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Health-related quality of life and health status in adolescent and adult people with haemophilia A without factor VIII inhibitors—A non-interventional study

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Abstract

Introduction: Real-world data on health-related outcomes in persons with haemophilia A (PwHA) can provide useful information for improving patient care. The global, non-interventional study (NIS; NCT02476942) prospectively collected high-quality data in PwHA, including those without factor VIII (FVIII) inhibitors treated according to local routine clinical practice.

Aim: To report health-related quality of life (HRQoL) and health status of adult/adolescent PwHA without FVIII inhibitors.

Methods: Participants were PwHA without FVIII inhibitors age ≥12 years; they remained on existing episodic treatment or prophylaxis. HRQoL was assessed by Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) or Haemophilia-Specific Quality of Life Assessment for Children and Adolescents Short Form (Haemo-QoL-SF II). Health status was assessed through EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) index utility score and visual analogue scale (EQ-VAS).

Results: Ninety-four participants enrolled; median age was 34.0 years (range 12–76). Forty-five received episodic treatment and 49 received prophylaxis for a median time of 27.7 weeks and 30.4 weeks, respectively. Mean (standard deviation) baseline Haem-A-QoL total scores were 40.1 (17.0) for the episodic group and 26.6 (14.6) for the prophylaxis group, indicating impairments in HRQoL, which remained consistent over time. Mean EQ-5D-5L IUS scores were similar between treatment regimens (0.8 episodic; 0.9 prophylaxis) and consistent over time. The mean EQ-VAS scores were similar between treatment regimens, and lower on days when bleeding occurred (79.0 vs 85.0 for episodic treatment; 77.0 vs 82.0 for prophylaxis, respectively).

Conclusions: Adult and adolescent PwHA without FVIII inhibitors had HRQoL impairments regardless of whether they were treated with episodic or prophylactic standard care with FVIII.

KEYWORDS
factor VIII, haemophilia A, health-related quality of life, inhibitors, non-interventional study, real-world data

1 | INTRODUCTION

The hallmark of the severe form of the bleeding disorder, haemophilia, is spontaneous recurrent bleeds, particularly into joints, and related debilitating haemophilic arthropathy. This has a substantial impact on physical health and health-related quality of life (HRQoL) of affected individuals.[1–3]

Prophylaxis for haemophilia A can prevent bleeding events and complications, but is associated with a high treatment burden; intravenous infusions of factor VIII (FVIII) are required 2–4 times per week to maintain protective trough levels and achieve adequate haemostatic coverage.[4] Extended half-life FVIII therapies are available, although generally require multiple infusions per week for adequate prophylaxis and therefore treatment burden is not assuaged. Difficulty in adhering to treatment can lead to suboptimal care.[4] Clinical and subclinical bleeds are still possible even with regular FVIII prophylaxis.[5–8] Greater understanding of the real-world impact of the disease and treatment on HRQoL and health status in persons with haemophilia A (PwHA) could provide valuable insights into patient needs and help inform treatment decisions.[9]

The global, multicentre, non-interventional study (NIS; NCT02476942) prospectively collected high-quality real-world data in PwHA with or without FVIII inhibitors treated according to local routine clinical practice. The primary endpoint, annualized bleed rate (ABR) for treated bleeds, other bleeding-related endpoints, adverse events (AEs) and HRQoL from participants ≥12 years old with FVIII inhibitors have been published previously.[10,11]

Here, we report on HRQoL data from the non-inhibitor population of PwHA; safety and efficacy outcomes have been reported previously.[12] No protocol-specified therapeutic interventions were applied during the NIS; however, eligible participants without FVIII inhibitors could subsequently enrol in a phase 3 emicizumab study (HAVEN 3), enabling intra-individual comparisons of data obtained before and during emicizumab prophylaxis.[13] Emicizumab (HEMLIBRA®; F. Hoffman–La Roche, Basel, Switzerland) is a subcutaneously administered recombinant, humanized, bispecific monoclonal antibody that bridges activated FIX and FX to replace the function of missing activated FVIII and restore haemostasis.[14]

2 | MATERIALS AND METHODS

2.1 | Study setting and design

Participants were enrolled from 4 April 2016 through to 22 July 2016; the final participant completed the NIS on 31 March 2017. The study complied with the International Conference on Harmonisation Guidelines for Good Clinical Practice and principles of the Declaration of Helsinki, and was approved by local ethics committees of participating centres. Participants and/or their legally authorized representatives provided prior written informed consent (assent for ages 12–17 years).

