SYNOPSIS

Name of Sponsor:

Catalyst Biosciences, Inc.
611 Gateway Boulevard, Suite 710
South San Francisco, CA 94080

Name of Finished Product: rFVIIa, MarzAA, Lyophilized Powder for Solution for Injection

Name of Active Ingredient: Marzeptacog alfa (activated)

Title of study:

Phase 1/2 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of Marzeptacog alfa (activated) in Treatment of Episodic Bleeding in Subjects with Inherited Bleeding Disorders

Protocol number: MAA-202

Investigators: List of Investigators appears in Appendix 16.1.4

Study centers: 14 sites located in India, Russia, Ukraine, United States, and Italy

Publication (reference):

Study period: May 2021 – November 2021	**Phase of development: Phase 1/2**

Objectives:

Primary:

Phase 1

- To evaluate the PK of ascending subcutaneous (SC) doses of MarzAA and confirm the Phase 2 dose

Phase 2

- To evaluate the efficacy of MarzAA for the on-demand treatment and control of bleeding episodes at 24 hours

Secondary:

Phase 1

- To determine the pharmacokinetics of intravenous (IV) and SC MarzAA
- To determine if the pharmacokinetics of IV and SC MarzAA are dose proportional
- To determine the pharmacodynamics of IV and SC MarzAA

Phase 2

- To assess the time to cessation of bleeding after the initial dose
- To assess the ability of MarzAA to achieve and maintain hemostasis in the treatment of bleeds at fixed time points
- To assess the number of doses and the cumulative dose needed to achieve adequate hemostasis for individual bleeds
- To assess the percentage of bleeds with treatment success at 24 hours that maintain hemostatic efficacy at 48 hours after the initial dose
- To assess the use and amount of rescue therapy needed in treatment failures
- To assess the pharmacokinetics and pharmacodynamics of MarzAA in the bleeding state

Safety:

- To evaluate safety parameters, treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- To evaluate the occurrence of thromboembolic events
- To record the development of antidrug antibodies (ADA) and to determine if these are neutralizing

Exploratory (By cohort for Phase 2 only):

- To assess pain at fixed time points (immediately prior to treatment and then hours 1, 3, 6, 9, 12, 24, and 48) using the Wong-Baker FACES™ Pain Rating Scale and analgesic use
- To assess time required from recognition of bleeding event to administer the reconstituted dose by SC injection; and time from bleed recognition to first dosing
- To assess resource utilization: number of home health visits, number of outpatient visits, number of emergency room visits, number of inpatient visits, and duration
- To assess subject and caregiver productivity: number of days off work and/or school

Methodology:

This multicenter, open-label Phase 1/2 study was designed to enroll ~ 24 to 60 male or female subjects with Factor VII deficiency (FVIID; Cohort 1), Glanzmann thrombasthenia (GT; Cohort 2), or Hemophilia A with inhibitors on emicizumab prophylaxis (HAwI-E; Cohort 3) ≥12 years of age into 1 of 3 disease-defined cohorts. The two phases entailed the following:

Phase 1

Subjects were to receive a single dose of IV MarzAA followed by ascending doses of SC MarzAA.

Phase 2

Subjects were to be treated for mild, moderate, or severe traumatic or spontaneous joint, muscle, or mucocutaneous bleeding with variable doses of SC MarzAA by cohort.

For completion of Phase 2 of the study, ≥30 individual eligible bleeding episodes must have been treated in Cohorts 1 and 2, as well as ≥15 individual eligible bleeding episodes must have been treated in Cohort 3.

