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LETTER TO THE EDITOR

Patient preference for emicizumab versus prior factor therapy in people with haemophilia A: Results from the HAVEN 3 and HAVEN 4 studies

To the Editor

The treatment burden for people with haemophilia A (PwHA) can be significant. Optimal therapy has been to prevent bleeds with prophylactic intravenous factor (F)VIII infusions multiple times per week. However, this burdensome approach has contributed to many PwHA choosing to administer FVIII on demand to treat bleeding events, which can lead to progressive haemophilic arthropathy. Emicizumab, a recombinant bispecific monoclonal antibody that bridges activated FIX and FX, mimicking the function of activated FVIII and restoring thrombin generation and haemostasis, provides a novel treatment option. Multiple clinical trials and real-world data have shown emicizumab to be effective for bleed prevention, with an acceptable safety profile, in PwHA with or without FVIII inhibitors.[1–4] Emicizumab is self-administered subcutaneously, with its half-life of approximately 30 days allowing for versatile maintenance dosing once weekly (QW), every 2 weeks (Q2W), or every 4 weeks (Q4W).

In the practice of evidence-based medicine, the importance of involving PwHA in decision making with regard to treatment choice is increasingly being recognized.[5] It has been demonstrated that efficacy and other clinical endpoints are not necessarily the main driving force behind treatment preference.[6] Many psychological, physical, and social factors contribute to treatment satisfaction and quality of life.[7] As the development of new therapies for PwHA takes us closer to the WFH guidelines' goal of achieving zero bleeds for all PwHA, patient-reported outcomes will be essential for evaluating how new treatments compare with those already available.

HAVEN 3 (NCT02847637) and HAVEN 4 (NCT03020160) were phase III clinical trials evaluating the efficacy and safety of emicizumab prophylaxis in adult/adolescent PwHA (Figure S1).[3,4] In HAVEN 3, PwHA aged ≥12 years without FVIII inhibitors who had received prior episodic (on-demand) FVIII ($n = 89$) were randomized 2:2:1 to receive emicizumab prophylaxis QW (Arm A), Q2W (Arm B), or no prophylaxis (Arm C). Patients on prior prophylactic FVIII ($n = 63$) received emicizumab prophylaxis QW (Arm D).[3] In HAVEN 4, PwHA aged ≥12 years with/without FVIII inhibitors who had been treated with prior episodic or prophylactic bypassing agents (BPAs; $n = 5$) or FVIII ($n = 36$), respectively, received emicizumab prophylaxis Q4W.[4]

Both studies included questionnaires developed to evaluate the preference of PwHA for emicizumab compared with their pre-study treatment. The Emicizumab Preference (EmiPref) survey was developed following a review of preference measures in the literature. As there were no existing measures in haemophilia designed to compare novel therapies, patient preference questionnaires employed in oncology trials were used as the basis for development (Figure 1).[8,9] The EmiPref survey underwent content validation by RTI Health Solutions (Research Triangle Park, NC, USA) as part of a study including six participants. Cognitive interviews with these participants led to minor modifications in the wording of the instructions, resulting in simplification and clarification. With these modifications, the EmiPref was deemed easy to understand and complete. The survey underwent linguistic validation as part of the pre-study process to translate it into the different languages of the participants in the HAVEN 3 and 4 studies.

The EmiPref survey consisted of three questions to make its interpretation clear and intuitive. Participants were initially asked which treatment they preferred: their previous haemophilia treatment, the new study treatment, or no preference. Those who expressed a preference were then asked to rank the top three factors that influenced their choice. Importantly, by design, participants chose the reasons for their preference choice from a pre-defined list of 14 options. No items related to efficacy (e.g., bleeding rate) were included on this list, as efficacy was captured by the primary and secondary endpoints of the HAVEN 3 and 4 studies. Finally, participants had an option to provide additional free text responses about their experience with emicizumab. The EmiPref survey was administered at Week 17 in both HAVEN 3 and 4. Week 17 was chosen so that participants had gained sufficient experience with emicizumab, while still being able to reliably recall their experience with prior therapy. The questionnaire was self-administered by participants on an electronic tablet, without involvement of a staff member, and site personnel could not view the entries. This allowed participants to complete the EmiPref privately, without concern about meeting their providers' expectations.

