PO058

Exogenous Factor Consumption in Participants With Hemophilia A or B Without Inhibitors Receiving Marstacimab in the BASIS Trial

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INTRODUCTION

- Hemophilia is a genetic bleeding disorder characterized by the deficiency of clotting factors, primarily factor VIII (FVIII; hemophilia A) or factor IX (FIX; hemophilia B).[1]
- Standard of care for people with hemophilia includes intravenous (IV) infusions of factor replacement therapy (FRT), either on-demand (OD) or routine prophylaxis (RP).[1]
- The challenges of FRT, including the development of inhibitors to exogenous FVIII and FIX and low adherence to IV infusions, have led to the development of non-factor alternatives.[1-5]
  - However, current non-factor products are only indicated for prophylaxis of bleeding events, and additional FRT is required to manage acute bleeding episodes.[2,5,6]
  - There is a theoretical increased risk of thrombosis when modulating hemostasis across different mechanisms, and both emicizumab and concizumab have been associated with thromboembolic events.[2,5,6]
- Marstacimab is a tissue factor pathway inhibitor (TFPI) antibody in development for the treatment of severe hemophilia A (FVIII <1%) or moderately severe to severe hemophilia B (FIX ≤2%), with or without inhibitors.[7-9]
- The efficacy and safety of marstacimab 150 mg subcutaneous (SC) once-weekly (QW) in the non-inhibitor cohort, compared with previous FRT, was demonstrated in the pivotal phase 3 BASIS trial, with a reduction in annualized bleeding rate (ABR) beyond 12 months and up to an additional 16 months in the open-label extension (OLE).[10-12]

OBJECTIVE

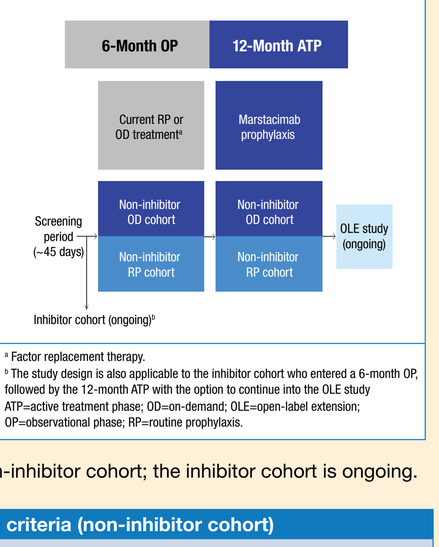
- Evaluate the impact of marstacimab on exogenous FRT consumption in BASIS.

METHODS

Study Design

- BASIS (NCT03938792) is an open-label, single-arm, one-way cross-over, multicenter, pivotal phase 3 trial to assess the efficacy and safety of marstacimab over a 12-month active treatment phase (ATP) (**Figure 1**).
  - The primary efficacy endpoint, ABR for treated bleeding events with marstacimab compared with prior OD or RP therapy, was previously reported.[10]
- Eligible participants (males aged 12 to <75 years with severe hemophilia A or moderately severe to severe hemophilia B) 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.

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.

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

Key inclusion criteria	Key exclusion criteria
• Male • Age ≥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–FRT, or any previous gene therapy product • Current immunomodulatory drugs

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

- Participants were grouped according to the treatment received (OD and RP) during a 6-month observational phase (OP), before entering the 12-month ATP.
- Dosing procedures involved an initial 300 mg SC loading dose of marstacimab, 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 dose to marstacimab 300 mg SC QW.
- Participants could take their prescribed FRT, according to the approved product labeling, for breakthrough bleeds, planned sport/physical activity (ie, unrelated to bleeding), or peri- and post-surgical/medical procedures.
  - Total FRT consumption was recorded by participants or caregivers on an electronically administered bleed and infusion diary (eDiary).
- FRT use was analyzed in the modified intent-to-treat population (including participants who completed the OP and received ≥1 dose of marstacimab in the ATP).