Number of subjects (planned and analyzed):

Approximately 24 to 60 male or female subjects were planned for enrollment across 3 cohorts. At the time of early termination of the study, 15 subjects had been consented and screened, of whom 6 (all male) were enrolled and treated with MarzAA in the study.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria:

Subject must have met all of the following inclusion criteria to be eligible for participation in this study:

1) Confirmed diagnosis for enrollment into one of three cohorts:
   a) Cohort 1: Confirmed diagnosis of congenital FVIID
   b) Cohort 2: Confirmed diagnosis of GT (ie, via platelet function analyzer and/or mutational analysis)
   c) Cohort 3: Confirmed diagnosis of HAwI-E who have been treated with the same dose of emicizumab for at least 4 weeks with one of the following:
      i) Titer ≥5 Bethesda units (BU)
      ii) Titer ≥0.6 BU but expected to have a high anamnestic response to FVIII, as demonstrated from the subject's medical history, precluding the use of FVIII products to treat bleeding as documented by the Investigator
      iii) Titer ≥0.6 BU but expected to be refractory to increased dosing of FVIII, as demonstrated from the subject's medical history, precluding the use of FVIII products to treat bleeding as documented by the Investigator

   Note: Documentation of highest historic titer should be recorded.

2) History of bleeding for subjects initially enrolling in the study into:
   a) Phase 1: No annual bleeding rate (ABR) requirement
   b) Phase 2: For subjects enrolled directly into Phase 2 without participation in Phase 1, the following ABRs are required 6 months before screening for their respective cohorts:
      i) Cohort 1: ABR of ≥8 for FVIID

ii) Cohort 2: ABR of ≥8 for GT

iii) Cohort 3: ABR of ≥1 for HAwI-E

3) Male or female, age ≥12 years
4) Agreement to use highly effective birth control throughout the study if the subject has childbearing potential
5) If female, then the subject must meet the following criteria:
   a) Not currently be breastfeeding
   b) Not plan on becoming pregnant during the study
   c) Be surgically sterile, or at least 2 years postmenopausal, or have a negative serum pregnancy test at Screening (Visit 1)
6) Affirmation of informed consent with signature confirmation and assent for children from age 12 to 17 years before any study-related activities

   Note: Study related activities are any procedures that would not have been performed during normal clinical management of the subject
7) Stated willingness to comply with all study procedures and availability for the duration of the study
8) Investigator confirmed subject's ability to rapidly assess a bleeding episode and respond appropriately
9) Investigator confirmed subject's ability to administer MarzAA SC at home

Exclusion Criteria:

Subjects who met any of the following criteria **were not eligible** for participation in this study:

1) Cohort 1: genotype of FVIID subjects with following mutations:
   a) P.A354V-p.464Hfs
   b) P.Ser112-Stop (homozygous)
   c) Ala294Val + Del C
   d) 100GlnArg
   e) Ser103Gly

   Note: Documentation of historic genotype was acceptable.
2) Inability to discontinue and washout any prophylactic (except emicizumab for subjects in Cohort 3) or episodic treatment for 5 days (10 days for platelet transfusion), prior to dosing
3) Previous participation in a clinical study involving SC administration of rFVIIa (NovoSeven or MOD-5014) or any study using a modified amino-acid sequence FVIIa (other than MarzAA) such as: NN1731 or BAY86-6150.

   Note: Prior participation in a study of IV LR769, rFVIIa-FP (CSL689), or MarzAA was permissible.
4) Previous participation in a clinical study with treatment within the previous 30 days or ≤5 half-lives of the investigational product or absence of clinical effect, whichever is longer
5) Known positive antibody to FVIIa or variants thereof detected during screening or prior to Day 1
6) Known hypersensitivity to plasma-derived Factor VIIa, plasma-derived Factor VII, wt-rFVIIa, or MarzAA or any of the excipients or related products
7) Treatment with anticoagulants or antiplatelet therapy within 1 week of enrollment or anticipated need during the study
8) Planned elective surgery within 12 months following study entry
9) History of other clinically relevant coagulation blood disorders
10) Platelet count <50,000 /μL based on screening laboratory assessments

