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Health-related quality of life and caregiver burden of emicizumab in children with haemophilia A and factor VIII inhibitors—Results from the HAVEN 2 study

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Abstract

Introduction: Persons with haemophilia A (PwHA) with factor (F)VIII inhibitors, including children, have impaired health-related quality of life (HRQoL). The HAVEN 2 study (NCT027955767) of paediatric PwHA with FVIII inhibitors demonstrated that subcutaneous emicizumab prophylaxis resulted in low annualizedbleed rates.

Aim: We assessed the impact of emicizumab prophylaxis on the HRQoL of children and their caregivers participating in HAVEN 2.

Methods: Children aged 8-11 years self-reported HRQoL using the Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form (Haemo-QoL SF II). Caregivers of children aged 0-11 years completed the Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden. All scores were transformed to a 0-100 scale, where lower scores reflect a better HRQoL. The number of missed days from school/day care and hospitalizations was also recorded.

Results: In HAVEN 2 (n = 88), the median age was 6.5 years (range: 1-15 years); 85 participants were aged < 12 years and included in this analysis, and 34 participants were aged 8-11 years, thereby eligible to complete the Haemo-QoL SF II questionnaire. The mean (standard deviation, n) baseline Haemo-QoL SF II 'Total' score was 30.2 (14.9, 30), indicating moderate impairment; with emicizumab, mean score decreased by −9.62 (7.73, 17) points to 23.0 (13.93, 20) by Week 49. The most improved domains were 'Sports & School' and 'Physical Health'. Caregivers reported similar improvements.

Conclusion: Prophylactic emicizumab is accompanied by substantial and sustained improvements in HRQoL of paediatric PwHA with FVIII inhibitors and their caregivers.

KEYWORDS
caregiver burden, children, emicizumab, haemophilia, health-related quality of life, inhibitors

1 | INTRODUCTION

Haemophilia A (HA), a congenital bleeding disorder characterized by deficiency of coagulation protein factor (F)VIII, has a negative impact on the health-related quality of life (HRQoL) of affected people.[1-3] A clinical hallmark of severe HA is recurrent spontaneous bleeds, particularly into joints, and a substantial corresponding impact on physical health and HRQoL.[4-8]

Approximately 30% of previously untreated persons with haemophilia A (PwHA) develop one of the most challenging complications of haemophilia treatment: neutralizing alloantibodies (inhibitors) against FVIII,[9-11] preventing effective FVIII prophylaxis.[12,13]

Standard treatment for PwHA with FVIII inhibitors is bypassing agents (BPAs); however, their haemostatic effects are suboptimal and unpredictable, and their use is further burdened by the need for frequent intravenous injections over prolonged periods of time.[14-16] As a result of these complex disease- and treatment-related burdens, PwHA with FVIII inhibitors have worse HRQoL as compared with those without FVIII inhibitors.[17,18] Previous analyses using haemophilia-specific HRQoL questionnaires have shown that PwHA with FVIII inhibitors experience impairments in HRQoL across a range of domains assessing both physical and psychosocial functioning.[19] This is a particular concern in children, for whom full integration into a 'normal' social life can depend on good physical health.[18]

Not only does HA affect the lives of PwHA, it also places burden on their caregivers and families, particularly for those of younger patients. Caregivers report burden from emotional stress associated with the disease, problems associated with treatment administration, and difficultly dealing with the pain their child is going through. Furthermore, caregivers of children with FVIII inhibitors were found to be significantly more burdened than caregivers of children without FVIII inhibitors. The burden of caregivers is an important aspect to consider when assessing the management of PwHA.[19-24]

Emicizumab, a bispecific, humanized, monoclonal antibody, bridges activated FIX and FX, thereby restoring the function of missing activated FVIII in PwHA.[25] It is approved for the prophylaxis of PwHA of all ages both with and without FVIII inhibitors in the United States, EU and other countries worldwide.[26,27] Emicizumab, the first approved subcutaneous (SC) prophylactic therapy for HA, can be administered weekly (QW), every 2 weeks (Q2W) or every 4 weeks (Q4W).[28,29] HAVEN 2 is the largest prospective bleed prevention study in children with HA with FVIII inhibitors. Primary analyses demonstrated that QW SC emicizumab prophylaxis resulted in a very low bleeding rate (annualized bleeding rate [ABR] 0.3 [95% confidence interval [CI], 0.17-0.50]), with 77% of participants having no treated bleeding events.[30] Similar bleeding rates were reported for participants receiving Q2W and Q4W treatment. Remarkably, 100% of all pre-existing target joints resolved during the study period.[30] Furthermore, an intra-individual comparison demonstrated a 99% reduction in ABR with emicizumab versus BPA prophylaxis in a preceding non-interventional study.[31]

Here, we report the impact of emicizumab prophylaxis on HRQoL outcomes in paediatric participants and associated caregiver burden in the HAVEN 2 study.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

