Matching-Adjusted Indirect Comparison of Etranacogene Dezaparvovec Versus Marstacimab for the Treatment of Severe Hemophilia B

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Conflict of Interest Statements

- **Robert Klamroth:** Research grants, consultancy fees, speaker honoraria, advisory board fees and/or travel support from Bayer, Biomarin, Biotest, Chugai, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Swedish Orphan Biovitrum, Tangram and Takeda
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- **Songkai Yan, Douglass Drelich, Hongseok Kim, and Radovan Tomic:** Employees of CSL Behring
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Background

HEMOPHILIA B (or FACTOR IX [FIX] deficiency)

Caused by F9 gene mutations which encode for coagulation FIX[1,2]. Prophylactic medications to prevent bleeding are the current standard of care. Novel treatments include gene and non-factor therapies.

ETRANACOGENE DEZAPARVOVEC (EDZ)

An adeno-associated virus 5 (AAV5) vector–based gene therapy designed to enable endogenous production of FIX.

One-time treatment

VS

MARSTACIMAB

A monoclonal antibody targeting the tissue factor pathway inhibitor.

Once-weekly injections

At the time of development, EDZ and marstacimab were the first approved gene therapy and non-factor prophylactic treatment, respectively, for patients without inhibitors.

There are no head-to-head trials comparing EDZ and marstacimab.

[1]Hart DA-O, Matino D, Astermark J, Dolan G, d'Oiron R et al. (2022) International consensus recommendations on the management of people with haemophilia B. *Ther Adv Hematol* 13 (2040-6207 (Print)).
[2]Konkle BA, Nakaya Fletcher S (2000 Oct 2 [Updated 2025 Aug 7]). *Hemophilia B. BTI - GeneReviews(®)*. (Adam MP BS, Mirzaa GM,, eds). University of Washington, Seattle.
[3] Phillippo, D., et al., NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE, in NICE Decision Support Unit Technical Support Documents. 2016, NICE Decision Support Unit: Sheffield.

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Abbreviations: AAV5, adeno-associated virus 5; EDZ, etranacogene dezaparvovec; FIX, factor IX; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; TSD, Technical Support Document.

Objective

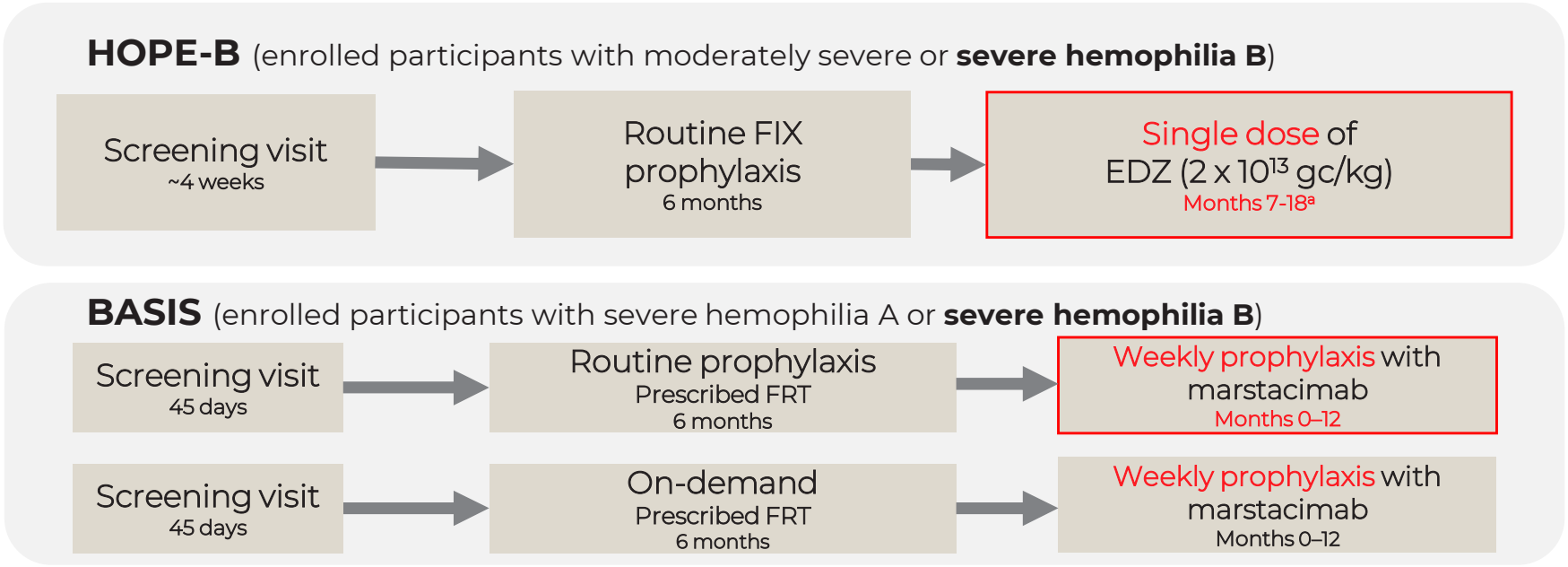
Objective: Compare the efficacy of EDZ vs marstacimab for the treatment of severe hemophilia B without inhibitors in patients who received prior routine prophylaxis using matching-adjusted indirect comparison (MAIC), following guidance from NICE TSD[3].