A total of 95/134 (71%) PwHA from Arms A, B, or D receiving emicizumab prophylaxis in HAVEN 3 completed the EmiPref survey. Eighty-nine participants (94% of respondents) reported preferring

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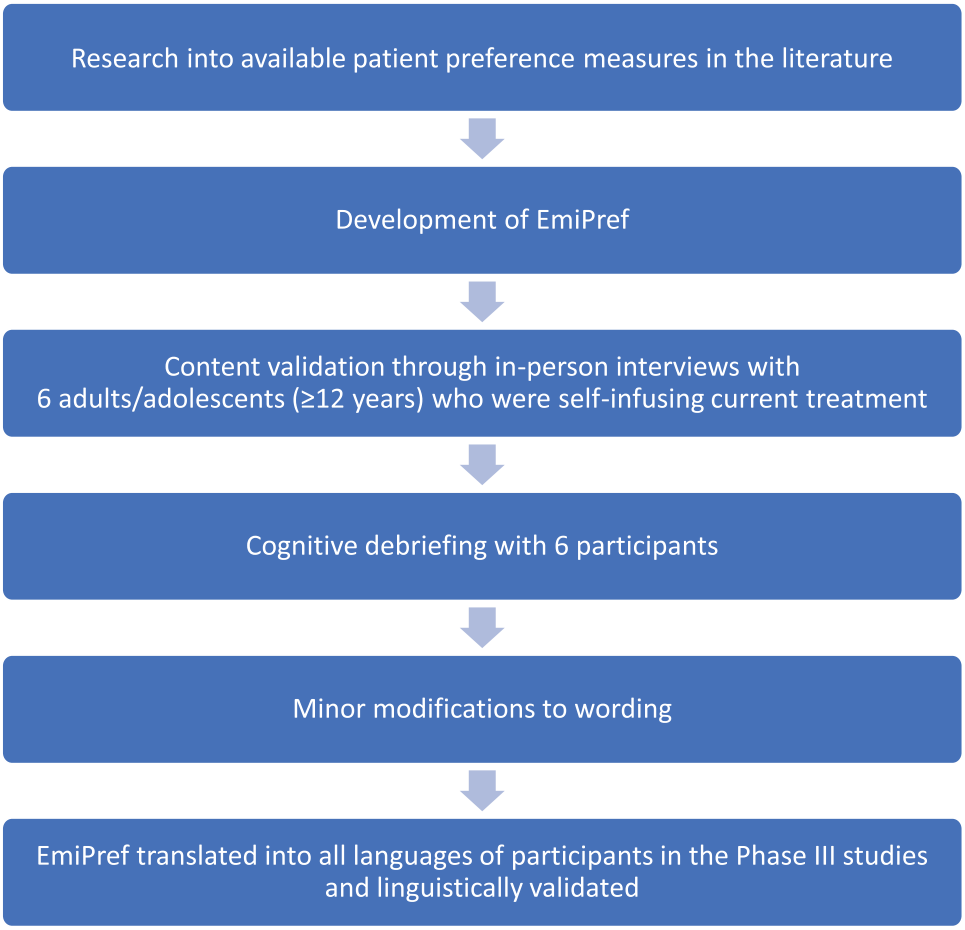

FIGURE 1 Steps in the development of the EmiPref questionnaire

emicizumab to their previous treatment and only two participants (2%), both from Arm B (Q2W dosing), favoured their previous episodic FVIII treatment. Four participants (4%) indicated no preference. In HAVEN 4, all 41 (100%) participants completed the EmiPref survey, with all (100%) reporting a preference for emicizumab over their prior treatment. For those whose prior treatment was prophylaxis, whether with FVIII or BPA, 75/76 (99%) favoured emicizumab, while among those who had previously been receiving episodic treatment, 55/60 (92%) preferred emicizumab. Notably, all participants in HAVEN 3 and 4, including those who did not indicate a preference for emicizumab, continued to receive emicizumab beyond the primary analysis, thereby corroborating the consistent preference for emicizumab.