RESULTS

Patient Demographics and Clinical Characteristics

- 128 participants without inhibitors entered the OP (37 in the OD group, 91 in the RP group) (**Table 2**).
- Of these, 116 entered the ATP and received ≥1 dose of marstacimab.
- The median (range) treatment duration in the ATP was 364 (344–392) days for the OD group (n=33) and 364 (28–383) days for RP group (n=83).

Table 2: Baseline demographics and characteristics of participants (safety population)

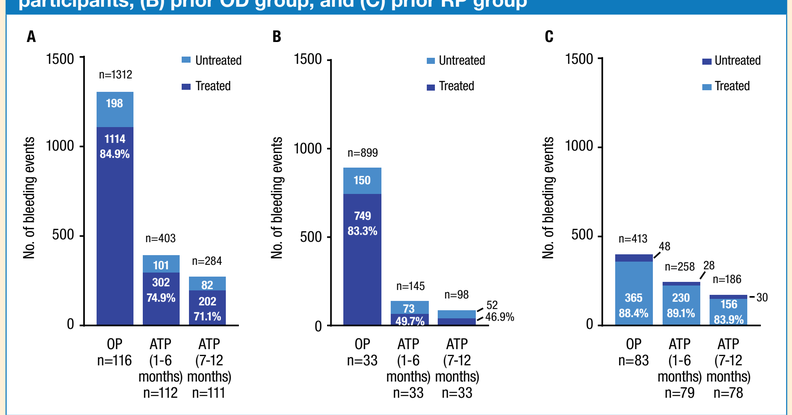
	Baseline (OP)		
	OD n=37	RP n=91	Overall N=128
Age, median (range), y	29.0 (15–58)	31.0 (13–66)	30.0 (13–66)
Adolescent (≥12 to <18 y), n (%)	2 (5.4)	18 (19.8)	20 (15.6)
Adult (≥18 to <75 y), n (%)	35 (94.6)	73 (80.2)	108 (84.4)
Hemophilia type, n (%)			
HA	29 (78.4)	72 (79.1)	101 (78.9)
HB	8 (21.6)	19(20.9)	27 (21.1)
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

Incidence of Treated and Untreated Bleeds

- The total number of treated and untreated bleeds was reduced with marstacimab during the ATP compared with prior OD or RP treatment in the OP (**Figure 2A**).
- During the ATP, the OD group had a lower proportion of treated bleeds compared with the RP group (**Figure 2B** and **2C**, respectively).

Figure 2: Number of treated and untreated bleeding events of (A) all BASIS participants, (B) prior OD group, and (C) prior RP group

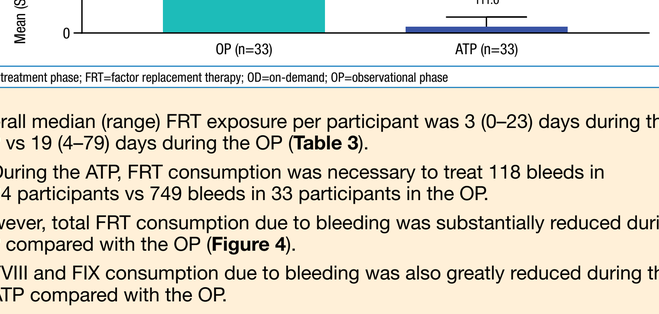


ATP=active treatment phase; OD=on-demand; OP=observational phase; RP=routine prophylaxis

FRT Consumption in the On-Demand Group

- In the OD group, the mean (SD) annualized total FRT consumption was lower during the ATP (111 [168] IU/kg) vs the OP (1276 [1181] IU/kg) (**Figure 3**).

