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# Mental and emotional impact of emicizumab treatment in people with hemophilia A: Post hoc analysis of the HAVEN 3 and 4 studies

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## Summary

Reducing the mental and emotional burden of hemophilia A (HA) in progressing towards a hemophilia-free mind remains a central treatment goal for people with HA (PwHA)

The participant-reported mental and emotional impact of HA, before and after treatment with emicizumab, was evaluated in PwHA from the Phase 3 HAVEN 3 and 4 clinical trials

These findings complement the low bleed rates and favorable safety profile observed in PwHA treated with emicizumab in HAVEN 3 and 4, representing a step towards a hemophilia-free mind

In this exploratory analysis, emicizumab prophylaxis was associated with long-term improvements in mental and emotional wellbeing, as measured by the Haem-A-QoL

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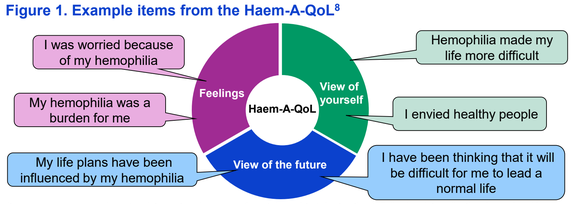
## Background

- As the treatment landscape for hemophilia A (HA) continues to evolve, there is an increasing focus on reducing the mental and emotional burdens experienced by people with HA (PwHA).[1,2]
- The concept of a "hemophilia-free mind" encompasses freedom from the physical and psychological constraints of hemophilia, including being free from pain, bleeds, arthropathy, and the fears and restrictions associated with hemophilia and its treatment;[3,4] this remains a central treatment goal for PwHA and within the hemophilia community.
- Although the psychological burden of hemophilia is well-recognized, longitudinal data exploring mental health outcomes among people with hemophilia are limited.[5]
- In the Phase 3 HAVEN 3 (NCT02847637)[6] and HAVEN 4 (NCT03020160)[7] clinical trials, emicizumab was well-tolerated and associated with low bleed rates. Here, we report results from an exploratory post hoc analysis, evaluating long-term participant-reported mental, emotional, and anxiety- and depression-related outcomes over 5 years of follow up in PwHA receiving emicizumab in HAVEN 3 and 4.

## Long-term participant-reported mental, emotional, and anxiety- and depression-related outcomes were evaluated in HAVEN 3 and 4

- The study populations included people with severe HA aged ≥12 years without factor (F)VIII inhibitors (HAVEN 3 and 4) and PwHA with inhibitors (HAVEN 4). Both studies were open label; HAVEN 3 was randomized and HAVEN 4 was a single-arm study
  - Following the emicizumab loading regimen, the maintenance dosing regimens were 1.5 mg/kg once weekly or 3 mg/kg twice weekly in HAVEN 3 and 6 mg/kg every 4 weeks in HAVEN 4.[6,7]
- Participants aged ≥18 years completed The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)[8] at specified assessment points throughout the analysis, which evaluated 14 items related to mental and emotional outcomes within three domains: "Feelings about hemophilia burden", "View of yourself", and "View of the future" over the past month (**Figure 1**).
- The EuroQol 5-Dimension 5-Level (EQ-5D-5L)[9] questionnaire was used to evaluate feelings of anxiety and depression in all participants on the day of the survey.

**Figure 1. Example items from the Haem-A-QoL[8]**




Items were assessed using a 5-point Likert scale, ranging from 1 (never) to 5 (all the time). Following data collection, "never" and "rarely" were combined into one response, as were "often" and "all the time"; the raw scores within each domain were transformed to a scale of 0–100, with higher scores reflecting greater impairment. Thus, a reduction in scores from one assessment point to the next reflected improvement. Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults.

## A total of 199 PwHA were included in this post hoc analysis

- Data cut-off was May 12, 2022 for HAVEN 3 and June 29, 2022 for HAVEN 4, representing 716.2 patient-years; participant characteristics are shown in **Table 1**.

