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

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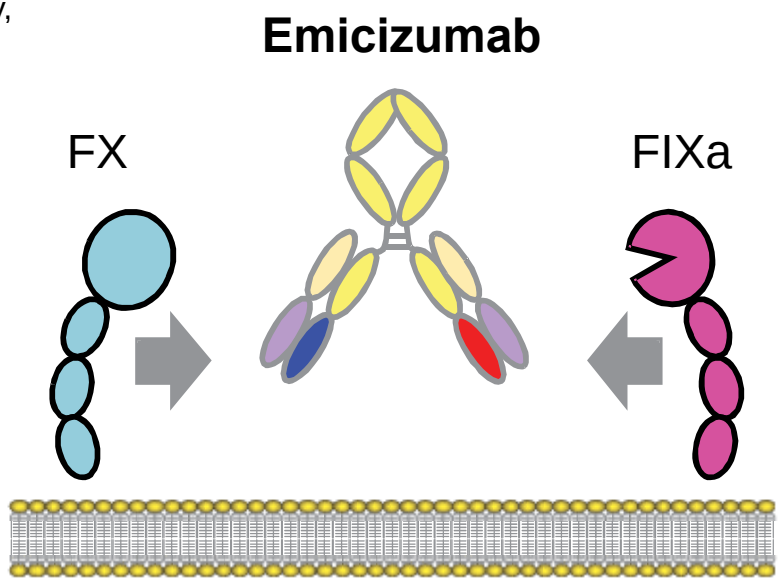
Beyond bleed prevention: exploring the potential effect of emicizumab prophylaxis on bone & joint health

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 cascade[2]

Emicizumab:

- Bridges FIXa and FX to replace the function of missing FVIIIa in PwHA, restoring hemostasis[3]
- Has a positive benefit–risk profile in PwHA with or without FVIII inhibitors when administered SC: QW, Q2W or Q4W[4-7]
- 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]



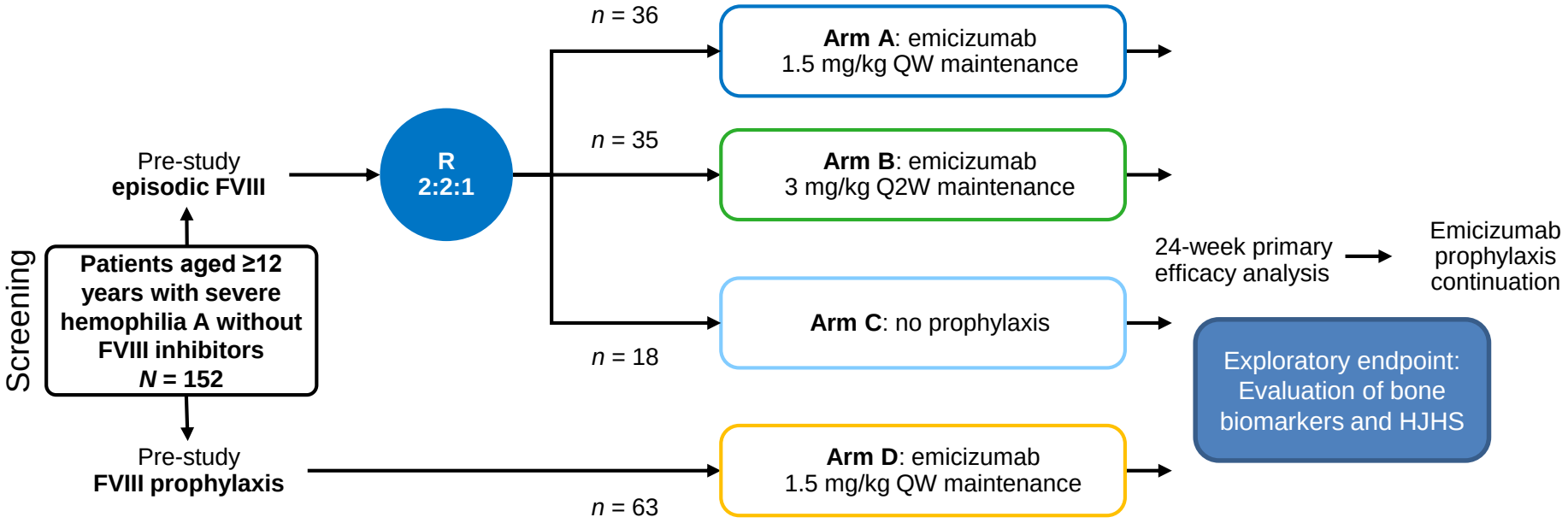
Analysis aim:

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

A, activated; F, factor; HA, hemophilia A; PwHA, persons with hemophilia A; QW, once weekly Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous.