[1]Hart DA-O, Matino D, Astermark J, Dolan G, d'Oiron R et al. (2022) International consensus recommendations on the management of people with haemophilia B. *Ther Adv Hematol* 13 (2040-6207 (Print)).
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Study Design

- HOPE-B (CSL Behring)[1] and BASIS (Pfizer)[2,3] are both phase 3, open-label, multi-center studies. There were differences in eligibility and enrollment with respect to disease subtype and severity:
  - HOPE-B enrolled participants with moderately severe or severe hemophilia B.
  - BASIS permitted enrollment of participants with severe hemophilia A and moderately severe or severe hemophilia B, but ultimately only enrolled participants with severe disease. **The focus of the MAICs was severe hemophilia B only.**

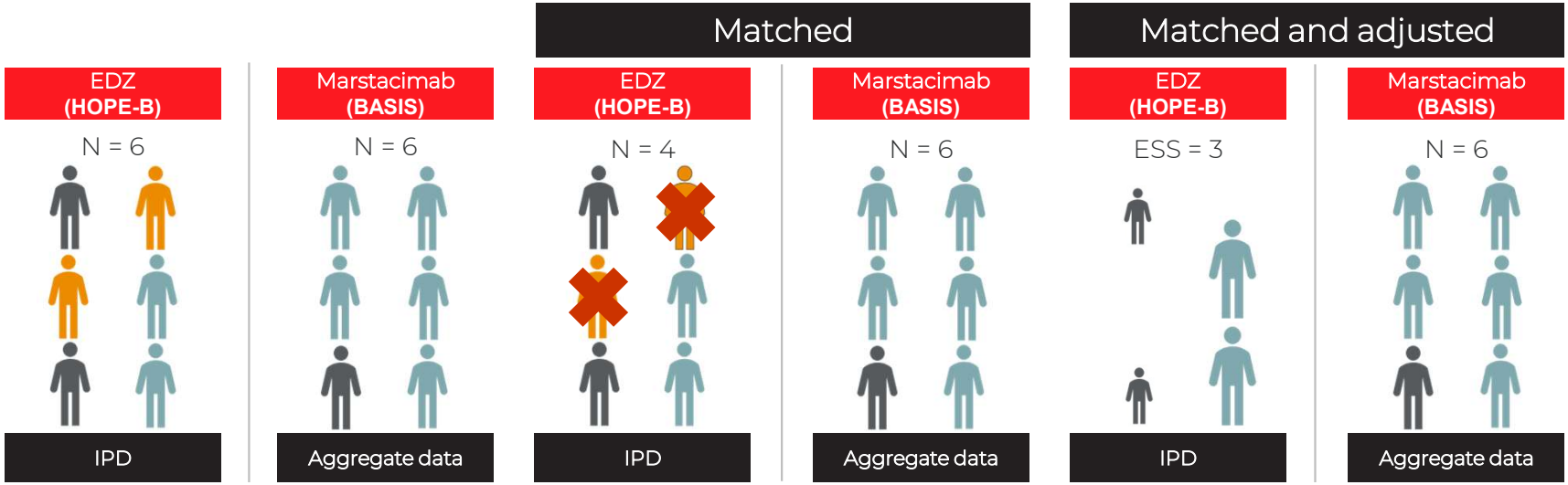


The MAICs compared HOPE-B and BASIS participants with severe hemophilia B who received routine FIX prophylaxis prior to study drug.

