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Pharmacokinetics and biomarkers in persons with haemophilia A (PwHA) receiving emicizumab every 2 or 4 weeks

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INTRODUCTION

- Haemophilia A is a genetic disorder resulting from the absence or dysfunction of coagulation factor VIII (FVIII).[1]
- Emicizumab▼, a recombinant, humanized, bispecific monoclonal antibody, bridges activated factor IX and factor X, restoring the function of missing activated FVIII, and thereby haemostasis, in people with haemophilia A (PwHA).[2,3]
- In three phase 3 studies: HAVEN 2 (NCT02795767),[4] HAVEN 3 (NCT02847637),[5] and HAVEN 4 (NCT03020160),[6] emicizumab given every 2 (Q2W) or 4 weeks (Q4W) demonstrated clinically meaningful bleed reduction and a favourable safety profile in PwHA with or without FVIII inhibitors.
- Here, we report pharmacokinetic (PK) and pharmacodynamic (PD) biomarker data for these dosing regimens.

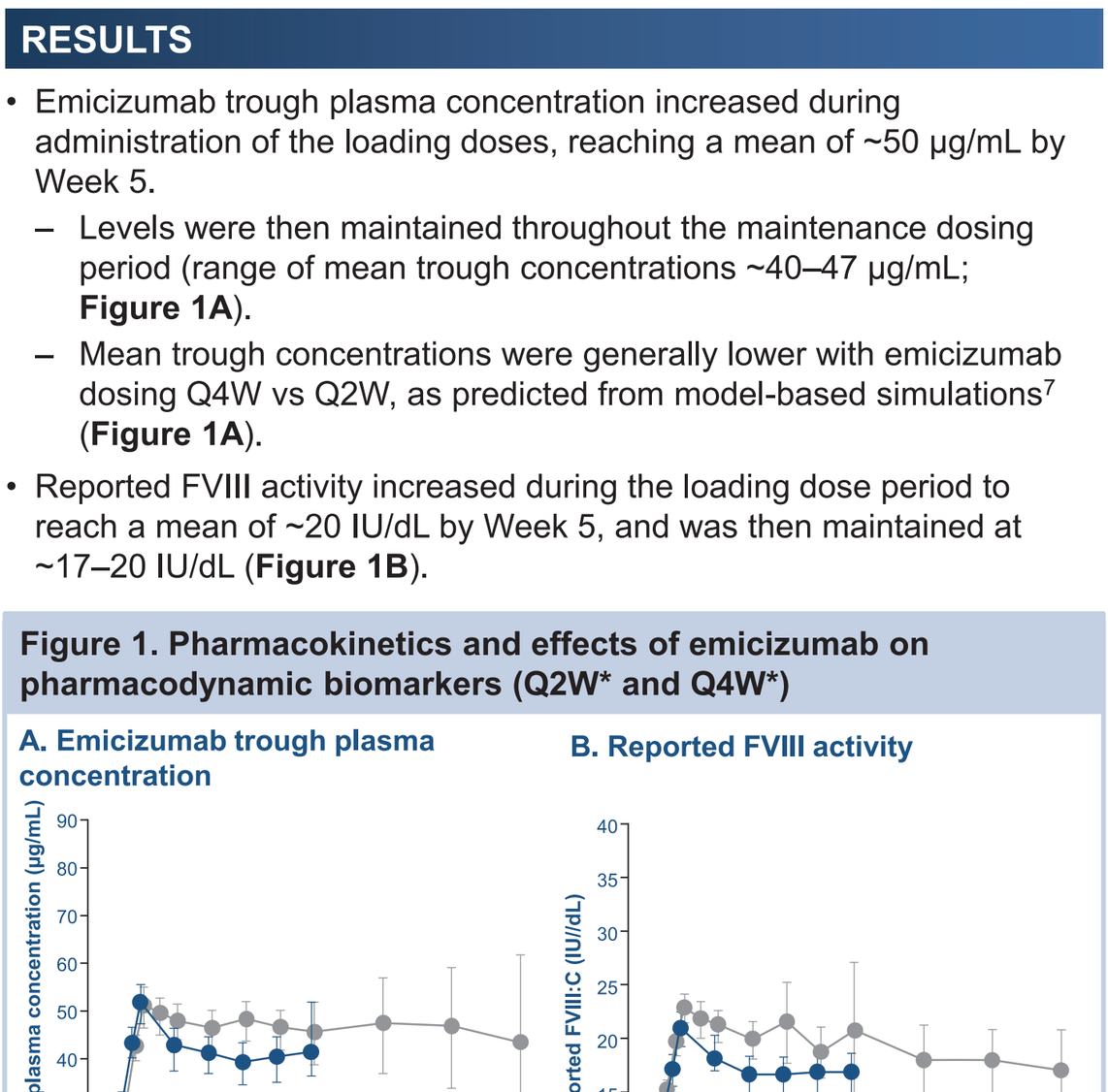
METHODS

- Eligible participants of all ages with or without FVIII inhibitors received emicizumab prophylaxis: four weekly loading doses of 3 mg/kg, followed by 3 mg/kg Q2W (n=10 HAVEN 2; n=48 HAVEN 3) or 6 mg/kg Q4W (n=10 HAVEN 2; n=8 HAVEN 4) maintenance dosing.[4–6]
- Emicizumab concentration was measured via a validated ELISA assay.
- PD biomarkers were assessed via a FVIII chromogenic activity assay with human FIXa and FX (emicizumab and FVIIIa co-factor properties are not identical, so this assay provides an approximation of emicizumab haemostatic activity) and FXIa-triggered thrombin generation (TG).
- Activated partial thromboplastin time (aPTT), prothrombin time (PT), antigen levels of FIX and FX, D-dimer and prothrombin fragment 1 and 2 (F1+2) were determined at multiple visits over time.
- FVIII inhibitor titres were measured via a Chromogenic Bethesda Assay with bovine FIXa and FX, which are insensitive to emicizumab.

RESULTS

