A Phase 2 Study of Oral Difelikefalin for Moderate-to-Severe Pruritus in Subjects With Notalgia Paresthetica (KOMFORT)

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SYNOPSIS

Notalgia Paresthetica (NP) is a common sensory neuropathy of the back characterized by chronic intense itching and paresthesias. People with chronic kidney disease undergoing hemodialysis (KDOQI Stage 5) are at increased risk of developing NP.

Methods

The KOMFORT study evaluated the safety and efficacy of oral difelikefalin (DFK) 2 mg twice daily (BID) for the treatment of NP in subjects with chronic kidney disease undergoing hemodialysis. The study was a double-blind, placebo-controlled phase 2 study (NCT04706975). A total of 126 subjects were randomized (placebo, n=63; DFK, n=62) to receive oral DFK 2 mg BID for 8 weeks.

RESULTS

Baseline demographics and disease characteristics were similar between groups (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=63)</th>
<th>DFK 2 mg (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>42 (16.1)</td>
<td>42 (16.1)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m</td>
<td>28.7 (5.2)</td>
<td>28.7 (5.2)</td>
</tr>
<tr>
<td>White</td>
<td>98 (33.9)</td>
<td>98 (33.9)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (12.7)</td>
<td>8 (12.7)</td>
</tr>
<tr>
<td>Median (IQR), WI-NRS score</td>
<td>7.6 (2.4)</td>
<td>7.6 (2.4)</td>
</tr>
<tr>
<td>Median (IQR), daily non-missing WI-NRS score for the week</td>
<td>7.6 (2.4)</td>
<td>7.6 (2.4)</td>
</tr>
</tbody>
</table>

DFK resulted in a significant reduction from baseline in the weekly mean WI-NRS score at week 8 compared with placebo (Figure 1).

Reduction in itch intensity was observed with DFK at day 1 compared with placebo (Figure 2).

Efficacy

By day 1, DFK resulted in a significant reduction from baseline in the weekly mean WI-NRS score at week 8 compared with placebo (Figure 1).

At week 8, a significantly greater proportion of subjects receiving DFK achieved a complete response (WI-NRS of 0 or 1 on at least 70% of the daily non-missing WI-NRS scores for the week) compared with placebo (Figure 3).

Safety

DFK was generally well tolerated. Headache, dizziness, constipation, and increased urine output were more commonly reported in DFK-treated subjects.

Table 3. Most Commonly Reported TEAEs

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Placebo (n=63)</th>
<th>DFK 2 mg (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>11 (17.4)</td>
<td>18 (29.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (8.1)</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (11.1)</td>
<td>13 (21.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (11.1)</td>
<td>10 (16.1)</td>
</tr>
<tr>
<td>Abnormal laboratory values</td>
<td>12 (19.0)</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td>Other adverse events</td>
<td>10 (16.1)</td>
<td>12 (19.3)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• The phase 2 KOMFORT study demonstrated that oral DFK significantly reduced itch intensity compared with placebo in subjects with NP.

• The onset of action was evident at day 1 and maintained through week 8.

• A significantly greater proportion of subjects receiving DFK at placebo achieved a complete response.

• DFK was generally well tolerated.

• The most commonly reported AEs were headache, transient dizziness, constipation, and increased urine output.

• The results of this phase 2 trial support the role of the kappa-opioid receptor activation for the control of neuropathic itch.

• These findings underscore that DFK has the potential to fill a significant unmet need and warrants further clinical development in NP.

REFERENCES


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CORRESPONDENCE

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DISCLOSURES

The authors report no relevant conflicts of interest. This study was supported by Cara Therapeutics, Stamford, CT, USA.

Figure 1. KOMFORT Study Design

Figure 2. Primary Endpoint: Orange Line Baseline in WI-NRS at 8 Weeks

Figure 3. Achievement of ≥4-Point Improvement in WI-NRS

Figure 4. Change from Baseline in Daily WI-NRS Scores During Week 1

Figure 5. Achievement of Complete Response in WI-NRS

Table 1. Baseline Demographic and Disease Characteristics

Table 2. Most Commonly Reported AE

Table 3. Most Commonly Reported TEAEs

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