[a]The timing of outcome assessments was designed to allow full gene expression to occur prior to outcome assessment, which was pre-defined for HOPE-B.
Abbreviations: FIX, factor IX; FRT, factor replacement therapy; gc, genome copies; kg, kilogram; MAIC, matching-adjusted indirect comparison.
[1]Pipe SW, Leebeek FWG, Recht M (2023) Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. *New England Journal of Medicine* 388 (8): 706-718.
[2]Matino D, Acharya SS, Taylor CT, Sun P, Agathon D et al. (2026) Efficacy and safety of marstacimab prophylaxis in hemophilia A/B with inhibitors: results from the phase 3 BASIS trial. *Blood* 147 (9): 920-931.
[3]Matino D, Palladino A, Taylor CT, Hwang E, Raje S et al. (2025) Marstacimab prophylaxis in hemophilia A/B without inhibitors: results from the phase 3 BASIS trial. *Blood* 146 (14): 1654-1663.

Overview of Unanchored Matching-Adjusted Indirect Comparison

MAICs match and adjust IPD to allow more balanced comparisons of efficacy.



Published trials differ on eligibility criteria, trial enrollment, and participant characteristics

Participants who would not have been eligible for or enrolled in the comparator trial are excluded

Participants in the trial with IPD are weighted to align with the averages reported in the comparator trial; ESS reflects estimated[a,1] sample size after adjusting

Adjustment is based on **treatment-effect modifiers** and **prognostic factors**.

[a]ESS is an estimate of sample size required by an unweighted sample to achieve the same level of precision.

[1]Zhang L, Bujkiewicz S, Jackson D. Three new methodologies for calculating the effective sample size when performing population adjustment. BMC Med Res Methodol. 2024 Nov 20;24(1):287. doi: 10.1186/s12874-024-02412-1. PMID: 39567920; PMCID: PMC11577712.

Abbreviations: ESS, effective sample size; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; N, number of patients.

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Identification of Key Baseline Characteristics for Matching and Adjustment

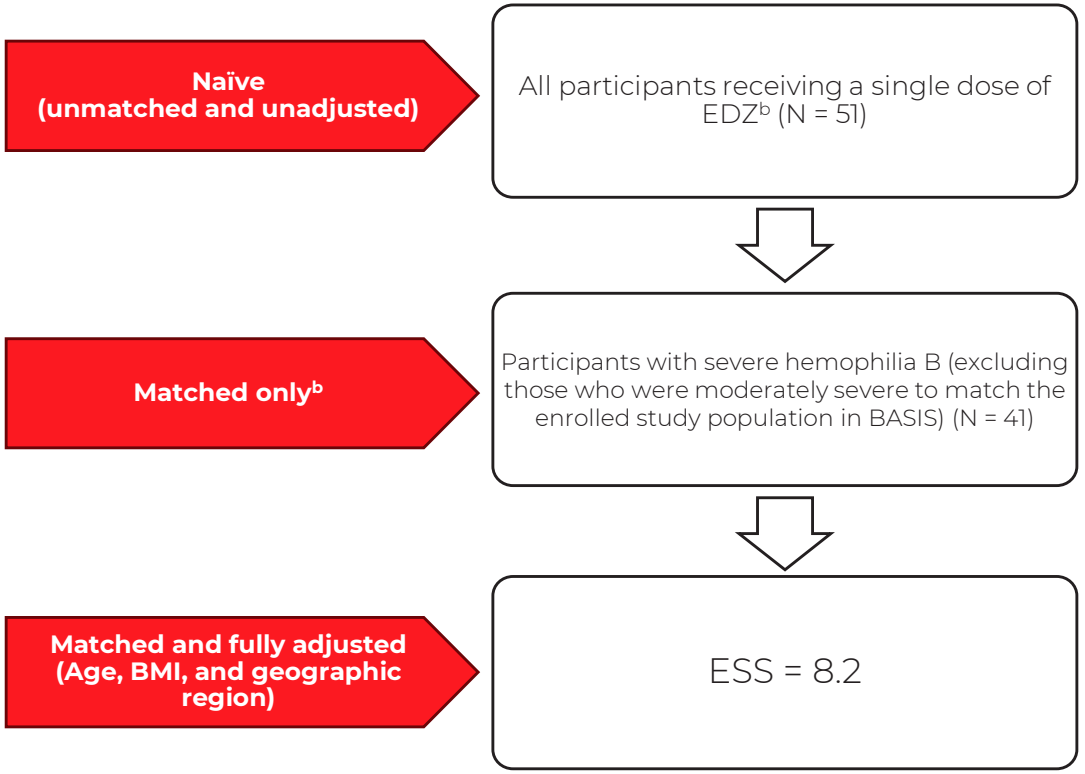
Baseline characteristics potentially influencing prognosis or treatment effects were identified *a priori* → Clinical experts assigned a rating to each characteristic → Final adjustment variables based on: availability, balance across both populations, and sample size

