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Clinical haemophilia

Pain-Related Quality of Life Outcomes in People With Haemophilia A Receiving Emicizumab: A Post Hoc Analysis of the HAVEN 1, 3 and 4 and STASEY Studies

Cedric Hermans[1] | Mark W. Skinner[2,3] | Brittany Gentile[4] | Elise Lim[5] | Miranda Minhas[6] | Katya Moreno[7] | Eunice Tzeng[8] | Tyler W. Buckner[9]

[1]Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Catholic University of Louvain (UCLouvain), Brussels, Belgium | [2]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada | [3]Institute for Policy Advancement Ltd, Washington, District of Columbia, USA | [4]Product Development, Genentech, Inc., South San Francisco, California, USA | [5]Data & Statistical Sciences OMNI, Genentech, Inc., South San Francisco, California, USA | [6]US Medical Affairs, Genentech, Inc., South San Francisco, California, USA | [7]Global Product Development/Medical Affairs (PDMAO), F. Hoffmann-La Roche Ltd, Basel, Switzerland | [8]Rare Blood Disease, US Medical Affairs, Genentech, Inc., South San Francisco, California, USA | [9]Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA

Correspondence: Cedric Hermans (cedric.hermans@uclouvain.be; hermans.cedric@gmail.com)

Received: 27 June 2024 | **Revised:** 25 October 2024 | **Accepted:** 6 November 2024

Funding: This study was supported by F. Hoffmann-La Roche Ltd.

Keywords: arthralgia | emicizumab | haemophilia | haemarthrosis | pain | prophylaxis | quality of life

ABSTRACT

Introduction: People with haemophilia A (PwHA) experience acute and chronic pain associated with reduced quality of life (QoL).

Aims: This post hoc analysis of pooled data from the HAVEN 1 (NCT02622321), 3 (NCT02847637), 4 (NCT03020160) and STASEY (NCT0319179) studies assessed the impact of emicizumab prophylaxis on pain-related QoL in PwHA.

Methods: PwHA received emicizumab during the four studies. In this analysis, pain was assessed using patient-reported responses to pain-specific questions from the Haem-A-QoL/Haemo-QoL-SF and the pain/discomfort dimension of the EQ-5D-5L. Responses were recorded at baseline and at regular intervals for up to 78 weeks following treatment initiation. Additional analyses evaluated the population with target joints at baseline, and the overall population stratified by age, factor (F)VIII inhibitor status and prior treatment.

Results: At the data cut-off, 504 PwHA had been treated across the four studies; 464 and 470 completed the Haem-A-QoL/Haemo-QoL-SF and the EQ-5D-5L, respectively. Improvements in pain-related QoL were observed by Week 13 of emicizumab prophylaxis and maintained through Week 78. In the overall population, responses of 'never/rarely' for 'my swellings hurt' and 'pain in joints' increased from 37.0% and 30.0% at baseline to 84.0% and 61.0% by Week 13, suggesting reductions in acute and chronic pain, respectively. Similar improvements were seen in the target joint population, and across all strata. Greater improvements were observed in younger versus older PwHA.

Conclusion: Pain-related QoL improved with emicizumab prophylaxis regardless of target joints, age, FVIII inhibitor status or prior treatment. Haemophilia-specific assessments are needed to accurately capture and characterize pain in PwHA.

1 | Introduction

Congenital haemophilia A (HA) is a rare X-linked bleeding disorder characterized by a deficiency of factor (F)VIII [1]. This deficiency leads to impaired thrombin generation, resulting in frequent bleeding into joints, muscles and soft tissues [1].

Around 80.0% of all bleeds in people with HA (PwHA) affect the joints [2], leading to substantial pain. Pain in PwHA can be broadly categorized into acute and chronic, with acute pain often being associated with bleeding into joints and joint swelling, and chronic pain being associated with long-term degeneration from recurrent bleeds that leads to haemophilic arthropathy [2, 3]. Acute and chronic pain are experienced by many PwHA: in a 2013–2014 study of 381 males with haemophilia and a history of joint pain/bleeding, 20.0% had experienced acute pain, 34.0% had experienced chronic pain and 32.0% had experienced both acute and chronic pain in the last 6 months [4].

The impacts of acute and chronic pain are wide-ranging and greatly impair the quality of life (QoL) of PwHA [3], even among people with mild or moderate HA [5]. Acute and chronic pain have been reported to interfere with activities of daily life, limit mobility [7], link to obesity [4], reduce participation in physical activity, work and school, and have been associated with early retirement and unemployment [6–9]. Pain can also be detrimental to mental health, as PwHA with acute or chronic pain are more likely to be affected by depression and anxiety [4, 9].

First approved in 2017 by the Food and Drug Administration [10], emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated FIX and FX to substitute for the function of deficient activated FVIII and restore haemostasis in PwHA [11]. As of June 2024, more than 25,000 people have been treated with emicizumab globally [12]. Emicizumab has demonstrated haemostatic efficacy and safety across all severities of HA, with and without inhibitors, and from newborns to adulthood. Joint bleed prevention and reduction and target joint resolution, demonstrated across the phase 3 clinical trials and subsequent post-marketing phase 3b trials [13–19], may be expected to improve acute and chronic pain and, consequently, pain-related QoL.

In this post hoc analysis of pooled data from the HAVEN 1, 3 and 4 and STASEY clinical studies, the impact of emicizumab prophylaxis on pain-related QoL was assessed in adults and adolescents with HA, with and without FVIII inhibitors. As factors such as age, clinical characteristics (such as the presence of target joints or FVIII inhibitors) and prior treatment regimens have been associated with pain intensity and functional disability [3, 20, 21], the population in this post hoc analysis was also stratified by these factors.

2 | Methods

2.1 | Study Design and Participants

This was a post hoc analysis of pooled data from four phase 3 studies: HAVEN 1, 3 and 4 and STASEY, which included adults and adolescents with severe HA. The full study designs have been previously published [13, 15, 16, 19]. In this analysis, data from the four studies were pooled, excluding any periods when individuals received no emicizumab prophylaxis as part of a control arm.

HAVEN 1 (NCT02622321) included people with FVIII inhibitors [13], HAVEN 3 (NCT02847637) included people without FVIII inhibitors [15] and HAVEN 4 (NCT03020160) included people with or without FVIII inhibitors [16]. In HAVEN 1, 3 and 4 emicizumab prophylaxis was given as subcutaneous (SC) loading doses of 3 mg/kg weekly (QW) for 4 weeks. In HAVEN 1, this was followed by SC maintenance dosing of 1.5 mg/kg QW; in HAVEN 3, by maintenance dosing of 1.5 mg/kg QW or 3 mg/kg every 2 weeks; in HAVEN 4, by maintenance dosing of 6 mg/kg every 4 weeks. For all three studies, the data cut-off for the present analysis was 15 May 2020. STASEY (NCT03191799) included people with FVIII inhibitors, with emicizumab prophylaxis given as a loading dose of 3 mg/kg QW for 4 weeks, followed by maintenance dosing of 1.5 mg/kg QW [19]; the data cut-off for the present analysis was 11 January 2021.

