PHASE 2/3 TRIAL OF SUBCUTANEOUSLY ADMINISTERED MARZEPTACOG ALFA (ACTIVATED) AN ENGINEERED FVIIA IN HEMOPHILIA WITH INHIBITORS - PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND EFFICACY

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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
- 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

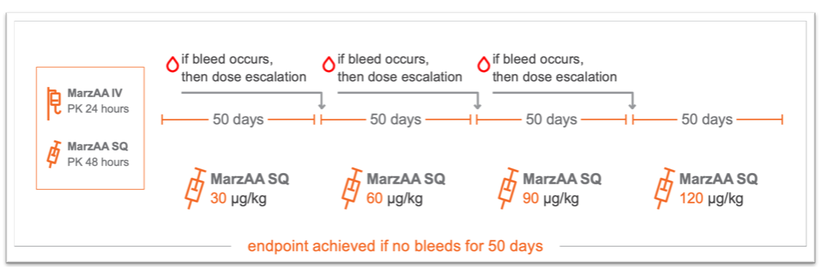
Part 1

- 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
- 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
- Annualized Bleed Rate (ABR) was be compared to the subjects prior ABR

MAA-201 TRIAL SCHEMA



RESULTS

- 13 subjects have been consented and 7 enrolled (Median ABR 18.2; Range 12.2-26.7)
- 5 subjects have completed dosing with clinically significant reduction in ABR
- 4 subjects had no bleeds at their final dose level
- IV half-life of 3.8 hours was increased to SQ half-life of 9.5 hours
- No anti-drug antibodies have been detected to date
- After more than 300 SQ injections, only a single moderate injection site hematoma that resolved without sequelae, was reported

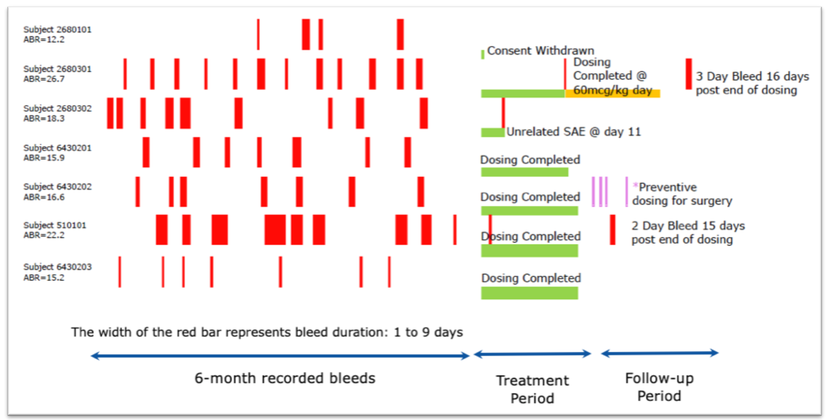
SUBJECT DEMOGRAPHICS AND DISPOSITION

Subject ID	Age	Highest Inhibitor level BU	Age when inhibitor diagnosed	Hemophilia A or B	ABR	ABR on treatment	Proportion of days with bleeding	Proportion of days with bleeding on treatment
2680101	36	16	15	A	12.2	Revoked consent	Revoked consent	Revoked consent
2680301	18	5	14	A	26.7	Zero at 60 µg/kg 3.8 overall	18%	Zero at 60 µg/kg 1% overall
2680302	30	2.7	26	A	18.3	Fatal unrelated SAE	11%	Fatal unrelated SAE
6430201	29	4.2	27	A	15.9	Zero	12%	Zero
6430202	35	4.7	35	A	16.6	Zero	11%	Zero
0510101	43	5.5	39	A	22.2	Untreated traumatic hematoma Day 4. ABR 7.3	22%	2%
6430203	23	4.5	21	A	15.2	Zero	4%	Zero
0510102	33	----------	21	B	29.8	Screen fail	16%	Screen fail
0510103	57	1.9	28	A	27.7	Screen fail	13%	Screen fail

