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Original Research

Patient Experience With Efanesoctocog Alfa for Severe Hemophilia A: Results From the XTEND-1 Phase 3 Clinical Study Exit Interviews

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ABSTRACT

Purpose: Hemophilia A is a rare bleeding disorder that leads to recurrent hemarthrosis, which can ultimately result in reduced mobility and poor quality of life. Qualitative exit interviews provide insights into patient perspectives and support the interpretation of quantitative trial data, such as patient-reported outcome measures. In the Phase 3 XTEND-1 study (NCT04161495) of efanesoctocog alfa in participants with severe hemophilia A, exit interviews were conducted to understand pre- and post-study experiences with pain and physical functioning and to evaluate participants' treatment experiences.

Methods: In XTEND-1, participants (≥12 years old) received once-weekly efanesoctocog alfa prophylaxis 50 IU/kg for 52 weeks (Arm A) or on-demand efanesoctocog alfa 50 IU/kg for 26 weeks followed by 26 weeks once-weekly prophylaxis (50 IU/kg; Arm B). Optional qualitative exit interviews were conducted using a semi-structured guide in a subset of participants following study completion. Interviews included open-ended questions about participants' pre- and post-study experiences with hemophilia A and targeted questions relating to improvements in patient-reported outcomes assessed during XTEND-1, including the Haemophilia Quality of Life Questionnaire for Adults Physical Health subscale (Haem-A-QoL PH). Content validity of the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity 3a measure was also assessed, particularly the worst pain item.

Findings: Exit interviews were conducted with 29 of 159 patients enrolled in XTEND-1 (mean [range] age 40 [16–73] years). Of 17 participants enrolled in Arm A, 13 (76.5%) reported a "wearing off" feeling with pre-study treatment, including more aches/pain, breakthrough bleeds, and limited physical activities. Joint pain was the most reported pre-study symptom (96.6%; n = 28/29), followed by a reduced ability to move without pain (89.7%, n = 26/29). Improvements following efanesoctocog alfa prophylaxis in ≥1 Haem-A-QoL PH domain were reported by 89.7% (n = 26/29) of participants, with improvements in joint pain, the ability to move without pain, and painful swellings reported by at least 21 (84%) participants. Participants reported that the PROMIS Pain Intensity 3a items were relevant, clear, and easy to answer. Most participants (96.6%) were "quite satisfied" or "very satisfied" with efanesoctocog alfa prophylaxis. All participants preferred efanesoctocog alfa over pre-study treatment.

Implications: The exit interviews demonstrated that once-weekly efanesoctocog alfa prophylaxis resulted in patient-relevant and meaningful improvements in pain and physical functioning, consistent with the quantitative

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findings from XTEND-1. These results support the validity of the Haem-A-QoL PH and PROMIS Pain Intensity 3a assessed during XTEND-1, demonstrating the potential for change with efficacious treatment.
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Trial Registration Number: NCT04161495
Registry URL: https://clinicaltrials.gov/study/NCT04161495

Introduction

Hemophilia A is a rare X-linked bleeding disorder, characterized by deficiency or dysfunction of the coagulation factor VIII needed to maintain hemostasis.[1] Despite treatment advances, life-threatening bleeding still occurs in patients with hemophilia, as well as bleeding into the joints and musculoskeletal system. This can result in hemophilic arthropathy, chronic pain, impaired physical functioning (including limited range of motion, deformity, and functional disability), and reduced health-related quality of life.[2–4] The primary goal for people living with hemophilia A is to prevent bleeding by maintaining higher factor VIII levels.[5,6] A trough factor VIII level of 3 to 5 IU/dL or higher is considered a preferable target for prophylaxis by many physicians, according to the World Federation of Hemophilia.[5,6] Standard of care for hemophilia includes prophylaxis with factor replacement therapies, which are either plasma-derived or recombinant clotting factor concentrates.[5] However, despite prophylaxis, patients can still experience spontaneous bleeding requiring on-demand treatment.[7–9] In addition, frequent administrations are often required, creating a substantial treatment burden for patients with hemophilia and highlighting the need for more efficacious treatments.[5,10]

Efanesoctocog alfa is a first-in-class FVIII replacement therapy designed to provide high sustained factor activity levels for longer and overcome the von Willebrand factor-imposed half-life ceiling.[11–13] Once-weekly efanesoctocog alfa was approved in February 2023 by the United States Food and Drug Administration for adults and children with hemophilia A, based on the results of the pivotal Phase 3 XTEND-1 study (NCT04161495).[14] The European Medicines Agency accepted the marketing authorization application for efanesoctocog alfa in May 2023.[15] Efanesoctocog alfa was also approved in Japan in September 2023 and in Taiwan in August 2023.[16] Results from the XTEND-1 study demonstrated that efanesoctocog alfa prophylaxis provided superior protection from bleeding in patients who switched from pre-study standard of care FVIII prophylaxis.[17] The primary endpoint was achieved; prophylaxis with efanesoctocog alfa resulted in an estimated mean annualized bleeding rate of 0.71 (95% confidence interval: 0.52, 0.97) and median annualized bleeding rate of 0.00 (interquartile range: 0.00; 1.04).[17] Statistically significant and clinically meaningful improvements from baseline in patient-reported outcome measures including the Haemophilia Quality of Life (Haem-A-QoL) Questionnaire for Adults Physical Health (PH) subscale and Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity-Short Form 3a measure worst pain item (within the previous 7 days), were also reported.[17]