**Table 1. Participant characteristics**

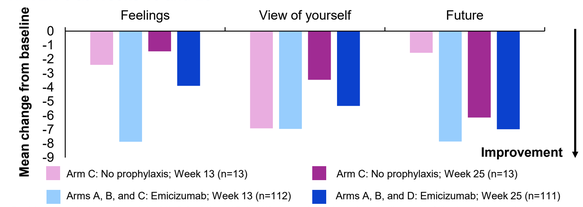
| | Participants in HAVEN 3 and 4 (N=199) |
|---|---|
| **Median (range) age, years** | 38.0 (13.0–77.0) |
| **Age group, years, n (%)** | |
| 13–17* | 12 (6.0) |
| 18–34 | 70 (35.2) |
| 35–49 | 72 (36.2) |
| 50–80 | 45 (22.6) |
| **Male, n (%)** | 199 (100) |
| **FVIII inhibitors status at emicizumab baseline, n (%)** | |
| Without inhibitors | 189 (95.0) |
| With inhibitors | 10 (5.0) |
| **Median (range) number of bleeds 24 weeks prior to study entry** | 8.0 (0.0–128.0) |
| **Number of target joints at study entry, n (%)** | |
| 0 | 67 (33.7) |
| 1 | 38 (19.1) |
| 2–8 | 94 (47.2) |
| **Prior prophylactic/episodic treatment in the last 24 weeks†, n (%)** | |
| Prophylactic | 80 (40.2) |
| Episodic | 96 (48.2) |
| Prophylactic and episodic | 22 (11.1) |
| **Median (range) duration of emicizumab treatment, efficacy period, years** | 4.2 (0.1–5.5) |

*Haem-A-QoL outcomes displayed are for participants ≥18 years. †Data for one participant were unavailable. F, factor; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults.

## In HAVEN 3, participants treated with emicizumab reported improved quality-of-life outcomes compared with those not on prophylaxis

- Improved mean Haem-A-QoL scores were generally observed across all three domains at Weeks 13 and 25 among participants in HAVEN 3 treated with emicizumab versus no prophylaxis for the first 24 weeks (**Figure 2**).

**Figure 2. Mean change from baseline in Haem-A-QoL domain scores among participants* aged ≥18 years receiving emicizumab versus no prophylaxis in HAVEN 3 at Weeks 13 and 25**

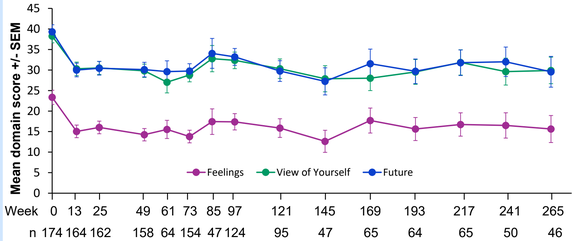



Participants assigned to Arms A (n=36), B (n=31), and D (n=52) received emicizumab according to the following dosing regimens: 1.5 mg/kg QW, 3 mg/kg Q2W, and 1.5 mg/kg QW, respectively; participants assigned to Arm C (n=14) did not receive prophylaxis. Participants in Arm D had received prior FVIII prophylaxis. *Includes participants with ≥1 data points available at baseline and post-baseline. F, factor; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; QW, every week; Q2W, every 2 weeks.

## Mean overall Haem-A-QoL domain scores improved from baseline to Week 265

- Overall, mean scores for all three domains improved by Week 13 and were maintained until Week 265 (**Figure 3**)
  - At Week 13, the proportion of participants achieving an improvement in score by 10 points or more was 39.6%, 48.8%, and 52.4% in the "Feelings", "View of Yourself", and "Future" domains, respectively.
- Participants reporting that hemophilia was "never/rarely" a burden increased from 55.2% at baseline to 75.6% at Week 13 and 78.3% at Week 265. Trends were similar for the 'View of yourself' and 'Future' domains.

**Figure 3. Mean Haem-A-QoL domain scores over time in participants* ≥18 years in HAVEN 3 and 4†**

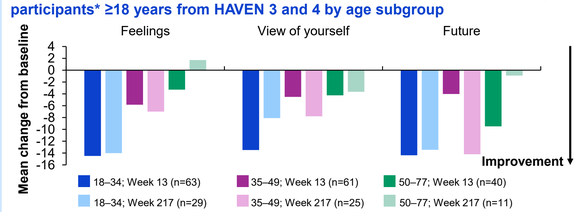



*Includes only participants with scores available at baseline and post-baseline. †Higher scores reflect greater impairment. Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; SEM, standard error of the mean.

## Improvements in mean Haem-A-QoL domain scores were observed across all three age subgroups

- Greater improvements in mean scores from baseline were generally observed among participants in younger age subgroups (**Figure 4**).