11) Current or history of advanced atherosclerotic disease (ie, known history of coronary artery disease, ischemic stroke, etc.), or deep venous thrombosis within 24 months of dosing or considered to be at a high risk of venous thromboembolic event or pulmonary embolism as judged by the Investigator
12) If known HIV positive, documentation of CD4 T cell count of <200 cells/mm^3 within the screening period
13) Compromised hepatic or renal function:
    a) Alanine aminotransferase and aspartate aminotransferase levels ≥5 × the upper limit of normal (ULN)
    b) Total bilirubin level ≥2 mg/dL (>35 µmol/L) unless there is a known history of Gilbert's syndrome
    c) Serum creatinine level >1.25 × ULN
14) Inability or medical, psychosocial, or familial issues that might prevent full participation and cooperation with the procedures and requirements of the clinical trial as determined by the Investigator
15) Weight ≥105 kg (231 lbs.)

Test product, dose, mode of administration, lot number:

MarzAA Dose, Route, and Timing of Administration:

PHASE 1:

Cohort 1: Factor VII Deficiency

Table S-1 MarzAA Dose and Mode of Administration for FVIID

Stage	Dose [a]	Route	Number of doses	Frequency, Timing [b]
1A	18 µg/kg	IV	1	Once, Day 1
1B	10 µg/kg	SC	1	Once, at least 5 days after Stage 1A
1C	20 µg/kg	SC	1	Once, at least 5 days after Stage 1B
1D	30 µg/kg	SC	1	Once, at least 5 days after Stage 1C
1E	2 × 20 µg/kg [c] (40 µg/kg/day)	SC	2	Twice at 3-hour intervals, at least 5 days after Stage 1D
1F	3 × 20 µg/kg [d] (60 µg/kg/day)	SC	3	Three times at 3-hour intervals, at least 5 days after Stage 1E
1G	60 µg/kg	SC	1	Once, at least 5 days after Stage 1F

Abbreviations: FVIID=Factor VII deficiency; IV=intravenous; MarzAA=marzeptacog alfa (activated); SC=subcutaneous.

a. For subjects requiring more than one vial of study drug, the number of SC injections should correspond with the number of vials needed.
b. For all SC stages, a maximum of 11 days may elapse between the 72-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol).
c. 20 µg/kg MarzAA (total dose 40 µg/kg/day) administered at two separate time points with three-hour intervals between each dose and in the same anatomical location.
d. 20 µg/kg MarzAA (total dose 60 µg/kg/day) administered at three separate time points with three-hour intervals between each dose and in the same anatomical location.

Cohort 2: Glanzmann thrombasthenia

Table S-2 Dose and Mode of administration for GT

Stage	Dose [a]	Route	Number of doses	Frequency, Timing [b]
2A	18 µg/kg	IV	1	Once, Day 1
2B	30 µg/kg	SC	1	Once, at least 48 Hours after Stage 2A
2C	45 µg/kg	SC	1	Once, at least 5 days after Stage 2B
2D	60 µg/kg	SC	1	Once, at least 5 days after Stage 2C
2E	2 x 60 µg/kg [c] (120 µg/kg/day	SC	2	Twice at 3-hour intervals, at least 5 days after Stage 2D
2F	3 x 60 µg/kg [d] (180 µg/kg/day)	SC	3	Three times at 3-hour intervals, at least 5 days after Stage 2E

Abbreviations: GT= Glanzmann thrombasthenia; IV=intravenous; MarzAA=marzeptacog alfa (activated); SC=subcutaneous.

a. For subjects requiring more than one vial of study drug, the number of SC injections should correspond to the number of vials needed.
b. For all SC stages, a maximum of 11 days may elapse between the 72-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol).
c. 60 µg/kg MarzAA (total dose 120 µg/kg/day) administered at two separate time points with three-hour intervals between each dose and in the same anatomical location.
d. 60 µg/kg MarzAA (total dose 180 µg/kg/day) administered at three separate time points with three-hour intervals between each dose and in the same anatomical location.

