

Bone and Joint Health Markers in Persons with Hemophilia A (PwHA) Treated with Emicizumab in HAVEN 3

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Beyond bleed prevention: exploring the potential effect of emicizumab prophylaxis on bone & joint health

Hemophilia A:

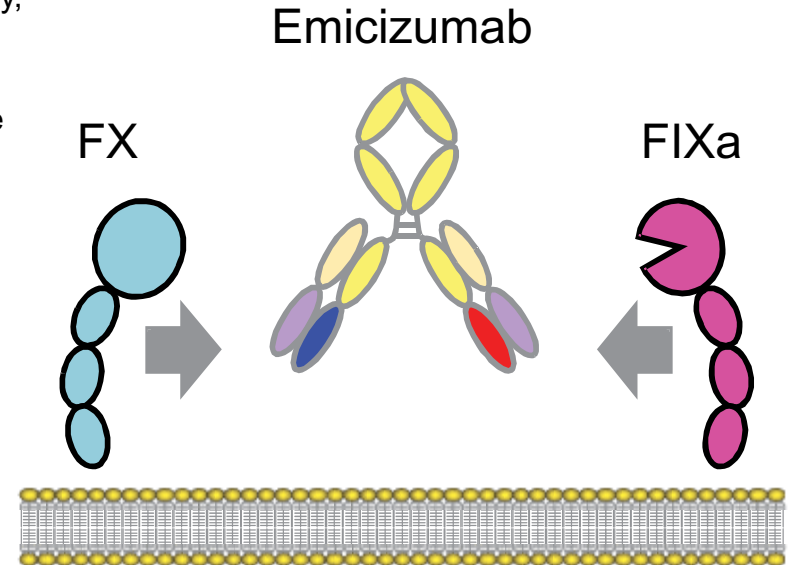
- Characterized by deficient coagulation due to missing FVIIIa activity, which predisposes to recurrent joint bleeds and hemophilic arthropathy
- Associated with decreased bone mineral density,¹ speculated to be due to missing FVIII activity outside of the coagulation cascade²

Emicizumab:

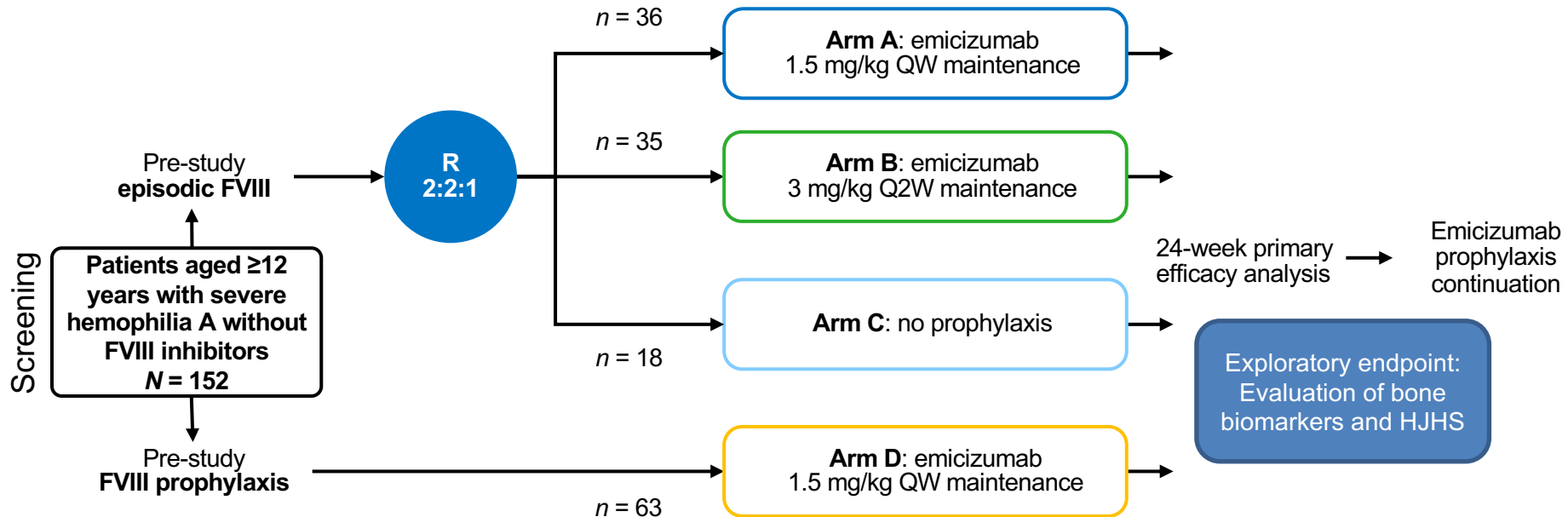
- Bridges FIXa and FX to replace the function of missing FVIIIa in PwHA, restoring hemostasis³
- Has a positive benefit–risk profile in PwHA with or without FVIII inhibitors when administered SC: QW, Q2W or Q4W⁴⁻⁷
- Significantly reduced risk of treated joint bleeds compared with previous episodic FVIII: 96% and 97% reductions with QW and Q2W prophylaxis ($p < 0.0001$)⁵