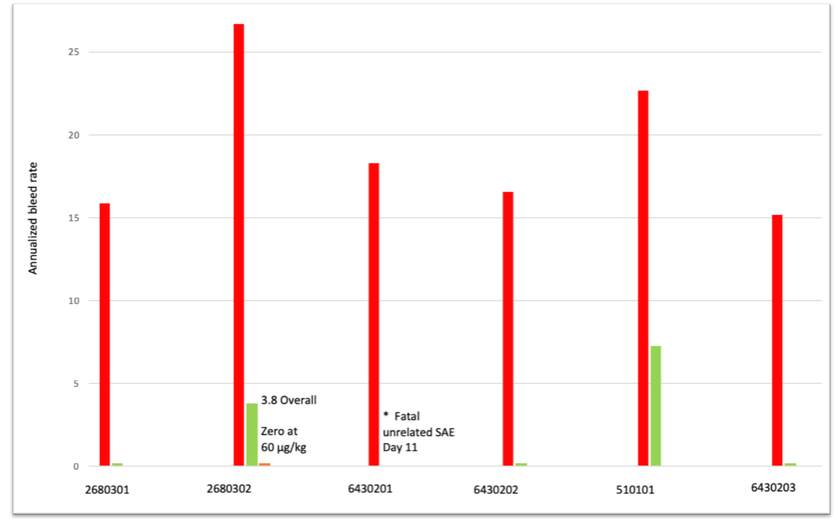
PHARMACOKINETICS OF INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION OF MARZEPTACOG ALFA (ACTIVATED)

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 (%)
IV Mean ± SD Median Range	278.1 ± 75.9 309.8 191.5-333.1	1.1 ± 1.6 0.1 0.1-3	1.7 ± 0.07 1.7 1.6-1.7	3.8 ± 0.75 3.8 3.1-4.6	3.7 ± 1.3 3.1 2.8-5.2	929 ± 262 881 694-1212	874 ± 182 879 690-1054	35 ± 3.6 35 32.4-37.5
SQ Mean ± SD Median Range	32.3 ± 0.4 32.3 32-32.6	5 5 5	-	9.5 ± 0.14 9.5 9.4-9.6	14.7 ± 0.21 14.7 14.5-14.8	471 ± 30 471 450-492	453 ± 31 453 431-475	

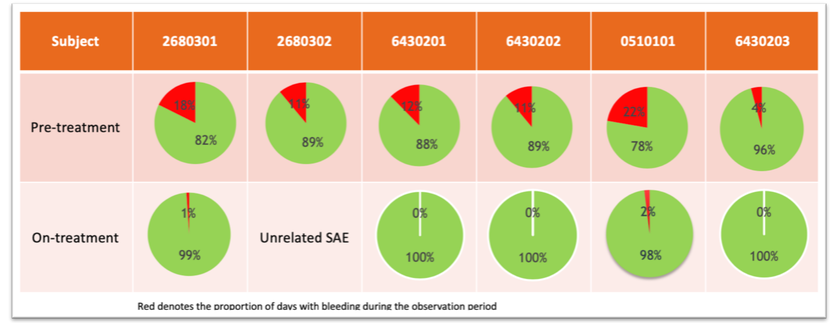
BLEED HISTORY FOR PRIOR 6 MONTHS, DURING AND POST-TREATMENT



PRIOR ANNUALIZED BLEEDING RATE (ABR) AND ON-TREATMENT ABR



PROPORTION OF DAYS BLEEDING FOR PRIOR 6 MONTHS AND DURING TREATMENT



- The average percentage of days of bleeding in the pre-treatment period was 13.2% (standard deviation 6.3%) [median 11.9%]
- In the treatment period, these percentages were reduced to 1.9% (standard deviation 3.2%) [median 0.5%]
- The analysis of these pairwise differences by a randomization paired t-test yields p=0.03 (and p=0.036 by Wilcoxon signed-rank test)

CONCLUSION

- Increased potency of MarzAA and these pharmacokinetic and clinical results support a target of achieving zero ABR with individualized dosing using daily subcutaneous injections

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Disclosures:
H. Levy and F. Del Greco, are employees, and Frank Booth is a consultant of CATALYST BIOSCIENCES