Cohort 3: Hemophilia A with Inhibitors on emicizumab prophylaxis

Table S-3 Cohort 3 Dose and Mode of Administration for HAwI-E

Stage	Dose [a]	Route	Number of doses	Frequency, Timing [b]
3A	18 µg/kg	IV	1	Once, Day 1
3B	30 µg/kg	SC	1	Once, at least 48 hours after Stage 3A
3C	45 µg/kg	SC	1	Once, at least 5 days after Stage 3B
3D	60 µg/kg	SC	1	Once, at least 5 days after Stage 3C
3E	2 x 60 µg/kg [c] (120 µg/kg/day	SC	2	Twice at 3-hour intervals, at least 5 days after Stage 3D
3F	3 x 60 µg/kg [d] (180 µg/kg/day)	SC	3	Three times at 3-hour intervals, at least 5 days after Stage 3E

Abbreviations: HAwI-E= Hemophilia A with inhibitors on emicizumab prophylaxis; IV=intravenous; MarzAA=marzeptacog alfa (activated); SC=subcutaneous.

a. For subjects requiring more than one vial of supplied study drug, the number of SC injections should be commensurate with the number of vials needed.
b. For all SC stages, a maximum of 11 days may elapse between the 72-hour blood draw and when the next stage commences (unless delayed because of dose interruption as specified in the protocol).
c. 60 µg/kg MarzAA (total dose 120 µg/kg/day) administered at two separate time points with three-hour intervals between each dose and in the same anatomical location.
d. 60 µg/kg MarzAA (total dose 180 µg/kg/day) administered at three separate time points with three-hour intervals between each dose and in the same anatomical location.

PHASE 2

Planned Doses:

Cohort 1: FVIID: 20 µg/kg Q3H prn for a maximum of three doses at 3-hour intervals

Cohort 2: GT: 60 µg/kg Q3H prn for a maximum of three doses at 3-hour intervals

Cohort 3: HAwI-E: 60 µg/kg Q3H prn for a maximum of three doses at 3-hour intervals

Lot Numbers:

Details of batch numbers are provided in Appendix 16.1.6

Duration of treatment:

The estimated time of treatment duration was expected to be 18 months. At the time of study termination, the actual duration was 7.5 months.

Reference therapy, dose, mode of administration, lot number:

Not applicable

Criteria for evaluation:

Efficacy (primary)

Phase 1

- Pharmacokinetics of ascending SC doses of MarzAA and confirm the Phase 2 dose

Phase 2

- Percentage of bleed treatments resulting in effective hemostasis at 24 hours

Efficacy (secondary)

Phase 1

- Pharmacokinetics of IV and SC MarzAA
- Pharmacokinetic assessment of dose proportionality
- Pharmacodynamics of IV and SC MarzAA

Phase 2

- Time to cessation of bleeding after the initial dose
- Percentage of bleed treatment resulting in effective hemostasis at the time points of 1, 3, 6, 9, 12, and 48 hours after initial dose
- Number of doses and the cumulative dose needed to achieve hemostasis for individual bleeds
- Percentage of bleeds with treatment success at 24 hours that maintain hemostatic efficacy at 48 hours after the initial dose
- Use and amount of rescue therapy needed in treatment failures

Safety

- TEAEs and SAEs
- Occurrence of thromboembolic events
- Occurrence of ADAs and whether these are inhibitory or cross-reactive to FVIIa or FVII or variants thereof

Exploratory (By cohort for Phase 2 only)

- Pain at fixed time points (immediately prior to treatment and then at 1, 3, 6, 9, 12, 24, and 48 hours) using the Wong-Baker FACES™ Pain Rating Scale and use of analgesics
- Time required to administer the reconstituted dose by SC injection, and the time from bleed recognition to first dosing
- Resource utilization: number of home health visits, number of outpatient visits, number of emergency room visits, numbers of inpatient visits and their duration
- Subject and caregiver productivity: number of days off work and/or school

Statistical methods:

Primary Analysis Plan:

- Pharmacokinetic analysis by route of administration, dose level/stage/cohort
- Pharmacokinetic analysis for assessment of dose proportionality
- Appropriate statistics of all recorded, measured, and calculated parameters will be reported, including 95% confidence intervals, n, mean, standard deviation, median, minimum, and maximum
- The proportion of bleeding events treated with MarzAA achieving hemostatic efficacy (Excellent or Good) using a 4-point scale according to the Investigator's assessment at 24 hours

