










The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies

Mark W. Skinner^{1,2}  | Claude Négrier³  | Ido Paz-Priel⁴ | Sammy Chebon⁵ | Victor Jiménez-Yuste⁶  | Michael U. Callaghan⁷ | Michaela Lehle⁵ | Markus Niggli⁵ | Johnny Mahlangu⁸  | Amy Shapiro⁹  | Midori Shima¹⁰  | Avrita Campinha-Bacote⁴ | Gallia G. Levy^{4,11} | Johannes Oldenburg¹²  | Sylvia von Mackensen¹³  | Steven W. Pipe¹⁴ 

¹ Institute for Policy Advancement Ltd, Washington, District of Columbia, USA

² McMaster University, Hamilton, Canada

³ Louis Pradel University Hospital, Claude Bernard University Lyon 1, Lyon, France

⁴ Genentech Inc., South San Francisco, California, USA

⁵ F. Hoffmann-La Roche Ltd, Basel, Switzerland

⁶ La Paz University Hospital, Autónoma University, Madrid, Spain

⁷ Central Michigan University, Detroit, Michigan, USA

⁸ University of the Witwatersrand and NHLS, Johannesburg, South Africa

⁹ Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, USA

¹⁰ Nara Medical University Hospital, Kashihara, Japan

¹¹ Spark Therapeutics, Inc., Philadelphia, Pennsylvania, USA

¹² Universitätsklinikum Bonn, Bonn, Germany

¹³ Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

¹⁴ Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Introduction: Severe haemophilia A (HA) has a major impact on health-related quality of life (HRQoL).

Aim: Assess the impact of emicizumab on HRQoL in persons with severe HA (PwHA) without factor VIII (FVIII) inhibitors in the phase 3 HAVEN 3 and 4 studies.

Methods: This pooled analysis examines the HRQoL of PwHA aged ≥ 18 years treated with emicizumab prophylaxis via Haemophilia-Specific Quality of Life Questionnaire for Adults (Haem-A-QoL) and EuroQoL 5-Dimensions 5-levels (EQ-5D-5L). In particular, changes from baseline in Haem-A-QoL 'Physical Health' (PH) domain and 'Total Score' (TS) are evaluated.

Results: Among 176 evaluable participants, 96 (55%) had received prior episodic treatment and 80 (45%) prophylaxis; 70% had ≥ 1 target joint and 51% had experienced ≥ 9 bleeds in the previous 24 weeks. Mean Haem-A-QoL PH and TS improved after emicizumab initiation. Mean (standard deviation) -12.0 (21.26)- and -8.6 (12.57)-point improvements were observed in PH and TS from baseline to Week 73; Week 73 scores were 27.9 (24.54) and 22.0 (14.38), respectively. Fifty-four percent of participants reported a clinically meaningful improvement in PH scores (≥ 10 points) by Week 73. Subgroups with poorer HRQoL prior to starting emicizumab (i.e. receiving episodic treatment, ≥ 9 bleeds, target joints) had the greatest improvements in PH scores, and corresponding reductions in missed workdays; change was not detected among those previously taking prophylaxis. No change over time was detected by the EQ-5D-5L questionnaire.

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Correspondence

Mark W. Skinner, Institute for Policy Advancement Ltd, 1155 23rd Street NW #3A, Washington, DC 20037, USA.
Email: mskinner@ipaltd.com

Funding information

F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd

Conclusions: Emicizumab prophylaxis in PwHA without FVIII inhibitors resulted in persistent and meaningful improvements in Haem-A-QoL PH and less work disruption than previous treatment.

KEYWORDS

emicizumab, haemophilia A, health-related quality of life, prophylaxis, therapeutic, work

1 | INTRODUCTION

Severe haemophilia A (HA) is a congenital bleeding disorder that has a major impact on health-related quality of life (HRQoL).^{1–5} Bleeds can lead to arthropathy and functional deficits,⁴ which can negatively impact emotional, social and physical well-being.⁶ Even with factor VIII (FVIII) prophylaxis, bleeding events occur.⁷ HRQoL can also be affected by treatment burden, such as from frequent and time-consuming intravenous FVIII administration for prophylaxis.⁶ Treatment burden can detrimentally affect adherence, leading to increased bleeding, joint damage and decline in HRQoL.^{5,8}

Emicizumab is a bispecific, humanized, monoclonal antibody that bridges activated factor IX and factor X to restore effective haemostasis in persons with HA (PwHA).⁹ High subcutaneous bioavailability and a half-life of approximately 30 days⁹ enables administration once weekly (QW), every 2 weeks (Q2W) or every 4 weeks (Q4W).^{10–13} The efficacy of emicizumab for the prevention of bleeding was demonstrated in HAVEN 3 (NCT02847637), a study in adolescent and adult PwHA without FVIII inhibitors, and in HAVEN 4 (NCT03020160), in PwHA with or without FVIII inhibitors.^{12,13} At primary analysis of HAVEN 3 (data cut-off 15 September 2017), 56% (20/36) who had previously received episodic FVIII treatment had no treated bleeding while taking emicizumab prophylaxis 1.5 mg/kg QW.¹² Similarly, 60% (21/35) of those administered 3 mg/kg Q2W had no treated bleeding, while all 18 PwHA not given prophylaxis had bleeding events.¹² In those who had previously received FVIII prophylaxis 1.5 mg/kg QW, 56% (35/63) had no treated bleeding.¹² In HAVEN 4 (emicizumab 6 mg/kg Q4W), 23/41 (56%) participants reporting no treated bleeding events during a median (range) of 25.6 (24.1–29.4) weeks.¹³ Long-term efficacy and a favourable safety profile was observed in a pooled analysis (N = 401) of HAVEN 3 and 4, as well as HAVEN 1 and 2, across a median (interquartile range) of 120.4 (89.0–164.4) weeks emicizumab exposure.¹⁴ In HAVEN 3 and 4, 94% (95% confidence intervals [CI] 87, 98) and 100% (95% CI 91, 100), respectively, of the 95 and 41 eligible participants expressed a preference for emicizumab over their previous FVIII concentrate or bypassing agent (BPA), potentially due to reduced treatment burden.^{12,13}

The HAVEN studies found overall improvements in HRQoL through 25 weeks with emicizumab prophylaxis in adolescent and adult PwHA with or without FVIII inhibitors,^{12,13,15} as measured by the Haemophilia-Specific Quality of Life Questionnaire for Adults (Haem-A-QoL) and Adolescents (Haemo-QoL-SF).^{16,17} The 'Physical Health' (PH) domain reflects the detrimental impact of HA on physical health status; a 10-point reduction in PH is the threshold for clinically mean-

ingful improvement in the physical health of PwHA.^{18,19} In HAVEN 3, the mean (standard deviation [SD]) change in PH scores from baseline to Week 25 was -12.2 (26.78) and -15.2 (19.52) in PwHA taking emicizumab QW and Q2W, compared to +1.9 (22.50) without prophylaxis. In HAVEN 4, PH scores changed -15.1 (21.91) from baseline to Week 25 of Q4W emicizumab.

Here we report secondary/exploratory objectives of the HAVEN 3 and 4 studies assessing the impact of up to 73 weeks of prophylactic emicizumab on HRQoL, via the PH and Treatment domains, and the 'Total Score' (TS) of the Haem-A-QoL in adult PwHA. As all PwHA in HAVEN 3 and the majority of those in HAVEN 4 did not have FVIII inhibitors, this analysis focuses on that population.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The study designs and eligibility criteria for HAVEN 3 and 4 have been previously described.^{12,13} HAVEN 3 is a phase 3, open-label, multicentre, randomized trial including 152 adults/adolescents (≥ 12 years) with severe congenital HA without FVIII inhibitors who were receiving episodic or prophylactic FVIII (Figure 1A). The HAVEN 3 data cut-off for these analyses was 4 October 2018. HAVEN 4 is a phase 3, open-label, multicentre trial in adults/adolescents (≥ 12 years) with severe congenital HA, with or without FVIII inhibitors, who were receiving either FVIII or BPAs at enrolment (Figure 1B). The expansion cohort included 41 participants who received maintenance emicizumab 6 mg/kg Q4W. This analysis only includes those without FVIII inhibitors, with a data cut-off of 11 October 2018.

Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocols were approved by the relevant independent ethics committee and all participants provided written informed consent.

2.2 | HRQoL and health status measures

In HAVEN 3 and 4, HRQoL was assessed in participants aged ≥ 18 years^{12,13} using the Haem-A-QoL.^{16,17} Participants aged < 18 years were assessed using a different, age-appropriate tool (Haemo-QoL Short Form), but their results are not presented here due to their limited number. The Haem-A-QoL is a validated haemophilia-specific instrument for assessing self-reported HRQoL in adults with

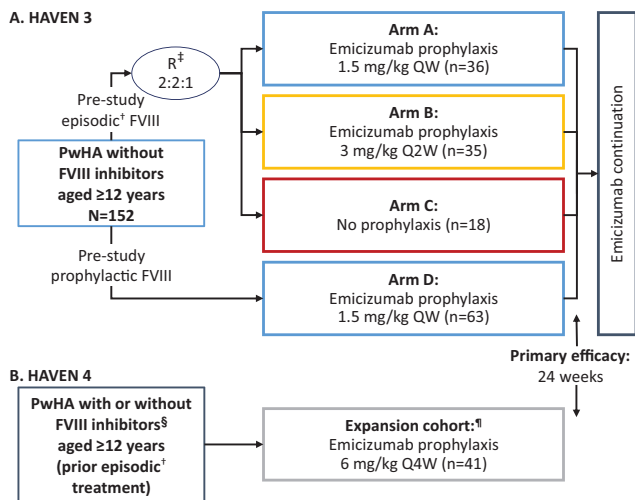


FIGURE 1 Study design for A, HAVEN 3 and B, HAVEN 4. All emicizumab regimens received a loading dose of 3 mg/kg QW emicizumab for 4 weeks and maintenance dosing as indicated was started at Week 5. [†]24-week bleed rate ≥ 5 for participants receiving episodic FVIII. [‡]Randomization (R) stratified based on 24-week bleed rate of < 9 or ≥ 9 episodes. [§]Undergoing treatments with either FVIII concentrates or bypassing agents. [¶]HAVEN 4 also included a run-in cohort that was not included in this analysis. Data cut-offs: HAVEN 3, 4 October 2018; HAVEN 4, 11 October 2018. Abbreviations: FVIII, factor VIII; PwHA, persons with haemophilia A; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomized

haemophilia.^{17,20} The questionnaire consists of 46 items pertaining to 10 domains ('Physical Health' (5 items), 'Feelings' (4), 'View of Yourself' (5), 'Sports & Leisure' (5), 'Work & School' (4), 'Dealing with Haemophilia' (3), 'Treatment' (8), 'Future' (5), 'Family Planning' (4) and 'Partnerships & Sexuality' (3)), with five-point Likert-scale responses ranging from 'never' to 'all the time' (Supplement). Each domain is transformed into a scale ranging from 0–100 with lower scores reflecting better HRQoL, and a TS is generated from all 10 domains.

Health status was assessed in HAVEN 3 and 4^{12,13} using the Euro-QoL 5-Dimensions 5-levels (EQ-5D-5L) questionnaire.^{21,22} Two components of the EQ-5D-5L: the Index Utility Score (IUS), a five-item health state profile, and a Visual Analogue Scale (VAS) measure overall health. Five dimensions of the IUS assess mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five response levels ('no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to/extreme problems'). The five dimensions are combined into a single score using the UK crosswalk value set; scores range from -0.594 (extreme problems on all dimensions) to 1 (no problems on all dimensions).²³ The EQ-VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health) on which patients provide a global assessment of their health.

The impact of treatment on work was assessed by recording missed workdays.

In both studies, Haem-A-QoL, EQ-5D-5L, and questions on expected and missed workdays, were administered at baseline (defined as a valid assessment on or before study day 1) and at scheduled timepoints.

This analysis includes assessments completed by the data cut-off, for HAVEN 3: Weeks 1, 13, 25, 49 and 73, and for HAVEN 4: 12-weekly assessments from Week 1 through to Week 61. Participants in HAVEN 3 and 4 completed study questionnaires at study sites using an electronic tablet.

2.3 | Data analysis

Data from HAVEN 3 and 4 were pooled. For continuous variables, CIs were produced assuming that the mean and SD for the population of interest was not known and was estimated based on the data available (i.e., using t-distribution). For response rates, the CIs were calculated via the Clopper-Pearson method.²⁴ No formal hypothesis testing was performed for this post-hoc analysis and therefore all analyses were descriptive. As there was no imputation when the selected score (corresponding to a domain or to the total across domains) was missing at a particular visit (only complete case analyses were performed), missing data were considered to be missing completely at random. However, a domain score could be calculated when at least 50%–60% of the items within the respective domain were answered, in which case the domain score (and potentially the total score across domains) would not be considered missing. This assumption was considered as acceptable given the low discontinuation rate and low number of up-titrations observed in both studies.

The questionnaire completion rate at each scheduled timepoint was calculated by dividing the number completed by the total number expected. Haem-A-QoL PH, Treatment, and TS, EQ-5D-5L and work data were pooled from the HAVEN 3 and 4 studies regardless of patient baseline characteristics or treatment. Haem-A-QoL, EQ-5D-5L, and missed workdays were also analysed by subgroups based on prior treatment, presence of target joints at baseline,²⁵ 24-week bleeding rate (a randomization stratification factor used in HAVEN 3), treated annualized bleed rate (ABR; during the first 24 weeks or at discontinuation if < 24 weeks), treated joint ABR (AJBR; during the first 24 weeks or at discontinuation if < 24 weeks) and dosing regimen. The proportions of participants at each timepoint with improvement larger than the responder threshold^{18,19} were calculated for the Haem-A-QoL PH and TS. Only those participants with data both at baseline and the timepoint of interest are included in score change calculations.

Among employed participants, the proportion with no missed workdays was calculated by dividing the self-reported missed workdays by the expected days at work in the previous 28 days.

3 | RESULTS

3.1 | Study population

Participant populations for the HAVEN 3 and 4 studies have been described previously.^{12,13} In HAVEN 3 and 4, 143 and 38 emicizumab recipients, respectively (181 altogether), were ≥ 18 years and thus eligible to complete the Haem-A-QoL questionnaire. Five participants in

TABLE 1 Participant demographics and baseline characteristics (participants without inhibitors receiving emicizumab and eligible to complete the Haem-A-QoL, aged ≥ 18 years)

Baseline characteristic	HAVEN 3 N = 143	HAVEN 4 N = 33	Total N = 176
Median age, years (range)	39.0 (19–77)	41.0 (20–66)	39.0 (19–77)
Bleeds in the past 24 weeks, mean (SD)	13.5 (16.5)	9.6 (16.7)	12.8 (16.5)
≥ 9 , n (%)	79 (55)	10 (30)	89 (51)
< 9 , n (%)	64 (45)	23 (70)	87 (49)
One or more target joints prior to study entry, n (%)	100 (70)	24 (73)	124 (70)
Prior treatment, n (%)			
Episodic	87 (61)	9 (27)	96 (55)
Prophylactic	56 (39)	24 (73)	80 (45)

Abbreviations: Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; SD, standard deviation.

