Joint Health Outcomes With Efanesoctocog Alfa Prophylaxis for Patients With Severe Hemophilia A: Third Interim Analysis of the Phase 3 XTEND-ed Study

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HJHS total score
improved or remained constant in
85.6%
of evaluable participants (n=90) from XTEND-1 baseline to XTEND-ed Month 36

Plain language summary

1 **This research studied joint health in adults and teenagers with severe hemophilia A who took efanesoctocog alfa once weekly for up to 4 years in the XTEND clinical trial program**

2 **Approximately 8 out of 10 people taking efanesoctocog alfa experienced stable or improved joint health**

Introduction

- Efanesoctocog alfa is a first-in-class, high-sustained factor VIII (FVIII) replacement therapy (also referred to as ultra-long half-life FVIII) that overcomes the von Willebrand factor–imposed half-life ceiling[1-3]
- The Phase 3 XTEND-1 study[4] (NCT04161495) showed once-weekly efanesoctocog alfa (50 IU/kg) prophylaxis was well tolerated in adults/adolescents with severe hemophilia A, providing superior bleed prevention over prior factor VIII prophylaxis
- Participants completing XTEND-1 could continue weekly efanesoctocog alfa (50 IU/kg) in the long-term extension study, XTEND-ed (NCT04644575) Arm A
- The second interim analysis of XTEND-ed showed that overall improvements in total Hemophilia Joint Health Score (HJHS) observed after 12 months of efanesoctocog alfa prophylaxis in XTEND-1 were maintained at Month 24[5]

Objective

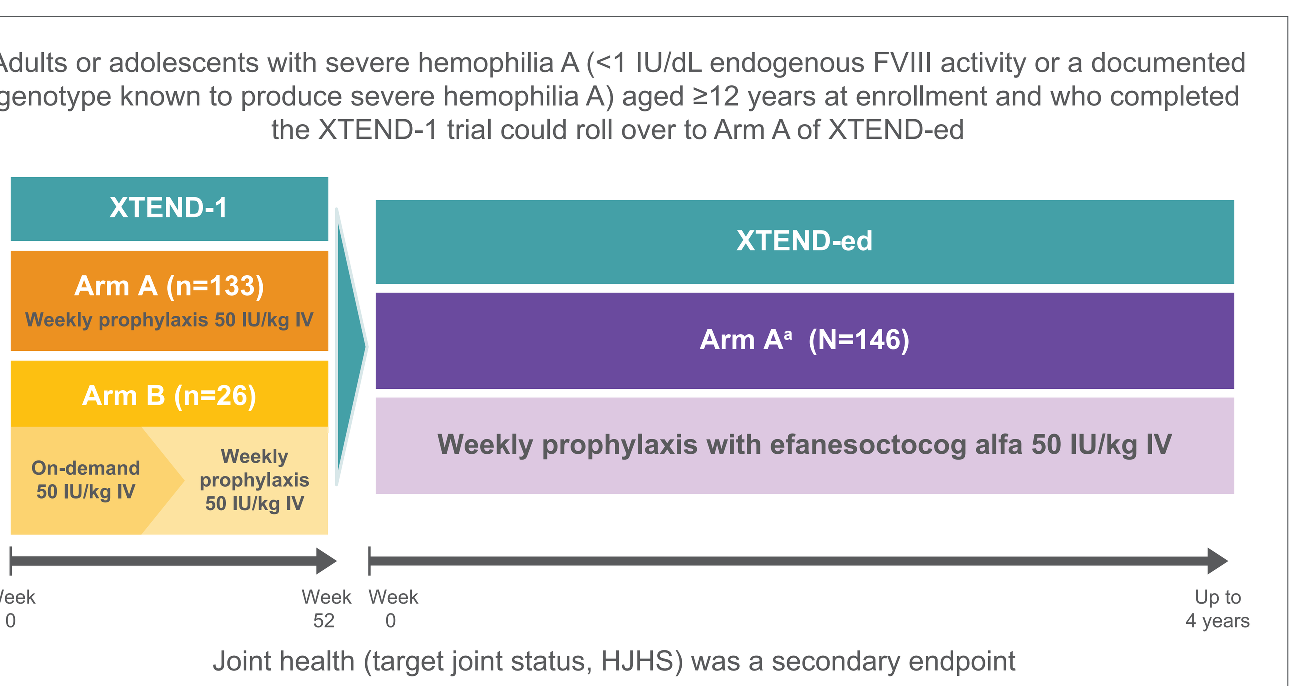
- To report long-term joint health with efanesoctocog alfa in adults/adolescents aged ≥12 years from XTEND-1 baseline through XTEND-ed third interim analysis (data cut: February 21, 2025)