HAVEN 2 is a phase 3, non-randomized, open-label, multicentre study assessing the efficacy, safety, pharmacokinetics and HRQoL of emicizumab prophylaxis in paediatric PwHA with FVIII inhibitors (NCT02795767).[30] All participants from a previous non-interventional study (NCT02476942) who met the eligibility criteria for this study were permitted to enrol in HAVEN 2 (group A). Paediatric PwHA <12 years of age, or adolescents 12-17 years of age who weighed <40 kg, with FVIII inhibitors, who were receiving episodic or prophylactic treatment including FVIII (long- and short-acting) and BPAs (activated prothrombin complex concentrate [aPCC] or recombinant activated FVII [rFVIIa]) were eligible to participate. Emicizumab was administered SC at a loading dose of 3.0 mg/kg QW for 4 weeks, followed by a maintenance dose of either 1.5 mg/kg QW (group A), 3.0 mg/kg Q2W (group B) or 6.0 mg/kg Q4W (group C) for a minimum of 52 weeks (or until unacceptable toxicity or study discontinuation occurred). Individuals aged <2 years or 12-17 years could enrol in group A only. To investigate the possibility of flexible dosing in paediatric PwHA, groups B and C were added to the study after the complete enrolment of group A.[30]

The study was conducted in 27 centres in ten countries[30] in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The relevant independent ethics committee/institutional review board at each centre approved the study protocol. Written informed consent was obtained from parents or legally acceptable representatives, and informed assent was obtained from children (aged 8-11 years) and adolescents (aged 12-17 years) where applicable.

Full inclusion and exclusion criteria, and additional methods have been published previously.[30]

2.2 | Participant-reported outcomes measures

2.2.1 | HRQoL

Participants (ages 8-11 years only) and caregivers of participants age < 12 years provided HRQoL assessments.

Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form (Haemo-QoL SF II)

Participants aged 8-11 years completed the Haemo-QoL SF II, a validated self-reported and haemophilia-specific instrument for assessing HRQoL in paediatric PwHA.[32] The questionnaire contains 35 items, covering nine domains ('Physical Health', 'Feeling', 'View

of Self', 'Family', 'Friends', 'Other People', 'Sports & School', 'Dealing with Haemophilia' and 'Treatment'), which are combined to create a 'Total' score. The questionnaire is linguistically validated in several languages.[33] Individual questions are rated on a 5-point Likert scale with the following response options: 'never' (1), 'seldom' (2), 'sometimes' (3), 'often' (4) and 'all the time' (5). Some items of the 'View of Yourself', 'Friends', 'Sports & School' and 'Dealing with Haemophilia' domains were reverse-scored. All scores were transformed to a 0-100 scale, with lower scores indicative of better HRQoL.

Adapted Inhibitor-Specific Quality of Life Assessment with Aspect of Caregiver Burden (Adapted Inhib-QoL)

Caregiver assessment of their children's HRQoL and aspects of caregiver burden were collected from caregivers for all children <12 years using the Adapted Inhib-QoL.[33] The questionnaire comprises two parts with a total of 34 questions. The first part asks the caregiver for their opinion of their child's HRQoL and consists of two domains: 'Physical Health' and 'Treatment'. The second part focuses on the impact of their child's HA on the caregiver and consists of six domains (five if the child does not have siblings): 'General Condition', 'Dealing with Inhibitor', 'Perceived Treatment', 'Family Life', 'Siblings' and 'Contact with Others'. A 'Total' score is calculated as the sum of all domains. Individual questions are rated on a 5-point Likert scale with the same response options as the Haemo-QoL SF II. All scores were transformed to a 0-100 scale, with lower scores indicative of better HRQoL and less caregiver burden.

2.2.2 | School/day care absences and hospitalizations

At each clinic visit, the number of missed days from school/day care for children (if applicable) during the previous 4 weeks, and the number of days they should have attended, were gathered from caregivers. The number of days the child was hospitalized (if applicable) was collected for the 24 weeks prior to study treatment, and obtained from the electronic case report form.

2.3 | Data collection and analysis

Both questionnaires were completed using an electronic handheld device at each clinic visit before treatment administration, at baseline, Weeks 13, 25, 37, 49 and 57, and every 24 weeks thereafter. For the Haemo-QoL SF II and Adapted Inhib-QoL questionnaires, descriptive analyses including summaries of change from baseline for each individual subscale and the overall score were performed. Change from baseline is calculated for those participants for whom data are available at both time points (ie, those who completed questionnaires at both baseline and the given week). The number of days of missed school/day care and days hospitalized was analysed using descriptive statistics with 95% CIs or standard deviation (SD). The proportion of missed days of school/day care was calculated for each participant by dividing the number of missed days by the number of days they were expected to attend, and the 95% CI was calculated. Data are presented for all eligible participants across the three dosing regimens (QW, Q2W and Q4W). The data cut-off for the analyses presented was 9 October 2018.

TABLE 1 Baseline demographics and disease characteristics

Demographics	All participants (N = 88)
Age in years (%)	
Median (range)	7.0 (1-15)
0-7	51 (58.0)
8-11	34 (38.6)
≥12	3 (3.4)[a]
Race—no. (%)	
White	54 (61.4)
Asian	13 (14.8)
Black	12 (13.6)
Multiple	2 (2.3)
Unknown	7 (8.0)
Haemophilia severity at baseline—no. (%)	
Mild	2 (2.3)
Moderate	1 (1.1)
Severe	85 (96.6)
Previous regimen—no. (%)	
Episodic	22 (25.0)
Prophylactic	66 (75.0)
Highest historical inhibitor titre[b] (BU/mL)	
Median (Range)	200 (5-7200)
Previously treated with ITI	
Yes	63 (71.6)
No	25 (28.4)

Abbreviations: BU, Bethesda Units; ITI, immune tolerance induction.
[a]Excluded from these analyses.
[b]Historical peak was unknown for two participants.

