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Factor VIII use in the treatment of breakthrough bleeds in hemophilia A patients without inhibitors on emicizumab prophylaxis: the phase III HAVEN 3 study experience

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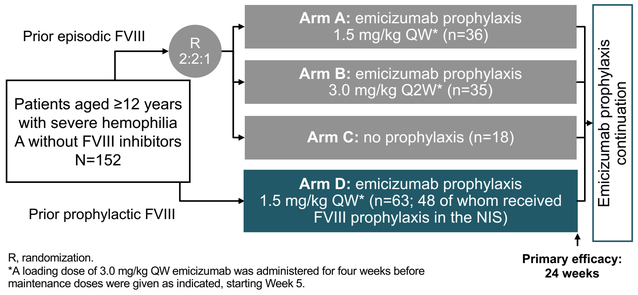
INTRODUCTION

- Emicizumab – a bispecific antibody – binds activated factor IX (FIXa) and FX to restore the hemostatic function of missing FVIIIa in persons with hemophilia A (PwHA).[1]
- HAVEN 3 (NCT02847637), a phase III study in adolescent/adult PwHA without FVIII inhibitors, demonstrated the efficacy and safety of emicizumab prophylaxis once every week (QW) or once every 2 weeks (Q2W).[2]
  - A 68% decrease in bleeds was observed with emicizumab prophylaxis over previous FVIII prophylaxis (1.5 versus 4.8, p<0.0001) in an intra-individual comparison of 48 PwHA who received FVIII prophylaxis in a non-interventional study (NIS) prior to enrollment in HAVEN 3.[2]
- On-demand FVIII was prescribed at the investigator's discretion in the NIS and in HAVEN 3. In HAVEN 3, investigators were advised to treat breakthrough bleeds (BTBs) with the lowest FVIII dose expected to achieve hemostasis.
- *Aim:* to characterize the dose and frequency of replacement FVIII used for the treatment of BTBs in the 48 PwHA previously enrolled in the NIS who were subsequently treated with emicizumab during HAVEN 3.

METHODS

- In HAVEN 3 (**Figure 1**), eligible participants were aged ≥12 years with severe congenital hemophilia A, without current FVIII inhibitors (<0.6 Bethesda units/mL), who were managed with episodic or prophylactic FVIII.[2]

Figure 1. HAVEN 3 study design.[2] These analyses focus on patients from Arm D who received prior FVIII prophylaxis as part of the NIS.



R, randomization.
*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.

- These analyses compare on-demand FVIII treatment for BTBs while receiving prophylactic FVIII during the NIS versus while receiving emicizumab prophylaxis during HAVEN 3 (Arm D; intra-patient comparison).
  - 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 ≤72 hours apart were considered the same bleed. Any injection to treat the bleed, taken >72 hours after the preceding injection, is 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 in these analyses.
- Annualized on-demand FVIII use was calculated by dividing by the total days in the efficacy period and multiplying the resulting daily consumption by 365.25.
- No formal statistical inferences (i.e. calculation of p-values) have been conducted.
- Clinical cut-off date for these analyses: October 4, 2018.

RESULTS

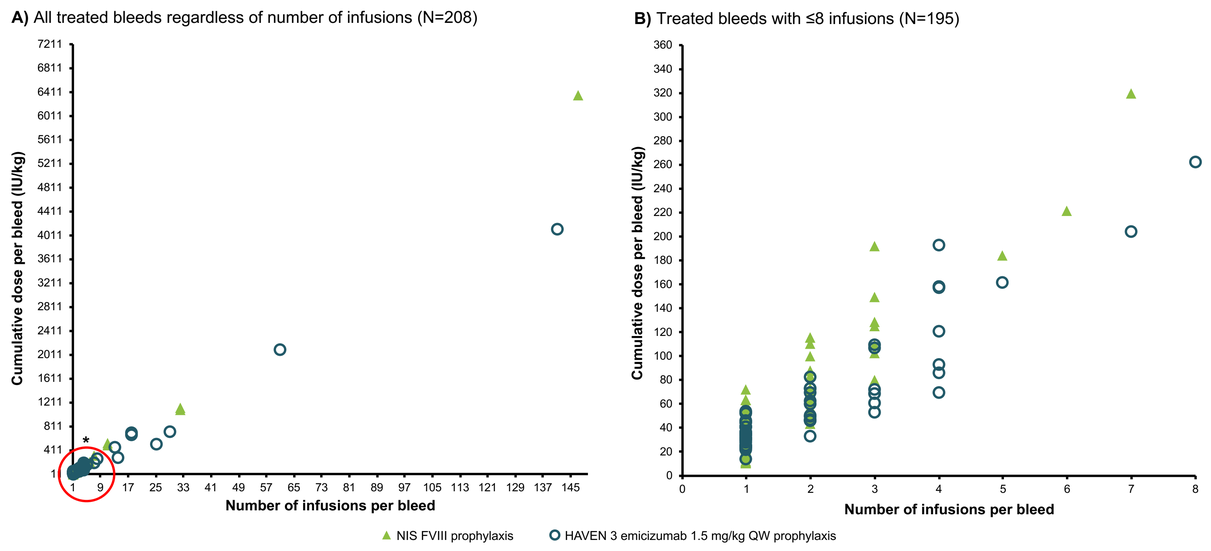
- Of 48 participants receiving FVIII prophylaxis in the NIS, 29 (60.4%) experienced a total of 137 treated bleeds. While receiving emicizumab prophylaxis during HAVEN 3, 27 of the same 48 participants (56.3%) experienced 71 treated bleeds (**Table 1**).
- Both the annualized infusion rate and the cumulative dose of on-demand FVIII per participant were higher while receiving FVIII prophylaxis during the NIS than when receiving emicizumab prophylaxis during HAVEN 3 (**Table 1**).
- At the individual bleed level, 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**).
- Further characterization of the treated bleeds in this intra-patient analysis showed similar rates of joint bleeds and muscle bleeds between the NIS and HAVEN 3 exposure periods (57 versus 61%; and 17 versus 14%, respectively).