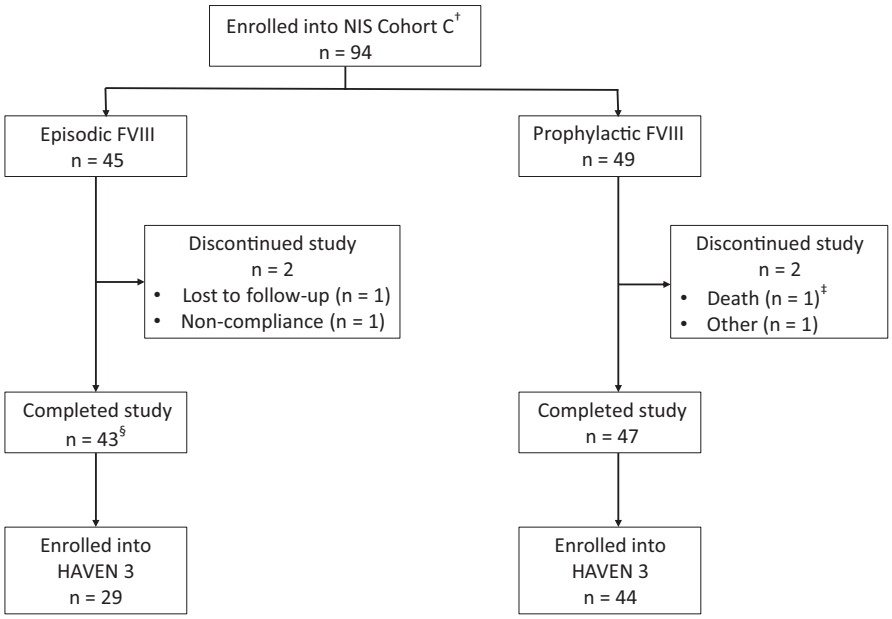

FIGURE 1 NIS Cohort C study design. †Cohort C included persons with haemophilia A without inhibitors against FVIII who were age ≥18 years or ages 12–17 years. ‡Cause of death was myocardial infarction. §Among the 43 participants in the episodic group who completed the NIS, three switched to prophylaxis during the efficacy period. FVIII, factor VIII; NIS, non-interventional study

The design of the NIS has been previously described.[11] Participants were enrolled in three cohorts. Cohort A included PwHA with FVIII inhibitors age ≥12 years, Cohort B included PwHA with FVIII inhibitors age <12 years and Cohort C included PwHA without FVIII inhibitors age ≥12 years.[10–12,15] Within each cohort, patients were categorized into either an episodic group or prophylactic group based on treatment received prior to study entry. Enrolled PwHA without FVIII inhibitors were followed for approximately 6 months, after which eligible participants could enrol in the interventional phase 3 emicizumab study, HAVEN 3 (NCT02847637; Figure 1).[13]

2.2 | Study participants

Key eligibility criteria included persons age ≥12 years with severe HA (FVIII activity <1%) without FVIII inhibitors, with recorded use of episodic or prophylactic FVIII for ≥150 days prior to study entry. Participants receiving episodic treatment must have had ≥5 bleeds in the preceding 6 months. Full eligibility criteria have been described in Kruse-Jarres et al.[12]

2.3 | Outcomes and assessments

All haemophilia-related assessments herein were conducted according to local routine clinical practice. Self-reported HRQoL was assessed using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) in persons age ≥18 years; and the Haemophilia-Specific Quality of Life Assessment for Children and Adolescents Short Form (Haemo-QoL-SF II) questionnaire for those ages 12–17 years.[16–18] Haem-A-QoL is a validated, 46-item questionnaire designed to assess HRQoL in adult PwH across 10 domains: 'Physical Health', 'Feelings', 'View of Yourself', 'Sports & Leisure', 'Work & School', 'Dealing with Haemophilia', 'Treatment', 'Future', 'Family Planning' and 'Partnership & Sexuality'.[19–22] The Haemo-QoL-SF II is a validated questionnaire for children and adolescent PwH ages 8–17 years.[17,18] It is composed of 35 items in nine domains: 'Physical Health', 'Feelings', 'View of Yourself', 'Family', 'Friends', 'Other People', 'Sports & School', 'Dealing with Haemophilia' and 'Treatment'. Scores for both questionnaires were transformed to a 0–100 scale, with higher scores reflecting greater HRQoL impairment.

Health status was assessed among all participants using the European Quality of Life 5 Dimensions 5 Levels version (EQ-5D-5L). 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.[23] These dimensions were combined into an index utility score (IUS) using the UK 'crosswalk' value set; scores ranged from −0.594 (extreme problems on all dimensions) to 1 (no problems on all dimensions).[24] Participants also provided an assessment of their general health using the EQ visual analogue scale (EQ-VAS). The EQ-VAS ranges from 0 to 100, where 0 is 'the worst health you can imagine' and 100 is 'the best health you can imagine'.[23]

2.4 | Data collection

Demographic data and medical history were collected from medical records on an electronic case report form (eCRF). Further details on data captured during this NIS have been previously published.[12]

The Haem-A-QoL or Haemo-QoL-SF II questionnaires assess the participants' perception across the preceding 4 weeks. Participants completed these questionnaires every 4 weeks from baseline until study completion (approximately 6 months in total).

Participants were asked to report their health status reflective of the day the EQ-5D-5L was completed. Participants completed the questionnaire every 4 weeks, and on days when bleeding occurred. The number of missed days of work/school was collected during the same clinic visit.

2.5 | Analyses

Analyses of HRQoL data were descriptive only. Summary statistics for the Haem-A-QoL and Haemo-QoL-SF II questionnaires and the EQ-5D-5L IUS and EQ-VAS were calculated at each scheduled assessment; no statistical testing was performed. The comparison of IUS and EQ-VAS at scheduled assessments vs unscheduled assessments (on a day when a bleed occurred) included only participants with at least one scheduled and one unscheduled assessment. The completion rates for HRQoL and health status were calculated by dividing the number of completed questionnaires by the number of those expected at each time point (determined from the number of eligible participants on-study). Completion rates for unscheduled EQ-5D-5L IUS and EQ-VAS were calculated as the number of unscheduled questionnaires completed, divided by the number of bleeding days. Further information on the methods has been published previously by Kruse-Jarres et al.[12]

3 | RESULTS

3.1 | Study population

A total of 94 participants were enrolled across 20 centres in 10 countries, of whom 45 received episodic treatment and 49 received prophylaxis (Figure 1).[12] Five participants switched from episodic to prophylactic treatment (standard half-life FVIII, n = 4; extended half-life FVIII, n = 1) during the efficacy period and were assigned to the episodic group for the purposes of data analysis. The median observation time and median efficacy period were 27.7 weeks (range 15.4–47.7) in the episodic group and 30.4 weeks (range 12.4–45.1) in the prophylactic group.