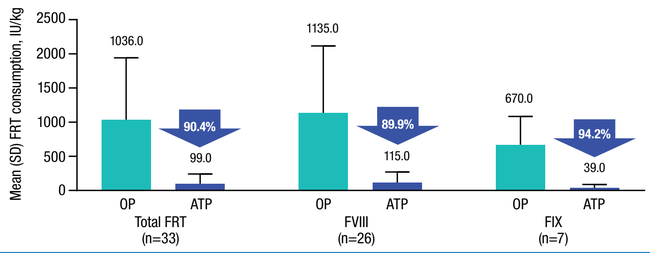
Figure 3: Total annualized FRT use of participants with prior OD



ATP=active treatment phase; FRT=factor replacement therapy; OD=on-demand; OP=observational phase

- Overall median (range) FRT exposure per participant was 3 (0–23) days during the ATP vs 19 (4–79) days during the OP (**Table 3**).
  - During the ATP, FRT consumption was necessary to treat 118 bleeds in 24 participants vs 749 bleeds in 33 participants in the OP.
- However, total FRT consumption due to bleeding was substantially reduced during the ATP compared with the OP (**Figure 4**).
  - FVIII and FIX consumption due to bleeding was also greatly reduced during the ATP compared with the OP.

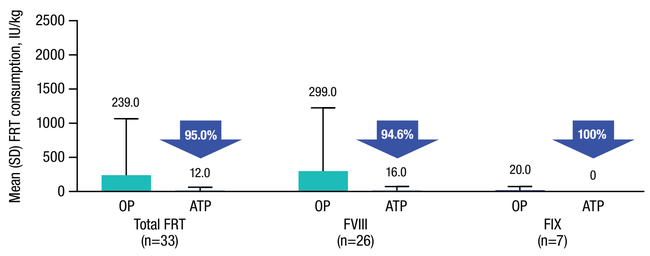
Figure 4: Annualized FRT use of participants with prior OD related to bleeding events for total FRT, FVIII, and FIX consumption (mITT population)



ATP=active treatment phase; FIX=factor IX; FRT=factor replacement therapy; FVIII=factor VIII; mITT=modified intent-to-treat; OD=on-demand; OP=observational phase

- Total FRT consumption unrelated to bleeding (consisting of prophylaxis infusions or preventative infusions for sports/physical activity) was substantially reduced during the ATP compared with the OP (**Figure 5**).
  - FVIII and FIX consumption unrelated to bleeding was greatly reduced during the ATP compared with the OP.

Figure 5: Annualized FRT use of participants with prior OD unrelated to bleeding events for total FRT, FVIII, and FIX consumption (mITT population)

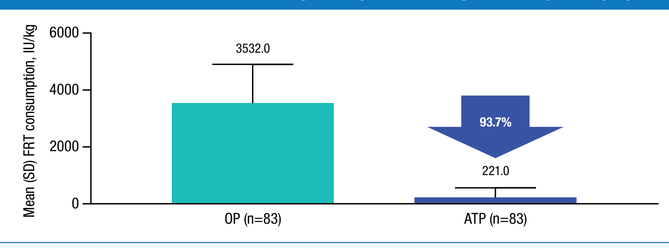


ATP=active treatment phase; FIX=factor IX; FRT=factor replacement therapy; FVIII=factor VIII; mITT=modified intent-to-treat; OD=on-demand; OP=observational phase

FRT Consumption in the Routine Prophylaxis Group

- In the RP group, the mean (SD) annualized total FRT consumption was lower during the ATP (221 [339] IU/kg) vs the OP (3532 [1370] IU/kg) (**Figure 6**).

Figure 6: Total annualized FRT use of participants with prior RP (mITT population)



ATP=active treatment phase; FRT=factor replacement therapy; mITT=modified intent-to-treat; OP=observational phase; RP=routine prophylaxis

- Overall median (range) FRT exposure per participant was 3 (0–42) days during the ATP vs 2 (0–47) days during the OP (**Table 3**).
  - During the ATP, on-demand FRT consumption due to bleeding was necessary to treat 386 bleeds of 55 participants vs 365 bleeds of 56 participants during the OP.

