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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial

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KEY POINTS

- **Marstacimab, a monoclonal antibody, targets the tissue factor pathway inhibitor to rebalance hemostasis.**
- **Marstacimab reduced bleeding events and was generally well tolerated with no unanticipated side effects.**

Marstacimab targets the tissue factor pathway inhibitor to rebalance hemostasis. Previous phase 1 and 2 trials established marstacimab safety and efficacy in adults with severe hemophilia A (HA) or B (HB). BASIS is an open-label, marstacimab phase 3 trial in males aged 12 to 74 years with severe HA (factor VIII <1%) or moderately severe to severe HB (factor IX ≤2%). Participants without inhibitors received on-demand (OD) or routine prophylaxis (RP) therapy during a 6-month observational phase (OP) before receiving once-weekly subcutaneous 150 mg marstacimab during a 12-month active treatment phase (ATP). Primary end points were annualized bleeding rate (ABR) for treated bleeds vs previous OD or RP during the OP, and safety. Of 128 participants enrolled in the OP, 116 received marstacimab in the ATP. In the OD group (n = 33), mean ABR decreased from 39.86 (95% confidence interval [CI], 33.05-48.07) in the OP to 3.20 (95% CI, 2.10-4.88) in the ATP, demonstrating superiority of marstacimab (estimated ABR ratio, 0.080 [95% CI, 0.057-0.113]; *P* < .0001). In the RP group (n = 83), mean ABR decreased from 7.90 (95% CI, 5.14-10.66) in the OP to 5.09 (95% CI, 3.40-6.78) in the ATP, demonstrating noninferiority and superiority of marstacimab (estimated ABR difference, –2.81 [95% CI, –5.42 to –0.20]; *P* = .0349). There were no deaths or thromboembolic events. Weekly subcutaneous marstacimab reduced ABR vs OD or RP therapy in the OP in individuals with severe HA or moderately severe to severe HB without inhibitors. Marstacimab was safe and well tolerated with no unanticipated side effects. This trial was registered at www.clinicaltrials.gov as #NCT03938792.

Introduction

Recommended treatments for hemophilia include IV administration of replacement factor VIII (FVIII) and FIX for hemophilia A and B, respectively, either prophylactically or on-demand (OD).[1] However, treatment challenges, including inhibitory antibodies, low adherence to intravenous injections, venous access difficulties, restricted geographic access, and inconsistent hemostatic protection associated with standard prophylaxis, led to the development of nonfactor alternatives requiring less frequent subcutaneous administration.[1-4]

Emicizumab was the first nonfactor prophylactic agent approved for treatment of hemophilia A; however, it is not indicated for hemophilia B and has been associated with thromboembolic events.[1,5] Similarly, thromboembolic events have been reported with other nonfactor agents including antitissue factor pathway inhibitor (TFPI) antibodies, concizumab, and befovacimab. Concizumab is approved for treatment of hemophilia A and B with inhibitors, but nonfatal thromboembolic events were reported during the phase 3 study in 3 participants with concomitant therapy and known risk factors.[6] Befovacimab was in development for treatment of

hemophilia A and B with or without inhibitors but was prematurely discontinued after the development of central nervous thromboses in 3 participants of the phase 2 study.[7] The antithrombin small interfering RNA fitusiran is approved for treatment of hemophilia A and B with or without inhibitors. The fitusiran phase 2 study was initially suspended because of a fatal cerebral sinus vein thrombosis and additional nonfatal thrombotic events. The reported thrombotic events occurred in conjunction with risk factors (the use of coagulation factor concentrates or bypassing agents or in association with antithrombin levels of <10%). To mitigate the risk of thrombotic events, a revised antithrombin-based dosing regimen was implemented to target antithrombin levels of 15% to 35%, along with recommendations for reduced doses of procoagulants used for managing breakthrough bleeding.[8-10] These risk mitigation measures reduced the risk of thrombotic events in the phase 3 open-label extension study, with thrombotic events (1 deemed treatment related) reported in 4 of 213 participants.[11] All were associated with predisposing clinical risk factors. As such, an unmet need for alternative therapies for hemophilia with an improved benefit-risk profile remains.

Marstacimab is a monoclonal antibody recently approved in the United States for prophylactic treatment of patients with hemophilia A or hemophilia B.[12-15] Marstacimab targets TFPI to alleviate inhibition of activated FX– and FVII–tissue factor complex and increase thrombin generation and clot formation independently of FVIII and FIX.[14] A phase 1b/2 study and its long-term phase 2 follow-up provided evidence for the safety, efficacy, and dose-level pharmacokinetics and pharmacodynamics of marstacimab in adults with severe hemophilia A or B, with or without inhibitors.[12,13] We present efficacy and safety results from the pivotal phase 3 marstacimab trial.

Methods

Trial design and oversight

BASIS (ClinicalTrials.gov identifier: NCT03938792) is an open-label, 1-way crossover, multicenter, phase 3 trial of marstacimab administered over a 12-month active treatment phase (ATP; supplemental Figure 1, available on the *Blood* website), conducted at 52 centers across 19 countries (supplemental Appendix 1).

