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 FIX\(a\) and FX to replace the function of missing FVIII 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

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HAVEN 3: Emicizumab prophylaxis in PwHA without FVIII inhibitors

Patients aged ≥12 years with severe hemophilia A without FVIII inhibitors, N = 152

Pre-study episodic FVIII

R 2:2:1

\( n = 36 \)

Arm A: emicizumab 1.5 mg/kg QW maintenance

\( n = 35 \)

Arm B: emicizumab 3 mg/kg Q2W maintenance

\( n = 18 \)

Arm C: no prophylaxis

\( n = 63 \)

Arm D: emicizumab 1.5 mg/kg QW maintenance

24-week primary efficacy analysis

Emicizumab prophylaxis continuation

Exploratory endpoint: Evaluation of bone biomarkers and HJHS

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

\( n = 117 \)

\( n = 29 \)

\( n = 78 \)

\( n = 39 \)

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, TNFα)

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PwHA in HAVEN 3 with evaluable HJHS, n = 107</th>
<th>PwHA in HAVEN 3 with biomarker data, n = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (min–max), years</td>
<td>35.7 (13–77)</td>
<td>38.4 (13–77)</td>
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<tr>
<td>Age groups, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>≥65 years</td>
<td>2 (1.9)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>7 (6.5)</td>
<td>7* (6.0)</td>
</tr>
<tr>
<td>Mean BMI (min–max), kg/m²</td>
<td>26.0 (19.2–40.6)</td>
<td>26.0 (16.8–40.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64 (59.8)</td>
<td>80 (68.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>28 (26.2)</td>
<td>22 (18.8)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>5 (4.7)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.9)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (8.4)</td>
<td>9 (7.7)</td>
</tr>
<tr>
<td>Prior FVIII, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>47 (43.9)</td>
<td>50 (42.7)</td>
</tr>
<tr>
<td>Episodic</td>
<td>60 (56.1)</td>
<td>67 (57.3)</td>
</tr>
<tr>
<td>Target joints, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>36 (33.6)</td>
<td>38 (32.5)</td>
</tr>
<tr>
<td>≥1</td>
<td>71 (66.4)</td>
<td>79 (67.5)</td>
</tr>
<tr>
<td>History of HIV infection†, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 (15.0)</td>
<td></td>
<td>31 (26.5)</td>
</tr>
<tr>
<td>Osteoporosis†, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>1 (0.9)</td>
<td>5* (4.3)</td>
</tr>
<tr>
<td>Treated</td>
<td>1 (0.9)</td>
<td>4* (3.4)</td>
</tr>
</tbody>
</table>

*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.

The diagram shows the percentage of PwHA with HJHS scores <12 vs ≥12* at baseline by treatment and by target joint status.

In the prophylactic FVIII group (n = 47), 51% had HJHS scores <12, while 49% had scores ≥12. In the episodic FVIII group (n = 60), 73% had HJHS scores <12, and 27% had scores ≥12.

In the group with no target joints (n = 36), 50% had HJHS scores <12, and 50% had scores ≥12. In the group with 1 or more target joints (n = 71), 70% had HJHS scores <12, and 30% had scores ≥12.
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 joint-specific domain.† Results were significant in the exploratory sense with 95% CI not including 0.

<table>
<thead>
<tr>
<th>Mean improvement from baseline to Week 49</th>
<th>Total HJHS</th>
<th>HJHS joint-specific domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean at baseline (SD): 25.6 (20.2)</td>
<td>-2.25</td>
<td>-2.23</td>
</tr>
<tr>
<td>Mean at baseline (SD): 15.5 (16.3)</td>
<td>-1.17</td>
<td>-1.22</td>
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†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 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-1\(\beta\) samples but one were BLQ and so are not shown here; \(^*\)Missing observation at baseline for \(n=1\).*

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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

*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

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  - Study investigators, coordinators, and site personnel
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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:

- **Prophylactic FVIII**
  - N = 47
- **Episodic FVIII**
  - N = 60

Individual baseline HJHS scores of PwHA with or without target joints:

- **No target joints**
  - N = 36
- **1+ target joints**
  - N = 71

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.
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.