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Timing of treated spontaneous bleeding in persons with haemophilia A (PwHA) with inhibitors in the HAVEN 1 study

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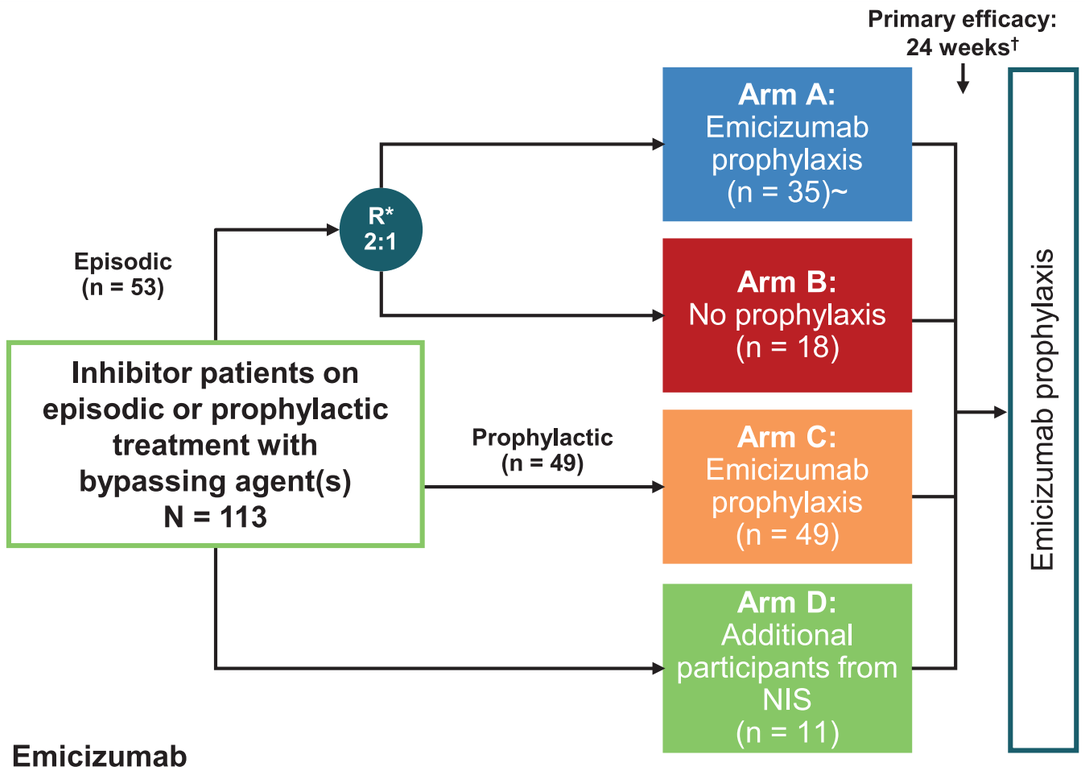
INTRODUCTION

- Emicizumab▼ is a bispecific humanized monoclonal antibody that binds activated factor IX (FIXa) and factor X (FX) to restore the function of missing FVIII in persons with haemophilia A (PwHA).[1]
- HAVEN 1 (NCT02622321) was a phase III study of weekly emicizumab treatment in adolescent or adult PwHA with FVIII inhibitors.[2]
  - Emicizumab prophylaxis resulted in a significant reduction in treated spontaneous bleed rates of 92% (p<0.001) compared with no prophylaxis.[2]
- Here, we present the results of a retrospective, post-hoc analysis evaluating the pattern of treated spontaneous bleeds within the weekly emicizumab dosing interval in HAVEN 1.

METHODS

- In HAVEN 1 (**Figure 1**), eligible patients were ≥12 years of age, had a history of FVIII inhibitor ≥5 Bethesda units/mL and were receiving episodic or prophylactic treatment with bypassing agents.[2]
  - Patients included those who previously participated in a non-interventional study (NIS) of bypassing agent therapy in real-world practice (NCT02476942).[2]

Figure 1. HAVEN 1 study design



Emicizumab

- Loading dose: 3 mg/kg/week for 4 weeks
- Maintenance dose: 1.5 mg/kg/week starting Week 5‡

*Stratified by 24-week bleed rate <9 or ≥9.
†When last patient completed 24 weeks on-study or discontinued study participation, whichever occurred first.
‡Option to increase dose in emicizumab arms if suboptimal response or rollover from control to emicizumab arm.
Episodic bypassing agent(s) could be used in all treatment arms to manage breakthrough bleeds.

- The primary study endpoint was the rate of treated bleeding events over at least 24 weeks and was used to compare between participants in Arms A and B.[2]
- PwHA receiving emicizumab by either treatment assignment or switch to emicizumab following initial assignment of no prophylaxis were included in the current analysis.
- Bleeds were defined per protocol using the 72-hour rule: bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections were ≤72 hours apart, were considered the same bleed.
- 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.
- Each treated spontaneous bleed was categorised by the day of the patient's dosing interval on which it occurred (e.g. 1, 2, 3, etc.).
  - The incidence of bleeding was compared across the days.
- An updated database cut-off (8 September 2017) was used for this analysis to capture additional bleeds and longer follow-up than the published primary data (25 October 2016 cut-off).