Participants were enrolled into 2 cohorts, depending on the presence of inhibitors (inhibitor or noninhibitor cohorts). We report results for the noninhibitor cohort. BASIS began on 9 March 2020. The primary completion date for the noninhibitor cohort was 17 April 2023. Participants who completed the parent study could enroll in the open-label extension study (ClinicalTrials.gov identifier: NCT05145127).

The sponsor, Pfizer, was responsible for overall trial design, site selection, monitoring, data management, and data storage. The protocol design was reviewed by regulatory agencies in the United States, Canada, and Europe. Information regarding data handling and quality assurance is in supplemental Section 1. Analyses were performed by the sponsor. All authors had access to the primary clinical trial data. The academic authors could request additional analyses. The first draft of the manuscript was written by a medical writer contracted by Pfizer under direction of the authors; all authors critically reviewed the manuscript, provided substantive input during drafting, contributed to revisions, approved the final version submitted for publication, and vouch for the completeness and accuracy of the data and for the trial's fidelity to the protocol.

Participants

Eligible participants were male, aged 12 to <75 years, with severe hemophilia A (FVIII levels of <1%) or moderately severe to severe hemophilia B (FIX levels of ≤2%), with body weight of ≥35 kg at screening, and consented to participate in the study (full criteria in supplemental Section 2). The noninhibitor cohort had no detectable or documented history of inhibitors against FVIII or FIX and were receiving either OD or routine prophylaxis (RP) before enrollment. Participants receiving RP (defined as treatment by IV infusion of factor concentrate to prevent bleeding) treatment with FVIII/FIX replacement in the observational phase (OP) were required to have demonstrated at least 80% adherence with scheduled prophylaxis regimen during 6 months before enrollment, and willing to continue to receive RP treatment with FVIII/FIX replacement during the OP.

Procedures

Participants were grouped according to treatment received (OD or RP group) during a 6-month OP and progressed into a 12-month ATP during which they received a single loading dose of 300 mg subcutaneous marstacimab administered as 2 150-mg injections, followed by once-weekly 150 mg with a prefilled syringe. The dosing strategy was chosen from previous marstacimab studies that determined a 300 mg loading dose followed by once-weekly 150 mg was the minimal effective dose (supplemental Section 3).[12,13,16] Dose escalation to 300 mg was allowed per the local investigator's discretion after day 180 for participants who met protocol-specified criteria based on breakthrough bleeding (supplemental Section 3). Participants who discontinued or did not enter the open-label extension study completed a 1-month follow-up phase. Participant treatment adherence with their prescribed treatment regimen or marstacimab was assessed by review of the factor infusions or study intervention injections in the electronic diary at each study visit (ie, at each telephone contact and in-person study visit) by the study investigator and site study staff. Participants were to maintain at least 80% adherence with their prescribed treatment regimen during the OP and with weekly subcutaneous dosing of marstacimab during the ATP.

End point

The primary efficacy end point was annualized bleeding rate (ABR) for treated bleeding events with marstacimab treatment compared with previous OD or RP therapy during the OP. ABR was calculated as number of treated bleeds ÷ (days on treatment period ÷ 365.25).

Key secondary end points included ABR for specific bleed types (joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeding events [treated and untreated]) and patient-reported health-related quality of life (HRQoL) outcomes (Haemophilia QoL Questionnaire for Adults, [Haem-A-QoL]). The Haemophilia QoL Questionnaire for Children and Adolescents (Haemo-QoL) and Hemophilia Joint Health Score (HJHS) were additional secondary end points. The EuroQol 5 dimensions 5 level (EQ-5D-5L) and visual analog scale (EQ-VAS) were key end

points in the hierarchical testing sequence for the RP group only. Safety assessments included adverse events of special interest (including thrombotic events, injection site reaction [ISR], hypersensitivity, and anaphylactic reaction), laboratory tests, and immunogenicity (anti-marstacimab antibodies and neutralizing antibodies). Exploratory end points included pharmacokinetic/pharmacodynamic parameters, target joints, and factor replacement consumption. Additional details of end points and assessments are provided in supplemental Sections 4 and 5.

Statistical analysis

Type 1 error across primary and key secondary end points was controlled through a predetermined hierarchical testing approach (supplemental Section 4). A sample size of 25 participants was estimated to provide at least 90% power to demonstrate superiority of marstacimab vs OD. Superiority was declared when the 2-sided 95% confidence interval (CI) for the ratio of the ABR for treated bleeds (marstacimab:OD) is <0.5. A sample size of 60 participants was estimated to provide at least 90% power (1-sided test with α = .025) to demonstrate noninferiority of marstacimab vs RP in mean ABR difference (margin, 2.5 ABR). If noninferiority was established, superiority was tested in mean ABR difference (margin, <0 ABR). Within each group, data were analyzed using repeated-measures negative binomial models with number of bleeds as response variables. For OD, the model included treatment as a factor using the log link. For RP, the model included treatment and the interaction by treatment and year (without the intercept) using the identity link.

