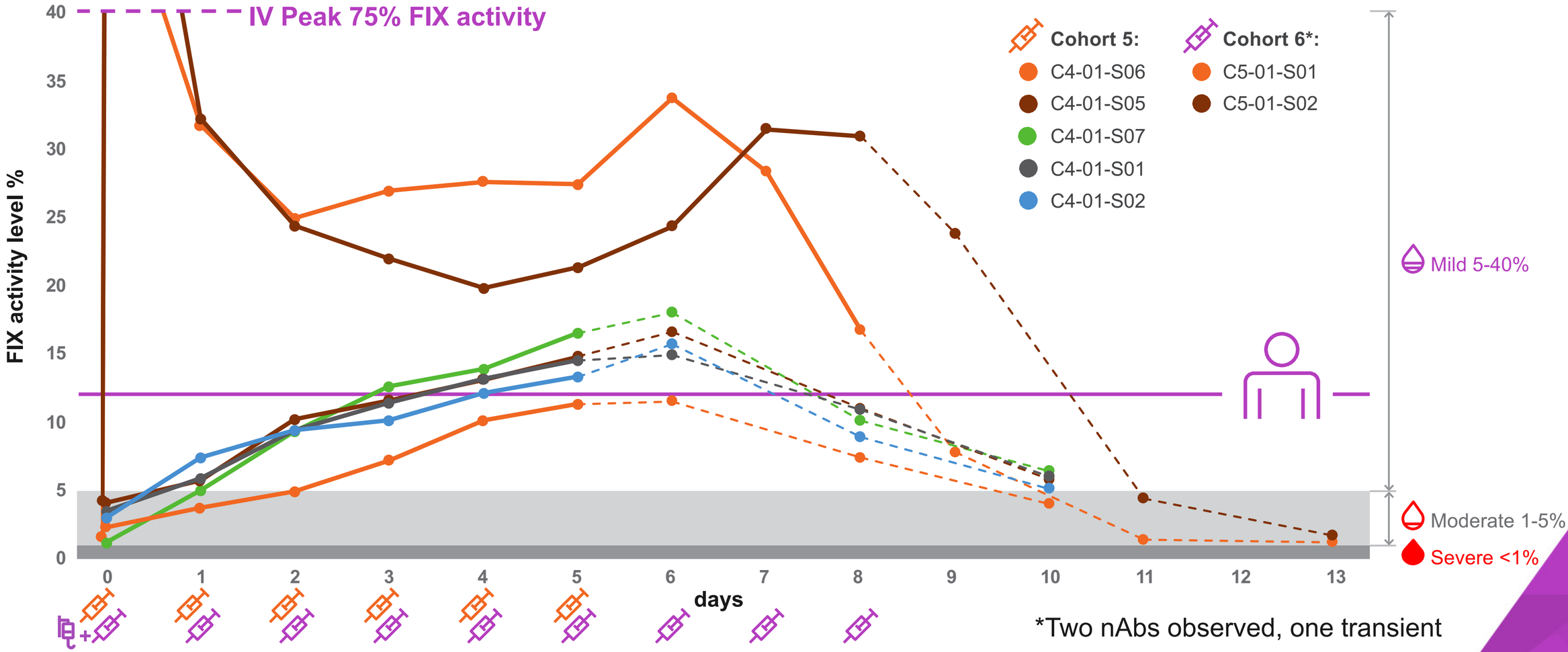
Cohort 2 & 3: PK activity profiles after IV and SQ Dalcinonacog alfa administration

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 ± SD	3.4 (n=1)	242.2 ± 365.5	29.0 ± 16.3 h	306 ± 148	19.8 ± 5.2%
	Median [25%-75%]		98.7 [60.0-369.4]	24 h [19.5-48]	352 [138-410]	18.5% [15.4-24.7%]

DalcA Phase 1/2 clinical trial FIX activity results

Nasdaq: CBIO

Trough levels >12% are sufficient to protect against spontaneous joint bleeds



*Two nAbs observed, one transient

Conclusions on the dalcinonacog alfa program

Continuing clinical development after an extensive immunogenicity risk assessment

Preclinical immunogenicity assessment showed that dalcinonacog alfa is equivalent to that of competitors such as BeneFIX

A comprehensive evaluation of the drug product showed comparable quality to marketed rFIX products

KoLs and subject experts agree with the immunogenicity risk assessment and proceeding with the P2b to evaluate the safety and efficacy of dalcinonacog alfa

