Nasdaq: CBIO

CRIMSON 1

A PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SUBCUTANEOUS MARZEPTACOG ALFA (ACTIVATED) FOR ON-DEMAND TREATMENT OF BLEEDING EVENTS IN SUBJECTS WITH HEMOPHILIA A OR B, WITH INHIBITORS

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Speakers Bureau	**Takeda/Shire, Pfizer**
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Scientific Advisory Board	**Sanofi, Sigilon, Takeda**

Treatments for Bleeds in Patients with Hemophilia with Inhibitors

Effective but Intravenous and Burdensome

+ Persons with Hemophilia A (HA) or Hemophilia B (HB) who develop inhibitors against FVIII or FIX, respectively, require bypassing agents (BPA) to treat bleeds

+ Subcutaneous emicizumab prophylaxis: approved for HA with inhibitors[1,2] but cannot be utilized for episodic bleed treatment

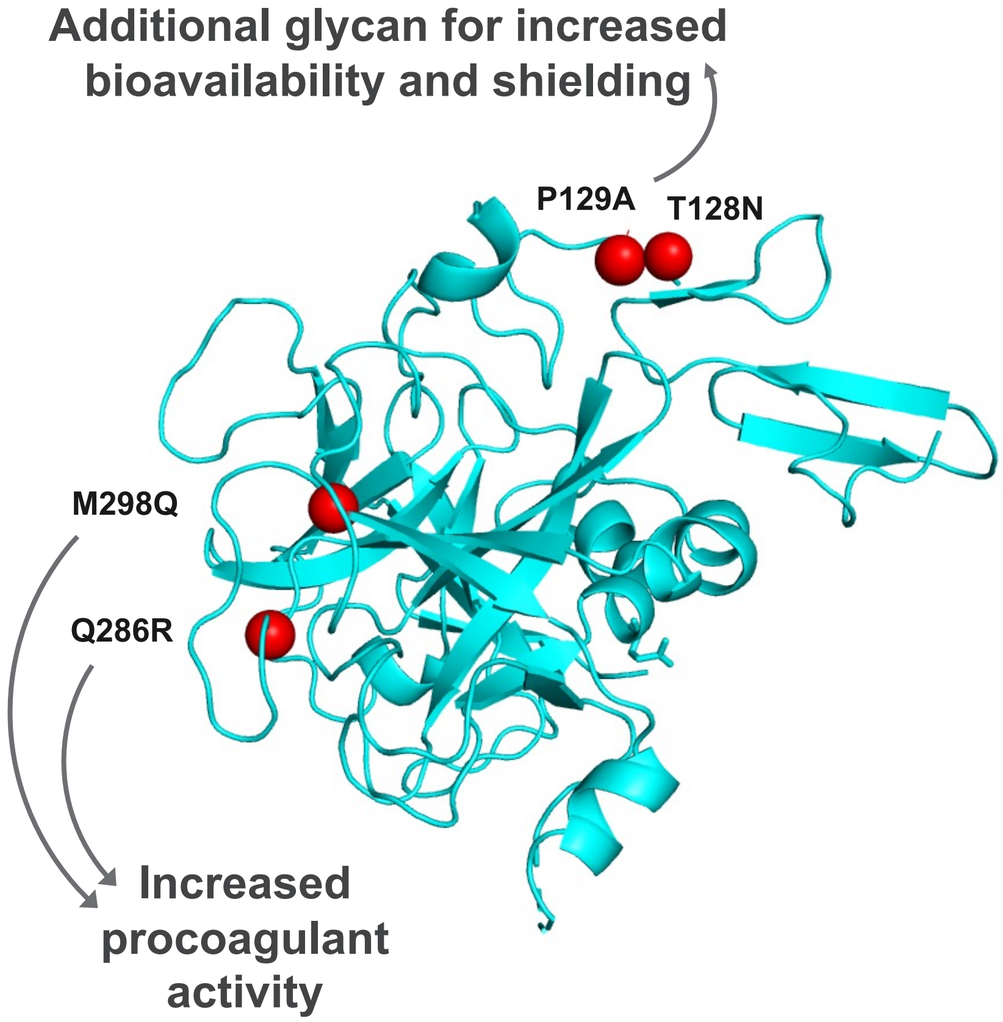
+ Standard of care BPAs—activated prothrombin complex concentrate (aPCC) and recombinant activated factor VII (rFVIIa)-–both require intravenous (IV) administration
  - Need adequate venous access
  - aPCC may take approximately 45 minutes to infuse
  - rFVIIa may require multiple IV infusions to stop bleed