2.2 | Objectives

Herein, we aimed to describe the relationship between emicizumab and pain-related QoL of the overall population of adults/adolescents with severe HA (with and without FVIII inhibitors), and in those with target joints at baseline, who enrolled in the HAVEN 1, 3 and 4 studies, or the STASEY study. Additional analyses assessed the overall population by age, FVIII inhibitor status and prior treatments received to explore factors that may impact pain-related QoL.

2.3 | Data Collection

Baseline demographics and disease characteristics were collected in each of the four studies. Pain medication use in the 4 weeks prior to initiating emicizumab was based on retrospective recall by study participants. Pain was assessed via patient-reported outcomes (PROs); responses to pain-specific questions from the Physical Health domain of the Haem-A-QoL and Haemo-QoL-SF (based on the past month) were evaluated in this analysis, along with responses to the pain/discomfort dimension of the EQ-5D-5L (based on the day of assessment) [22–25]. Responses were recorded at baseline and at regular prespecified assessment points for up to 78 weeks following initiation of emicizumab prophylaxis. The Haemo-QoL-SF was completed by participants 12–17 years old, and this analysis included three pain-related questions ('my swellings hurt,' 'pain in joints' and 'painful to move'); the Haem-A-QoL was completed by participants ≥18 years old, and this analysis included five pain-related questions (those included in the Haemo-QoL-SF plus 'difficulty walking as far as wanted to' and 'needed more time to prepare') [23, 24]. The EQ-5D-5L assessment was completed by adolescents (aged 12–17 years) and adults (aged ≥18 years) and included one pain-related question, which was 'pain/discomfort' [25]. Response options for the Haem-A-QoL/Haemo-QoL-SF were 'never,' 'seldom/rarely,' 'sometimes,' 'often' and 'always/all the time,' whereas response options for the EQ-5D-5L pain/discomfort dimension were 'extreme,' 'severe,' 'moderate,' 'slight' and 'no' pain/discomfort.

2.4 | Data Analysis

In this analysis, pain-related QoL measures were assessed in the overall population and in those who had target joints at baseline (according to the ISTH definition [26]). Additional analyses of the overall population were stratified by age, FVIII inhibitor status, and prior treatment approach (prophylactic or episodic). As assessment time points varied between studies, similar assessment time points were grouped to allow for pooling of the data. Only descriptive statistics are reported.

3 | Results

3.1 | Participant Demographics and Clinical Characteristics

At the time of data cut-off, data from 504 PwHA who were enrolled across the four clinical studies were available for analysis (Table 1); the median emicizumab exposure was 2.04 (range 0.02–4.25) years, representing 1150 patient-years. At baseline, 336 (66.7%) participants had target joints, 283 (56.2%) had FVIII inhibitors and 265 (52.6%) had arthropathy (of whom 191 had target joints). The median age (range) was 33 (12–80) years. Prior to enrolment, 173 (34.4%) PwHA had received prophylactic treatment, 281 (55.9%) had received episodic treatment and 49 (9.7%) had received both prophylactic and episodic treatment (data missing for one participant). Participants without FVIII inhibitors who received prophylaxis typically received FVIII replacement products and participants with FVIII inhibitors received bypassing agents. Within the 24 weeks prior to study entry, 296 (58.7%) participants had <9 bleeds and 207 (41.1%) had ≥9 bleeds (data missing for one participant). The median emicizumab exposure was similar between participants with and without target joints.

Of the overall population (N = 504), 210 (41.7%) participants reported taking pain medication in the 4 weeks prior to initiating emicizumab: 99 (19.6%) took opioids, 126 (25.0%) took NSAIDs and 91 (18.1%) took non-opioids/non-NSAIDs. Pain medication use during the 4 weeks prior to starting emicizumab was more common in older participants compared with younger participants (12–17 years: 19.3% of participants; 18–34 years: 36.2%; 35–49 years: 47.1%; 50–80 years: 63.5%), and in participants who were previously receiving episodic treatment only (47.3%) or both prophylactic and episodic treatment (49.0%) compared with participants previously receiving prophylaxis only (30.6%). No notable trends were observed with respect to pain medication use when the population was stratified by the presence of FVIII inhibitors, nor when comparing the overall population to the population of PwHA with target joints at baseline.

TABLE 1 | Baseline demographics and characteristics in the overall population.

	Overall pooled population $N = 504$
Age, years	
Mean (SD)	34.6 (15.8)
Median (range)	33.0 (12.0–80.0)
Age group, *n* (%)	
12–17 years	83 (16.5)
18–34 years	185 (36.7)
35–49 years	140 (27.8)
≥50 years	96 (19.0)
Race, *n* (%)[a]	
American Indian or Alaska Native	20 (4.0)
Asian	100 (19.8)
Black or African American	27 (5.4)
Native Hawaiian or other Pacific Islander	3 (0.6)
White, Hispanic or Latino in Ethnicity	32 (6.4)
White, Not Hispanic or Latino in Ethnicity	292 (57.9)
White, Not Reported or Unknown in Ethnicity	7 (1.4)
Unknown	23 (4.6)
FVIII inhibitors at study entry, *n* (%)[a]	
Yes	283 (56.2)
No	221 (43.9)
Target joints at study entry, *n* (%)[a]	
0	167 (33.1)
1	102 (20.2)
≥2	234 (46.4)
Missing	1 (0.2)
Haemophilic arthropathy at baseline, *n* (%)[b]	
No	239 (47.4)
Yes	265 (52.6)
Therapy prior to enrolment, *n* (%)[c]	
Prophylactic only	173 (34.3)
Episodic only	281 (55.8)
Prophylactic and episodic	49 (9.7)
Missing	1 (0.2)
Pain medication received in the 4 weeks prior to emicizumab, *n* (%)	
Any pain medication	210 (41.7)
Opioids	99 (19.6)
NSAID	126 (25.0)
Non-opioid/non-NSAID	91 (18.1)

Abbreviation: FVIII, Factor VIII; NSAID, nonsteroidal anti-inflammatory drug; PwHA; People with haemophilia A; SD, standard deviation.

[a]Percentages may not add to 100.0% due to rounding of data.

[b]The number of PwHA with arthropathy at baseline includes individuals with events of haemophilic arthropathy, arthropathy, arthroplasty, synovectomy and synoviorthesis reported by participants in prior, or prior and concomitant, periods in their medical history.

[c]Data missing for one participant.

3.2 | Pain-Related QoL in the Overall Population

In the overall population, at baseline, 464 PwHA completed the questions related to pain in the Haem-A-QoL/Haemo-QoL-SF and 470 PwHA completed the pain/discomfort dimension of the EQ-5D-5L.