Matching Factors (based on eligibility criteria and enrollment)		
Disease severity and bilirubin threshold		
Adjustment Factors		
Rated Clinical Importance	Baseline Variable	Adjusted for in MAICs
High	Disease severity	No (used as a matching factor)[a]
	Age	Yes
	BMI	Yes
	Race/ethnicity	No (substantial heterogeneity with BASIS after matching; geographic region used instead)[b]
	Weight (kg)	No (BMI used instead)
	Number of bleeding episodes in prior year	No (NR for BASIS)
	≥1 Target joint	No (NR for HOPE-B)
	Geographic Region	Yes
Low	Pre-study FIX therapy	No (Used to define the population of interest)
	HIV-positive	No (NR for BASIS)
	HCV-positive	No (NR for BASIS)
	Percent of adolescents (12-17 years)	No (Adjusted for mean age)

[a]Disease severity was applied as a matching criteria instead of an adjustment criteria due to all participants enrolled in BASIS being categorized as "severe."
[b]While race was ranked as highly important and deemed an important adjustment factor, geographic region was selected for the analysis instead due to substantial differences in the populations after matching which made it infeasible to adjust for this characteristic.

Abbreviations: BMI, body mass index; FIX, factor IX; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IPD, individual patient data; kg, kilogram; MAIC, matching-adjusted indirect comparison; NR, not reported.

Analysis Overview



Compared Outcomes and Data Sources[a]

Outcome	Data Source
Annualized Bleeding Rate for Treated Bleeds (ABR)	G-BA[1] & HAS[2]
Annualized Spontaneous Bleeding Rate for Treated Bleeds (AsBR)	G-BA[1]
Annualized Joint Bleeding Rate for Treated Bleeds (AjBR)	G-BA[1] & HAS[2]
Proportion of Participants with 0 Treated Bleeds	G-BA[1] & HAS[2]
Annualized FIX consumption (IU/kg/year)	Kim et al., 2025[3]

