

INTRODUCTION

- In hemophilia patients with inhibitors, hemostasis can be achieved using bypass agents: activated plasma-derived prothrombin complex concentrates (aPCC), recombinant Factor VIIa (FVIIa), or emicizumab that can only treat hemophilia A
- Marzeptacog alfa (activated) (MarzAA) has four amino acid substitutions that were introduced using rational design and has enhanced biological properties including 7-fold increased catalytic activity, measured by the rate of Factor Xa generation *in vitro*, in the presence and absence of tissue factor, and prolonged duration of effect *in vivo* compared with wild-type rFVIIa
- Daily subcutaneous (SQ) dosing in dogs demonstrated achievement of stable trough levels of MarzAA that are believed to be effective for prophylaxis
- A human intravenous (IV) single-dose escalation study up to 30 µg/kg showed a half-life of 3.5 hours and dose-dependent pharmacodynamic effects on prothrombin time, aPTT and thrombin generation with a good safety profile (NTC01439971)

AIMS

- Phase 2 Study MAA-201 complies with the Declaration of Helsinki, is approved by recognized medical ethics committees, will enroll 12 subjects with inhibitors and an annual bleeding rate (ABR) ≥12 who sign informed consent to determine if SQ MarzAA can provide effective prophylaxis (NCT03407651)
- The objective is to find an individualized dose that provides prophylaxis without spontaneous bleeding

METHODS

- Part 1
- 18 µg/kg MarzAA was infused IV and pharmacokinetics (PK) and coagulation parameters were measured for 24 hours
 - 30 µg/kg MarzAA was injected SQ and PK, bioavailability and coagulation parameters were measured for 48 hours
- Part 2
- Daily 30 µg/kg MarzAA SQ therapy was injected for up to 50 days
 - If no spontaneous bleeding events occurred the subject proceeded to safety follow up 3 weeks after the last dose
 - If spontaneous bleeding was reported, then dose escalation occurred sequentially to 60, 90 or 120 µg/kg for 50 days, as needed
 - Functional FVIIa was measured 7 hours after SQ dosing at prescribed intervals
 - Subjects were tested for anti-drug antibodies to MarzAA, as well as FVII levels (>50% reduction defined as significant) at screening and every 7 days during treatment
 - ABR will be compared to the subjects prior ABR