Improvements in pain were consistently observed from baseline through to the final assessment at Weeks 73–78, across all pain-related QoL outcomes (Figure 1). Improvements were observed from the first common assessment time point across studies

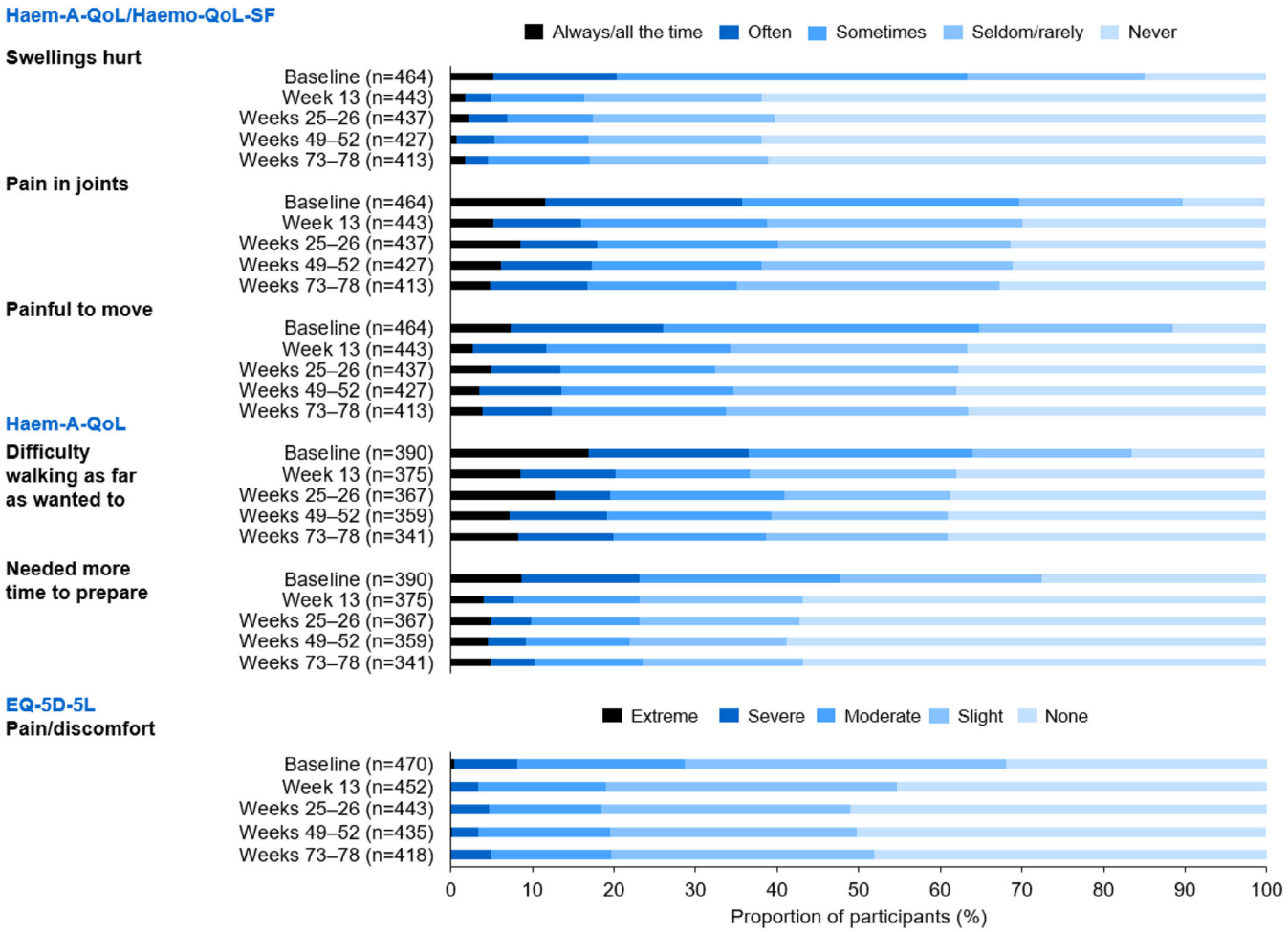

FIGURE 1 | Pain-related QoL outcomes from the Haem-A-QoL/Haemo-QoL-SF and EQ-5D-5L in the overall population. QoL, quality of life.

(Week 13, although HAVEN 1 had additional earlier assessments, where similar improvements in pain-related questions were observed at Weeks 5 and 9) and were sustained through to the last assessment time point (Weeks 73–78).

For the Haem-A-QoL/Haemo-QoL-SF, the largest improvement was in 'my swellings hurt,' with 'never/rarely' responses increasing from 37.0% (170/464) at baseline to 84.0% (371/443) by Week 13. 'Never/rarely' responses for 'pain in joints' also increased from 30.0% (140/464) at baseline to 61.0% (271/443) by Week 13. For the EQ-5D-5L, 71.0% (335/470) of PwHA had 'no/slight' pain/discomfort at baseline; this improved to 81.0% (366/452) by Week 13. All improvements observed in the pain-related dimensions of the Haem-A-QoL/Haemo-QoL-SF and EQ-5D-5L were maintained through Weeks 73–78.

3.3 | Pain-Related QoL in the Target Joint Population

Of the 336 people with target joints, 308 completed the questions related to pain in the Haem-A-QoL/Haemo-QoL-SF, and 313 completed the pain/discomfort dimension of the EQ-5D-5L. Similar trends of improvement were observed in the target joint population compared with the overall population (Figure 2).

3.4 | Pain-Related QoL Stratified by Age, Presence of FVIII Inhibitors and Prior Treatment Approach

Improvements in pain were consistently observed from baseline through to the final assessment at Weeks 73–78, irrespective of age, FVIII inhibitors, or prior treatment approach.

PwHA aged 12–17 years showed the most improvement when the overall population was stratified by age: 43.0% (33/76) responded 'never'/'rarely' at baseline versus 93.0% (64/69) at Week 13 for 'my swellings hurt' and 51.0% (39/76) responded 'never'/'rarely' at baseline versus 86.0% (59/69) at Week 13 for 'pain in joints' (Figure 3). This was in comparison with PwHA aged ≥ 50 years, who showed the smallest improvement: 26.0% (23/87) 'never'/'rarely' at baseline versus 76.0% (63/83) at Week 13 for 'my swellings hurt' and 20.0% (17/87) 'never'/'rarely' at baseline versus 42.0% (35/83) at Week 13 for 'pain in joints.'