Efficacy assessments were performed on a modified intention-to-treat basis in all participants who completed the OP and received ≥1 dose of marstacimab in the ATP (excluding those who changed to inhibitor cohort on or before ATP day –7 testing). For participants who received dose escalation, the duration on an escalated dose was not included in the primary end point assessment to avoid overestimation of the effect of the intended dose. For HRQoL end points, change from baseline at 6 months was compared between the OP and ATP using the Wilcoxon signed rank test and cumulative distribution frequency.

Safety analyses included (1) all participants in the RP group who received ≥1 prophylactic or OD therapy during the OP and all participants in the OD group who completed any OP baseline procedures, and (2) all participants who received ≥1 dose of marstacimab in the ATP. See supplemental Section 6 for further details of statistical analyses.

The protocol was approved by relevant review boards and ethics committees responsible for each site. The study was conducted in accordance with the International Council for Harmonisation good clinical practice guidelines and ethical principles of the Declaration of Helsinki.

Results

Participants

Of 179 screened male participants with hemophilia, 128 without inhibitors entered the 6-month OP, and 116 entered the 12-month ATP and received ≥1 dose of marstacimab (Figure 1; supplemental Table 1). In the OD group, 34 of 37 (91.9%) completed the OP, and 33 entered and completed the ATP. In the RP group, 84 of 91 (92.3%) completed the OP, 83 entered the ATP, and 78 completed the study. Among those who entered the OP, 101 (78.9%) had hemophilia A and 27 (21.1%) had hemophilia B, and 20 (15.6%) were adolescents and 108 (84.4%) were adults. Median age was 30.0 years (range, 13-66), and most were White (50.8%) or Asian (47.7%). At baseline, 97.3% and 58.2% of participants in the OD and RP groups, respectively, had ≥1 target joint (Table 1).

Study drug exposure

The median marstacimab treatment duration was 364.0 days for both OD (range, 344-392) and RP (range, 28-383) groups (supplemental Table 2), and adherence was 97% and 98.8%, respectively. Overall, 47 participants (14 in the OD group and 33 in the RP group) met the protocol-defined criteria for dose escalation based on breakthrough bleeding. Of those that qualified for dose escalation, 3 participants in the OD group and 11 in the RP group received dose-escalation to 300 mg once weekly.

Efficacy outcomes

Primary and secondary efficacy outcomes are in supplemental Table 3. Mean ABR of treated bleeds was 3.20 (95% CI, 2.10-4.88) with marstacimab in the ATP vs 39.86 (95% CI, 33.05-48.07) with previous OD in the OP (estimated ABR ratio, 0.080; 95% CI, 0.057-0.113; P < .0001), demonstrating superiority over OD therapy (92.0% reduction; Figure 2A). Median ABR was 2.02 (interquartile range [IQR], 0.00-4.25) with marstacimab in the ATP vs 35.73 (IQR, 22.48-55.75) with OD therapy in the OP. Mean ABR was 5.09 (95% CI, 3.40-6.78) with marstacimab vs 7.90 (95% CI, 5.14-10.66) with previous RP (estimated ABR difference, –2.81 [95% CI, –5.42 to –0.20; P = .0349]), demonstrating noninferiority then superiority over RP (35.5% [95% CI, 6.2-55.7] reduction; Figure 2B). Median ABR was 2.02 (IQR, 0.00-6.09) with marstacimab vs 2.59 (IQR, 0.00-10.09) with RP. The proportion of participants without any treated bleeds with marstacimab was 30.3% (n = 10/33) in the OD group and 34.9% (n = 29/83) in the RP group. Results by hemophilia type, age, and geographic subgroups are shown in supplemental Figure 2. Results of supplementary and sensitivity analyses are in supplemental Table 4 for participants who received dose escalation, supplemental Table 5 and supplemental Figure 3 for each 6-month period in the ATP, and supplemental Figure 4 by baseline number of target joints. The ABR for all key secondary bleeding end points was consistently superior with marstacimab vs OD therapy (P < .0001) and noninferior vs RP (Figure 2C-D; supplemental Table 3).

Overall, changes in HRQoL from baseline to 6 months of the ATP vs OP were not significantly different for the OD group and were noninferior for the RP group (Figure 3; supplemental Table 6). The cumulative distribution frequency for Haem-A-QoL showed separation vs OD (physical health domain) and RP (physical health domain and total score), and negligible separation for EQ-5D-5L and EQ-VAS vs RP (supplemental Figures 5 and 6). For the HJHS, estimated median differences from baseline at 6 months between the OP and ATP were negligible for both OD and RP groups (supplemental Table 6). Mean number of target joints during the OP and ATP is shown in

