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); MarzAA

Title of study:

Phase 3 Study to Evaluate the Efficacy and Safety of Subcutaneous Marzeptacog Alfa (Activated) For On-Demand Treatment and Control of Bleeding Episodes in Subjects with Hemophilia A or Hemophilia B, with Inhibitors: The Crimson 1 Study

Protocol number: MAA-304

Investigators: List of Investigators appears in Appendix 16.1.4

Study centers: 31 sites; 15 countries (Armenia, Taiwan, Denmark, Georgia, Hungary, India, Italy, Malaysia, Mexico, Poland, Russia, South Africa, Spain, Turkey, and Ukraine)

Publication (reference):

Study period:	**Phase of development: Phase 3**
Date of first subject enrolled: 15 May 2021 Date of last subject completed: 01 December 2021	

Objectives:

Primary:

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

Secondary:

- 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 after the initial dose
- 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 required
- To assess the subcutaneous (SC) population pharmacokinetics (PopPK) of MarzAA

Safety:

- To evaluate safety parameters (treatment-emergent adverse events, serious adverse events)
- To evaluate the occurrence of thrombotic events
- To record the development of anti-drug antibodies (ADA) and to determine if these are neutralizing and cross reactive

Exploratory:

- To assess patient satisfaction with the Treatment Satisfaction Questionnaire for Medicine 9 (TSQM-9)
- To assess pain at fixed time points using the Visual Analogue Scale (VAS), and use of analgesics
- To assess the proportion of bleeds treated vs untreated

- To assess time required to administer the reconstituted dose (inclusive of insertion of venous access and infusion or injection time), and the time from bleed recognition to initial dosing
- To assess resource utilization: number of home health visits; number of outpatient visits; number of emergency room visits; and number of inpatient visits and their duration
- To assess subject and caregiver productivity: number of days off work and/or school

Methodology:

This multi-center, global, open label, randomized, cross-over Phase 3 study evaluated the efficacy and safety of MarzAA for on demand treatment and control of spontaneous or traumatic bleeding episodes compared to the standard of care (SOC) in adolescents and adult subjects with congenital HA or HB with inhibitors. Approximately 60 male or female subjects, ≥12 years of age with congenital HA or HB with inhibitors and a historical annual bleed rate (ABR) of ≥8, were to be enrolled and randomized to treat a total of ≥244 eligible bleeds with MarzAA and a total of ≥244 eligible bleeds were to be treated with SOC and 80% of patients have ≥3 bleeds treated with each treatment. Pharmacokinetic assessments were to be obtained during the MarzAA treatment period in the nonbleeding (Appendix 16.1.1 [MAA-304, Amendment 1, Appendix A, Table 18-3]) and if possible, the bleeding state (Appendix 16.1.1 [MAA-304, Amendment 1, Appendix A, Table 18-4]). Individual spontaneous or traumatic joint, muscle, or mucocutaneous bleeding episodes, each with a bleeding severity of mild, moderate, or severe were to be eligible for treatment. Subjects >17 years of age were randomized in blocks to treat approximately 5 bleeds with MarzAA and 5 bleeds with SOC in either Sequence A or Sequence B. Subjects 12 to 17 years of age were enrolled in the study after a positive Data Safety Monitoring Board (DSMB) assessment of 30 eligible bleeds have been treated with MarzAA.

Sequence A - MarzAA then SOC: Subjects were to be observed until ≤5 eligible bleeds were to have been treated with MarzAA or a total of 130 eligible bleeding events were observed in this treatment period, whichever came first. This was to be followed by treatment of ≤5 eligible bleeds with SOC or until a total of ≥244 eligible bleeding events were treated with SOC for the study (cumulative from both sequences).

Sequence B - SOC then MarzAA: Subjects were to be observed until ≤5 eligible bleeds had been treated with SOC or a total of 130 eligible bleeding events were observed in this treatment period, whichever came first. This was to be followed by treatment for ≤5 eligible bleeds with MarzAA or until a total ≥244 eligible bleeding events with MarzAA for the study (cumulative from both sequences).

The study was to be concluded when ≥244 bleeds were treated with MarzAA (cumulative from both sequences) and ≥244 bleeds were treated with SOC (cumulative from both sequences) and ≥80% of subjects had ≥3 eligible treated bleeds.

Number of subjects (planned and analyzed):

Approximately 60 male or female subjects were planned for enrollment to treat a total of ≥244 individual eligible bleeds each with SOC and with MarzAA.

