PO048

Surgical and Medical Procedures in Participants With Hemophilia A or B Without Inhibitors Receiving Marstacimab in the BASIS and Open-Label Extension Trials

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INTRODUCTION

- Hemophilia is characterized by the deficiency of clotting factors, specifically factor VIII (FVIII) in hemophilia A and factor IX (FIX) in hemophilia B.[1]
- People with hemophilia often require surgical procedures during their lifetime.[1-3]
  - Some procedures are unrelated to the disease, however, procedures that treat joint damage due to hemarthrosis are related to the condition itself.
- People with hemophilia have increased risk of bleeding, poor wound healing, and infection when undergoing surgery.[1-3]
  - People with hemophilia may therefore require management with hemostatic therapy during the peri-operative period.
- The current standard of care for hemophilia includes prophylaxis with factor replacement therapy (FRT), which involves regular intravenous infusions of the missing clotting factor, or other hemostatic products to prevent bleeding.[1]
  - However, these treatments are associated with several challenges, including the development of inhibitors to FVIII or FIX replacement therapies, rendering the treatment ineffective.[1,4]
- Marstacimab, an anti-tissue factor pathway inhibitor (TFPI) antibody, represents a novel prophylactic option for people with hemophilia.[5,6]
  - Marstacimab works by targeting and inhibiting TFPI, thereby enhancing thrombin generation and improving hemostasis.
- The efficacy and safety of marstacimab were demonstrated in patients with hemophilia A or B without inhibitors in the pivotal BASIS phase 3 trial with a reduction in annualized bleeding rate (ABR) during a 12-month treatment period and up to an additional 16 months in the open-label extension (OLE).[7]
- Marstacimab has recently been approved for routine prophylaxis in patients with hemophilia A and B without inhibitors in Europe[8] and the United States.[9]
  - However, there are limited prospective data on the management and outcomes of people receiving marstacimab prophylaxis and undergoing surgical procedures.

OBJECTIVE

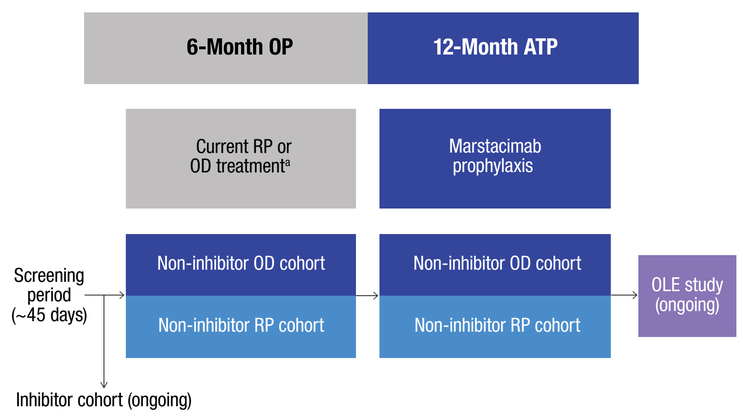
- Describe surgical/medical procedures in BASIS and its OLE in participants without inhibitors.

METHODS

Study Design

- BASIS (NCT03938792) is a phase 3 trial designed to evaluate the efficacy and safety of subcutaneous (SC) marstacimab prophylaxis administered once weekly (QW).
- Participants were enrolled into 1 of 2 cohorts depending on the presence of inhibitors (inhibitor vs non-inhibitor cohorts).
  - We report the results for the non-inhibitor cohort; the inhibitor cohort is ongoing.
- The study includes a 6-month observational phase (OP) during which participants continued to receive their prescribed FRT – either on-demand or routine prophylaxis – before entering the 12-month active treatment phase (ATP) with marstacimab (**Figure 1**).
- Participants who completed the ATP were eligible to enroll in an OLE trial (NCT05145127).

