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Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study.

Pipe SW[1], Shima M[2], Lehle M[3], Shapiro A[4], Chebon S[3], Fukutake K[5], Key NS[6], Portron A[3], Schmitt C[3], Podolak-Dawidziak M[7], Selak Bienz N[3], Hermans C[8], Campinha-Bacote A[9], Kiialainen A[3], Peerlinck K[10], Levy GG[9], Jiménez-Yuste V[11].

Author information

Abstract

BACKGROUND: Emicizumab, a subcutaneously administered, humanised, bispecific, monoclonal antibody, is approved to treat people with haemophilia A of all ages with and without coagulation factor VIII (FVIII) inhibitors. HAVEN 4 assessed emicizumab prophylaxis administered as one dose every 4 weeks in adults and adolescents with haemophilia A, regardless of FVIII inhibitor status.

METHODS: In this phase 3, multicentre, open-label, two-stage study, patients aged 12 years and older with severe congenital haemophilia A (<1% of normal FVIII activity in blood) or haemophilia A with FVIII inhibitors, undergoing treatment with either FVIII concentrates or bypassing agents were recruited from three sites in Japan and Spain for a run-in cohort, and from 17 sites in Australia, Belgium, Japan, Poland, Spain, and the USA for a subsequent expansion cohort. Participants in the run-in and expansion cohorts were given emicizumab subcutaneously 6 mg/kg every 4 weeks for 24 weeks or more; for patients in the expansion cohort this regimen was preceded by four loading doses of 3 mg/kg once weekly. In the run-in cohort, we assessed pharmacokinetics after single and multiple (every 4 weeks) subcutaneous administration of 6 mg/kg emicizumab and safety. In the expansion cohort, the efficacy endpoint was efficacy of prophylactic emicizumab in maintaining adequate bleed prevention, assessed in all patients who received at least one dose of emicizumab and reported as annualised bleed rates for treated bleeds, all bleeds (treated and untreated), treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds. Safety was assessed in all participants given emicizumab. This study is registered with ClinicalTrials.gov, number NCT03020160, and is ongoing.

FINDINGS: Between Jan 30, 2017, and Feb 27, 2017, seven patients were enrolled into the initial run-in cohort, which confirmed the expected pharmacokinetic profile and safety of the regimen based on model-based simulations, providing sufficient evidence for opening of the expansion cohort (n=41), which was recruited and enrolled between May 24, 2017, and June 30, 2017. The annualised rate of treated bleeds was 2·4 (95% CI 1·4-4·3). 23 (56·1%; 95% CI 39·7-71·5) of 41 reported no treated bleeds and 37 (90%; 76·9-97·3) reported zero to three treated bleeds. The annualised bleed rate was 4·5 (95% CI 3·1-6·6) for all bleeds, 0·6 (0·3-1·5), for treated spontaneous bleeds, 1·7 (0·8-3·7) for treated joint bleeds, and 1·0 (0·3-3·3) for treated target joint bleeds. The most frequent treatment-related adverse event was injection-site reaction (nine [22%] of 41 patients). We observed no thrombotic events or development of de-novo antidrug antibodies with neutralising potential or FVIII inhibitors.

INTERPRETATION: Emicizumab given once every 4 weeks showed clinically meaningful bleed control while being well tolerated. This regimen could improve patient care by decreasing treatment burden and increasing adherence to effective prophylaxis, potentially decreasing the development of secondary complications for people with haemophilia A.

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