HAVEN 4 had FVIII inhibitors and were excluded from this analysis, resulting in 176 PwHA included (Table 1). Overall, 96 (55%) participants had prior episodic treatment and 80 (45%) had prior prophylaxis; these groups, respectively, had mean (SD) 17.5 (13.2) and 7.0 (18.4) bleeds in the 24 weeks before initiating emicizumab. In total, 124 (70%) participants had target joint(s) prior to study entry; of these, 82 (66%) had been on episodic treatment only and 42 (34%) prophylaxis. Also, 89 (51%) of participants had ≥ 9 bleeds in the previous 24 weeks. At data cut-offs, participants in this long-term analysis had received a median (interquartile range) of 80.3 (68.1–89.1) weeks of therapy; those in HAVEN 3 had 83.9 (79.1–92.1) weeks and HAVEN 4 had 68.0 (64.1–68.1) weeks of emicizumab.

3.2 | Completion rates

The questionnaire completion rates across all scheduled timepoints were 94.3% in HAVEN 3 and 99.0% in HAVEN 4. Among participants who were dosed with emicizumab, none discontinued from HAVEN 4, and 2 discontinued from HAVEN 3 (1 lost to follow-up, another due to AE).

3.3 | Haemophilia-specific quality of life (Haem-A-QoL)

In this pooled analysis, participants who completed Haem-A-QoL questionnaires at baseline ($n = 170$) had mean (SD) PH, Treatment, and TS of 40.2 (23.19), 35.5 (17.96) and 33.0 (15.99). Mean PH, Treatment, and TS improved by the Week 13 assessment and were maintained throughout the study follow-up to Week 73 (Figures 2A–C). From baseline, mean (SD) PH scores improved by -9.8 (21.08) points ($n = 157$) at

Week 25 and by -12.0 (21.26) points ($n = 113$) at Week 73. The mean (SD) Treatment change from baseline was -18.3 (17.48) at Week 25 ($n = 157$) and -17.9 (17.81) at Week 73 ($n = 113$). Mean (SD) TS improved by -8.1 (12.73) points ($n = 157$) at Week 25 and by -8.6 (12.57) points ($n = 113$) at Week 73; subgroup analyses of TS mirrored the trends seen in the full population (Figure S1A–F).

Among those with available PH scores at baseline, 54% had a clinically meaningful improvement at Week 73 (Figure 3). The overall improvements observed in PH scores were also reflected across subgroups analysed by type of prior treatment, dosing regimen, 24-week bleed rate, treated ABR, treated AJBR and presence of target joints at baseline (Figures 4A–F). However, the level of improvement between subgroups (change in PH score from baseline to Week 73) was higher in subgroups with worse PH scores at baseline, specifically, those: on episodic treatment, with ≥ 9 bleeds in the 24 weeks before study start and with target joints at baseline (Table 2). Because the baseline PH scores were worse in participants taking episodic treatment than prophylaxis, the change from baseline to Week 73 was larger. In participants who had ≥ 9 bleeds before study start, the mean (SD) change from baseline to Week 73 was -16.9 (21.35), reflecting a larger physical health improvement than in those with < 9 bleeds (-6.2 [19.81]) following from different baseline starting points (Table 2). Contrastingly, minimal differences were observed in PH scores from baseline to Week 73 in participants with a treated ABR of 0 versus > 0 or a treated AJBR of 0 versus > 0 (Table 2). While those with target joints at baseline also reported improvement in mean PH scores from baseline to Week 73, those without target joints only had minimal improvement (Table 2); those without target joints at baseline had lower initial scores, reflecting better physical health than those with target joints, therefore their potential for improvement was reduced. No substantial difference in HRQoL was observed between emicizumab dosing regimens (QW and Q2W; the Q4W regimen only had two participants with evaluable data) (Figure 4B).

3.4 | Health status (EQ-5D-5L)

Score changes in EQ-VAS and IUS of 7 and 0.07 points, respectively, are considered clinically meaningful.^{26–28} In this pooled analysis, no notable changes over time were observed by EQ-5D-5L. At baseline ($n = 170$) and Week 73 ($n = 118$), mean (SD) IUS for the pooled population was 0.74 (0.20) and 0.79 (0.17), respectively, yielding a mean (SD) change from baseline of 0.03 (0.15) among 113 evaluable participants. Similarly, there was little change in mean (SD) EQ-VAS scores in the same population (baseline, 77.0 [17.47]; Week 73, 81.8 [15.59]; mean (SD) change 3.1 [14.32]). Subgroup analyses by type of prior treatment, presence of target joints at baseline, number of bleeds (< 9 or ≥ 9) at baseline and dosing regimen also showed no notable changes over time (Figures S2 and S3; other subgroup analyses data not shown). Analysis of the Mobility domain demonstrates a slight trend towards improvement over time, with 76.3% of PwHA reporting ‘no problems’ or ‘slight problems’ at Week 73 ($n = 90/118$) compared with 70.6% at baseline ($n = 120/170$).

