Poster #36

Bone and joint health markers in persons with hemophilia A (PwHA) treated with emicizumab in the HAVEN 3 clinical trial

Anna Kiialainen,[1] Markus Niggli,[1] Christine Kempton,[2] Giancarlo Castaman,[3] Tiffany Chang,[4] Ido Paz-Priel,[4] Joanne I. Adamkewicz[4]

Summary

Hemophilia A (HA) can impact bone and joint health.[1]

Treatment of HA with emicizumab was shown to be efficacious and well tolerated in the HAVEN clinical trials.[2–5]

The effect of emicizumab on bone and joint health was assessed in the HAVEN 3 clinical trial.

Treatment with emicizumab led to clinically relevant improvements in joint function in those with target joints (a joint with multiple bleeds). Bone and joint biomarkers remained within the normal range during emicizumab prophylaxis.

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[1]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]Careggi University Hospital, Florence, Italy; [4]Genentech, Inc., South San Francisco, CA, USA

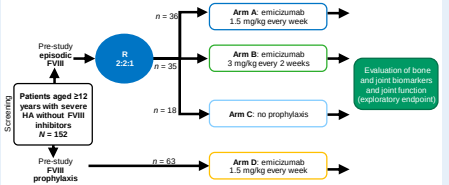
Introduction

- Bone health depends upon multiple factors, including physical activity, lifestyle, and diet.
- Diseases such as HA can also impact bone health. Repeat bleeding into joints can cause permanent damage and lead to conditions such as arthritis.[6] HA is also associated with lower bone density.[7]
- In the HAVEN 3 trial (NCT02847637), treatment with emicizumab (a HA treatment with a unique mechanism) was shown to reduce bleeding rates in persons with HA (PwHA) without clotting factor VIII (FVIII) inhibitors.[2] Treatment was well tolerated, and annualized bleeding rates were significantly lower (68%) than with previous FVIII prophylaxis (p<0.001).
- The HAVEN 3 trial also investigated the effect of emicizumab prophylaxis on bone and joint health in persons with hemophilia A without FVIII inhibitors.[2]

The HAVEN 3 study investigated emicizumab safety, efficacy, and other effects such as joint function in persons with HA.

- HAVEN 3 was a Phase III trial of adult and adolescent persons with severe HA without FVIII inhibitors (**Figure 1**), who had previously taken FVIII as **episodic** or **prophylactic** treatment.

Figure 1. Study design of HAVEN 3.

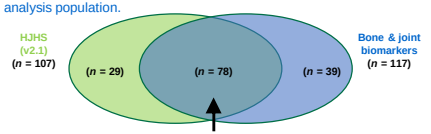


All patients treated with emicizumab were given a loading dose of 3.0 mg/kg weekly for 4 weeks, followed by the indicated maintenance dose, starting Week 5. The primary efficacy analysis was performed at 24 weeks. Emicizumab prophylaxis continued after the primary efficacy analysis.
FVIII, factor VIII; HA, hemophilia A; kg, kilogram; mg, milligram; R, randomization.

- Joint function was assessed through the Hemophilia Joint Health Score (HJHS) at baseline and Week 49 of emicizumab prophylaxis, and annually thereafter. Lower scores indicate better joint health.
- Bone and joint health biomarkers were assessed via blood samples taken after overnight fasting before starting emicizumab, and at 13, 25, 49, and 73 weeks of emicizumab prophylaxis.

Over a hundred PwHA from HAVEN 3 supplied joint function and biomarker data, through data cut-off: October 4, 2018 (Figure 2).

Figure 2. PwHA who supplied HJHS and biomarker data formed the analysis population.



Biomarkers are chemicals relating to bone and joint health. HJHS, Hemophilia Joint Health Score; PwHA, persons with hemophilia A.

Characteristics of HAVEN 3 participants with evaluable HJHS and biomarker measurements (Table 1).

- At the time of this analysis (October 4, 2018), the participants in HAVEN 3 had been followed for a median of 87.4 weeks.

Table 1. The participants in HAVEN 3 treated with emicizumab were pooled for this analysis.