[a]Due to the lack of hemophilia B subgroup data available in the primary publication of BASIS, publicly available SLD was obtained from the German G-BA submission dossier and French HAS decision document for bleeding outcomes. For ABR and proportion of participants without any treated bleeds, slightly different results were reported in each document, so separate MAICs were run. Figures in Kim et al., EAHAD 2025 poster were the source for FIX Consumption.[1-3]
[b]3 additional participants were excluded compared to published results; 1 participant removed due to data privacy laws; 1 participant receiving only a partial dose of EDZ, and 1 participant with only 1.09 days at risk who was deemed an outlier.
[c]While BASIS included participants with moderately severe to severe hemophilia B (FIX ≤2%) per trial inclusion criteria, only those with severe disease were enrolled. Therefore, participants without severe disease were removed from the HOPE-B analysis population.
Abbreviations: ABR, annualized bleeding rate for treated bleeds; AjBR, annualized joint bleeding rate for treated bleeds; AsBR, annualized spontaneous bleeding rate for treated bleeds; BMI, body mass index; EAHAD, European Association for Haemophilia and Allied Disorders; EDZ, etranacogene dezaparvovec; ESS, effective sample size; FIX, factor IX; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; IU, international unit; kg, kilogram; N, number of patients; SLD, summary-level data.
[1]Haute Autorité de Santé (2025). Décision n° 2025.0072/DC/SEM du 6 mars 2025 du collège de la Haute Autorité de santé portant refus d'accès précoce de la spécialité marstacimab (marstacimab). Available online at: https://www.has-sante.fr/upload/docs/application/pdf/2025-03/marstacimab_decision_et_avisct_ap444.pdf.
[2]Gemeinsamer Bundesausschuss (2025). Nutzenbewertungsverfahren zum Wirkstoff Marstacimab (schwere Hämophilie A, ≥ 12 Jahre, ohne Faktor VIII-Inhibitoren). Available online at: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1171/.
[3]Kim HK, Taylor CT, McDonald R, Sun P, Gould T et al. (2025) Exogenous Factor Consumption in Participants With Haemophilia A or B Without Inhibitors Receiving Marstacimab in the Basis Trial [Poster Presentation]. (#PO058) EAHAD. Milan, Italy. February 4–7, 2025.

Baseline Characteristics Before and After MAIC

- Populations were **well-balanced** for the adjusted factors after MAIC

Characteristic	BASIS (marstacimab)[a]	HOPE-B (EDZ)				
		Naïve (Unmatched & Unadjusted)	Matched & Unadjusted	Matched and adjusted for age	Matched and adjusted for age and BMI	Matched and adjusted for age, BMI, and geographic region
	N = 91	N = 51	N = 41	ESS = 24.3	ESS = 12.1	ESS = 8.2
Age						
N reported[b]	91	51	41	41	41	41
Mean (SD)	33 (14.76)	40.4 (15.0)	40.5 (14.6)	33.0 (15.0)	33.0 (15.1)	33.0 (15.1)
BMI						
N reported[b]	91	51	41	41	41	41
Mean (SD)	23.9 (4.2)	27.3 (5.2)	27.7 (5.2)	28.5 (7.4)	23.9 (4.3)	23.9 (4.3)
Geographic Region						
N reported[b]	91	51	41	41	41	41
Rest of World, %[c]	87.9%	62.7%	68.3%	58.6%	58.5%	87.9%
North America, %[c]	12.1%	37.3%	31.7%	41.4%	41.5%	12.1%

[a]Baseline characteristics for BASIS were reported for the entire prophylaxis cohort, it is assumed these baseline characteristics are representative of the hemophilia B subpopulation.
[b]For adjusted analyses, N reported reflects the number of participants with non-missing data in the original sample.
[c]Only % is reported for adjusted analyses.

Abbreviations: BMI, body mass index; EDZ, etranacogene dezaparvovec; ESS, effective sample size; FIX, factor IX; MAIC, matching-adjusted indirect comparison; N, number of patients; SD, standard deviation.

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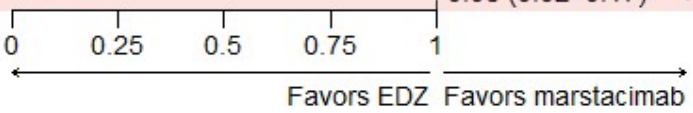
Summary of Results

Bleed Rates

- EDZ had statistically significantly lower bleed rates (ABR, AsBR, AjBR) compared to marstacimab, for the naïve and matched and fully adjusted analyses for the hemophilia B population. There is high concordance between the naïve and matched and fully-adjusted analyses.