Both PwHA with and without FVIII inhibitors demonstrated improvement similar to the overall population (Figure 4). A greater improvement from baseline was seen in people with versus without FVIII inhibitors, particularly for 'my swellings hurt': 31.0% (79/256) 'never'/'rarely' at baseline versus 86.0% (212/246) at Week 13 for PwHA with FVIII inhibitors compared

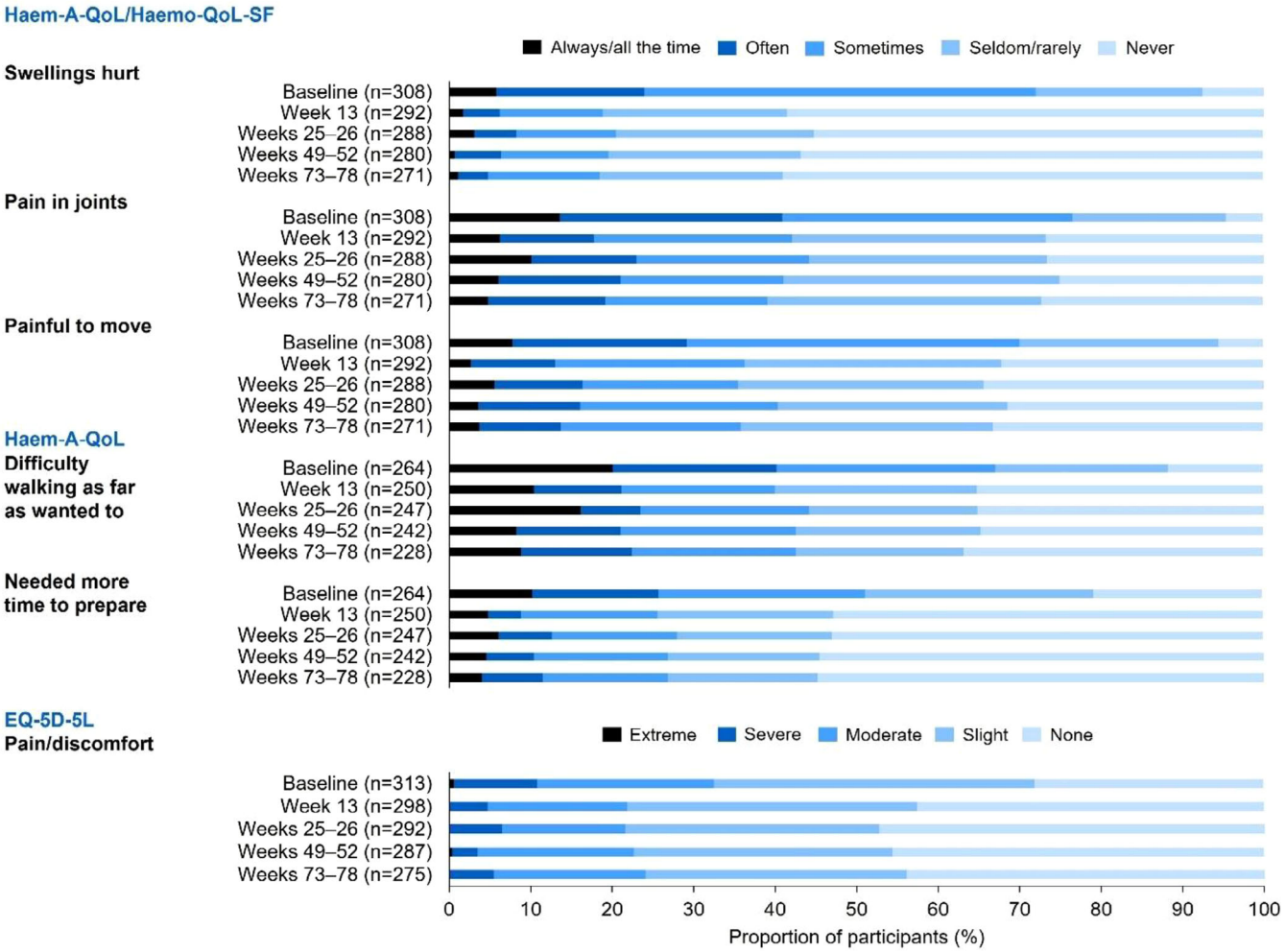

FIGURE 2 | Pain-related QoL outcomes from the Haem-A-QoL/Haemo-QoL-SF and EQ-5D-5L in the target joint population. QoL, quality of life.

with 44.0% (91/208) at baseline versus 81.0% (159/197) for PwHA without FVIII inhibitors.

When stratified by prior treatment (prophylaxis, episodic treatment, or both), improvements in the proportion of people responding 'never'/'rarely' were comparable with those seen in the overall population (Figure 5). In those who received prior prophylactic treatment, there was a 41.7% increase in those who responded 'never'/'rarely' from baseline to Week 13 for 'my swellings hurt,' and a 29.2% increase for 'pain in joints.' In those who received prior episodic treatment, there was a 51.8% increase in those who responded 'never'/'rarely' from baseline to Week 13 for 'my swellings hurt,' and a 35.6% increase for 'pain in joints.'

4 | Discussion

Clinical studies of emicizumab prophylaxis in PwHA have demonstrated lower annualized bleeding rates (ABRs) versus no prophylaxis by over 96% (in participants with no FVIII inhibitors) and 87% (in participants with FVIII inhibitors) in the HAVEN 3 and HAVEN 1 trials, respectively [13, 15]. Further, intra-participant analyses have shown that emicizumab prophylaxis resulted in an ABR 68% lower than participants on prior FVIII prophylaxis in HAVEN 3 [15], and 79% lower than participants receiving prior bypassing agent prophylaxis in HAVEN 1 [13]. These data are supported by results from HAVEN 4, STASEY, and other trials in the HAVEN program, including long-term outcomes [16-19, 27], and are consistent with real-world experience [28–30]. Expanding on these previously reported reductions in bleeding events observed with emicizumab prophylaxis, this post hoc pooled analysis of four phase 3/3b clinical studies found early and sustained improvements in pain-related QoL when emicizumab prophylaxis was administered to adults and adolescents of all ages with HA, with or without FVIII inhibitors, as measured by the Haem-A-QoL/Haemo-QoL-SF and the ED-5Q-5L pain-specific questions. Improvements in responses to questions such as 'my swellings hurt' and 'pain in joints' are likely to be associated with a reduction in acute and chronic pain, respectively. The potential for a treatment to offer improvements in long-term chronic pain that has accumulated over years of joint bleeding may have a significant impact on QoL in PwHA. Sustained prophylactic treatment with emicizumab decreases joint haemorrhages and rebleeding into joints, likely resulting in reduced synovial inflammation and associated pain. The results of this post hoc analysis illustrate the clinical benefits of emicizumab prophylaxis beyond the sustained bleed protection and target joint resolution documented throughout the HAVEN studies [13–18], the STASEY study [19], and in real-world