Methods

Study design and population

- Participants provided informed consent; the study was approved by applicable review boards
- The XTEND clinical trial program is shown in **Figure 1**

Figure 1: XTEND clinical trial program


Adults or adolescents with severe hemophilia A (<1 IU/dL endogenous FVIII activity or a documented genotype known to produce severe hemophilia A) aged ≥12 years at enrollment and who completed the XTEND-1 trial could roll over to Arm A of XTEND-ed
XTEND-1
Arm A (n=133)
Weekly prophylaxis 50 IU/kg IV
Arm B (n=26)
On-demand 50 IU/kg IV
Weekly prophylaxis 50 IU/kg IV
XTEND-ed
Arm A[a] (N=146)
Weekly prophylaxis with efanesoctocog alfa 50 IU/kg IV
Week 0
Week 52
Week 0
Up to 4 years
Joint health (target joint status, HJHS) was a secondary endpoint

[a]Patients in XTEND-ed Arm A will continue to receive efanesoctocog alfa prophylaxis for up to 4 years, unless efanesoctocog alfa is commercially available in their participating country.
FVIII, factor VIII; HJHS, Hemophilia Joint Health Score; IU, international unit; IV, intravenous.

Outcome measures

- Changes in HJHS (range 0–124) from parent study (XTEND-1) baseline up to XTEND-ed Month 36 are presented descriptively
- Higher HJHS denotes worse joint health
- Individual joints (left/right elbows, knees, ankles) were scored according to 8 HJHS domains to obtain total joint score; gait score was determined based on walking and climbing stairs and ranged from 0 to 4
 - HJHS assessments within 2 weeks after a joint or muscle bleed were excluded
 - Joint scores following joint surgeries were replaced using the last observation carried forward method
- Improved/worsened HJHS was defined as decrease/increase of ≥4 points, and unchanged (or constant) HJHS as decrease/increase of -3 to +3 points[6]

Results

- Overall, 146 adults/adolescents rolled over from XTEND-1 to Arm A of XTEND-ed (**Table 1**)
 - Median (range) treatment duration and exposure days from XTEND-1 baseline were 212.2 (46.3–244.8) weeks and 216.5 (47–254) days, respectively

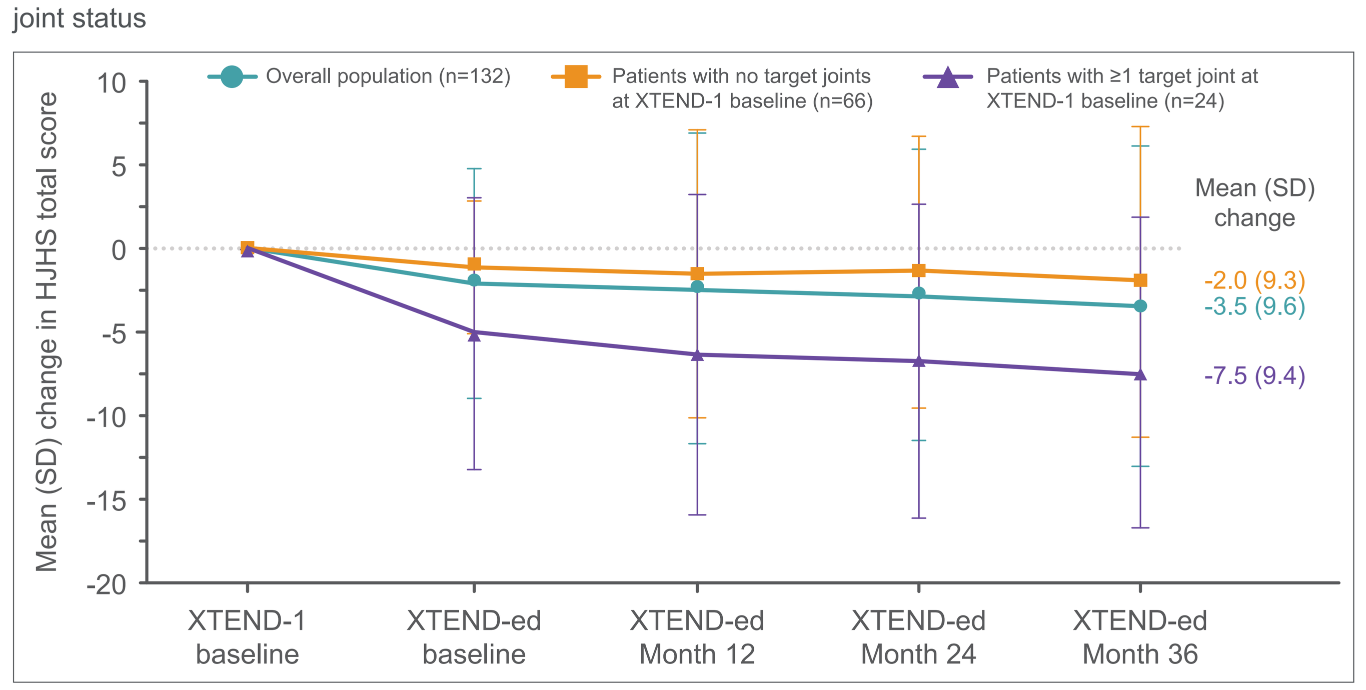
Table 1: Participant demographics and baseline characteristics