At the time of termination, 29 subjects had been consented and screened, of whom 18 subjects were randomized and enrolled with 16 subjects treated with MarzAA or SOC. A total of 74 individual eligible bleeding events treated with MarzAA or SOC were observed.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria:

Study candidates must have met all the following **inclusion** criteria to be eligible for participation in this study:

1) Confirmed diagnosis of congenital HA or HB, with inhibitors, with confirmation of one of the following:
   a) Titer of ≥5BU
   b) Titer of ≥0.6 BU but expected to have a high anamnestic response to FVIII or FIX, as demonstrated from the subject's medical history, precluding the use of FVIII or FIX products to treat bleeding as documented by the Investigator
   c) Titer ≥0.6 BU but expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the subject's medical history, precluding the use of FVIII or FIX products to treat bleeding as documented by the Investigator

   Note: Documentation of highest historic titer should be recorded.

2) History of bleeding with an ABR of ≥8
3) Male or Female, ≥12 years of age
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 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 between ages 12 to 17 years before any study related activities

   Note: Study related activities are any procedure 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 and infuse SOC at home

Exclusion Criteria:

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

1) Previous participation in a 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. Prior participation in a study of intravenous (IV) LR769, rFVIIa-FP (CSL689), or MarzAA is permissible
2) Previous participation in a clinical study with subsequent treatment within the previous 30 days or ≤5-half-lives or absence of clinical effect, whichever is longer
3) Known positive antibody to FVIIa or variants thereof detected during screening and prior to Day 1
4) Known hypersensitivity to pd-FVIIa, pd-FVII, wt rFVIIa or MarzAA or any of the excipients or related products
5) Treatment with anticoagulants or antiplatelet therapy within one week of enrollment or anticipated need during the study
6) Planned elective surgery within 12 months following study entry
7) History of other clinically relevant coagulation disorder(s)
8) Platelet count <50,000 /μL based on screening laboratory assessments
9) Current or history of advanced atherosclerotic disease (ie, known history of coronary artery disease [CAD], ischemic stroke, etc.), or deep venous thrombosis (DVT) or pulmonary embolism (PE) within 24 months of dosing or considered to be at a high risk of venous thromboembolic event (VTE) as judged by the Investigator
10) CD 4 T Cell count of <200 cells/ mm3
11) Compromised hepatic or renal function:
   a) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≥5 × the upper limit of normal (ULN)
   b) Total bilirubin (TBIL) level ≥2 mg/dL (>35 μmol/L) unless there is a known history of Gilbert's syndrome (GS)
   c) Serum creatinine (Cr) level >1.25 × ULN
12) Inability or medical, psychosocial, or familial issues that might prevent full participation and cooperation with the procedures and requirements of the clinical study as determined by the potential subject and Investigator
13) Weight ≥105 kg (231 lbs.)

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

MarzAA Dose, Route, and Timing of Administration:

At 3-hour intervals for a maximum of 3 doses as needed for hemostasis (Table S-1).

Dosing, route, and frequency of administration are provided in Table S-1.

Table S-1 MarzAA Dose & Route & Timing of Administration

Dose Number	Dose	Route	Timing	Timing of Dosing window
1	60 µg/kg	SC	Hour 0	NA
2 (if needed)			No sooner than 3 hours after Dose 1	+3 hours
3 (if needed)			No sooner than 3 hours after Dose 2	+1 hour

Abbreviations: MarzAA=marzeptacog alfa (activated); NA=not applicable; SC=subcutaneous.

NOTE: For subjects requiring more than 1 vial of MarzAA, the number of SC injections should be commensurate with the number of vials needed.

Lot Numbers:

Details of batch numbers are provided in Appendix 16.1.6

Duration of treatment:

The estimated time of treatment duration was 15 months. The actual duration by early termination of the study was 6.5 months.

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

The reference therapy for this study is the subject's SOC. Standard of care products include NovoSeven, NovoSevenRT, SevenFact, and FEIBA.

SOC Dose, Route, and Timing of Administration Guidelines are provided in Table S-2.

Table S-2 Guidelines for SOC Dose, Dosing Frequency, & Route of Administration

SOC (units)	Dose	Route	Timing	Max Doses
NovoSeven (µg/kg) or equivalent	90 (±30)	IV	Every 2 hours prn	3
	270 (±30)		One time	1
SevenFact (µg/kg)	75 (±25)		Every 3 hours prn	3
	225 (±25)		One time	1
FEIBA (units/kg)	50 (±15)		Every 6 to 12 hours prn	2
	100 (±15)			

Abbreviations: IV=intravenous; Max=maximum; prn=pro re nata (as needed).