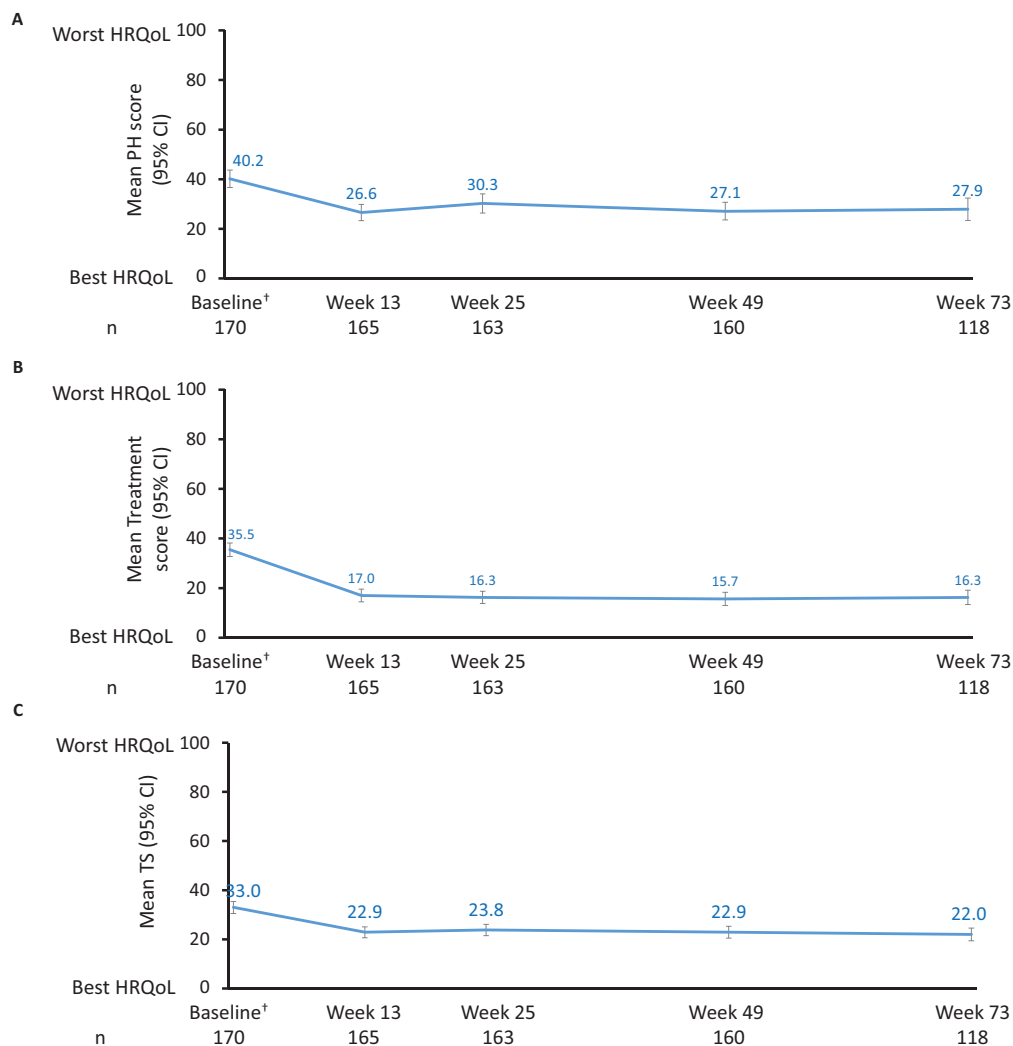


FIGURE 2 Mean (95% CI) Haem-A-QoL: A, PH domain score, B, ‘Treatment’ domain score, and C, TS over time in adults with haemophilia A without FVIII inhibitors who received emicizumab during the HAVEN 3 and 4 studies. Reductions in Haem-A-QoL PH domain score, ‘Treatment’ domain score and TS denote an improvement in health-related quality of life. [†]Baseline assessment was the last valid assessment on or before study day 1. Abbreviations: CI, confidence interval; FVIII, factor VIII; Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; HRQoL, health-related quality of life; PH, physical health; TS, total score

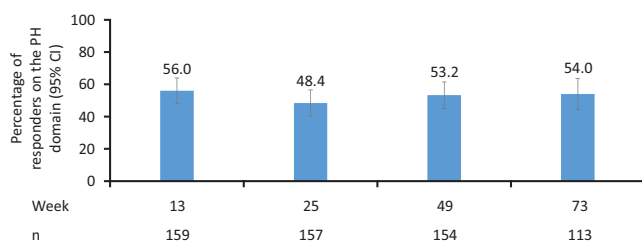


FIGURE 3 Percentage of adults with haemophilia A without FVIII inhibitors with improvements in Haem-A-QoL PH score greater than the responder threshold (≥ 10 points) from baseline in pooled data from emicizumab recipients in the HAVEN 3 and 4 studies. Error bars depict 95% CIs. n denotes the number of participants with available data to calculate the change from baseline. Abbreviations: CI, confidence interval; FVIII, factor VIII; Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; PH, physical health

3.5 | Work absences

With emicizumab, fewer employed participants missed workdays than in the 28 days prior to study enrolment (Figure 5). Improvements were more pronounced in those with prior episodic treatment, ≥ 9 bleeds or target joints at baseline (Figures 6A–C, respectively). Those previously taking prophylaxis already had a low rate of missed days at baseline and little room for improvement.

4 | DISCUSSION

With emicizumab, clinically meaningful improvements were observed in Haem-A-QoL PH scores in more than half of adult PwHA without FVIII inhibitors in HAVEN 3 and 4. These improvements are complementary to demonstrated efficacy of emicizumab in bleed

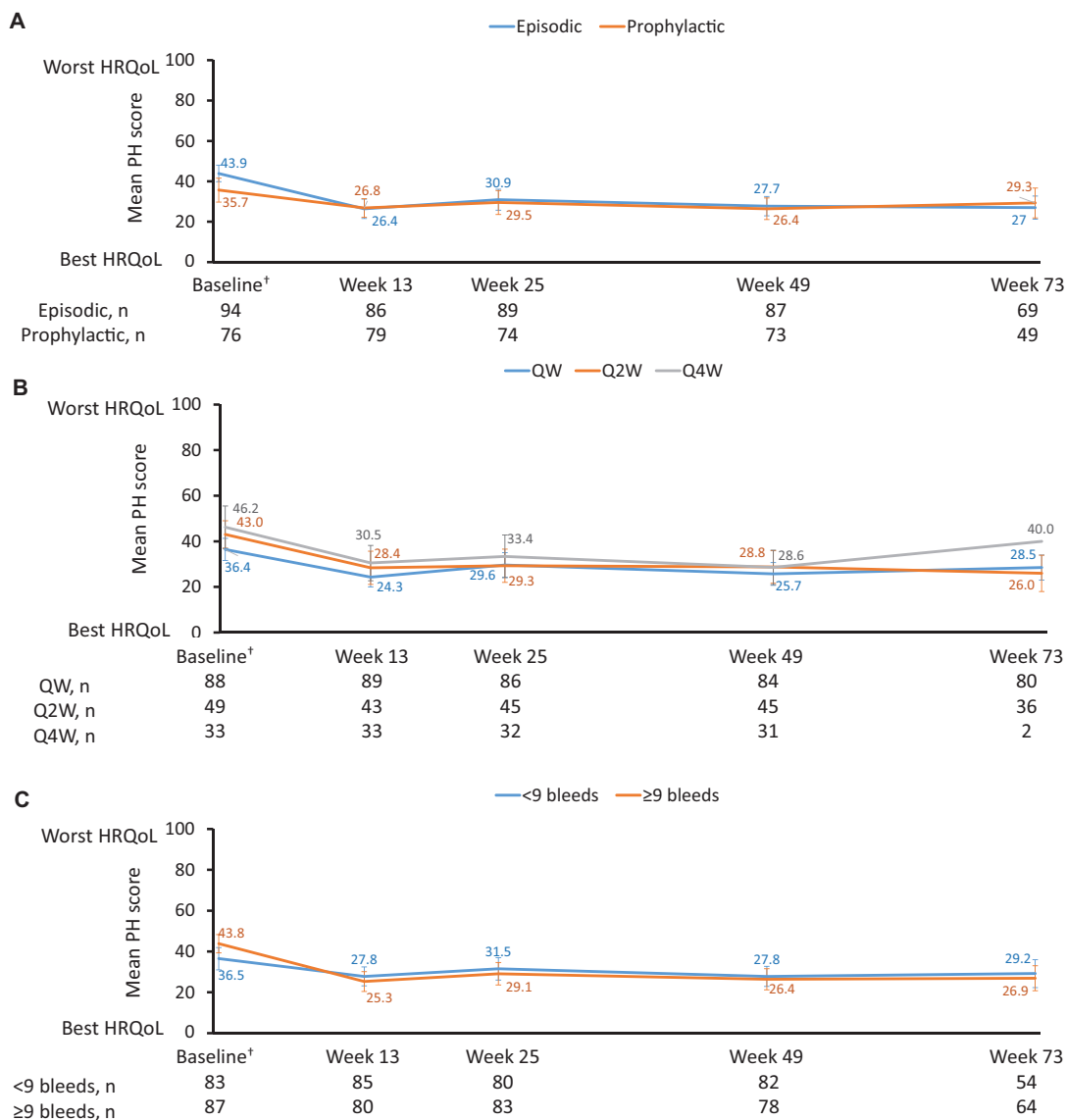


FIGURE 4 Mean (95% CI) Haem-A-QoL PH domain scores over time in adults with haemophilia A without FVIII inhibitors treated with emicizumab in the HAVEN 3 and 4 studies by A, type of prior treatment, B, emicizumab dosing regimen[‡], C, 24-week bleed rate of < 9 or ≥ 9 episodes (randomization stratification factor used in HAVEN 3), D, on treatment ABR (in the first 24 weeks on emicizumab or up to early discontinuation if the treatment duration is less than 24 weeks, and before treatment up-titration), E, on treatment joint ABR (in the first 24 weeks on emicizumab or up to early discontinuation if the treatment duration is less than 24 weeks, and before treatment up-titration), and F, presence of target joints at baseline. Reductions in Haem-A-QoL PH domain scores denote an improvement in health-related quality of life. n denotes the number of participants in each subgroup with an available score at each timepoint. [†]Baseline assessment was the last valid assessment on or before study day 1. [‡]At Week 73, HAVEN 4 data were not available, which singularly affects the Q4W dosing regimen. For Q4W, 95% CIs are not shown for Week 73 where n = 2. Abbreviations: ABR, annualized bleed rate; AJBR, annualized joint bleed rate; FVIII, factor VIII; Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; PH, physical health; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks

prevention.^{12,13} In contrast, no improvement was seen in Group C of HAVEN 3 during 24 weeks of no prophylaxis (+1.9 [22.50]). Improvements in HRQoL observed early with emicizumab were maintained long term, shown by relatively consistent PH and TS to Week 73. Furthermore, greater improvements in HRQoL were observed in sub-analyses of those with higher scores at baseline (reflecting poorer HRQoL), including those with regular bleeding or target joints, or taking episodic treatment. Notably, those taking episodic treatment had many more bleeds in the 24 weeks before switching

to emicizumab (mean [SD] 17.5 [13.2]) compared with those taking factor prophylaxis (7.0 [18.4]), likely leading to greater impairment in their HRQoL and, therefore, greater room for improvement. These findings are consistent with other studies that have shown a correlation between frequent bleeding and/or target joints and a significant negative impact on HRQoL.^{29,30} Previous studies have also demonstrated that prophylaxis is associated with better HRQoL compared with episodic treatment, potentially because of improved physical health.^{30,31}

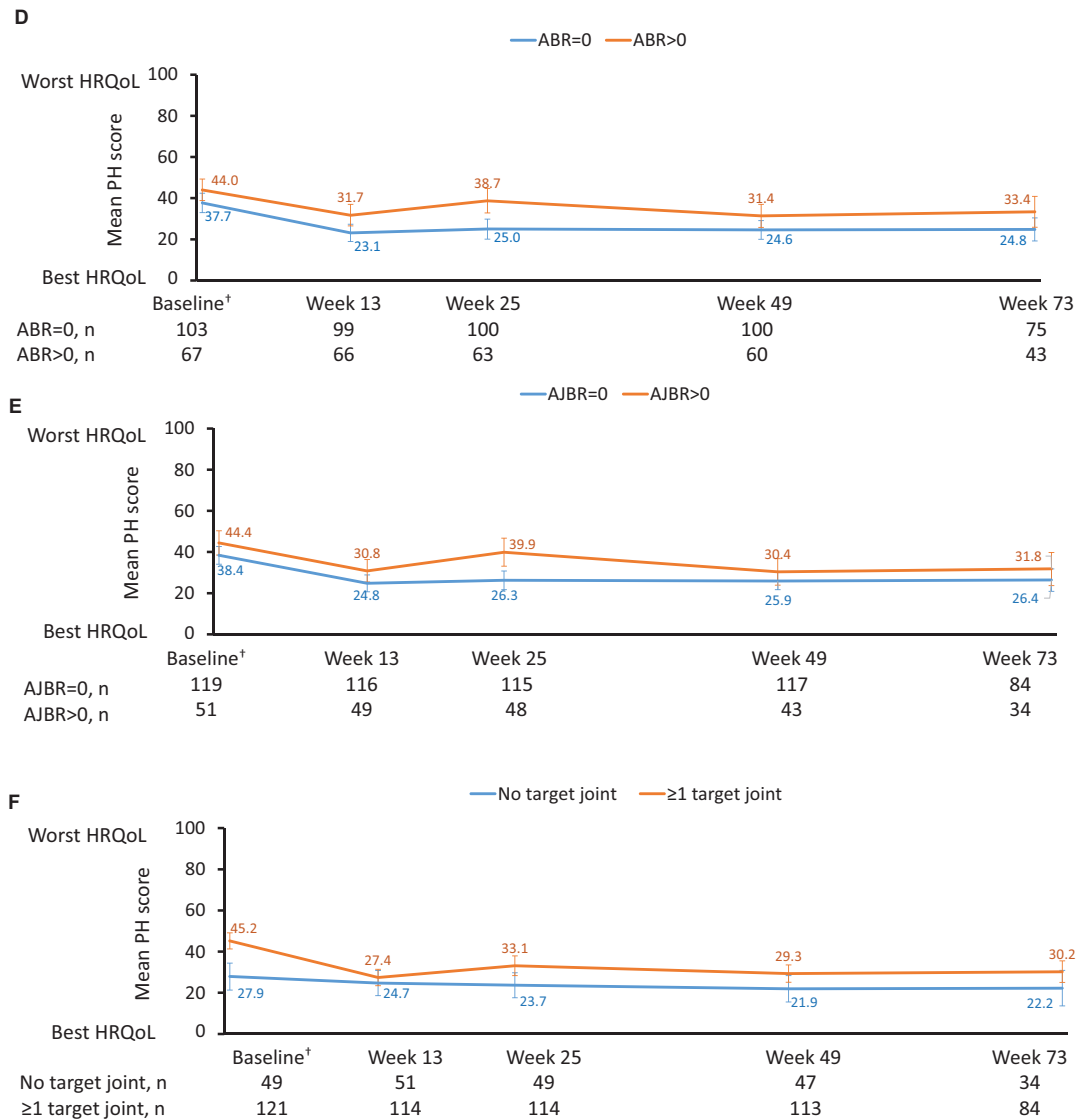


FIGURE 4 Continued

The improvement in HRQoL described in PwHA without FVIII inhibitors here is less than observed in PwHA with inhibitors in HAVEN 1, consistent with the observation that those with compromised HRQoL have a greater improvement with emicizumab than those with relatively high HRQoL.¹⁵ Importantly, the PH scores were consistent in PwHA with¹⁵ or without FVIII inhibitors. In this pooled analysis, an improvement in mean PH score from baseline was observed at Week 25 and was maintained through 73 weeks. In comparison, during HAVEN 1, those previously taking episodic or prophylactic BPAs had respective reductions of -19.8 (95% CI $-28.8, -10.8$) and -15.0 (95% CI $-36.2, 6.2$) at Week 25.¹⁵ In keeping with previous studies that found a higher disease burden in those with FVIII inhibitors than without,^{29,32} in HAVEN 1 higher mean baseline PH scores were observed for those previously taking episodic BPAs 52.4 (95% CI 44.4, 60.4) and those taking prophylactic BPAs 59.5 (95% CI 48.0, 71.1),¹⁵ signifying poorer physical health, than in this analysis of PwHA without FVIII inhibitors 40.2 (95% CI 36.7, 43.7). Although the PH scores of

those with FVIII inhibitors were poorer at the start of each study than in those without, by the end, the scores of those with FVIII inhibitors¹⁵ were within the same range as those without (both groups ~ 30). This is not unexpected given the mechanism of action of emicizumab, which enables coagulation independent of activated FVIII. Collectively, these data indicate that emicizumab improves aspects of HRQoL regardless of FVIII inhibitor status.