Qualitative interviews with patients in a clinical trial setting enable the exploration of the relevance and clinical meaningfulness of a specific treatment beyond clinical outcome assessments and side effects.[18] The results from such interviews can be used to help validate quantitative patient-reported outcomes and provide further insight into a patients' treatment experience. In rare disorders, these interviews can be especially beneficial, given the difficulty in recruiting for these trials due to relatively low patient numbers.[18] Here, we report the results of qualitative exit interviews conducted following participation in the XTEND-1 study. The objectives of these interviews were to understand patients' pre-study experiences with respect to pain and physical functioning and impact of prior treatments, to evaluate the patients' experience with efanesoctocog alfa and any improvements observed, and to obtain feedback on the use of the PROMIS Pain Intensity 3a measure, particularly the item measuring worst pain and the Haem-A-QoL PH.

Participants and Methods

Study Design

The full description of the Phase 3 XTEND-1 open-label multicenter study (ClinicalTrials.gov identifier: NCT04161495) has previously been published.[17] Eligible participants were aged 12 years or older, with an endogenous factor VIII activity of less than 1 IU/dL (<1%), or a documented genotype known to produce severe hemophilia A, who had previously received treatment for hemophilia A. Participants received once-weekly prophylaxis with efanesoctocog alfa (50 IU/kg) for 52 weeks (Arm A) or on-demand efanesoctocog alfa (50 IU/kg) for 26 weeks followed by 26 weeks once-weekly efanesoctocog alfa prophylaxis (50 IU/kg; Arm B).

Clinical sites in 6 countries (Argentina, United States, South Korea, France, United Kingdom, and Italy) invited participants in the XTEND-1 study to take part in exit interviews up to 6 months after end-of-treatment (52-week) visit, but before end-of-study was declared (3 February 2022). All patients who had completed their end-of-treatment (Week 52) were eligible for an exit interview. Selection of these sites for interview activities was based on feasibility and the timing required to obtain appropriate institutional review board/ethics committee reviews and subsequent consenting, as well as the number of patients enrolled in the XTEND-1 study that would be eligible by the time these approvals were obtained. No clinical or demographic participant quotas were targeted during recruitment for interview activities. Since all eligible participants at the selected sites were contacted for recruitment into the study, it was anticipated that the overall interview study sample would be reasonably representative of the overall study population.

Patient-Reported Outcome Endpoints Administered in XTEND-1

Patient-reported outcome measures in XTEND-1 included the Haem-A-QoL total score and PH subscales, all items of the PROMIS Pain Intensity 3a measure (both secondary endpoints) and the Patient Global Impression of Severity and Change assessments (both exploratory endpoints).[17] The Haem-A-QoL PH subscale and PROMIS Pain Intensity 3a worst pain item were used in the hierarchical testing procedure. The Haem-A-QoL PH domain was used to assess the impact of treatment on patients, and consists of 5 items pertaining to physical health: painful swelling, joint pain, ability to move without pain, ability to walk desired distance, and time needed to get ready.[19,20] The questionnaire asks about the experience with these items in the past 4 weeks (never, rarely, sometimes, often, all the time, not applicable) and was assessed at baseline, Week 26 and Week 52. The PROMIS Pain Intensity 3a instrument measures how intense pain is at its worst, average pain, and current level of pain and was assessed at baseline, Week 26, and Week 52. The questionnaire uses a 5-point Likert scale (1 = no pain, 5 = very severe pain). The Patient Global Impression of Severity is a single item scale in which patients indicate an overall assessment of their joint symptoms over the past week (1 = no joint symptoms, 5 = very severe joint symptoms) at baseline, Week 26, and Week 52. The Patient Global Impression of Change consists of one item that evaluates all aspects of patients' overall health and assesses if there has been an improvement, decline, or no change in their overall status since they started receiving the study medication (1 = very much improved, 7 = very much worse), administered at Week 26 and Week 52.

