Safety and Efficacy of the Anti-Tissue Factor Pathway Inhibitor Marstacimab in Participants With Severe Hemophilia Without Inhibitors: Results From the Phase 3 BASIS Trial and Ongoing Long-Term Extension Study

Suchitra S Acharya[1], Davide Matino[2], Andrew Palladino[3], Eunhee Hwang[3], Regina McDonald[4], Carrie Turich Taylor[5], John Teeter[5]

[1]Cohen Children's Medical Center, Northwell Hemostasis and Thrombosis Center, Northwell Health, New Hyde Park, NY, USA; [2]McMaster University, Hamilton, ON, Canada; [3]Pfizer Inc, Collegeville, PA, USA; [4]Pfizer Inc, New York, NY, USA; [5]Pfizer Inc, Groton, CT, USA

BACKGROUND

- Hemophilia A (HA) and hemophilia B (HB) are recessive, X-linked bleeding disorders associated with a deficiency of clotting factors VIII (FVIII) or IX (FIX), respectively.[1]
- Standard of care for HA and HB includes intravenous infusions of factor replacement therapy, either on-demand (OD) or through routine prophylaxis (RP).[1]
  - Challenges to factor replacement therapy include the development of inhibitors to exogenous FVIII and FIX and low adherence to intravenous injections. Thus, an unmet clinical need remains for alternative therapies for people with HA or HB.[1-4]
- Marstacimab (PF-06741086) is an investigational antibody that targets tissue factor pathway inhibitor to promote blood clot formation independently of FVIII- and FIX-dependent coagulation (intrinsic pathway).[5,6]
- Data from the marstacimab phase 1b/2 study (N=26) and its long-term follow-up phase 2 study (N=20) provided evidence that subcutaneous (SC) once-weekly (QW) dosing of marstacimab 150–450 mg was safe and effective for reducing the annualized bleeding rate (ABR) in participants with HA and HB with or without inhibitors.[7,8]
- BASIS (NCT03938792) is the pivotal phase 3 trial assessing the safety and efficacy of marstacimab for people with severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%), with or without inhibitors.

OBJECTIVE

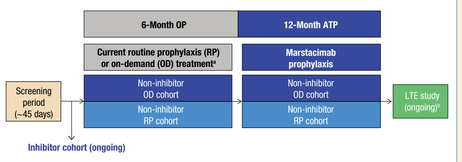
- Evaluate the safety and efficacy of marstacimab in participants without inhibitors compared with their previous factor replacement therapy.

METHODS

Study Design

- BASIS is a one-way, cross-over, open-label, multicenter, pivotal phase 3 trial that enrolled male participants with severe HA or moderately severe to severe HB with or without inhibitors.
- Patients were enrolled into 1 of 2 cohorts, depending on the presence of inhibitors (inhibitor cohort or non-inhibitor cohort).
  - We report the results for the non-inhibitor cohort; the inhibitor cohort is ongoing.
- Following screening, participants entered a 6-month observational phase (OP) wherein they continued their prescribed factor replacement therapy, either OD or as RP, before entering the 12-month active treatment phase (ATP).
- Participants who completed the ATP were eligible to continue into the long-term extension (LTE) study (NCT05145127) (**Figure 1**).

Figure 1: Study design of BASIS and its LTE



[a] Factor replacement therapy.
[b] Patients who completed the ATP were eligible to enter the ongoing LTE study. For each patient, the LTE study will continue for 7 years or until marstacimab is available in the patient's market, whichever comes earlier. Participants who discontinued or did not roll over to the LTE study were to complete a 1-month follow-up phase.
ATP=active treatment phase; LTE=long-term extension; OD=on-demand; OP=observational phase; RP=routine prophylaxis

Patient Population

- Males were aged 12 to <75 years with severe HA or moderately severe to severe HB, with or without inhibitors, and were receiving factor FVIII or FIX replacement therapy (**Table 1**).
- Following screening, participants were evaluated according to the treatment received during a 6-month OP (OD or RP) before entering the 12-month ATP.

