Long-Term Efficacy and Adverse Event Characterization of Dichlorphenamide for the Treatment of Primary Periodic Paralysis

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Introduction

- Primary periodic paralysis (PPP) is a rare condition caused by genetic mutations in skeletal muscle sodium, calcium, and potassium channels, resulting in attacks or muscle weakness/
stiffness.
- Dichlorphenamide (DCP) is now administered daily for up to 1 year, having been shown to reduce the frequency, severity, and duration of attacks in PPP.

Methods

- Study Design and Patients
  - Data were analyzed from a 6-week phase 3, randomized, double-blind, placebo (PBO)-controlled phase and a 52-week open-label extension phase (Figure 1).
- In the phase 3 DCP trial, patients were randomly assigned to receive DCP (current DCP dose if taking a prior antihypokalemic agent) or PBO for 9 weeks during the double-blind phase, followed by a 52-week open-label phase (Figure 1).
- Patients in the open-label DCP group continued at the same dose they were taking at the end of the double-blind phase (dose adjustments permitted to mimic clinical practice).
- In the open-label phase, patients could switch to DCP 50 mg twice daily.

Assessments and Statistical Analyses

- The study completor population included patients in the intent-to-treat (ITT) population (all patients completing 1 week of DCP treatment).
- Changes from baseline at Week 61 in attack rates and severity-weighted attack rates were analyzed for within- and between-group differences
- Within-group median differences were assessed for significance using Wilcoxon signed rank test between treatment groups. Discontinuation due to event assessments were assessed using blocked Wilcoxon rank sum test.

Results

Demographic and Baseline Characteristics

- Table 1 shows demographic and baseline characteristics of patients:
- Majority of the 63 patients were male (61.9%), white (84.1%), and had hypokalemic periodic paralysis (68.3%).

Table 1. Demographic and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Completer Population</th>
<th>PBO/DCP Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>59 (81.0)</td>
<td>56 (84.1)</td>
</tr>
<tr>
<td>Race (%)</td>
<td>White 45 (66.7)</td>
<td>43 (66.1)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hypokalemic 46 (68.3)</td>
<td>42 (65.6)</td>
</tr>
<tr>
<td>Attack rate</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.25 (1.75, 3.00)</td>
<td>2.25 (1.75, 3.00)</td>
</tr>
</tbody>
</table>
| Median % decrease from baseline to Week 61 | Based on median decrease from baseline to Week 61 within a group.

Efficacy

- For patients in the study completor population, the median weekly attack rate (Table 2; Figure 2) and median severity-weighted attack rate (Table 2; Figure 2) improved significantly from baseline to Week 61 in both treatment groups.

Table 2. Summary of Efficacy From Baseline to Week 61

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Completer Population</th>
<th>PBO/DCP Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median weekly attack rate</td>
<td>Baseline 2.25 (1.75, 3.00)</td>
<td>Baseline 2.25 (1.75, 3.00)</td>
</tr>
<tr>
<td>Median decrease from baseline to Week 61</td>
<td>0.06 (0.00, 0.12)</td>
<td>0.06 (0.00, 0.12)</td>
</tr>
</tbody>
</table>

Conclusions

- Long-term (61 weeks) DCP treatment was efficacious and provided durable reduction in attack frequency in patients with PPP.
- Patients and cognition-related AEs tended to be mild or moderate in intensity and usually managed by dose adjustments.
- These AEs rarely resulted in discontinuation from the study and were sometimes managed by DCP dose reductions.

Acknowledgements

- Disclosures

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