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The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study

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Introduction: Persons with haemophilia A (PwHA) with inhibitors to factor VIII often experience decreased health-related outcomes. In HAVEN 1 (NCT02622321), there was a statistically significant reduction in bleeding with emicizumab prophylaxis versus no prophylaxis.

Aim: Describe health-related outcomes in PwHA with inhibitors in HAVEN 1.

Methods: PwHA with inhibitors aged ≥12 years previously on episodic bypassing agents (BPAs) were randomized to emicizumab prophylaxis (Arm A; n = 35) or no prophylaxis (Arm B; n = 18); participants previously on BPA prophylaxis received emicizumab prophylaxis (Arm C; n = 49). Health-related outcomes assessed at baseline and monthly thereafter: Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), Haemophilia-specific Quality of Life Questionnaire for Children Short Form (Haemo-QoL SF), EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) index utility score (IUS) and visual analogue scale (EQ-VAS) and work/school days. Days hospitalized also recorded.

Results: At week 25, differences (ANCOVA) in adjusted mean scores (95% confidence interval) favoured Arm A versus B for Haem-A-QoL "Total" score (14.0 [5.6, 22.5]; $P = 0.002$) and "Physical Health" (21.6 [7.9, 35.2]; $P = 0.003$); EQ-VAS (−9.7 [−17.6, −1.82]; $P = 0.017$); and IUS (−0.16 [−0.25, −0.07]; $P = 0.001$); mean scores are comparable in Arms A and C. Throughout the study, a greater proportion of participants on emicizumab prophylaxis than no prophylaxis exceeded questionnaire-specific responder thresholds. Mean proportion of missed work days and number of days hospitalized were lower with emicizumab prophylaxis than no prophylaxis.

Conclusions: In PwHA with inhibitors, emicizumab prophylaxis was associated with substantial and meaningful improvements in health-related outcomes.

KEYWORDS

emicizumab, factor VIII inhibitors, haemophilia A, health-related quality of life, prophylaxis

1 | INTRODUCTION

Despite advances in the treatment of haemophilia A in the past decades,[1] current standard approaches continue to require frequent and time-consuming intravenous infusions of factor VIII (FVIII) concentrates.[1-3] Up to 20% of persons with haemophilia A (PwHA) develop alloantibodies (inhibitors) to FVIII treatments, typically within the first 10-15 days of treatment.[4,5] Inhibitors are classified as low titre (<5 Bethesda units [BU]/mL) or high titre (>5 BU/mL at least once) based on the highest documented inhibitor level and the occurrence of an anamnestic response after re-exposure to factor concentrate.[6] Among PwHA with inhibitors, therapeutic options have been more limited, particularly burdensome and suboptimally effective.[7-12] Current guidelines recommend immune tolerance induction (ITI) to eliminate high-titre inhibitors as first-line treatment in these individuals, which can enable effective replacement therapy and make prophylaxis feasible in order to prevent or lessen the negative impact of persistent inhibitors on patients' morbidity and quality of life.[13-18] However, ITI is associated with high costs, involves frequent, prolonged infusions and is not always effective.[19,20] Bleeding in PwHA with inhibitors requires bypassing agents (BPAs; ie, activated prothrombin complex concentrates, recombinant factor VIIa).[12]

Until recently, the only prophylaxis regimens for PwHA with inhibitors with acceptable outcomes required intravenous infusions of BPAs every other day, with dosing regimens varying from three times a week to daily in clinical practice.[10-12,21] Despite BPA prophylaxis, PwHA with inhibitors have significant breakthrough bleeding,[10,12] and often experience poor health-related quality of life (HRQoL), increased health care costs, joint pain and other orthopaedic issues, and missed days of work and school due to bleeding.[22-26]

Emicizumab (HEMLIBRA®; F. Hoffmann-La Roche, Basel, Switzerland) was developed to address the unmet needs of PwHA with inhibitors for effective, less burdensome prophylaxis. Emicizumab is a humanized bispecific antibody that bridges activated factor IX and factor X, restoring the function of missing activated FVIII and haemostasis even in the presence of FVIII inhibitors. High subcutaneous bioavailability[27] and a 4- to 5-week half-life[28] allow emicizumab to be administered subcutaneously once weekly.[29] Emicizumab has been approved in several countries for prophylaxis to prevent or reduce bleeding frequency in adult and paediatric PwHA with FVIII inhibitors.

In the HAVEN 1 Phase 3 clinical study of PwHA with inhibitors (NCT02622321), emicizumab prophylaxis was associated with statistically significant and clinically meaningful reductions in bleeding versus no prophylaxis. Annualized bleeding rate (95% confidence interval [CI]) for treated bleeds was 2.9 (1.7, 5.0) with emicizumab prophylaxis and 23.3 (12.3, 43.9) with no prophylaxis (episodic BPAs only); representing an 87% difference in favour of emicizumab prophylaxis (risk ratio: 0.13; $P < 0.001$).[29] Zero-treated bleeding events were experienced by 63% on emicizumab prophylaxis and 6% on no prophylaxis. In an intra-individual comparison among those previously using BPA prophylaxis in a prospective non-interventional study (NIS; NCT02476942), emicizumab prophylaxis resulted in a 79% decrease in bleeding rates ($P < 0.001$).[29]

The purpose of the present paper is to provide a detailed description of HRQoL and health status outcomes in PwHA with inhibitors in HAVEN 1.