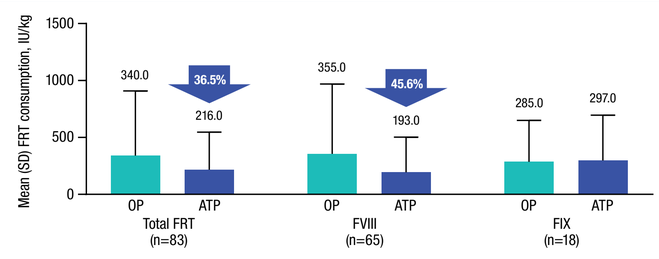
Table 3: FRT exposure days per participant during BASIS due to bleeding events (mITT population)

	OD		RP	
Per participant	6-month OP n=33	12-month ATP n=24	6-month OP n=56	12-month ATP n=55
No. of treated bleeds	749	118	365	386
Exposure days receiving FRT				
Median (min, max)	19 (4, 79)	3 (0, 23)	2 (0, 47)	3 (0, 42)
No. of infusions				
Median (min, max)	19 (5, 79)	3 (0, 23)	2 (0, 54)	3 (0, 42)

ATP=active treatment phase; FRT=factor replacement therapy; max=maximum; min=minimum; mITT=modified intent-to-treat; OD=on-demand; OP=observational phase

- Total FRT consumption due to bleeding was substantially reduced during the ATP compared with the OP (**Figure 7**).
  - FVIII consumption due to bleeding was greatly reduced during the ATP compared with the OP.
  - Changes in FIX consumption from the OP to ATP were negligible and was influenced by 2 adolescents with traumatic bleeds during the ATP who required FRT: one had 14 bleeds and the other had 11 traumatic bleeds.

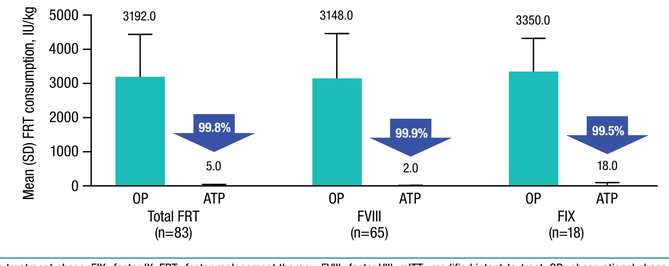
Figure 7: Annualized FRT use of participants with prior RP related to bleeding events for total FRT, FVIII, and FIX consumption (mITT population)



ATP=active treatment phase; FIX=factor IX; FRT=factor replacement therapy; FVIII=factor VIII; mITT=modified intent-to-treat; OP=observational phase; RP=routine prophylaxis

- FRT consumption unrelated to bleeding (consisting of prophylaxis infusions or preventative infusions for sports/physical activity) was substantially reduced during the ATP compared with the OP (**Figure 8**).
  - FVIII and FIX consumption unrelated to bleeding was greatly reduced during the ATP compared with the OP.

Figure 8: Annualized FRT use of participants with prior RP unrelated to bleeding events for total FRT, FVIII, and FIX consumption (mITT population)



ATP=active treatment phase; FIX=factor IX; FRT=factor replacement therapy; FVIII=factor VIII; mITT=modified intent-to-treat; OP=observational phase; RP=routine prophylaxis

CONCLUSIONS

- Consistent with the observed reduction in mean ABR of treated bleeds in BASIS,[10] the use of marstacimab markedly reduced the consumption of FRT (total, related to bleeding and unrelated to bleeding) and exposure to FRT compared with previous OD and RP treatment.
- These results highlight the potential impact of marstacimab at reducing treatment burden for participants with hemophilia A or hemophilia B without inhibitors.

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DISCLOSURES

RM: Former employee and an equity holder in Pfizer. **HKK, CTT, PS, TG, AP:** Employees of and equity holders in Pfizer.

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