Eighty participants were adults and eligible to complete the Haem-A-QoL, including 37 receiving episodic treatment and 43 receiving prophylaxis. Fourteen participants were eligible to complete the Haemo-QoL-SF II, including eight receiving episodic treatment and six receiving prophylaxis.

The median age of participants receiving episodic treatment was 33.0 years (range 12–76), of which 82.2% were ≥18 years old. The median age of participants receiving prophylaxis was 35.0 (13–68), of which 87.8% were ≥18 years old (Table 1). The median (range) number of bleeds during the 6 months prior to study entry was 8.0 (5–32) among the patients receiving episodic treatment and 1.0 (0–13) among those receiving prophylaxis. The most common previous conditions were hepatitis C and human immunodeficiency virus infection, further details of which have been reported previously.[12]

3.2 | HRQoL in adults: Haem-A-QoL

The majority of adults completed the Haem-A-QoL at baseline (91.9% episodic, 95.3% prophylactic). Questionnaire completion rates remained above 75% throughout the study (Table S1). The variation of completion rates over time ranged between 91.9% and 75.7% for episodic treatment and between 95.3% and 76.7% with prophylaxis.

In participants receiving episodic treatment who completed the Haem-A-QoL at baseline (n = 34), the mean (95% confidence interval [CI]) Haem-A-QoL 'Total Score' was 40.1 (34.1–46.0). At week 25, the mean 'Total Score' was 42.3 (34.0–50.6) (n = 23). By contrast, participants receiving prophylaxis (n = 41) had a mean 'Total Score' of 26.6 (22.1–31.2) at baseline and 25.6 (20.0–31.2) at week 25 (n = 33) (Figure 2). Little variability in the scores for both treatment regimens was observed during the efficacy period through week 25, and the mean 'Total Score' per visit was consistently higher in participants receiving episodic treatment compared with participants receiving prophylaxis, indicating poorer HRQoL in the episodic group (Figure 3). The 'Physical Health' scores at baseline and week 25, respectively, were 50.1 (42.8–57.5) and 49.3 (39.1–59.6) for participants receiving episodic treatment and 27.9 (21.9–34.0) and 30.0 (22.1–37.9) for those receiving prophylaxis (Figure 3).

For participants in both groups, 'Sports & Leisure' and 'Future' were the most impacted domains (ie highest scores) at baseline. Regarding 'Sports & Leisure', 52.9% of participants receiving episodic treatment reported that they often/always refrain from sports that they like; this was true for fewer participants receiving prophylaxis, affecting 24.4% (Figure S1). Also, 38.3% of participants taking episodic treatment never/rarely did as much sport as others at baseline, whereas this affected 29.3% of participants taking prophylaxis. Regarding 'Future', 52.9% of participants receiving episodic treatments reported that they often/always had life plans influenced by haemophilia; fewer participants receiving prophylaxis reported this (31.7%; Figure S2). In participants receiving episodic treatment, 'Physical Health' was their third most impacted domain, with 52.9% who had often/always 'pain in their joints' at baseline and 35.3% who reported that their 'swellings hurt' (Figure S3), whereas those receiving prophylaxis reported higher impairments in the domain 'Treatment' at baseline: 80.5% felt often/always 'dependent on the factor concentrate' and 24.4% felt dependent on their physician (Figure S4). For all domains in both groups, differences between the responses at baseline and those at week 25 were not substantial (Figures S1–S4).

TABLE 1 NIS Cohort C participant characteristics

Characteristic	Episodic n = 45	Prophylaxis n = 49	All N = 94
Age			
Median (min–max) years	33.0 (12–76)	35.0 (13–68)	34.0 (12–76)
≥12 and <18 years, n (%)	8 (17.8)	6 (12.2)	14 (14.9)
≥18 years, n (%)	37 (82.2)	43 (87.8)	80 (85.1)
Race, n (%)			
White	16 (35.6)	37 (75.5)	53 (56.4)
Asian	13 (28.9)	9 (18.4)	22 (23.4)
Black/African American	6 (13.3)	1 (2.0)	7 (7.4)
Multiple race[a]	1 (2.2)	1 (2.0)	2 (2.1)
Unknown	9 (20.0)	1 (2.0)	10 (10.6)
Bleeds in previous 6 months[b]			
Participants, n	43[c]	32[d]	75
Mean (SD)	10.6 (7.5)	2.6 (3.7)	7.2 (7.3)
Median (min–max)	8.0 (5–32)	1.0 (0–13)	5.0 (0–32)

Abbreviations: max, maximum; min, minimum; NIS, non-interventional study; SD, standard deviation.

[a]More than one race selected.

[b]Collected from participant medical records and documented in an electronic case report form.

[c]Numbers of previous bleeds excluded for two participants: one with 13 bleeds but a history of a condition listed as 'unknown' and one with number of bleeds listed as unknown.

[d]A high proportion of participants on prophylaxis did not report number of bleeds in previous 6 months because it was not an inclusion criterion for this treatment group. one participant with zero bleeds excluded because history of condition listed as 'unknown.'