2 | MATERIALS AND METHODS

HAVEN 1 was a multicentre, open-label, randomized, Phase 3 trial conducted in 43 centres in 14 countries worldwide. The protocol was approved by the institutional review board at each centre and adhered to Good Clinical Practice guidelines. The protocol for the HAVEN 1 clinical trial has been described previously[29] and is summarized briefly here and in Figure 1.

PwHA (any severity) with inhibitors aged ≥12 years were enrolled if they had a history of high-titre FVIII inhibitors (≥5 BU/mL), had received BPAs to treat or control bleeding for ≥24 weeks before study entry and, in the previous 24 weeks, had ≥6 bleeds while on episodic BPAs or ≥2 bleeds while on prophylactic BPAs.

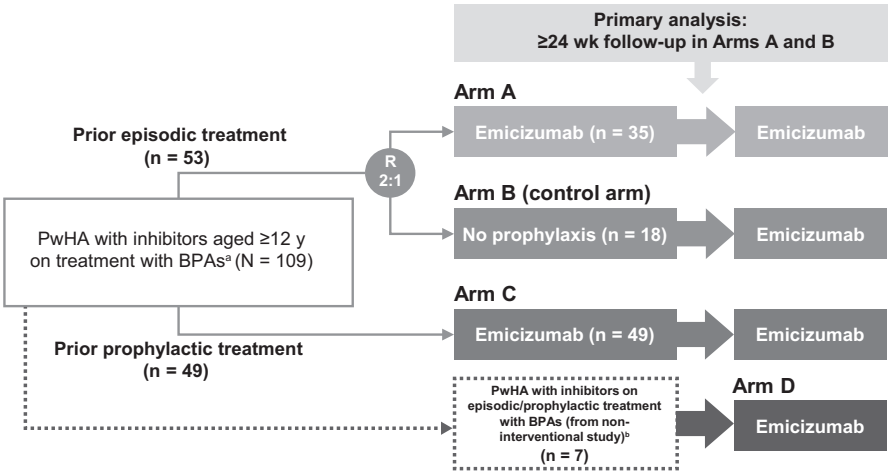

FIGURE 1 HAVEN 1 Study design. BPA, bypassing agent; PwHA, persons with haemophilia A; R, randomization. [a]Non-interventional study (NCT02476942) collected real-world data on bleed rates and standard-of-care treatments in PwHA with inhibitors; participants subsequently had the option to enrol into HAVEN 1. [b]Participants unable to enrol into Arms A, B or C before they closed to enrolment were enrolled in Arm D for compassionate reasons

Participants on episodic BPA treatment before study entry were randomized 2:1 to receive subcutaneous emicizumab prophylaxis (Arm A) or no prophylaxis (Arm B; only episodic BPAs allowed). Participants previously on prophylactic BPAs all received emicizumab prophylaxis (Arm C). Participants who had previously participated in the NIS, but were unable to enrol into Arms A, B or C before enrolment closed, received emicizumab prophylaxis in Arm D (Figure 1). The results for Arm D are not included in the present report because there were too few participants (n = 7) for a meaningful analysis of their outcomes.

Emicizumab prophylaxis was administered at 3.0 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly.

2.1 | Outcome measures

2.1.1 | Quality of life

Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)

The Haem-A-QoL is a validated, haemophilia-specific instrument for evaluating HRQoL in PwHA aged ≥18 years.[30-32] This 46-item measure consists of 10 domains ("Physical Health," "Feelings," "View of Yourself," "Sports & Leisure," "Work & School," "Dealing with Haemophilia," "Treatment," "Future," "Family Planning" and "Partnerships & Sexuality"), each scored separately and combined to create a "Total" score. Response options range from "Never" (1) to "All of the time" (5) on a 5-point Likert scale, with an additional "Not applicable" option available for "Sports & Leisure," "Family Planning" and "Work & School." In order to score all responses in the same direction, some items of the domains "View of Yourself," "Sports & Leisure," "Work & School," "Dealing with Haemophilia," "Treatment" and "Future" were reverse-scored.

Haemophilia-specific Quality of Life assessment for children and adolescents Short Form (Haemo-QoL SF)

The Haemo-QoL SF is a validated, haemophilia-specific instrument for evaluating HRQoL in PwHA in two age groups (I: 4-7 years; II: 8-17 years).[33] The 35-item measure for age group II is composed of nine domains ("Physical Health," "Feelings," "View of Yourself," "Family," "Friends," "Other People," "Sports & School," "Dealing with Haemophilia" and "Treatment"), each scored separately and combined to create a "Total" score. Response options ranged from "Never" (1) to "Always" (5) on a 5-point Likert scale. Some items of the domains "View of Yourself", "Friends," "Sports & School" and "Dealing with Haemophilia" were reverse-scored as above.

For both Haem-A-QoL and Haemo-QoL SF scales, participants were asked to consider their experience in the previous 4 weeks when responding. On both scales, all domain scores were transformed to a 0-100 scale with higher scores indicating greater impairment.

2.1.2 | Health status

Health status was assessed using the European Quality of Life 5-Dimensions 5-levels (EQ-5D-5L) questionnaire and visual analogue scale (EQ-VAS).[34,35] The five dimensions of the EQ-5D-5L assess mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each with five levels of severity ranging from "no problems" to "extreme problems".[35,36] The five dimensions were combined into an index utility score (IUS) using the UK crosswalk value set; scores range from −0.594 (extreme problems on all dimensions) to 1 (no problems on all dimensions).[37] On the EQ-VAS, participants indicated their health status on a thermometer ranging from 0 (worst imaginable) to 100 (best imaginable). For both EQ-5D-5L and EQ-VAS, participants were asked to report the severity experienced on the day the questionnaire was completed.