1. Kempton CL, et al. *Haemophilia*. 2014;20:121–8; 2. Recht M, et al. *Haemophilia.* 2013;19(6):908–912; 3. Kitazawa T, et al. *Thromb Haemost* 2017;117:1348–57; 4. Oldenburg J, et al. *N Engl J Med* 2017;377:809–18; 5. Mahlangu J, et al. *N Engl J Med* 2018;379:811–22; 6. Emicizumab USPI. 2019; 7. Pipe S, et al. *Lancet Haematol* 2019; 6:e295–e305.

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

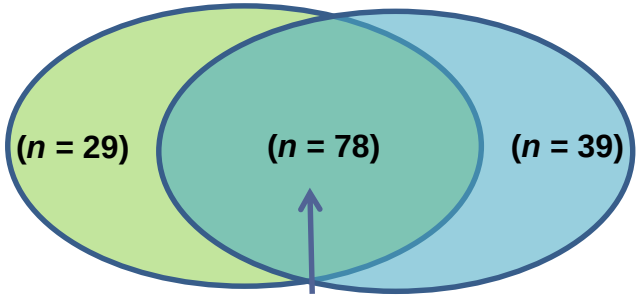
One participant was lost to follow up and not treated. ABR, annualized bleeding rate; NIS, non-interventional study; R, randomization.

1. Mahlangu J, et al. *N Engl J Med* 2018;379:811–822.

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

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, TNFα)

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)

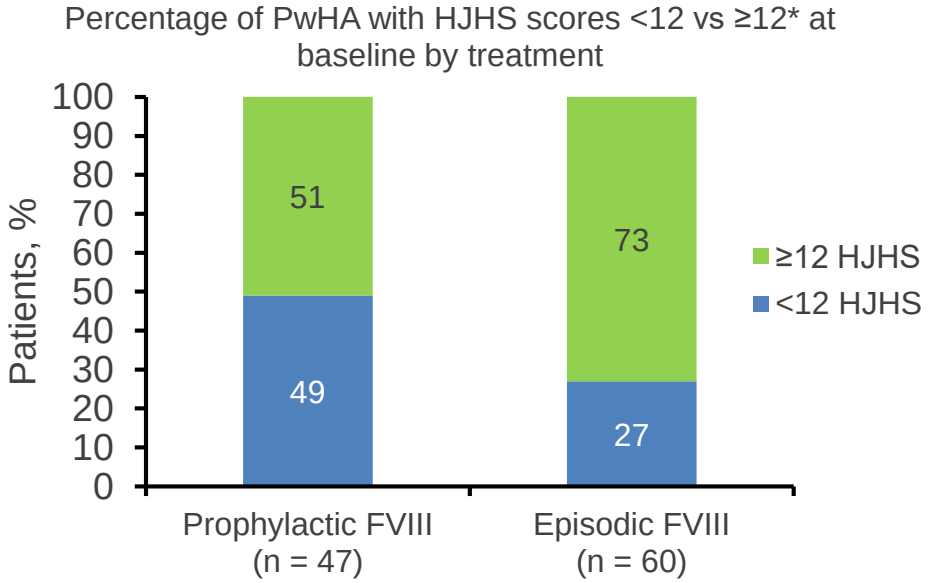
Data cut-off date: Oct 2018; Bone biomarker samples were collected after overnight fasting.
COMP, cartilage oligomeric matrix protein; CS846, aggrecan chondroitin sulfate epitope 846; CTX-1, C-terminal telopeptide of type I collagen; HJHS, hemophilia joint health scores; IL, interleukin; OC, osteocalcin; OPG, osteoprotegerin; P1NP, N-terminal propeptide of type I procollagen; sRANKL, soluble receptor activator of nuclear factor- kappaB ligand; TNFα, tumor necrosis factor alpha.