- Emicizumab trough plasma concentration increased during administration of the loading doses, reaching a mean of ~50 µg/mL by Week 5.
  - Levels were then maintained throughout the maintenance dosing period (range of mean trough concentrations ~40–47 µg/mL; **Figure 1A**).
  - Mean trough concentrations were generally lower with emicizumab dosing Q4W vs Q2W, as predicted from model-based simulations[7] (**Figure 1A**).
- Reported FVIII activity increased during the loading dose period to reach a mean of ~20 IU/dL by Week 5, and was then maintained at ~17–20 IU/dL (**Figure 1B**).

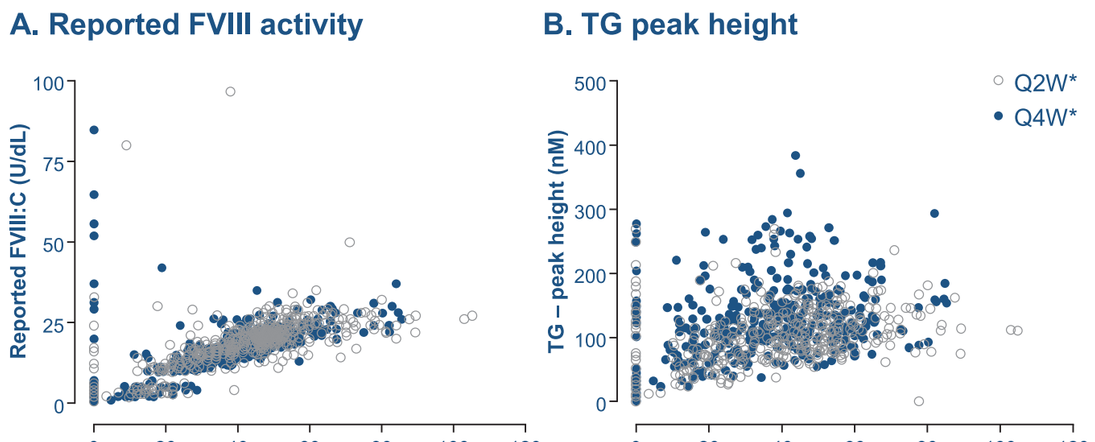
Figure 1. Pharmacokinetics and effects of emicizumab on pharmacodynamic biomarkers (Q2W* and Q4W*)



*Four weekly loading doses of 3 mg/kg, followed by 3 mg/kg Q2W (n=10 HAVEN 2; n=48 HAVEN 3) or 6 mg/kg Q4W (n=10 HAVEN 2; n=41 HAVEN 4). Data are presented as mean (95% CI). aPTT, activated partial thromboplastin time; Q2W, every 2 weeks; Q4W, every 4 weeks; TG, thrombin generation.

- Mean TG peak height (HAVEN 3 and HAVEN 4; HAVEN 2 not included due to limitations in paediatric blood volume sampling) also increased until Week 5, with levels sustained >100 nM thereafter during the maintenance dosing phase (**Figure 1C**).
  - There was larger variability in TG peak height in the Q4W group, and some overlap between values across both maintenance dosing regimens.
  - TG peak height for Q4W dosing was already slightly higher than for Q2W dosing at the end of the loading period, despite the same loading dose being administered across regimens. The higher mean TG peak height with Q4W dosing was not expected based on emicizumab PK.
- aPTT was normalized after the first emicizumab dose, and remained so throughout the dosing period (**Figure 1D**).
- PK/PD relationships were similar regardless of dosing regimen.
  - Reported FVIII activity and TG peak height generally increased with increasing emicizumab concentration (**Figure 2**).