2.1.3 | Work and school absences

Every 4 weeks, participants were asked to report how many days of work or school they missed during the previous 4 weeks due to haemophilia A, and how many days they should have been at work or school.

2.1.4 | Hospitalizations

Hospitalizations were recorded in the serious adverse events page of the electronic case report forms (eCRFs) by investigators.

TABLE 1 Participant demographics and baseline characteristics[29]

Characteristic	Previously on episodic BPAs[a]		Previously on prophylactic BPAs[a]
	Arm A: Emicizumab prophylaxis (n = 35)	Arm B: No prophylaxis (n = 18)	Arm C: Emicizumab prophylaxis (n = 49)
Median age, y (range)	38.0 (12-68)	35.5 (13-65)	17.0 (12-75)
Age groups			
<18 y, n (%)	4 (11.4)	2 (11.1)	26 (53.1)
≥18 y, n (%)	31 (88.6)	16 (88.9)	23 (46.9)
Race, n (%)			
Asian	10 (28.6)	3 (16.7)	8 (1.36)
Black or African American	4 (11.4)	4 (22.2)	3 (6.1)
White	21 (60.0)	10 (55.6)	33 (67.3)
Other[b]	0 (0.0)	1 (5.6)	5 (10.2)
Bleeding events in previous 24 wk, n (%)			
<9	11 (31.4)	5 (27.8)	23 (46.9)
≥9	24 (68.6)	13 (72.2)	26 (53.1)
Severe haemophilia at baseline, n (%)	31 (88.6)	18 (100.0)	47 (95.9)
Previously treated with ITI, n (%)	14 (40.0)	7 (38.9)	33 (67.3)
Highest historical inhibitor titre levels,[c] median BU (range)	288.9 (5-1570)	706.8 (18-4500)	815.7 (11-5000)

BPA, bypassing agents, bypassing agent; BU, Bethesda units; ITI, immune tolerance induction.
[a]Includes prothrombin complex concentrate, recombinant factor VIIa and factor VIII.
[b]Includes Native American, Alaskan Native, Native Hawaiian, other Pacific Islanders and unknown.
[c]No participants under 5 BU.

2.2 | Data collection and analysis

All outcomes, except for hospitalizations, were recorded by participants using an electronic, handheld device provided during the week 1 visit and before administration of study medication. Participants were asked to record all HRQoL and health status outcomes every 4 weeks. In addition to scheduled assessments, they were asked to complete the EQ-5D-5L on any day during which bleeding occurred.

Demographic data, medical history and hospitalizations were collected from participants' medical records on an eCRF by clinicians. Analysis of covariance (model included treatment group, baseline score and the treatment-by-baseline interaction term as covariates) was used to compare the adjusted mean scores for Haem-A-QoL "Physical Health" and "Total" score and the EQ-5D-5L IUS and EQ-VAS between Arms A and B which were included as type 1 error-controlled secondary endpoints. The analysis of EQ-5D-5L IUS and EQ-VAS when a bleed occurred (unscheduled assessments) as compared with when no bleed occurred (monthly scheduled assessments) only included participants who had at least one scheduled and one unscheduled assessment.

Cumulative distribution function (CDF) plots of the change from baseline to week 25 in Haem-A-QoL "Physical Health" domain and "Total" scores were calculated for Arms A and B.

The proportion of participants achieving an improvement at week 25 larger than a previously published responder threshold was calculated for Haem-A-QoL "Total" score (−7), Haem-A-QoL "Physical Health" score (−10), EQ-5D-5L IUS (+0.07) and EQ-VAS (+7).[38-41]

The rate of participant compliance with the completion of each questionnaire (Haem-A-QoL, Haemo-QoL SF and scheduled EQ-5L-5D) at each time point was calculated by dividing the number of questionnaires by the total number expected at that time.

All analyses were based on the data cut-off used for the primary analysis.[29]

3 | RESULTS

3.1 | Study population

The participant population for the HAVEN 1 study has been described previously[29] and is summarized briefly here. Participants previously receiving episodic BPAs were randomized 2:1 to emicizumab prophylaxis (Arm A, n = 35) or no prophylaxis (Arm B, n = 18; episodic BPAs only), and 49 participants previously receiving prophylactic BPAs received emicizumab prophylaxis in Arm C. Nearly all participants had severe haemophilia at diagnosis, and >50% in each treatment arm had experienced ≥9 bleeding events in the previous 24 weeks. Participants in Arm C were younger and had a higher rate of previous ITI than those in Arms A and B (Table 1).

TABLE 2 Haemophilia-related quality of life in adults. Mean Haem-A-QoL domain and total scores at baseline