3 | RESULTS

3.1 | Study population

Overall, 88 male participants were enrolled in HAVEN 2, with a median age of 6.5 years (range: 1-15 years). The majority of participants had severe HA (97%), had previously undergone ITI (72%) and were receiving treatment with prophylactic BPAs (75%) (Table 1). In those PwHA who received episodic treatment in the 24 weeks prior to study entry, the majority had taken rFVIIa (79.5%) and/or aPCC (53.8%), with a minority taking long- or short-acting FVIII (7.7% and 2.6%, respectively) or another therapeutic agent (2.6%). For those

TABLE 2 Baseline Haemo-QoL SF II domain scores and changes over the follow-up period

Haemo-QoL SF II domains	Baseline n = 30[a]	Week 13 n = 33[a]	Week 25 n = 32[a]	Week 37 n = 30[a]	Week 49 n = 20[a]
Physical Health, mean (SD)	27.7 (23.5)	12.31 (13.9)	9.4 (13.3)	11.0 (15.8)	10.9 (13.0)
Change from baseline[b]	–	−15.7	−18.1	−22.4	−15.4
Feelings, mean (SD)	24.0 (22.8)	19.3 (22.0)	9.4 (14.5)	9.0 (15.5)	18.1 (20.5)
Change from baseline[b]	–	−6.9	−17.2	−16.8	−10.7
View of Self, mean (SD)	24.2 (24.7)	24.2 (23.4)	16.4 (20.6)	15.8 (22.9)	22.2 (20.6)
Change from baseline[b]	–	0.0	−7.4	−9.0	−8.1
Family, mean (SD)	40.6 (21.5)	32.2 (20.8)	31.5 (22.0)	28.5 (24.3)	33.8 (23.9)
Change from baseline[b]	–	−8.8	−9.2	−14.7	−5.9
Friends, mean (SD)	25.0 (24.0)	33.8 (30.2)	28.1 (31.9)	29.0 (33.2)	34.2 (33.9)
Change from baseline[b]	–	8.1	0.9	2.2	3.9
Other Persons, mean (SD)	21.9 (21.5)	19.3 (20.5)	13.9 (21.1)	12.5 (19.7)	14.7 (16.9)
Change from baseline[b]	–	−2.6	−6.3	−10.6	−13.2
Sports & School, mean (SD)	55.2 (27.7)	42.2 (30.6)	38.9 (33.1)	33.8 (31.0)	38.8 (33.2)
Change from baseline[b]	–	−13.8	−15.0	−22.6	−14.3
Dealing with Haemophilia Score, mean (SD)	16.0 (18.8)	17.6 (15.7)	14.5 (16.9)	10.8 (15.9)	14.1 (18.5)
Change from baseline[b]	–	0.2	−4.0	−7.2	−2.6
Treatment Score, mean (SD)	35.6 (20.5)	24.2 (24.3)	18.4 (20.9)	22.9 (24.3)	23.1 (19.8)
Change from baseline[b]	–	−12.7	−18.3	−14.4	−16.9
Total Score, mean (SD)	30.2 (14.9)	24.8 (14.0)	19.8 (13.5)	19.0 (13.9)	23.0 (13.9)
Change from baseline[b]	–	−6.2	−10.8	−13.2	−9.6

Note: Scores were transformed and range from 0 to 100. Higher values indicate greater impairment in HRQoL Larger decreases from baseline indicate greater improvement in HRQoL.

Abbreviations: Haemo-QoL SF II, Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form II; HRQoL, health-related quality of life; SD, standard deviation.

[a]Haemo-QoL SF II was completed by participants aged 8-11 y only. For each week, n is the number of participants who completed the questionnaire.

[b]Change from baseline includes only those participants who competed the questionnaire at baseline and at least one other time point: Week 13, n = 29; Week 25, n = 28; Week 37, n = 26; Week 49, n = 17.

who received prophylactic treatment in this time period, this was most likely to be aPCC (51.5%), followed by rFVIIa (33.8%), short-acting FVIII (19.1%), another therapeutic agent (16.2%) or long-acting FVIII (13.2%). Eighty-five participants were aged <12 years and were therefore eligible for inclusion in this analysis; three participants aged ≥12 years (<40 kg) were excluded from this analysis. In total, 34 participants aged 8-11 years were eligible to complete the Haemo-QoL SF II questionnaire. All caregivers of participants <12 years (N = 85) were eligible to complete the Adapted Inhib-QoL questionnaire. However, not all eligible participants/caregivers completed the questionnaires at all designated weeks. Hence, reported numbers vary by time point.

3.2 | Questionnaire completion rate

High completion rates were consistently observed from baseline to Week 49 for both Haemo-QoL SF II (>88.2%) and Adapted Inhib-QoL (>91.8%). At Week 57, technical difficulties with the tablet provided to centres for data collection prevented questionnaire completion and reduced compliance rates (68.2% [15/22] for Haem-QoL SF II; 75.0% [42/56] for Adapted Inhib-QoL). As such, Week 57 data are not presented.

