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

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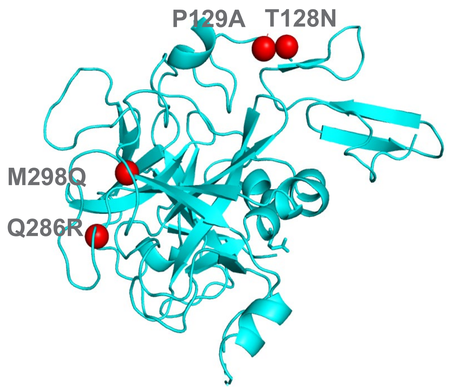
## Conclusion

**The Phase 1 MAA-102 study demonstrates the potential of MarzAA to achieve and maintain prolonged therapeutic levels to allow treatment of acute bleeding events with subcutaneous injections in hemophilia subjects with and without inhibitors**

## Background

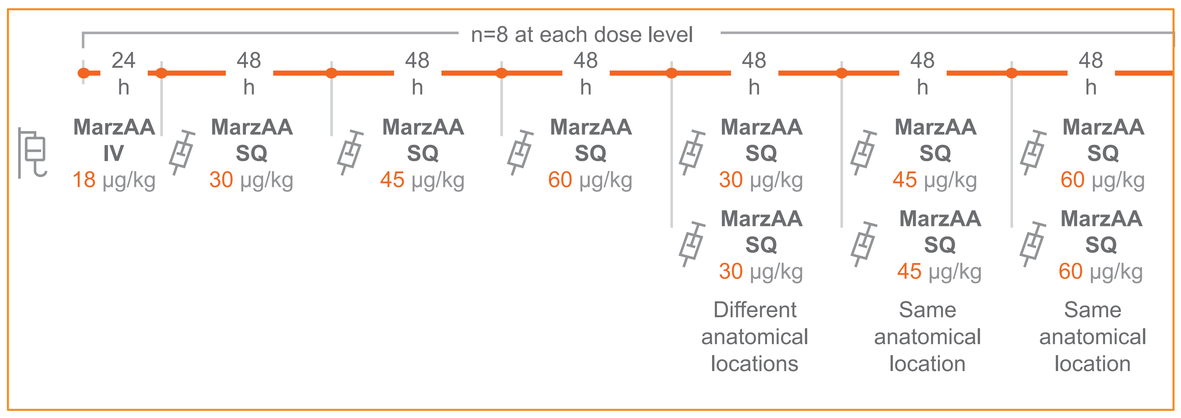
+ Currently available therapies for hemophilia patients with inhibitors include rFVIIa (eptacog alfa (activated); NovoSeven) and activated prothrombin complex concentrates (aPCC; marketed as FEIBA) to treat bleeding or when additional coverage is required
+ All hemophilia patients including those on emicizumab prophylaxis require intravenous (IV) access to treat a bleed, with associated pain, required expertise and compliance issues, that create delays in treatment
+ Marzeptacog alfa (activated) (MarzAA) is a novel rFVIIa differentiated by increased potency for subcutaneous (SQ) administration to rapidly achieve pharmacologically relevant plasma concentrations
+ 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 additional substitutions in the EGF2 domain of the light chain (T128N and P129A) create an additional N-linked glycosylation site




## Study Design

+ 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 doses of MarzAA in adult subjects with Hemophilia A or B, with or without inhibitors
+ Each enrolled subject may receive MarzAA in 7 dosing stages
+ Investigators record MarzAA administration, route of administration, anatomical location, injection site assessment, subject AEs, any bleeding episodes, concomitant treatments and any anti-drug antibodies (ADAs)

### Clinical study design




## Primary Objective

To evaluate the pharmacokinetics of ascending SQ doses of MarzAA

## Secondary Objective

+ To determine the pharmacokinetics and pharmacodynamics of single dose IV and SQ MarzAA
+ To determine if 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 ADAs
+ To evaluate the safety of IV and SC MarzAA

## Key Inclusion/Exclusion Criteria

| Inclusion | Exclusion |
|---|---|
| Male, age 18 or older | Previous participation in a SQ trial with 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 disorder |

## Subject demographics

| Subject | Age | Weight (kg) | Hemophilia Type | Hemophilia Severity | Factor Inhibitor status | Ethnicity | Race |
|---|---|---|---|---|---|---|---|
| 1 | 47 | 114 | A | Severe | N | Not Hispanic or Latino | White |
| 2 | 35 | 90 | B | Severe | N | | |
| 3 | 36 | 65 | B | Moderate | N | | |
| 4 | 40 | 75 | A | Moderate | N | | |
| 5 | 46 | 70 | A | Severe | N | | |
| 6 | 38 | 30 | A | Severe | N | | |
| 7 | 20 | 69 | A | Moderate | N | | |
| 8 | 31 | 91 | A | Severe | Y | | |