+ High treatment burden of IV BPAs[3] suggest unmet need for SC treatment of bleeds with efficacy that is at least on-par with SOC

1. Oldenburg J, et al. *New Engl J Med.* 2017;377:809-818. 2. Young G, et al. *Blood*. 2019;134:2127-2138. 3. Krumb E, et al. *Haemophilia*. 2021;27:736-743.

Marzeptacog alfa (activated) – MarzAA: Extended $t_{1/2}$, SC rFVIIa

Addresses Unmet Need in Multiple Bleeding Disorders, Including Hemophilia with Inhibitors, for both Prophylactic and On-Demand Use



5- to 10-fold higher activity *vs* NovoSeven

+ Potency allows **low volume SC dosing** with **prolonged half-life**

Preclinical efficacy of SC on-demand treatment

+ HA mouse; HA dog; HA rat – all dosed after bleeding had started; dog and rats after spontaneous ‘clinical’ bleeds

Proof of Concept & safety in HA or HB with inhibitors

+ Total of 61 subjects treated in Phase 1/2/3 incl. single dose IV, up to 3 SC doses/day, daily SC up to 97 days

Several FDA Fast Track and Orphan Drug Designations

+ FTD & ODD for on-demand use in HA/HB with inhibitors
+ FTD for on-demand use in FVII deficiency & ODD for FVII deficiency (broadly)
+ ODD for prophylaxis for hemophilia with inhibitors

FTD = Fast Track Designation, ODD = Orphan Drug Designation

Crimson 1: Study Design

Study Objectives & Study Population

- **Primary Objective**

  Control of bleeding episodes at 24 hours after initial dose

- **Secondary Objectives**

  Time to bleeding cessation after initial dose

  Hemostasis at fixed time points after initial dose

  Number of doses and cumulative dose to achieve hemostasis

  Among bleeds stopped at 24 hours after initial dose, percentage of hemostasis maintained at 48 hours

