EAHAD
European Association for Haemophilia and Allied Disorders
2025

18th ANNUAL CONGRESS OF THE EUROPEAN ASSOCIATION FOR HAEMOPHILIA AND ALLIED DISORDERS

MILAN, ITALY
4-7 FEBRUARY 2025

Indirect Treatment Comparison of Marstacimab versus Emicizumab in Haemophilia A

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BACKGROUND

- Haemophilia A is a rare bleeding disorder that impairs blood clotting
- Primarily affecting males, it can lead to prolonged bleeding after injury, surgery, and/or spontaneous bleeding[1]
- Current prophylactic treatment options include factor replacement therapy or emicizumab as outlined within the World Federation of Hemophilia (WFH) guidelines[2]
- Marstacimab is the first and only anti-tissue factor pathway inhibitor (anti-TFPI) approved in the European Union (EU) for the treatment of haemophilia A or B and the first haemophilia medicine to be administered via a pre-filled, auto-injector pen
- Specifically, the European Commission (EC) has granted marketing authorization for marstacimab for the routine prophylaxis of bleeding episodes among individuals aged 12 years or older who have severe haemophilia A or B and who have not developed inhibitors against factor VIII or factor IX

OBJECTIVES

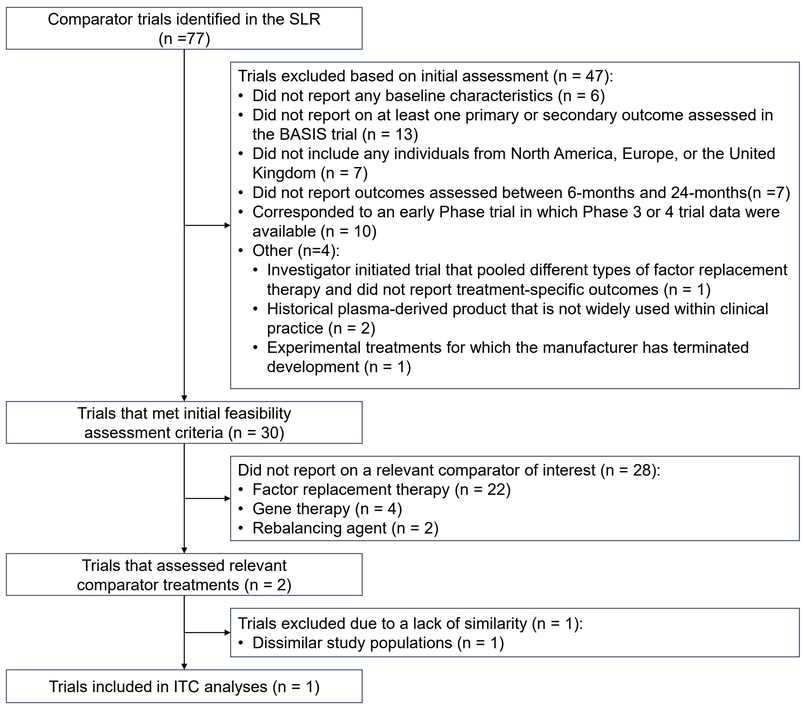
- To compare the efficacy of marstacimab relative to emicizumab among adults and adolescents with severe haemophilia A, without inhibitors, and who received prior prophylaxis

METHODS

Identification of evidence base

- 79 unique trials were identified for inclusion in a systematic literature review (SLR) of which 2 assessed marstacimab (the BASIS trial [NCT03938792] and a Phase 2 trial [NCT03363321]) and 77 examined other treatments
- Following the SLR, the feasibility of conducting an indirect treatment comparison (ITC) of marstacimab relative to other treatments identified was assessed (**Figure 1**), two trials (HAVEN-3[3] and HAVEN-4[4]) both evaluated emicizumab among individuals with haemophilia A and were further evaluated
- While stratified outcome data for the without inhibitors subgroup was reported for the HAVEN-4 trial, data specific to the prior prophylaxis subgroup was not available, making it incomparable to the without inhibitor, prior prophylaxis subgroup of the BASIS trial

Figure 1: Results of the feasibility assessment



Effect modifier and prognostic factors

- Relevant effect modifiers and/or prognostic variables were identified based on a literature review, input from clinical experts, and results from a series of regression analyses
- Based on these results, the following covariates were controlled for in the analyses: 1) prior total annualized bleeding rate (ABR); 2) target joints; 3) age; 4) body mass index (BMI); and 5) race/ethnicity