Haem-A-QoL domain	Previously on episodic BPAs		Previously on prophylactic BPAs
	Arm A: Emicizumab prophylaxis n = 29 Mean score[a] (95% CI)	Arm B: No prophylaxis n = 16 Mean score[a] (95% CI)	Arm C: Emicizumab prophylaxis n = 21 Mean score[a] (95% CI)
Physical Health	52.4 (44.4, 60.4)	57.2 (46.1, 68.3)	59.5 (48.0, 71.1)
Feelings	36.9 (27.2, 46.5)	32.4 (18.0, 46.8)	47.9 (32.6, 63.2)
View of Yourself	45.3 (37.6, 53.1)	48.8 (38.7, 58.8)	52.1 (40.9, 63.4)
Sports & Leisure[b]	58.0 (45.4, 70.6)	66.9 (55.4, 78.4)	67.3 (47.8, 86.8)
Work & School[b]	36.7 (23.4, 49.9)	42.3 (31.2, 53.4)	50.3 (33.4, 67.1)
Dealing with Haemophilia	26.7 (19.2, 34.3)	21.9 (14.0, 29.8)	28.2 (14.7, 41.7)
Treatment	36.3 (26.6, 46.0)	45.7 (34.0, 57.4)	48.5 (37.5, 59.5)
Future	48.4 (38.7, 58.1)	55.3 (41.6, 69.0)	54.5 (44.0, 65.0)
Family Planning[b]	27.1 (9.5, 44.7)	44.9 (21.8, 68.0)	43.8 (9.7, 77.8)
Partnership & Sexuality	26.4 (12.6, 40.3)	15.6 (4.4, 26.8)	34.9 (19.2, 50.7)
Total score	41.1 (34.0, 48.3)	44.6 (36.7, 52.5)	49.4 (40.4, 58.4)

BPA, bypassing agents; CI, confidence limit; Haem-A-QoL; Haemophilia Quality of Life Questionnaire for Adults.
[a]Scales range from 0 (no impairment) to 100 (high impairment).
[b]Participants had the option to choose "not applicable" for these domains. At week 1, the number of respondents (n) for Arms A, B and C, respectively, was 20, 13 and 12 for "Sports & Leisure," 14, 11 and 8 for "Family Planning" and 20, 13 and 16 for "Work & School".

3.1.1 | Compliance

Compliance with completion of all questionnaires across all time points was ≥90% for all outcome measures in all treatment arms.

3.1.2 | Haemophilia-specific Quality of Life in adults (Haem-A-QoL)

Baseline mean Haem-A-QoL "Total" and domain scores are listed in Table 2.

Improvements in Haem-A-QoL domain and total scores with emicizumab prophylaxis were seen as early as week 5, maintained through week 25 and generally similar regardless of previous treatment regimen (Figure 2A and 3A). Among participants previously treated with episodic BPAs, the difference in adjusted mean scores between the emicizumab prophylaxis group (Arm A) and the no prophylaxis group (Arm B) at week 25 was statistically significant in favour of emicizumab for both "Total" (Δ = 14.01; 95% CI: 5.56, 22.45; $P = 0.0019$) and "Physical Health" domain (Δ = 21.55; 95% CI: 7.89, 35.22; $P = 0.0029$) scores.

Throughout the study, a greater proportion of participants in the emicizumab prophylaxis groups (Arms A and C) than the no prophylaxis group (Arm B) achieved an improvement from baseline exceeding responder thresholds[38] for "Total" (−7 points) and "Physical Health" domain (−10 points) scores (Figure S1A,B). In the cumulative distribution plots of change from baseline to week 25 for both the "Total" and "Physical Health" domain scores, there was a clear separation between Arms A and B throughout all potential levels of change (Figure 2B and 3B).

Emicizumab prophylaxis also produced notable improvements from baseline in other domains of the Haem-A-QoL (Table 3), and improvements were qualitatively similar regardless of previous treatment regimen. There was no notable change in the no prophylaxis group (Arm B) in "Total" or domain scores at any time during the study.

3.1.3 | Haemophilia-specific Quality of Life in adolescents (Haemo-QoL SF)

The impact of emicizumab prophylaxis on Haemo-QoL SF is only presented for those participants previously treated with prophylactic BPAs (Arm C) because too few adolescents completed this questionnaire in Arms A (n = 3) and B (n = 2) for meaningful analysis.

At baseline, mean (95% CI) Haemo-QoL SF "Total" score was 30.7 (24.3, 37.2). Improvements from baseline with emicizumab prophylaxis were seen in most domains of the Haemo-QoL SF and in the "Total" score (Table 4). Improvements were seen as early as week 5 and maintained through week 25.

3.1.4 | Health status

At baseline, mean (95% CI) EQ-VAS scores were 70.7 (63.6, 77.9), 76.3 (69.1, 83.5) and 75.8 (68.4, 83.2) in Arms A, B and C, respectively. Baseline mean (95% CI) EQ-5D-5L IUS scores were 0.72 (0.63, 0.81), 0.67 (0.52, 0.82) and 0.74 (0.67, 0.81) in Arms A, B and C, respectively. For some dimensions of the EQ-5D-5L (eg, anxiety), a considerable number of participants reported "never" having a