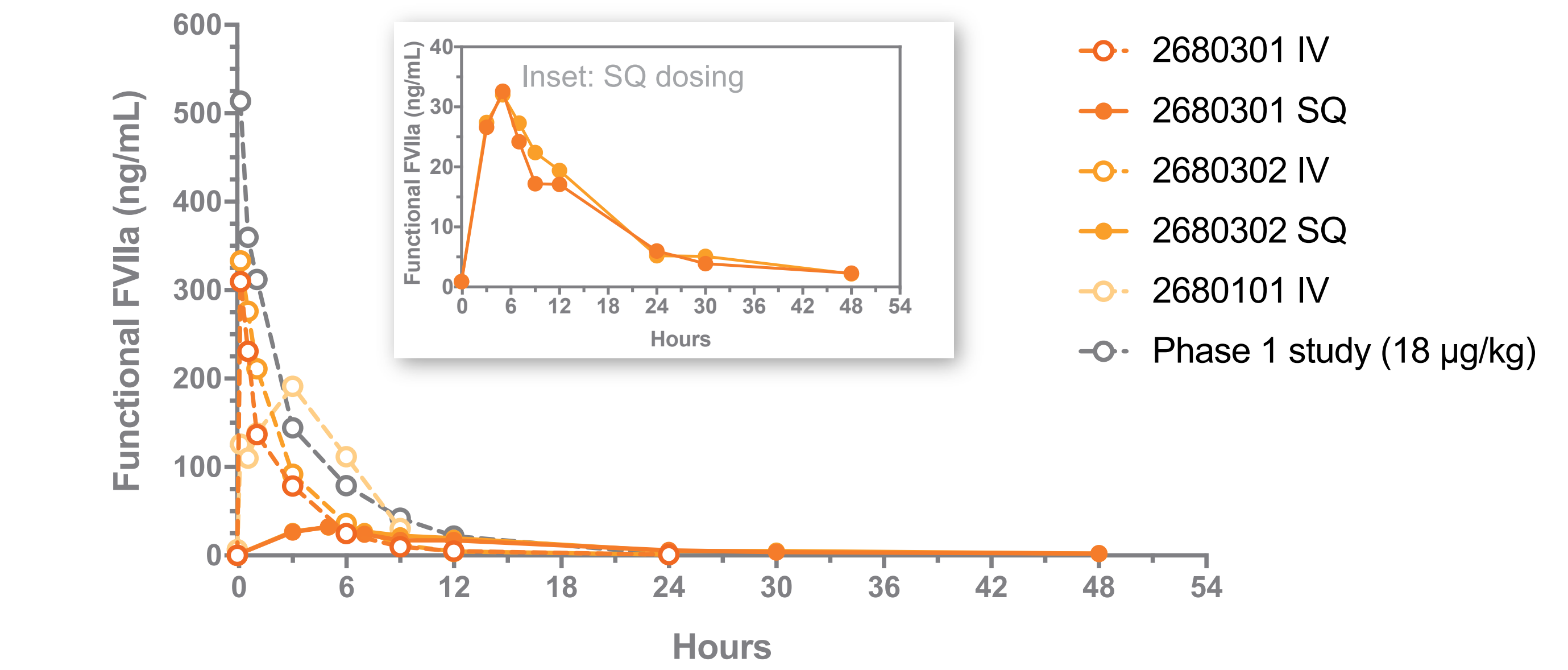
MAA-201 TRIAL SCHEMA



RESULTS

- 5 subjects have been enrolled (Median ABR 16.6; Range 12.2-26.7)
- 1 subject with historical ABR 26.7 has completed the study and had a spontaneous bleed 16 days after dosing termination in the follow-up period
 - No bleeding at 60 µg/kg for 50 days, after bleed on Day 46 at 30 µg/kg
- A fatal hemorrhagic stroke that was not related to study drug occurred on Day 11 in a subject with previously-treated but currently-untreated hypertension: BP 195/95 mmHg on admission
- Levels of MarzAA at Tmax 5 hours after SQ injection were similar to levels at 6 hours after IV infusion
- Median subcutaneous bioavailability was 35%; Range 32.4-37.5%
- IV half-life of 3.5 hours was increased to SQ half-life of 9.5 hours
- Daily SQ dosing of 30 µg/kg had MarzAA trough levels of 5-10 ng/mL and increased 7 hours after administration to 30-35 ng/mL
- Daily SQ dosing of 60 µg/kg MarzAA reached levels of 40-50 ng/mL 7 hours after administration
- Prothrombin Time baseline of 12-12.7 seconds reduced to 8-9 seconds after 18 µg/kg IV infusion (normal 9.4-12.5 seconds)
- Prothrombin Time gradually reduced to 8.6-8.7 seconds after 7 days of 30 µg/kg SQ injection
- No anti-drug antibodies have been detected to date

FVIIa FUNCTIONAL ACTIVITY AFTER INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION OF MARZEPTACOG ALFA (ACTIVATED)