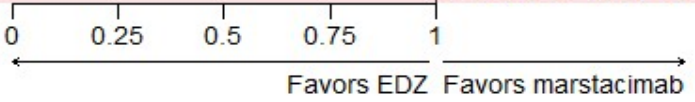
Naive - Bleeding Rates

Outcome	N EDZ	N marstacimab	Rate EDZ	Rate marstacimab	RR (95% CI)	P-value
ABR (G-BA)	51	18	0.50	4.60	0.11 (0.04–0.29)	< 0.0001
ABR (HAS)	51	18	0.50	4.71	0.11 (0.04–0.28)	< 0.0001
AsBR (G-BA)	51	18	0.13	2.88	0.04 (0.01–0.16)	< 0.0001
AjBR (G-BA)	51	18	0.21	3.87	0.06 (0.02–0.17)	< 0.0001



MAIC (age, BMI, and geographic region) - Bleeding Rates

Outcome	ESS EDZ	N marstacimab	Rate EDZ	Rate marstacimab	RR (95% CI)	P-value
ABR (G-BA)	8.2	18	0.28	4.60	0.06 (0.01–0.43)	0.0049
ABR (HAS)	8.2	18	0.28	4.71	0.06 (0.01–0.42)	0.0045
AsBR (G-BA)	8.2	18	0.17	2.88	0.06 (0.01–0.56)	0.0134
AjBR (G-BA)	8.2	18	0.24	3.87	0.06 (0.01–0.54)	0.0120



Abbreviations: ABR, annualized bleeding rate for treated bleeds; AjBR, annualized joint bleeding rate for treated bleeds; AsBR, annualized spontaneous bleeding rate for treated bleeds; BMI, body mass index; CI, confidence interval; EDZ, etranacogene dezaparvovec; ESS, effective sample size; N, number of patients; RR, rate ratio.

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Summary of Results

Proportion of Participants with 0 Treated Bleeds

- EDZ had statistically significantly more participants without any treated bleeds compared to marstacimab for the naïve and matched and fully adjusted analyses for the hemophilia B population. There is high concordance between the naïve and matched and fully-adjusted analyses.

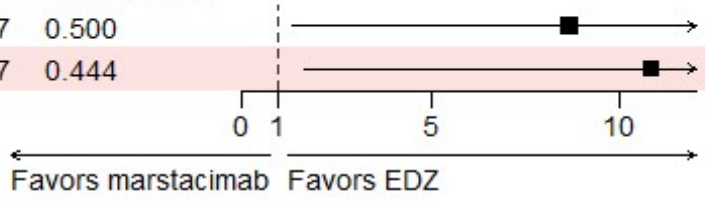
Naive - Proportion with 0 Treated Bleeds

Outcome	N EDZ	N marstacimab	Prop. EDZ	Prop. marstacimab	OR (95% CI)	P-value
Prop. 0 Treated Bleeds (G-BA)	51	18	0.765	0.500	3.25 (1.16–9.09)	0.0248
Prop. 0 Treated Bleeds (HAS)	51	18	0.765	0.444	4.06 (1.42–11.66)	0.0092



MAIC (age, BMI, and geographic region) - Proportion with 0 Treated Bleeds

Outcome	ESS EDZ	N marstacimab	Prop. EDZ	Prop. marstacimab	OR (95% CI)	P-value
Prop. 0 Treated Bleeds (G-BA)	8.2	18	0.897	0.500	8.67 (1.36–55.41)	0.0225
Prop. 0 Treated Bleeds (HAS)	8.2	18	0.897	0.444	10.84 (1.67–70.26)	0.0125



Abbreviations: BMI, body mass index; CI, confidence interval; EDZ, etranacogene dezaparvovec; ESS, effective sample size; FIX, factor IX; IU, international unit; kg, kilogram; MD, mean difference; N, number of patients; OR, odds ratio.