Criteria for evaluation:

Efficacy (primary)

- Percentage of treated bleeding episodes resulting in effective (Excellent or Good) hemostasis at 24 hours after the initial dose

Efficacy (secondary)

- Time to cessation of bleeding after the initial dose
- Percentage of treated bleeding episodes resulting in effective hemostasis at the time points (Hours 1, 3, 6, 9, 12, and 48) after the 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 response at 48 hours after the initial dose
- Use and amount of rescue therapy needed
- Population pharmacokinetics of subcutaneous MarzAA

Safety

- Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Occurrence of thrombotic events
- Occurrence of an antibody response and whether it is neutralizing or cross-reactive to FVIIa or FVII or variants thereof

Exploratory

- Patient satisfaction with Treatment Satisfaction Questionnaire for Medicine-9
- Pain at fixed time points (Hours 1, 3, 6, 9, 12, 24, and 48) using the Visual Analogue Scale and the use of analgesics
- Proportion of bleeds treated vs untreated
- Time required to administer the reconstituted dose (inclusive of insertion of venous access and infusion or injection time), and the time from bleed recognition to initial dosing
- Resource utilization: number of home health visits, number of outpatient visits, number of emergency room visits, number of inpatient visits and their duration
- Subject and caregiver productivity: number of days missed work and/or school

Statistical methods:

Primary Analysis Plan:

- 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 were to be compared to that observed during the SOC treatment period. The goal was to show a lack of inferiority of the former compared to the latter using a non-inferiority margin of −0.12. A one-sided 97.5% confidence interval for the difference of the proportion of efficacious treatments with MarzAA and SOC. The confidence interval was to be formulated allowing for the potential clustering of outcomes within subjects using a generalized estimating equations (GEE) approach. Superiority of MarzAA over SOC was to be demonstrated if the non-inferiority margin is exceeded at the upper bound.

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 AEs were to 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 were to be documented. Verbatim terms on case report forms (CRFs) 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 from baseline

Sample Size Justification:

The sample size for Study MAA-304 was based on the presumption of a two-arm study evaluating individual mucocutaneous, joint, or muscle bleeds on a 4-point scale with a primary endpoint of the proportion of treated bleeds resulting in effective hemostasis (Excellent or Good) at 24 hours. The goal of the study was to demonstrate that the true proportion of effective results in the MarzAA-treated bleeds is not inferior to the same proportion for the bleeds treated with standard of care. A non-inferiority margin for the former of −0.12 was to be used.

Using a baseline efficacy of 0.85 for SOC, with a −12% margin of non-inferiority treatment of 244 individual bleeds in each group provides 90% power with a one-sided 2.5% significance level to demonstrate that MarzAA-treated bleeds were non-inferior to SOC-treated bleeds. This calculation assumed that a one-sided 97.5% confidence interval for the difference of two proportions based on large-sample theory were to be used but adjusting the standard error of the estimate of the difference by the potential intra-subject correlation in the outcomes, which was assumed to be 0.1.

Using the Kish design effect (1 + [m-1]ρ, where m is the average cluster size of 4 and ρ is the intra-subject correlation of 0.1), the sample size was to be inflated from a non-cluster adjusted value of 187 per group to a final result of 244 (after rounding up to a value divisible by 4) by incorporating the calculated design effect into the calculation of the effective sample size. Also, note that although the same subjects were to be in both groups, the sampling unit here was an individual bleed, which was not paired between the study arms.

Analysis Sets

Intent to treat (ITT):	Any subject who received at least one dose of MarzAA or SOC to treat a bleeding event. This population was to be used for safety analysis and a global efficacy analysis that includes 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 or SOC for an eligible and evaluable bleed and had an assessment of hemostasis. Any bleed that was not assessed would be considered missing.

Safety:

The safety of MarzAA and SOC was to be monitored closely by the medical monitor, the Sponsor, and the DSMB 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 (IRB)/Ethics Committees (EC), about the closing of Study MAA-304. After end of treatment, Catalyst followed all subjects enrolled in MAA-304 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 29 male subjects were screened, of whom 18 subjects were randomized and enrolled with 16 subjects treated. No adolescent subjects were enrolled in the study.

Efficacy results

Baseline characteristics of the study population were relatively well-matched between subjects treated with MarzAA and SOC.