XTEND-1 Exit Interviews

All interviews were conducted in each country's native language using translated guides where applicable. Interviews were conducted by trained interviewers. The qualitative web-based interviews (~60 minutes) were conducted using a semi-structured interview guide that included open-ended questions intended to encourage the participants to talk about their experiences with hemophilia A, including symptoms and impacts. More targeted questions followed to address the specific study objectives, including: patient experiences with hemophilia A before XTEND-1 (particularly regarding pain and physical functioning); impact of efanesoctocog alfa on pain intensity and physical functioning (Haem-A-QoL PH subscale); experiences with global impressions of changes in joint pain (Patient Global Impression of Change, Patient Global Impression of Severity-joint severity score) and overall status and the meaningfulness of those changes, if any; and assessment of the content validity of PROMIS Pain Intensity 3a measure. Pre- and post-study experiences were collected during the exit interviews. The interviews were audio recorded, transcribed into English if needed, and de-identified. Currently, no clear guidance exists on the minimum or maximum number of participants required for qualitative interviews. However, qualitative studies can reach saturation at relatively small sample sizes,[21] given the concepts explored here, the sample size was deemed sufficient.

Data Analysis

Analysis of the qualitative interview data was performed using de-identified interview transcripts and the ATLAS.ti 9 software. Data were analyzed and summarized in aggregate for the overall sample and participant quotes from the interview transcripts were used to illustrate the data. Dominant trends were identified and compared across interviews to describe the way participants talked about their experience with hemophilia A and efanesoctocog alfa and any important changes experienced during XTEND-1. Formal hypotheses were not tested in this qualitative study.

Compliance With Ethics Guidelines

The XTEND-1 study was conducted in accordance with the Declaration of Helsinki[17] and was approved by an Institutional Review Board of each participating center before study conduction. Local ethics approval was obtained from each of the respective interview sites in Argentina, Canada, United States, South Korea, France, United Kingdom, and Italy; site staff obtained informed consent for the interviews from patients (as well parental consent and assent for adolescents).

Results

Patient Population

Exit interviews were completed with a total of 29 participants from the 6 participating countries (18.2%). Baseline characteristics for the interview cohort are presented in Table 1. The mean age at study entry was 40.0 years (standard deviation ±14.2) and all but one participant (96.6%) were male. Seventeen (58.6%) participants were enrolled in Arm A and 12 (41.4%) in Arm B. Most patients were from Argentina (n = 12) and the US (n = 9). The baseline demographics of the exit interview cohort were in line with the overall XTEND-1 population (n = 159) in which the mean age was 35.4 years (standard deviation ±15.1) and 99% of patients were male.[17]

Prestudy Experiences With Hemophilia A

Of the 17 participants in Arm A (who all received prophylaxis with factor VIII prior to enrolment) in XTEND-1, 13 (76.5%) reported a "wearing off" feeling of their product. Patients described "wearing off" as having more aches/pains and stiffness, feeling unprotected, having breakthrough bleeds, feeling the need to be more cautious, and limiting their physical activities (e.g., walking, working out at the gym). A few patients noted merely that they "felt" that they needed another infusion. Participant quotes describing pre-study experiences are shown in Table 2.

Table 1
Baseline demographic data exit interview participants.

Characteristic	Total (N = 29)
Age, years	
Mean (SD), range	40 (14.2), 16–73
Age at diagnosis, years	
Mean (SD), range	1.9 (2.7), 0–12
Males, n (%)	28 (96.6)
XTEND-1 treatment arm	
Arm A (prophylaxis), n (%)	17 (58.6)
Arm B (on-demand followed by prophylaxis), n (%)	12 (41.4)
Country, n (%)	
Argentina	12 (43.4)
United States	9 (31.0)
South Korea	4 (13.8)
France	2 (6.9)
United Kingdom	1 (3.4)
Italy	1 (3.4)

SD = standard deviation.

Pain was the most frequently reported pre-study symptom, with 28 (96.6%) participants reporting that they experienced some level of hemophilia-related pain (i.e., joint pain) before starting the trial. Episodes of intense pain were generally associated with acute bleeds, twisted joints, or pulled muscles, whereas chronic pain was generally attributed to cumulative joint damage that had occurred over a number of years and/or arthritis. All 28 patients described their pain to be of at least moderate or severe intensity. When describing hemophilia-related pain/aches before the study, 26 (92.9%) participants described it as occurring in more than one joint and with varying degrees of severity (Table 2).

Concepts Assessed by the Haem-A-QoL PH Subscale Prior to Starting XTEND-1 Study

Four of the 5 concepts assessed in the Haem-A-QoL PH subscale were experienced by at least 25 (86.2%) of the interview participants prior to entering the study (Figure 1A). Joint pain was the most commonly reported pre-study symptom, experienced by 28 (96.6%) participants, with acute bleeds and cumulative joint damage commonly reported. Participant quotes describing the concepts assessed by the Haem-A-QoL PH are shown in Table 2. The majority of participants (89.7%) also reported a reduced ability to move without pain, with common factors including aches, pain, and swelling in the joints (Figure 1A and Table 2). Limitations in the ability to walk desired distances were reported by 25 (86.2%) participants, associated with joint pain, joint swelling, and decreased mobility in the lower extremities. While reported less frequently, a substantial portion of the sample (41.4%) also reported that they needed more time to get ready due to their hemophilia.