Analysis of the Treatment domain of the Haem-A-QoL indicated an improvement in the HRQoL associated with changing from at least twice-weekly factor replacement by intravenous infusion to subcutaneous injection with emicizumab prophylaxis administered every 1, 2 or 4 weeks. Although the Haem-A-QoL was developed at a time when subcutaneous regimens were not available for haemophilia and therefore the Treatment domain may not be fully applicable to emicizumab prophylaxis, these results complement the participant preferences for treatment reported in the EmiPref survey in the primary analyses of HAVEN 3 and 4 at Week 25, wherein 98% and 100% of

TABLE 2 Mean (SD) Haem-A-QoL PH domain scores in participants of HAVEN 3 and 4 studies receiving emicizumab

Baseline FVIII treatment	Baseline		Week 73		Change ^c	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Episodic	94	43.9 (20.06)	69	27.0 (23.80)	67	-17.2 (19.87)
Prophylaxis	76	35.7 (25.99)	49	29.3 (25.74)	46	-4.6 (21.21)
Emicizumab dosing						
QW	88	36.4 (22.82)	80	28.5 (24.72)	77	-8.6 (21.86)
Q2W	49	43.0 (20.89)	36	26.0 (23.48)	34	-19.0 (18.58)
Q4W	33	46.2 (26.13)	2	40.0 (49.50)	2	-25.0 (7.07)
Bleeds ^a						
≥ 9	87	43.8 (20.94)	64	26.9 (24.31)	62	-16.9 (21.35)
< 9	83	36.5 (24.92)	54	29.2 (24.99)	51	-6.2 (19.81)
Treated ABR ^b						
0	103	37.7 (23.97)	75	24.8 (24.22)	71	-13.3 (19.93)
> 0	67	44.0 (21.57)	43	33.4 (24.42)	42	-9.9 (23.44)
Treated AJBR ^b						
0	119	38.4 (23.89)	84	26.4 (25.06)	80	-11.3 (20.34)
> 0	51	44.4 (21.11)	34	31.8 (23.12)	33	-13.8 (23.59)
Baseline target joints						
Yes	121	45.2 (21.52)	84	30.2 (24.21)	81	-15.3 (20.75)
No	49	27.9 (22.75)	34	22.2 (24.78)	32	-3.9 (20.66)

Abbreviations: ABR, annualized bleed rate; AJBR, annualized joint bleed rate; FVIII, factor VIII; Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; PH, physical health; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks; SD standard deviation.

n denotes evaluable participants. At Week 73, HAVEN 4 data were not available, which singularly affects the Q4W dosing regimen.

^aDuring 24 weeks prior to study entry and before treatment up-titration.

^bIn the first 24 weeks of emicizumab treatment or up to early discontinuation if the treatment duration is less than 24 weeks, and before treatment up-titration.

^cOnly patients with numbers at both baseline and Week 73 are included in the change value.

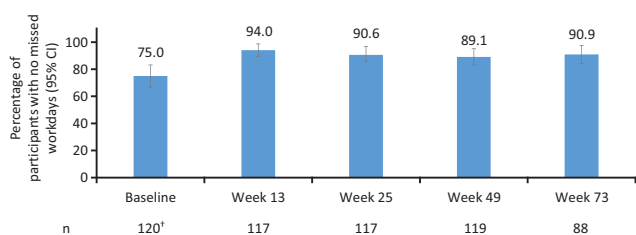


FIGURE 5 Percentage of employed adult participants without FVIII inhibitors who self-reported no missed workdays in the previous 28 days. Pooled data from emicizumab recipients in the HAVEN 3 and 4 studies. Error bars depict 95% CIs. n is the number of employed participants at each timepoint. [†]Reflects the work period 28 days prior to enrolment. Abbreviations: CI, confidence interval; FVIII, factor VIII

participants previously taking FVIII or BPA prophylaxis preferred emicizumab, respectively (45/46; 95% CI 88, 100; 41/41; 95% CI 91.4, 100).^{12,13} As the Treatment domain constitutes 8 items within the Haem-A-QoL,¹⁸ these changes may make an important contribution alongside the PH to the observed improvement in TS.

A previous non-interventional study demonstrated that PwHA without FVIII inhibitors experience bleeds on prophylaxis with FVIII³³

and associated impairments in HRQoL.³⁴ Moreover, the study demonstrated a need for a treatment that reduces the burden of PwHA without FVIII inhibitors³⁴; improved long-term HRQoL in those taking emicizumab has now been demonstrated. Concomitantly, the proportion of participants with no missed workdays increased from 75% at baseline to > 90% at Week 73 with emicizumab prophylaxis.

The health status measured by EQ-5D-5L IUS and EQ-VAS indicated no notable improvement over time in HAVEN 3 and 4, with the exception of a slight trend towards improvement over time in the Mobility domain. As mobility is directly impacted by physical health, this improvement in Mobility is congruent with the changes described in Haem-A-QoL PH. A notable improvement in EQ-5D-5L may be precluded by high baseline health status with mean (SD) IUS at baseline of 0.74 (0.20) and EQ-VAS scores of 77.0 (17.47), or could be due to only a small change in health status while taking emicizumab. For context, a healthy population had a mean EQ-5D-5L IUS of 0.93 in ages 18–24 years (UK VAS value set) with scores decreasing further with age (e.g., ≥ 75 years: 0.73) and EQ-VAS scores ranging across countries from 79–89 in ages 18–24 years and scores again decreasing with age (e.g., ≥ 75 years: 54–76).³⁵ In contrast to HRQoL as measured by Haem-A-QoL, which broadly assesses the impact of disease on daily life and functioning (physical, social, emotional, etc.), health status as