3.3 | Haemophilia-specific HRQoL in children (Haemo-QoL SF II)

Mild to moderate impairments were reported across multiple domains of the Haemo-QoL SF II at baseline (Table 2). Domains that were most severely impacted were related to 'Sports & School', 'Family' and 'Treatment'. At baseline (n = 30), mean (SD) 'Physical Health' and 'Total' scores were 27.7 (23.5) and 30.2 (14.9), respectively, indicating moderate impairment. Mean scores improved towards zero during treatment with emicizumab (Figure 1), indicating reduced impairment and improved HRQoL. Score improvements with emicizumab prophylaxis were seen as early as Week 13 (n = 29): both 'Physical Health' and'Total' scores had decreased from baseline by a mean (SD, n) of −15.7 (26.8, 29) and −6.2 (11.4, 29), respectively. These improvements in both domain scores were maintained for up to 1 year of emicizumab treatment (Table 2). Across the study period, changes in the 'Physical Health' domain showed near-maximal improvement from baseline, with scores approaching the minimum score possible on the scales. By Week 49, the mean (SD, n) 'Physical Health' score was 10.9 (13.0, 20), an improvement of 15.4 (20.0, 17) points from baseline (Figure 1A).

Starting from Week 13, the majority of the other domains ('Feeling', 'View of Self', 'Family', 'Other Persons', 'Sports &

School','Dealing with Haemophilia' and'Treatment') also displayed improvements from baseline, which were sustained throughout the study (Table 2). At baseline, 17/30 (56.7%) respondents reported that their haemophilia was 'never' or 'seldom' a burden to them. By Week 49, this proportion increased to 75% (15/20). The proportion of children reporting 'never' or 'seldom' feeling pain in their swellings (haematomas), joints, or while moving increased by 43.3, 35.0 and 21.7 percentage points, respectively, over the emicizumab treatment period, although the proportion of children reporting feeling pain in their joints or while moving 'often' or 'always' remained relatively similar (Figure 2).

3.4 | Caregiver-reported HRQoL and caregiver burden (Adapted Inhib-QoL)

At baseline, moderate impairments were reported across all domains of the Adapted Inhib-QoL (n = 78). Domains that were most severely impacted were 'Dealing with Inhibitors', 'Perceived Treatment' and 'Family Life'. Caregiver reporting of 'Physical Health' impairment was consistent with that reported by the children. The mean 'Physical Health' (SD, n) score at baseline was 34.6 (22.0, 78), which decreased by −28.1 (24.7, 77) by Week 13. Similarly, the mean (SD, n) 'Total' score at baseline was 41.3 (13.7, 78) and decreased by −18.8 (14.3, 77) points at Week 13 (Table 3). These improvements from baseline in both 'Physical Health' and 'Total' scores were sustained through Week 49 (n = 60; Figure 3).

Marked improvements were also observed in other Adapted Inhib-QoL domains particularly indicative of caregiver burden, such as 'Dealing with Inhibitor', 'Family Life', 'Perceived Condition' and 'Perceived Treatment' (Week 49, n = 60; Table 3). In response to individual questions in the Adapted Inhib-QoL questionnaire, similar to their child's reporting, an increasing proportion of caregivers reported their child 'never' or 'seldom' feeling pain in their swellings, joints, or while moving over the course of emicizumab treatment, compared with baseline (Figure 4). In addition, at baseline 46.2% and 29.5% of caregivers reported their child 'often' or 'always' as having bruises or bleeds, respectively, but this reduced to 1.7% and 0%, respectively, by Week 49 (Figure 4).

3.5 | School/day care attendance

At baseline, 59/85 (75.6%) participants were enrolled in school/day care. In the 4 weeks before study entry, these participants missed a mean (95% CI) of 41% (29-53) of days they were expected to attend school/day care. By Week 49, 50/60 (83.3%) participants enrolled in school/day care who responded to the questionnaire had missed a mean (95% CI) of 15% (6-24) of days they were expected to attend school/day care in the past 4 weeks. At baseline, 23/59 (39.0%) participants enrolled in school/day care reported no missed days; by Week 49, this had increased to 39/50 (78.0%) participants.