The factors that many participants in both HAVEN 3 and HAVEN 4 considered as the most important for influencing their preference for emicizumab were related to the convenience of treatment administration. The item 'frequency of treatments was lower' was selected as the most important reason by 22% of respondents in HAVEN 3 and 22% of respondents in HAVEN 4, while 'route of administration was easier' was selected by 24% in HAVEN 3 and 20% in HAVEN 4 (Figure 2). In HAVEN 3, 'worries about having bleeds were less' was the next most frequently selected reason for preferring emicizumab (18%). In HAVEN 4, 'quality of life in general was better' (15%) and 'effect on other activities was less' (12%) were the next most frequently selected reasons for emicizumab preference (Figure 2). One of the two participants who reported a preference for their prior episodic FVIII therapy stated that the most important reason for their response was 'effect on other activities was less', while the other gave 'frequency of treatments was lower' as the most important reason.

The development of emicizumab has provided PwHA with a subcutaneously administered treatment option with a lower frequency of administration compared with FVIII prophylaxis. These factors were demonstrated to be major driving forces for participants stating a preference for emicizumab in the EmiPref. However, a variety of other reasons were given as being most important for respondents' preference, demonstrating the complexity and interpatient variability associated with treatment choice in haemophilia A.

Satisfaction with emicizumab treatment has also been reported for Arm D of the HAVEN 3 study using the Satisfaction Questionnaire–Intravenous Subcutaneous Haemophilia Injection (SQ-ISHI), and this corroborated the findings of the EmiPref.[10] Overall, 92% of respondents indicated that they were 'much more' or 'a lot more' satisfied with their current emicizumab prophylaxis compared with their prior FVIII prophylaxis, while none indicated that they were less satisfied.[10]

Together, these findings further highlight the importance of involving PwHA when making decisions about their treatment. Obtaining high-quality patient-reported outcome data that reflect how