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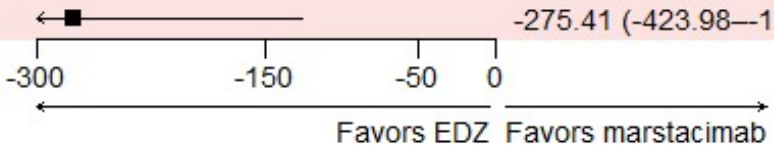
Summary of Results

Annualized FIX Consumption (IU/kg/year)

- EDZ had statistically significantly lower annualized FIX consumption compared to marstacimab for the naïve and matched and fully adjusted analyses for the hemophilia B population. There is high concordance between the naïve and matched and fully-adjusted analyses.

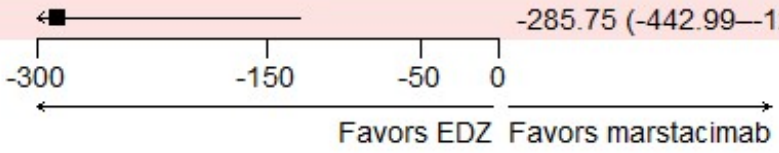
Naive - Annualized FIX Consumption (IU/kg/year)

Outcome	N EDZ	N marstacimab	Mean EDZ	Mean marstacimab	MD (95% CI)	P-value
Annualized FIX Consumption (IU/kg)	51	18	39.59	315	-275.41 (-423.98–-126.84)	3e-04



MAIC (age, BMI, and geographic region) - Annualized FIX Consumption (IU/kg/year)

Outcome	ESS EDZ	N marstacimab	Mean EDZ	Mean marstacimab	MD (95% CI)	P-value
Annualized FIX Consumption (IU/kg)	8.2	18	29.25	315	-285.75 (-442.99–-128.52)	4e-04



Abbreviations: BMI, body mass index; CI, confidence interval; EDZ, etranacogene dezaparvovec; ESS, effective sample size; FIX, factor IX; IU, international unit; kg, kilogram; MD, mean difference; N, number of patients; OR, odds ratio.

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Strengths and Limitations

Strengths



HOPE-B IPD enabled matching and adjustment for heterogeneity



HOPE-B and BASIS populations were well-balanced after adjustment



Comparable outcome definitions



All available data was assessed with a rigorous feasibility assessment

Limitations



Unanchored MAICs require assumptions and cannot exclude residual confounding



Baseline characteristics for pooled hemophilia A and B populations used due to lack of reporting for the hemophilia B population alone



Limited study sample sizes (HOPE-B N=51, BASIS N=18)[a] and low MAIC ESS (8.2)



Due to lack of available data from BASIS, only select highly-ranked factors could be adjusted for

[a]These sample sizes reflect the hemophilia B population in each study.
Abbreviations: ESS, effective sample size; MAIC, matching-adjusted indirect comparison.

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Conclusions

After matching and adjustment, the MAICs showed favorable and statistically significant results for EDZ for:

-ABR (G-BA RR: 0.06 [95% CI: 0.01–0.43], HAS RR: 0.06 [95% CI: 0.01–0.42])

-AsBR (RR: 0.06 [95% CI: 0.01–0.56])

-AjBR (G-BA RR: 0.06 [95% CI: 0.01–0.54])

-Proportion of Participants with No Treated Bleeds (G-BA OR: 8.67 [95% CI: 1.36–55.41], HAS OR: 10.84 [95% CI 1.67–70.26])

-Annualized FIX Consumption (IU/kg/year) (MD: -285.75 [95% CI: -442.99– -128.52])

Given the small effective sample size and unadjusted prognostic factors, these findings should be interpreted with caution.

A single dose of EDZ may reduce bleeds and required FIX products, compared to routine prophylaxis with marstacimab.

Abbreviations: ABR, annualized bleeding rate for treated bleeds; AjBR, annualized joint bleeding rate for treated bleeds; AsBR, annualized spontaneous bleeding rate for treated bleeds; BMI, body mass index; FIX, factor IX; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; IU, international unit; kg, kilogram; MAIC, matching-adjusted indirect comparison; MD, mean difference; OR, odds ratio; RR, rate ratio.

THANK YOU

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1. Hart DA-O, Matino D, Astermark J, Dolan G, d'Oiron R et al. (2022) International consensus recommendations on the management of people with haemophilia B. *Ther Adv Hematol* 13 (2040-6207 (Print)).

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