Timing of treated spontaneous bleeding in persons with haemophilia A receiving emicizumab ▼ prophylaxis 6 mg/kg once every 4 weeks

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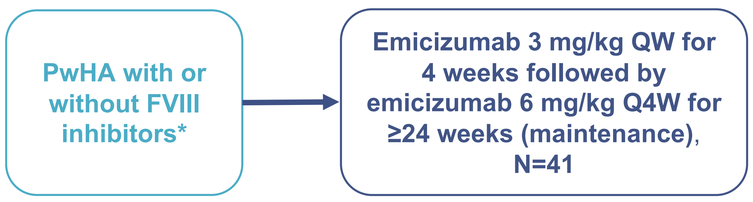
INTRODUCTION

- Emicizumab ▼ is a bispecific humanised monoclonal antibody that binds activated factor IX (FIXa) and FX to restore the function of missing activated FVIII in persons with haemophilia A (PwHA).[1]
- Emicizumab is approved as three maintenance dosing regimens for prophylaxis for PwHA: 1.5 mg/kg once a week (QW), 3 mg/kg once every 2 weeks (Q2W), and 6 mg/kg once every 4 weeks (Q4W); each regimen follows a loading dose of emicizumab 3 mg/kg QW for 4 weeks.[2]
- HAVEN 4 (NCT03020160; **Figure 1**) was a phase III, multicentre, open-label study of the emicizumab Q4W dosing regimen in persons with severe congenital haemophilia A ≥12 years with or without FVIII inhibitors. The objectives were to assess the pharmacokinetics, efficacy and safety of emicizumab prophylaxis administered Q4W.[3]

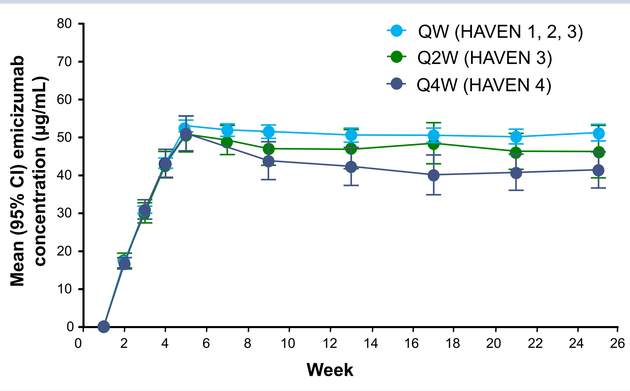
Figure 1. HAVEN 4 study design[3]



PwHA, persons with haemophilia A; Q4W, every 4 weeks; QW, every week; *Only patients in the expansion cohort were considered for inclusion in this analysis.

  - Emicizumab Q4W prophylaxis provided consistent and clinically meaningful bleed control, with an annualised treated bleed rate of 2.4 (95% CI: 1.4–4.3).[3]
  - Emicizumab Q4W prophylaxis also sustained levels of trough plasma concentrations at a level associated with efficacy (approximately 40 µg/mL), which was slightly lower than in those given emicizumab QW or Q2W (**Figure 2**).[3]

Figure 2. PK profiles of the HAVEN 4 expansion cohort and the HAVEN 1–3 study participants[3]



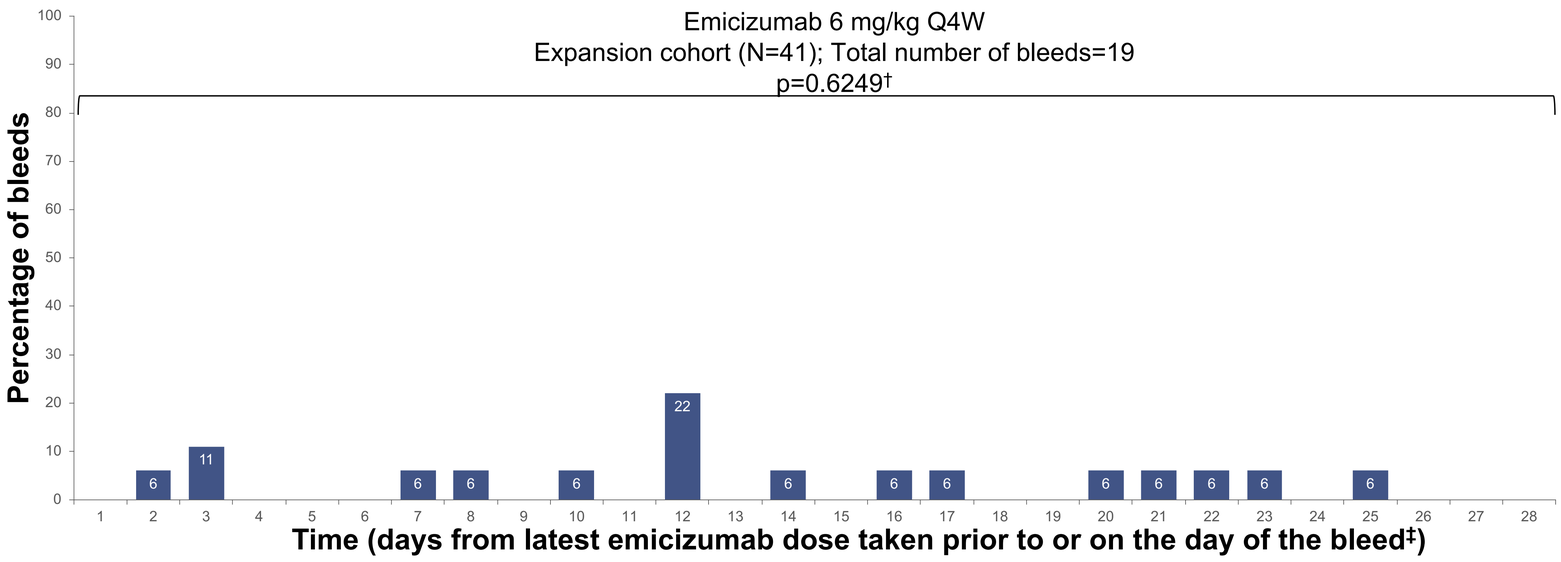
CI, confidence interval; PK, pharmacokinetic; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week.