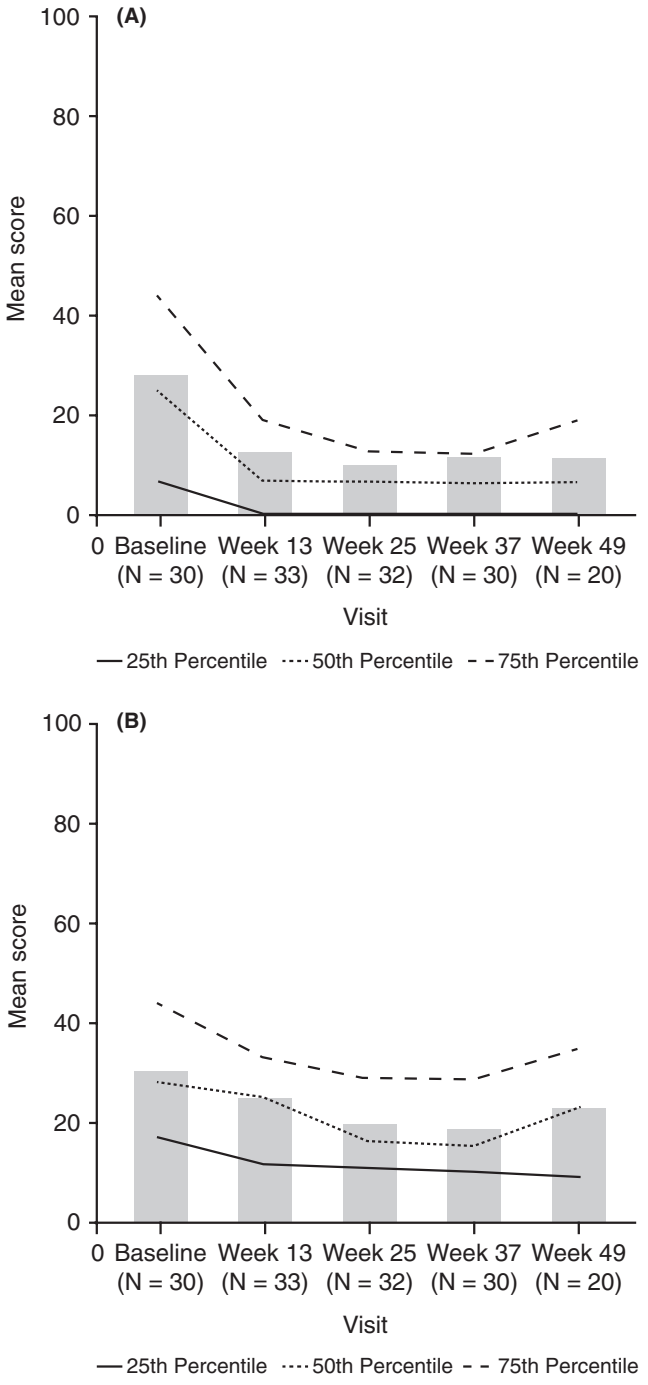

FIGURE 1 Haemo-QoL SF II mean 'Physical Health' (A) and 'Total' (B) scores by visit. Includes data before up-titration only, for participants whose dose was up-titrated. For each visit, N is the number of participants responding to these scales. Haemo-QoL SF II was completed by participants aged 8-11 y only. Higher scores indicate poorer HRQoL. Haemo-QoL SF II, Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form II; HRQoL, health-related quality of life

3.6 | Hospitalization

At baseline, 25/88 (28.4%) participants had been hospitalized in the 24 weeks prior to study entry. The median (range) number of days

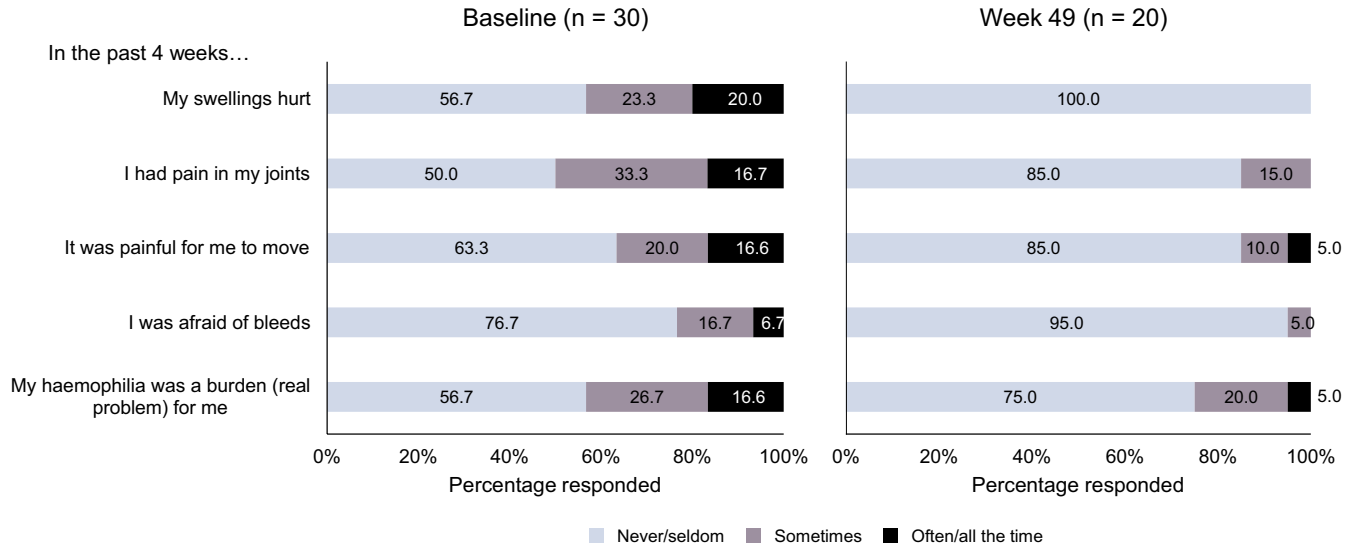

FIGURE 2 Distribution of Haemo-QoL SF II responses to individual questions. Only items demonstrating the highest improvements are shown here. Includes data before up-titration, for participants whose dose was up-titrated. Haemo-QoL SF II was completed by participants aged 8-11 y only. For each visit, n is the number of participants responding to each question. Haemo-QoL SF II, Haemophilia-Specific Quality of Life Assessment Instrument for Children and Adolescents Short Form II [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Baseline Adapted Inhib-QoL domain scores