Table 1: Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Male • ≥12 to <75 years of age • Severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%) • No detection or history of inhibitors against FVIII or FIX • OD group: ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion during the 6 months prior to enrollment • RP group: ≥80% compliance with FVIII/FIX regimen 6 months prior to enrollment	• Previous/current treatment for coronary artery diseases, venous or arterial thrombosis, ischemic disease, unstable liver or biliary disease, other hemostatic defects • eGFR <30 mL/min/1.73 m^2 • Current RP with bypassing agent, non-coagulation non-factor replacement therapy, or any previous gene therapy product • Current immunomodulatory drugs • Planned surgery during study period • Platelet count <100,000/µL • Hemoglobin level <10 g/dL • ALT >2× ULN; bilirubin >1.5× ULN; serum albumin <LLN

ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate; FIX=factor IX; FVIII=factor VIII; HA=hemophilia A; HB=hemophilia B; LLN=lower limit of normal; OD=on-demand; RP=routine prophylaxis, ULN=upper limit of normal

Dosing Procedures

- Participants in the ATP received a single loading dose of 300 mg marstacimab (administered as two 150 mg SC injections), followed by 150 mg SC QW doses.
  - After 6 months, participants who met prespecified dose escalation criteria could have their dose increased to 300 mg SC QW.
  - Dosing considerations were determined from previous phase 1/2 studies, as well as supporting evidence from publicly available information of other investigational compounds.[8,9]
- Participants who completed the ATP continued their dosing regimen in the LTE study.

Study Endpoints

- Safety assessments included monitoring of serious adverse events (SAEs) and adverse events of special interest (AESIs; including thrombotic or embolic events, injection site reactions, hypersensitivity, and anaphylactic shock).
  - During screening and the 6-month OP, AEs were collected during 2 clinic visits and 3 phone calls. During the 12-month ATP, AEs were collected during 9 clinic visits and 5 phone calls.
- Immunogenicity was assessed through antidrug antibodies (ADA) or neutralizing antibodies (NAb).
- The primary efficacy endpoint was the ABR for treated bleeds with marstacimab compared with prior OD and RP therapy in the OP:
  - Superiority vs prior OD therapy.
  - Non-inferiority vs prior RP.
- The secondary efficacy endpoints included the ABR for the bleed categories: joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds (treated and untreated).
- The primary completion date for the non-inhibitor cohort was April 17, 2023.
  - We present efficacy and immunogenicity data from BASIS with up to an additional 16 months of follow-up with continued marstacimab prophylaxis in the LTE study.
  - Safety data for the current analysis was from BASIS and the later data cutoff up to an additional 23 months in the LTE study.

Statistical Analysis

- ABR was calculated as the number of bleeds requiring treatment / (days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
- Mean estimated ABR was based on a repeated-measure negative binomial regression model via a generalized estimating equation approach with a log link function for comparison vs OD and with an identity link function for comparison vs prior RP.
- The primary hypotheses and decision rules for the primary endpoint of ABR for treated bleeds were applied during the BASIS study. Bleed rates during the LTE were descriptively summarized and compared.
  - OD group during ATP: P values are for the null hypothesis that ABR ratio (marstacimab prophylaxis / OD) = 0.5. The superiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI was <0.5.
  - RP group during the ATP: P values are for the null hypothesis that the difference (marstacimab prophylaxis – routine prophylaxis) = 0. Non-inferiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI was <2.5. Superiority was declared when the upper bound of the 95% CI was <0.
- Primary efficacy analysis evaluated the efficacy of marstacimab 150 mg dose via censoring bleeding records on or after a dose increase to 300 mg. Duration of escalated dose was not included in the primary endpoint assessment.

RESULTS

Patients

- 128 participants (median age 30 [range 13–66] years) entered the OP (OD: HA n=29, HB n=8; RP: HA n=72, HB n=19) (**Table 2**).
  - The majority of participants were adults (84.4%), with HA (78.9%) and ≥1 target joint (69.5%).

Table 2: Baseline demographics and characteristics

	Baseline (OP)		
	OD n=37	RP n=91	Overall N=128
Age, median (range), y	29.0 (15–58)	31.0 (13–66)	30.0 (13–66)
Adolescent (≥12 to <18 y), n (%)	2 (5.4)	18 (19.8)	20 (15.6)
Adult (≥18 to <75 y), n (%)	35 (94.6)	73 (80.2)	108 (84.4)
Hemophilia type, n (%)			
HA	29 (78.4)	72 (79.1)	101 (78.9)
HB	8 (21.6)	19 (20.9)	27 (21.1)
Race, n (%)			
Asian	24 (64.9)	37 (40.7)	61 (47.7)
Black	0	1 (1.1)	1 (0.8)
White	13 (35.1)	52 (57.1)	65 (50.8)
Not reported	0	1 (1.1)	1 (0.8)
Region, n (%)			
Asia	23 (62.2)	31 (34.1)	54 (42.2)
Europe	8 (21.6)	39 (42.9)	47 (36.7)
North America	4 (10.8)	11 (12.1)	15 (11.7)
Middle East	2 (5.4)	10 (11.0)	12 (9.4)
BMI ± SD, kg/m^2	23.7 ± 5.6	23.9 ± 4.2	23.8 ± 4.6
No. target joints at BL assessment, n (%)			
0	1 (2.7)	38 (41.8)	39 (30.5)
1	8 (21.6)	21 (23.1)	29 (22.7)
2	16 (43.2)	15 (16.5)	31 (24.2)
≥3	12 (32.4)	17 (18.7)	29 (22.7)