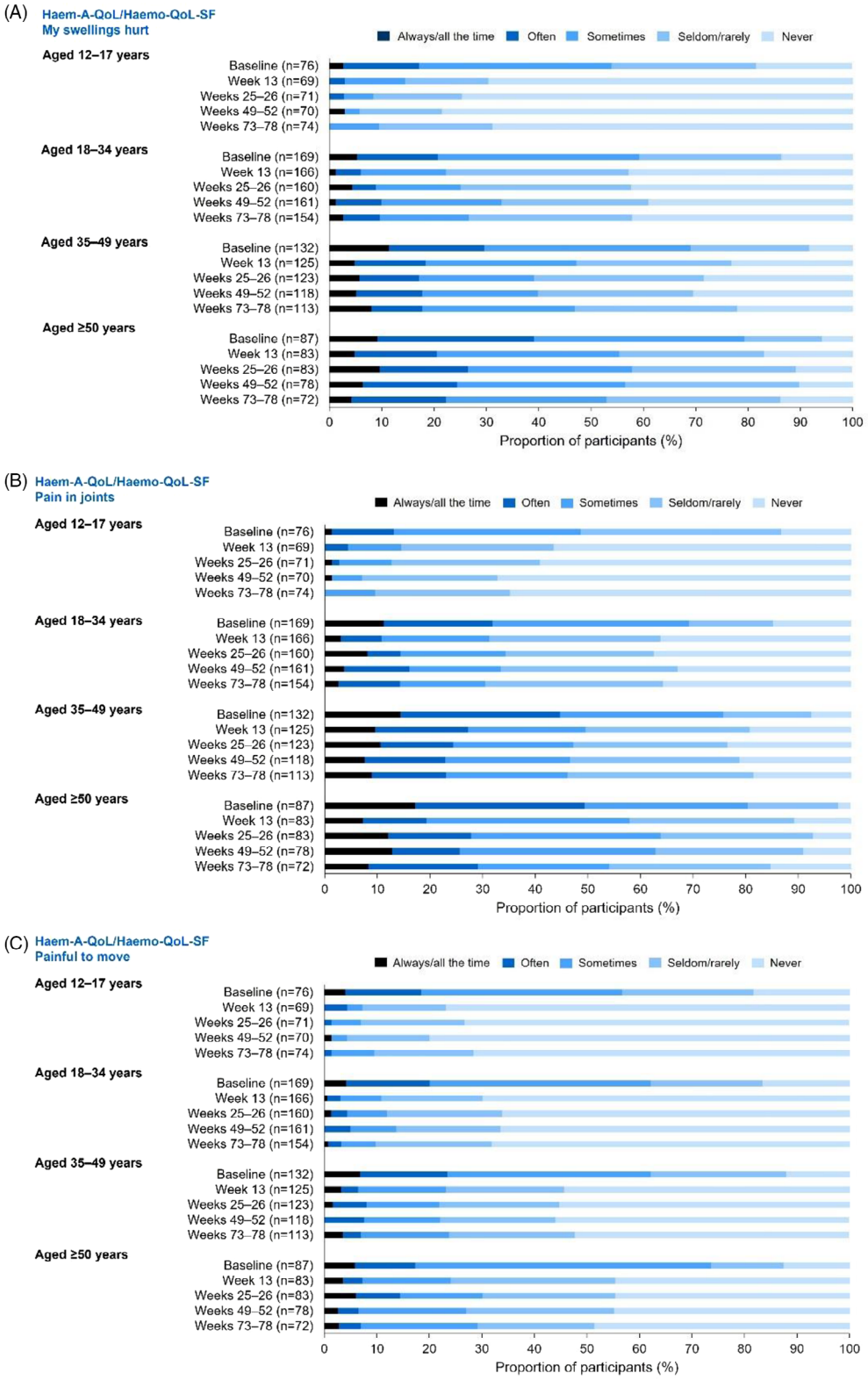

FIGURE 3 | Pain-related QoL outcomes stratified by age from the Haem-A-QoL/Haemo-QoL-SF and EQ-5D-5L: (A) 'my swellings hurt'; (B) 'pain in my joints'; (C) 'painful to move'; (D) 'difficulty walking'; (E) 'needed more time to prepare' and (F) 'pain/discomfort.' QoL, quality of life.

experience [28–32], and are aligned with previously reported broad health-related outcomes [33–35].

PwHA aged 12–17 years had greater improvement in pain-related QoL upon initiation of emicizumab compared with those aged 35 years and older. This is unsurprising, as younger PwHA have less advanced joint disease and therefore greater scope for improvement in pain-related QoL [36]. Indeed, clinically relevant improvements in the Haemophilia Joint Health Score were observed in younger PwHA after 48 weeks of emicizumab