Improvements in Haem-A-QoL PH Concepts During the XTEND-1 Study

Among the 28 patients who noted pre-study issues, 26 (89.7%) reported improvements in at least one Haem-A-QoL PH concept during the XTEND-1 study. Improvements in the concepts assessed in the Haem-A-QoL PH subscale, including joint pain, the ability to move without pain, and painful swellings, were reported by at least 21 (84%) participants (Figure 1B). Improvements in the ability to walk desired distances and time to get ready were reported by a slightly lower proportion of

Table 2
Participant quotes from exit interviews.

Interview objective	Example participant quotes	Country
Pre-study experiences with hemophilia A	*"It's almost like you can feel that you need an injection…I don't know how to describe it. I was aware…I felt different immediately after, you know, the hours after an injection, compared to say, 4 days later before I did an injection. I was aware that I needed to [infuse]."*	UK
	"I think just the pain, in general, was what…impacts my ability to do my life…. You can have arthritic swelling and you can also have bleed swelling or both at the same time, and it's hard to know the difference…."	US
Experiences with concepts assessed by the Haem-A-Qol PH subscale prior to starting XTEND-1 study	*"I do have joint inflammation symptoms so that is why I'm uncomfortable. It bothers me to the degree that it annoys me a little, like that. It's not like it hurts continuously like when I'm bleeding, it doesn't feel like that… I am feeling pain because of the accumulated joint damage in the body… when it bleeds, the pain continuously damages the joints on and on."*	South Korea
	"The swelling didn't let me walk. The severe pain wasn't even the problem, it was the swelling. The knee was swollen generally. I couldn't stretch it. It rested bent for a couple of days."	Argentina
	"Yes, [hemophilia] totally affects that person's life because you can't live a normal life. Due to the pain, the inability to move…not just because of the swelling but also because of all the collateral damages that the continuous hemorrhages in the joints cause."	Argentina
	"[Pain interfered with distance walked] My primary method of exercising these days is going on walks. And if I would go beyond about 30 to 40 minutes, I can expect some flare-up from that."	US
	"I definitely leave extra time to get ready, particularly in the mornings when I wake up and my limbs are just a bit stiffer"	UK
Improvements in Haem-A-QoL PH concepts during the XTEND-1 study and meaningfulness of changes	*"I noticed a lot of improvements…The most important thing is that pain gets better instead of worsening…I have also noticed an improvement in the movement of my elbows: they are freer in the movement."*	Italy
	"There is much less pain, and my range of activity has expanded, so it is significant to have more things that I am able to do."	South Korea
	"A lot of improvement [was important] …Since I had many less bleedings …that caused less damage of the joint, less pain and when there was a bleeding, I recovered quickly… [Change was meaningful as] that allowed me to resume my normal activities faster, without having to rest as much."	Argentina
	"[Change is meaningful] Because now I can go out for walks. It was something I didn't do before."	Argentina
Improvements beyond pain and physical functioning	*"Yes, clearly [improvements are important]. It's better on a daily basis… Well, I can do a lot more things, I am less tired in the evening and at the end of the week, I can move about more…. For example, when I go for walks with my dog in the woods, I stay for a longer period of time…. It also makes me feel a bit more confident to go on longer walks without having to wonder whether my knees will hurt, or my ankles will hurt…."*	France
Improvements in PGIS-Joint Symptoms and overall status, and the definition of meaningful change	*"Thanks to this treatment I am able to walk and exercise (not sport, but gymnastics) much more frequently and safely."*	Italy
	"Any improvement is always acceptable…any improvement would be good for me."	US
	"…It would be a big improvement even if I could stay where I am at mild…mild is already a big improvement for me."	US
	"I just think any improvement is important no matter the scale, I think. Anything moving in a positive direction is important."	US
	"Yes because, since it helped me become independent…That's what a person with hemophilia wants the most."	Argentina
Treatment satisfaction	*"I am very, very satisfied. Yes, I truly am because this medication stopped the bleedings. I don't bleed…it was totally efficient. And if there are no bleedings, the joint doesn't get damaged further."*	Argentina
	"[Efanesoctocog alfa] because with this one, I know I won't have any problems in the future. Tomorrow for instance, I know that I will be okay because I always have a level of factor VIII in blood which prevents bleeding episodes."	Argentina

Haem-A-QoL PH = Haemophilia Quality of Life Questionnaire for Adults Physical Health subscale; PGIS = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Information System; UK = United Kingdom; US = United States.