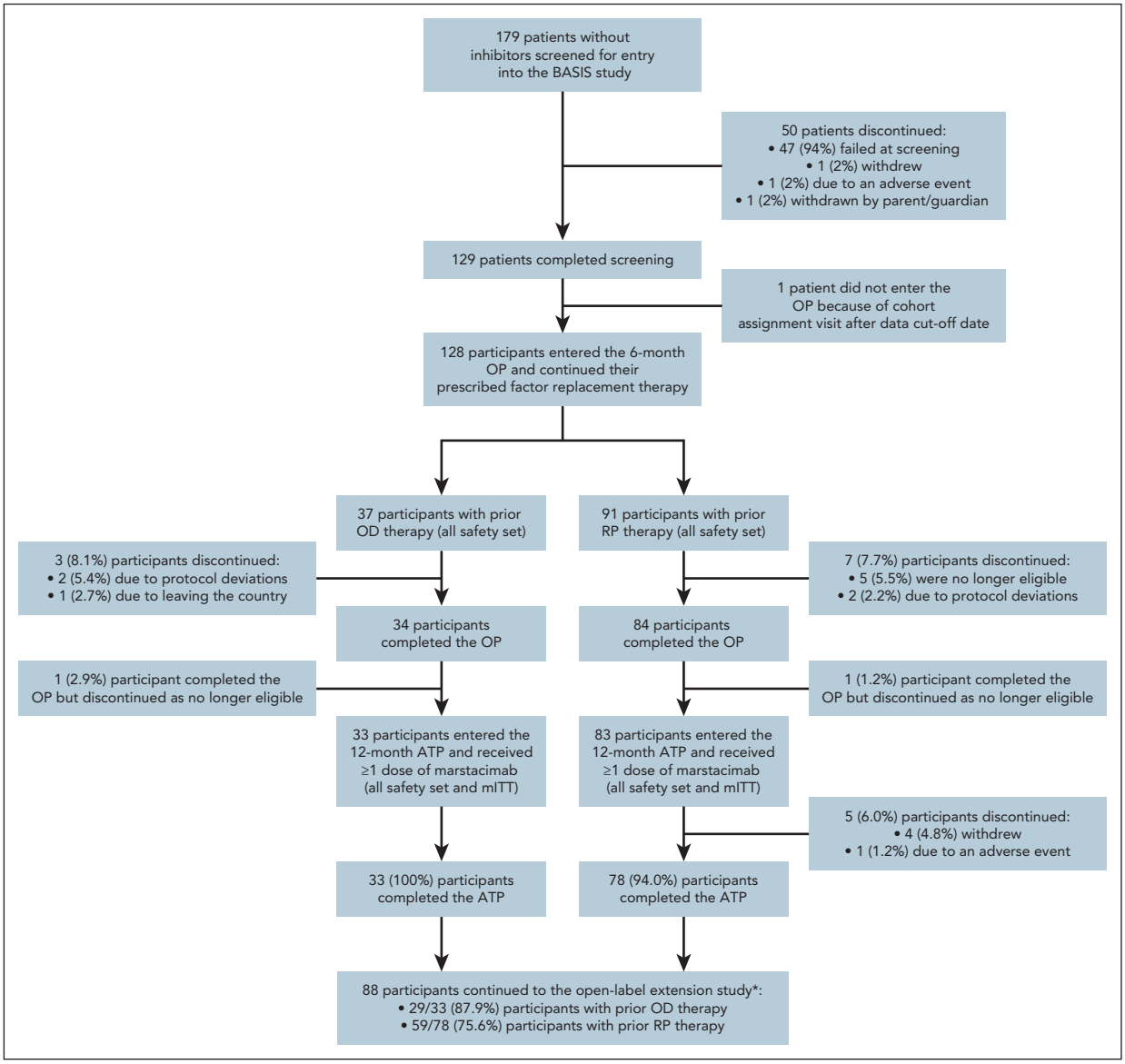

Figure 1. Screening, enrollment, dosing, and progression in the BASIS study. Screening for patients without inhibitors to enter the BASIS study, enrollment into the OP, entry into the ATP, dosing with marstacimab, and progression to the ongoing open-label extension study. *Number of participants before the phase 3 study primary completion date (data cutoff, 17 April 2023). mITT, modified intent to treat.

supplemental Figure 7. Days requiring factor replacement and total consumption are shown in supplemental Table 7.

Safety outcomes

No deaths or thromboembolic events occurred during the ATP, and 74 participants experienced adverse events, most of which were mild to moderate in severity. The most common adverse events (in ≥5% of participants in either the OD or RP group) were COVID-19–related, pruritus, upper respiratory tract infection, decreased range of joint motion, headache, and contusion.

Overall, 7 participants experienced ≥1 serious adverse event during the ATP (all in the RP group); 1 event was assessed as treatment related (grade 1 peripheral swelling; Table 2). One participant in the RP group with a serious adverse event of meningioma (not treatment related) discontinued the study for potential risk of thrombosis after surgical resection and radiotherapy. Adverse events of special interest are shown in Table 2. ISRs occurred in 2 (6.1%) participants in the OD group and 9 (10.8%) in the RP group and were generally mild and of short duration. In the OD group, 1 participant with a history of hemorrhoids experienced adverse events of grade 1 and 2 thrombosed hemorrhoids successfully treated with incisional drainage without treatment disruption. Adverse events for 14 participants who received dose escalation are in supplemental Section 7. None were serious or led to study discontinuation.