Figure 1: Study design of BASIS and its OLE



[a] Factor replacement therapy.
ATP=active treatment phase; OD=on-demand; OLE=open-label extension; OP=observational phase; RP=routine prophylaxis

Participant Population

- Inclusion criteria required male participants aged ≥12 to <75 years with severe hemophilia A (FVIII <1%) or moderately severe to severe hemophilia B (FIX ≤2%), with or without inhibitors.

Study Treatment

- 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.
  - Following 6 months in the ATP, participants meeting protocol-defined criteria could increase their marstacimab dose to 300 mg SC QW.

Study Assessments

- The primary efficacy endpoint, ABR for treated bleeding events with marstacimab compared with prior therapy, was previously reported.[7]
- During the study, surgeries and medical procedures were permitted on a case-by-case basis.
- Surgeries and medical procedures were identified from Case Report Forms and analyzed descriptively.

RESULTS

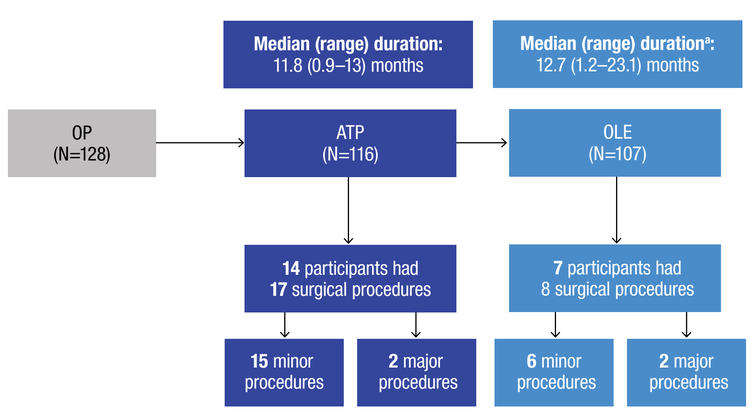
Participant Population

- Overall, 128 participants without inhibitors entered the OP and 116 participants entered the ATP and received ≥1 dose of marstacimab.
  - The median duration in the ATP was 11.8 (range, 0.9–13) months.
- Of the participants who entered the ATP, 107 had transitioned into the OLE at the time of data cutoff (October 9, 2023).
  - The median duration in the OLE was 12.7 (range, 1.2–23.1) months.

Surgical/Medical Procedures in the ATP and OLE

- Overall, 14 (12%) participants had 17 procedures in the ATP and 7 (7%) participants had 8 procedures in the OLE (**Figure 2**).
- Most procedures (21/25; 17/21 minor procedures and 4/4 major procedures) were conducted with FRT.

Figure 2: Surgical/medical procedures in the BASIS ATP and OLE



[a] Data cutoff date, October 9, 2023.
ATP=active treatment phase; OLE=open-label extension; OP=observational phase

Marstacimab Administration in the Peri-Operative Period

- Marstacimab administration continued as scheduled during minor procedures in the ATP and in the OLE (**Table 1**).
  - 3 participants were dosed on procedure day (wound treatment, n=1; tooth extraction, n=1; endodontic procedure, n=1).
- Marstacimab treatment temporarily discontinued for major procedures in the ATP and in the OLE.
  - A detailed description of marstacimab scheduling is provided below for each major procedure (see sections *FRT for Major Procedures in the ATP and FRT for Major Procedures in the OLE*).

FRT for Minor Procedures in the ATP and OLE

- During the ATP, 12 minor procedures were conducted with FRT (**Table 1**).
  - 3 procedures were conducted with preventative FRT administered on the day of the procedure; treatment ranged 1 to 3 days.
  - 9 procedures were conducted with on-demand FRT; the majority started on procedure day; treatment ranged 1 to 10 days with the exception of one participant who received FRT for the duration of an extended dental procedure, finishing FRT 18 days after the procedure was completed.
- In the OLE, 5 minor procedures were conducted with FRT (**Table 1**).
  - 3 procedures were conducted with preventative FRT administered on the day of the procedure, 1 procedure was conducted with preventative FRT administered starting on Day 4; treatment ranged 1 to 23 days.
  - 1 procedure was conducted with on-demand FRT administered on the day of the procedure and continuing for 4 days.

