PO065

Health-Related Quality of Life Outcomes for Marstacimab in Participants With Severe Hemophilia A or Moderately Severe to Severe Hemophilia B Without Inhibitors: Results From the Phase 3 BASIS Trial

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INTRODUCTION

- Hemophilia is a genetic bleeding disorder characterized by the deficiency of clotting factors, primarily factor VIII (FVIII) in hemophilia A (HA) or factor IX (FIX) in hemophilia B (HB).[1,2]
- Standard of care treatment for people with hemophilia includes intravenous infusions of factor replacement therapy (FRT), either on-demand (OD) or as routine prophylaxis (RP).[1,2]
- Challenges associated with FRT include the development of inhibitors to exogenous FVIII and FIX, limited venous access, and inadequate adherence to regular intravenous injections.[1-5]
- The burden of management and the clinical sequelae of hemophilia negatively impact health-related quality of life (HRQoL) and self-reported health status.[6,7]
- Alternative non-factor agents have shown increased risk of thromboembolic events and lack of efficacy in HB.[1,5,8]
- As such, an unmet need for alternative therapies for people with hemophilia remains.
- Marstacimab is a tissue factor pathway inhibitor (TFPI) antibody for the treatment of severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%), with or without inhibitors.[9-11]
- In the pivotal phase 3 BASIS trial, a 150 mg subcutaneous (SC) weekly (QW) dose of marstacimab resulted in a significant reduction in annualized bleeding rate (ABR) compared with previous FRT over a 12-month active treatment phase (ATP) and up to an additional 16 months in the open-label extension (OLE).[12]

OBJECTIVE

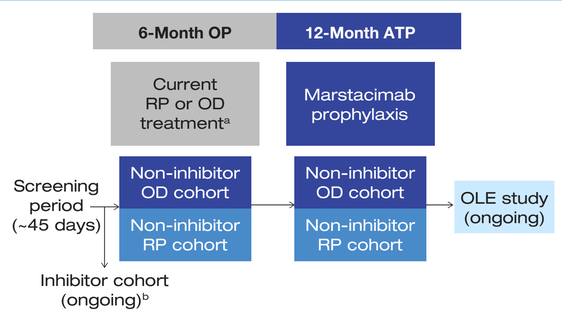
- To evaluate HRQoL outcomes participants without inhibitors in BASIS.

METHODS

Study Design and Patient Population

- BASIS (NCT03938792) is an open-label, single arm, one-way cross-over, multicenter, pivotal phase 3 trial assessing the efficacy and safety of marstacimab over a 12-month ATP (**Figure 1**).
  - The primary efficacy endpoint, ABR for treated bleeding events with marstacimab compared with prior OD or RP therapy, was previously reported.[12]

Figure 1: Study design of BASIS and its OLE



[a] Factor replacement therapy.
[b] The study design is also applicable to the inhibitor cohort who entered a 6-month OP, followed by the 12-month ATP with the option to continue into the OLE study.
ATP=active treatment phase; OD=on-demand; OLE=open-label extension; OP=observational phase; RP=routine prophylaxis

- Eligible participants (males aged 12 to <75 years) with severe HA or moderately severe to severe HB were enrolled into 1 of 2 cohorts depending on the presence of inhibitors (inhibitor vs non-inhibitor cohorts) (**Table 1**).
  - Here we report results for the non-inhibitor cohort; the inhibitor cohort is ongoing.
- Participants were grouped according to the treatment received (OD or RP) during a 6-month observational phase (OP) before entering the 12-month ATP to receive marstacimab.
- Marstacimab dosing procedures consisted of an initial 300 mg SC loading dose administered as two 150 mg SC injections, followed by a 150 mg SC QW dose during the 12-month ATP.
  - After 6 months in the ATP, participants meeting protocol-defined criteria could increase their marstacimab dose to 300 mg SC QW.
- Participants who completed the ATP were eligible to continue into the OLE (NCT05145127).

Table 1: Key inclusion and exclusion criteria (non-inhibitor cohort)

Key inclusion criteria	Key exclusion criteria
• Male • Aged ≥12 to <75 years • 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 before enrollment during the 6-month period prior to enrollment • RP group: ≥80% compliance with FVIII/FIX regimen 6 months before enrollment	• Previous/current treatment for coronary artery diseases, venous or arterial thrombosis, ischemic disease, unstable liver or biliary disease, and other hemostatic defects • Scheduled surgery during the study period • Platelet count <100,000/μL • Hemoglobin level <10 g/dL • ALT >2× ULN; bilirubin >1.5× ULN; serum albumin <LLN • 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

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

Evaluation of HRQoL

- The evaluation of HRQoL was a planned secondary study objective with the following endpoints:
  - Haemophilia Quality of Life Questionnaire (Haem-A-QoL for participants ≥17 years old) physical health domain (OD and RP groups) and total scores (RP group only).
  - EQ-5D-5L index score (RP group only).
  - EQ-5D visual analog scale (EQ-VAS) score (RP group only).
- HRQoL outcomes were evaluated with marstacimab at Month 6 of the ATP and compared with prior OD or RP therapy in the 6-month OP.
- Change from baseline (CFB) to Month 6 in Haem-A-QoL scores during the OP and ATP were analyzed using cumulative distribution function (CDF) plots. Clinically meaningful within-patient change was evaluated using existing thresholds from published literature.[13,14]

RESULTS

- A total of 128 participants without inhibitors entered the OP (n=37 in the OD group, n=91 in the RP group) (**Table 2**).