No clinically significant laboratory abnormalities were observed. Antidrug antibodies (ADAs) were detected in 23 of 116 (19.8%) participants (supplemental Table 8); titers were low, and 22 of 23 cases resolved by end of study. ADA status had no impact on ABR (supplemental Table 9), incidence of adverse events (supplemental Table 10), or pharmacokinetic or

Table 1. Baseline demographics and clinical characteristics

n (%)*	OD group (n = 37)	RP group (n = 91)	Total (N = 128)
Sex, male	37 (100)	91 (100)	128 (100)
Age, y			
<18	2 (5.4)	18 (19.8)	20 (15.6)
Mean (SD)	31.4 (10.54)	33.0 (14.76)	32.5 (13.65)
Median (range)	29.0 (15.0-58.0)	31.0 (13.0-66.0)	30.0 (13.0-66.0)
Hemophilia A	29 (78.4)	72 (79.1)	101 (78.9)
Hemophilia B	8 (21.6)	19 (20.9)	27 (21.1)
Race			
Asian	24 (64.9)	37 (40.7)	61 (47.7)
Black or African American	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)
Ethnicity			
Hispanic or Latino	4 (10.8)	9 (9.9)	13 (10.2)
Geographical region			
Asia	23 (62.2)	31 (34.1)	54 (42.2)
Europe	8 (21.6)	39 (42.9)	47 (36.7)
Middle East	2 (5.4)	10 (11.0)	12 (9.4)
North America	4 (10.8)	11 (12.1)	15 (11.7)
Mean body mass index (SD), kg/m^2	23.7 (5.6)	23.9 (4.2)	23.8 (4.6)
Target joints† at baseline			
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)

SD, standard deviation.

*Unless otherwise specified.

†Target joints are defined as major joints (eg, hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (≥3 spontaneous bleeds into a single joint within a consecutive 6-month period).

pharmacodynamic end points (supplemental Figures 8-13). Neutralizing antibodies were detected in 6 participants; titers were transient and resolved by end of study.

Pharmacokinetics and pharmacodynamics

Pharmacokinetic and pharmacodynamic results after once-weekly subcutaneous administration of marstacimab (150 mg and 300 mg) are summarized in supplemental Section 8. After subcutaneous administration, marstacimab plasma concentrations appeared to reach steady state by ~60 days, and treatment-related changes were observed for all pharmacodynamic assessments. Marstacimab pharmacokinetics was not clinically significantly affected by race, hemophilia type, presence of ADAs, and mild renal or hepatic impairment.

Discussion

In the BASIS study of participants aged 12 to 74 years with severe hemophilia A or moderately severe to severe hemophilia B without inhibitors, once-weekly subcutaneous prophylaxis with 150 mg marstacimab in the ATP significantly reduced the ABR of treated bleeds compared with previous OD therapy or RP in the OP; a finding that showed noninferiority (primary end point for RP) and superiority (primary end point for OD, secondary end point for RP) of marstacimab compared with previous treatment. Improvements in ABR were also observed for the 14 (12.1%) participants who escalated dose to 300 mg, suggesting treatment adjustments could be considered by physicians to improve outcomes in patients with hemophilia A or B with a greater number of bleeds. ABR reductions were generally consistent across subgroups; however, the CIs are broad for some subgroups (eg, hemophilia B participants in the OD group) and the upper bound of the CI for ABR difference exceeded 2.5 for some subgroups. These analyses should be interpreted with caution because sample sizes were small, and the study was not powered to assess noninferiority or superiority in subgroups. A general trend in the lowering of ABR for treated bleeds over time was observed in both OD and RP