BL=baseline; BMI=body mass index; HA=hemophilia A; HB=hemophilia B; OD=on-demand; OP=observational phase; RP=routine prophylaxis

- Of the participants enrolled in the OP, 116 (OD n=33, RP n=83) received ≥1 dose of marstacimab in the ATP.
- At the time of the primary completion date, 87 participants continued treatment in the LTE and had efficacy and immunogenicity data (at 16-month data cutoff, OD n=29, RP n=58).
- At the later data cutoff (Month 23), 107 participants continued treatment in the LTE and had safety data (at data cutoff, OD n=32, RP n=75).
- Marstacimab treatment duration and exposure are shown in **Table 3**.

Table 3: Summary of marstacimab exposure during BASIS and the LTE study

Duration of treatment (days)[a]	OD	RP	Overall
BASIS, n	33	83	116
Median (range)	364.0 (334.0–392.0)	364.0 (28.0–383.0)	364 (28.0–392.0)
LTE (≤16 months), n	29	58	87
Median (range)	220.0 (36.0–435.0)	180.0 (34.0–483.0)	193.0 (34.0–483.0)
LTE (≤23 months), n	32	75	107
Median (range)	416.5 (36.0–654.0)	343.0 (147.0–693.0)	380.0 (36.0–693.0)
Exposure days per participant[b]			
BASIS, n	33	83	116
Median (range)	52.0 (40.0–56.0)	52.0 (4.0–54.0)	52.0 (4.0–56.0)
LTE (≤16 months), n	29	58	87
Median (range)	31.0 (5.0–62.0)	25.5 (5.0–68.0)	28.0 (5.0–68.0)
LTE (≤23 months), n	32	75	107
Median (range)	59.0 (5.0–93.0)	48.0 (21.0–98.0)	54.0 (5.0–98.0)

[a] Defined as the last dose date – the first dose date + 7.
[b] Total number of days injections occurred per participant, ie, the total number of exposure days on which marstacimab was administered.
LTE=long-term extension; OD=on-demand; RP=routine prophylaxis

Safety

Serious Adverse Events

- No deaths or thromboembolic events were reported during BASIS or the LTE study (**Table 4**).
- In the ATP, no participants experienced SAEs in the OD group, and 7/83 (8.4%) participants experienced SAEs in the RP group (**Table 4**).
  - 1 participant experienced an SAE of grade 1 peripheral swelling (calf) considered to be treatment-related that was diagnostically confirmed to be unrelated to a bleeding or thrombotic event.
  - 1 participant discontinued the ATP due to a non–treatment-related SAE of meningioma requiring surgery.
- In the LTE, no participants in the OD group experienced SAEs vs 5/75 (6.7%) in the RP group (**Table 4**).
  - No SAEs were considered treatment-related.
  - No participants discontinued due to SAEs.
- The incidence of AESIs are shown in **Table 4**.
  - In the OD group, AESIs occurred in 24.3% of participants in the OP, 42.4% in the ATP, and none in the LTE study.
  - In the RP group, AESIs occurred in 16.5% of participants in the OP, 55.4% in the ATP, and 20% in the LTE study.

Table 4: Summary of serious adverse events and adverse events of special interest

	OD		RP		OD	RP
	OP n=37	Marstacimab prophylaxis during ATP n=33	OP n=91	Marstacimab prophylaxis during ATP n=83	Marstacimab prophylaxis during LTE n=32	Marstacimab prophylaxis during LTE n=75
SAEs[a]	1 (2.7)	0	2 (2.2)	7 (8.4)	0	5 (6.7)
Treatment-related	NA	0	NA	1 (1.2)	0	0
Discontinued due to AEs	0	0	0	1 (1.2)[b]	0	0
Patients with an AESI, n (%)	9 (24.3)	14 (42.4)	15 (16.5)	46 (55.4)	0	15 (20.0)
AESIs (≥5%)[c], n (%)						
COVID-19	0	2 (6.1)	3 (3.3)	19 (22.9)	0	4 (5.3)
Hemorrhage	1 (2.7)	0	5 (5.5)	13 (15.7)	0	4 (5.3)
Hepatic disorders	7 (18.9)	7 (21.2)	3 (3.3)	4 (4.8)	0	0
Hypersensitivity	0	2 (6.1)	2 (2.2)	6 (7.2)	0	4 (5.3)
Hypertension	1 (2.7)	2 (6.1)	2 (2.2)	5 (6.0)	0	2 (2.7)
Injection site reactions	0	2 (6.1)	0	9 (10.8)	0	6 (8.0)
Deaths or SAEs related to thromboembolism	0	0	0	0	0	0