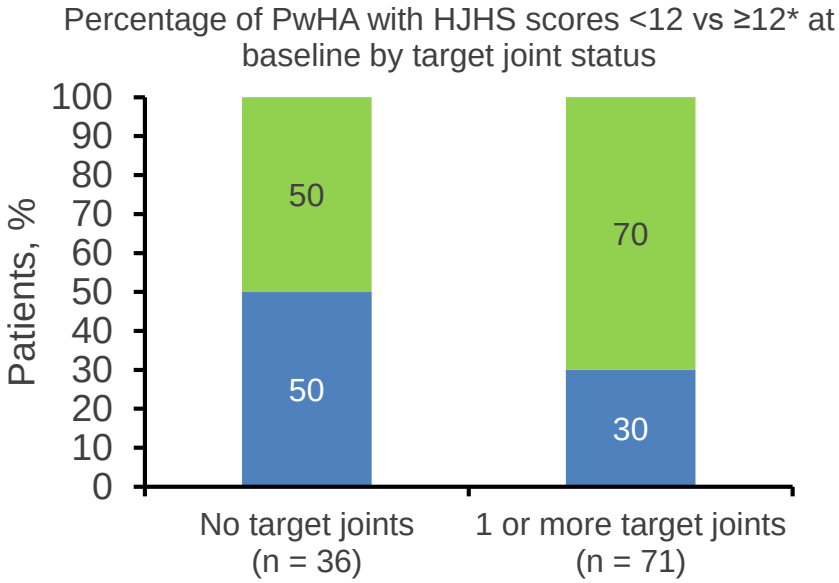
Characteristics of HAVEN 3 participants with evaluable HJHS and biomarker measurements

Characteristics		PwHA in HAVEN 3 with evaluable HJHS, *n* = 107	PwHA in HAVEN 3 with biomarker data, *n* = 117
Mean age (min–max), years		35.7 (13–77)	38.4 (13–77)
Age groups, *n* (%)	≥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, *n* (%)	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, *n* (%)	Prophylaxis	47 (43.9)	50 (42.7)
	Episodic	60 (56.1)	67 (57.3)
Target joints, *n* (%)	None	36 (33.6)	38 (32.5)
	≥1	71 (66.4)	79 (67.5)
History of HIV infection†, *n* (%)		17 (15.0)	31 (26.5)
Osteoporosis†, *n* (%)	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

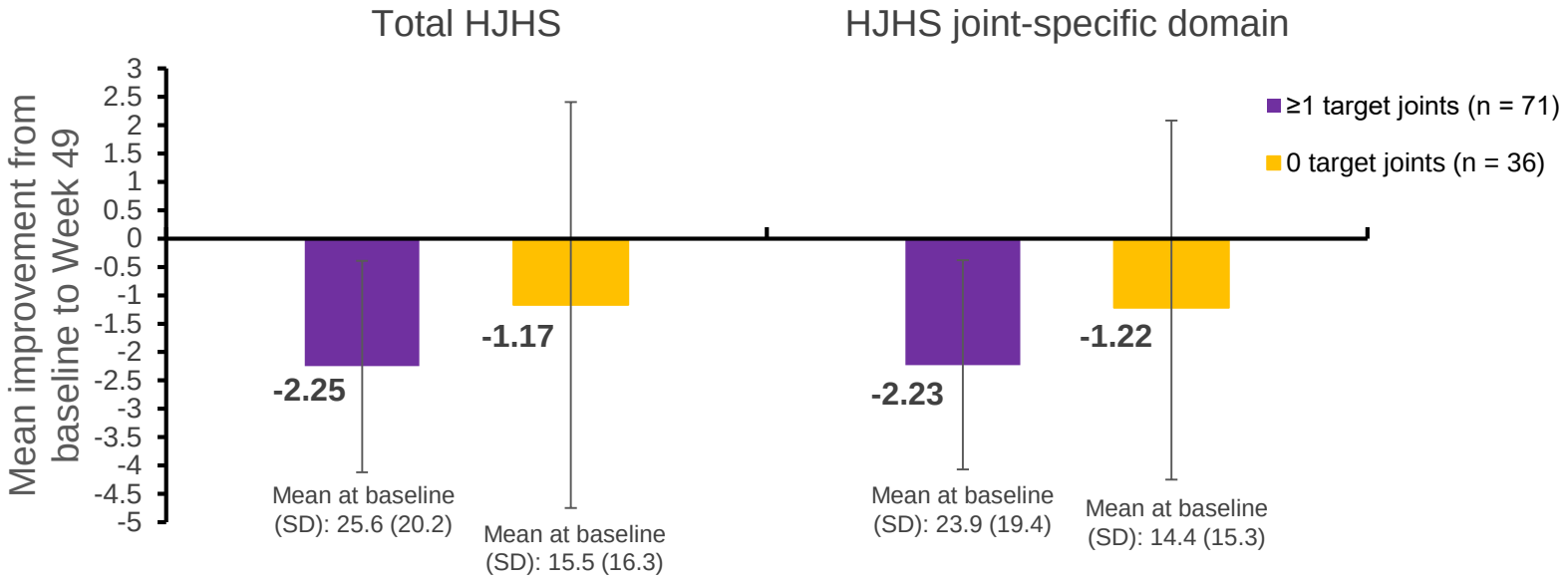
PwHA previously on FVIII prophylaxis and with no target joints have lower HJHS scores at baseline