Analysis aim:

- Explore the effect of emicizumab prophylaxis on bone & joint health in PwHA without FVIII inhibitors enrolled in HAVEN 3



HAVEN 3: Emicizumab prophylaxis in PwHA without FVIII inhibitors



Emicizumab

- Loading dose: 3.0 mg/kg QW for 4 weeks
- Maintenance dose: as indicated, starting Week 5

NCT02847637

One participant was lost to follow up and not treated. ABR, annualized bleeding rate; NIS, non-interventional study; R, randomization.

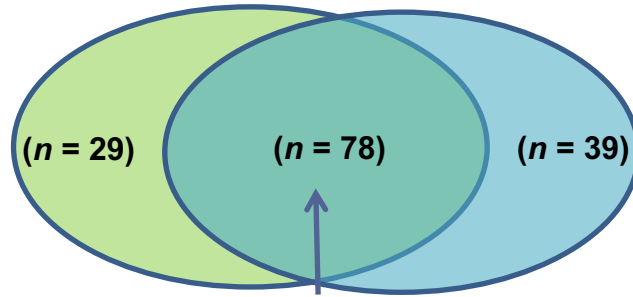
Measures of bone & joint health

HJHS (v2.1)

Evaluated at baseline and Week 49 of emicizumab prophylaxis
(*n* = 107)

Bone & Joint Biomarkers

Measured at baseline and after 3, 6, 12, & 18 months of treatment
(*n* = 117)



Both HJHS and biomarkers

Analyses performed

- Change over time in HJHS and biomarkers
- Correlations within biomarkers and between biomarker levels and HJHS
- Sub-group analyses based on target joint status and previous treatment (episodic and prophylactic)

Bone & joint biomarkers assessed

- Bone formation (OC, P1NP)
- Bone resorption (CTX-I)
- Osteoblasts (OPG)
- Osteoclastogenesis (sRANKL)
- Cartilage turnover (COMP)
- Cartilage degradation (CTX-II)
- Cartilage synthesis/repair (CS846)
- Inflammation (IL-1 beta, IL-6, TNF α)

Characteristics of HAVEN 3 participants with evaluable HJHS and biomarker measurements

