

Factor VIII use in the treatment of breakthrough bleeds in persons with hemophilia A without inhibitors from emicizumab prophylaxis: The phase III HAVEN 3 study experience

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Summary

- Persons with hemophilia A (PwHA) had fewer bleeds with emicizumab bleed prevention (prophylaxis) than previously when taking factor (F) VIII prophylaxis.
- In this analysis, researchers took a closer look at how on-demand FVIII treatment was used for breakthrough bleeds (BTBs) when taking FVIII versus emicizumab prophylaxis.
- Because PwHA receiving emicizumab had fewer BTBs, they needed less on-demand FVIII for treating BTBs than when taking FVIII prophylaxis (lower annualized infusion rate for BTBs [AIRB]).
- The amount of FVIII treatment used per BTB was similar irrespective of the prophylaxis received or the location of bleed.

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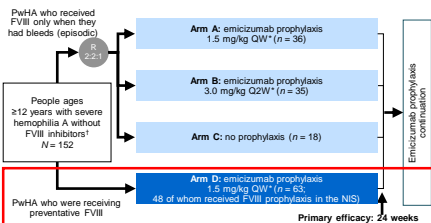
Introduction

- Clinical and subclinical bleeds (breakthrough bleeds; BTBs) are still possible even with regular FVIII prophylaxis.¹ Recurring bleeds can lead to joint disease.²
- The Phase III HAVEN 3 study (NCT02847637) compared how well emicizumab (a hemophilia A [HA] treatment with a unique mechanism) prevented bleeds versus no prophylaxis in adolescent and adult PwHA without FVIII inhibitors.³ Those who received emicizumab had a smaller number of bleeds compared to those who did not have prophylaxis. Emicizumab was efficacious and well tolerated.⁴
- A portion of the participants in HAVEN 3 (Arm D) had already received FVIII prophylaxis through routine clinical practice as observed through a separate 'non-interventional study' (NIS) that used similar data collection (Figure 1).⁵
- After they switched to emicizumab prophylaxis (HAVEN 3, Arm D), they had significantly fewer bleeds per year than when taking FVIII prophylaxis (1.5 vs 4.8; p<0.0001), but it was not known how much 'on-demand' FVIII was given for BTBs. This analysis looks at the amount of FVIII given for BTBs.

Methods

This analysis looks only at the 48 PwHA who received FVIII prophylaxis as part of the NIS and then switched to emicizumab prophylaxis in the HAVEN 3 study (Figure 1).

Figure 1. HAVEN 3 study design⁴.



- *A loading dose of 3.0 mg/kg QW emicizumab was administered for four weeks before maintenance doses were given as indicated, starting Week 5; \pm0.6 Bethesda units/mL. FVIII, factor eight; NIS, non-interventional study; PwHA, persons with hemophilia A; QW, once per week; Q2W, once every 2 weeks; R, randomization (people in the study were randomly allocated to a study arm).
- In both the NIS and HAVEN 3, doctors treated PwHA with BTBs with 'on-demand' FVIII at their discretion. In HAVEN 3, doctors were advised to use the lowest dose possible to treat bleeds.
 - A 'bleed' was defined starting from the first sign of bleeding and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or for which injections were \leq 72 hours apart were considered the same bleed. Any injection to treat the bleed, taken >72 hours after the preceding injection, was considered the first injection to treat a new bleed at the same location.
 - Only on-demand FVIII use for the treatment of BTBs is included in these analyses; any other use of FVIII (e.g., prophylactic FVIII, preventative dosing prior to activity, treatment for surgical procedures) was not included.
- To see the number of on-demand FVIII infusions used during the year ('the annualized infusion rate for BTBs' [AIRB]) the total amount given per day was divided by the total days in the study period and multiplied by 365.25.
- No formal statistical analysis was conducted.

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Results

PwHA in Arm D of HAVEN 3 needed fewer 'on-demand' treatments for BTBs when they were switched to emicizumab, compared with when they previously received FVIII during the NIS (Table 1).

- Of 48 participants receiving FVIII prophylaxis in the NIS, 29 (60.4%) experienced a total of 137 treated bleeds. While receiving emicizumab prophylaxis during HAVEN 3, 27 of the same 48 participants (56.3%) experienced 71 treated bleeds.
- Both the average number of treatments per year (AIRB) and amount of on-demand FVIII they were given (the total dose per person) for BTBs were lower during the HAVEN 3 study, compared to when participants received FVIII prophylaxis during the NIS (Table 1).

Table 1. Analysis of BTBs that were treated in PwHA, both in the NIS when they received FVIII prophylaxis and when they switched to emicizumab prophylaxis (Arm D) in HAVEN 3.