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)

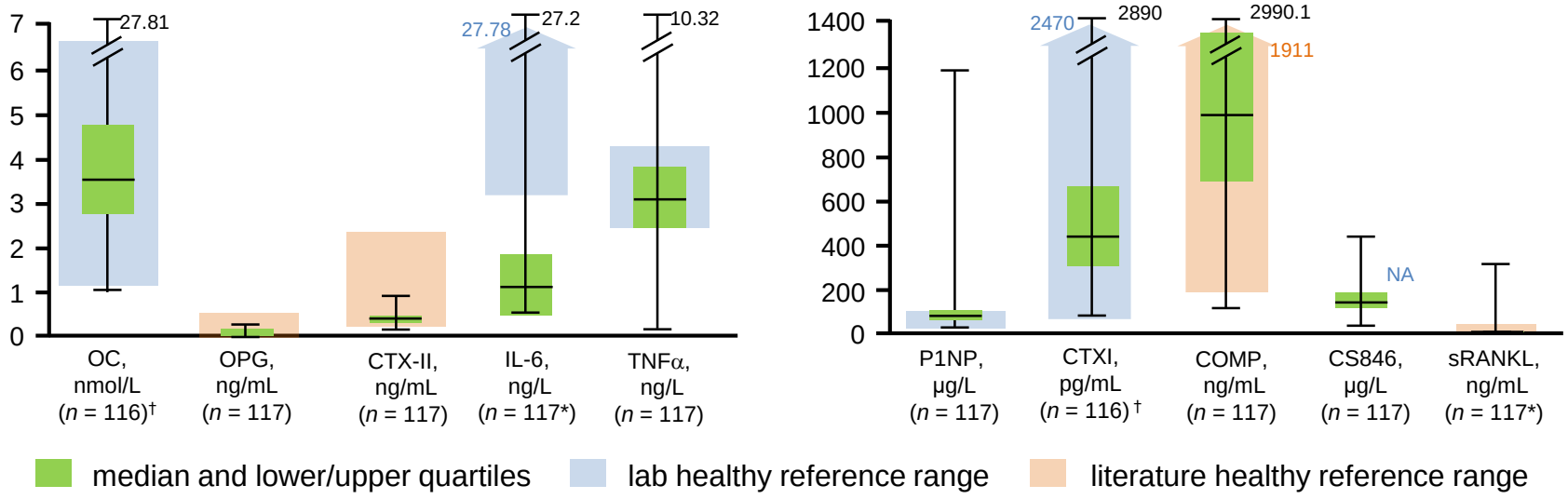
* A HJHS higher score indicates worse joint health. Clinically relevant improvements are defined as a ≥4-point reduction in Total HJHS or a ≥2-point reduction in HJHS joints domain.[1] Results were significant in the exploratory sense with 95% CI not including 0.

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

1. Kuijlaars IAR, et al. *Haemophilia*. 2017;23:934–940.

Baseline values of most bone and joint biomarkers were within normal ranges or similar to published levels in healthy individuals[1-4]

