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

INTRODUCTION

• Haemophilia A is a genetic disorder resulting from the absence or dysfunction of coagulation factor VIII (FVIII).

• 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).1,2,5

• In three phase 3 studies: HAVEN 2 (NCT02795677),1 HAVEN 3 (NCT02847673),1 and HAVEN 4 (NCT03029154),2,6 emicizumab given every 2 weeks (2QW) or 4 weeks (4QW) demonstrated clinically meaningful bleed reduction and a favourable safety profile in PwHA with or without FVIII.

• 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.5

• Emicizumab concentration was measured via a validated ELISA assay. PD biomarkers were assessed via a FVIII chromogenic 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 FVIIIa-agonized 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 dosing regimens, 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 simulations2 (Figure 1A).

• Reported FVIII activity increased during the dosing period to reach a mean of ~20% ILT, by Week 5, and was then maintained at ~17–20% ILT (Figure 1B).

• Mean TG peak height (HAVEN 3 and HAVEN 4) was ~140 cm 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 dosing period, despite the same dosage being administered across regimens. The higher mean TG peak height with Q4W dosing was not expected based on emicizumab PK.

• aPTT decreased 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).

• 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 newly FVIII inhibitors in any of the studies.

CONCLUSIONS

• PD biomarkers demonstrated on-target activity of FVIII 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.2,5

REFERENCES


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f This material is submitted to a scientific journal. This will allow public dissemination of new public data, ensure transparency to permit any subsequent analyses, and thus be shared in the way that is beneficial to the public at large and accessible by any interested parties.