Joint Health in Participants With Hemophilia A and Hemophilia B Without Inhibitors Treated With Marstacimab From the Phase 3 BASIS Trial

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Plain Language Summary

What is marstacimab?

- Marstacimab is an antibody being studied by researchers as a treatment for people with hemophilia A or B.
- Marstacimab works by attaching to a protein in the blood called Tissue Factor Pathway Inhibitor (TFPI for short).
- TFPI is a protein that naturally slows down blood clotting. Marstacimab helps balance blood flowing freely or clotting when needed. Marstacimab attaches to TFPI and stops it from slowing down blood clotting.
- This means that treatment with marstacimab can help blood to clot in people with hemophilia.

Why was this study done?

- Researchers are looking at the effects of marstacimab in men with severe hemophilia A and men with moderately severe and severe hemophilia B in a study called BASIS.
- The researchers wanted to see how marstacimab affected the men's joints compared with the treatment they had before marstacimab. The men previously had on-demand treatment (to manage bleeding) or prophylaxis (to stop bleeding in severe cases).

What were the results of the study?

After receiving marstacimab for 1 year:

In the on-demand group:

- 91% ↓ The number of bleeding events in joints decreased by 91%
- 92% ↓ The number of bleeding events in target joints* decreased by 92%
- Men had fewer target joints*

In the prophylaxis group:

- 27% ↓ The number of bleeding events in joints decreased by 27%
- 25% ↓ The number of bleeding events in target joints* decreased by 25%
- There was a small improvement in the men's joint health scores
- The effect of marstacimab on reducing bleeding events continued after 1 year

*A target joint is a joint where there have been 3 or more bleeds in a 6-month time span.

Plain Language Summary (PLS)
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Plain Language Study Results Summaries are descriptions in everyday language of the design and results of clinical studies. These summaries (also called layperson summaries, plain language summaries, lay language summaries, simple summaries, and trial results summaries) are intended to make the clinical results of these studies understandable and accessible to patients, healthcare providers, caregivers, researchers, and a general audience.

BACKGROUND

- Hemophilia is an X-linked recessive bleeding disorder characterized by spontaneous or traumatic bleeding manifestations at the joints, muscles, skin, mucosal soft tissues, internal organs, and brain.[1]
- Hemophilia A (HA) and hemophilia B (HB) are caused by deficiencies of clotting factors VIII (FVIII) and IX (FIX), respectively.
- Standard of care for people with hemophilia includes intravenous infusions of factor replacement therapy, either on-demand (OD) or routine prophylaxis (RP).[1]
  - Challenges to factor replacement therapy include the development of inhibitors to exogenous FVIII and FIX.
  - As such, there still remains an unmet need for alternative therapies for people with hemophilia.[1,2]
- Marstacimab (PF-06741086) is an investigational antibody for the treatment of people with severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%), with or without inhibitors.[1,3,4]
  - Marstacimab targets the K2 domain of tissue factor pathway inhibitor to alleviate factor VII and factor X inhibition to promote thrombin production and clot formation.[4,5]
- Data from the phase 1b/2 study (N=26) and its long-term follow-up study (N=20) of participants with HA and HB, with or without inhibitors, demonstrated that once-weekly (QW) subcutaneous (SC) marstacimab (150–450 mg) was safe and effective for reducing annualized bleeding rate (ABR).[3,6]
- Data on the impact of marstacimab musculoskeletal outcomes have not been analyzed previously.

OBJECTIVE

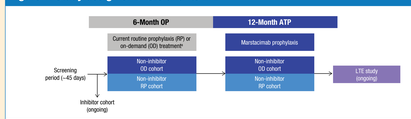
- To examine joint health data of BASIS participants without inhibitors.

METHODS

Study Design

- BASIS (NCT03938792) is a single-arm, open-label, multicenter, pivotal phase 3 trial that compared the safety and efficacy of marstacimab for people with severe HA or moderately severe to severe HB, with or without inhibitors, over a 12-month active treatment phase (ATP) vs prior factor replacement therapy during a 6-month observational phase (OP).
  - Participants who completed the ATP were eligible to continue into the long-term extension (LTE) study (NCT05145127) (**Figure 1**).
  - During the 6-month OP, participants received either OD treatment or RP factor replacement therapy.