  Use and amount of rescue therapy required

  Population pharmacokinetics of SC MarzAA

- **Safety Objectives**

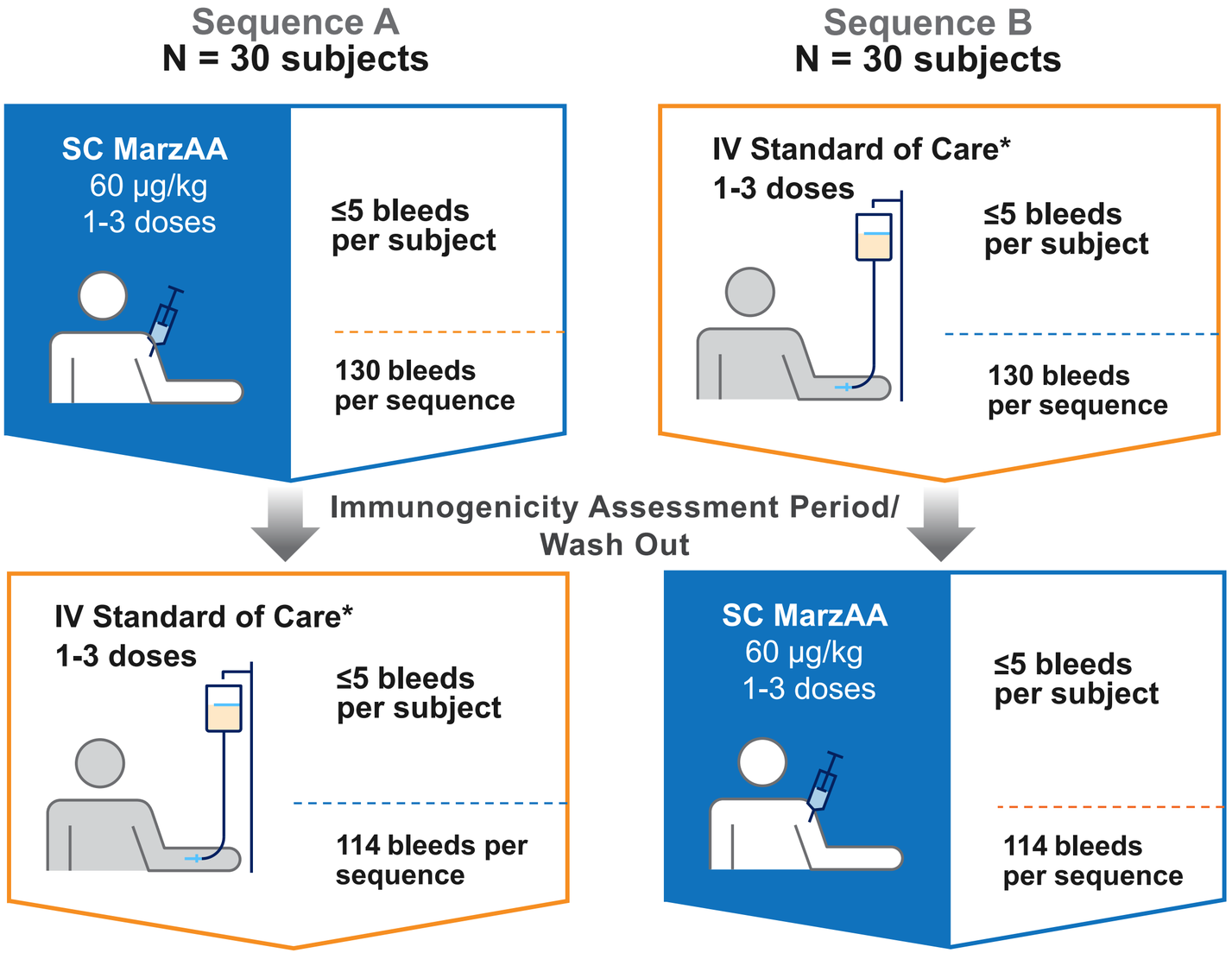
  Adverse events, thrombotic events, anti-drug antibodies (ADAs)

Planned Study Population

+ Approximately 60 male or female subjects
+ ≥12 years of age with congenital HA or HB with inhibitors
+ Historical annualized bleeding rate (ABR) of ≥8

Crimson 1: Study Design

Multi-Center, Global, Randomized, Open-Label, Cross-Over Phase 3 Study



- **Primary endpoint**
  Non-inferior hemostatic efficacy: standard 4-point severity scale at 24 hours
- **Secondary endpoints**
  Time to bleed resolution; number of doses; rescue meds
- **Safety**
  Adverse events, thromboembolism, ADAs

Statistics

+ Standard of Care (SOC) estimate: **85%** of treated bleeds rated as ‘Excellent’ or ‘Good’
+ Non-inferiority margin: **12%**
+ **2.5%** significance, one-sided
+ **90%** power