Table 2: Baseline demographics and characteristics of participants

	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. of 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 these, 116 (n=33 OD, n=83 RP) entered the ATP and received ≥1 dose of marstacimab and 111 completed the ATP (n=33 OD; n=78 RP).
  - Median (range) treatment duration was 364 (28–392) days in the ATP.
- In the OD group, the estimated median difference from baseline to Month 6 of the ATP for the Haem-A-QoL physical health domain numerically favored marstacimab compared with prior OD treatment in the OP. The effect size of 0.53 SD units indicated a discernable effect, but did not reach statistical significance (**Table 3**).
- In the RP group, the estimated median difference from baseline to Month 6 of the ATP for Haem-A-QoL physical health domain and total score demonstrated non-inferiority of marstacimab compared with prior RP in the OP. The effect size indicated a negligible effect of marstacimab over prior RP (**Table 3**).

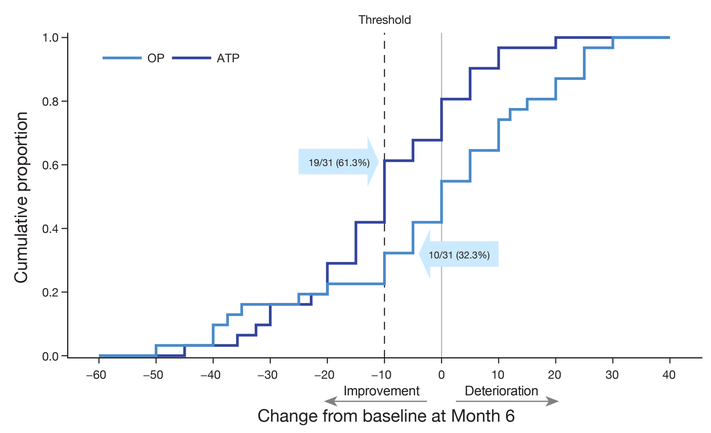
Table 3: Change from baseline to Month-6 in Haem-A-QoL[a] scores

	Estimated change from baseline[b], median (95% CI)		Estimated median difference (95% CI)	P value (effect size)[c]
	OP	ATP		
OD group (n=31)				
Physical health domain	–1.1 (–12.2, 10.0)	–12.4 (–19.6, –5.1)	–10.7 (–24.0, 2.6)	0.1161 (0.53)
RP group (n=63)				
Total score	–1.2 (–3.5, 1.1)	–3.7 (–6.8, 0.6)	–2.8 (–6.6, 1.0)	0.1493 (0.17)
Physical health domain	–3.0 (–8.2, 2.2)	–6.1 (–12.6, 0.4)	–2.2 (–9.1, 4.6)	0.5223 (0.08)

[a] Evaluated for participants aged 17 to <75 years. Transformed Scale Score is reported; it ranges from 0 to 100, with higher score indicating worse quality of life.
[b] Change from baseline at Month 6 of the ATP is presented as the treatment duration for OP was 6 months.
[c] Exact CI using Walsh averages, P value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption. Effect Size is calculated as lestimated median differencel / (SD at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
Non-inferiority criterion was upper bound of 95% CI <7 for the total score and upper bound of 95% CI <10 for physical health domain score.
ATP=active treatment phase; MAR=missing at random; OD=on-demand; OP=observational phase; RP=routine prophylaxis

- In the OD group, the CDF plot for the Haem-A-QoL physical health domain showed a clear separation between marstacimab prophylaxis and OD treatment, suggesting a clinically relevant difference (**Figure 2**).
  - The threshold for clinically meaningful within-patient change from baseline (–10 points) was met by 19 of 31 (61.3%) participants receiving marstacimab prophylaxis at Month 6 of the ATP compared with 10 of 31 (32.3%) participants receiving OD treatment during the OP.
  - The physical health domain demonstrated a less clear separation between marstacimab prophylaxis and RP (**Figure 3**) than that seen in the OD group (**Figure 2**).