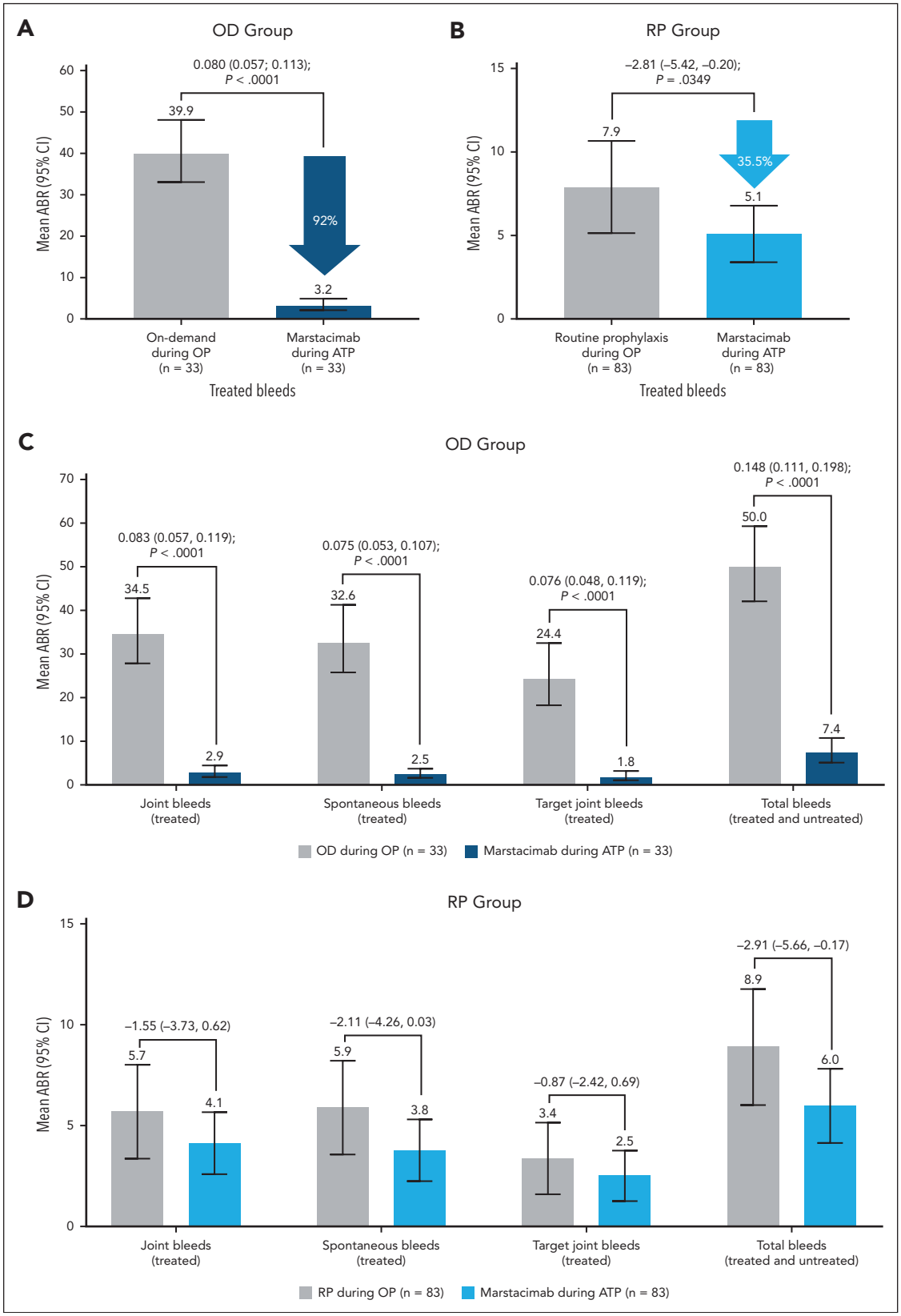

Figure 2. Results of primary and key secondary efficacy end points. The model-based ABR during the (A-B) OP and ATP for the primary end point (treated bleeds) and (C-D) key secondary end points in the OD group (A,C) and the RP group (B,D). Ratio estimate, 95% CI and *P* value are shown for marstacimab vs previous OD therapy; difference estimate and 95% CI are shown for marstacimab vs previous RP (*P* values not shown because comparisons did not reach significance). The analyses include participants who received ≥1 dose of marstacimab prophylaxis in the ATP. ABR was calculated for time on treatment in each phase. For participants who had a dose escalation, the duration on marstacimab 300 mg was not included. For the OD group, *P* values are for the null hypothesis that the ABR ratio (marstacimab prophylaxis to OD treatment) equals 0.5. For the RP group, *P* values are for the null hypothesis that the difference (marstacimab prophylaxis minus RP) equals 0.0. Hierarchical testing precluded superiority testing for the secondary end points in the RP group (panel B) because superiority was not demonstrated in the physical health domain of the Haem-A-QoL.