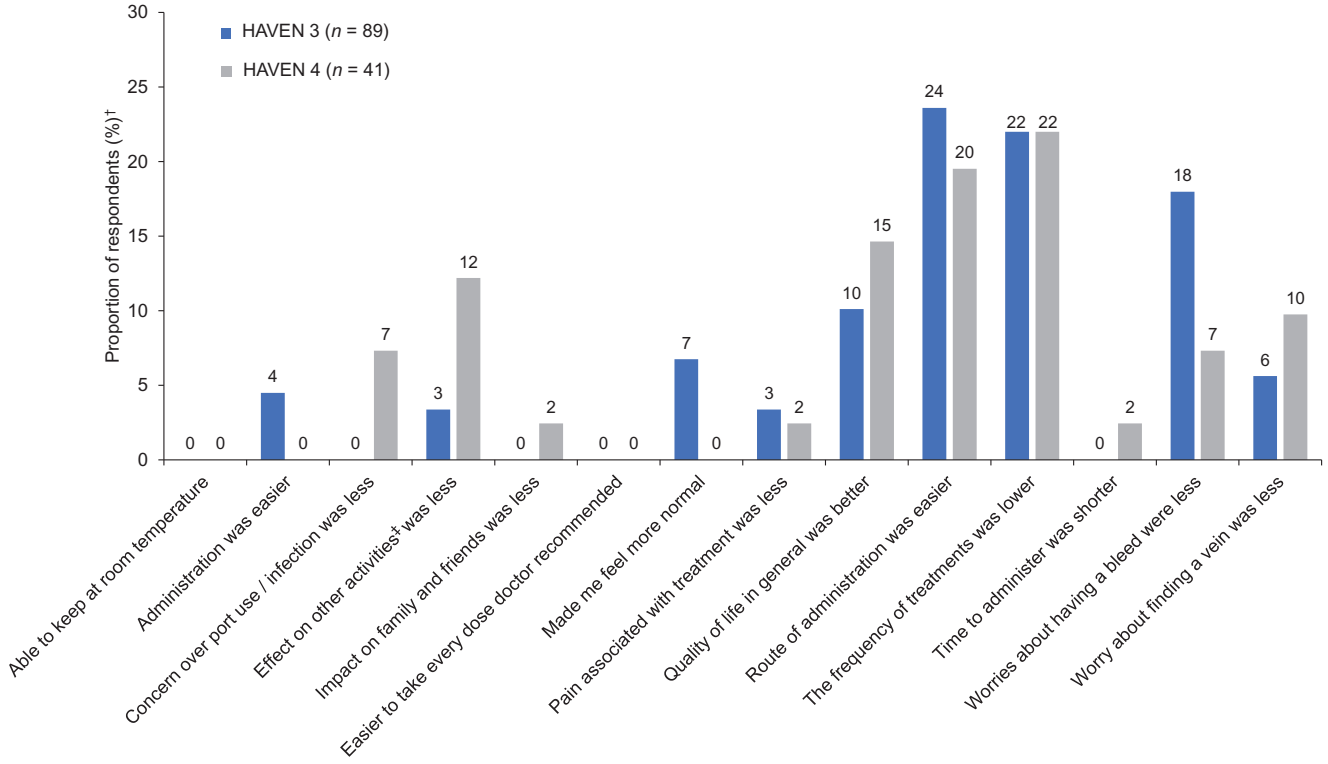

FIGURE 2 Factors selected by respondents as most important for influencing preference of emicizumab over prior therapy. †Includes only participants who stated a preference for emicizumab. ‡Other activities include work, school, sports, and social interactions

different treatments are perceived by PwHA often involves administration of multifaceted questionnaires. The EmiPref survey was designed to be a simple and intuitive means by which to capture a patient's treatment preference and the reasons behind their decision, with interpretation of the responses not requiring sophisticated statistical analyses.

One potential limitation of this study is that the EmiPref survey relies on the patient's memory of their previous treatment. For this reason, intermediate timing was selected so that participants could recall details of their previous treatment, but had also gained adequate experience with emicizumab to be able to assess its impact on their quality of life. Since all participants had undergone many years of factor treatment, they would be unlikely to forget this experience in a few months. In addition, while the list of pre-provided reasons for treatment preference was wide-ranging, there may have been other factors that affected respondents' choices. In HAVEN 3, 39 (29%) of the 134 participants did not complete the EmiPref. This could be attributed to the EmiPref being the only questionnaire scheduled for the Week 17 visit, which may have led to sites forgetting to administer it or not scheduling an office visit at that time. Indeed, in 16 of the 39 cases, sites specifically reported that the questionnaire was not administered. As this was identified as an operational issue and not patient-related, occurring completely at random, it is unlikely to have introduced a selection bias. Furthermore, due to additional briefing of the HAVEN 4 sites, all participants completed the EmiPref in this latter study. Bias due to the clinical trial setting should also be considered as a potential limitation. However, the magnitude of the preference was high, with 96% of 136 respondents favouring emicizumab, and all participants elected to remain on emicizumab following the HAVEN 3 and 4 studies, rather than resuming their pre-study therapy, thereby demonstrating consistency between stated and revealed preference.

In conclusion, focused surveys like EmiPref can capture the patient's voice in a simple and intuitive way, with the responses providing information that is complementary to the bleed-related clinical outcome data for informing patients' and physicians' treatment decisions.

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AUTHOR CONTRIBUTIONS

Aric Parnes contributed to acquisition, analysis and interpretation of data, writing of first draft, and review and revision of drafts. Johnny N. Mahlangu contributed to acquisition, analysis and interpretation of data, and review and revision of drafts. Steven W. Pipe contributed to acquisition, analysis and interpretation of data, and review and revision of drafts. Ido Paz-Priel contributed to questionnaire and study design, analysis and interpretation of data, and review and revision of drafts. Michaela Lehle contributed to interpretation of data, and review and revision of drafts. Peter C. Trask contributed to questionnaire and study design, analysis and interpretation of data, and review and revision of drafts. Víctor Jiménez-Yuste contributed to acquisition, analysis and interpretation of data, and review and revision of drafts. All authors revised the manuscript critically and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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