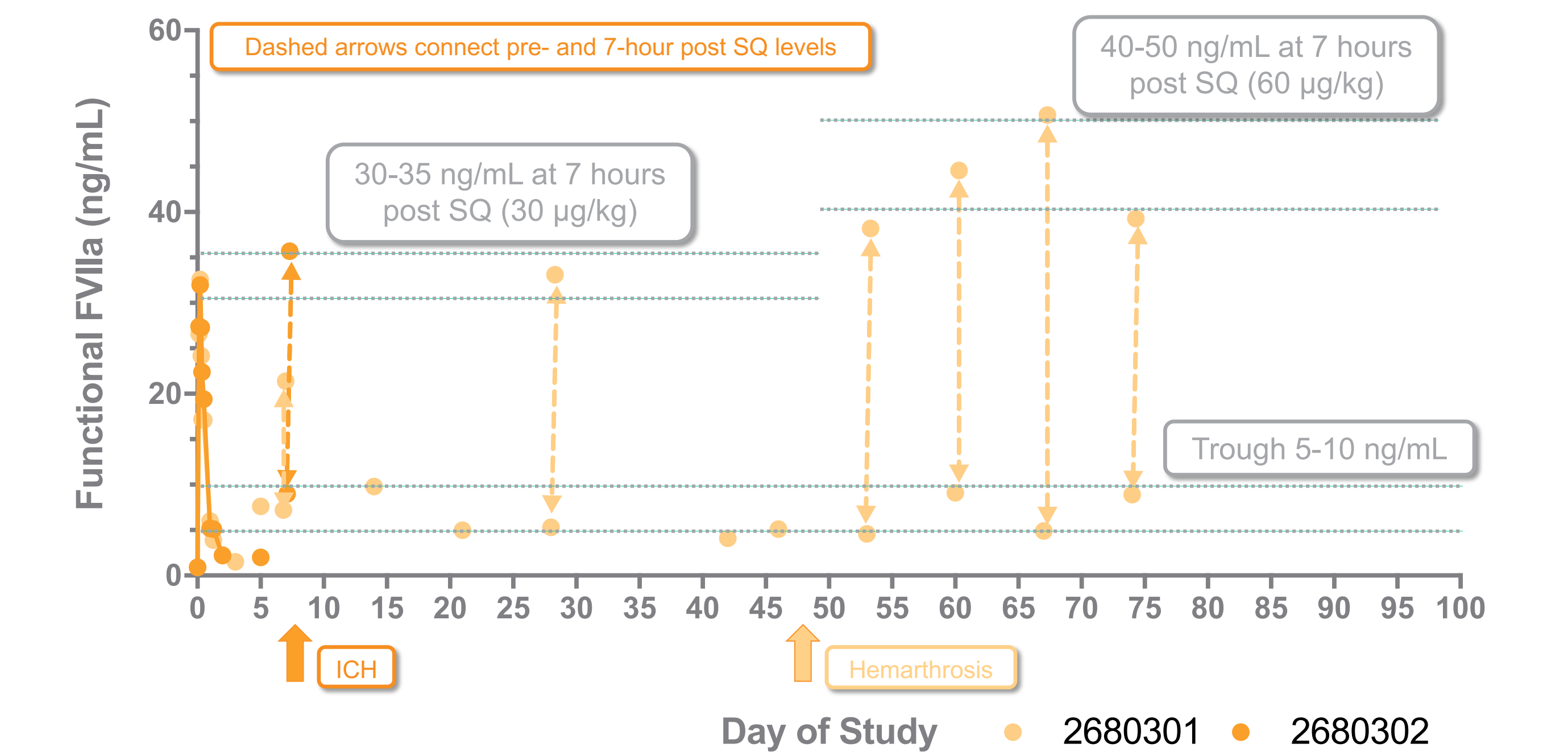


PHARMACOKINETICS OF INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION OF MARZEPTACOG ALFA (ACTIVATED)