Adapted Inhib-QoL domains	Baseline n = 78[a]	Week 13 n = 84[a]	Week 25 n = 82[a]	Week 37 n = 81[a]	Week 49 n = 60[a]
Physical Health Score,[b] mean (SD)	34.6 (22.0)	6.6 (8.5)	5.8 (7.2)	5.6 (7.2)	8.5 (11.0)
Change from baseline[c]	–	−28.1	−29.2	−30.3	−28.7
Treatment Score, mean (SD)	32.2 (27.7)	18.3 (21.3)	15.1 (21.1)	14.4 (18.9)	17.3 (19.1)
Change from baseline[c]	–	−13.6	−17.1	−18.1	−14.4
Perceived Condition Score, mean (SD)	37.7 (21.5)	27.6 (18.5)	24.5 (20.3)	24.2 (18.7)	22.4 (18.2)
Change from baseline[c]	–	−9.3	−12.7	−13.4	−14.8
Dealing with Inhibitor Score, mean (SD)	57.8 (17.2)	37.6 (20.6)	32.3 (17.3)	34.5 (18.7)	31.1 (19.3)
Change from baseline[c]	–	−19.7	−25.4	−23.7	−26.4
Perceived Treatment Score,[d] mean (SD)	43.9 (16.3)	30.8 (14.7)	29.1 (14.6)	31.3 (15.4)	29.1 (14.6)
Change from baseline[c]	–	−14.1	−15.8	−13.6	−15.2
Family Life Score, mean (SD)	41.9 (24.5)	17.2 (18.3)	14.7 (15.6)	13.7 (16.9)	13.9 (15.6)
Change from baseline[c]	–	−24.4	−26.9	−28.0	−28.7
Contact with Others Score, mean (SD)	25.8 (26.4)	9.1 (17.2)	8.5 (16.8)	7.4 (17.1)	6.5 (14.8)
Change from baseline[c]	–	−15.9	−16.5	−17.9	−20.4
Total Score, mean (SD)	41.3 (13.7)	22.5 (9.3)	20.0 (9.6)	20.5 (8.7)	20.0 (9.5)
Change from baseline[c]	–	−18.8	−21.4	−21.3	−21.9
	n = 51[e]	**n = 59[e]**	**n = 57[e]**	**n = 57[e]**	**n = 43[e]**
Siblings Score,[e] mean (SD)	24.5 (29.8)	18.2 (26.2)	14.0 (22.7)	14.0 (22.2)	16.3 (23.7)
Change from baseline[f]	–	−6.4	−10.2	−10.9	−6.4

[a]HRQoL, health-related quality of life; SD, standard deviation. Adapted Inhib-QoL was completed by all caregivers of participants aged <12 y (N = 85). For each week, n is the number of caregivers who completed the questionnaire. Scores ranged from 0 to 100. Higher values indicate greater impairment. Larger decreases from baseline indicate greater improvement in HRQoL.

[b]Caregiver perception of child's physical health.

[c]Change from baseline includes only those caregivers who competed the questionnaire at both time points. Week 13, n = 77; Week 25, n = 76; Week 37, n = 74; Week 49, n = 54.

[d]Caregiver perception of treatment affecting their child.

[e]Reported only for those with siblings (n = 51).

[f]Change from baseline includes only those caregivers who completed the questionnaire at baseline and at least one other time point: Week 13, n = 51; Week 25, n = 49; Week 37, n = 48; Week 49, n = 35.