	Overall cohort (N=146)
Mean (SD) age (at XTEND-ed enrollment), years	37.0 (15.1)
Age category (at XTEND-ed enrollment), n (%)	
12–17 years	21 (14.4)
18–64 years	120 (82.2)
≥65 years	5 (3.4)
Sex, n (%)	
Male	145 (99.3)
Female	1 (0.7)
Race, n (%)	
White	100 (68.5)
Black or African American	4 (2.7)
Asian	27 (18.5)
Not reported	13 (8.9)
Other	2 (1.4)
Mean (SD) weight, kg	78.0 (19.4)
Mean (SD) body mass index, kg/m²	25.6 (5.2) *(n=145)*

HJHS total and domain scores

- In total, 132/146 participants had evaluable HJHS scores at XTEND-1 baseline
 - Median (range) HJHS total score was 19 (0–98)
 - Mean (standard deviation [SD]) HJHS total score was 20.5 (18.4)
 - Gradual improvements in HJHS total score at 12-month intervals were observed with up to 4 years of efanesoctocog alfa prophylaxis (**Figure 2**)

Figure 2: Change in HJHS total score from XTEND-1 baseline to XTEND-ed Month 36 according to target joint status


Overall population (n=132)
Patients with no target joints at XTEND-1 baseline (n=66)
Patients with ≥1 target joint at XTEND-1 baseline (n=24)
Mean (SD) change in HJHS total score
Mean (SD) change
-2.0 (9.3)
-3.5 (9.6)
-7.5 (9.4)
XTEND-1 baseline
XTEND-ed baseline
XTEND-ed Month 12
XTEND-ed Month 24
XTEND-ed Month 36

Mean (SD) HJHS Total Score (0–124) Overall population	XTEND-1 Baseline		XTEND-ed Baseline		XTEND-ed Month 12		XTEND-ed Month 24		XTEND-ed Month 36	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total score	132	20.5 (18.4)	133	17.6 (17.1)	114	16.5 (15.9)	122	17.0 (16.7)	96	14.8 (14.9)
Change from XTEND-1 baseline	–	–	128	-2.1 (6.9)	107	-2.4 (9.3)	115	-2.8 (8.7)	90	-3.5 (9.6)

An HJHS total score could be calculated if all 48 individual item scores (8 domains × 6 joints, total joint score) and the gait score were present.
HJHS, Hemophilia Joint Health Score; SD, standard deviation.

