Immunogenicity of emicizumab in people with hemophilia A: results from the HAVEN 1–4 studies

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Emicizumab is a humanized, IgG4, bispecific monoclonal antibody. Bridges FIXa and FX to replace the function of FVIIIa in PwHA.

- Optimized structure to minimize development of anti-emicizumab antibodies.
- Half-life of ~30 days.
- Administered subcutaneously with high bioavailability.
- Demonstrated favorable safety and effective bleed prevention in adolescents/adults and pediatric PwHA with or without inhibitors (HAVEN 1–4).
- Approved in the US for PwHA of all ages, with or without FVIII inhibitors, with QW, Q2W, or Q4W dosing.

References:
Background: anti-drug antibodies (ADAs)

- Biological products may induce ADAs with variable clinical significance, e.g.
  - No clinical effect
  - Change in drug clearance rate
  - Reduced drug efficacy
  - Safety impact: hypersensitivity, infusion reaction, cross reaction with endogenous proteins

- In the emicizumab phase I/II study, four participants (4/18), treated at low dose levels, tested positive for ADAs without clinical impact\(^1\)

- Initial analyses of HAVEN studies did not identify any participants with ADAs

- Assay sensitivity has been improved by establishing a disease-specific threshold for ADA positivity according to guidelines\(^2,3\)

- The goal of the current analysis was to characterize the incidence and clinical significance of anti-emicizumab antibodies based on a revised, validated detection threshold


Methods: ADA definitions

**ADA positive**

**Treatment induced**: ADAs that develop *de novo* following drug exposure

**Treatment boosted**: ADAs detectable at baseline whose titer increases ≥4-fold following drug exposure

**Transient ADA**

ADA detected only at one sampling time point during treatment or follow-up observation period (excluding the last sampling time point)

**Persistent ADA**

ADA detected at two or more sampling time points during the treatment or follow-up observation period, or detected at the last sampling time point

**Neutralizing ADAs**

Inhibit or reduce *in vitro* the pharmacological activity by preventing target binding

**Non-neutralizing ADAs**

Bind the biological drug *in vitro* but do not inhibit its pharmacological activity

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Methods: bioanalytical approach to anti-emicizumab ADA detection

- **ADA detection**
  - Bridging immunoassay, 1-step sandwich ELISA
    - ADA bridges the plate-bound biotin-emicizumab (emicizumab\textit{Bio}) and digoxigenin-labeled emicizumab (emicizumab\textit{Dig})
    - Emicizumab\textit{Bio}—ADA—emicizumab\textit{Dig} complex detected
  - Assay detects ≥100 ng/mL of positive control in presence of therapeutic concentration of emicizumab
    - Sensitivity in accordance with immunogenicity guidance

- Specificity confirmed by repeating the ELISA assay in the presence of excess emicizumab
  - Signal quenching indicates specific anti-emicizumab antibody

- A disease-specific threshold for ADA positivity was established based on baseline (pre-exposure) samples
- The revised cut point was applied to all plasma samples from HAVEN 1, 2, 3 and 4
  - ADA positive or negative status was reassigned to all HAVEN samples

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ELISA, enzyme-linked immunosorbent assay
Methods: participants and sampling

- Analyses included all participants in the HAVEN studies who:
  - Received at least one dose of emicizumab and
  - Had at least one sample tested for ADA after exposure

- Per protocol, blood samples collected for ADA assessment at predetermined time points
  - Concurrent samples collected for PK and PD analyses

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**Adults and adolescents (HAVEN 1, 3, and 4)**
- Pre-dose
- At Weeks 5, 9, 13, 17, 21, and 25
- Every 8–12 weeks thereafter

**Children (HAVEN 2)**
*Reduced sampling due to blood volume constraints*
- Pre-dose
- At Weeks 5, 17, 33, and 49
- Every 12 weeks thereafter

For participants who discontinue: 24 weeks after last dose

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PD, pharmacodynamic; PK, pharmacokinetic
Results: ADAs were observed in 3.5% of participants across HAVEN studies

- Overall, **14/398** (3.5%, 95% CI 1.9–5.8) participants tested positive for ADAs