Figure 1: Study design of BASIS and its LTE



* Factor replacement therapy.
ATP=active treatment phase; LTE=long-term extension; OP=observational phase

Dosing Procedures

- Participants in the ATP received a single loading dose of 300 mg marstacimab administered as two 150 mg SC injections, followed by SC 150 mg QW doses. After 6 months, participants who met prespecified dose escalation criteria could increase their dose to 300 mg QW.
  - Dosing considerations included safety, tolerability, efficacy, pharmacokinetic and pharmacodynamic parameters and modeling results, immunogenicity, and biopharmaceutics observations in non-inhibitor participants from previous phase 1b/2 and phase 2 studies, as well as supporting evidence from publicly available information of other investigational compounds.[3,6]

Patient Population

- Males aged 12 to <75 years with severe HA or moderately severe to severe HB, with or without inhibitors, were screened for enrollment into the 6-month OP (**Table 1**).

Table 1: Key inclusion and exclusion criteria

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

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

Primary Study Endpoint

- The primary study endpoint for BASIS was ABR for treated bleeds with marstacimab compared with prior OD and RP therapy.
  - These data have been presented elsewhere but are included here for context.[7]

Joint Health Assessment Measures

- ABR for joint and target joint bleeds were compared with prior OD and RP therapy.
- Change from baseline in the Hemophilia Joint Health Score (HJHS; v2.1) was used to evaluate joint total and global gait scores.[8]
  - The HJHS total score ranges from 0 to 124, with a lower score indicative of better joint health.
- The reference treatment duration in the OP was 6 months. As marstacimab prophylaxis was administered for 12 months, the main comparison time point between the OP and ATP is 6 months.
  - Effect size was calculated as [estimated median difference] / (SD at OP baseline); small effect size = 0.2 SD units; medium effect size = 0.5; large effect size = 0.8.
- The number of target joints were compared with prior OD and RP therapy.
  - Target joint was defined as a major joint such as the hip, elbow, wrist, shoulder, knee, and ankle, into which ≥3 spontaneous bleeds occurred in a single joint within a consecutive 6-month period.
  - The number of target joints was derived from an eDiary tallied during the treatment period.
- No joint imaging modalities were utilized as a component of joint health assessment in this study.

RESULTS

Patient Demographics and Clinical Characteristics

- In total, 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%), had HA (78.9%), and had ≥1 target joint (69.5%).
- Of those enrolled, 116 participants (**OD** n=33, **RP**, n=83) received ≥1 dose of marstacimab in the ATP.
  - Median (range) treatment duration was 364 (28–392) days in the ATP.
- A total of 87 participants continued treatment in the LTE; at the time of data cut: **OD:** n=29, **RP:** n=58.
  - Median (range) treatment duration was 193 (34–483) days in the LTE.
    - Data were unavailable by the cutoff date for 1 RP participant and were not included in the LTE safety analysis set; thus, 87/88 participants who entered the LTE were evaluated for joint health.

Table 2: Participant demographics at baseline

	Baseline (OP)		
	OD n=37	RP n=91	Overall N=128
Age, median (range), y	29.0 (15.0–58.0)	31.0 (13.0–66.0)	30.0 (13.0–66.0)
Adolescent (≥12 to <18 y), n (%)	2.0 (5.4)	18.0 (19.8)	20.0 (15.6)
Adult (≥18 to <75 y), n (%)	35.0 (94.6)	73.0 (80.2)	108.0 (84.4)
Hemophilia type, n (%)			
Hemophilia A	29.0 (78.4)	72.0 (79.1)	101.0 (78.9)
Hemophilia B	8.0 (21.6)	19.0 (20.9)	27.0 (21.1)
Race, n (%)			
Asian	24.0 (64.9)	37.0 (40.7)	61.0 (47.7)
Black	0	1.0 (1.1)	1.0 (0.8)
White	13.0 (35.1)	52.0 (57.1)	65.0 (50.8)
Not reported	0	1.0 (1.1)	1.0 (0.8)
Region, n (%)			
Asia	23.0 (62.2)	31.0 (34.1)	54.0 (42.2)
Europe	8.0 (21.6)	39.0 (42.9)	47.0 (36.7)
North America	4.0 (10.8)	11.0 (12.1)	15.0 (11.7)
Middle East	2.0 (5.4)	10.0 (11.0)	12.0 (9.4)
BMI ± SD, kg/m^2	23.7 ± 5.6	23.9 ± 4.2	23.8 ± 4.6
Number of target joints at baseline assessment, n (%)			
0	1.0 (2.7)	38.0 (41.8)	39.0 (30.5)
1	8.0 (21.6)	21.0 (23.1)	29.0 (22.7)
2	16.0 (43.2)	15.0 (16.5)	31.0 (24.2)
≥3	12.0 (32.4)	17.0 (18.7)	29.0 (22.7)