As described in the methods, differences in study phase duration and frequency of provider assessments of AEs should be considered when comparing safety data between the study periods.
[a] Number of participants with SAEs.
[b] Discontinued after surgical resection for non–treatment-related SAE of atypical meningioma.
[c] AESIs are listed by event type by standardized MedDRA query (MedDRA v25.1 coding dictionary was applied).
AE=adverse event; AESI=adverse event of special interest; ATP=active treatment phase; LTE=long-term extension; OD=on-demand; OP=observational phase; RP=routine prophylaxis; SAE=serious adverse event

Immunogenicity

- ADAs developed in 23/116 participants (19.8% incidence), of which titers were low and resolved in 22 participants by end of the ATP.
  - Of the 23 participants positive for ADAs, 6 were also positive for NAbs, all of which were treatment-induced and resolved by the end of the ATP.
- In the LTE study, 1/44 (2.3%) participant was persistently ADA-positive.
  - The ADA titer was negative in the OP but positive at the end of the ATP (titer 2.48), positive at Day 180 in the LTE (titer 2.41), and the participant tested negative for NAbs at both timepoints.

Dose Escalation

- In the ATP, 14 participants (OD n=3, RP n=11) met dose-escalation criteria and increased marstacimab dose from 150 mg to 300 mg SC QW.
- Of these participants, 10 continued into the LTE study and received 300 mg SC QW. An additional 4 participants had their dose escalated during the LTE study (total participants with escalated dose: OD n=3, RP n=11).

Incidence of Treated Bleeds

- Marstacimab significantly lowered the mean ABR for treated bleeds vs prior OD therapy (superiority; P<0.0001; **Figure 2A**) and prior RP therapy (non-inferiority and superiority; P=0.0376; **Figure 2B**).
  - Mean ABR declined over the first 6 months and continued to decrease in the second 6 months of the ATP (**Table 5**).

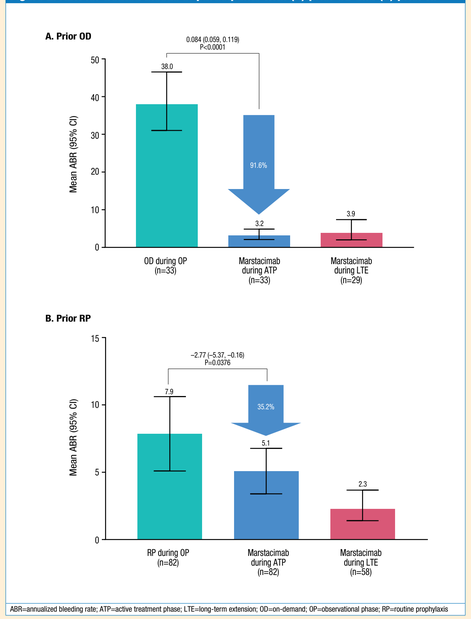
Table 5: Time profile of the ABR of treated bleeding events in the ATP

Group[a]	OD		RP	
Treatment phase	ATP Months 1–6 marstacimab prophylaxis n=33	ATP Months 7–12 marstacimab prophylaxis n=33	ATP Months 1–6 marstacimab prophylaxis n=83	ATP Months 7–12 marstacimab prophylaxis n=79
Mean estimated ABR (95% CI)	3.93 (2.35, 6.57)	2.39 (1.53, 3.72)	5.36 (3.72, 7.73)	3.61 (2.44, 5.35)
Median ABR (range)	2.00 (0.00–35.93)	2.03 (0.00–10.15)	2.00 (0.00–39.92)	0.00 (0.00–30.95)

[a] The time interval of marstacimab treatment starts from the ATP and includes participants who received ≥1 dose of marstacimab prophylaxis in the ATP after completing the OP.
ABR=annualized bleeding rate; ATP=active treatment phase; OD=on-demand; OP=observational phase; RP=routine prophylaxis

- In the LTE, bleed rates up to an additional 16 months were consistent with the ATP for the OD group (**Figure 2A**), and reductions continued for the RP group (**Figure 2B**).