3.3 | HRQoL in adolescents: Haemo-QoL-SF II

Among participants ages <18 years, 75.0% receiving episodic treatment and 83.3% receiving prophylaxis completed the Haemo-QoL-SF II questionnaire at baseline; the overall completion rate varied across scheduled assessments between 75.0% and 37.5% for participants receiving episodic treatment and between 83.3% and 66.7% for those receiving prophylaxis (Table S1).

Among adolescents who completed the Haemo-QoL-SF II, the mean (95% CI) 'Total Score' was 31.4 (22.1–40.8) at baseline (n = 6) and 35.4 (25.5–45.2) at week 25 (n = 4) for participants receiving episodic treatment. For participants receiving prophylaxis, the scores at baseline (n = 5) and week 25 (n = 4) were 19.6 (8.0–31.1)

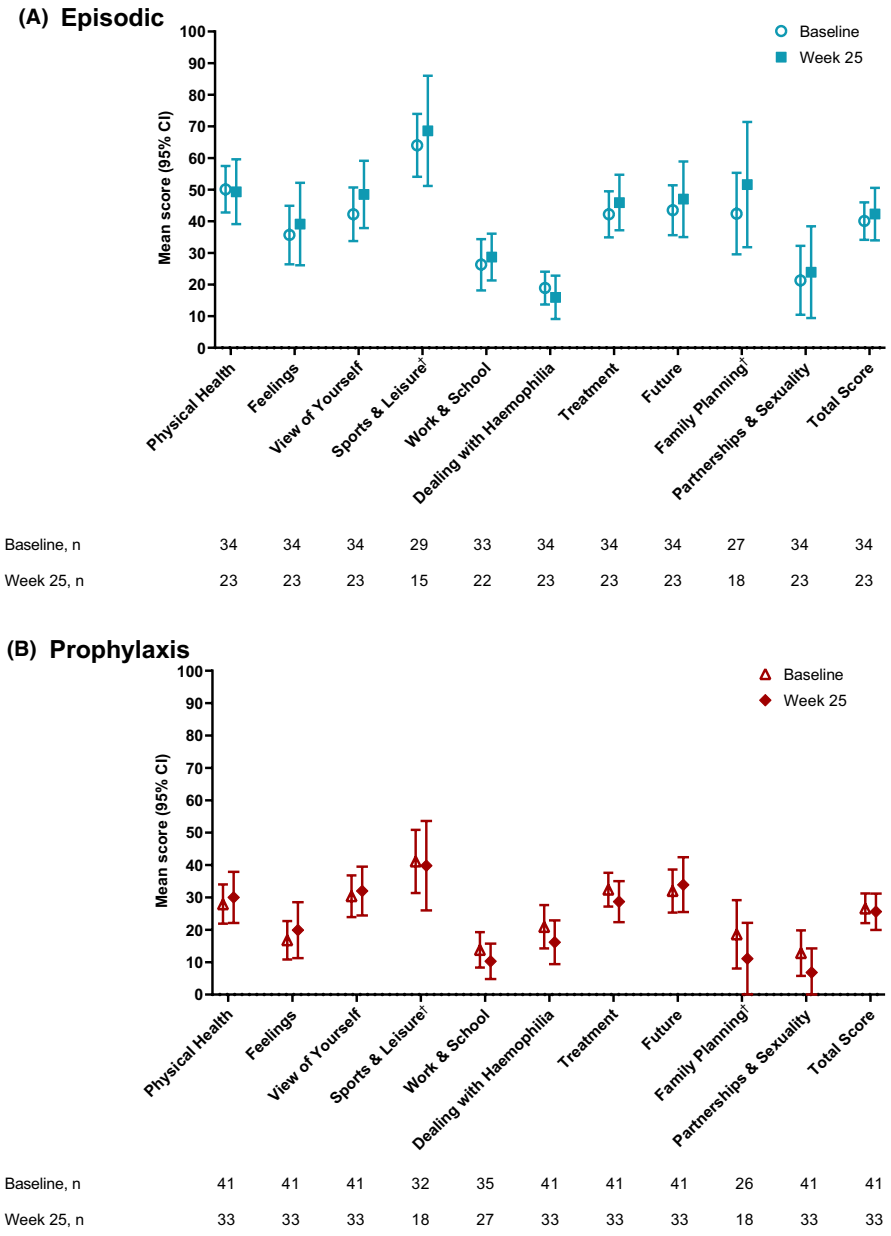

FIGURE 2 Haem-A-QoL domain and 'Total' scores for participants demonstrate impaired HRQoL across a range of domains in adult PwHA (≥18 years old) without FVIII inhibitors receiving episodic treatment (A) or prophylaxis (B). Scale ranges from 0 (no impairment) to 100 (high impairment). †Participants had the option to choose 'not applicable' for these domains. CI, confidence interval; FVIII, factor VIII; Haem-A-QoL, Haemophilia-specific Quality of Life Questionnaire for Adults; HRQoL, health-related quality of life; PwHA, persons with haemophilia A [Colour figure can be viewed at wileyonlinelibrary.com]