BMI=body mass index; OD=on demand; OP=observational phase; RP=routine prophylaxis

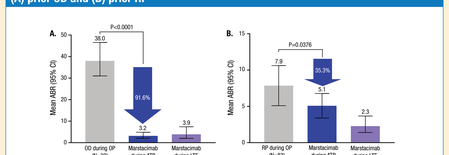
Incidence of Treated Bleeds

- Marstacimab demonstrated superiority (P<0.0001) over prior OD, with a reduction in mean ABR of 91.6%. Efficacy was maintained in the LTE (**Figure 2A**).
- Marstacimab demonstrated superiority and non-inferiority (P<0.0376) to prior RP, with a reduction in mean ABR of 35.3%. Further reductions were observed in the LTE (**Figure 2B**).

Incidence of Joint Bleeds

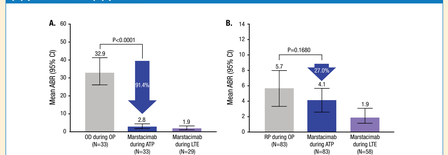
- Marstacimab demonstrated superiority (P<0.0001) over prior OD, with a reduction in mean ABR of 91.4% (**Figure 3A**).
  - Further numerical reductions in mean (95% CI) ABR were observed in the LTE: 1.9 (95% CI: 1.1, 3.3).
- Marstacimab demonstrated non-inferiority to prior RP, with a reduction in mean ABR of 27.0% (**Figure 3B**).
  - Further numerical reductions in mean (95% CI) ABR were observed in the LTE: 1.9 (1.1, 3.1).

Figure 2: ABR for treated bleeds during the OP, ATP, and LTE for participants with (A) prior OD and (B) prior RP



ABR was based on a repeated measure negative binomial regression model via a generalized estimating equation approach with a log link function.
For prior OD, P value for the null hypothesis that the ratio=0.5. The superiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI was below 0.5.
For prior RP, P value for the null hypothesis of difference=0. Non-inferiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI lies below 2.5. Superiority was declared when the upper bound of the 95% CI lies below 0. Percentage reduction between OP and ATP treatment calculated using mean ABR values.
ABR=annualized bleeding rate; ATP=active treatment phase; LTE=long-term extension; OD=on-demand; OP=observational phase; RP=routine prophylaxis

Figure 3: ABR for joint bleeds during the OP, ATP, and LTE for participants with (A) prior OD and (B) prior RP

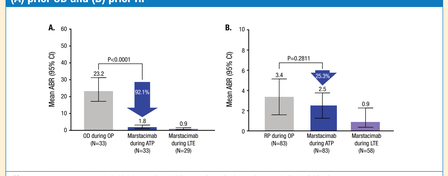


ABR was based on a repeated measure negative binomial regression model via a generalized estimating equation approach with a log link function.
For prior OD, P values for the null hypothesis that the ratio=0.5 for all bleed-related parameters. The superiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI was below 0.5.
For prior RP, P value for the null hypothesis of difference=0. Non-inferiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI lies below 2.5. If non-inferiority was established, then a testing for superiority was conducted. Percentage reduction between OP and ATP treatment calculated using mean ABR values.
ABR=annualized bleeding rate; ATP=active treatment phase; LTE=long-term extension study; OD=on demand; OP=observational phase; RP=routine prophylaxis

Incidence of Target Joint Bleeds

- Marstacimab demonstrated superiority (P<0.0001) over prior OD, with a reduction in mean ABR of 92.1% (**Figure 4A**).
  - Further numerical reductions in mean (95% CI) ABR were observed in the LTE: 0.9 (0.5, 1.6).
- Marstacimab demonstrated non-inferiority to prior RP, with a reduction in mean ABR of 25.3% (**Figure 4B**).
  - Further numerical reductions were observed in the LTE: 0.9 (95% CI: 0.4, 2.3).