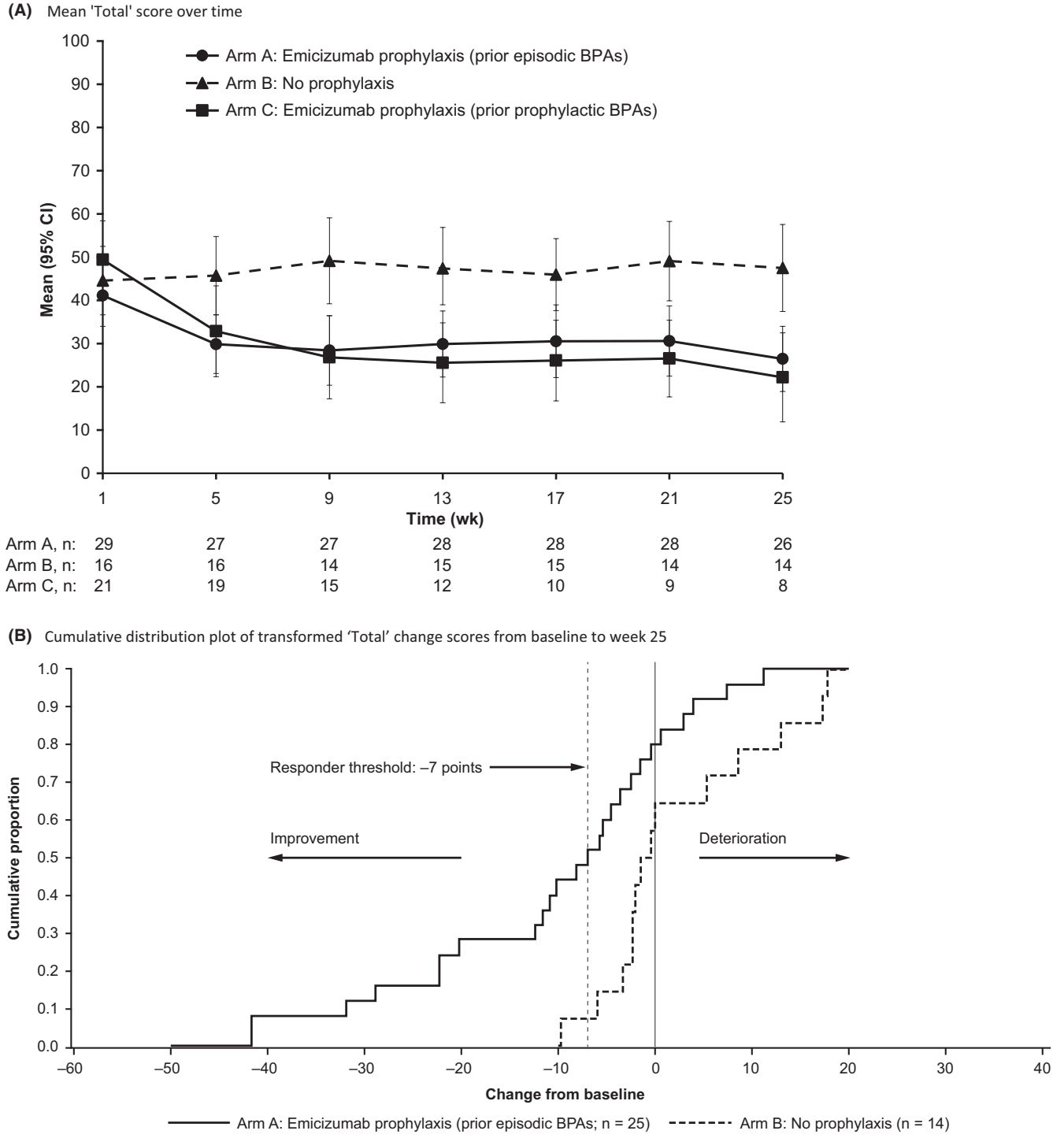

FIGURE 2 Haem-A-QoL (adults) "Total" score. Scale ranges from 0 (no impairment) to 100 (high impairment). BPA, bypassing agent; CI, confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; QW, once a week. A. Mean score over time. B. Cumulative distribution plot of transformed "Total" change scores from baseline to week 25

problem at baseline, and this may have limited the ability to detect an improvement in some items.

Improvements in EQ-VAS and EQ-5D-5L IUS with emicizumab prophylaxis were seen as early as week 5, maintained through week 25, and similar regardless of previous treatment regimen (Figure 4). In the no prophylaxis group (Arm B), EQ-VAS and EQ-5D-5L IUS scores remained near baseline levels or decreased slightly during the study.

Among participants previously treated with episodic BPAs, the difference in adjusted mean scores between the emicizumab prophylaxis group (Arm A) and the no prophylaxis group (Arm B) at week 25 was statistically significant in favour of emicizumab for both the EQ-VAS (Δ = −9.72; 95% CI: −17.6, −1.82; $P = 0.0171$) and IUS (Δ = −0.16, 95% CI: −0.25, −0.07; $P = 0.0014$). Throughout the study, a greater proportion of participants in the emicizumab prophylaxis groups