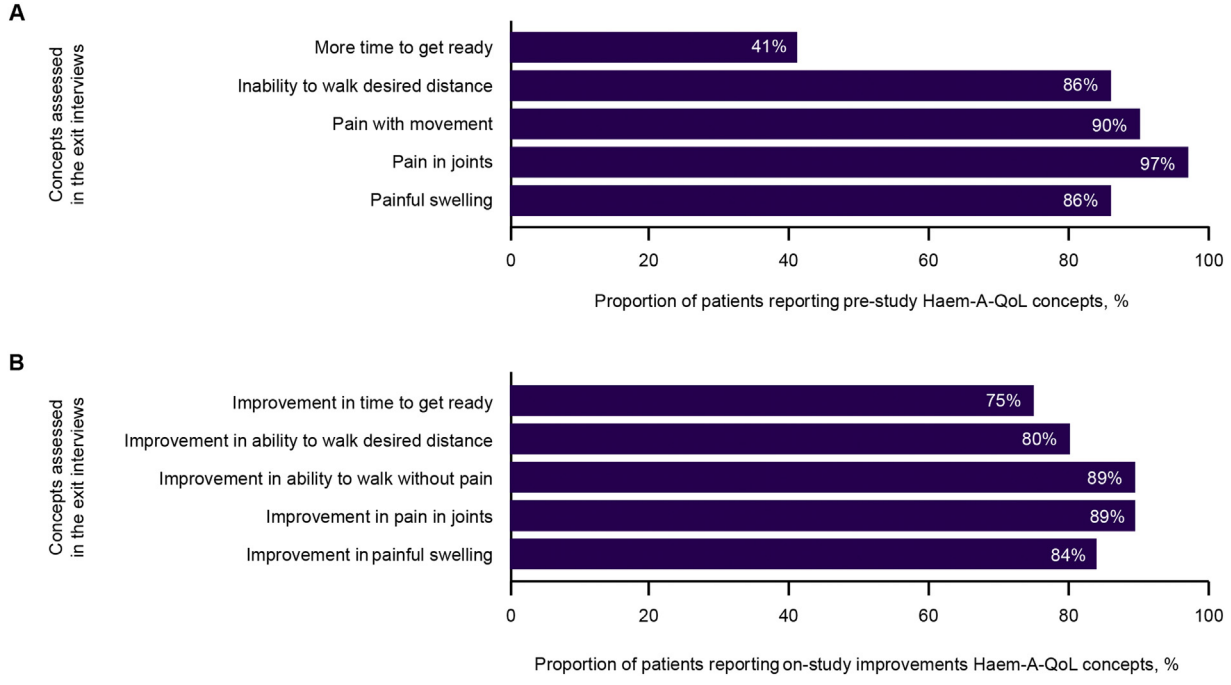

Figure 1. (A) Pre-study and (B) on-study experience of dealing with hemophilia A according to the Haem-A-QoL PH domain. [a]Calculated from the number of participants that reported the symptom/impact pre-study. Two participants were not asked about improvements in the ability to walk desired distance. Haem-A-QoL PH, Haemophilia Quality of Life Questionnaire for Adults Physical Health subscale.

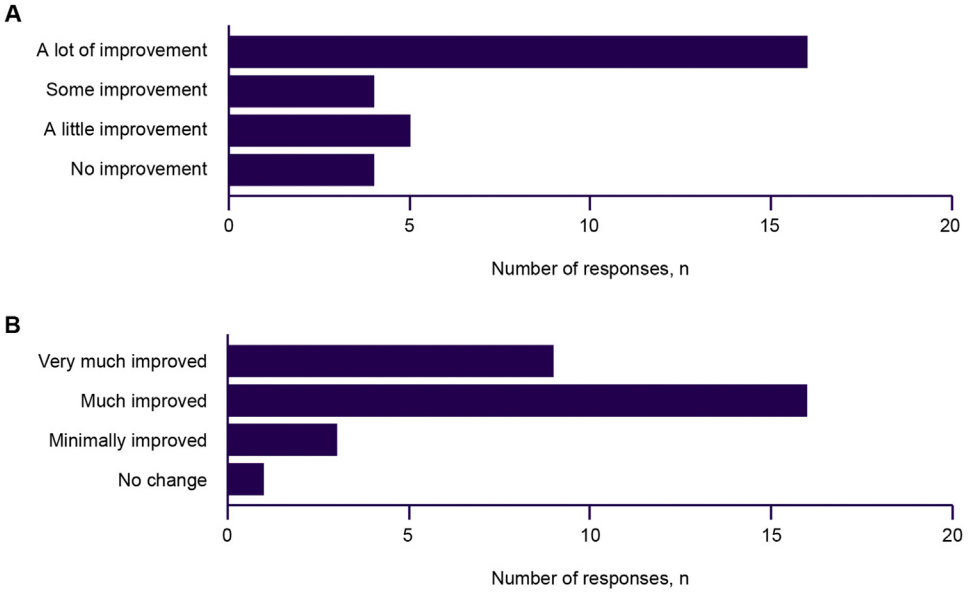

Figure 2. Patient global impression items following study treatment for (A) PGIS-Joint symptoms and (B) PGIC following study treatment. PGIC, patient global impression of change; PGIS, patient global impression of severity.

participants (80.0% and 75%, respectively). Participant quotes describing improvements in Haem-A-QoL PH concepts are presented in Table 2.