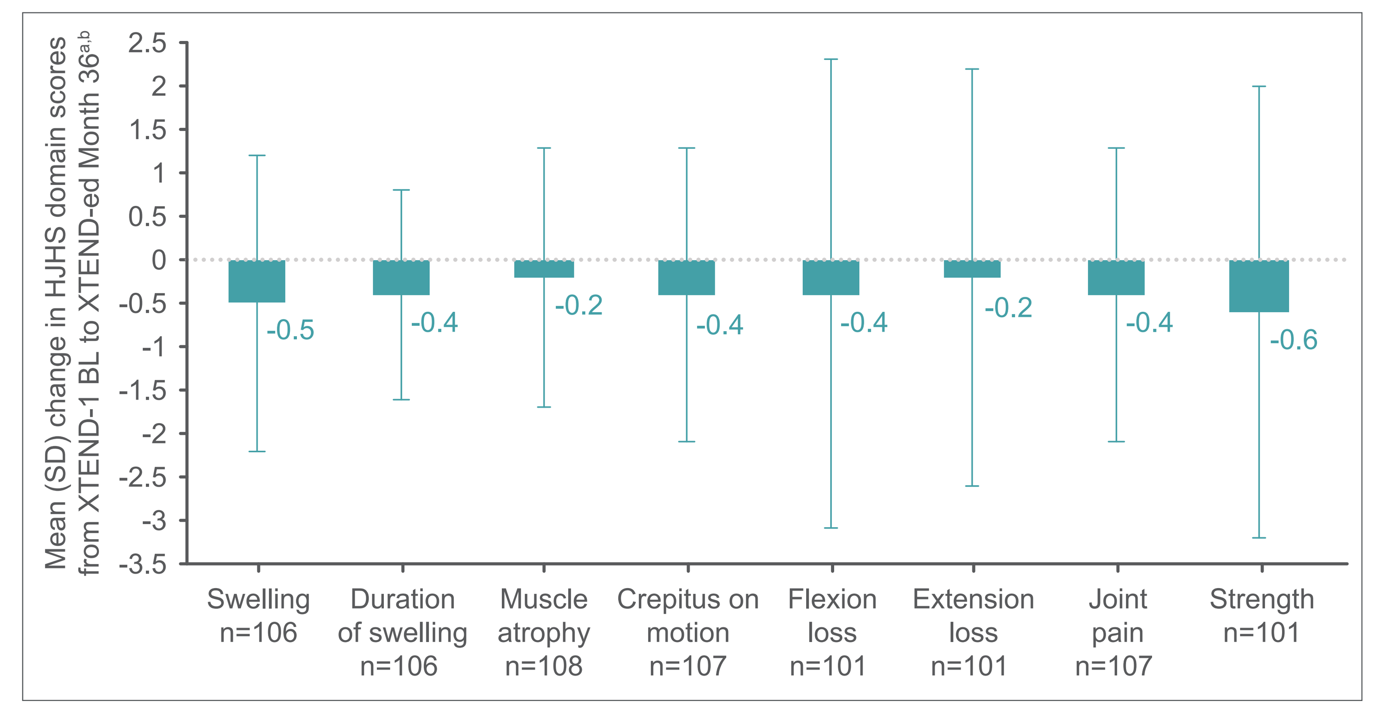
Conclusions

1 **Long-term once-weekly prophylaxis with efanesoctocog alfa for up to 4 years continues to improve or maintain joint health in adults and adolescents with severe hemophilia A**

2 **The greatest improvements in HJHS total score were observed in people with the worst joint health at XTEND-1 baseline (HJHS >29; quartile 4) and those aged ≥50 years**

- At Month 36, relative to XTEND-1 baseline:
 - Greatest mean (SD) changes in HJHS domain scores were observed for strength -0.6 (2.6) and swelling -0.5 (1.7) (**Figure 3**)
 - Mean (SD) HJHS gait score remained constant at 1.5 (1.6) (XTEND-1 baseline, 1.7 [1.6])
 - HJHS total score improved or remained constant[6] in 85.6% of participants (77/90)

Figure 3: Change in HJHS domain scores from XTEND-1 baseline to XTEND-ed Month 36