Safety Analysis Plan:

- Subject disposition (ie, number of subjects treated, subjects who completed the study, subjects who discontinued and the primary reasons for discontinuation) were to be tabulated
- All adverse events will be listed by preferred term and system organ class as classified by using the Medical Dictionary for Regulatory Activities (MedDRA) and type, frequency, course, outcome, severity, and causality to study drug were to be documented. Verbatim terms on case report forms were to be mapped to preferred terms and related system organ class using MedDRA.
- Vital signs (blood pressure, heart rate, temperature, respiratory rate) and laboratory values with descriptive statistical summaries of shifts for each stage

Sample size justification:

The sample size estimate is based on PK guidance for the development of hemostatic factors published by regulatory agencies and to demonstrate proof of concept for efficacy.

Analysis Sets for Phase 1

Safety:	Any subject who received at least one dose of MarzAA. The Intent-to-Treat (see below) and Safety populations were identical for this study, so both populations are interchangeable for analytic purposes.
PK Population:	Any subject who completed an entire stage, including the PK assessments, and had adequate samples for analyses.

Analysis Sets for Phase 2

Intent-to-Treat:	Any subject who received at least one dose of MarzAA. This population was to be used for safety analysis. A global efficacy analysis was to include all dosed subjects where any eligible bleed that was not assessed would be imputed as treatment failure.
Per Protocol Efficacy:	Any subject who received at least one dose of MarzAA for both an eligible and evaluable bleed and had an assessment of hemostasis. Any eligible bleed that was not assessed would be considered missing.

Safety:

The safety of MarzAA was to be monitored closely by the medical monitor and the Sponsor on an ongoing basis. All SAEs were to be reported to the medical monitor and the Sponsor.

Summary and Conclusions:

On 12 November 2021, Catalyst Biosciences, Inc., announced that the clinical development of marzeptacog alfa, activated (MarzAA; subcutaneous, extended half-life, recombinant factor VIIa) would be discontinued. This was a business decision and not due to any safety concerns regarding the investigational medicinal product (IMP) or impact on the enrolled subjects. On 15 November 2021, Catalyst officially notified active clinical trial sites, as well as Regulatory Health Authorities outside of the US and Institutional Review Boards/Ethics Committees, about the closing of Study MAA-202. After end of treatment, Catalyst followed all subjects enrolled in MAA-202 through the end-of-study (EOS) visit. After the EOS visit, subjects were monitored per their routine, pre-trial standard of care treatment and schedule by their personal physician. Data collected until EOS from this study were compiled and included in this clinical study report. By the EOS, a total of 15 adult subjects were screened, of whom 6 (3 males and 3 females: 1 in FVIID cohort, 3 in GT cohort and 2 in HAwI-E cohort) were enrolled and treated. No adolescent subjects were enrolled in the study.

PK results

- For SC single doses, mean (SD) T_{max} for subjects with FVIID, GT, and HAwI-E were 6.1 (0.09), 5.5 (3.24), and 7.3 (2.19) hours, respectively; for the 2-dose SC stage (60 µg/kg x 2, with 3 hours between doses), mean (SD) T_{max} for subjects with FVIID and GT were 5.9 (N/A) and 15.0 (12.73) hours, respectively; for the 3-dose SC stage (60 µg/kg x 3, with 3 hours between doses) for subjects with GT was 18.0 (8.49) hours.

