Reduction in Pain during and between Attacks in Patients with Acute Hepatic Porphyria Treated with Givosiran: A Post-Hoc Analysis of the Phase 3 ENVISION Study

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Acute Hepatic Porphyria (AHP) and Givosiran

Disease Overview and Pathophysiology

- Family of rare, genetic diseases resulting from deficiency in one of the enzymes responsible for heme biosynthesis in the liver, leading to accumulation of neurotoxic intermediates ALA/PBG\textsuperscript{1,2}
- Characterized by acute neurovisceral attacks with common symptoms of severe abdominal pain and muscle weakness\textsuperscript{3,4}
  - Without proper treatment, attacks can progress to paralysis, respiratory failure, and death
- Patients also experience chronic debilitating symptoms, most commonly severe pain\textsuperscript{3–5}
- Acute attacks often require hospitalization with supportive care, opioid analgesics, and hemin\textsuperscript{4}

Givosiran

- RNAi therapeutic targets ALAS1, decreasing ALA/PBG that are causal for disease manifestations\textsuperscript{6,7}
- Approved in the US for the treatment of adults with AHP and in the EU for treatment of AHP in adults and adolescents aged ≥12 years\textsuperscript{8,9}
  - In patients with AIP (most common AHP type), givosiran significantly reduced the annualized rate of porphyria attacks, urinary ALA and PBG, days of hemin use, and improved multiple other disease manifestations compared with placebo, with an acceptable and monitorable safety profile
  - Daily worst pain\textsuperscript{a} (p=0.0530 [pre-specified ANCOVA]; p=0.0455 [post-hoc Wilcoxon]) and analgesic use were reduced compared with placebo

\textsuperscript{a}Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method

AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; ALAS1, delta-aminolevulinic acid synthase 1; ANCOVA, analysis of covariance; EU, European Union; PBG, porphobilinogen; RNAi, RNA interference

ENVISION Phase 3 Study Design
Randomized, Double-Blind, Placebo-Controlled Study in Patients with AHP

94 patients enrolled at 36 sites in 18 countries

Patient Population (N=94)
- Age ≥12 years
- Diagnosis of AHP
- ≥2 attacks within prior 6 months
- Willing to discontinue and/or not initiate hemin prophylaxis

Primary Endpoint
- Composite annualized attacks (attacks requiring hospitalization, urgent health care, or IV hemin administration at home) in AIP at 6 months\(^a\)

Secondary Endpoints\(^b\)
- ALA and PBG
- Hemin doses
- Composite annualized attacks in AHP over 6 months\(^a\)
- Pain
- Fatigue
- Nausea
- PCS of SF-12

Aim of current post-hoc analysis of ENVISION
- Assess reduction in pain and analgesic use during and between attacks over 6 months

\(^a\)Attacks requiring hospitalization, urgent health care, or IV hemin administration at home; composite annualized attack rate calculated for each patient by dividing the total number of porphyria attacks by the total number of days in the treatment period before multiplying by 365.25. \(^b\)Endpoints evaluated in genetically confirmed AIP patients, unless otherwise noted.

**Demographics and Baseline Characteristics of Patients with AHP**

**Baseline Characteristics Were Generally Balanced between Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo&lt;sup&gt;a&lt;/sup&gt; (n=46)</th>
<th>Givosiran (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, years, median (range)</td>
<td>36 (20, 60)</td>
<td>42 (19, 65)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>41 (89)</td>
<td>43 (90)</td>
</tr>
<tr>
<td>Years since diagnosis, median (range)</td>
<td>6.11 (0.1, 38.5)</td>
<td>6.98 (0.2, 43.3)</td>
</tr>
<tr>
<td>Prior hemin prophylaxis, n (%)</td>
<td>18 (39)</td>
<td>20 (42)</td>
</tr>
<tr>
<td>Historical AAR&lt;sup&gt;b&lt;/sup&gt;, median (range)</td>
<td>7.0 (0&lt;sup&gt;a&lt;/sup&gt;, 46)</td>
<td>8.0 (4, 34)</td>
</tr>
<tr>
<td>Chronic symptoms daily or most days between attacks, n (%)</td>
<td>26 (57)</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Opioid use daily or most days between attacks, n (%)</td>
<td>13 (28)</td>
<td>14 (29)</td>
</tr>
</tbody>
</table>

<sup>a</sup>One patient in the placebo group did not meet inclusion criterion of ≥2 attacks requiring hospitalization, urgent healthcare visit, or IV hemin at home within 6 months prior to screening (patient had 2 attacks that were treated at home without IV hemin)