The primary endpoint of this study was the percentage of treated bleeding episodes resulting in effective (Excellent or Good) hemostasis at 24 hours after the initial dose. The primary efficacy endpoint trended toward a positive outcome, with the collected data prior to early termination of the study. Based on the 29 and 37 evaluable bleeding events in each group of subjects randomized to initially receive treatment with MarzAA or SOC, respectively, the proportion of treatment success (effective hemostasis) at 24 hours after the initial dose was essentially equivalent (86.5% versus 86.2% for subjects treated with SOC versus MarzAA). For the same number of evaluable bleeds, rates of effective hemostasis prior to 3 hours were observed to be more favorable for SOC compared to MarzAA, whereas rates of effective hemostasis beyond the first 3 hours through 48 hours post-treatment were more favorable for MarzAA compared to SOC. While IV SOC can achieve hemostasis quickly, it is also known to have limited duration of clinical effect, sometimes requiring multiple infusions to maintain hemostasis and prevent re-bleeding (NovoSeven RT US Package Insert, 2019; SevenFact US Package Insert, 2020). In contrast, the prolonged maintenance (beyond 3 and up to 48 hours) of hemostatic efficacy achieved with MarzAA (T_{max} >18 hours) administered subcutaneously is particularly noteworthy, especially as a subcutaneous, bypassing agent for on-demand treatment, something that has heretofore not been demonstrated. Furthermore, the mean time to cessation of bleeding for subjects treated with MarzAA was shorter than for subjects treated with SOC (770 minutes versus 855 minutes). In addition, of the eligible bleeding events treated with MarzAA versus SOC, the time to administer MarzAA was also shorter compared to that for SOC, with MarzAA never exceeding 7 minutes versus >10 minutes required for 2 bleeding events treated with FEIBA. Therefore, based on the limited data collected prior to early trial termination, clinical efficacy outcomes for SC

rFVIIa, MarzAA, trend similarly or better compared to those reported for approved IV SOC products (e.g., NovoSeven and FEIBA).

Overall, these results of MarzAA as a subcutaneous injection for treatment of bleeds are promising for HA/HB patients with inhibitors, for whom current episodic treatment options are limited and the IV route of administration remains a significant barrier to timely and effective treatment, particularly for pediatric patients or those with poor venous access.

Safety results

Overall, MarzAA has an acceptable safety profile. During the study, no safety concerns, drug-related AEs, or thromboembolic events were observed. There was 1 unrelated SAE of ureterolithiasis that was reported. While one subject (out of 16 total) was found to have low-titer, cross-reactive but non-neutralizing ADAs, these were transient and resolved by the time of the final study visit, 2 months after his last exposure to MarzAA. The incidence rate for ADAs observed in this study is in line with the reported rates (between 3-7%) for recombinant FVIIa (Napolitano, 2013; Eshghi, 2019) and other FVIII biologics that are used to treat severe hemophilia A (Mahlangu, 2014; Mahlangu, 2016; Paz-Priel, 2018). Per communication with this subject's PI after database lock, clinically, he has fared well when using FEIBA for treatment of bleeding events and has not experienced any safety events since ending study participation. In summary, MarzAA was well-tolerated and not associated with any serious, treatment-related SAEs, drug-related AEs, or thromboembolic events.

Conclusions

Currently approved therapies for cessation of bleeds in HA/HB patients with inhibitors require IV access, which may preclude treatment in those with poor venous access, be associated with an increased risk of infection and/or thrombosis if administered through a central venous catheter, delay treatment initiation, and require technical expertise by themselves or caregivers to administer. Multiple infusions may be required to achieve hemostasis, requiring additional time for treatment administrations, bleed cessation, and prevention of re-bleeding. First-hand accounts from patients and caregivers with congenital bleeding disorders provided to the FDA suggest there remains a need for potential therapies that reduce joint deterioration and pain, are fast and simple to administer, retain sufficient activity exposure longer than the current available therapy, and alleviate socio-psychological burden associated with hemophilia, with or without inhibitors (FDA, 2016). The clinical evidence from MAA-304 suggests that MarzAA, with its enhanced potency, prolonged durability, and simple SC route of administration, has the potential to provide a substantial improvement for bleed treatment in HA/HB patients with inhibitors over available IV therapies, such as NovoSeven or FEIBA.

The findings from this study that was terminated early suggest essential equivalence in efficacy for treatment of bleeds in HA/HB patients with inhibitors using MarzAA or SOC, with favorable rates of effective hemostasis following MarzAA compared to SOC beyond the first 3 hours through 48 hours post-treatment. Notably, this was achieved with MarzAA being administered subcutaneously, which has not been previously possible for on-demand treatment of bleeding events. In addition, MarzAA was 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 that is transient and does not appear to be associated with cross-reactive neutralizing antibodies or clinical sequelae. Based on the data included herein, MarzAA may provide an important bleed treatment option and contribution to patient care by directly addressing unmet medical needs while also potentially reducing the risk of development of hemophilic arthropathy and other bleeding-related comorbidities due to suboptimal bleeding control.

Date of Report: 25 March 2022