Characteristics		PwHA in HAVEN 3 with evaluable HJHS, <i>n</i> = 107	PwHA in HAVEN 3 with biomarker data, <i>n</i> = 117
Mean age (min–max), years		35.7 (13–77)	38.4 (13–77)
Age groups, <i>n</i> (%)	≥65 years	2 (1.9)	5 (4.3)
	<18 years	7 (6.5)	7* (6.0)
Mean BMI (min–max), kg/m ²		26.0 (19.2–40.6)	26.0 (16.8–40.6)
Race, <i>n</i> (%)	White	64 (59.8)	80 (68.4)
	Asian	28 (26.2)	22 (18.8)
	Black/African American	5 (4.7)	5 (4.3)
	Other	1 (0.9)	1 (0.8)
	Unknown	9 (8.4)	9 (7.7)
Prior FVIII, <i>n</i> (%)	Prophylaxis	47 (43.9)	50 (42.7)
	Episodic	60 (56.1)	67 (57.3)
Target joints, <i>n</i> (%)	None	36 (33.6)	38 (32.5)
	≥1	71 (66.4)	79 (67.5)
History of HIV infection [†] , <i>n</i> (%)		17 (15.0)	31 (26.5)
Osteoporosis [†] , <i>n</i> (%)	Any	1 (0.9)	5* (4.3)
	Treated	1 (0.9)	4* (3.4)

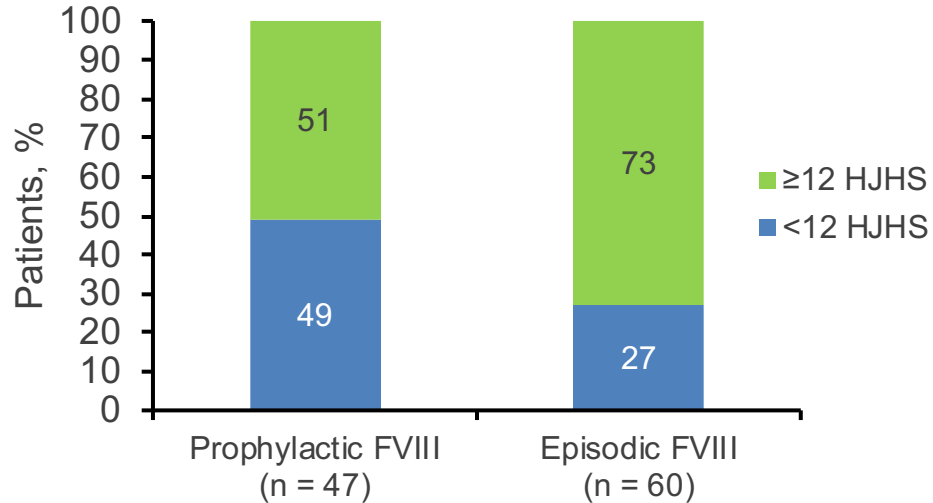
*All in Arm D of HAVEN 3 (participants who had received prior FVIII prophylaxis, and received loading doses of 3 mg/kg emicizumab QW for 4 weeks followed by 1.5 mg/kg QW maintenance).

[†]HIV and osteoporosis numbers are based on CSR information applied on these subsets.

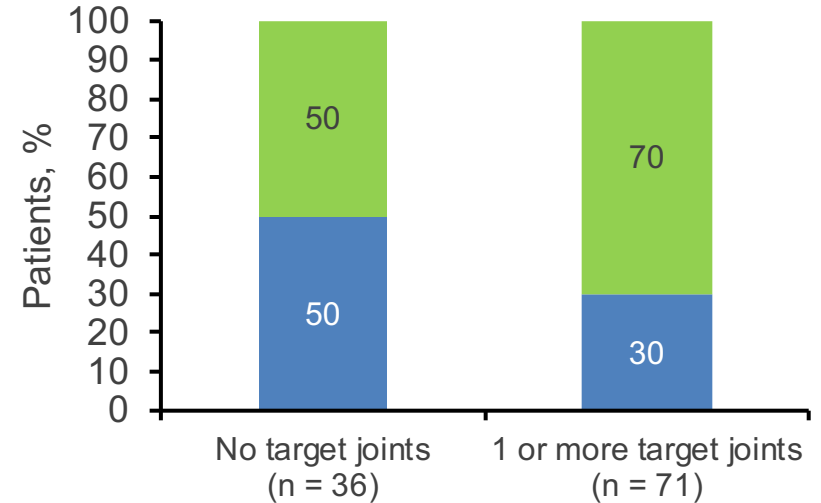
BMI, body mass index; HIV, human immunodeficiency virus. Data cut-off date: Oct 2018