- For SC single doses, dose normalized mean (SD) C_{max} for subjects with FVIID, GT, and HAwI-E were 0.5 (0.17), 0.5 (0.26), and 0.6 (0.09) (ng/mL)/(µg/kg), respectively; for the 2-dose SC stage (60 µg/kg x 2, with 3 hours between doses), dose normalized mean (SD) C_{max} for subjects with FVIID and GT were 0.7 (N/A), and 0.3 (0.26) (ng/mL)/(µg/kg), respectively; for the 3-dose SC stage (60 µg/kg x 3, with 3 hours between doses), dose normalized mean (SD) C_{max} for subjects with GT was 0.2 (0.21) (ng/mL)/(µg/kg).
- The apparent $T_{1/2}$ was prolonged from 3.6 hours after IV administration to 12.7 to 21.4 hours after SC administration, indicating flip-flop kinetics.

These observed PK results (T_{max} and $T_{1/2}$) are similar to those observed in the previously completed MarzAA trials in HA/HB with or without inhibitors. In the MAA-102 study (Neuman, 2020), single SC doses yielded a mean T_{max} of 6.0 to 9.0 hours, and multiple SC doses yielded a mean T_{max} of 8.5 to 12.0 hours, with a $T_{1/2}$ averaging 3.45 hours after IV administration and 13.18 to 22 hours after SC administration. In the MAA-201 study (Mahlangu, 2021), mean T_{max} was calculated to be 7 hours, with $T_{1/2}$ for IV averaging 3.65 hours and 17 hours after SC administration). Therefore, these data show predictable dose-dependent increases in MarzAA concentrations after SC dosing with both single and multiple administrations that is similar across all bleeding disorders studied to date.

Safety results

Overall, MarzAA has an acceptable safety profile. During the study, no safety concerns, drug-related AEs, or thromboembolic events were observed in the study.

One (out of 6 total) subject was found to have low-titer, cross-reactive ADAs that appeared to be non-neutralizing at the final, end of study visit, 3 months after his last exposure to MarzAA. Unfortunately, samples collected to assess the neutralizing capacity of these ADAs were not deemed valid for analysis, due to prolonged thawing of the sample during shipment from the site to the reference laboratory for analysis. The incidence rate for ADAs observed in this study is in line with the reported rates (in previous MarzAA studies, as well as for recombinant FVIIa (Napolitano, 2013; Eshghi, 2019) and other FVIII biologics that are used to treat severe hemophilia A (Mahlangu, 2016; Paz-Priel, 2018; Mahlangu, 2014). There were no other samples that tested positive for the presence of ADAs in any of the other subjects.

In summary, MarzAA was well tolerated and not associated with any serious, treatment-related SAEs, drug-related AEs, or thromboembolic events.

Conclusions

Current therapies to treat episodic bleeding in patients with inherited bleeding disorders, including FVIID, GT, and HAwI-E, have short half-lives, often requiring frequent IV administrations; this may delay treatment due to poor venous access, prolonged infusion time, and/or the need for frequent, repeat dosing to achieve hemostasis. The results of the early-terminated MAA-202 study suggest consistent achievement of a prolonged half-life with SC MarzAA, while being well-tolerated and having a safety profile consistent with other biologic products approved for the treatment of the same and related bleeding disorders studied. In addition, the PK profiles across the FVIID, GT, and HAwI-E cohorts herein were similar to those observed in the previously completed MarzAA clinical trials in patients with HA/HB, with or without inhibitors. The PK and PD of MarzAA are promising, and further exploration and clinical studies will be needed to fully understand the clinical effect of MarzAA for the treatment of inherited bleeding disorders.

There were no safety concerns, related AEs, or thromboembolic events observed during the conduct and completion of the study.

MarzAA administered by SC has an acceptable safety profile, is well-tolerated, and in combination with the experience from other MarzAA clinical trials (Gruppo, 2018; Mahlangu, 2021; Neuman, 2020), has a low rate of ADA formation which does not appear to be associated with cross-reactive neutralizing antibodies, although this too needs to be studied in future clinical trials.

The main limitation of this study is that it was terminated early, before all PK sample collections and analyses for each of the 3 cohorts could be completed. In addition, the small sample size precluded more rigorous statistical analysis of our initial findings. Overall, these results support the further study of SC MarzAA as a prophylactic and/or episodic treatment for patients with inherited bleeding disorders.
Date of Report: 25 March 2022