and 12.7 (0.0–37.9), respectively (Table 2). Similar to adult participants, mean 'Total Score' per visit was higher throughout the study in those taking episodic treatment, suggesting greater HRQoL impairment with episodic treatment, though there was greater variation in score between time points compared with scores in adults (Figure 4). The 'Physical Health' scores at baseline (n = 6) and week 25 (n = 4), respectively, were 21.9 (12.8–30.9) and 28.1 (4.5–51.8) for participants receiving episodic treatment. For participants receiving prophylaxis, the 'Physical Health' scores were 23.8 (0.0–53.0) at baseline (n = 5) and 26.6 (0.0–83.0) at week 25 (n = 4; Table 2). These mean (95% CI) scores varied across visits through week 25, but continued to be higher for the episodic group than for the prophylaxis group (Figure 4). For both treatment regimens, 'Sports & School' and 'Family' were the most impacted domains at baseline (n = 6, episodic; n = 5, prophylactic). Participants receiving episodic treatments reported 'Treatment' as their third most impacted domain, whereas those receiving prophylaxis reported 'Friends' within the top three most impacted domains. At week 25, the top three most impacted domains remained consistent for the episodic group, but had changed to 'Physical Health', 'Family' and 'Dealing with Haemophilia' for the prophylaxis group (n = 4, episodic; n = 4, prophylactic) (Table 2).

3.4 | Health status: EQ-5D-5L IUS and EQ-VAS

For health status, data from the adults and adolescents within each treatment regimen were pooled. The EQ-5D-5L completion rate was >91% at baseline assessment with both treatment regimens and remained >68% until the majority of the participants enrolled in HAVEN 3. At baseline, mean (SD) EQ-5D-5L IUS was 0.8 (0.1) for participants receiving episodic treatment (n = 41) and 0.9 (0.1)

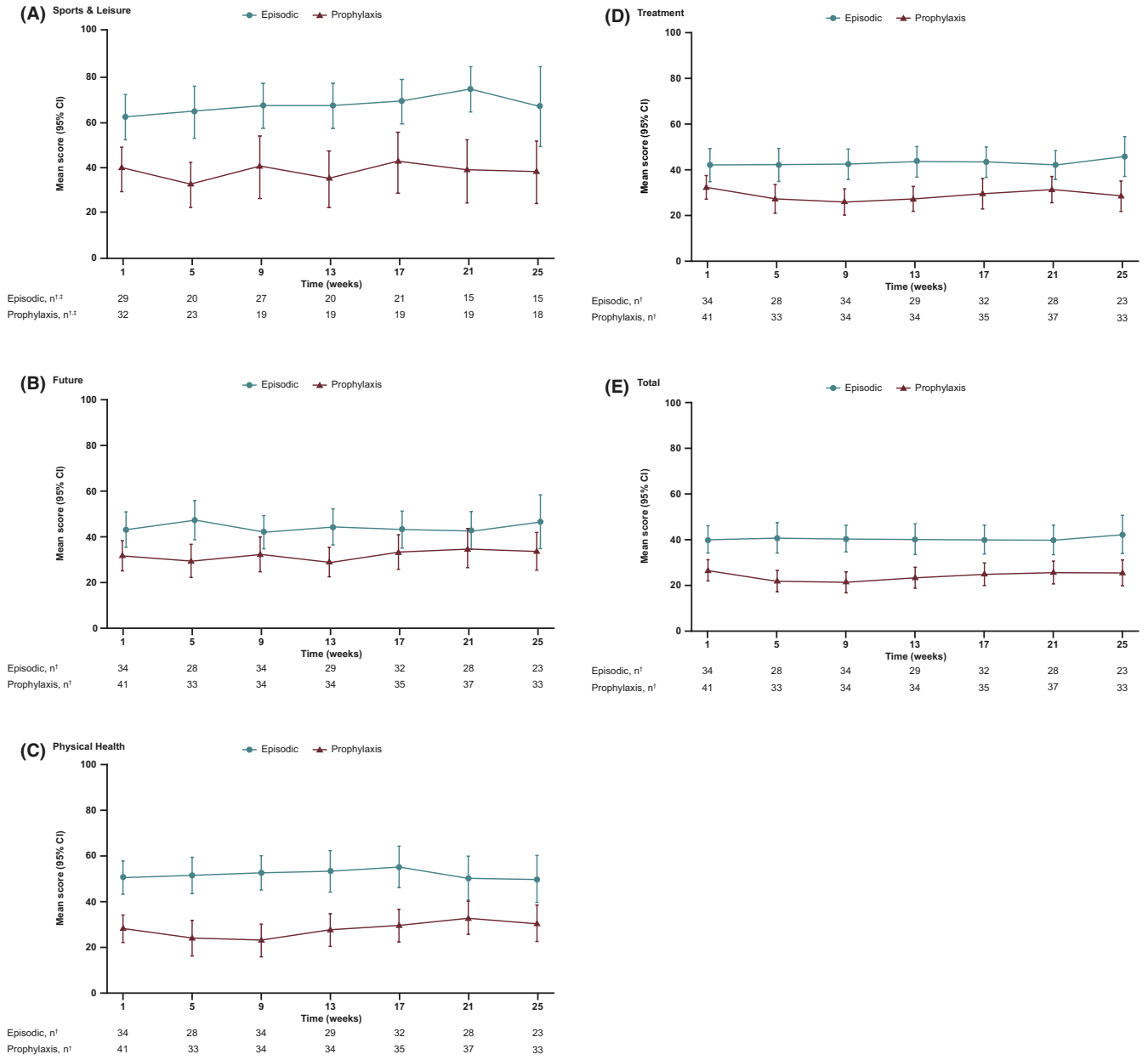

FIGURE 3 HRQoL over time in adult PwHA (≥18 years old) without FVIII inhibitors receiving episodic treatment or prophylaxis with FVIII according to usual clinical practice. Haem-A-QoL most impacted domains and 'Total Scores' over time. Scale ranges from 0 (no impairment) to 100 (high impairment). †Only participants age ≥18 years eligible to complete this questionnaire. ‡Participants had the option to choose 'not applicable' for the 'Sports & Leisure' domain. CI, confidence interval; FVIII, factor VIII; Haem-A-QoL, Haemophilia-Specific Quality of Life Questionnaire for Adults; HRQoL, health-related quality of life; PwHA, persons with haemophilia [Colour figure can be viewed at wileyonlinelibrary.com]