<table>
<thead>
<tr>
<th></th>
<th>HAVEN 1</th>
<th>HAVEN 2</th>
<th>HAVEN 3</th>
<th>HAVEN 4</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants exposed to emicizumab</td>
<td>112</td>
<td>88</td>
<td>151</td>
<td>48</td>
<td>399</td>
</tr>
<tr>
<td>≥1 post-baseline assessment, n</td>
<td>111</td>
<td>88</td>
<td>151</td>
<td>48</td>
<td>398</td>
</tr>
<tr>
<td>Median duration of exposure, weeks (IQR)</td>
<td>91.1</td>
<td>53.1</td>
<td>50.1</td>
<td>44.1</td>
<td>55.1</td>
</tr>
<tr>
<td>ADA negative, n (%)</td>
<td>109 (98.2)</td>
<td>84 (95.5)</td>
<td>145 (96.0)</td>
<td>46 (95.8)</td>
<td>384 (96.5)</td>
</tr>
<tr>
<td>ADA positive, n (%)</td>
<td>Treatment induced</td>
<td>2 (1.8)</td>
<td>4 (4.5)</td>
<td>5 (3.3)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Treatment boosted</td>
<td>0</td>
<td>0</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>2 (1.8)</td>
<td>4 (4.5)</td>
<td>6 (4.0)</td>
<td>2 (4.2)</td>
</tr>
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CI, confidence interval; IQR, interquartile range
Results: ADAs were frequently transient

Transitory ADAs were detected in 7/14 ADA-positive participants

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<td>111</td>
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<td>151</td>
<td>48</td>
<td>398</td>
</tr>
<tr>
<td>1 positive, n (%)</td>
<td>0</td>
<td>2 (2.3)</td>
<td>4 (2.6)</td>
<td>1 (2.1)</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>≥2 positive, n (%)</td>
<td>2 (1.8)</td>
<td>2 (2.3)</td>
<td>2 (1.3)</td>
<td>1 (2.1)</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>All</td>
<td>2 (1.8)</td>
<td>4 (4.5)</td>
<td>6 (4.0)</td>
<td>2 (4.2)</td>
<td>14 (3.5)</td>
</tr>
</tbody>
</table>

ADA detected only at one sampling time point during treatment or follow-up observation period (excluding the last sampling time point)
Results: ADAs with neutralizing potential were observed in <1% of the study population

- In the absence of a neutralizing antibody assay, PK and PD profiles were used to identify ADAs with neutralizing potential
  - ADAs with neutralizing potential were defined as ADAs associated with decline in PK and corresponding reduced PD effects

- ADAs with neutralizing potential were identified in 3/398 (0.75%, 95% CI 0.2–2.2) participants
  - One participant discontinued due to a loss of efficacy
  - One participant remained on study without any bleed for 48 weeks since ADA detection
  - One participant discontinued due to personal preference

- Importantly, ADAs without neutralizing potential were not associated with reduced efficacy
Results: illustrative profiles of ADAs with neutralizing potential

- Typical participant (no ADA detected)

- ADAs detected at Week 5
  - Sharp decline in emicizumab concentration and reported FVIII activity
  - Up-titration to 3 mg/kg QW at Week 9 without improvement in PK or PD was observed
  - Discontinued from the study due to lack of efficacy and resumed previous treatment

- ADAs detected at Week 33
  - Gradual decline in emicizumab concentrations to ~15 µg/mL with a corresponding decline in reported FVIII activity
  - Continues emicizumab at original dose without a bleed for 48 weeks since ADA detection

*Sample confirmed positive after initial snapshot (data cut-off: 30 April 2018)
Results: most ADAs were detected early

- Duration of exposure was >36 weeks for 88.5% of patients (N=398)
- ADAs were detected between 5–33 weeks on study
  - Seven participants before Week 14
  - Six participants between Week 14–25
  - One participant after Week 25
Results: the presence of ADAs did not impact safety

- The safety profile of the 14 participants who tested positive for ADAs was similar to that of patients without ADAs
  - ADAs did not affect the frequency or type of adverse events
  - No cases of anaphylaxis or hypersensitivity occurred
  - No events indicative of potential immune complex deposition were observed
  - The frequency or severity of injection-site reactions did not increase following development of ADAs
- The safety profile of the 14 participants who tested positive for ADAs did not change after the detection of ADAs
- Anti-emicizumab ADAs do not cross-react with endogenous proteins
  - ADAs did not affect FIX or FX antigen levels
  - ADAs were not associated with development of FVIII inhibitors
Conclusions

- Emicizumab treatment is associated with a low rate of ADA development (14/398 participants, 3.5%), as expected for a humanized monoclonal antibody.
- ADAs with neutralizing potential were observed in <1% of participants.
- Nearly all ADAs were detected in the first 6 months of exposure to emicizumab.
- The presence of ADAs was not associated with a change in safety profile, anaphylaxis, or hypersensitivity reaction.
- In itself, detection of ADAs has limited impact on clinical management, suggesting that routine surveillance is not warranted.
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