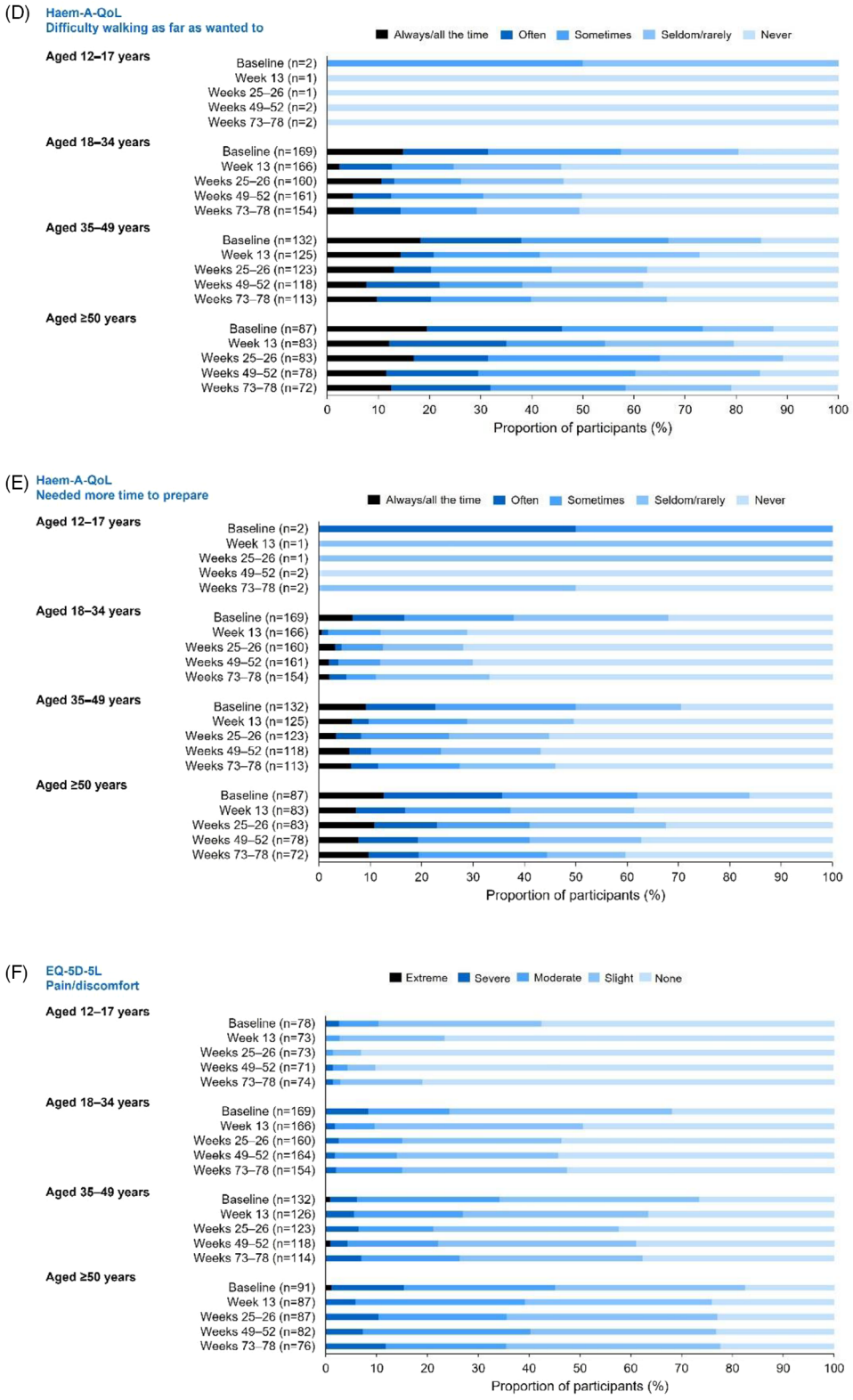

FIGURE 3 | (Continued)

prophylaxis in HAVEN 3; no change was reported in participants aged ≥40 years, likely due to the degree of joint damage, which might be irreversible in some cases [37]. The propensity of older PwHA to have more advanced joint disease is borne out by the clinical characteristics of the population in this analysis: people aged ≥50 years had more target joints and higher rates of haemophilic arthropathy compared with the younger participants (data not shown). It is likely that the older population has lived a longer duration with a higher burden of disease, given the historically lower prophylaxis rates that may have progressively and irreversibly impacted their joint health. Moreover, the use of pain medication prior to emicizumab initiation, which provides

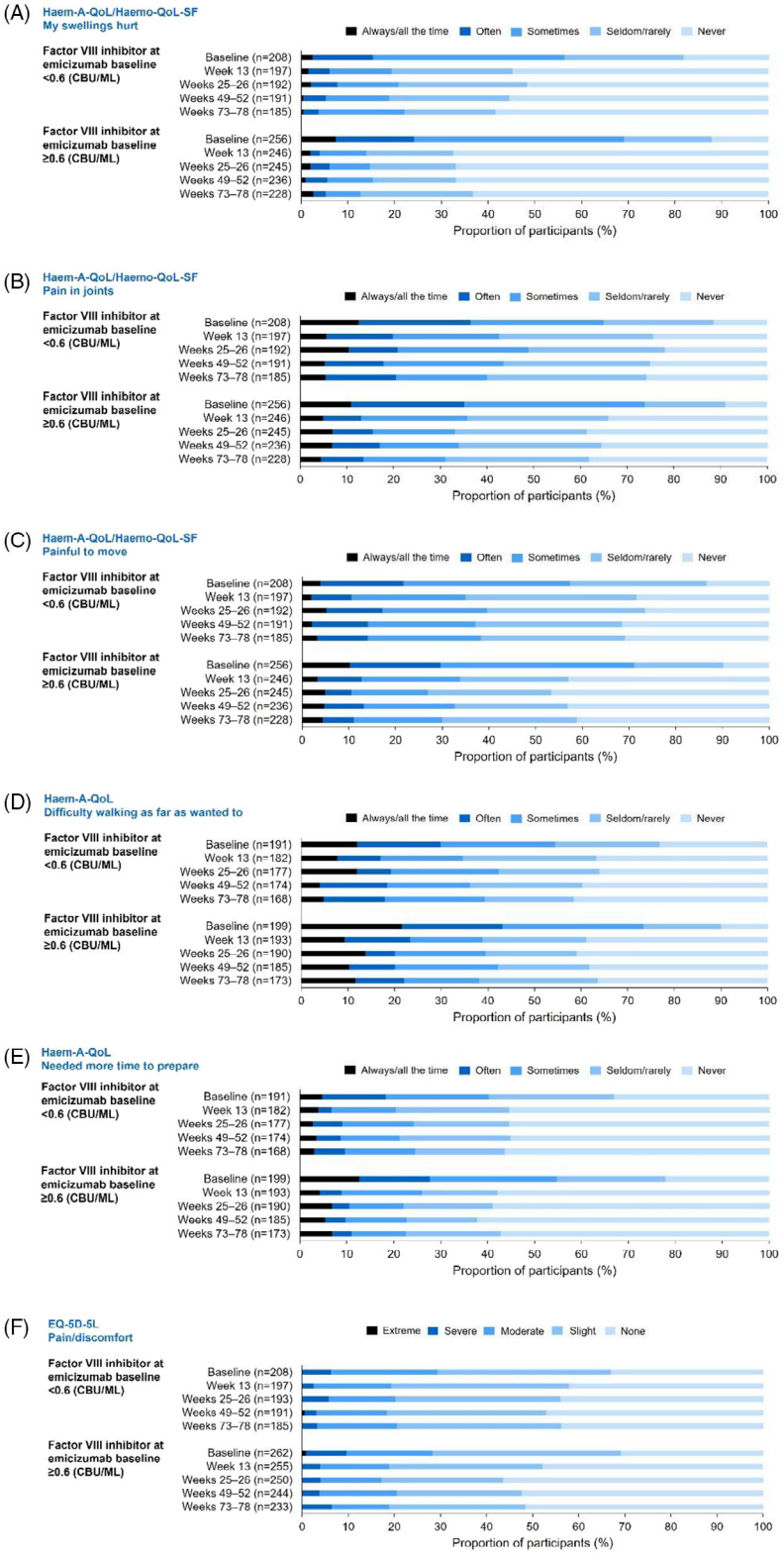

FIGURE 4 | Pain-related QoL outcomes stratified by inhibitor status from the Haem-A-QoL/Haemo-QoL-SF and EQ-5D-5L: (A) 'my swellings hurt'; (B) 'pain in my joints'; (C) 'painful to move'; (D) 'difficulty walking'; (E) 'needed more time to prepare' and (F) 'pain/discomfort.' QoL, quality of life.

insight into the pain experienced by this HA population at baseline, showed a correlation with age. By this surrogate measure, a greater proportion of older PwHA experienced pain prior to emicizumab treatment than younger PwHA. Nonetheless, PwHA aged over 35 years old in this analysis still reported improvements in pain-related QoL, irrespective of the presence of target joints at baseline or prior treatment approach.