Figure 2: ABR for treated bleeds of participants with (A) prior OD and (B) prior RP

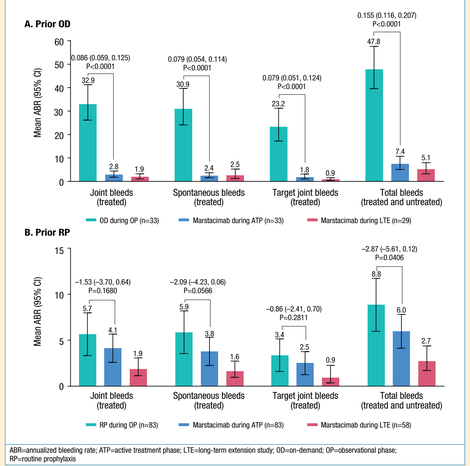


ABR=annualized bleeding rate; ATP=active treatment phase; LTE=long-term extension; OD=on-demand; OP=observational phase; RP=routine prophylaxis

ABR for Bleed Categories

- Marstacimab significantly reduced ABR across all secondary bleed categories vs OD (superiority; P<0.0001; **Figure 3A**) and numerically reduced ABR vs RP (non-inferiority; **Figure 3B**).
- The reductions in ABR during the ATP were maintained or further reduced in the LTE (**Figure 3**).

Figure 3: ABR for bleed categories of participants with (A) prior OD and (B) prior RP



ABR=annualized bleeding rate; ATP=active treatment phase; LTE=long-term extension study; OD=on-demand; OP=observational phase; RP=routine prophylaxis

CONCLUSIONS

- Marstacimab 150 mg SC QW was safe and well tolerated over the 12-month ATP and for up to 23 months of the LTE study.
  - No deaths or thrombotic or embolic events were observed.
- Marstacimab significantly reduced the ABR of treated bleeds vs prior OD (superiority; P<0.0001) and RP therapy (non-inferiority and superiority; P=0.0376) in the ATP.
  - Bleed rates declined over the first 6 months and continued to Month 12 of the ATP.
- Marstacimab significantly reduced ABR across all secondary bleed categories vs prior OD therapy (superiority; P<0.0001) and numerically reduced ABR vs prior RP (meeting all non-inferiority criteria) in the ATP.
- Reductions in ABR for all primary and secondary bleed categories continued to decline or were maintained up to an additional 16 months of follow-up in the LTE study.
- Overall, long-term marstacimab prophylaxis was safe and effective in participants with severe HA or moderately severe to severe HB without inhibitors.

REFERENCES

1. Srivastava A, et al. Haemophilia 2020;26(suppl 6):1-158. **2.** Berntorp E, et al. Nat Rev Dis Primers 2021;7:45. **3.** Jiménez-Yuste V, et al. Haemophilia 2021;27:340-50. **4.** Mancuso ME, et al. Lancet 2021;397:630-40. **5.** Nogami K, Shima M. Blood 2019;133:399-406. **6.** Pittman DD, et al. Res Pract Thromb Haemost 2022;6:e12679. **7.** Apgar J, et al. Res Pract Thromb Haemost 2020;4(suppl 1):abstr PB0240. **8.** Mahlangu JN, et al. Br J Haematol 2023;200:229-39. **9.** Mahlangu J, et al. Br J Haematol 2023;200:240-8.

DISCLOSURES

SSA: Advisory board: Bayer, Pfizer. **DM:** Research funding: Bayer, Novo Nordisk, Octapharma, Pfizer, Roche Sanofi, Spark Therapeutics; honoraria: Bayer, Novo Nordisk, Octapharma, Pfizer, Sanofi, Sobi. **EH and JT:** Were employees of Pfizer at the time of study conduct; shareholders in Pfizer. **AP, RM, and CTT:** Employees and shareholders in Pfizer.

ACKNOWLEDGMENTS

This study was funded by Pfizer. Medical writing support was provided by Jake Evans, PhD, of Engage Scientific Solutions and funded by Pfizer.

Electronic Poster

Please scan this QR code with your smartphone app to view or obtain a copy of this poster. If you don't have a smartphone, access the poster via the Internet at: https://scientificpubs.congressposter.com/p/u3t0yg0k7gxwdmpe

Presented at the Thrombosis & Hemostasis Societies of North America (THSNA) Summit, April 4–6, 2024, Chicago, IL, USA