**Figure 4. Change in mean Haem-A-QoL domain scores from baseline among participants* ≥18 years from HAVEN 3 and 4 by age subgroup**

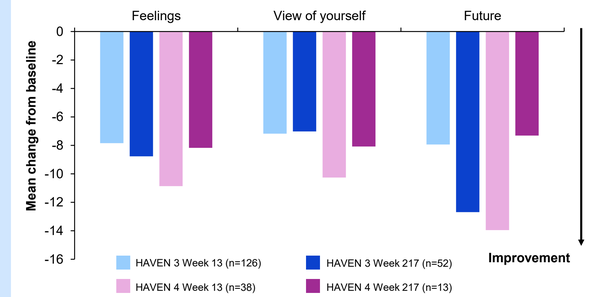



Data beyond Week 217 are not displayed due to a small number of participants remaining in HAVEN 4. *Includes participants with ≥1 data points available at baseline and post-baseline. Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults.

## In both HAVEN 3 and HAVEN 4, mean Haem-A-QoL domain scores improved from baseline to Week 13 and Week 217

- The changes in mean Haem-A-QoL scores from baseline to Week 13 and Week 217 were generally comparable between the two studies, despite the difference in dosing frequency (HAVEN 3: once weekly or every 2 weeks; HAVEN 4: every 4 weeks; **Figure 5**).
- The greatest improvements were observed in the "Future" domain among participants in HAVEN 3 at Week 217 and HAVEN 4 at Week 13.

**Figure 5. Mean change from baseline in Haem-A-QoL domain scores among participants* ≥18 years from HAVEN 3 and 4 by study**




Data beyond Week 217 are not displayed due to a small number of participants remaining in HAVEN 4. The emicizumab maintenance dosing regimens were 1.5 mg/kg QW or 3 mg/kg Q2W in HAVEN 3 and 6 mg/kg every Q4W in HAVEN 4. *Includes participants with ≥1 data points available at baseline and post-baseline. Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; QW, once weekly; Q2W, twice weekly; Q4W, every 4 weeks.

## Most participants continued to report being not anxious or depressed, or slightly anxious or depressed through to Week 265

- By Week 13, the proportion of participants reporting that they were not anxious or depressed or were slightly anxious or depressed at the time of EQ-5D-5L completion improved from 90.3% at baseline to 94.2% (**Table 2**).

**Table 2. EQ-5D-5L responses in all participants***

| n (%) | Baseline (n=185) | Week 13 (n=173) | Week 265 (n=48) |
|---|---|---|---|
| I am not/I am slightly anxious or depressed | 167 (90.3) | 163 (94.2) | 44 (91.7) |
| I am moderately anxious or depressed | 15 (8.1) | 8 (4.6) | 3 (6.3) |
| I am severely/I am extremely anxious or depressed | 3 (1.6) | 2 (1.2) | 1 (2.1) |

Dimensions were scored on a 5-level Likert severity scale, ranging from level 1 (no problems) to 5 (extreme problems). Following data collection, responses "I am not anxious or depressed" and "I am slightly anxious or depressed" were combined into one response, as were "I am severely anxious or depressed" and "I am extremely anxious or depressed". *Includes participants with ≥1 data points available at baseline and post-baseline. EQ-5D-5L, EuroQol 5-Dimension 5-Level.

## Limitations

- The number of participants completing the Haem-A-QoL decreased from 174 at baseline to 46 at Week 265, predominantly due to study completion.
- Most participants reported they were not or were slightly anxious or depressed at baseline, which may reflect the "disability paradox" whereby people with chronic conditions often report a high quality of life[10]
  - It is important to note that the EQ-5D-5L is not specific to HA and may lack sensitivity for detecting changes in health-related quality of life unique to PwHA.

## Conclusions

- Long-term exploratory data from HAVEN 3 and 4 show early and sustained improvements over 5 years in self-reported mental and emotional outcomes among PwHA receiving emicizumab.
- The proportion of participants reporting no or slight anxiety or depression remained relatively stable over time, indicating that these outcomes were unaffected by emicizumab treatment.
- Alongside its established clinical efficacy,[6,7,11] these findings suggest that emicizumab may provide mental health benefits for PwHA and represent a step towards a hemophilia-free mind, in line with real-world evidence.[12]

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