for prophylaxis (n = 47). The mean EQ-VAS score (higher score corresponds to better health status on a 0–100 scale) at baseline was 85.4 (11.3) for episodic treatment (n = 41) and 85.2 (15.1) for prophylaxis (n = 47), remaining at a consistent level across time through week 25 (Figure S5). Median EQ-VAS scores were lower on days in which bleeding occurred than on the regular scheduled reporting days (79.0 vs 85.0 for episodic treatment and 77.0 vs 82.0 for prophylaxis, respectively; Figure 5).

3.5 | Hospitalizations and work/school absences

Work absenteeism was assessed in 73 participants: 33 treated episodically and 40 receiving prophylaxis. The mean (SD) proportion of missed-to-expected workdays was 0.10 (0.2) for episodic treatment and 0.03 (0.2) for prophylaxis. Those receiving episodic FVIII had a higher mean number of days away from work compared with those receiving prophylaxis (8.4 vs 1.2 days, respectively).

TABLE 2 Haemo-QoL-SF II scores demonstrate impaired HRQoL across a range of domains in adolescent PwHA (12–17 years old) without FVIII inhibitors

	Episodic		Prophylaxis	
Domain	**Baseline (n = 6)**	**Week 25 (n = 4)**	**Baseline (n = 5)**	**Week 25 (n = 4)**
Physical Health, mean (95% CI)	21.9 (12.8–30.9)	28.1 (4.5–51.8)	23.8 (0.0–53.0)	26.6 (0.0–83.0)
Feelings, mean (95% CI)	21.9 (0.0–48.0)	26.6 (0.0–57.4)	11.3 (0.0–25.1)	7.8 (0.0–32.7)
View of Yourself, mean (95% CI)	26.0 (0.0–54.9)	26.6 (4.5–48.6)	13.8 (0.0–28.7)	4.7 (0.0–14.2)
Family, mean (95% CI)	50.0 (23.4–76.6)	54.7 (23.9–85.5)	33.8 (0.0–71.6)	23.4 (0.0–85.5)
Friends, mean (95% CI)	26.4 (0.0–67.6)	22.9 (0.0–62.5)	36.7 (21.0–52.4)	6.3 (0.0–26.1)
Other People, mean (95% CI)	12.5 (1.5–23.5)	34.4 (15.3–53.4)	7.5 (0.0–16.0)	4.7 (0.0–19.6)
Sports and School, mean (95% CI)	52.1 (24.1–80.1)	64.1 (39.2–88.93)	36.3 (11.5–61.0)	12.5 (0.0–35.5)
Dealing with Haemophilia, mean (95% CI)	34.4 (0.0–73.2)	21.9 (4.7–39.1)	6.3 (0.0–19.7)	14.1 (0.0–40.2)
Treatment, mean (95% CI)	36.5 (14.0–59.0)	35.9 (0.0–79.2)	11.3 (0.0–27.2)	12.5 (0.0–40.6)
Total Score, mean (95% CI)	31.4 (22.1–40.8)	35.4 (25.5–45.2)	19.6 (8.0–31.1)	12.7 (0.0–37.9)

Note: Haemo-QoL-SF II domain scores and 'Total Scores' for participants receiving episodic or prophylactic treatment. Scale ranges from 0 (no impairment) to 100 (high impairment).

Abbreviations: CI, confidence interval; FVIII, factor VIII; Haemo-QoL-SF II, Haemophilia-Specific Quality of Life Assessment for Children Short Form; HRQoL, health-related quality of life; PwHA, persons with haemophilia A.

Additionally, 23 participants receiving episodic treatment and 25 participants receiving prophylaxis were enrolled in school. The mean (SD) proportion of missed school days was 0.16 (0.3) for the episodic and 0.03 (0.1) for prophylaxis. Those receiving episodic FVIII had a higher mean number of days away from school during the efficacy period compared with those receiving prophylaxis (7.8 vs 1.9 days, respectively).

4 | DISCUSSION

In this real-world setting with treatment according to local routine clinical practice, PwHA without FVIII inhibitors age ≥12 years experienced impairments in both HRQoL and overall health status despite their prophylactic use of standard FVIII.