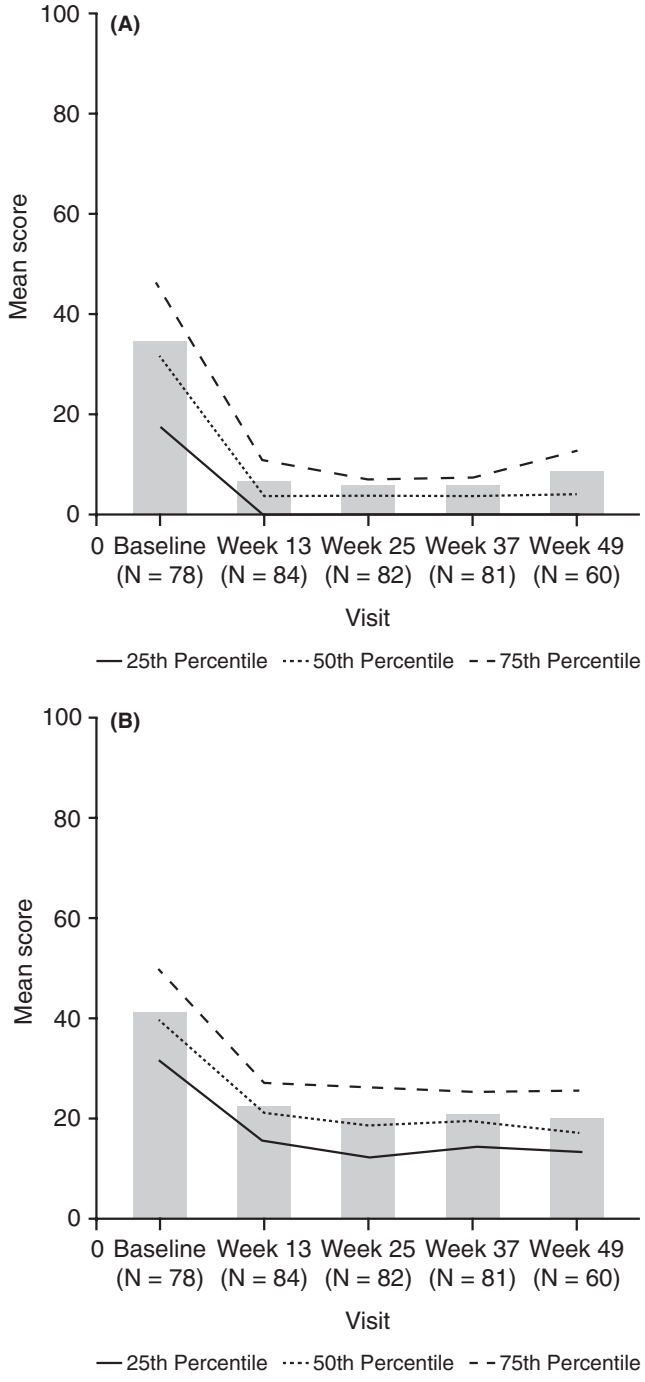

FIGURE 3 Adapted Inhib-QoL mean 'Physical Health' (A) and'Total' (B) scores by visit. Includes data before up-titration only, for participants whose dose was up-titrated. For each visit, N is the number of participants responding to these scales. Higher scores indicate poorer HRQoL. Adapted Inhib-QoL, Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden; HRQoL, health-related quality of life

these children were hospitalized was 3.0 (1-66); the mean (SD) was 9.3 (14.7). As of data cut-off, 19/88 (21.6%) participants had been hospitalizedin the last 24 weeks. The 19 hospitalized children spent a median (range) of 4.0 (2-15) days in hospital; the mean (SD) was 5.6 (3.7).

4 | DISCUSSION

In this analysis, emicizumab prophylaxis is compared with prior treatment (either BPA episodic or prophylaxis). While it may be expected that adding changing from episodic to a prophylactic regimen of any kind would improve HRQoL outcomes due to a reduction in bleeding (and consequently pain) in PwHA previously receiving BPA, the efficacy of BPA prophylaxis is variable and highly burdensome (especially in patients with poor venous access or recurrent CVAD infections), which could negatively impact HRQoL.[34] As such, emicizumab prophylaxis was compared to each participant's baseline HRQoL, regardless of their prior treatment.

Consistent with the substantial efficacy and tolerability previously reported in children treated with emicizumab prophylaxis from HAVEN 2,[30] improvements in HRQoL for children were observed as early as the first scheduled time point of Week 13 and were sustained throughout the treatment period across multiple domains of both the Haemo-QoL SF II and Adapted Inhib-QoL questionnaires. Baseline scores for 'Physical Health' in this population were similar to those reported in other studies using the Haemo-QoL SF II to assess HRQoL in children with HA with FVIII inhibitors receiving episodic or prophylactic aPCC or and rFVIIa.[19,35,36] Furthermore, the domains 'Family' and 'Sports & School' were the most impacted domains for those receiving both episodic or prophylactic FVIII,[20,35,36] as was the case for HAVEN 2 participants at baseline.[31]

Following prophylaxis with emicizumab, improvements in domains related to physical activity including 'Physical Health' and 'Sports & School' showed rapid and sustained improvements, with an almost maximal improvement from baseline in 'Physical Health', approaching the minimal score possible. Such improvements in physical health and HRQoL may have contributed to reduced absence from school/day care. The improvements in the self-reported outcomes for children likely result from a combination of substantially reduced bleeding rates, increasing target joint resolution, and the low rate of mostly mild adverse events as well as the SC mode of administration for emicizumab.[30] There were also fewer hospitalizations for the children in this study after they began receiving emicizumab prophylaxis. The decrease of 6.8% was not as substantial as may be expected given the improvements in HRQoL; however, there may be different reasons for the hospitalizations recorded while receiving prophylaxis. One such reason could be the removal of central venous access devices (CVADs) from 49% of the children who had these devices at baseline,[30] although this interpretation is only speculative.

In addition to the effect of emicizumab on the HRQoL of children in this study, caregivers reported similar improvements in their children. As two scales on the Adapted Inhib-QoL questionnaire refer to the caregiver view of their child's treatment and physical health, they were able to observe changes that occurred in their children consistent with their child's self-report. Caregivers thought that the physical health of their child was moderately impaired at baseline and observed similar improvements to their child's reports of physical health changes while on emicizumab.