At baseline, PwHA previously receiving episodic treatment were more likely to report use of pain medication in the 4

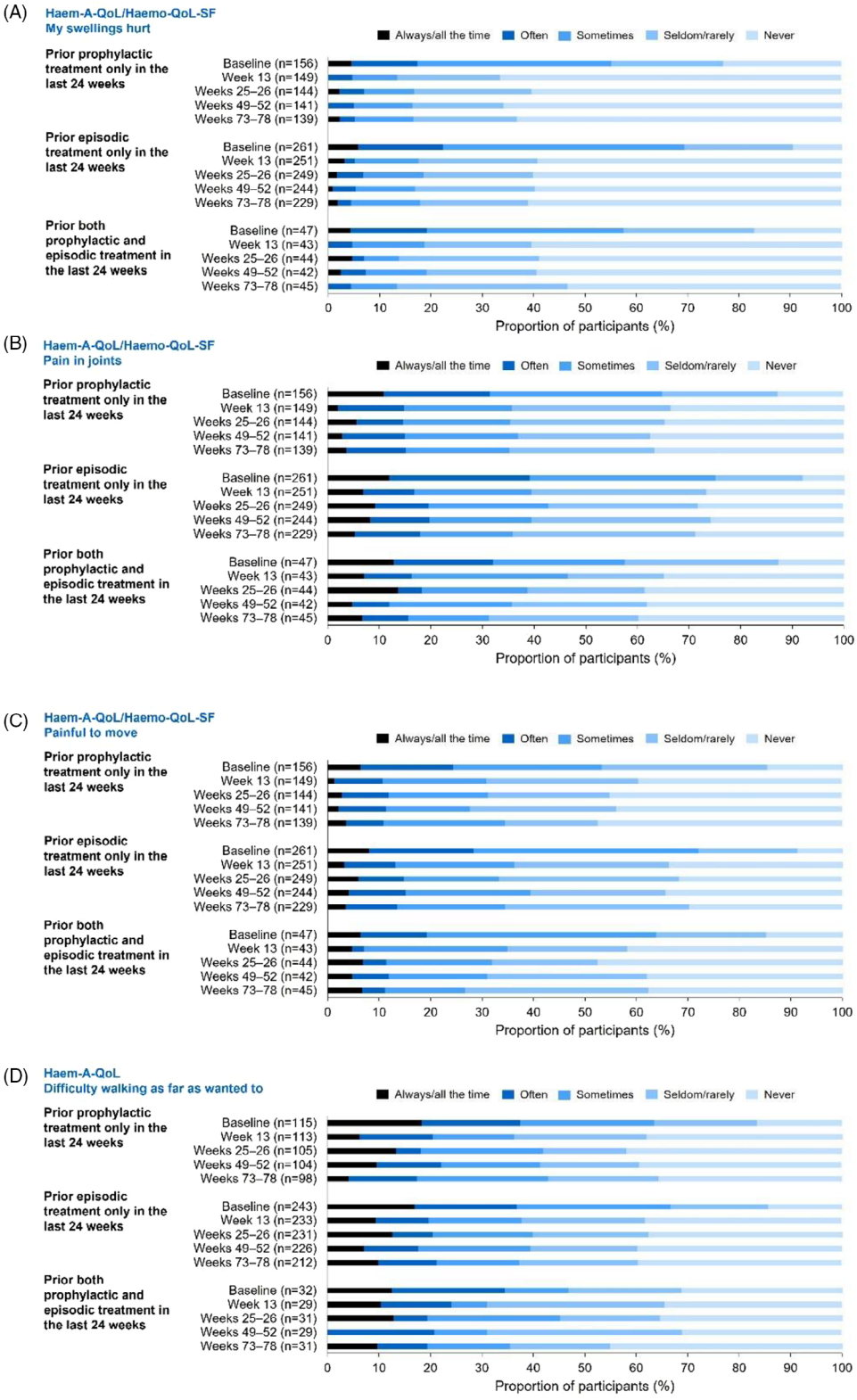

FIGURE 5 | Pain-related QoL outcomes stratified by prior treatment approach from the Haem-A-QoL/Haemo-QoL-SF and EQ-5D-5L: (A) 'my swellings hurt'; (B) 'pain in my joints'; (C) 'painful to move'; (D) 'difficulty walking'; (E) 'needed more time to prepare' and (F) 'pain/discomfort.' QoL, quality of life.

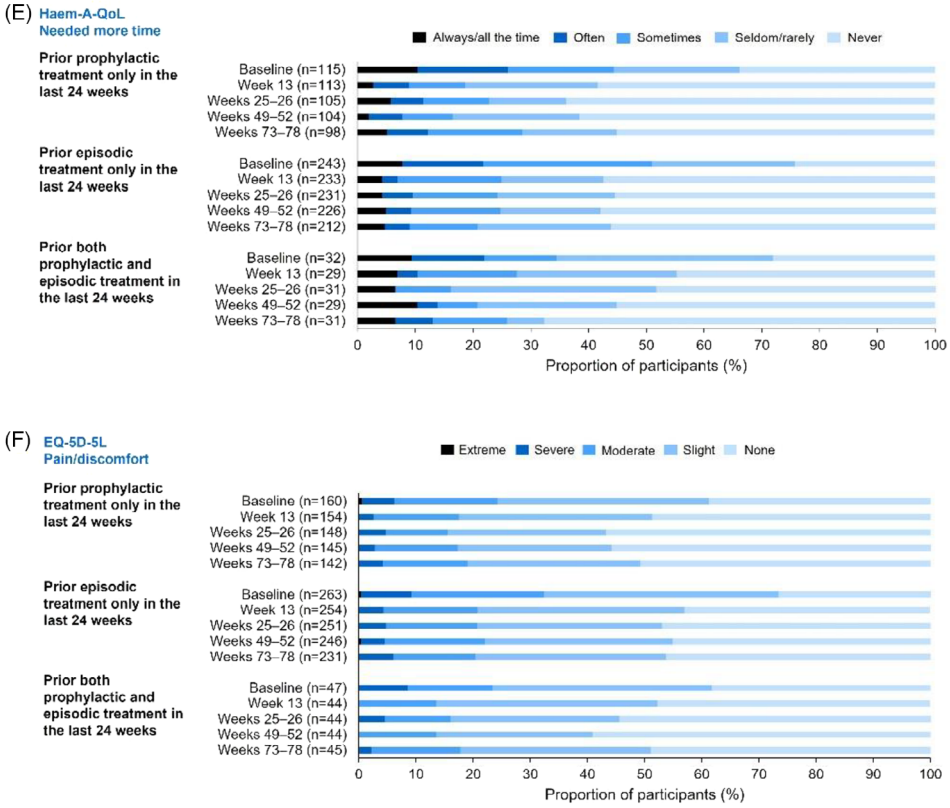

FIGURE 5 | (Continued)

weeks prior to initiating emicizumab prophylaxis, compared with those previously receiving prophylaxis. These data, alongside the higher proportion of older PwHA reporting pain medication use, emphasize the benefit of prescribing primary prophylaxis early in life in PwHA [38, 39], to reduce the risk of chronic pain in later life. The type of prophylaxis may also be consequential. In a post hoc analysis of the A-LONG study [24], similar to this post hoc analysis, pain was assessed using the Haem-A-QoL and EQ-5D-3L questionnaires at baseline and at the end of the study in PwHA treated with extended half-life FVIII prophylaxis, who had been previously treated episodically (26.0%) or prophylactically (74.0%) with standard half-life FVIII [21]. A significantly greater proportion of individuals did not experience painful swellings or pain in their joints at the end of the study versus baseline. In the present analysis, improvements in pain-related QoL were also observed even in people previously receiving prophylaxis, suggesting that emicizumab may offer additional clinical benefit over FVIII prophylaxis, considered standard-of-care at the time of initiation of the HAVEN 1, 3, and 4 and STASEY studies.