PwHA previously on FVIII prophylaxis and with no target joints have lower HJHS scores at baseline

Percentage of PwHA with HJHS scores <12 vs $\geq 12^*$ at baseline by treatment



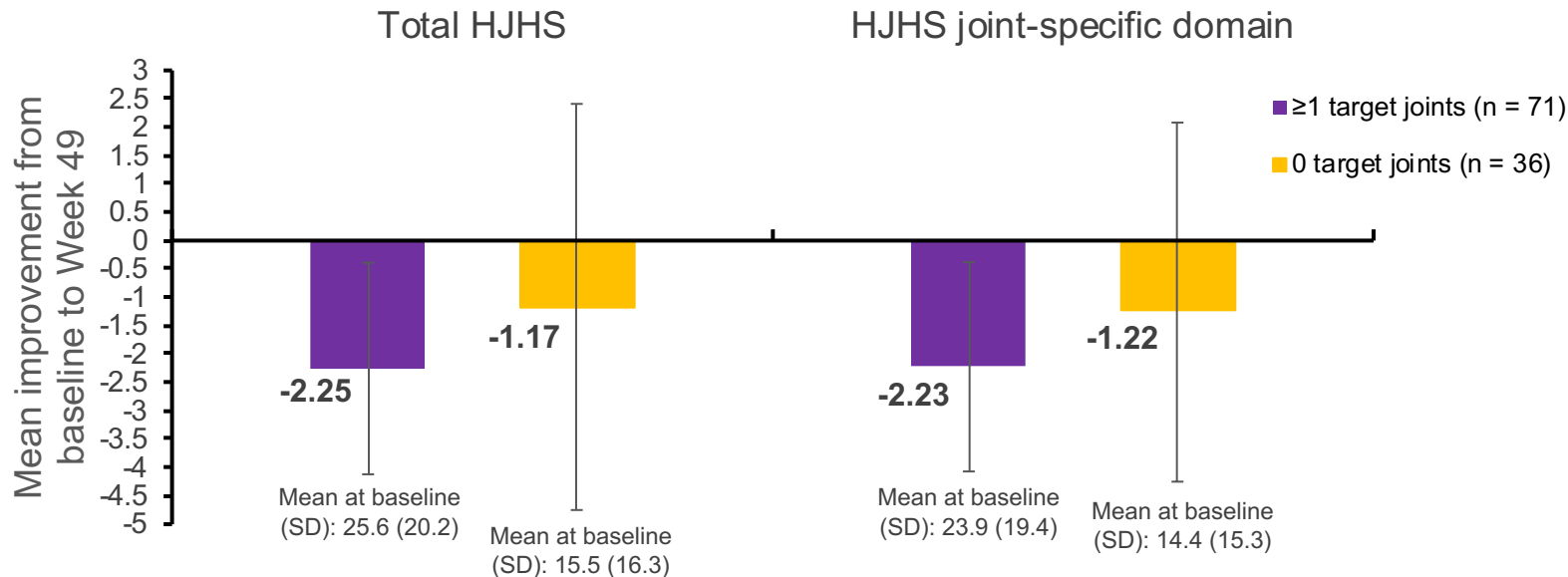
Percentage of PwHA with HJHS scores <12 vs $\geq 12^*$ at baseline by target joint status



The HJHS 2.1 consists of 8 item scores on joint level and a global gait score. Scores range from 0 to 20 per joint and the global gait score ranges from 0 to 4, resulting in a HJHS-total score (0 to 124). A higher score indicates worse joint health.

*A cut-off score of 12 was used, as this was the median in the FVIII prophylaxis population based on our data; CI, confidence interval.