Table 1. Analyses of treated bleeds. NIS FVIII prophylaxis versus HAVEN 3 emicizumab prophylaxis (Arm D).

	NIS FVIII prophylaxis N=48	**HAVEN 3 Arm D** 1.5 mg/kg emicizumab QW N=48
Total exposure period of prophylaxis, 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
Annualized number of infusions per participant (AIR) Mean AIR (SD) Median AIR (IQR, Q1, Q3)	 15.3 (43.6) 3.6 (15, 0, 15)	 7.2 (16.8) 0.6 (5, 0, 5)
Annualized cumulative dose, FVIII IU/kg per participant Mean (SD) Median (IQR, Q1, Q3)	 602.4 (1822.3) 75.5 (473, 0, 473)	 209.0 (459.8) 19.1 (139, 0, 139)
Number of infusions per bleed, median (IQR) Treated bleeds Treated joint bleeds	 1.0 (1.0) 1.0 (1.0)	 2.0 (3.0) 2.0 (3.0)
Cumulative dose per bleed, IU of FVIII/kg, median (IQR) Treated bleeds Treated joint bleeds	 43.5 (35.1) 48.2 (31.9)	 50.0 (72.7) 53.5 (84.3)

IQR, interquartile range; IU, international units; Q, quartile; SD, standard deviation.

Figure 2. Number of infusions and cumulative dose (IU/kg) per treated BTB. NIS FVIII prophylaxis versus HAVEN 3 emicizumab prophylaxis (Arm D).



*Data contained within the red circle are expanded and shown in Figure 2B.

CONCLUSIONS

- These analyses revealed a lower annualized infusion rate and a correspondingly lower annualized cumulative dose of on-demand FVIII treatment for BTBs with emicizumab prophylaxis in HAVEN 3 (Arm D) compared with FVIII prophylaxis in the NIS as a result of the overall reduction in bleed frequency.
- The amount of on-demand FVIII used per bleeding episode was comparable between the NIS and HAVEN 3 and similar by location of bleed.
- The treatment of individual bleeds was similar regardless of the type of prophylaxis (emicizumab versus FVIII) administered.

REFERENCES

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2. Mahlangu J, et al. N Eng J Med 2018;379:811–22.

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DISCLOSURES

MC: consultancy (F. Hoffmann-La Roche Ltd/Genentech Inc., Bayer, Shire/Takeda, Bioverativ/Sanofi, Global Blood Therapeutics, Spark Therapeutics, Biomarin, Pfizer, Novo Nordisk, Kedrion, Octapharma, Grifols), equity ownership interests (Alnylam), research funding (F. Hoffmann-La Roche, Pfizer, Takeda), speaker's bureau (F. Hoffmann-La Roche Ltd, Novo Nordisk, Bayer, Shire/Takeda); **TC**, **AP**, **BT**: employment (Genentech Inc.), equity ownership interests (F. Hoffmann-La Roche Ltd/Genentech Inc.); **CD** and **MN**: employment (F. Hoffmann-La Roche Ltd); **RK**, **LL**, **MS**, **UT**: employment (Genentech Inc.); **JM**: consultancy (Baxalta, Catalyst Biosciences, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Spark), research funding (Biomarin, Baxalta, Catalyst Biosciences, CSL Behring, Novartis, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, Spark, Unique), honoraria (Baxalta, Catalyst Biosciences, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Spark), speakers' bureau (Baxalta, Catalyst Biosciences, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Spark).

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