	FVIII prophylaxis n = 48	Emicizumab prophylaxis n = 48
Total exposure period in person years	28.6	75.8
Per-participant exposure years, median (IQR)	0.58 (0.19)	1.70 (0.20)
Total participants with treated bleeds, n	29	27
Total treated bleeds, n	137	71
AIRB per participant		
Mean (SD)	15.3 (43.6)	7.2 (16.8)
Median (IQR, Q1, Q3)	3.6 (15, 0, 15)	0.6 (5, 0, 5)
Annualized cumulative dose, FVIII IU/kg per participant		
Mean (SD)	602.4 (1822.3)	209.0 (459.8)
Median (IQR)	75.5 (473, 0, 473)	19.1 (139, 0, 139)
Number of infusions per bleed, median (IQR)		
Treated bleeds	1.0 (1.0)	2.0 (3.0)
Treated joint bleeds	1.0 (1.0)	2.0 (3.0)
Cumulative dose per bleed, IU of FVIII/kg, median (IQR)		
Treated bleeds	43.5 (35.1)	50.0 (72.7)
Treated joint bleeds	48.2 (31.9)	53.5 (84.3)

Clinical cut-off date: October 4, 2018.
 AIRB, annualized infusion rate for BTBs; IQR, interquartile range; IU, international units; Q, quartile; SD, standard deviation.

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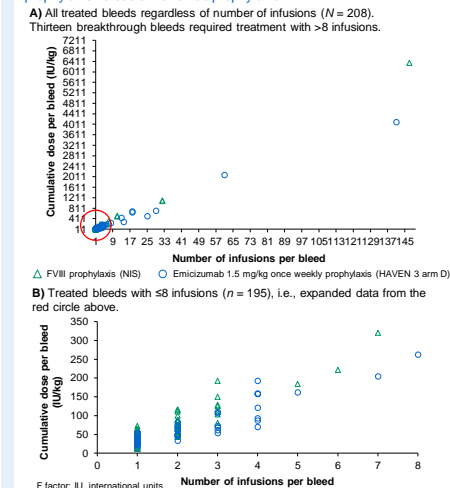
Disclosures

MC: consultancy (F. Hoffmann-La Roche Ltd/Genentech, Inc.; Bayer, Shire/Takeda, Bioventris/Sanofi, Global Blood Therapeutics, Spark Therapeutics, BioMarin, Pfizer, Novo Nordisk, Kedron, Octapharma, Grifols), equity ownership interests (Ahlstrom), research funding (F. Hoffmann-La Roche Ltd, Pfizer, Takeda), speakers' bureau (F. Hoffmann-La Roche Ltd, Novo Nordisk, Bayer, Shire/Takeda). TC: AMP, BT, employment (Genentech, Inc.), equity ownership interests (F. Hoffmann-La Roche Ltd/Genentech, Inc.), CEO, MNC employment (F. Hoffmann-La Roche Ltd, Genentech, Inc.). RM, LL, HB, ET: PIP employment (Genentech, Inc.). All consultancy (Basilea, Catalyt Biotechnologies, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Spark), research funding (BioMarin, Basilea, Catalyt Biotechnologies, CSL Behring, Novartis, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, Spark, Uniqum), honoraria (Basilea, Catalyt Biotechnologies, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Spark), speakers' bureau (Basilea, Catalyt Biotechnologies, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Spark).

PwHA who needed no on-demand FVIII to treat BTBs received similar amounts of FVIII in the NIS as received during HAVEN 3 (Table 1, Figure 2).

- Looking at individual bleeds, the number of on-demand FVIII infusions and the total cumulative FVIII dose per treated bleed indicate that participants were administered a similar amount of medication to treat bleeds during both the NIS and HAVEN 3 study periods (Table 1, Figure 2).
- Looking specifically at joint and muscle bleeds, they also found similar rates occurring during the NIS and HAVEN 3 (57% versus 61%; and 17% versus 14%, respectively).

Figure 2. Number of on-demand FVIII infusions and cumulative dose (IU/kg) per treated breakthrough bleed while receiving FVIII prophylaxis versus emicizumab prophylaxis.



Conclusions

- PwHA who switched from FVIII prophylaxis in the NIS to emicizumab prophylaxis in the HAVEN 3 study had significantly fewer bleeds per year on the latter prophylaxis (4.8 vs 1.5; p<0.0001).
- Since less BTBs required treatment, PwHA receiving emicizumab needed less frequent and lower yearly doses of on-demand FVIII, compared with when they received FVIII prophylaxis as part of the NIS. The median number of FVIII infusions for BTBs per year [AIRB] reduced by 6-fold from 3.6 to 0.6 on emicizumab prophylaxis.
- The amount of FVIII used to treat individual bleeds was similar regardless of the type of prophylaxis (emicizumab or FVIII) used.