- 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

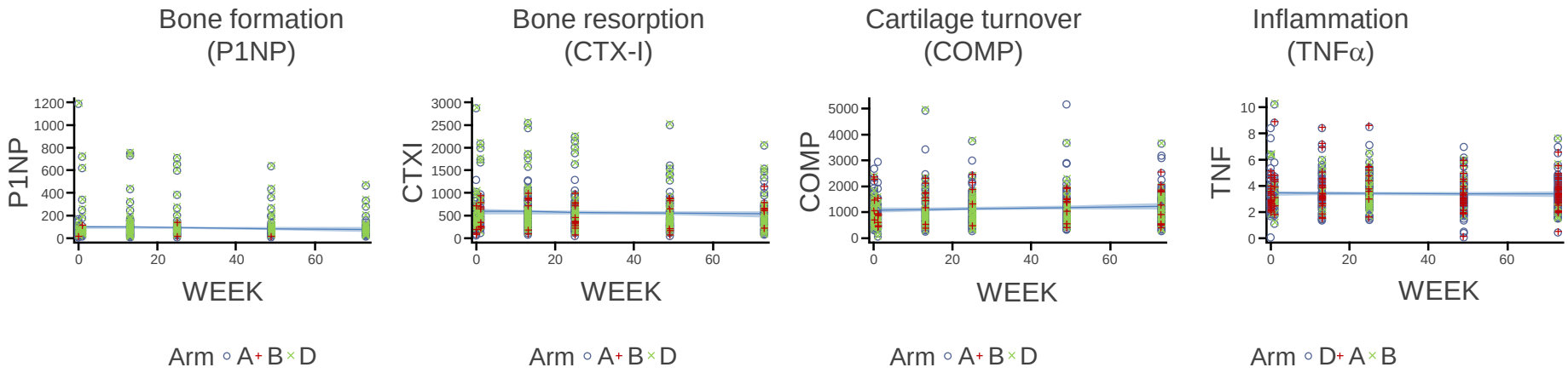


*Values below the limit of quantification (BLQ) are imputed with half of that limit of quantification; 57% of values for sRANKL, and 49% of values for IL-6 were BLQ; all IL-1β samples but one were BLQ and so are not shown here; †Missing observation at baseline for n=1.

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:



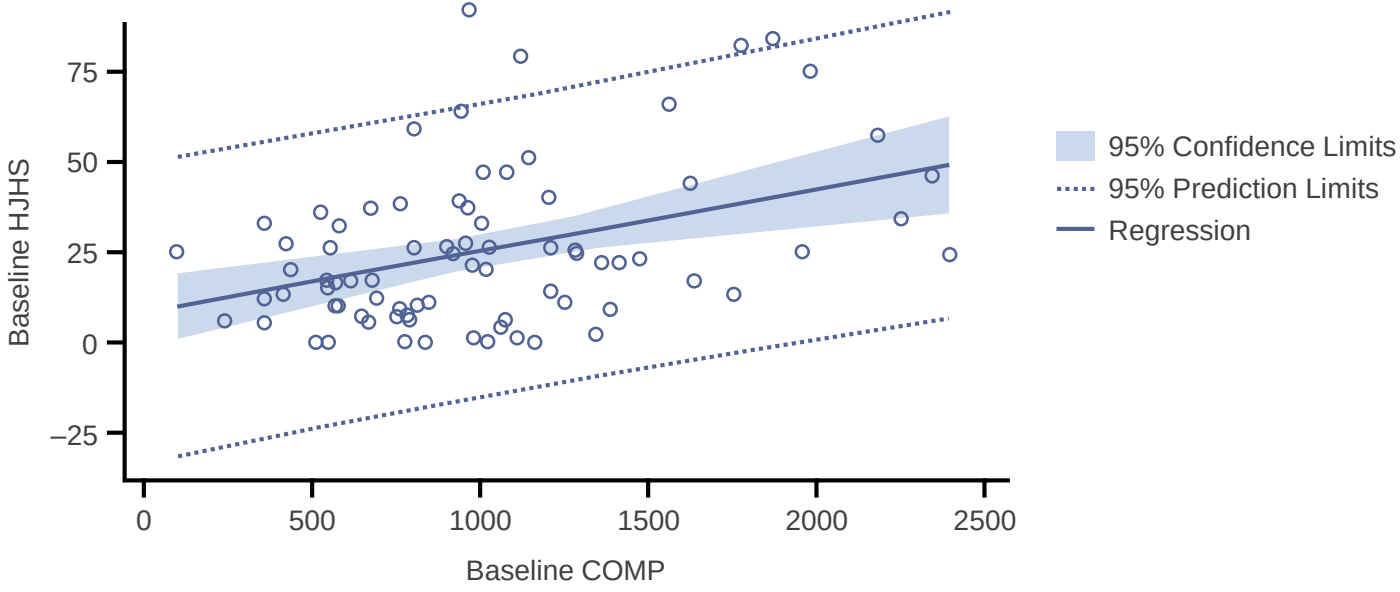
- Higher OC, P1NP, and CTX-I levels were observed in adolescents, consistent with reported increases of these biomarkers during skeletal growth[1,2]

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

1. Bayer M. *Osteoporos Int.* 2014;25:729–736;
2. Rauchenzauner M, et al. *J Clin Endocrinol Metab.* 2007;92:443–449.

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



*Includes only patients ≥18 years, including Arm C

Conclusions

- Clinically relevant improvements in HJHS (defined as a ≥2-point reduction in HJHS joints domain[1]) 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

1. Kuijlaars IAR, et al. *Haemophilia*. 2017;23:934–940.

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