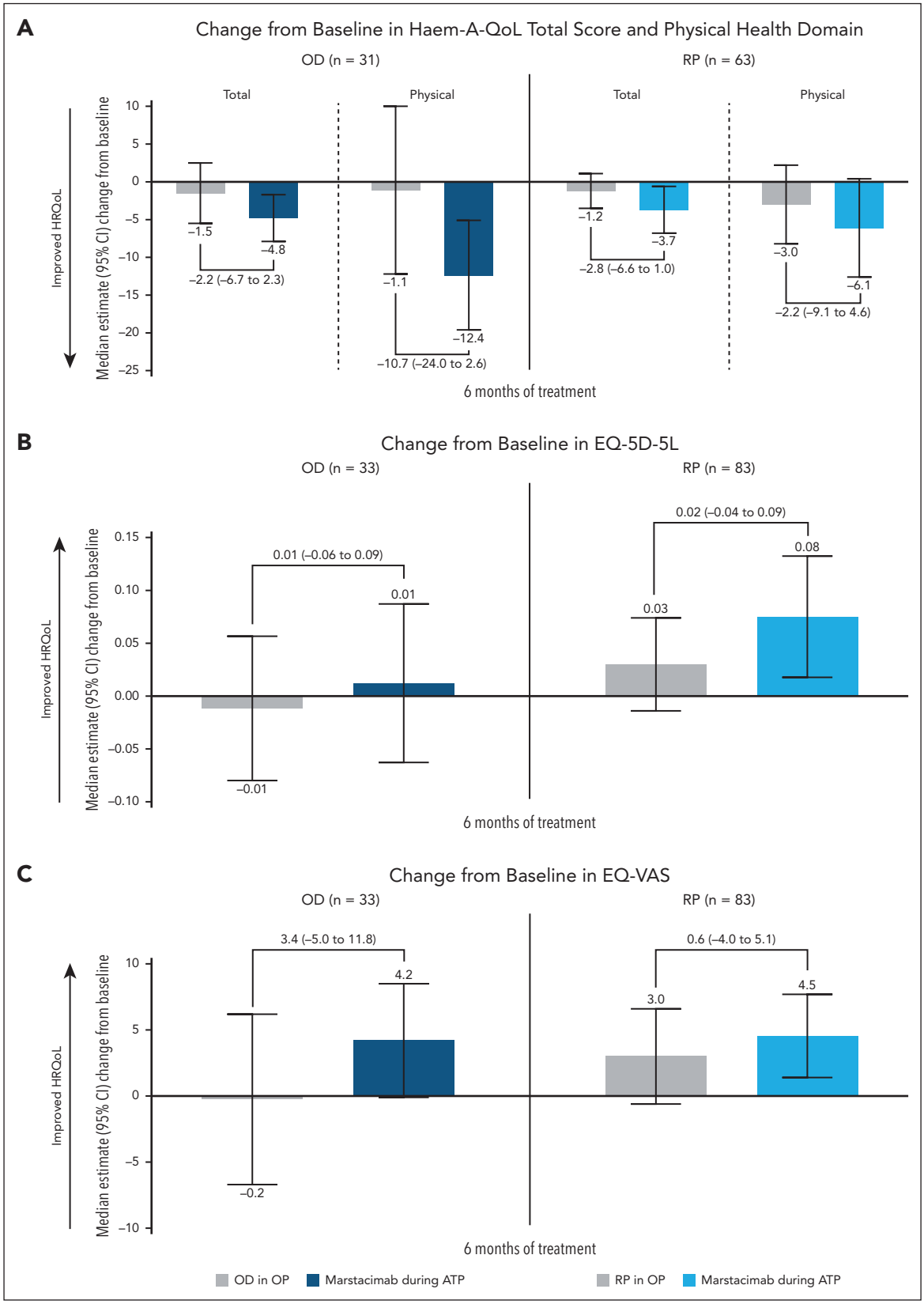

Figure 3. Key patient-reported outcomes for HRQoL. Nonparametric analysis of change from baseline to month 6 during the OP and from last day of the OP to month 6 of the ATP for the Haem-A-QoL (A), EQ-5D-5L (B), and EQ-VAS (C) measures. Estimated median difference (95% CI) of marstacimab vs previous OD therapy and RP. Missing values were imputed using multiple imputation methods based on missing at random assumption.

Table 2. Adverse events

Event, n (%)	OD group		RP group	
	OP OD therapy (n = 37)	ATP Marstacimab prophylaxis (n = 33)	OP RP therapy (n = 91)	ATP Marstacimab prophylaxis (n = 83)
Any event	9 (24.3)	12 (36.4)	20 (22.0)	62 (74.7)
Treatment related	NA	4 (12.1)*	NA	19 (22.9)†
Reported in ≥5% of participants‡				
COVID-19	0	2 (6.1)	3 (3.3)	18 (21.7)
Headache	0	1 (3.0)	0	6 (7.2)
Contusion	0	0	0	5 (6.0)
Dental caries	2 (5.4)	0	0	4 (4.8)
Pruritus	0	2 (6.1)	0	2 (2.4)
Upper respiratory tract infection	0	2 (6.1)	1 (1.1)	1 (1.2)
Joint range of motion decreased	1 (2.7)	2 (6.1)	0	0
Any serious event	1 (2.7)§	0	2 (2.2)¦	7 (8.4)¶
Treatment related	NA	0	NA	1 (1.2)#
Event leading to treatment discontinuation	0	0	0	1 (1.2)**
Embolic and thrombotic events	0	0	1 (1.1)††	0
Events of special interest‡‡	9 (24.3)	14 (42.4)	15 (16.5)	46 (55.4)
Reported in ≥5% of participants				
COVID-19	0	2 (6.1)	3 (3.3)	19 (22.9)
Hemorrhages	1 (2.7)§	0	5 (5.5)	13 (15.7)
Hepatic disorders	7 (18.9)	7 (21.2)	3 (3.3)	4 (4.8)
Hypersensitivity§§	0	2 (6.1)	2 (2.2)	6 (7.2)
Hypertension	1 (2.7)	2 (6.1)	2 (2.2)	5 (6.0)
Injection site reactions	0	2 (6.1)	0	9 (10.8)

NA, not applicable.

*Including pruritus (n = 2), gastrointestinal disorders (n = 1; hemorrhoids and thrombosed hemorrhoids), injection site hematoma (n = 1), injection site pain (n = 1).

†Including injection site pruritus (n = 4), injection site erythema (n = 3), and prothrombin fragment 1.2 increased (n = 3).

‡Shown are the number and percent of participants with ≥1 treatment-emergent adverse event. Participants are only counted once per treatment group per preferred term.

§Gastric hemorrhage.

¦Esophagitis and device occlusion.

¶One occurrence each of: tympanic membrane perforation, chest pain, peripheral swelling, tonsillitis, traumatic hemorrhage, hemarthrosis, meningioma, and hemorrhage.

#Grade 1 peripheral calf swelling considered to be treatment related that was diagnostically confirmed to be unrelated to a bleeding or thrombotic event.

**Participant with meningioma requiring surgical resection and follow-up therapy permanently discontinued from the study because there was potential elevated risk for development of thrombosis in the postoperative recovery phase and the planned follow-up radiotherapy treatment.