<sup>b</sup>Composite porphyria attacks are attacks requiring hospitalization, an urgent healthcare visit, or IV hemin treatment at home

AAR, annualized rate of composite porphyria attacks
Improvement in Number and Severity of Attacks in Givosiran-Treated Patients

<table>
<thead>
<tr>
<th>Attacks&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Overall</th>
<th>With Prior Hemin Prophylaxis</th>
<th>Without Prior Hemin Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=46)</td>
<td>Givosiran (n=48)</td>
<td>Placebo (n=18)</td>
</tr>
<tr>
<td>Total number of attacks</td>
<td>297</td>
<td>90</td>
<td>186</td>
</tr>
<tr>
<td>Number of patients with ≥1 attack, n (%)</td>
<td>38 (82.6)</td>
<td>24 (50.0)</td>
<td>17 (94.4)</td>
</tr>
<tr>
<td>Total number of attacks with median pain scores ≥7, n (%)</td>
<td>95/297 (32.0)</td>
<td>19/90 (21.1)</td>
<td>66/186 (35.5)</td>
</tr>
<tr>
<td>Number of patients with ≥1 attack with median pain scores ≥7, n (%)</td>
<td>24/38 (63.2)</td>
<td>10/24 (41.7)</td>
<td>13/17 (76.5)</td>
</tr>
</tbody>
</table>

Regardless of prior hemin prophylaxis use:
- Givosiran led to reduction in total attack number compared with placebo
- Givosiran had a lower proportion of patients with ≥1 attack compared with placebo
- Givosiran treatment resulted in a lower proportion of patients with ≥1 attack with severe pain (median daily worst pain score ≥7) compared with placebo

<sup>a</sup>Attacks included are those requiring hospitalization, urgent care, or at-home hemin use. Median pain scores of these attacks were calculated based on scores collected during each attack.
Reduced Daily Worst Pain Score during Attack-free Periods

- Fewer days with daily worst pain scores above baseline\(^a\) for givosiran-treated vs placebo
- Patients receiving givosiran reported nearly 50% fewer days with severe pain compared with placebo (proportion of days with scores ≥7: 6.8% vs 12.2%, respectively)

\(^a\)Baseline pain score is the mean score from 4 to 7 days prior to first dose of study drug, when patient is not experiencing an attack

NRS, numeric rating scale
Reduced Analgesic Use in Patients Receiving Givosiran

- Patients receiving givosiran had reductions in opioid use compared with placebo
  - Larger reductions were observed during attack-free periods

![Bar chart showing reduced analgesic use in patients receiving givosiran](chart.png)

- **During Attacks\(^a\)**
  - Placebo: 85.0%
  - Givosiran: 73.3%
  - Placebo: 75.0%
  - Givosiran: 60.0%
  - Placebo: 100.0%
  - Givosiran: 83.3%

- **During Attack-free Periods**
  - Opioid use: Placebo: 69.6%, Givosiran: 56.3%
  - Non-opioid use: Placebo: 67.4%, Givosiran: 62.5%
  - Either opioid or non-opioid use: Placebo: 95.7%, Givosiran: 85.4%

\(^a\)All investigator-adjudicated attacks are included
Improvement in Overall Bodily Pain Domain in SF-12\textsuperscript{a} Assessment

- Bodily pain domain had greater improvement (increase) with givosiran (7.3) vs placebo (2.2)
- Data suggest reduction in daily worst pain (along with decreased analgesic use) is clinically relevant as patients reported reduced interference with normal activities

![Bodily Pain Domain Graph](image)

\textsuperscript{a}The SF-12 is scored on a scale of 0–100, where higher scores indicate improvement. All investigator-adjudicated attacks are included.

\textsuperscript{b}SF-12 (version 2) was assessed using a recall period (the time period patients are asked to consider in responding to a PRO item or question) of 4 weeks.

SEM, standard error of the mean.
Summary of ENVISION Post-Hoc Analysis

Givosiran Reduced Pain in Patients with AHP during and between Attacks

• Patients with AHP can experience chronic pain even during attack-free periods and require high levels of analgesics, including opioids, to manage pain during and between attacks
• Givosiran treatment reduced both the number and severity of attacks compared with placebo, regardless of prior hemin prophylaxis use
• Givosiran treatment reduced the level of pain patients report compared with placebo, both during attacks and between attacks
  – Treatment-related reductions in pain were not due to higher analgesic use; givosiran treatment was associated with reduced analgesic use compared with placebo
  – Givosiran-treated patients reported greater improvement in the SF-12 Bodily Pain domain, suggesting reduction in daily worst pain was clinically relevant

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