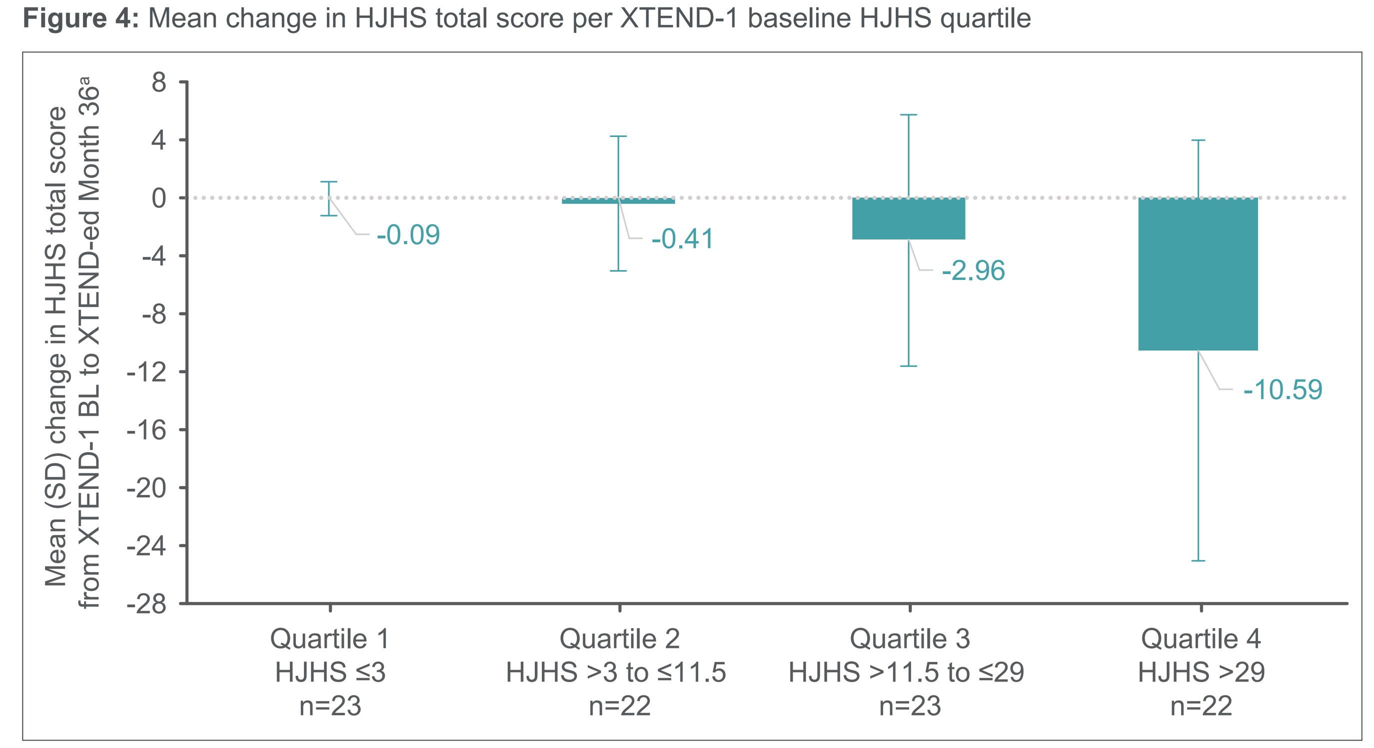

Mean (SD) change in HJHS domain scores from XTEND-1 BL to XTEND-ed Month 36[a,b]
-0.5
-0.4
-0.2
-0.4
-0.4
-0.2
-0.4
-0.6
Swelling n=106
Duration of swelling n=106
Muscle atrophy n=108
Crepitus on motion n=107
Flexion loss n=101
Extension loss n=101
Joint pain n=107
Strength n=101

[a]Mean change only determined for participants for whom data were available at XTEND-1 baseline and at each respective XTEND-ed follow-up time; [b]HJHS domains are assessed on the following ranges of scores: swelling (0–3); duration of swelling (0 or 1); muscle atrophy (0–2); crepitus on motion (0–2); flexion loss (0–3); extension loss (0–3); joint pain (0–2); strength (0–4).
BL, baseline; HJHS, Hemophilia Joint Health Score; SD, standard deviation.

Change in HJHS total score according to baseline HJHS quartile

- The greatest improvements in HJHS total score were observed in participants with the highest HJHS (>29; quartile 4) at XTEND-1 baseline (**Figure 4**)

Figure 4: Mean change in HJHS total score per XTEND-1 baseline HJHS quartile


Mean (SD) change in HJHS total score from XTEND-1 BL to XTEND-ed Month 36[a]
-0.09
-0.41
-2.96
-10.59
Quartile 1 HJHS ≤3 n=23
Quartile 2 HJHS >3 to ≤11.5 n=22
Quartile 3 HJHS >11.5 to ≤29 n=23
Quartile 4 HJHS >29 n=22