- Previously, we investigated the timing of spontaneous treated bleeds in relation to emicizumab administration in HAVEN 1 (QW dosing) and in HAVEN 3 (QW and Q2W dosing).[4,5]
- Here, we present the results of a retrospective, post-hoc analysis evaluating the pattern of treated spontaneous bleeds in PwHA receiving the emicizumab 6 mg/kg Q4W maintenance dosing regimen in the expansion cohort of HAVEN 4.

METHODS

- Each treated spontaneous bleed was categorised by when it occurred during the patient's maintenance dose interval (i.e., Day 1—the day of dosing, to Day 28).
  - The percentage of bleeds occurring on each day during emicizumab prophylaxis relative to the total number of bleeds in the dosing interval was then calculated.

Figure 3. Proportion of treated spontaneous bleeds since latest emicizumab Q4W dose*



Q4W, every 4 weeks.
*One bleed occurred during the loading dose phase, which is not included in the analysis. †One bleed occurred 34 days after one patient took their latest emicizumab dose, which is not included in the graph; the p-value for the analysis includes the 19th bleed on Day 34. The graph depicts the approved Q4W dosing interval (28 days). ‡Day 1 is the day the patient injected regardless of whether or not the patient injected as per the schedule.

Methods (continued)

  - The percentage of bleeds on a given day after adjusting for the number of days exposed to emicizumab was calculated for each day of the dosing interval (exposure-adjusted sensitivity analyses).
  - Bleed analyses were performed for the maintenance dosing period only.
- P-values were generated from the statistical test for the fixed effect for time from last emicizumab dose in a repeated-measures generalised linear model with a negative binomial link function and unstructured covariance.
- The data cut-off for this analysis was 11 October 2018.

RESULTS

Characteristics of the HAVEN 4 expansion cohort

- Overall, 41 male PwHA (median age [range]: 39 [14–68] years) received emicizumab Q4W.[2]
  - In the 24 weeks before study entry, the median (range) number of bleeds in the expansion cohort was 5.0 (0– 90).
  - At baseline, 25 PwHA the expansion cohort (61%) had target joints, 5 (12%) had a FVIII inhibitor, and 30 (73%) were taking a previous prophylactic regimen.

Emicizumab exposure

- The median time (IQR) on emicizumab for PwHA in the expansion cohort was 1.31 (1.29–1.33) years.

Table 1. Emicizumab exposure during HAVEN 4 in the expansion cohort, (N=41)

Total exposure years in the whole study period	51.58
Median (IQR) exposure years per patient in whole study period	1.31 (1.29–1.33)
Median (IQR) number of days since last emicizumab injection during maintenance period	28 (28–28)

IQR, interquartile range.

Treated spontaneous bleeds

- A sum of 10 PwHA in the expansion cohort experienced a total of 19 treated spontaneous bleeds during the maintenance dosing period.
- There was no evidence of an uneven distribution of bleeds across different days using the Q4W maintenance dosing regimen (p=0.6249; **Figure 3**).
- Exposure-adjusted sensitivity analyses of the percentage of bleeds on a given day revealed a consistent distribution of bleeds and no statistical trends during the dosing intervals (p=0.6074).

CONCLUSIONS

- In this analysis of HAVEN 4 data, there was no evidence of any association between the occurrence of bleeding and the timing of the last emicizumab Q4W dose; however, the analysis was limited by a low number of treated spontaneous bleeds.
- This finding is consistent with the long half-life of emicizumab and the sustained levels of trough plasma concentrations associated with efficacy previously reported with Q4W maintenance dosing.[1,3]
- This finding is also consistent with similar analyses of bleed distribution that have been conducted on the emicizumab QW and Q2W dosing regimens in the HAVEN 1 and HAVEN 3 studies.[4,5]

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DISCLOSURES

SWP: Consultancy (Apcintex, Bayer, Biomarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd./Genentech, Inc., Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure); **RHK:** Employment (F. Hoffmann-La Roche Ltd./Genentech, Inc.); **TC:** Employment and Shareholder (Genentech, Inc.); **ML:** Employment and Shareholder (F. Hoffmann-La Roche Ltd.); **NSB:** Employment (F. Hoffmann-La Roche Ltd.); **BT:** Employment and Shareholder (Genentech, Inc.); **MM:** Employment and Shareholder (Genentech, Inc.).

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