Twenty-five participants (89.3%) reported meaningful improvements in joint pain after switching to efanesoctocog alfa and one participant who did not report improvements in joint pain, reported improvements in the ability to move without pain and walk desired distances. The remaining 3 participants reported no change in joint pain intensity; however, they noted that improvements were not likely given the cumulative joint damage sustained with repeated joint bleeds over time. Many participants also reported improvements beyond pain and physical functioning, noting less fatigue, having more freedom, and a more convenient treatment (Table 2).

Reported levels of improvement varied across participants, ranging from minimal (common among individuals with mild impairments before the trial) to "dramatic" which were often associated with improvements in participants' overall functioning and health-related quality of life. Despite these differences in the magnitude of change, all participants reported that the improvements they experienced during the trial were meaningful to them. Specifically, participants consistently reported that any improvement in the concepts assessed by the Haem-A-QoL PH subscale would be meaningful to them, with one participant noting that remaining at the same level would also be meaningful since that would suggest that further damage to joints was not occurring.

Patient Global Impression Items

As measured by the Patient Global Impression of Severity-Joint Symptoms item, 16 (55.2%) participants reported having "a lot of improvement" in their joint symptoms (Figure 2A). Participants were also asked what a meaningful improvement in joint symptoms meant to them; 23 of 29 participants provided a response and of these the majority (n = 20; 87.0%) reported that any improvement in joint symptoms would be meaningful to them. Participant quotes describing improvements as measured by the Patient Global Impression of Severity-Joint Symptoms item are shown in Table 2. Three participants who reported "mild" joint symptoms noted that staying at that current level would be meaningful since this was already a significant improvement.

Participants were also asked to review the Patient Global Impression of Change item and report the level of change, if any, they saw in their overall health status since starting prophylaxis with efanesoctocog alfa (Figure 2B). Most participants (n = 16) reported "much improved" for the change in overall status. When asked what a meaningful improvement meant to them regarding change in overall status, all 21 participants who provided a response reported that any improvement (minimally improved or more) would be meaningful. Participants noted that any improvement in overall status increases the feeling of being protected and the ability to engage in physical activities (Table 2).

Evaluation of the PROMIS Pain Intensity 3a Measure

Participants reported that the PROMIS Pain Intensity 3a items were generally relevant, clear, and easy to answer using the response options provided. Participant quotes describing the evaluation of the PROMIS Pain Intensity 3a measure are presented in Table 3. Participant interpretations of the items, including "pain at its worst" as well as pain "right now" (i.e., during the exit interviews) were generally consistent. Three participants noted that their responses to the item assessing pain "right now" were based on the past few days to the past 7 days or even more broadly (today, in general, and at the moment).

All 29 participants were able to select responses for all 3 PROMIS Pain Intensity 3a items; however, 3 participants reported that the items addressing "pain at its worst" and "right now" were a bit easier to answer than the item referencing "average pain" (Table 3).

No participant indicated that concepts measuring pain intensity were missing from the instrument, providing strong support for the content validity of the scale. However, 6 participants did state that the questions could be more specific and/or capture additional details pertaining to hemophilia-related pain. All participants noted that hemophilia-related pain is very impactful, and, thus, any improvements or change in item responses would be meaningful to them and are important to measure.

Treatment Satisfaction

The majority of participants (96.6%) were either "quite" or "very satisfied" with efanesoctocog alfa prophylaxis (Table 4). Participants described improvement in symptoms and impacts, improved physical function, and decreased or completely eliminated bleeding events as key factors in their satisfaction ratings (Table 2). All 29 participants preferred efanesoctocog alfa prophylaxis over previous hemophilia treatments (Table 4).

Discussion

The present analysis reports the results of the XTEND-1 study exit interviews, which aimed to better understand participants' experiences with the outcomes of efanesoctocog alfa prophylaxis, focusing on the

Table 3
Participant quotes related to the evaluation of the PROMIS Pain Intensity 3a measure.