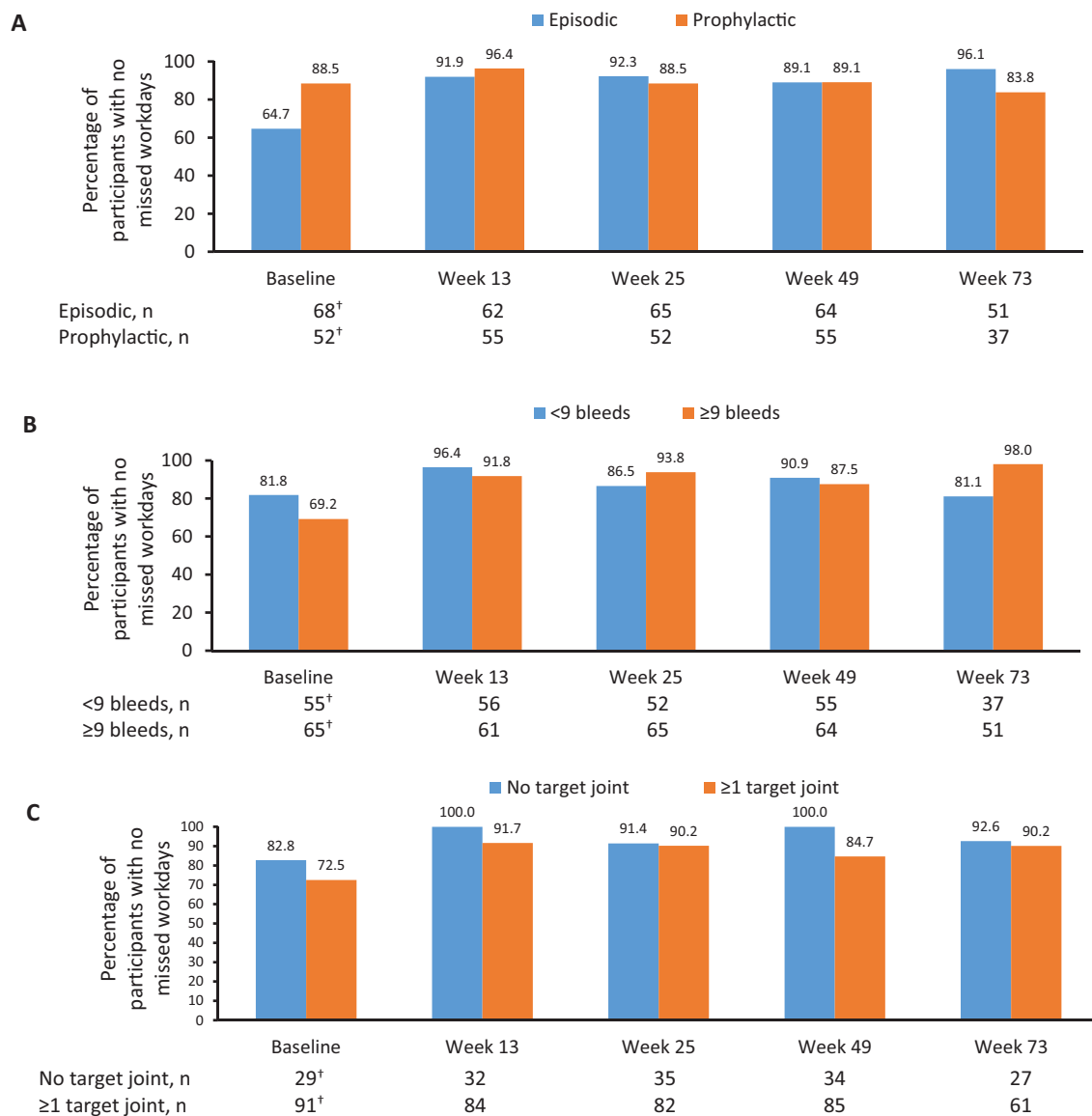


FIGURE 6 Percentage of employed adult participants without FVIII inhibitors who self-reported no missed workdays in the previous 28 days by A, type of prior treatment, B, 24-week bleed rate of < 9 or ≥ 9 episodes (randomization stratification factor used in HAVEN 3), and C, presence of target joints at baseline. Pooled data from emicizumab recipients in the HAVEN 3 and 4 studies. n is the number of employed participants at each timepoint. [†]Reflects the work period 28 days prior to enrolment. Abbreviation: FVIII, factor VIII

measured by EQ-5D-5L focuses on disease impact in terms of health economic evaluations. While both versions of the EQ-5D (3L or 5L) are frequently used for measuring health status in clinical research, and may in certain situations be able to detect meaningful differences between some patient subpopulations, it might not, as a generic tool, be able to adequately detect differences between all subgroups of PwHA, or detect changes over time.^{36,37} Recent research suggests that people with inherited and long-term conditions, such as haemophilia, may adapt to their health state and their HRQoL may be assessed as better than the general population using tools like EQ-5D-5L.³⁸ Overall, this highlights the need to use reliable and valid HRQoL tools and/or patient satisfaction/preference tools that are able to detect differences in the burden of administration of different prophylactic agents used by PwHA.

The Haem-A-QoL is a frequently utilized haemophilia-specific instrument for the evaluation of HRQoL in PwHA^{19,39} and use of this instrument is a strength of this study. Because of the high impact of HA on physical activities, the PH domain is an important facet of the Haem-A-QoL when measuring HA interference with HRQoL. A potential weakness of the study is the lack of sensitivity of Haem-A-QoL in detecting meaningful changes in the subpopulations with less severe HA and/or better bleed control prior to emicizumab; therefore, this instrument, developed in the era of standard half-life FVIII concentrates, may not be suitable for detecting change in those with good HRQoL prior to intervention with emicizumab (e.g., PwHA on routine prophylaxis, or with mild HA). Additionally, comparing dosing regimens is limited by potential confounders, such as the type of FVIII treatment before study entry. In particular, QW and Q2W data were



collected in HAVEN 3, while Q4W data were collected in HAVEN 4. Most of the HRQoL data from participants taking QW or Q4W emicizumab were collected from participants who previously took FVIII prophylaxis, while all the data on Q2W emicizumab were from participants who previously took episodic treatment.

Because of the range of dosing options, emicizumab can potentially accommodate the varying lifestyles and needs of different PwHA. Providing prophylaxis aligned to patients' needs has the potential to improve adherence, and thus reduce bleeds and increase HRQoL.

5 | CONCLUSIONS

This analysis of pooled HAVEN 3 and 4 data demonstrates that the substantial reductions in bleeding seen with emicizumab prophylaxis in PwHA without FVIII inhibitors were accompanied by meaningful improvements in Haem-A-QoL PH scores in those who previously had more severe HA and/or poorer bleed control. These improvements were apparent as early as Week 13 and persisted up to 73 weeks, and also led to reduced missed workdays, with more pronounced effects on work in those with prior episodic treatment, target joints or ≥ 9 bleeds at baseline. These findings add to the evidence suggesting that emicizumab can provide an improved HRQoL in PwHA without FVIII inhibitors with less burdensome prophylaxis.

ACKNOWLEDGEMENTS

Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Rebecca A Bachmann, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd. These studies were funded by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd.

DISCLOSURES

MWS has received research funding from Bayer, CSL Behring, Freeline, Novo Nordisk, F. Hoffmann-La Roche Ltd, Sanofi, Sobi, Takeda, and uniQure; and fees for Advisory Board or educational presentations from Bayer, BioMarin, Novo Nordisk, Pfizer (DMC), F. Hoffmann-La Roche Ltd/Genentech, Inc., and Spark (DMC). CN has received honoraria from Alnylam/Sanofi, Bayer, Catalyst Biosciences, CSL Behring, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Shire/Takeda, Sobi, and Spark Therapeutics; research funding from Bayer, CSL Behring, Freeline, Novo Nordisk, Octapharma, F. Hoffmann-La Roche Ltd, Shire/Takeda, Sobi, and Spark Therapeutics; and travel and accommodation expenses from CSL Behring, F. Hoffmann-La Roche Ltd, and Sobi. IP-P is an employee of Genentech, Inc. SC is an employee and holds shares in F. Hoffmann-La Roche Ltd. VJ-Y has provided consultancy (including expert testimony) for F. Hoffmann-La Roche Ltd, Novo Nordisk, Takeda, Sobi, and Pfizer; and received research funding from Grifols, Novo Nordisk, Sobi, Takeda, and Pfizer; as well as honoraria from F. Hoffmann-La Roche Ltd, Novo Nordisk, Takeda, Sobi, Pfizer, Grifols, Octapharma, CSL Behring, and Bayer. MUC has provided consultancy for F. Hoffmann-La Roche, Ltd/Genentech, Inc., Bayer,

Shire/Takeda, Bioverativ/Sanofi, Global Blood Therapeutics, Spark Therapeutics, BioMarin, Pfizer, Novo Nordisk, Kedrion, Octapharma, and Grifols; has equity ownership interests in Alnylam; has gained research funding from F. Hoffmann-La Roche Ltd, Pfizer, and Takeda; and honoraria for speaker's bureau participation from F. Hoffmann-La Roche Ltd, Novo Nordisk, Bayer, and Shire/Takeda. ML is an employee and holds stocks in F. Hoffmann-La Roche Ltd. MN is an employee of F. Hoffmann-La Roche Ltd. JM has received research grants from Bayer, Biogen, CSL Behring, Novo Nordisk and F. Hoffmann-La Roche Ltd, has served on Advisory Boards for Baxalta, Biogen, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, and Shire; and on speakers' bureaus for Amgen, Alnylam, Bayer, Biogen, Biotest and CSL Behring. AS has received honoraria; fees for consultation, advisory role, or speakers' bureau; research funding; and travel, accommodation, and expenses from Genentech, Inc. MS has received honoraria from Chugai Pharmaceutical Co., Ltd, CSL Behring, Bayer, Sanofi, Novo Nordisk, and Sysmex; fees for consultancy or advising Chugai Pharmaceutical Co., Ltd and Sanofi; research funding from Chugai Pharmaceutical Co., Ltd, Bayer, Novo Nordisk, Sanofi, Takeda, and CSL Behring; and patents royalties or other intellectual property income from Chugai Pharmaceutical Co., Ltd. AC-B is an employee of Genentech, Inc. and holds stocks in F. Hoffmann-La Roche Ltd. GGL was a previous employee and leader of Genentech, Inc., holds stocks in F. Hoffmann-La Roche Ltd and is a current employee of Spark Therapeutics, Inc. JO reports grants and personal fees (for travel support, participation in Advisory Boards and participation in symposia as chair or speaker) from Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, and Shire/Takeda; as well as personal fees from Chugai Pharmaceutical Co., Grifols, Pfizer, F. Hoffmann-La Roche Ltd, and Sobi. SvM has served as a consult or advisor for Sobi, F. Hoffmann-La Roche Ltd/Chugai Pharmaceutical Co., Takeda, and Bayer; in speakers' bureaus for Sobi and CSL Behring; and received research funding from Sobi and Novo Nordisk; as well as travel, accommodations, and expenses from Sobi and CSL Behring. SWP has served as a consultant to Apicintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd /Genentech, Inc., Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure.