*SOC: FEIBA or NovoSeven

Crimson 1: Baseline Characteristics

Balanced Across Both Groups, Inhibitor Titers Higher in Sequence A

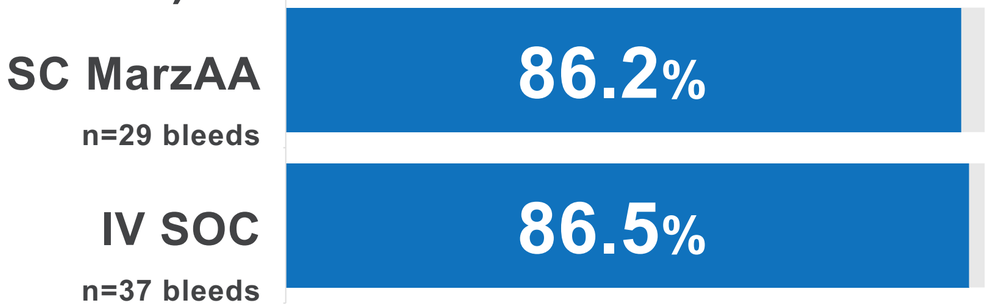
Characteristic	Sequence A SC MarzAA / IV SOC (N=9 subjects)	Sequence B IV SOC / SC MarzAA (N=7 subjects)	Total (N=16*)
Age (years): Mean (SD)	33.0 (9.67)	35.7 (10.73)	34.2 (9.89)
Male: n (%)	9 (100.0)	7 (100.0)	16 (100.0)
Race: n (%)			
Asian	6 (66.7)	5 (71.4)	11 (68.8)
White, Not Hispanic or Latino	2 (22.2)	2 (28.6)	4 (25.0)
Black or African American	1 (11.1)	0 (0.0)	1 (6.3)
BMI (kg/m^2): Mean (SD)	27.9 (5.17)	26.8 (3.43)	27.4 (4.39)
Annualized Bleeding Rate			
Mean (SD)	18.9 (11.97)	26.0 (32.49)	22.0 (22.62)
Median (IQR)	13.0 (11.0-24.0)	15.0 (9.0-20.0)	13.5 (11.0-22.0)
Hemophilia A with Inhibitor: n (%)	9 (100.0)	7 (100.0)	16 (100.0)
Highest Historical Inhibitor Level (BU)			
Mean (SD)	257.6 (362.77)	20.6 (25.87)	148.2 (284.95)
Median (IQR)	40.3 (16.0-768.0)	7.9 (1.9-40.8)	24.0 (7.7-64.0)
Most recent inhibitor level (BU)			
Mean (SD)	89.2 (186.91)	15.8 (22.10)	52.5 (133.41)
Median (IQR)	24.0 (4.4-40.3)	10.0 (1.9-17.6)	12.4 (4.0, 27.5)

BMI = body mass index; cm = centimeter; FVIII = Factor VIII; kg = kilogram; kg/m^2 = kilogram per square meter; N = number of subjects; n = number of subjects in the specified category; n (%) = count and percentage; SD = standard deviation; IQR = inter-quartile range; BU = Bethesda Units. *Study terminated early by Sponsor on 12 Nov 2021.

Crimson 1: Efficacy and Safety

74 Bleeds Reported Before Trial Termination, 66 Bleeds Evaluable for Efficacy

Treatment Success (Rated 'Excellent' or 'Good') at 24 Hours



Time to Cessation of Bleeding (minutes)

	SC MarzAA (N=8 subjects)	IV SOC (N=10 subjects)
Evaluable Bleeds	29	37
Mean (SD)	770.1 (645.5)	854.8 (954.2)
Median (IQR)	537.0 (180.0-1390.0)	360.0 (161.0-1380.0)

Essentially equivalent efficacy of SC MarzAA *vs* IV SOC at 24 hours

+ Slight differences in mean versus median time to bleeding cessation

Safe & well-tolerated

+ No injection site reactions (ISRs), drug-related adverse events, or thrombotic events
+ One serious adverse event unrelated to MarzAA or SOC (left vesico-ureteric junction calculus)
+ One subject with transient ADA

ISRs = injection site reactions, SAE = serious adverse event, ADA = anti-drug antibody

Additional Secondary Efficacy Endpoints

Higher Percentages of Bleeds had Effective Hemostasis Beyond First 3 Hours of Treatment with SC MarzAA *vs* IV SOC

Effective Hemostasis at X Hours After Initial Dose	Evaluable Bleeds SC MarzAA n=29 bleeds (%)	Evaluable Bleeds IV SOC n=37 bleeds (%)
1	7 (24.1)	16 (43.2)
3	14 (48.3)	22 (59.5)
6	21 (72.4)	25 (67.8)
9	24 (82.8)	26 (70.3)
12	25 (86.2)	28 (75.7)
48	26 (89.7)	32 (86.5)

Number of Doses and Cumulative Doses Administered for Successfully Treated Bleeds	Successfully Treated Bleeds SC MarzAA n=25 bleeds (%)	Successfully Treated Bleeds IV SOC n=32 bleeds (%)
1	10 (40.0)	22 (68.8)
2	8 (32.0)	9 (28.1)
3	4 (16.0)	0 (0.0)
≥4	3 (12.0)	1 (3.1)