Interview objective	Example participant quotes	Country
Overall impressions of PROMIS Pain Intensity 3a	*"I think [the response choices] are pretty appropriate… they are classified well."*	Argentina
	"I think they [response choices] cover the range pretty well"	US
Quotes supporting definitions of worst pain, average pain, and pain right now	*"I understand it [pain at its worst] as real pain. With specifying if it was caused by a hematoma or the arthritis…It doesn't specify if it because of the hematoma or because of arthritis, but it is understandable."*	Argentina
	"When there is a swelling, the average pain would be when the swelling isn't at its bleeding peak and so it will hurt less…when it has already started the process of healing. It's at the average point…it causes pain, but it is healing…there is when I think the pain subsides a bit."	Argentina
	"There's no memory involved. It's just kind of a quick status check of, okay well how am I feeling right now?"	US
Quotes supporting difficulty of quantifying average pain	*"[Average pain is hard to rate] …because it's so short…the moment when…when I get up, and I walk a couple of steps, and I start…it's like the pain disappears too fast so… [There isn't…there isn't enough time to say that there is an average pain]."*	Argentina
	"I don't even know how to average pain. I don't even know really what that means…. [I] understood Q1 and 3. Average pain harder to answer… I don't know a single person who would know how to average their pain, so I don't think number 2 makes sense to tell you the truth. I can average my speed in my car. I know how to do that, but I would have no clue how to average pain. It just doesn't make sense to me… I think we're trying to quantify something that's way too subjective to lend itself to this kind of objectivity… don't have a pain meter on my arm that registers some value."	US
Overall impressions of comprehensiveness of the PROMIS Pain Intensity 3a measure	*"I think these questions really cut to the heart of the issue that we're discussing."*	US
	"I think they [items] capture it very well. Pain is always a difficult subject because it is subjective and we all experience pain differently, but trying to measure the severity and the duration of pain and the type of pain as best we can, like it makes a solid comparison within the same person. So, I think these questions do about as well as can be done with the subject."	US
Quotes supporting meaningful change in pain intensity	*"I'm not expecting any kind of antihemophilic factor to resolve decades of joint issues, but I will say a little improvement [is] meaningful. Any movement from right to left on the scale would be meaningful."*	US
	"[A change in pain intensity from moderate to mild would be meaningful]. At least…that there is an improvement…. An improved towards walking well instead of towards a further damage of the body."	Argentina
Quotes supporting ability of PROMIS Pain Intensity 3a to measure changes in pain	*"If you asked me if I've had pain in the last 7 days, I would either think of either, A, did I have a bleed or B, did I have trouble maybe moving around, where there was some sort of pain. That's what comes to mind with those questions."*	US
	"These things [pain ratings] are changing throughout the day depending on what you're doing…"	US
Quotes supporting relevance of pain intensity	*"Yes, quite a lot [of importance], because it's like what defines your level of life, your quality of life, basically. We are very dependent on the pain, in our day-to-day, so, like the pain intensity, you measure it all the time."*	Argentina
	"I think it's important to be able to talk about the level of pain we feel and the level of difficulty to do something in life."	France

PROMIS = Patient-Reported Outcomes Information System; UK = United Kingdom; US = United States.

Table 4
Participants' responses to satisfaction with efanesoctocog alfa prophylaxis.

Satisfaction rating, n (%)	Total (N = 29)
Treatment satisfaction	
Not at all satisfied	0 (0.0)
A little satisfied	1 (3.4)
Moderately satisfied	0 (0.0)
Quite satisfied	3 (10.3)
Very satisfied	24 (82.8)
Treatment preference	
Prefer previous hemophilia treatment	0 (0.0)
Prefer efanesoctocog alfa	29 (100.0)

assessment of physical health and functioning and pain. Participant responses during the interviews highlighted the substantial morbidity associated with severe hemophilia A, with nearly all interview participants reporting that they experienced some level of hemophilia-related pain before enrolling in the XTEND-1 study, even when treated with standard of care prophylaxis. The majority of participants reported issues with being able to move without pain, walk desired distances (because of pain), and painful swelling, and a substantial number of participants also reported that they needed more time to get ready due to their hemophilia. These findings are largely consistent with previous studies which described pain as a major driver for decline in health-related quality of life.[22–25] One previous qualitative study of the association between pain and functional limitations reported that the level of pain experienced by patients (n = 78) was the most important parameter to predict functional limitations,[25] while another study (n = 675) stated that 89% of adults with hemophilia who completed patient-reported outcome surveys reported experiencing pain that interfered with activities, and 26% reporting that pain interfered with their daily life "extremely" or "quite a lot" in the past 4 weeks.[26]

After switching to efanesoctocog alfa (prophylaxis in Arm A, 26 weeks of on-demand followed by 26 weeks of prophylaxis in Arm B), most participants self-reported meaningful improvements in pain and physical functioning, as well as treatment satisfaction. Most participants also reported some level of improvement in their joint symptoms (as measured by the Patient Global Impression of Severity), with the majority stating that any positive change would be meaningful to them. Joint bleeds, which account for 70 to 80% of bleeding episodes in hemophilia, can make living with hemophilia extremely painful, which has a major impact on participants' health-related quality of life.[5,27] The overall health status of participants, as measured by the Patient Global Impression of Change, was also improved with efanesoctocog alfa prophylaxis, with participants stating that improvements increased the feeling of being protected from joint damage and the ability to engage in physical activities. Improvements in health status are likely a result of the sustained high levels of factor VIII provided by efanesoctocog alfa, and thus reduced risk of breakthrough bleeding.[17] While most participants did report improvements in physical functioning and pain after switching to efanesoctocog alfa, a small proportion did not report improvements during the study, although participants noted that having no increase in pain would still be beneficial to their health-related quality of life. It may be that 52 weeks of treatment was not enough to demonstrate benefit. These quality of life endpoints are planned to be assessed over longer periods in the Phase 3 extension study (XTEND-ed; ClinicalTrials.gov number, NCT04644575).