Table 1: Minor procedures in the ATP and OLE

Procedure	Marstacimab administration continued as scheduled	Category of FRT used	Start and end day of FRT administration following procedure (Procedure Day = Day 0) / FRT Daily Dose / SHL or EHL
In the ATP			
Dental procedures, n=8			
Dental care	✓	None	NA
Endodontic procedure	✓	None	NA
Tooth extraction	✓	Preventative	Day 0 / 1000 IU/day / SHL
Dental care	✓	On-demand	Days 8–18[a] / 1500–3000 IU/day / SHL
Dental cleaning	✓	On-demand	Day 0 / 500 IU/day / SHL
Tooth extraction	✓	On-demand	Days 0–2 / 1200 IU/day / SHL
Tooth extraction	✓	On-demand	Day 1 / 2000 IU/day / SHL
Tooth restoration	✓	On-demand	Days 0–1 / 1500–3500 IU/day / SHL
Hemorrhoid-related, n=2[b]			
Incisional drainage	✓	On-demand	Days 0–9 / 2200 IU/day / SHL
Drainage	✓	On-demand	Day 6 / 2200 IU/day / SHL
Other, n=5			
Cooling therapy	✓	None	NA
Tendon sheath incision	✓	Preventative	Days 0–1 / 1000–2000 IU / SHL
Inguinal hernia repair	✓	Preventative	Days 0 and 3 / 4000 IU / EHL
Wound treatment	✓	On-demand	Day 0 / 5000 IU / EHL
Cooling therapy	✓	On-demand	Days 2–3 / 1000 IU / SHL
In the OLE			
Dental procedures, n=3[c]			
Endodontic procedure	✓	None	NA
Endodontic procedure	✓	Preventative	Day 0 / 1000 IU / SHL
Tooth extraction	✓	Preventative	Day 0 / 1000 IU / SHL
Other, n=3			
Surgery[d]	✓	Preventative	Days 4–26 / 2000–4000 IU / EHL
Joint injection	✓	Preventative	Day 0 / 2000 IU / EHL
Splint application	✓	On-demand	Days 0–3 / 1500 IU / SHL

[a] Participant received dental treatment from November 2021 (Study Day 150) through to April 2022 (Study Day 293); on-demand FRT was initiated on Study Day 158 and continued through to Study Day 311 (18 days after the procedure finished).
[b] 2 procedures in the same participant; incisional drainage procedure for thrombosed hemorrhoids on Study Day 69 followed by drainage for thrombosed hemorrhoids on Study Day 72.
[c] 2 procedures in the same participant: tooth extraction on Study Day 70 and endodontic procedure on Study Day 93.
[d] Surgical procedure was undefined.
ATP=active treatment phase; Day 0=day of procedure; EHL=extended half life product FRT=factor replacement therapy; NA=not applicable; OLE=open-label extension; SHL=standard half life product

FRT for Major Procedures in the ATP

- During the ATP, 2 major procedures (tympanoplasty and ear tube insertion) in the same participant were conducted with preventative FRT. Details of peri- and post-operative dose and scheduling for marstacimab and FRT are shown in **Table 2**.

Table 2: Participant with tympanoplasty and ear tube insertion: peri- and post-operative marstacimab dose and schedule and FRT use

Baseline characteristics:
Asian, aged 13 y, with severe hemophilia A
On routine prophylaxis in the OP, with administration of SHL recombinant FVIII replacement therapy (1000 IU, 22.8 IU/kg) 3x/wk
Procedures:
Tympanoplasty and ear tube insertion on Study Day 291
Marstacimab dose and schedule:
150 mg QW, temporarily discontinued 10 days pre-procedure (Study Day 281) and resumed with a 300-mg loading dose 6 days post-procedure (Study Day 297)
FVIII replacement therapy use peri- and post-operatively:
Duration: 3 days total
Day of procedure (Study Day 291): preventative SHL FVIII replacement therapy 1500 IU BID
Post-procedure: SHL, 1500 IU BID on Study Days 292 and 293