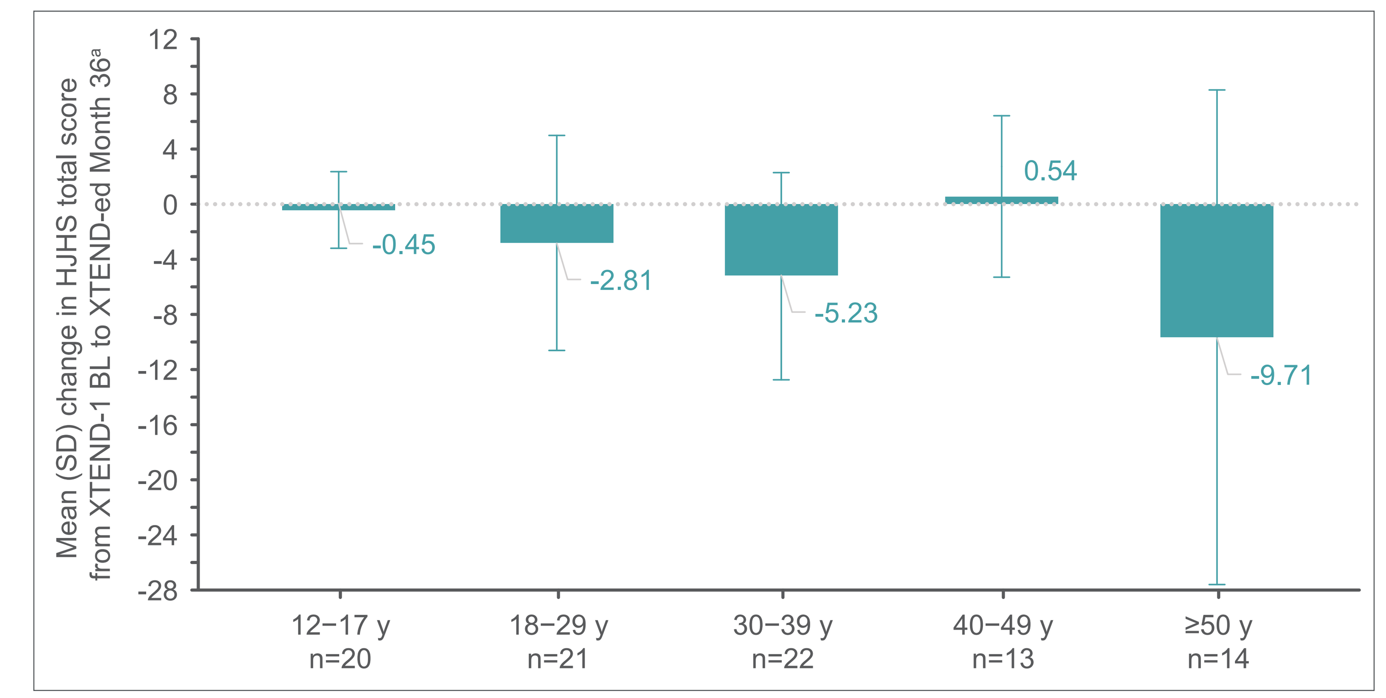
Mean (SD) HJHS Total Score (0–124)	XTEND-1 Baseline HJHS Quartile			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
XTEND-1 Baseline	0.61 (0.94)	7.09 (2.54)	22.04 (5.51)	41.45 (14.82)
XTEND-ed Month 36	0.52 (0.95)	6.68 (5.40)	19.09 (9.20)	30.86 (11.78)

Higher HJHS score denotes worse joint health. aIncludes patients who had HJHS data at both XTEND-1 baseline and XTEND-ed Month 36.
BL, baseline; HJHS, Hemophilia Joint Health Score; SD, standard deviation.

Change in HJHS total score according to baseline age

- The greatest improvements in HJHS total score were reported among participants aged ≥50 years, followed by those aged 30 to 39 years (**Figure 5**)
- Mean (SD) change in HJHS total score from XTEND-1 baseline to XTEND-ed Month 36 was -2.90 (6.7; median, 0) in participants aged <40 years (n=63) and -4.78 (14.3; median, 3.0) in participants aged ≥40 years (n=27)

Figure 5: Mean change in HJHS total score per XTEND-1 baseline age


Mean (SD) change in HJHS total score from XTEND-1 BL to XTEND-ed Month 36[a]
-0.45
-2.81
-5.23
0.54
-9.71
12–17 y n=20
18–29 y n=21
30–39 y n=22
40–49 y n=13
≥50 y n=14

Age group at XTEND-1 Baseline	Mean (SD) HJHS Total Score (0–124)	
	XTEND-1 Baseline	XTEND-ed Month 36
12–17 y	3.25 (5.76)	2.80 (6.73)
18–29 y	9.24 (11.07)	6.43 (6.71)
30–39 y	20.68 (12.59)	15.45 (11.13)
40–49 y	22.23 (12.88)	22.77 (13.91)
≥50 y	41.86 (19.15)	32.14 (10.97)

Higher HJHS score denotes worse joint health. [a]Includes patients who had HJHS data at both XTEND-1 baseline and XTEND-ed Month 36.
BL, Baseline; HJHS, Hemophilia Joint Health Score; SD, standard deviation; y, year.

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