Figure 2: CDF plot of CFB at 6 months of OP (with OD therapy) and 6 months of ATP (with marstacimab) in Haem-A-QoL physical health domain



The dotted vertical line represents the threshold of clinically meaningful within-patient change from baseline (solid line). CFB at Month 6 = Month 6 value – Baseline value.
ATP=active treatment phase; CDF=cumulative distribution function; CFB=change from baseline; Haem-A-QoL=Haemophilia Quality of Life Questionnaire; OD=on demand; OP=6-month observational phase

- Change from baseline at Month 6 of the ATP with marstacimab treatment in both the EQ-5D-5L index score and EQ-VAS score was non-inferior to that with prior RP, indicating preservation of patient health status (**Table 4**).

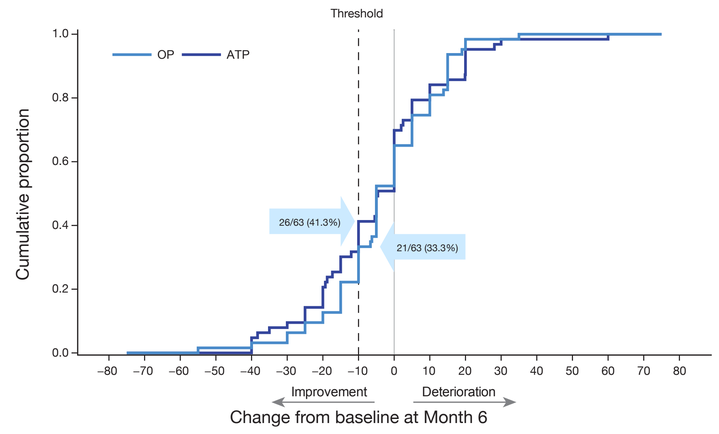
Table 4: Change from baseline to Month-6 in EQ-5D-5L[a] and EQ-VAS[b] scores

RP group (n=83)	Estimated change from baseline,[b] median (95% CI)		Estimated median difference (95% CI)	P value (effect size)[c]
	OP	ATP		
EQ-5D-5L	0.0300 (–0.0140, 0.0740)	0.0752 (0.0178, 0.1325)	0.0223 (–0.0432, 0.0877)	0.505 (0.12)
EQ-VAS	3.0 (–0.6, 6.6)	4.5 (1.4, 7.7)	0.6 (–4.0, 5.1)	0.8006 (0.03)

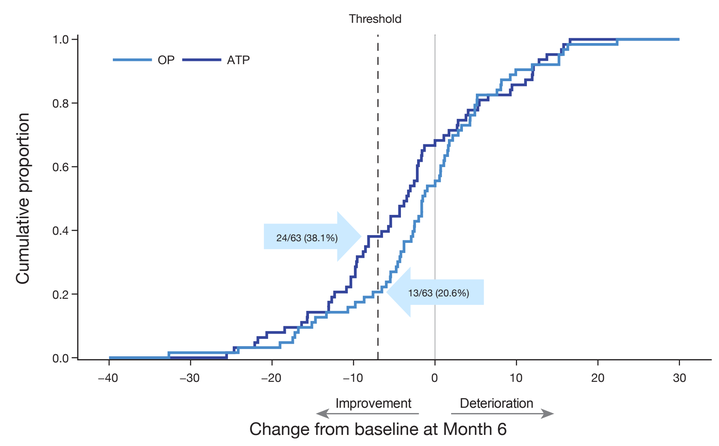
[a] Higher scores indicate better health states with the maximum value of 1. Measures participant self-rated health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
[b] Change from baseline at Month 6 of the ATP is presented as the treatment duration for OP was 6 months.
[c] Exact CI using Walsh averages, P value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption. Effect Size (ES) is calculated as lestimated median differencel / (SD at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
Non-inferiority criterion was lower bound of 95% CI > –0.1 for the EQ-5D-5L index and lower bound of 95% CI > –9.5 for the EQ-VAS.
ATP=active treatment phase; EQ-VAS=EuroQol visual analog scale; MAR=missing at random; OP=observational phase; RP=routine prophylaxis

Figure 3: CDF plot of CFB in Haem-A-QoL score at 6 months of OP with RP therapy and 6 months of ATP with marstacimab

A. Physical health domain



B: Total score



The dotted vertical line represents the threshold of clinically meaningful within-patient change from baseline (solid line). CFB at Month 6 = Month 6 value – Baseline value.
ATP=active treatment phase; CDF=cumulative distribution function; CFB=change from baseline; EQ-VAS=EuroQol visual analog scale; Haem-A-QoL=Haemophilia Quality of Life Questionnaire; OD=on demand; OP=6-month observational phase; RP=routine prophylaxis

CONCLUSIONS

- At Month 6 of the ATP, marstacimab was associated with improvements in HRQoL parameters compared with prior OD treatment in the OP. Marstacimab maintained HRQoL scores reported by participants with prior RP in the OP.
- These results support the potential impact of marstacimab to improve HRQoL and reduce treatment burden for people with severe HA or moderately severe to severe HB without inhibitors.
- Further follow-up of HRQoL measures to Month 12 of the ATP and throughout the OLE will provide further insights into the long-term impact of marstacimab.

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DISCLOSURES

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