Significant and clinically relevant improvements in HJHS* after 48 weeks of emicizumab in PwHA with ≥ 1 target joint†



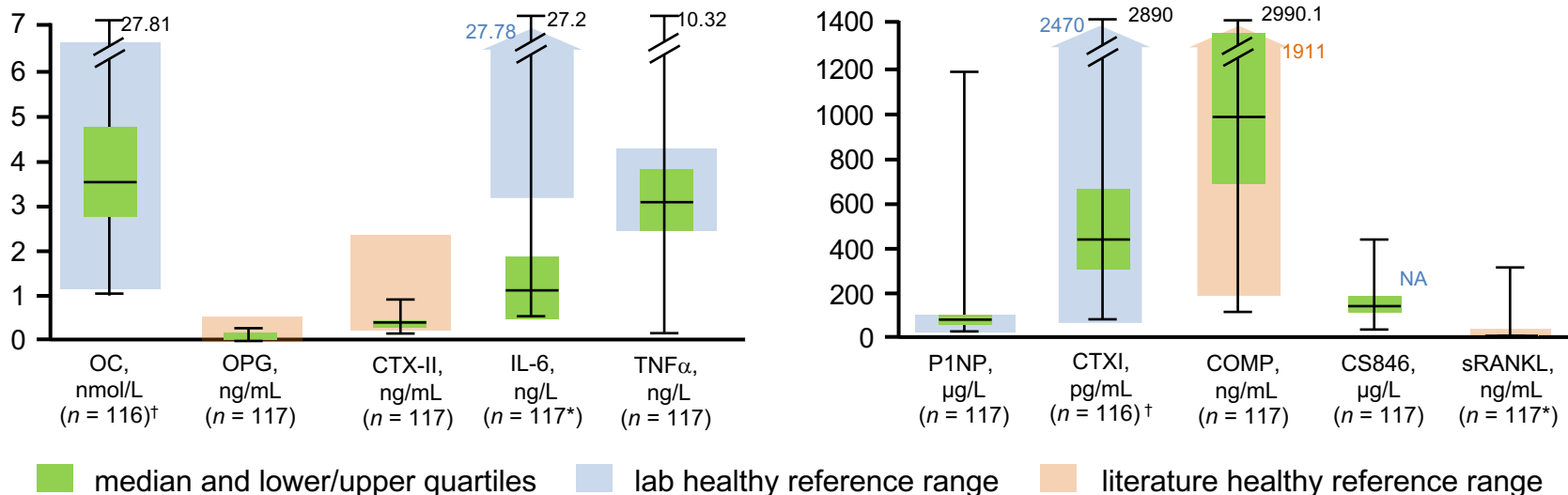
- Improvements were consistent across HJHS for different locations (knee, ankle, elbow)

* A HJHS higher score indicates worse joint health. Clinically relevant improvements are defined as a ≥ 4 -point reduction in Total HJHS or a ≥ 2 -point reduction in HJHS joints domain.† Results were significant in the exploratory sense with 95% CI not including 0.

†Excludes Arm C and includes only those with an evaluable HJHS score at both baseline and Week 49. CI, confidence interval.

Baseline values of most bone and joint biomarkers were within normal ranges or similar to published levels in healthy individuals¹⁻⁴

- Large variability in bone and joint biomarkers was observed between individuals
- No significant differences in baseline values were observed in the biomarkers of PwHA previously on FVIII prophylaxis versus episodic treatment, and in PwHA with target joints versus those without