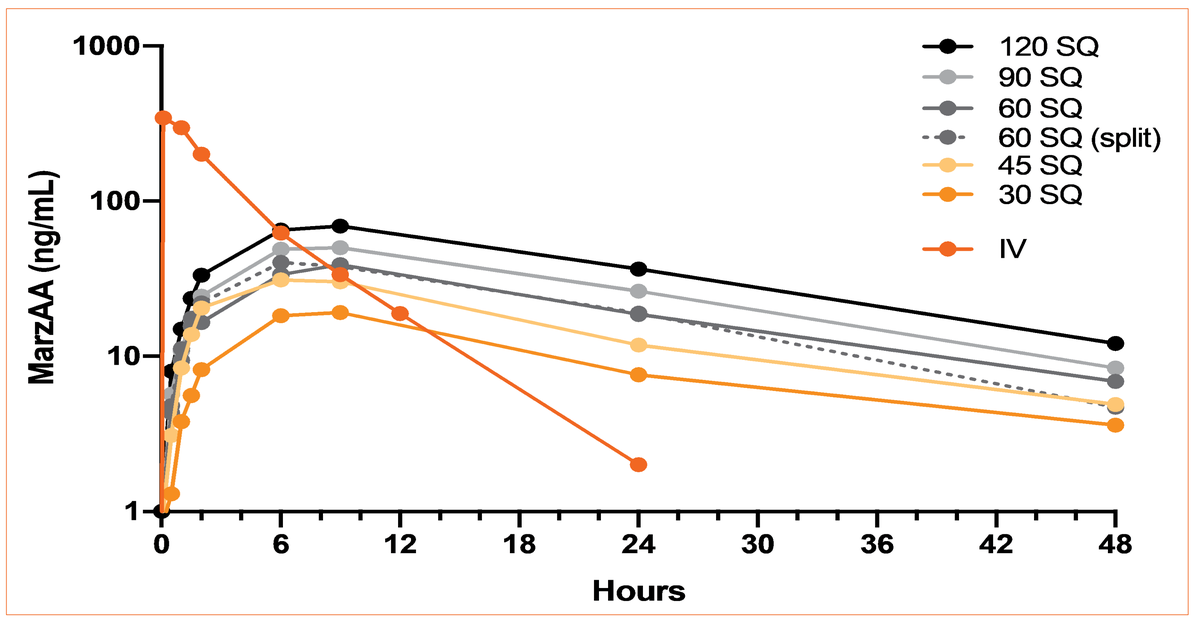
## Results

+ Interim data as of 20 Jan 2020 from Stages 1 to 7 are presented
  + A total of 8 subjects consented and enrolled per local ethics committee requirements and each completed all dose levels
+ After SQ administration PK results demonstrate:
  + MarzAA $T_{max}$, SQ=7.5 hours; IV=0.20 hours
  + SQ MarzAA $C_{max}$=range 18.7 to 54.2 ng/ml
  + MarzAA Mean Residence time, SQ=25.6 hours; IV=3.8 hours
+ No safety concerns observed:
  + 3 injection site reactions / 90 total SQ injections (single dose may require ≥1 injection)
  + No ADAs, related AEs, or thrombotic events were observed

### Pharmacokinetic Parameters

| PK Parameters (units) | Route of Administration & Dose Level (Mean ±SD) | | | | | | |
|---|---|---|---|---|---|---|---|
| | IV | SQ | | | | | |
| | 18 µg/kg n=8 | 30 µg/kg n=8 | 45 µg/kg n=8 | 60 µg/kg n=8 | 60 µg/kg (split) n=6 | 90 µg/kg n=6 | 120 µg/kg n=6 |
| $C_{max}$ (ng/mL) | 389 ±100 | 18.7 ±10.3 | 33.8 ±18.9 | 38.8 ±11.8 | 41.4 ±18.0 | 50.1 ±20.9 | 54.2 ±20.9 |
| $AUC_{0\text{-}inf}$ (ng/mL • hr) | 1375 ±424 | 493 ±171 | 864 ±338 | 1081 ±198 | 1030 ±389 | 1483 ±436 | 1787 ±702 |
| $AUC_{0\text{-}t}$ (ng/mL • hr) | 1368 ±420 | 417 ±179 | 707 ±269 | 934 ±209 | 968 ±356 | 1185 ±433 | 1302 ±413 |
| $T_{1/2}$ (hr) | 3.4 ±0.4 | 17.0 ±5.3 | | | | | |
| $T_{max}$ (hr) | 0.20 ±0.33 | 7.5 ±1.8 | | | | | |
| MRT (hr) | 3.8 ±0.43 | 25.6 ±7.1 | | | | | |
| Vol. of dist. (mL/kg) | 54.6 ±17.1 | 1688 ±764 | | | | | |
| Clearance (mL/kg/hr) | 14.4 ±4.9 | 64.9 ±21.4 | | | | | |

### Mean MarzAA pharmacokinetic levels




## Discussion

+ Current therapies to treat episodic bleeding require IV administration, which may delay treatment, often need repeated dosing, may result in suboptimal efficacy, and have reported safety issues
+ SQ MarzAA rapidly achieves and maintains therapeutic levels and was well tolerated and has the potential to treat acute bleeding in Hemophilia A and B
+ SQ injection presents a major advantage over IV administration as it enables expeditious at-home treatment, improved quality of life, and can help reduce health care costs

## Bibliography

+ NovoSeven Package insert, 2019, https://www.novo-pi.com/novosevenrt.pdf
+ FEIBA Package insert, 2018, https://www.shirecontent.com/PI/PDFs/FEIBA_USA_ENG.pdf

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