Outcomes

- Total ABR was chosen as the main outcome for the ITC
- The proportion of bleeding events that were treated was considerably lower in the HAVEN-3 trial than in the BASIS trial, which suggests that there were important differences in the clinical management of breakthrough bleeds
- In the HAVEN-3 trial, for example, only 23.9% of bleeding events were treated among individuals who received prior prophylaxis.[5] The majority of these untreated bleeds were located within joints (14.0%) or muscles (49.3%).[5] After excluding surgery or procedure-related bleeds, as done within the HAVEN-3 and BASIS trials, the proportion of treated bleeding events remained low at 34.6%.[5]
- In contrast, 83.3% of bleeding events that occurred after the initiation of marstacimab were treated in the BASIS trial
- These findings suggest that treated ABR is not directly comparable between the BASIS and HAVEN-3 trials

Statistical analyses

- An unanchored simulated treatment comparison (STC) using the conventional plug-in method was conducted using individual-level data from the BASIS trial and aggregate-level data from the Group D emicizumab arm of the HAVEN 3 trial (participants in Group D had been receiving factor VIII prophylaxis in a previous non-interventional study and were treated with emicizumab at a maintenance dose of 1.5 mg/kg)
- An STC was chosen over a matching-adjusted indirect comparison (MAIC) based on the 2020 NICE-DSU recommendations[6] and research suggesting that MAIC performs poorly when sample size is limited and there is a considerable lack of overlap in the distribution of baseline covariates, as was the case in the current study[7]

METHODS (CONTINUED)

Statistical analyses (continued)

- In the STC analyses, total ABR was modelled using negative binomial regression with log-time as an offset. The fitted outcome regression models were used to predict the conditional outcomes on marstacimab at the mean covariate values of the HAVEN-3 trial
- Relative treatment effects were estimated on the linear predictor scale and were expressed as rate ratios. Adjusted effects were reported alongside 95% CI and p-values
- All analyses were conducted in R

Sensitivity analyses

- In the BASIS trial, participants who met dose-escalation criteria after six months of treatment were permitted to increase their marstacimab dose from 150 mg to 300 mg QW following discussion with the medical monitor
- The primary analysis did not include data collected after dose modification and the ABR was modelled using bleeding rates up until dose modification
- To assess the impact of this exclusion on the results of this investigation, a sensitivity analysis was conducted in which bleeding events that occurred after a marstacimab dose-escalation were included in the analyses

RESULTS

- A total of 128 individuals were included in the analyses, 65 for marstacimab (BASIS) and 63 for emicizumab (HAVEN 3, Group D)
- The BASIS trial population had a more severe bleeding phenotype at baseline in terms of having a higher mean prior total ABR and higher percent with target joints (**Table 1**)
- In addition, the BASIS trial population was younger and had a higher proportion of non-White participants compared to the HAVEN-3, Group D (prior prophylaxis) comparator arm (absolute standardized difference (ASD) > 0.1)

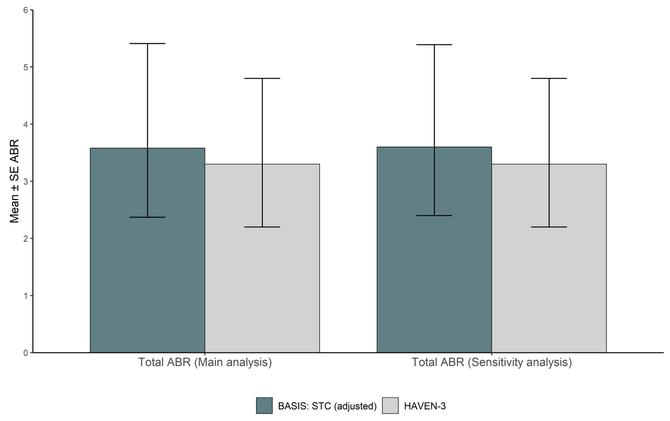
Table 1: Baseline characteristics of individuals with severe haemophilia A, without inhibitors, who received prior prophylaxis in the BASIS trial (N = 65) and HAVEN 3 trial, Group D (N = 63)

Baseline characteristics	BASIS (n = 65)	HAVEN 3, Group D (n= 63)	ASD
Patient characteristics			
Age, year (mean, SD)	31.63 (14.2)	36.4 (14.4)	0.336
Hispanic/Latino (%)	13.85%	11.1%	0.083
White (%)	52.31%	74.6%	0.476
BMI (mean, SD)	23.91 (4.3)	25.56[a]	-
Disease characteristics			
Prior total ABR (mean, SD)	10.26 (14.8)	6.4[a]	-
Target Joint (%)	56.92%	41.3%	0.317

[a]Prior total ABR and BMI were not available in the primary HAVEN 3 publication and were instead captured from Astermark et al. (2023)[8], respectively
Abbreviations: ABR = annualized bleed rate; ASD = absolute standardized difference; BMI = body mass index; n = number of patients; SD = standard deviation

- After adjusting for baseline differences in the distribution of effect modifiers and prognostic factors, there were no statistically significant differences between marstacimab and emicizumab with respect to total ABR (rate ratio: 1.08; 95% CI: 0.61 to 1.91; p = 0.79) (**Figures 2 and 3, Table 2**)
- In sensitivity analyses, the findings were similar after including bleeding events that occurred after a marstacimab dose-escalation (**Figures 2 and 3, Table 2**)