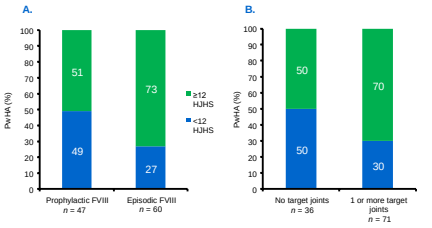
Participant characteristics		PwHA with evaluable HJHS (*n* = 107)	PwHA with biomarker data (*n* = 117)
Median age (IQR), years		35 (26–45)	38 (27–48)
Age groups, *n* (%)	≥65 years	2 (1.9)	5 (4.3)
	<18 years	7 (6.5)	7 (6.0)
Median BMI (IQR), kg/m²		25.0 (23.0–28.0)	25.4 (22.8–28.3)
Race, *n* (%)	White	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)

*HIV and osteoporosis numbers are based on clinical study report information applied to these subsets.
BMI, body mass index; HIV, human immunodeficiency virus; HJHS, Hemophilia Joint Health Score; IQR, interquartile range; PwHA, persons with hemophilia A.

PwHA had better joint health if they had previously taken preventative replacement FVIII rather than on-demand FVIII.

- The HJHS scale ranges from 0 to 20 per joint, with higher scores indicating worse joint health.
- For the analysis below, we used a cut-off score of 12, as this was the median in the HAVEN 3 FVIII prophylaxis population. Scores above 12 indicate bone health in the lower half of scores of the overall HAVEN 3 population (**Figure 3**).
- At study entry (baseline), PwHA who had previously taken prophylactic (regular, preventative) FVIII had better joint health than those who had taken episodic FVIII.

Figure 3. HJHS scores above/equal to (≥) or below (<) 12 at baseline by treatment (A) or target joint status (B).

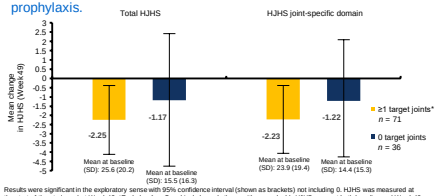


A cut-off score of 12 was used, as this was the median in the FVIII prophylaxis population based on our data.
FVIII, clotting factor VIII; HJHS, Hemophilia Joint Health Score; PwHA, persons with hemophilia A.

Significant improvements in joint health were seen with emicizumab treatment (Figure 4).

- Clinically relevant improvements in HJHS are defined as a ≥2-point reduction in the joint-specific domain or a ≥4-point reduction in Total HJHS.
- The average change in joint-specific and total HJHS after 48 weeks of emicizumab prophylaxis were -2.23 and -2.25, respectively, for PwHA with at least one target joint.
- Around half this level of improvement was seen for PwHA without target joints.
- Improvements were consistent across HJHS for different locations (knee, ankle, elbow).

Figure 4. Improvement in joint health at Week 49 of emicizumab prophylaxis.

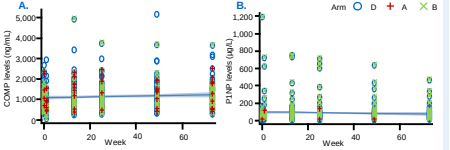


Results were significant in the exploratory sense with 95% confidence interval (shown as brackets) not including 0. HJHS was measured at the start of the study and at Week 49. *Excludes Arm C and includes only those with an evaluable HJHS score at both baseline and Week 49.
HJHS, Hemophilia Joint Health Score; SD, standard deviation.

No significant changes in bone and joint biomarkers were observed during the HAVEN 3 trial (Figure 5).

- Baseline biomarker levels were within normal ranges, but variable between individuals.
- During the follow-up period, biomarker levels (e.g. COMP and P1NP) remained stable within the normal range.

Figure 5. Measures of cartilage turnover (A. COMP) and bone formation (B. P1NP) did not change significantly over time with emicizumab prophylaxis (*n* = 94).*



Biomarkers were measured at the start of the study, and at 13, 25, 49, and 73 weeks. *Includes only patients ≥18 years, and excludes Arm C.
Bone & joint biomarkers assessed bone formation (OC, P1NP); bone resorption (CTX-I); osteoblastis (OPG); osteoclastogenesis (sRANKL); cartilage degradation (CTX-II); cartilage synthesis/repair (CS846); inflammation (IL-1β, IL-6, TNFα).
L, liter; mL, milliliter (of blood); ng, nanogram; µg, microgram.

Conclusions

Clinically relevant improvements in joint function were seen in persons with hemophilia A with target joints treated with emicizumab.

Bone and joint biomarkers remained within normal ranges during the follow-up period.

Further research is required to understand the long-term effect of emicizumab prophylaxis on bone and joint health.

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Disclosures

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