††Device occlusion of a blocked port-a-cath over the right subclavicular region without surrounding swelling and tenderness. In 1 attempt, blood was drawn easily and flushed with normal saline without resistance.

‡‡Adverse events of special interest are listed by event type by standardized Medical Dictionary for Regulatory Activities query (version 25.1) coding dictionary was applied.

§§Systemic and localized allergic reactions: conjunctivitis, eczema, pruritus, rash, and rhinitis allergic.

groups during the first and second 6 months of the ATP. Similar time-dependent improvements have also been observed in a pooled analysis of emicizumab phase 3 studies.[1,17,18] However, the marstacimab open-label extension study will further explore long-term efficacy and safety outcomes.

This study population had a high prevalence of target joints at baseline, with 69.5% having ≥1 target joint, of whom 18.7% in the RP group had ≥3 target joints despite being compliant with previous RP during the OP. The mean number of target joints remained consistent between RP and marstacimab prophylaxis. Compared with OD, marstacimab reduced target joints and consistently reduced ABR regardless of the number of baseline target joints, demonstrating efficacy in a population with considerable target joint bleeds. Reductions in ABR translated to negligible improvements in HJHS, possibly because marstacimab does not resolve previous joint damage or because more time is required to detect further changes.

Hemophilia is associated with impaired HRQoL, exacerbated by burden of treatment.[19,20] Therapies with reduced dosing frequency may enhance adherence and acceptance of prophylaxis

by reducing the infusion-schedule burden.[14] Marstacimab prophylaxis was associated with reduced frequency and factor replacement consumption, indicative of improved clinical outcomes. Adherence was high overall (≥97%) but noteworthy in the OD group, in which participants enrolled without recent experience of routine administration of prophylaxis, which demonstrates the feasibility of switching from OD to marstacimab prophylaxis. Changes in HRQoL measures were observed with marstacimab prophylaxis during the first 6 months of the ATP compared with previous therapy during the 6-month OP. However, improvements in HRQoL measures were not significant and will be explored further in the open-label extension study to determine whether changes in HRQoL are time dependent.

Marstacimab was safe and well tolerated over 12 months, with no deaths or thromboembolic events. Safety, immunogenicity, and laboratory parameters were consistent with previous studies[12,13] and contrast other investigational nonfactor treatments associated with thromboembolic complications.[6,7] Although these treatments target TFPI, differences among their specific epitope binding sites and differences in their binding affinities (marstacimab, K_D = 3.7 nM; concizumab, K_D = 0.025 nM; befovacimab, K_D < 0.01 nM)[21-23] may contribute to their distinct clinical safety profiles. ISRs were relatively infrequent with marstacimab and did not lead to discontinuation, suggesting the tolerability of subcutaneous delivery may have contributed to high adherence. ADAs can affect the therapeutic effect of biologics.[6,24-26] In this study, <20% of participants developed antibodies to marstacimab, which resolved in most (95.7%) by the study completion and did not affect safety, pharmacokinetics, or efficacy. Extended follow-up and real-world evidence of nonfactor therapies will determine whether adverse events are time dependent and whether nonhemostatic side effects may arise as a consequence of treatment.[27] The ongoing open-label extension of marstacimab will provide further insight into long-term safety and efficacy of BASIS participants.

Limitations of the study include a limited sample size to fully characterize thrombotic events, of which none were reported and which rules out >2.55% of the true thromboembolic rate with 1-sided 95% confidence. Although the COVID-19 pandemic had potential to affect recruitment, treatment suspension, and HRQoL assessments, there was minimal impact on the conduct of the study.

Nonfactor therapies requiring less frequent subcutaneous administration could expand treatment options for patients with hemophilia.[1-4] Emicizumab is approved for hemophilia A but is not indicated for hemophilia B.[1,5] A strength of BASIS is the inclusion of participants with hemophilia A and B, with or without inhibitors, because marstacimab acts independently of FVIII and FIX and may represent an effective treatment regardless of hemophilia type and inhibitor status.[14] Furthermore, no thromboembolic events were reported with marstacimab, unlike other nonfactor agents,[5-7,10] and will continue to be monitored in the long-term extension study.

In conclusion, these findings demonstrate the efficacy and safety of once-weekly subcutaneous marstacimab prophylaxis up to 12 months in adolescents and adults with severe hemophilia A or severe to moderately severe hemophilia B without inhibitors.

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Authorship

Contribution: A.P., C.T.T., E.H., and J.T. contributed to the study design; D.M., S.S.A., J.M., V.J.-Y., N.C., R.Y., M.A.-K., Y.W., J.M.A., Y.-S.P., and O.B.Z. participated as study investigators and provided patients or study materials; D.M., S.S.A., J.M., V.J.-Y., N.C., R.Y., M.A.-K., Y.W., J.M.A., Y.-S.P., O.B.Z, A.P., C.T.T., E.H., and J.T. participated in the collection and assembly of data; A.P., C.T.T., E.H., S.R., S.N., R.M., and J.T. contributed to data analysis; and all authors participated in data interpretation and critical review and revision of this manuscript and provided approval of the manuscript for submission.

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Footnotes

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Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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