Figure 2: Mean Total ABR after STC adjustment



Note: Total ABR refers to the negative binomial model-derived ABR; STC was adjusted for baseline age, prior total ABR, percent with target joints, percent Hispanic/latino, percent white and BMI; Sensitivity analysis refers to BASIS dose-escalation, in which the STC was repeated after including bleeding events that occurred after a marstacimab dose-escalation
Abbreviations: ABR = annualized bleed rate; CI = confidence interval; STC = simulated treated comparison

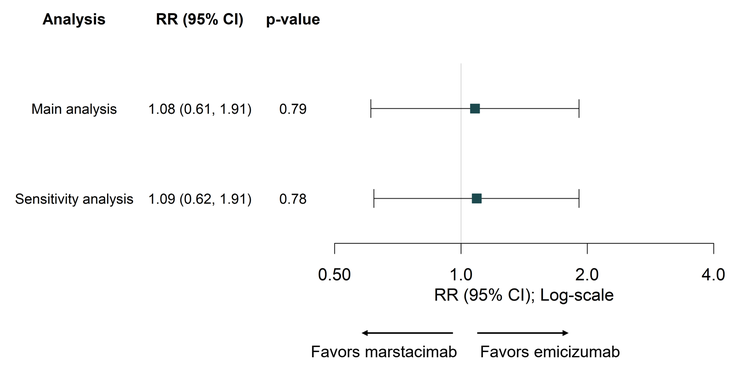
Table 2: Results from an unanchored STC of marstacimab (BASIS trial) versus emicizumab (HAVEN-3 trial, Group D) among individuals with severe haemophilia A, without inhibitors, and who received prior FVIII prophylaxis

Scenario	Trial Arm	n	Total ABR[a] (95% CI)	Rate Ratio (95% CI)	P-value
Main analysis	BASIS: STC[b]	65	3.58 (2.37 to 5.41)	1.08 (0.61 to 1.91)	0.79
	HAVEN-3	63	3.3 (2.2 to 4.8)	Ref.	-
Sensitivity analysis[c]	BASIS: STC[b]	65	3.60 (2.40 to 5.39)	1.09 (0.62 to 1.91)	0.78
	HAVEN-3	63	3.3 (2.2 to 4.8)	Ref.	-

[a]Refers to the negative binomial model-derived ABR
[b]Adjusted for baseline age, prior total ABR, percent with target joints, percent Hispanic/latino, percent white and BMI
[c]Sensitivity analysis refers to BASIS dose-escalation, in which the STC was repeated after including bleeding events that occurred after a marstacimab dose-escalation
Abbreviations: ABR = annualized bleed rate; CI = confidence interval; n = number of individuals; STC = simulated treated comparison

RESULTS (CONTINUED)

Figure 3: Relative treatment effect from an unanchored STC of marstacimab (BASIS trial) versus emicizumab (HAVEN-3 trial, Group D) for total ABR, main and sensitivity analyses



Note: RR represents the rate ratio of marstacimab versus emicizumab (reference); Values less than 1 indicates a lower total ABR for marstacimab compared with emicizumab (favors marstacimab); Sensitivity analysis refers to BASIS dose-escalation, in which the STC was repeated after including bleeding events that occurred after a marstacimab dose-escalation
Abbreviations: ABR = annualized bleed rate; CI = confidence interval; RR = rate ratio; STC = simulated treated comparison

LIMITATIONS

- These results should be interpreted with caution because there is a high risk of bias and high degree of uncertainty due to the following factors:
  - Potential residual differences in the distribution of measured and unmeasured effect modifiers and prognostic factors
  - Between-trial geographic and temporal differences that could not be fully accounted for within the analyses
  - Potential differences between the marginal outcome and the conditional outcome for marstacimab that could bias the STC results
  - Lack of precision due to the limited sample sizes

CONCLUSION

- An unanchored STC was conducted to compare the efficacy of marstacimab relative to emicizumab using individual-level data from the BASIS trial and aggregate-level data from the prior prophylaxis, emicizumab arm (Group D) of the HAVEN 3 trial
- Results suggest that the efficacy of marstacimab is comparable to that of emicizumab with respect to the control of total bleeding events among adults or adolescents with severe haemophilia A, without inhibitors, and who received prior prophylaxis
- In the absence of a direct head-to-head comparison, these findings represent the best available comparative efficacy evidence. However, these results should be interpreted with caution due to the high risk of bias and high degree of uncertainty

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DISCLOSURE

- AS, TG, JC and MI are employees and shareholders of Pfizer Inc. YW, AN, HJ, JU, KL, DB are employees of IQVIA, Inc, which received funding from Pfizer to conduct this study and to develop this poster

Presented at the 18th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), February 4-7, 2025, Milan, Italy