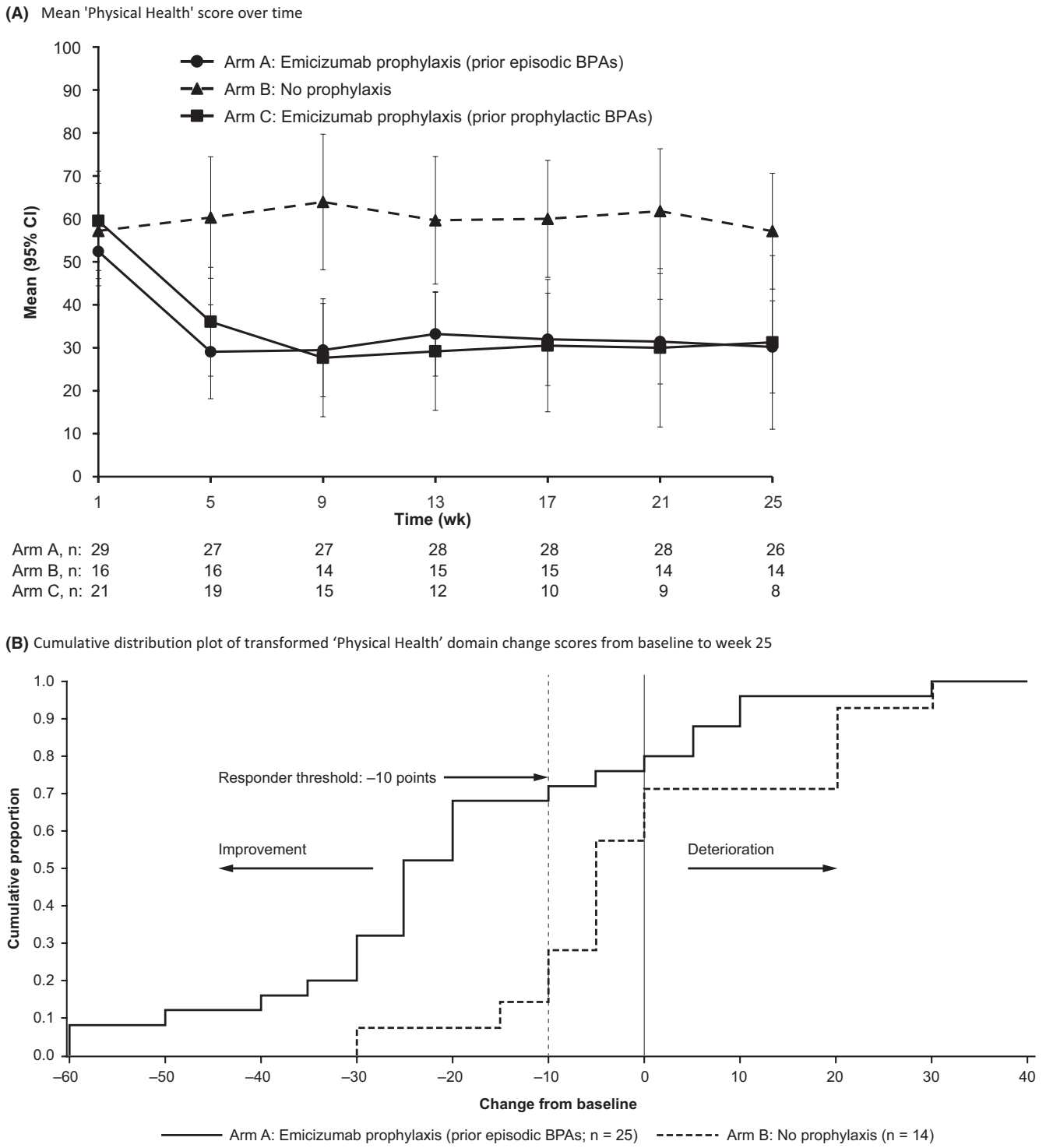

FIGURE 3 Haem-A-QoL (adults) Physical Health Domain score. Scale ranges from 0 (no impairment) to 100 (high impairment). BPA, bypassing agent; CI, confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; QW, once a week. A, Mean score over time. B, Cumulative distribution plot of transformed "Physical Health" domain change scores from baseline to week 25

(Arms A and C) than in the no prophylaxis group (Arm B) achieved an improvement exceeding responder thresholds (Figure S1C,D).[39,40]

Mean EQ-VAS and EQ-5D-5L IUS scores were generally lower (worse) on days when bleeding occurred than on regularly scheduled reporting days (Figure S2).

3.1.5 | Work/school absences and hospitalizations

The number of participants working before and during the study was 11 in the emicizumab prophylaxis group (Arm A) and 7 in the no prophylaxis group (Arm B). In the 4 weeks before study entry, the

TABLE 3 Effect of emicizumab prophylaxis on haemophilia-related quality of life in adults. Mean change from baseline to week 25 in Haem-A-QoL domain and total scores[a]

Domain	Previously on episodic BPAs		Previously on prophylactic BPAs
	Arm A: Emicizumab prophylaxis n = 25[b] Mean Δ (95% CI)	Arm B: No prophylaxis n = 14[b] Mean Δ (95% CI)	Arm C: Emicizumab prophylaxis n = 8[b] Mean Δ (95% CI)
Physical Health[c]	−19.8 (−28.8, −10.8)	0.4 (−9.2, 9.9)	−15.0 (−36.2, 6.2)
Feelings	−14.8 (−25.9, −3.6)	6.7 (−1.2, 14.6)	−14.1 (−35.1, 7.0)
View of Yourself	−12.2 (−19.9, −4.6)	2.5 (−6.0, 11.0)	−6.3 (−21.0, −8.5)
Sports & leisure[c,d]	−9.8 (−21.6, 2.0)	2.1 (−5.7, 9.8)	−40.8 (−115.6, 33.9)
Work & School[d]	−13.1 (−20.8, −5.3)	8.3 (−9.8, 26.5)	−21.9 (−46.3, 2.6)
Dealing with Haemophilia	−4.0 (−11.7, 3.7)	8.3 (−2.0, 18.7)	−20.8 (−35.7, −5.9)
Treatment	−9.3 (−16.5, −2.0)	2.2 (−4.6, 9.1)	−24.6 (−50.1, 0.9)
Future	−13.8 (−23.6, −4.0)	−2.5 (−15.3, 10.3)	−17.5 (−36.1, 1.1)
Family Planning[d]	10.9 (−4.6, 26.3)	−3.1 (−16.5, 10.3)	−43.8 (NE)[e]
Partnerships & Sexuality	−2.3 (−12.6, 8.0)	3.6 (−5.4, 12.6)	−6.3 (−17.3, 4.8)
Total score[c]	−10.7 (−16.5, −4.8)	2.5 (−2.5, 7.4)	−16.4 (−33.4, 0.6)