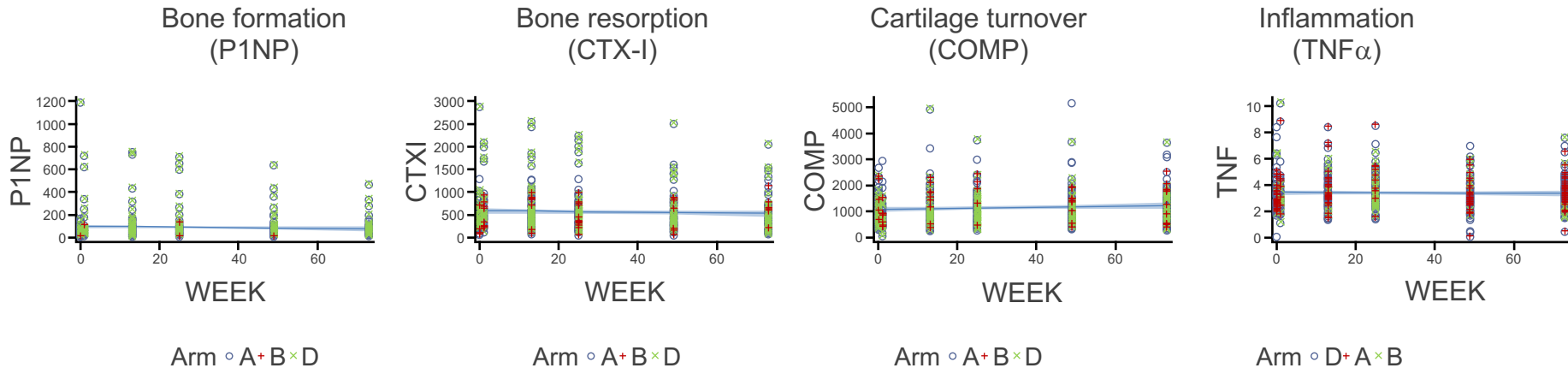


*Values below the limit of quantification (BLQ) are imputed with half of that limit of quantification; 57% of values for sRANKL, and 49% of values for IL-6 were BLQ; all IL-1β samples but one were BLQ and so are not shown here; †Missing observation at baseline for n=1.

1. Kudlacek S, et al. *Bone*. 2003;32:681-686; 2. Papassava M, et al. *Vitamin D. Epilepsy Behav*. 2019;97:192-196; 3. BioVendor. COMP ELISA insert; 4. Severino RM, et al. *Rev Bras Ortop*. 2015;50:331-335.

None of the measured biomarkers changed significantly during emicizumab prophylaxis across 18 months

- Select biomarkers in PwHA on emicizumab prophylaxis ($n = 94$)* in HAVEN 3:

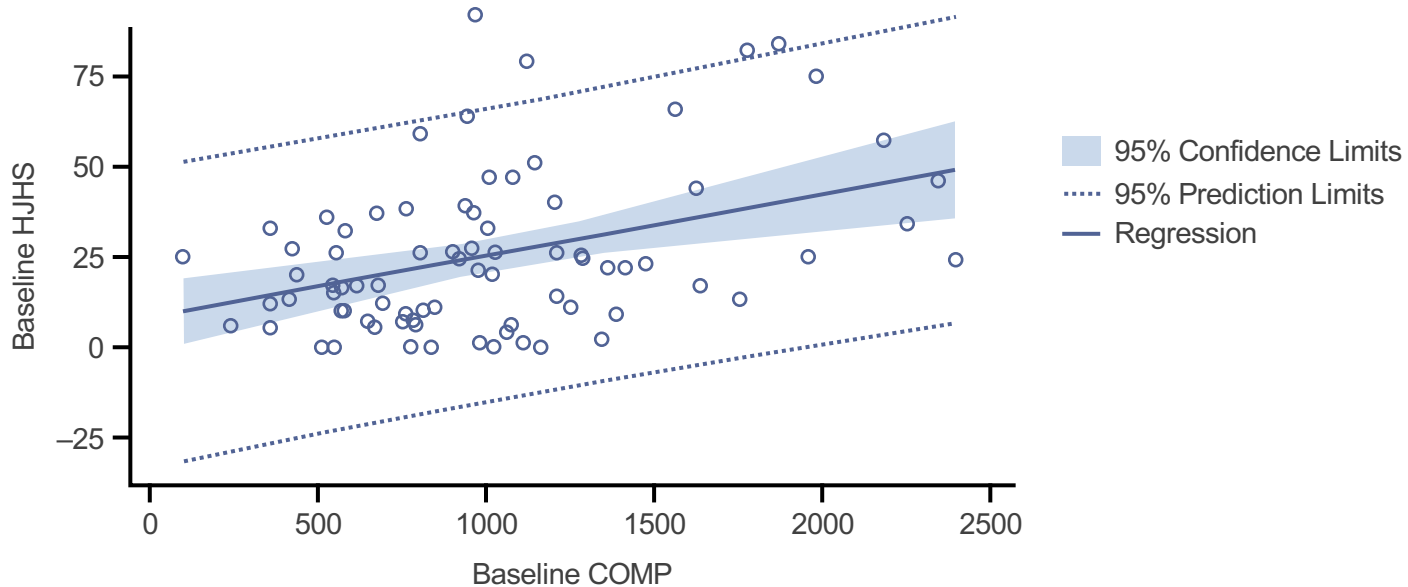


- Higher OC, P1NP, and CTX-I levels were observed in adolescents, consistent with reported increases of these biomarkers during skeletal growth^{1,2}

*Includes only patients ≥ 18 years, and excludes Arm C

At baseline, elevated levels of COMP, a biomarker of cartilage turnover, are associated with worse joint health

- Data suggest a potential association of COMP levels with HJHS scores at baseline (Pearson correlation coefficient 0.39, $p = 0.0003$; Spearman correlation coefficient: 0.32, $p = 0.0038$), $n = 79^*$
- Based on further investigations, this association may be substantially driven by age



Conclusions

- Clinically relevant improvements in HJHS (defined as a ≥ 2 -point reduction in HJHS joints domain¹) were observed for HAVEN 3 participants with target joints after as little as 48 weeks of emicizumab
- The biomarkers measured in blood as surrogates of bone and joint health did not show significant changes over the first 18 months of emicizumab prophylaxis
 - This may reflect the effects on the measured biomarkers by factors other than joint health (e.g., age, diet, physical activity)
 - For most, bone and joint biomarkers were already similar to levels reported in healthy individuals and there was little possibility for improvement
- There was no evidence of worsening in any bone and joint health markers in PwHA on emicizumab where FVIII exposure was reduced
- Additional data are needed to better understand the long-term effect of emicizumab prophylaxis on bone and joint health

Acknowledgments

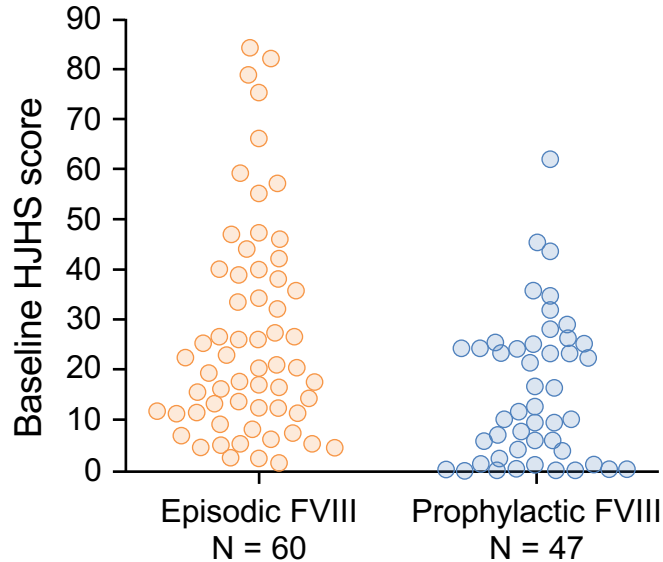
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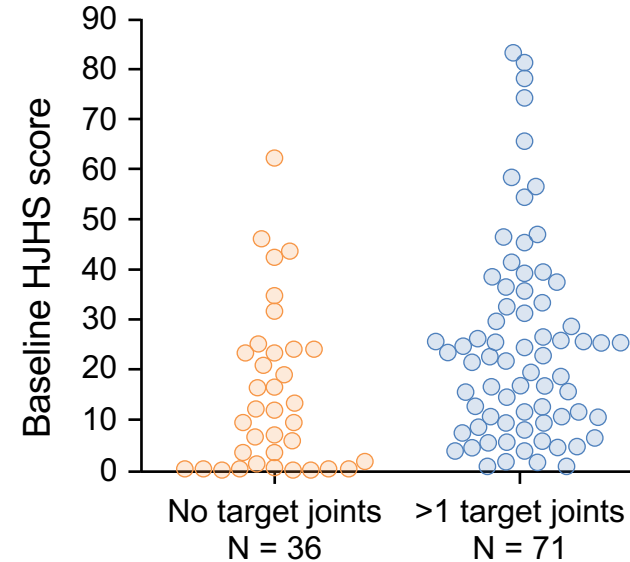
Backup slides