Figure 4: ABR of target joint bleeds during the OP, ATP, and LTE for participants with (A) prior OD and (B) prior RP

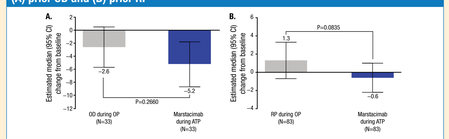


ABR was based on a repeated measure negative binomial regression model via a generalized estimating equation approach with a log link function.
For prior OD, P values for the null hypothesis show that the ratio=0.5 for all bleeding-related parameters. Superiority of marstacimab prophylaxis was declared when the upper bound of the 95% CI was below 0.5.
For prior RP, P value for the null hypothesis of difference=0. Non-inferiority of marstacimab prophylaxis is declared when the upper bound of the 95% CI lies below 2.5. If non-inferiority was established, then a testing for superiority was conducted. Percentage reduction between OP and ATP treatment calculated using mean ABR values.
ABR=annualized bleeding rate; ATP=active treatment phase; LTE=long-term extension study; OD=on demand; OP=observational phase; RP=routine prophylaxis

HJHS

- The estimated median change from baseline in HJHS total score was numerically lower for marstacimab compared with prior OD therapy, with a resulting estimated median (95% CI) difference of −2.8 (−7.6, 2.1) points, corresponding to an observed effect size of 0.17 SD units, indicating a negligible effect of marstacimab over OD (**Figure 5A**).
  - The observed reduction was maintained to Day 180 of the LTE: mean (SD) change from LTE baseline, 1.1 (2.5); n=19 (data not shown).
- The estimated median change from baseline in HJHS total score was numerically lower for marstacimab compared with prior RP therapy, with a resulting estimated median (95% CI) difference of −2.0 (−4.3, 0.3) points, corresponding to an observed effect size of 0.11 SD units, indicating a negligible effect of marstacimab over RP (**Figure 5B**).
  - The observed reduction was maintained to Day 180 of the LTE: mean (SD) change from LTE baseline, −2.7 (14.3); n=24 (data not shown).

Figure 5: Change from baseline in HJHS score at Month 6 for participants with (A) prior OD and (B) prior RP

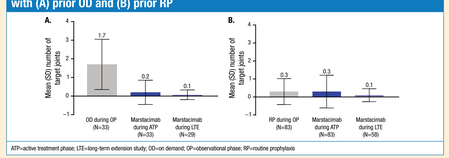


Exact CI using Walsh averages, P value from Wilcoxon signed rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.
ATP=active treatment phase; HJHS=Hemophilia Joint Health Score; MAR=missing at random; OD=on demand; OP=observational phase; RP=routine prophylaxis

Number of Target Joints

- The mean (SD) number of target joints was lower with marstacimab treatment in the ATP (0.2 [0.7]) compared with prior OD in the OP (1.7 [1.4]), and was maintained over the LTE (0.07 [0.258]) (**Figure 6A**).
- The mean (SD) number of target joints was similar for marstacimab treatment in the ATP (0.3 [0.9]) compared with prior RP in the OP (0.3 [0.7]), and was maintained over the LTE (0.1 [0.4]) (**Figure 6B**).

Figure 6: Mean number of target joints during the OP, ATP, and LTE for participants with (A) prior OD and (B) prior RP



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

CONCLUSIONS

- In participants with severe HA or moderately severe to severe HB, dosing with 150 mg QW SC marstacimab:
  - Significantly reduced the ABR of joint bleeds and target joint bleeds vs prior OD therapy, demonstrating superiority.
  - Was non-inferior to RP with regard to the ABR of joint bleeds and target joint bleeds vs prior RP.
    - Reductions were maintained in the LTE.
  - Resulted in a numerical improvement (negligible) in HJHS scores at 6 months of the ATP that continued in the LTE vs prior OD and RP.
  - Reduced the number of target joints vs prior OD therapy and maintained the number of target joints vs prior RP in the ATP and LTE.
    - The absence of imaging data for joint health is a limitation of this subanalysis.
- The discrepancy between the reductions observed in ABR of joint and target joint bleeds and minor improvements in HJHS scores may be attributed to the study population having a high degree of established hemophilic arthropathy that may lag behind an initial reduction in ABR.

REFERENCES

1. Srivastava A, et al. Haemophilia 2020;26(suppl 6):1-158. **2.** Jiménez-Yuste V, et al. Haemophilia 2021;27:340-50. **3.** Mahlangu JN, et al. Br J Haematol 2023;200:229-39. **4.** Pittman DD, et al. Res Pract Thromb Haemost 2022;6:e12679. **5.** Apgar J, et al. Res Pract Thromb Haemost 2020;4(suppl 1) 2020 ISTH congress [abstract]. **6.** Mahlangu J, et al. Br J Haematol 2023;200:240-8. **7.** Matino D, et al. Blood 2023;142:285. **8.** Gouw SC, et al. Haemophilia 2019;25:e1-e10.

DISCLOSURES

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