AUTHOR CONTRIBUTIONS

Michaela Lehle, Ido Paz-Priel, Avrita Campinha-Bacoteand Gallia G. Levy contributed to the study concept, design and data interpretation. Data analysis and interpretation was conducted by the trial statisticians (Sammy Chebon and Markus Niggli), who vouch for the completeness and accuracy of the data and analyses. Mark W. Skinner, Claude Négrier, Victor Jiménez-Yuste, Michael U. Callaghan, Johnny Mahlangu, Amy Shapiro, Midori Shima, Johannes Oldenburg, and Steven W. Pipe contributed data collection and interpretation, and Sylvia von Mackensen contributed data analyses and interpretation. All authors contributed to drafting of this article and revising it critically for important intellectual content. All authors approved the final manuscript as submitted and 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).

ORCID

Mark W. Skinner  <https://orcid.org/0000-0002-0934-0680>

Claude Négrier  <https://orcid.org/0000-0002-2905-055X>

Victor Jiménez-Yuste  <https://orcid.org/0000-0003-3937-3499>

Johnny Mahlangu  <https://orcid.org/0000-0001-5781-7669>

Amy Shapiro  <https://orcid.org/0000-0003-2821-7159>

Midori Shima  <https://orcid.org/0000-0002-5922-7061>

Johannes Oldenburg  <https://orcid.org/0000-0002-1585-4100>

Sylvia von Mackensen  <https://orcid.org/0000-0002-5926-0478>

Steven W. Pipe  <https://orcid.org/0000-0003-2558-2089>

REFERENCES

- Mahlangu J, Oldenburg J, Callaghan MU, et al. Health-related quality of life and health status in persons with haemophilia A with inhibitors: a prospective, multicentre, non-interventional study (NIS). *Haemophilia*. 2019;25(3):382-391.
- Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. *Eur J Haematol*. 2012;88(4):329-335.
- Witkop M, Guelcher C, Forsyth A, et al. Treatment outcomes, quality of life, and impact of hemophilia on young adults (aged 18–30 years) with hemophilia. *Am J Hematol*. 2015;90(Suppl 2):S3-S10.
- Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-e47.
- McLaughlin JM, Munn JE, Anderson TL, Lambing A, Tortella B, Witkop ML. Predictors of quality of life among adolescents and young adults with a bleeding disorder. *Health Qual Life Outcomes*. 2017;15(1):67.
- Wiley RE, Khoury CP, Snihur AWK, et al. From the voices of people with haemophilia A and their caregivers: challenges with current treatment, their impact on quality of life and desired improvements in future therapies. *Haemophilia*. 2019;25(3):433-440.
- Ljung R, Gretenkort Andersson N. The current status of prophylactic replacement therapy in children and adults with haemophilia. *Br J Haematol*. 2015;169(6):777-786.
- Berntorp E. Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens. *Haemophilia*. 2009;15(6):1219-1227.
- Kitazawa T, Esaki K, Tachibana T, et al. Factor VIIIa-mimetic cofactor activity of a bispecific antibody to factors IX/IXa and X/Xa, emicizumab, depends on its ability to bridge the antigens. *Thromb Haemost*. 2017;117:1348-1357.
- Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
- Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
- Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379(9):811-822.
- Pipe SW, Shima M, Lehle M, et al. 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. *Lancet Haematol*. 2019;6(6):e295-e305.
- Callaghan M, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with/without FVIII inhibitors from the HAVEN 1–4 studies. *Blood*. 2020;137(16):2231-2242.
- Oldenburg J, Mahlangu JN, Bujan W, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 study. *Haemophilia*. 2019;25(1):33-44.
- von Mackensen S, Gringeri A. Development and pilot testing of a disease-specific quality of life questionnaire for adult patients with haemophilia (Haem-A-QoL). *Blood*. 2004;104(11):2214-2214.
- von Mackensen S, Gringeri A. Quality of life in haemophilia. In: Preedy VR, Watson RR, eds. *Handbook of Disease Burdens and Quality of Life Measures*. New York, NY: Springer; 2010:1895-1920.
- Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. *Haemophilia*. 2015;21(5):578-584.
- von Mackensen S, Catalani O, Asikanius E, Paz-Priel I, Lehle M, Trask P. Determining meaningful health-related quality-of-life improvement in persons with haemophilia A using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL). *Haemophilia*. 2020;26(6):1019-1030.
- von Mackensen S, Eldar-Lissai A, Auguste P, et al. Measurement properties of the Haem-A-QoL in haemophilia clinical trials. *Haemophilia*. 2017;23(3):383-391.
- Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.
- Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717-1727.
- Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ*. 2018;27(1):7-22.
- Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26:404-413.
- Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939.
- Antunes SV, Tangada S, Stasyshyn O, et al. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia*. 2014;20(1):65-72.
- Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5:70.
- Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: eQ-5D and SF-6D. *Qual Life Res*. 2005;14(6):1523-1532.
- Oladapo AO, Lu M, Walsh S, O'Hara J, Kauf TL. Inhibitor clinical burden of disease: a comparative analysis of the CHES data. *Orphanet J Rare Dis*. 2018;13(1):198.
- Allhaidan MA, Almashaan AM, Alduaij AA, Altuwaijri HA, Alotaibi LA, Almomen AM. Health-related quality of life in adult patients with hemophilia, Riyadh, Saudi Arabia. *J Applied Hematol*. 2018;9(1):5-10.
- Oladapo AO, Epstein JD, Williams E, Ito D, Gringeri A, Valentino LA. Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a systematic review of results from prospective clinical trials. *Haemophilia*. 2015;21(5):e344-e358.
- Oladapo A, Walsh S, O'Hara J, Kauf TL. A descriptive comparison of disease burden between hemophilia patients with and without inhibitors: data from the CHES study. *Blood*. 2016;128:4756.



33. Kruse-Jarres R, Oldenburg J, Santagostino E, et al. Bleeding and safety outcomes in persons with haemophilia A without inhibitors: results from a prospective non-interventional study in a real-world setting. *Haemophilia*. 2019;25(2):213-220.
34. Oldenburg J, Tran H, Peyvandi F, et al. Health-related quality of life and health status in adolescent and adult people with haemophilia A without factor VIII inhibitors—a non-interventional study. *Haemophilia*. 2021;27(3):398-407.
35. Janssen B, Szende A. In: Szende A, Janssen B, Cabases J, eds. *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht (NL): Springer; 2014. Chapter 3 Population Norms for the EQ-5D.
36. Payakachat N, Ali MM, Tilford JM. Can the EQ-5D detect meaningful change? A systematic review. *Pharmacoeconomics*. 2015;33(11):1137-1154.
37. Grosse SD, Chaugule SS, Hay JW. Estimates of utility weights in hemophilia: implications for cost-utility analysis of clotting factor prophylaxis. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(2):267-283.
38. Nugent D, O'Hara J, Martin A, et al. Examining the hemophilia disability paradox. *Res Pract Thromb Haemost*. 2020;4. [abstract PB0817].
39. Trindade GC, Viggiano LGL, Brant ER, et al. Evaluation of quality of life in hemophilia patients using the WHOQOL-bref and Haemo-A-Qol questionnaires. *Hematol Transfus Cell Ther*. 2019;41(4):335-341.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Skinner MW, Négrier C, Paz-Priel I, et al. The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without Factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies. *Haemophilia*. 2021;1-12.

<https://doi.org/10.1111/hae.14363>