PwHA previously on FVIII prophylaxis and with no target joints have lower HJHS scores at baseline

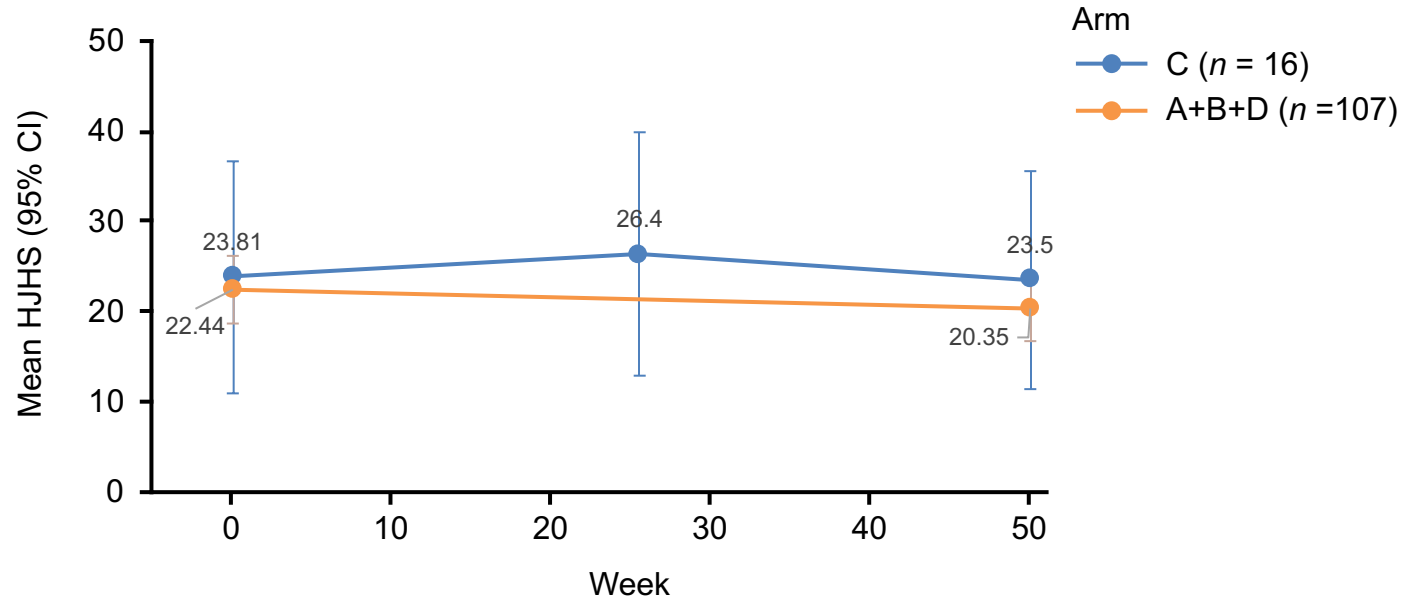
Individual baseline HJHS scores of PwHA previously on FVIII prophylaxis versus episodic treatment



Individual baseline HJHS scores of PwHA with or without target joints



Mean HJHS values decrease over 48 weeks of emicizumab prophylaxis, indicating improvement in joint function and health



The HJHS 2.1 consists of 8 item scores on joint level and a global gait score. Scores range from 0 to 20 per joint and the global gait score ranges from 0 to 4, resulting in a HJHS-total score (0 to 124). A higher score indicates worse joint health.