Dalcinonacog alfa phase 2b SQ clinical trial design

Nasdaq: CBIO

DLZ-201 enrolling

- Enrollment: 6 patients
- Single IV dose followed by 28 day SQ dosing

- Primary endpoint: Steady state FIX activity level above 12% with daily dosing
- Secondary endpoints: safety, lack of neutralizing antibody formation, pharmacokinetics, pharmacodynamics

Dalcinonacog alfa program

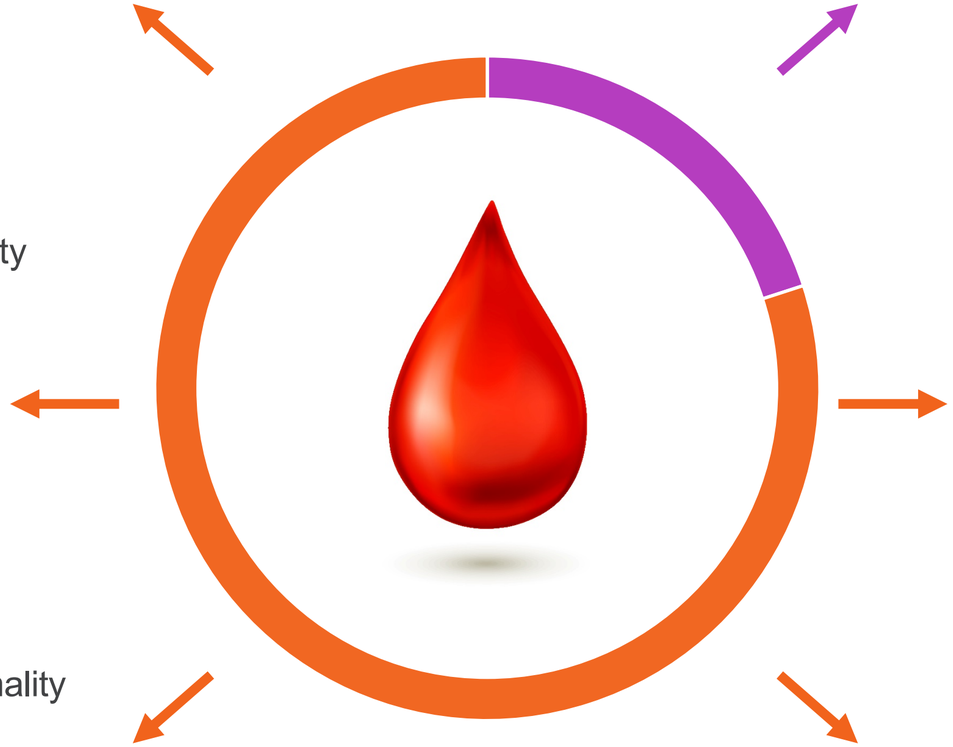
Moving forward in clinical development to address key unmet needs

- Robust SQ prophylaxis clinical efficacy demonstrated
- Safe and well tolerated
- Two anti-drug antibodies detected but low risk of immunogenicity
- Expected Top line Phase 2 results 4Q 2019

Addressing unmet needs in orphan bleeding disorders

Nasdaq: CBIO

MarzAA & DalcA



Hemophilia A with inhibitors

Anti-FVIII antibodies that neutralize activity

– 30% of Hem A patients

– Treatments: SQ Hemlibra®, IV FVIIa, FEIBA®

SQ treatment of bleeds & Hemlibra non-responders

Hemophilia B with inhibitors

Anti-FIX antibodies that neutralize activity

– 5% of Hem B patients

– Treatments: IV FVIIa, FEIBA

SQ prophylaxis & SQ treatment of bleeds

Factor VII deficiency – Glanzmann Thrombasthenia

Congenital lack of FVII – Platelet abnormality

– Treatments: IV plasma FVII or FVIIa

SQ prophylaxis in severe patients & SQ treatment of bleeds

Hemophilia B

Congenital lack of functional FIX

– Treated with IV FIX products

SQ prophylaxis

Hemophilia A

Congenital lack of functional FVIII

– Treatments: IV FVIII or SQ Hemlibra

SQ treatment of bleed

Acquired Hemophilia

Rare disorder, caused by anti-FVIII nAbs

– Treated with immunosuppressants + IV FVIIa, FEIBA or Obizur®

SQ treatment of bleeds & SQ prevention of re-bleeds

THANK YOU

CATALYST BIOSCIENCES