SC MarzAA

+ Median T_{max}: ~9 hours[1]
+ $t_{1/2}$: ~17 hours[1]

+ While more doses of SC MarzAA were administered *vs* IV SOC, all took <7 minutes from reconstitution to completion of injection

1. Neuman L, et al. *Res Pract Thromb Haemost*. 2020;4(Suppl 1):PB0941.

Additional Secondary Efficacy Endpoints

SC MarzAA and IV SOC Both Have High Rates of Treatment Success at 24 Hours that Are Maintained at 48 Hours and Rarely Require Rescue Therapy

Percentage of Bleeds with Treatment Success	Treatment Success SC MarzAA n/N (%)	Treatment Success IV SOC n/N (%)
At 24 Hours	25/29 (86.2)	32/37 (86.5)
Among at 24 Hours, maintained at 48 Hours	24/25 (96.0)	31/32 (96.9)

Number of Rescue Therapy Needed (Treatment >24 Hours after First Dose)	Evaluable Bleeds SC MarzAA n (Medication, Dose[s])	Evaluable Bleeds IV SOC n (Medication, Dose[s])
1	1 subject (FEIBA, 50 U/kg/dose)	0
2	0	0
3	0	0
4	0	1 subject (COAGIL VII, 111 mcg/kg/dose)

MarzAA Anti-Drug Antibody (ADA) Case

One of 11 Subjects Treated with SC MarzAA Had Transient, Cross-Reactive ADAs

Per protocol, planned immunogenicity assessments (against MarzAA, NovoSeven, FVIIa, FVII) occurred at Screening, monthly during treatment periods, during immunogenicity assessment period, and at end of study

+ Crimson 1: 1/29 (3.4%) screened subjects excluded due to prior or current antibody against FVIIa
+ Prior MarzAA studies (MAA-102 & MAA-201): Exclusion of 2/14 (14.3%)[1] & 3/17 (17.6%)[2] screened subjects, respectively, due to FVII/FVIIa antibody detected during Screening

29-year-old Asian male with HA with inhibitors, baseline ABR 14, who tested negative for MarzAA ADA at Screening and over first 3 months of MarzAA exposure

Month 4: First positive MarzAA ADA

+ Cross-reactive to NovoSeven, FVIIa, and FVII; no sample available to test for neutralizing capacity

Immunogenicity Assessment Period: Second positive MarzAA ADA

+ Cross-reactive to NovoSeven, FVIIa, and FVII; neutralizing antibody tests for MarzAA and FVIIa negative

End of Study (2 months after last MarzAA exposure): MarzAA ADA negative

1. MAA-102 (NCT04072237) Clinical Study Report. 2. Mahlangu J, et al. *Res Pract Thromb Haemost*. 2021; 5:e12576.

Study Summary

Limited Results Suggest Parity of SC MarzAA & IV SOC for Bleed Treatment at 24 Hours

Efficacy data collected on 14% (66/488) of planned, evaluable bleeds among HA subjects with inhibitors

+ Recruitment challenges, due to pandemic-related logistical challenges, competition for subjects, and increasing availability of prophylaxis therapy globally, led to corporate decision to terminate Crimson 1 early
+ 86.2% vs. 86.5% treatment success at 24 hours for SC MarzAA vs. IV SOC

Well-tolerated, with no ISRs, drug-related adverse events, or thrombotic events

One subject developed transient, cross-reactive ADAs while receiving MarzAA

+ Has not prevented effectiveness of FEIBA to treat all subsequent bleeds
+ rFVIIa ADAs infrequent but known (between 3-7% in congenital FVII deficiency[1,2]), and low MarzAA ADA frequency also in line with ADA rate of other FVIII biologics used to treat severe hemophilia A[3-5]

Further evaluation of MarzAA for prevention/treatment of other bleeding disorders is warranted

1. Napolitano M, et al. *Haematologica*. 2013;98:538-544. 2. Eshghi P, et al. *Haemophilia*. 2019;25:e345-e349. 3. Mahlangu J, et al. *Blood*. 2016;128:630-637.
4. Paz-Priel I, et al. *Blood*. 2018;132:633. 5. Mahlangu J, et al. *Blood*. 2014;123:317-325.

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Questions?

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