BID=twice per day; FRT=factor replacement therapy; FVIII=factor VIII; OP=observational phase; QW=once weekly; SHL=standard half life product

FRT for Major Procedures in the OLE

- During the OLE, 2 major procedures were conducted with preventative FRT. Details of peri- and post-operative dose and scheduling for marstacimab and FRT are shown in **Table 3** (knee arthroplasty) and **Table 4** (hip arthroplasty).

Table 3: Participant with knee arthroplasty: peri- and post-operative marstacimab dose and schedule and FRT use

Baseline characteristics:
Asian, aged 31 y, with severe hemophilia A
On routine prophylaxis in the OP, with administration of SHL FVIII replacement therapy and Von Willebrand factor (3000 IU, 48.4 IU/kg) QOD
Procedures:
Total left knee replacement on Study Day 202
Marstacimab dose and schedule:
300 mg QW, temporarily discontinued 11 days pre-procedure (Study Day 191) and had not resumed before the data cutoff date
FVIII replacement therapy use peri- and post-operatively:
Duration: 15 days total
Day of procedure (Study Day 202): preventative EHL FVIII replacement therapy (1 × 4000 IU and 1 × 3000 IU)
Post-procedure: EHL, 2000 IU QD for 5 days (Study Days 203–207), and then 3000 IU every third day in the following week (Study Days 210 and 213) until the last dose on Study Day 216

EHL=extended half life product; FRT=factor replacement therapy; FVIII=factor VIII; OP=observational phase; QD=once per day; QOD=every other day; QW=once weekly

Table 4: Participant with hip arthroplasty: peri- and post-operative marstacimab dose and schedule and FRT use

Baseline characteristics:
White, aged 47 y, with severe hemophilia A
On routine prophylaxis in the OP, with administration of SHL FVIII replacement therapy (2000 IU, 23 IU/kg) 3×/wk
Procedures:
Right hip replacement carried out on Study Day 178
Marstacimab dose and schedule:
150 mg QW, temporarily discontinued 8 days pre-procedure (Study Day 170) and resumed with a 150-mg dose 16 days post-procedure (Study Day 194)
FVIII replacement therapy use peri- and post-operatively:
Duration: 15 days total
Day of procedure (Study Day 178): preventative (4000 IU) and on-demand (2000 IU) SHL FVIII replacement therapy
Post-procedure: SHL, preventative FVIII replacement therapy 1 × 1000 IU / 1 × 1500 IU on Study Day 179, 2 × 1500 IU on Study Day 180, 1 × 1500 IU on Study Day 181, 1 × 1500 IU / 1 × 1000 IU on Study Days 182–184, 2 × 1000 IU on Study Days 185–189, followed by 1 × 1000 IU / 1 × 500 IU on Study Days 190 and 191 with a final 1000 IU QD on Day 192

BID=twice per day; FRT=factor replacement therapy; FVIII=factor VIII; OP=observational phase; QD=once per day; QW=once weekly; SHL=standard half life product

Safety Assessment

- No thromboembolic events in participants undergoing surgery were reported.

CONCLUSIONS

- Once-weekly marstacimab SC prophylaxis was well tolerated without discontinuation during minor procedures and with temporary discontinuation ≤11 days before major procedures.
- FRT was safely administered in combination with marstacimab to prevent and control excessive bleeding during the peri- and post-operative periods.

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DISCLOSURES

OB: Consultant: Bayer, CSL Behring, Octapharma, Pfizer, Roche, Sobi, Takeda; speaker bureau: Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda. **HKK, CTT, BM, PS, AP, RM:** Employees of and equity holders in Pfizer.

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