RESULTS

- In total, 113 patients were enrolled to receive emicizumab treatment, with a total of 129.6 emicizumab patient exposure-years (median duration [range]: 1.16 [0.0–1.8] years) (**Table 1**).
- Of the 113 patients analyzed, 181 spontaneous (both treated and untreated) bleeds occurred.
  - Of the 181 spontaneous bleeds, 116 bleeds in 37 patients were treated (**Table 2**).
  - The majority of these bleeds occurred in the joints (**Table 2**).

Table 1. Emicizumab exposure (ITT population)

	Emicizumab exposure (years)
Overall, n = 113 Mean (SE) Median (range)	 1.15 (0.04) 1.16 (0.00–1.81)
Arm A, n = 35 Mean (SE) Median (range)	 1.25 (0.08) 1.43 (0.00–1.81)
Arm B, n = 18 Mean (SE) Median (range)	 0.88 (0.07) 1.00 (0.09–1.19)
Arm C, n = 49 Mean (SE) Median (range)	 1.25 (0.04) 1.19 (0.46–1.74)
Arm D, n = 11 Mean (SE) Median (range)	 0.78 (0.09) 0.95 (0.46–1.16)

SE, standard error.
Emicizumab treatment period: Patients with emicizumab during standard treatment and up-titration periods.

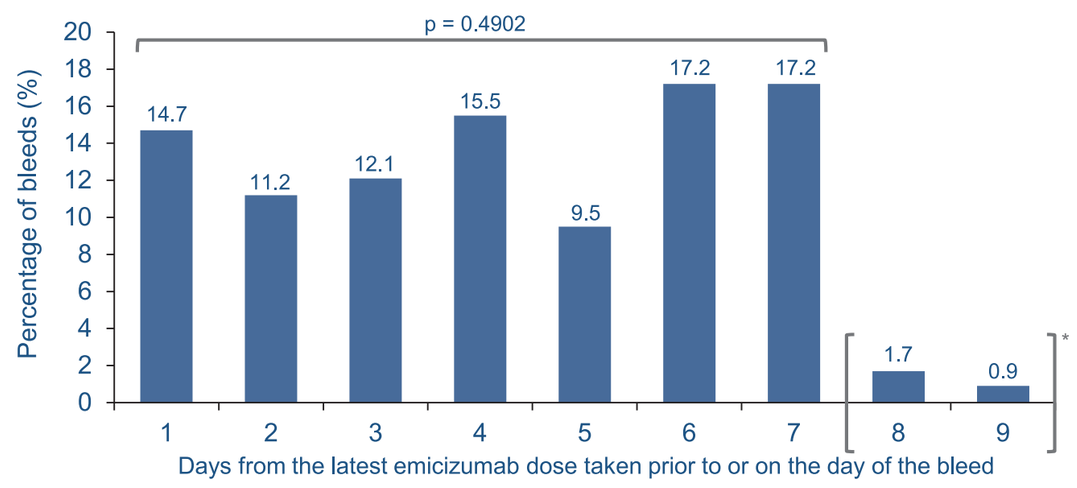
Table 2. Spontaneous treated bleeds and locations

Type of bleed	Number of bleeds (%)
Total	116 (100)
Joint	91 (78.4)
Muscle	13 (11.2)
Other	12 (10.3)

N = 113; total exposure-years = 129.60. Patients with emicizumab during standard treatment and up-titration periods.

- The incidence of treated spontaneous bleeding events within the emicizumab dosing interval appeared to be relatively similar amongst the days from the last dose of emicizumab (**Figure 2**).
- 91.1% of doses were administered within the weekly dosing schedule. Few bleeds occurred 8 or 9 days from the prior emicizumab dose (2 and 1, respectively) in the few patients receiving emicizumab on those days.
- Statistical tests indicated no evidence for a specific pattern of treated spontaneous bleeds across the emicizumab dosing schedule (p=0.4902; **Figure 2**).
- Additional sensitivity analyses were conducted to adjust for the exposure time to emicizumab at each day in Figure 2 and confirmed the unadjusted analysis of no evidence of a trend (p=0.2337).

Figure 2. Proportion of bleeds by days since latest emicizumab dose



*A handful of patients were treated outside of the weekly dosing schedule and due to small sample sizes no inference should be drawn beyond day 7 with respect to bleeds.
N = 113; total number of bleeds = 116. Patients with emicizumab during standard treatment and up-titration periods.

CONCLUSIONS

- **No relationship was detected between the timing of treated spontaneous bleeds and the number of days from the last dose of emicizumab.**
- **These findings are consistent with the long half-life of emicizumab and the sustained stable trough plasma concentrations previously reported with once-weekly maintenance dosing.[1–5]**

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DISCLOSURES

RK-J: grant/research support (CSL Behring, Pfizer, and Genentech), consultancy (CSL Behring, Grifols, Genentech, NovoNordisk, and Shire); **BT** and **KR**: employee and shareholder (Genentech); **ET**: employee (Genentech); **BPS**: employee (Genentech), shareholder (Roche); **RHK**: employee (Genentech).

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.