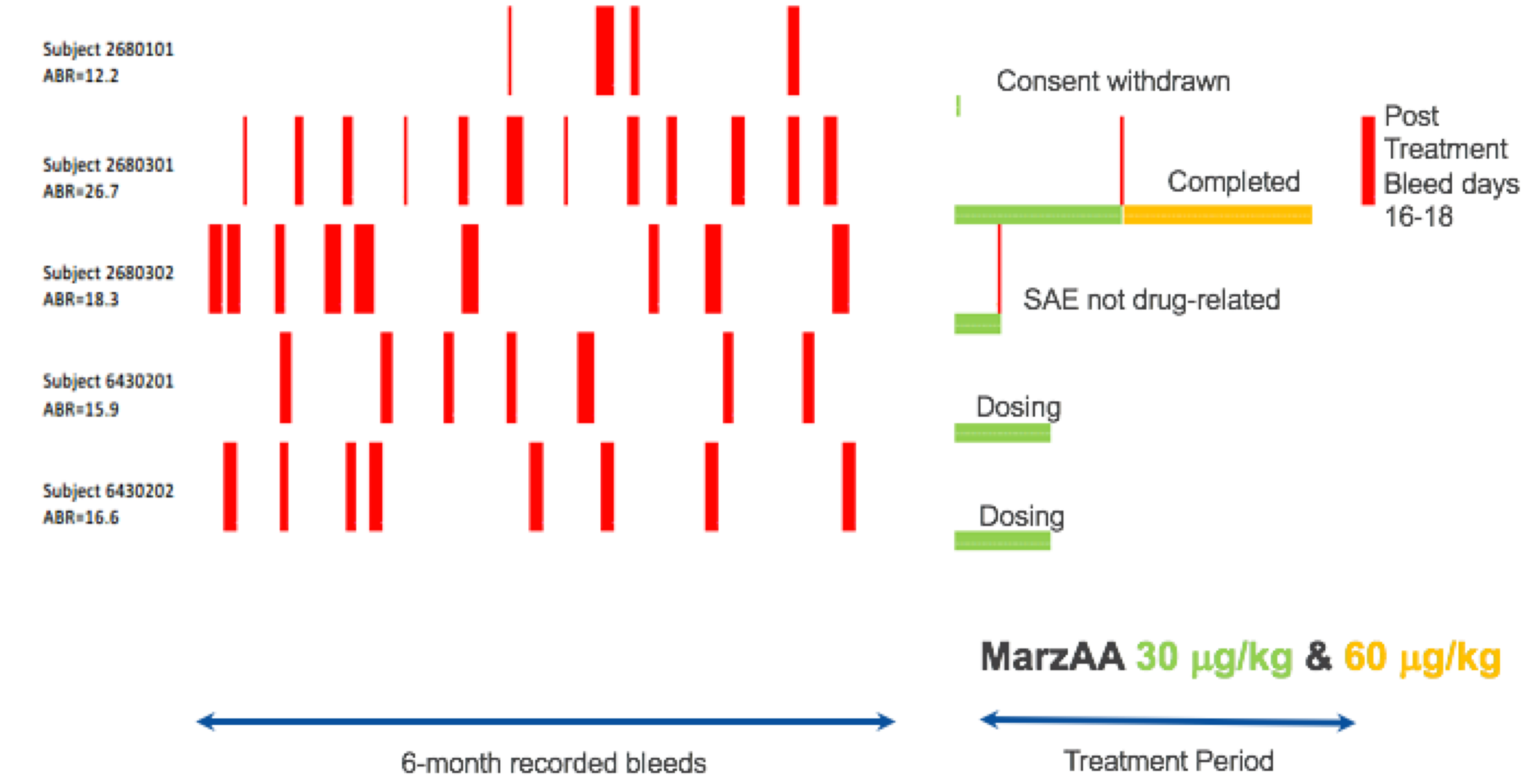
Subject	Route	Cmax (ng/mL)	Tmax (hr)	Half-life alpha (hr)	Half-life beta (hr)	Mean Residence Time (hr)	AUC _{0-∞} (ng/mL*hr)	AUC ₀₋₄ (ng/mL*hr)	Bioavailability
2680301	IV	309.8	0.08	1.7	3.8	3.1	694	690	37.5%
	SQ	32.6	5	-	9.6	14.8	450	431	
2680302	IV	333.1	0.08	1.6	3.1	2.8	881	879	32.4%
	SQ	32.0	5	-	9.4	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 FVIIa LEVELS AFTER SUBCUTANEOUS ADMINISTRATION OF MARZEPTACOG ALFA (ACTIVATED)



BLEED HISTORY FOR PRIOR 6 MONTHS, DURING AND POST-TREATMENT



The width of the red line indicates the bleed duration: 1, 2 or 3 days

CONCLUSION

- Increased potency of MarzAA and these pharmacokinetic and clinical results support a target of achieving significant reduction in ABR and achieving individualized normal coagulation pharmacodynamics with daily subcutaneous injections

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Disclosures:

H. Levy, F. Del Greco, A. Hetherington and J. Hillman are employees of CATALYST BIOSCIENCES