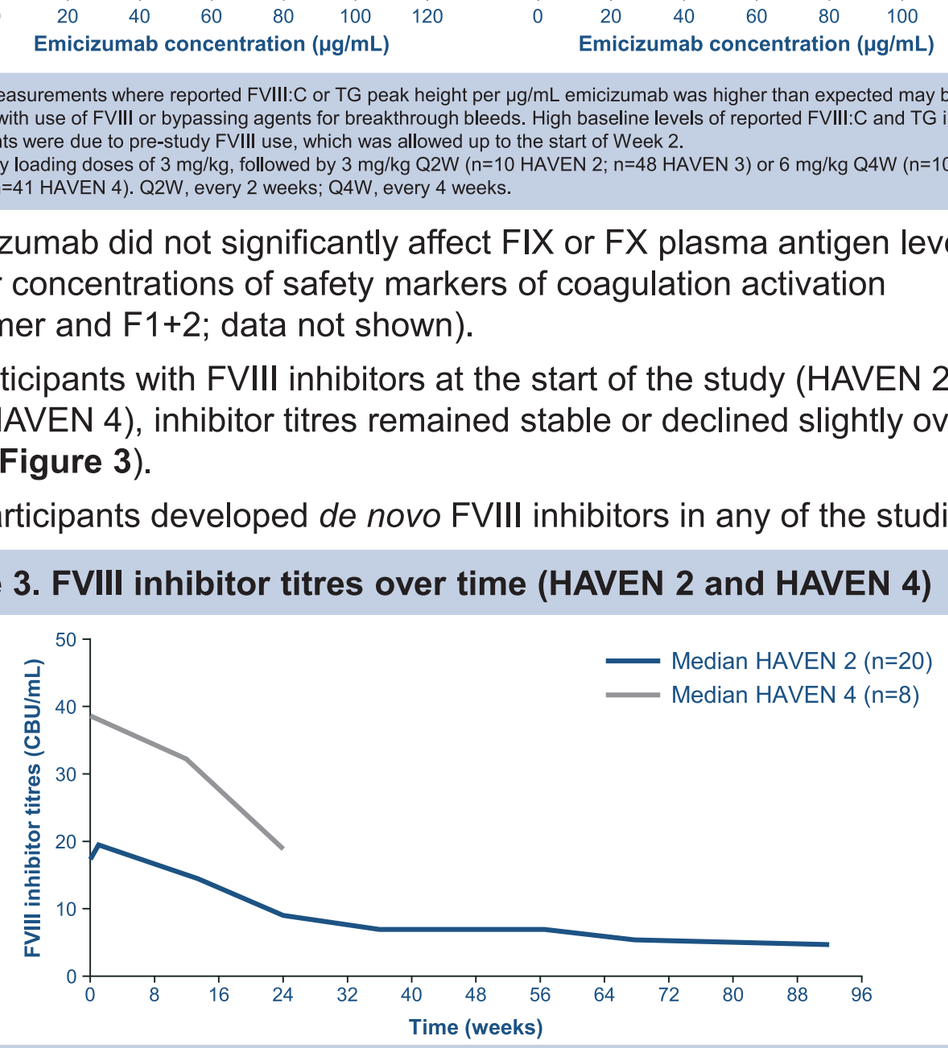
Figure 2. PK/PD relationships



Sporadic measurements where reported FVIII:C or TG peak height per µg/mL emicizumab was higher than expected may be associated with use of FVIII or bypassing agents for breakthrough bleeds. High baseline levels of reported FVIII:C and TG in some patients were due to pre-study FVIII use, which was allowed up to the start of Week 2.
*Four weekly loading doses of 3 mg/kg, followed by 3 mg/kg Q2W (n=10 HAVEN 2; n=48 HAVEN 3) or 6 mg/kg Q4W (n=10 HAVEN 2; n=41 HAVEN 4). Q2W, every 2 weeks; Q4W, every 4 weeks.

- Emicizumab did not significantly affect FIX or FX plasma antigen levels, PT, or concentrations of safety markers of coagulation activation (D-dimer and F1+2; data not shown).
- In participants with FVIII inhibitors at the start of the study (HAVEN 2 and HAVEN 4), inhibitor titres remained stable or declined slightly over time (**Figure 3**).
- No participants developed *de novo* FVIII inhibitors in any of the studies.

Figure 3. FVIII inhibitor titres over time (HAVEN 2 and HAVEN 4)



CONCLUSIONS

- **PD biomarkers demonstrated on-target activity of emicizumab irrespective of FVIII inhibitor status or dosing regimen.**
- **Emicizumab dosing Q2W or Q4W demonstrated sustained PK and PD, and comparable PK/PD characteristics as observed in PwHA with or without FVIII inhibitors who received the once-weekly dosing regimen.[8,9]**

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▼ 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.