4.1 | Study Limitations

Although results from this study show an association between emicizumab prophylaxis and reduced pain levels in PwHA, additional analyses are warranted to confirm the findings in a real-world setting. A limitation of this study is that it is a post hoc analysis; the four clinical trials included were not designed to specifically assess pain-related QoL or collect information about pain management. We therefore limited our analyses to descriptive statistics, which limit the strength of conclusions that can be drawn from the results.

Further, this analysis did not exclude data from PwHA who discontinued from the study. It is not anticipated, however, that reported improvements in pain are an artefact of study discontinuations, as attrition of participants was minimal. At baseline, there were a total of 464 participants, versus 413 at Weeks 73–78. Previous trials have indicated most discontinuations were due to the availability of commercial emicizumab, with few discontinuations due to AEs or lack of efficacy [13–19, 27]. Consequently, including data from the PwHA discontinuing study is not believed to change the outcomes reported.

In this analysis, pain-specific questions were evaluated from multidimensional questionnaires assessing overall health-related QoL rather than using pain-specific questionnaires. The EQ-5D-5L is a non-disease specific tool used to assess overall health status, and the Haem-A-QoL/Haemo-QoL-SF are validated for use in PwHA but are not pain-specific. Furthermore, although inferences can be made about which of the pain-specific questions may be applicable to acute and chronic pain, the questions were not designed to differentiate between the two. The development and validation of assessments for acute and chronic pain is critical to our understanding of how a new treatment impacts pain- and health-related QoL in PwHA. Additionally, improved assessments of pain intensity, interference and other pain dimensions may offer opportunities to aid in the diagnosis of acute bleeding episodes. Despite the question of 'difficulty walking' allowing speculation on the impact of emicizumab on physical activity, the questions do not provide

detailed insights on how pain may interfere with daily functions. Including measures of pain interference into clinical studies would strengthen future analyses of pain outcomes. Indeed, using the Patient Reported Outcomes Burdens and Experience (PROBE) questionnaire, Kucher et al. reported that reductions in interference with activities of daily living and frequency of pain interference occurrence were core patient-centric measures for pain [40].

5 | Conclusions

In adults and adolescents with HA with or without FVIII inhibitors receiving emicizumab prophylaxis, improved pain-related QoL was observed as early as Week 13 of emicizumab treatment, as measured by pain-specific questions from the Haem-A-QoL/Haemo-QoL-SF and the EQ-5D-5L. Improvements may reflect a reduction in chronic pain, a crucial outcome for PwHA with established joint damage. Improvements in pain were observed regardless of target joint status at study entry or prior treatment approach. A greater proportion of younger individuals (12–17 years old) demonstrated improvements compared with older individuals (≥50 years old). The development of a validated pain-specific assessment tool to accurately characterise and measure pain in PwHA is needed to improve understanding of pain-related QoL, and such measures should be included to enhance future clinical trials and observational studies. Nonetheless, these results highlight the clinical benefits of emicizumab prophylaxis beyond bleed prevention.

Author Contributions

C.H., M.M. and E.T. contributed to the study design. C.H. contributed to the study conduct. C.H., M.W.S., B.G., E.L., M.M., K.M., E.T. and T.W.B. contributed to data analysis and interpretation. All authors revised the manuscript critically and provided final approval of the version to be published, and all authors agree to be accountable for all aspects of the work.

Acknowledgements

The HAVEN 1, 3 and 4 studies and STASEY study were sponsored by F. Hoffmann-La Roche Ltd. Third party medical writing assistance, under the direction of the authors, was provided by Tiffany Blythe, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd. The authors would like to thank the study participants and their families, as well as the study investigators, research coordinators and nurses.

Ethics Statement

All participants enrolled in the four studies provided written informed consent. The study protocols were approved by institutional review boards or ethics committees at each centre. The studies were conducted in accordance with the Declaration of Helsinki, the Act on the Protection of Personal Information, the Ethical Guidelines for Medical and Biological Research involving Human Subjects, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable laws and regulations.

Conflicts of Interest

Cedric Hermans has received research funding from Bayer, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda, and Sobi; consulting fees from Bayer, Shire/Takeda, Novo Nordisk, CSL Behring, Sobi, Pfizer, CAF-DCF, and LFB; speakers bureau and honoraria from Bayer, BioMarin, CAF-DCF, CSL Behring, F. Hoffmann-La Roche Ltd, LFB, Novo Nordisk, Octapharma, Pfizer, Shire/Takeda, Sobi, and UniQure; support for attending meetings and/or travel from BioMarin, F. Hoffmann-La Roche Ltd, LFB, Novo Nordisk, and Sobi. Mark W. Skinner has received research support for the PROBE study and core outcomes studies as part of independent investigator-initiated research projects from Band Therapeutics, BioMarin, CSL Behring, Novo Nordisk, F. Hoffmann-La Roche Ltd, Sanofi, Takeda, and Vega Therapeutics; consulting fees from Bayer, and Sanofi; honoraria from Bayer, Novo Nordisk, Genentech, Inc., Sanofi, and Takeda; support for attending meetings and/or travel from Bayer, Novo Nordisk, Sanofi, Takeda; participation on a Data Safety Monitoring Board or advisory board for Pfizer and Spark Therapeutics, Inc.; serves on advisory or governance boards of Blue Cross Blue Shield MAP, ICER, NHF MASA, NORD and WFH USA. Brittany Gentile has nothing to disclose. Elise Lim, Eunice Tzeng and Miranda Minhas are employees of Genentech, Inc., and shareholders at F. Hoffmann-La Roche Ltd. Katya Moreno is an employee and shareholder of F. Hoffmann-La Roche Ltd. Tyler W. Buckner has received research funding from NIH—NHLBI; consulting fees from BioMarin and Tremeau Pharmaceuticals; honoraria from Octapharma; participation on an advisory board for BioMarin, CSL Behring, and Novo Nordisk; board of directors for American Thrombosis and Hemostasis Network.

Data Availability Statement

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli. https://vivli.org/ourmember/roche/. For up-to-date 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://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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