No previous studies have examined the suitability of the PROMIS Pain Intensity 3a measure in hemophilia A; therefore, the insights gathered from these interviews may support future clinical trial endpoints. The PROMIS Pain Intensity 3a measure was positively received by participants in the XTEND-1 exit interviews, with all participants indicating that the questions were relevant, clear, and easy to answer with the response options provided, the recall period was appropriate, and the pain experience was adequately captured. Perhaps most importantly, all participants also noted that hemophilia-related pain is very impactful and, thus, an important concept to measure. These results strongly support the validity and importance of the PROMIS Pain Intensity 3a worst pain item to capture changes that are meaningful to patients.

All participants preferred efanesoctocog alfa prophylaxis over their pre-study treatment. The findings from these interviews support the primary results of the XTEND-1 study, where once-weekly prophylaxis with efanesoctocog alfa provided effective prevention of bleeding compared with standard of care factor VIII prophylaxis. The improved bleeding profile, reduced treatment burden, and sustained high FVIII levels demonstrated with efanesoctocog alfa translate to the statistically significant improvements in the secondary endpoints of Haem-A-QoL PH and PROMIS Pain Intensity 3a worst pain item, as well as the substantial improvements in physical functioning and pain further described by the participants during the exit interviews. Even participants with mild impairments pre-study reported substantial improvements in overall functioning and health-related quality of life after treatment with efanesoctocog alfa, highlighting its benefits over previous treatment regimens. Of note, only 2 interview participants were adolescents, and both reported little or no pain or issues with physical functioning. Further investigations are needed to confirm the findings from these interviews and examine the benefits of initiating efanesoctocog alfa prophylaxis at an early age and whether joint damage can be prevented. Taken together, the pre- and post-study experiences of participants regarding pain, physical functioning, and treatment satisfaction from both arms of the XTEND-1 study suggest that efanesoctocog alfa may provide patient-perceived meaningful and relevant improvements in overall health-related quality of life in patients with hemophilia A, regardless of the factor VIII treatment (prophylaxis or on-demand) used prior to starting the study.

Limitations

Both pre- and post-study experiences were discussed during the exit interviews, which may limit the reliability of patient recall; however, this is generally standard practice for within-trial interviews, as pre-study interviews can be logistically difficult and costly to conduct. While the number of exit interview participants was representative of the study with no evidence of selection bias, a larger sample size, including more adolescent participants, may improve the generalizability of the results and further confirm the benefits described by participants. However, despite the rarity of hemophilia A, the sample size obtained within this qualitative study still provides valuable insights into the patient experience. In some instances, participants expressed their concern with the PROMIS Pain Intensity 3a measure, stating that “average pain” was difficult to define, which was expected and the reason why only the first item (pain at its worst) was used as the secondary endpoint in the hierarchical testing.

Future studies could include interviews with patients as a trial activity, potentially enabling higher participation rates and a better opportunity to understand the patient experience. Furthermore, it would be beneficial to determine the effects of treatment on other stakeholders such as caregivers and the treating clinicians to gather a more rounded perspective on treatment with efanesoctocog alfa.

Conclusions

The XTEND-1 study interviews provided valuable and positive insights into patients’ experiences with hemophilia A and its treatment. Beyond the superior prevention of bleeds, efanesoctocog alfa prophylaxis resulted in patient-relevant and meaningful improvements in physical functioning and pain, while simultaneously decreasing burden of treatment with a once-weekly dosing regimen. These qualitative results confirmed that the quantitative improvements observed in the secondary endpoints of the PROMIS Pain Intensity 3a worst pain item and the Haem-A-QoL PH subscale represented clinically meaningful improvements for patients. The results from the exit interviews also support the content validity of the PROMIS Pain Intensity 3a worst pain item and demonstrate the potential for change in both physical functioning and pain intensity with efficacious treatment.

Data availability statement

Qualified researchers may request access to patient level data and related study documents. Patient level data will be anonymized, and study documents will be redacted, including to protect the privacy of our trial participants. Further details on Sanofi’s data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

Declaration of competing interest

Dana DiBenedetti is a full-time employee of RTI Health Solutions, an independent non-profit research organization, which was retained by Sanofi to conduct the research which is the subject of this manuscript. Her compensation is unconnected to the studies on which she works.

Daniela Neme has received personal or institutional honoraria from Biomarin, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda.

Brigitte Pan-Petesch has no conflicts of interest to declare.

Annemieke Willemze is an employee of Sanofi and may hold stock or stock options in Sanofi.

Tung Wynn has participated as a study PI for Sanofi, Takeda, Spark, and Sobi. Spouse was an employee of Takeda from October 2022 until June 2023.

Nana Kragh is an employee of Sobi and may have stock or stock options.

Amanda Wilson was an employee of Sanofi at the time the study was conducted and may hold stock or stock options in Sanofi.

CRediT authorship contribution statement

Dana DiBenedetti: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daniela Neme:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Brigitte Pan-Petesch:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Annemieke Willemze:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Tung Wynn:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Nana Kragh:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Amanda Wilson:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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