BPA, bypassing agent; CI, confidence interval; Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; NE, not evaluable.
[a]Scales range from 0 (no impairment) to 100 (high impairment); negative values indicate an improvement from baseline.
[b]Only includes those participants with results at both baseline and week 25.
[c]Responder thresholds defined for "Physical Health" (−10), "Sports and Leisure" (−10) and "Total" score (−7).[38]
[d]Participants could choose "not applicable" for these domains. The number of participants with results at both baseline and week 25 in Arms A, B and C, respectively, was 15, 11 and 3 for "Sports & Leisure," 9, 8 and 1 for "Family Planning" and 15, 9 and 6 for "Work & School".
[e]Only 1 participant had results at both baseline and week 25.

mean proportion of missed work days (95% CI) was 5% (0%, 12%) in Arm A and 13% (2%, 25%) in Arm B. This remained essentially unchanged in both groups (7% [0%, 15%] and 14% [8%, 19%], respectively) during the study. For participants previously treated with prophylactic BPAs (Arm C), the mean proportion of missed work days (95% CI) decreased from 9% (0%, 23%) in 4 weeks before study entry to 3% (0%, 8%) during emicizumab prophylaxis.

Only four participants in Arms A and B (previously treated with episodic BPAs) were attending school during the study. Seventeen participants previously treated with prophylactic BPAs (Arm C) were attending school, and the mean proportion of missed school days (95% CI) was 28% (6%, 50%) during 4 weeks before study entry and 5% (0%, 11%) during emicizumab prophylaxis.

The mean (95% CI) number of days hospitalized was 1.9 (0.0, 5.1) with emicizumab prophylaxis (Arm A), 4.2 (0.0, 8.9) with no prophylaxis (Arm B) and 0.7 (0.0, 1.5) with emicizumab prophylaxis in participants previously treated with prophylactic BPAs (Arm C).

4 | DISCUSSION

The results of this analysis demonstrate that participants receiving once weekly emicizumab prophylaxis in HAVEN 1 experienced statistically significant and clinically meaningful improvements in haemophilia-specific QoL and overall health status. On all measures, improvements were seen as early as week 5 and maintained through week 25. Moreover, improvements from baseline were similar regardless of whether previous BPA use was episodic or prophylactic. These improvements with emicizumab were likely due to a combination of substantial reductions in bleeding, the low rate of mostly mild adverse events and the once weekly subcutaneous dosing regimen.[29]

TABLE 4 Effect of emicizumab prophylaxis on haemophilia-related quality of life in adolescents. Mean change from baseline to week 25 in Haemo-QoL SF domain and "Total" scores[a]

Domain	Previously on prophylactic BPAs
	Arm C: Emicizumab prophylaxis n = 13[b] Mean Δ (95% CI)
Physical Health	−24.5 (−32.8, −16.3)
Feelings	−3.9 (−13.4, 5.7)
View of Yourself	−12.0 (−25.1, 1.1)
Family	−15.9 (−31.0, −0.7)
Friends	12.2 (−3.8, 28.2)
Other People	−12.5 (−20.2, −4.8)
Sports & School	−21.2 (−34.0, −8.3)
Dealing with Haemophilia	−8.2 (−17.2, 0.9)
Treatment	−11.1 (−18.5, −3.6)
Total score	−11.4 (−16.6, −6.3)

BPA, bypassing agent; CI, confidence interval; Haem-A-QoL, Haemophilia-Specific Quality of Life Assessment for Children.
[a]Scales range from 0 (no impairment) to 100 (high impairment); negative values indicate an improvement from baseline.
[b]Only calculated for those participants with results at both baseline and week 25.

During emicizumab prophylaxis in HAVEN 1, mean Haem-A-QoL and Haemo-QoL SF "Total" and "Physical Health" domain scores improved from near the middle of the scale to below the lower third of the scale regardless of previous treatment regimen, suggesting a marked improvement in haemophilia-related QoL. Improvements seen in Haem-A-QoL "Work & School" and "Sports & Leisure" domains and the Haemo-QoL SF "Sports & School" domain, as well as the low rate of hospitalizations and work or school absences, suggest an overall improvement in the ability to engage in activities of daily life. This is supported by the high rate of participants achieving responder thresholds on Haem-A-QoL "Total" and "Physical Health" domain scores. Currently, there is no consensus on how changes in HRQoL outcomes should be interpreted, but the responder thresholds used in this study provide an estimate of notable improvements that, when combined with other findings, suggest meaningful improvements in participants' lives.[38] Further longitudinal assessments are needed, however, to quantify how the HRQoL changes observed with emicizumab prophylaxis correspond to real-life improvements.

In addition to improvements in HRQoL, emicizumab prophylaxis resulted in statistically significant improvements in overall health status as measured by the EQ-VAS and EQ-5D-5L IUS. As has been seen in other studies,[24,42] EQ-5D-5L IUS scores were generally