The Haem-A-QoL is a frequently utilized instrument for evaluating HRQoL in adult PwH, as it specifically addresses haemophilia-related factors.[25,26] Because of the high impact of haemophilia on a person's physical activities, the 'Physical Health' domain is a particularly important facet of the Haem-A-QoL when measuring haemophilia interference with HRQoL; a 10-point reduction in this domain is considered a threshold for notable improvement in HRQoL in PwH.[27] In general, PwHA receiving episodic treatment had notably poorer 'Physical Health' scores than those receiving prophylaxis. The 'Physical Health' scores at baseline and week 25, respectively, were 50.1 (42.8–57.5) and 49.3 (39.1–59.6) for participants receiving episodic treatment and 27.9 (21.9–34.0) and 30.0 (22.1–37.9) for those receiving prophylaxis. These data trends are consistent with other reports of HRQoL in participants receiving episodic or prophylactic therapy.[28–30] This can be attributed to diminished control of bleeding; previously published bleed data for this cohort showed a negative binomial regression model-based ABR (95% CI) of 36.1 (30.8–42.3) treated bleeds for episodic treatment and 5.0 (3.3–7.5) for prophylactic treatment.[12]

These data trends are consistent with those reported in a systematic literature review evaluating the effects of prophylaxis on HRQoL in prospective clinical trials in PwHA or haemophilia B.[29] Out of 13 included trials, the majority showed an improvement in HRQoL (six significantly, four non-significantly) with prophylaxis compared with episodic treatment, mirroring the results found in this study.[29] Moreover, of the four trials which administered the Haem-A-QoL, all indicated a greater improvement in participants who previously received on-demand treatment and initiated prophylaxis during the clinical trial; these effects were most pronounced in the 'Physical Health' domain,[29] in agreement with the results reported in this manuscript.

A different result was observed in participants with FVIII inhibitors (Cohort A), in which no clear difference in HRQoL was seen between participants on episodic treatment or prophylaxis. For example, among participants who completed the Haem-A-QoL at baseline, mean (SD) Haem-A-QoL 'Physical Health' score was 53.1 (24.5) in the episodic group (n = 52) and 48.5 (19.8) in the prophylaxis group (n = 14),[10] reflecting, despite the strong impact of FVIII inhibitors on HRQoL in general, the high treatment burden and unsatisfactory bleed control of bypassing agent (BPA) prophylaxis.

Mean Haem-A-QoL scores were consistent across the 25 weeks analysed. The low variation was as expected given the stable nature of the disease and absence of new interventional treatment in this study. In contrast, Haemo-QoL-SF II scores varied over time; however, the results should be interpreted with caution due to the small number of adolescents in this study.

A potential limitation of the NIS is the required bleed incidence of ≥5 bleeds during the 6 months prior to study entry for patients on episodic treatment and therefore the results reflect HRQoL experiences of individuals with regular bleeding phenotypes. Additionally, NIS investigators may have selected participants with significant

