Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of ascending doses of subcutaneous marzeptacog alfa (activated) in adult subjects with hemophilia

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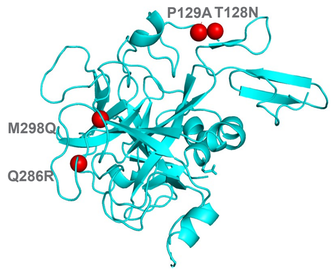
Conclusion

The Phase 1 MAA-102 study demonstrates the potential of subcutaneous marzeptacog alfa (activated) (MarzAA) to rapidly achieve and maintain therapeutic levels to treat acute bleeding events in hemophilia

Background

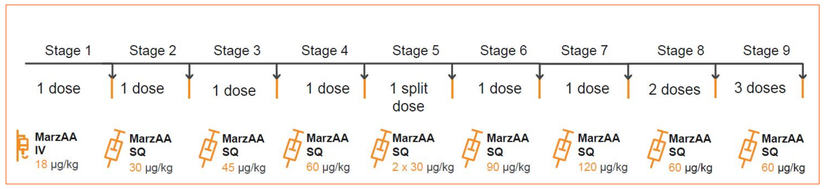
- Treatment of episodic bleeding for individuals with hemophilia who have inhibitors, including those on emicizumab prophylaxis, requires technical expertise, necessitates intravenous (IV) access associated with pain, and may have delays in administration of therapy
- Marzeptacog alfa (activated) (MarzAA) is a novel rFVIIa, differentiated by increased potency, allowing for subcutaneous (SQ) administration
- Therapeutic levels are quickly achieved and SQ administration results in a prolonged half-life
- Preliminary data for stages 1 to 7 was previously presented at EAHAD 2020 – abstract P128
- MarzAA has two amino acid substitutions in the protease domain (Q286R and M298Q) that increase catalytic activity for FX activation in the presence and absence of tissue factor
- Two substitutions in the EGF2 domain of the light chain (T128N and P129A) create an additional N-linked glycosylation site



Study design and methods

- MAA-102 is a Phase 1, open-label, multicenter clinical trial evaluating the pharmacokinetics, pharmacodynamics, and safety of a single IV dose and ascending SQ (single and multiple) doses of MarzAA in adult subjects with hemophilia A or B with or without inhibitors
- Each enrolled subject could participate in 9 stages with ascending dosing levels
- Investigators recorded the dose, route of administration, anatomic location, injection site assessment, adverse events, bleeding episodes, concomitant treatments, thrombotic events
- Chemistry, hematology, MarzAA activity, thrombin generation kinetics and total potential, prothrombin fragment 1+2, thrombin-antithrombin, D-dimer, and fibrinogen were measured to characterize pharmacodynamics
- Anti-drug antibodies (ADA) were measured at frequent time points during the trial and at 30 days after the last MarzAA exposure

Clinical study design



Clinicaltrials.gov: NCT04072237

Primary Objective

To evaluate the pharmacokinetics of ascending doses of SQ MarzAA

Secondary Objectives

- To determine the pharmacokinetics and pharmacodynamics of single IV and SQ doses and repeat SQ doses of MarzAA
- To determine if the pharmacokinetics behave in a dose proportional manner
- To determine whether split (2 different anatomic sites) injections of the same dose provide comparable pharmacokinetics to a single injection
- To evaluate the safety of IV and SQ MarzAA

Key Inclusion/Exclusion Criteria

Inclusion	Exclusion
Male, age 18 or older	Previous participation in a trial with SQ rFVIIa
Confirmed Hem A or B with or without inhibitors	Known positive antibody to FVII or FVIIa
Agreement to use highly effective birth control	History of other coagulation disorders

Demographics

Subject	Age	Weight (kg)	Hemophilia Type	Hemophilia Severity	Inhibitor status
1	47	120	A	Severe	N
2	35	90	B	Severe	N
3	36	64	B	Moderate	N
4	40	76	A	Moderate	N
5	46	70	A	Severe	N
6	38	60	A	Severe	N
7	20	69	A	Moderate	N
8	31	92	A	Severe	Y
9	36	65	A	Severe	N
10	38	75	A	Severe	Y

Results

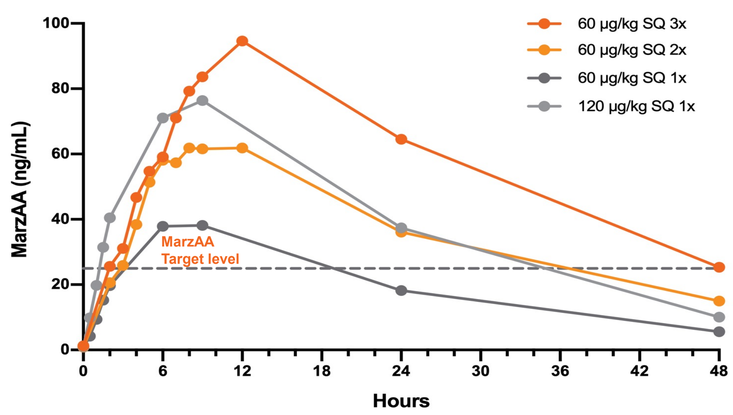
- Data from stages 1 to 9 are presented in the pharmacokinetic parameter table, and the median activity levels are displayed in the graph
  - A total of 11 subjects were consented and enrolled per local ethics committee requirements; 1 withdrew consent during stage 1 and 6 completed all stages
- No safety concerns, no ADA, related adverse events, or thrombotic events were observed
- 8 mild injection site reactions of 153 total SQ injections (single dose may require >1 injection)

Pharmacokinetic parameters

	Route of Administration & Dose Level (Mean)							
	IV	SQ						
PK Parameter (units)	18 µg/kg n=10	30 µg/kg n=8	45 µg/kg n=8	60 µg/kg n=16*	90 µg/kg n=8	120 µg/kg n=8	60 µg/kg twice (Q3H) N=8	60 µg/kg thrice (Q3H) N=8
C_{max} (ng/mL)	419.5	19.0	32.9	41.3	54.3	76.7	68.0	98.3
T_{max} (hr)	0.17	7.5	7.4	7.5	7.1	8.2	8.4	12.2
$T_{1/2}$ (hr)	3.3	18.6	19.3	14.4	15.5	15.0	18.8	18.1
MRT (hr)	3.8	28.3	28.1	22.4	23.4	22.8	29.0	29.3
AUC $_{0\text{-inf}}$ (µg · h/mL)	1390	516	849	1043	1488	2088	2108	3236
AUC $_{0\text{-t}}$ (µg · h/mL)	1383	430	693	928	1323	1868	1939	3038
Clearance (mL/kg/hr)	14.2	63.3	57.8	61.4	65.1	64.4	59.0	58.2
Bioavailability (%)	100	19	22	21	20	21	23	23

* Combines 60 µg/kg + 60 µg/kg split dose results

Mean MarzAA activity levels



Discussion

- Current therapies to treat episodic bleeding require IV administration, which may delay treatment due to access issues, reduce compliance, and often require repeat dosing
- SQ MarzAA rapidly achieves and maintains therapeutic levels and was well tolerated
- SQ administration presents a major advantage over IV infusion because of the prolonged period above target levels to treat bleeding that can be achieved
- MarzAA is the only SQ therapy that has the potential to treat acute bleeding
- These results support initiating a phase 3 study of SQ treatment of bleeding in individuals with hemophilia with inhibitors (CRIMSON1) in late 2020

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