Efficacy of emicizumab prophylaxis versus factor VIII prophylaxis for treatment of hemophilia A without inhibitors: network meta-analysis and sub-group analyses of the intra-patient comparison of the HAVEN 3 trial

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Dear Editor,

We have read with interest the article by Reyes et al [1]. The article describes a network meta-analysis (NMA) of trials including patients with hemophilia A without inhibitors, assessing the relative efficacy of emicizumab versus factor VIII (FVIII) prophylaxis.

While the authors accurately state that several assumptions and limitations apply to their study, we highlight below additional weaknesses that likely skewed their overall findings:

1. Despite the authors discovering a high degree of heterogeneity among the recombinant FVIII (rFVIII) prophylaxis trials, they pooled the annualized bleed rates (ABR) of the extended half-life (EHL) factor recombinant FVIII FC fusion protein (rFVIIIFc) with three standard half-life (SHL) factors, based on the assumption that the only advantage of an EHL rFVIII is reduction of treatment burden. This is not a correct assumption, as rFVIIIFc improves joint health, bleed rates, dosing frequency, and consumption as compared with SHL FVIII [2–4]. In the A-LONG study of rFVIIIFc, participants who received pre-study SHL factor prophylaxis achieved reduced ABRs on rFVIIIFc, which were further reduced in the A-LONG extension study, ASPIRE Table 1 [4]. In a longitudinal analysis of A-LONG and ASPIRE, there was a median spontaneous ABR of 0.0 in those receiving individualized prophylaxis (IP) for up to 5 years [6]. Furthermore, in a direct comparison of pre-study and on-study prophylaxis in A-LONG, median ABR was lower on-study than the 12-month pre-study median ABR [7]. Improved outcomes with rFVIIIFc have been supported by several real-world studies [8–10].

2. In the methods for the base-case analysis, the authors state, “When different doses or treatment regimens were published in the same trial, the licensed one was used in the model, i.e. the dose that was recommended in the label.” The label for rFVIIIIFc in Europe recommends 50 IU/kg every 3–5 days [11] and in the United States, 50 IU/kg every 4 days [12] with adjustments from 25–65 IU/kg in 3–5-day intervals for routine prophylaxis in both cases [11, 12], which is in line with the rFVIIIIFc IP arm in the A-LONG study [4]. However, only the weekly prophylaxis (WP) group was used in the NMA. The WP group (n=23) was an exploratory arm composed of subjects with high pre-study ABR who received pre-study on-demand rFVIII treatment and represents a smaller sample size compared with the IP group (n=117) Table 1 [4]. The inclusion of the much smaller arm with a higher ABR in subjects who did not receive the licensed recommended dosing regimen of rFVIIIIFc presents an obvious bias and deviation from defined methodology. Furthermore, the NMA excluded “individualized prophylaxis treatment arms” without providing scientific rationale for this exclusion. It would appear that had the IP arm been included in this analysis, the reported significant statistical difference between emicizumab and rFVIIIIFc prophylaxis would be lost.

3. The trials included in this analysis [4, 13–16] each had varying degrees of randomization. The A-LONG study did not meet the inclusion criteria provided for the base case. The randomized part of the study only included on-demand and WP, which is not the recommended dose in the EU and US labels, and thus should have been excluded. It is unclear what the rationale was for omitting other relevant studies,
as the included trials were not all similarly randomized.

4. In a publicly available report from an independent evaluation of information provided by Roche by a health technology assessment (HTA) body in Europe, indirect comparison of emicizumab with routine rFVIII prophylaxis showed there is no statistically significant difference in ABRs (for treated bleeds and joint bleeds) between the use of rFVIII prophylaxis and emicizumab [17]. Although assessed by different methodologies than that presented in the NMA, to date there is no HTA that has recognized superiority of emicizumab over FVIII prophylaxis in the non-inhibitor population.

In summary, prophylactic factor replacement that can be individualized to patient needs remains the cornerstone of hemophilia treatment, and factor replacement with rFVIIIFc is a single-agent therapy with a proven long-term record of efficacy for prevention of bleeds, management of acute bleeds, and perioperative hemostasis among patients of all ages. The safety and efficacy profile of rFVIIIFc is based on up to 5 years of study data and more than 5 years of real-world experience, including substantial experience in pediatric and physically active patients [4, 5, 7, 18, 19].

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