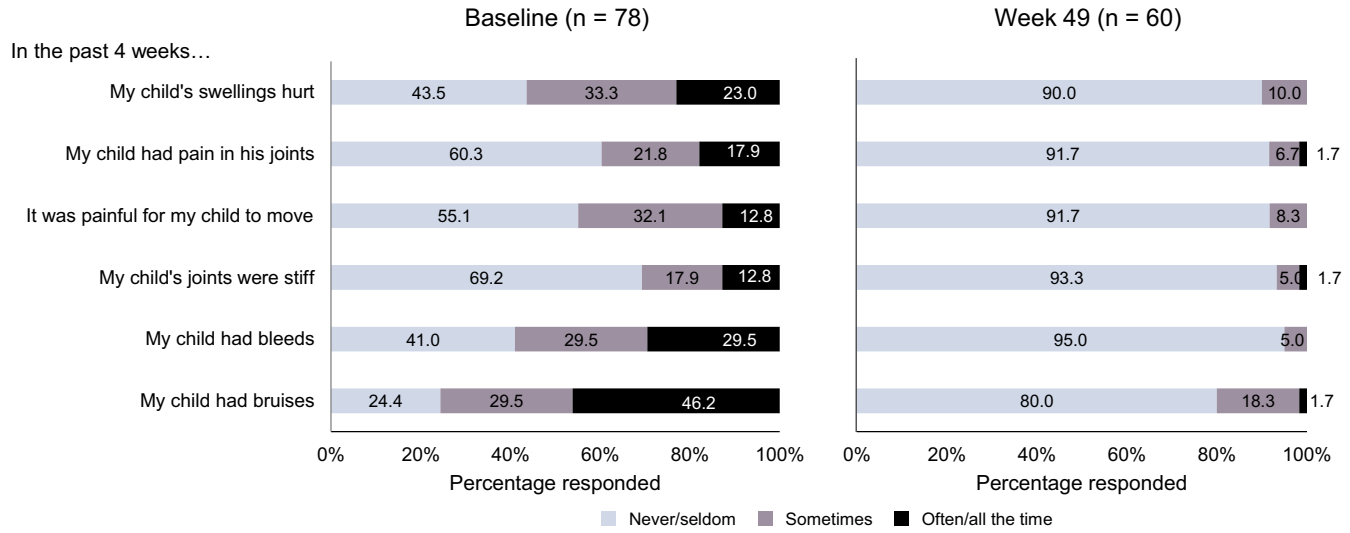

FIGURE 4 Distribution of Adapted Inhib-QoL responses to individual questions. Only items demonstrating the highest improvements are shown here. Includes data before up-titration, for participants whose dose was up-titrated. For each visit, n is the number of parents/carers responding to each question. Adapted Inhib-QoL, Adapted Inhibitor-Specific Quality of Life Assessment with Aspects of Caregiver Burden [Colour figure can be viewed at wileyonlinelibrary.com]

Prophylaxis with emicizumab resulted in rapid and sustained improvements in multiple domains, indicative of a potential reduction in caregiver burden, possibly aided by the visible improvement of their child's HRQoL. A 26.4-point improvement (n = 54) from baseline at Week 49 was observed in the 'Dealing with Inhibitor' domain, suggesting caregivers were less worried about the increased burdens of their child's FVIII inhibitor development and the associated risk of bleeding. Similar improvements in the 'Family Life' domain suggest that emicizumab prophylaxis may reduce the impact of HA on children and their families. Caregivers were also increasingly satisfied with their child's treatment while on emicizumab, with a 15.2-point improvement in the 'Perceived Treatment' domain at Week 49. This may be attributed to the SC mode of administration, which allowed CVAD removal in almost half of the participants who had the devices at baseline,[30] and reduced frequency of treatment compared with standard BPAs, lifting the burden of treatment administration from caregivers.

Caregivers of children with HA can report higher impairments in HRQoL than their child, linked to the emotional stress associated with the disease (such as financial burden, problems with treatment administration or difficulty dealing with the child's pain).[19] Moreover, the discrepancies in ratings between children and their caregiver are a known phenomenon in HRQoL research, especially regarding caregivers overestimating physical burdens experienced by their children.[37] The development of FVIII inhibitors in children provides an additional element of burden for caregivers, due to the additional management needed for these children.

Limitations of these analyses are reflective of the constraints of running clinical trials in rare diseases. The HAVEN 2 was a non-randomized trial; participants were aware that they were undergoing a new treatment, which may have impacted their perceptions in the short term; however, continued improvements were reported with treatment long term, eliminating any potential bias that may have originally occurred. In addition, the absence of a comparator arm and lack of validated thresholds for clinically meaningful response for both questionnaires restricts comprehensive interpretation of the results. The technical issues experienced with the questionnaires and subsequent reduced compliance at Week 57 also could have impacted the results obtained at that time point, which is why Week 49 results are presented. However, the magnitude of change in domain scores from baseline over time does suggest that the results are clinically meaningful.

5 | CONCLUSION

The impact of HA on the HRQoL of adults has been well established. There is also growing interest in understanding the impact of HA on younger PwHA and their caregivers. Results from the HAVEN 2 study demonstrate that the previously reported efficacy and safety profiles of emicizumab prophylaxis in children are accompanied by substantial and sustained improvements in the self-reported and proxy-reported HRQoL of paediatric PwHA along with reduced caregiver burden.[30] These results suggest that emicizumab prophylaxis not only offers a highly therapeutic and well-tolerated treatment option, but also one that alleviates the burden of treatment, and may allow children with HA to lead less-restricted social lives, similar to their peers without HA.

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AUTHOR CONTRIBUTIONS

PT, MU, TC and SvM contributed to the study design. MEM, JM, RS, MS, GY and JO contributed to the study design and collected the data for the study. PT, MU, TC and SvM participated in the analysis and interpretation of the data. All authors critically reviewed the manuscript, approved the final version and support this publication.

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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