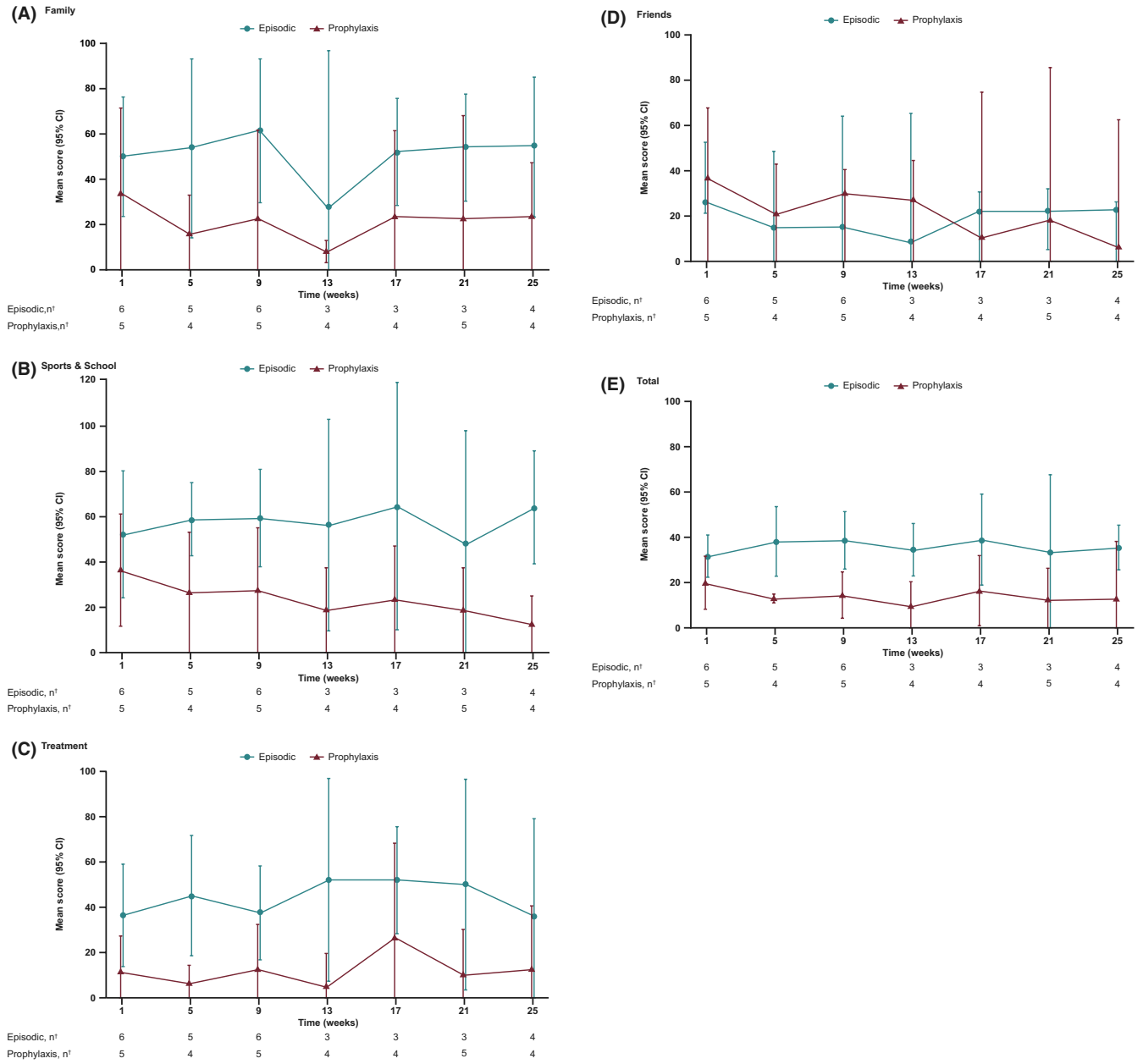

FIGURE 4 HRQoL over time in adolescent PwHA (12–17 years old) without FVIII inhibitors receiving episodic treatment or prophylaxis with FVIII according to usual clinical practice. Haemo-QoL-SF II most impacted domains and 'Total Scores' over time. Scales range from 0 (no impairment) to 100 (high impairment). †Only participants' ages 12–17 years were eligible to complete this questionnaire. CI, confidence interval; FVIII, factor VIII; Haemo-QoL-SF II, Haemophilia-specific Quality of Life Questionnaire for Children Short Form; HRQoL, health-related quality of life; PwHA, persons with haemophilia A [Colour figure can be viewed at wileyonlinelibrary.com]

bleeding on FVIII who would benefit more from emicizumab therapy in HAVEN 3.

Assessment of the most impacted domains may assist in identifying key factors that could be improved to ameliorate the HRQoL of PwHA. 'Sports & Leisure' and 'Sports & School' were among the most impacted domains in adults and adolescents, respectively, regardless of treatment regimen. This highlights that being unable to participate in physical activities may represent a significant burden on the HRQoL of PwHA. Adults receiving prophylaxis indicated 'Treatment' as one of their most impacted domains, highlighting that although the frequent intravenous administration of factor replacement therapy lowers ABR, it may also diminish HRQoL. Less frequent administration of a subcutaneous treatment such as emicizumab could alleviate this.

Impairments in health status were similar between the episodic and prophylactic treatment groups. Episodically treated participants, however, rated their health status lower on days when they had a bleed compared with days without. Impaired HRQoL had an impact on daily activities such as work or school, reflected by the fact that those on episodic FVIII—with reported higher HRQoL

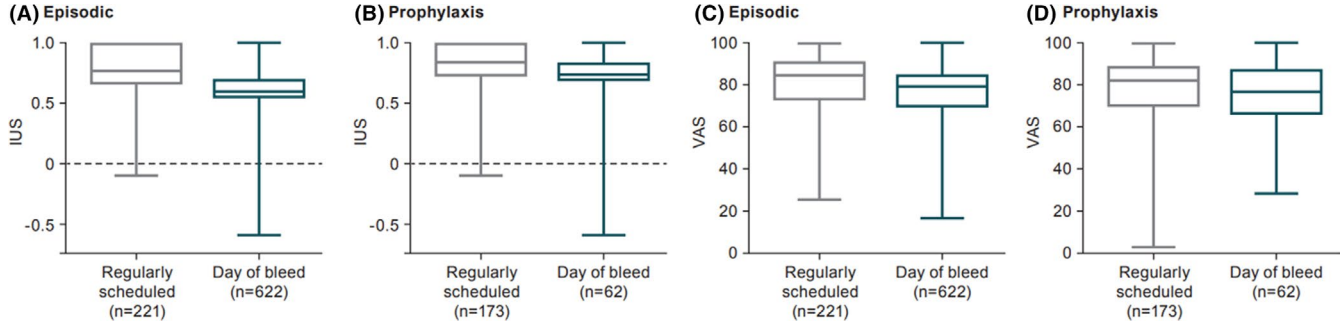

FIGURE 5 Effect of bleeding on health status of PwHA without FVIII inhibitors: A comparison of EQ-5D-5L IUS (A, B) and EQ-VAS (C, D) scores from regularly scheduled appointments vs those from days with bleeds. Box plot depicts median IUS or VAS score, with lower and upper quartiles, and overall minimum/maximum scores; n refers to the total number of EQ-5D-5L or EQ-VAS questionnaires completed during the study. EQ-5D-5L, European Quality of Life 5 Dimensions 5 Levels version; EQ-VAS, visual analogue scale of the EQ-5D; FVIII, factor VIII; IUS, index utility score; PwHA, persons with haemophilia A [Colour figure can be viewed at wileyonlinelibrary.com]

impairment—missed more days of work (8.4 vs 1.2 days) or school (7.8 vs 1.9 days) than those on prophylactic FVIII.

5 | CONCLUSION

Adult and adolescent PwHA without FVIII inhibitors experience impairments in HRQoL regardless of whether they are treated episodically or prophylactically with FVIII, as has been previously demonstrated for those with FVIII inhibitors primarily taking BPAs. This highlights an unmet need for a treatment that reduces the burden of PwHA without FVIII inhibitors.

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DISCLOSURE

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AUTHOR CONTRIBUTIONS

ML and PT contributed to the study concept, design and data interpretation. Data analysis and interpretation were conducted by the trial statistician (SC), who vouches for the completeness and accuracy of the data and analyses. JO, HT, FP, RN, JNM and VJ-Y contributed to data collection and interpretation, and SvM contributed to the 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).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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