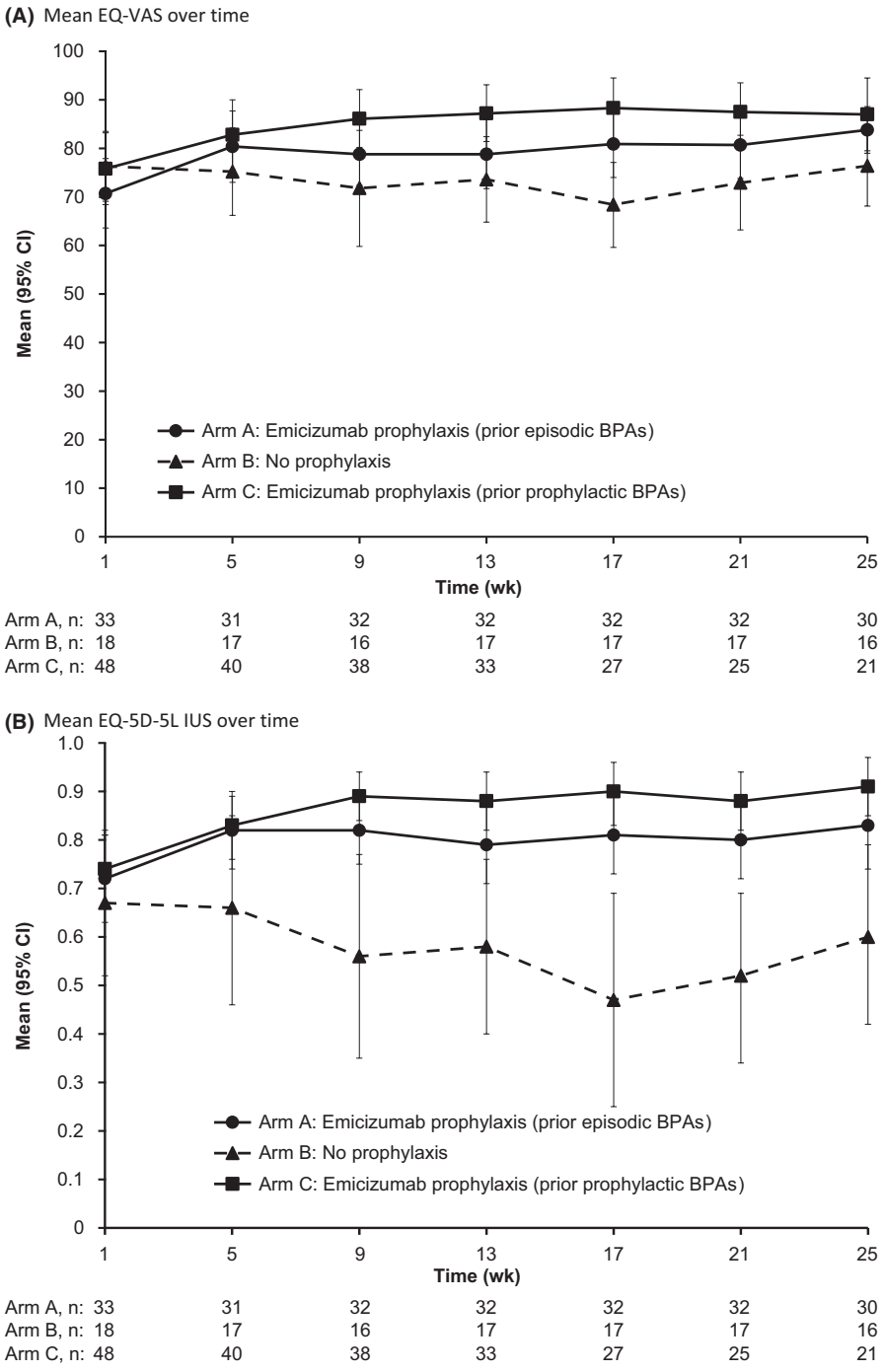

FIGURE 4 Health status as measured by the European Quality of Life 5-Dimensions 5-levels (EQ-5D-5L) visual analogue scale (EQ-VAS) and index utility score (IUS). On the EQ-VAS, scores ranged from 0 (worst imaginable) to 100 (best imaginable). On the IUS, scores ranged from −0.594 (extreme problems on all dimensions) to 1 (no problems on all dimensions). BPA, bypassing agent; CI, confidence interval. A, Mean EQ-VAS over time. B, Mean EQ-5D-5L IUS over time

worse on the days on which bleeding occurred than on regularly scheduled reporting days.

The strengths of this study include the use of psychometrically validated, haemophilia-specific and age-appropriate HRQoL instruments.[33,43] The inclusion of overall health status measures that are not disease-specific provides a valuable complement to the disease-specific outcomes. The separate analyses for participants on different previous treatment regimens are also a strength, providing insights on how switching to emicizumab prophylaxis affected outcomes for participants with different treatment histories. This study was limited by the small number of adolescents in Arms A and B, making it difficult to evaluate the impact of emicizumab prophylaxis versus no prophylaxis on HRQoL and school attendance in this age group.

5 | CONCLUSIONS

This analysis of HAVEN 1 demonstrates that the substantial reductions in bleeding seen with emicizumab prophylaxis[29] were accompanied by substantial and meaningful improvements in the daily lives of PwHA with inhibitors. Improvements in haemophilia-specific QoL and overall health status were apparent as early as the first assessment after the start of treatment and maintained throughout the study. Importantly, improvements among participants previously treated with prophylactic BPAs mirrored the improvements seen in participants previously on episodic BPAs. These findings suggest that emicizumab prophylaxis can help meet the needs of PwHA with inhibitors for effective, less burdensome prophylaxis.

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AUTHORS' CONTRIBUTIONS

PT, EA and JX contributed to study concept and design. Data analysis was conducted by EA, who vouches for the completeness and accuracy of the data and analyses. Specific direction from the authors (JO, JM, WB, PT, MC, GY, EA, FP, ES, RK-J, CN, CK, JX, JW, MS and SvM) informed the development of the first draft of the manuscript by Envision Pharma Group (funded by F. Hoffmann-La Roche Ltd). That draft was subsequently critically reviewed by all authors and revised according to their direction. All the authors had access to the data and confirm adherence to the protocol and statistical analysis plan during the conduct of the study.

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SUPPORTING INFORMATION

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

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