Open-Label Extension of a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Analgesic Efficacy of MNK-795 Controlled-Release Oxycodone/Acetaminophen Tablets (CR OC/APAP) in an Acute Pain Model

Neil Singla, MD; Thomas Barrett, PhD; Lisa Sisk; Kenneth Kostenbader, MD; Jim Young, PhD; Michael Giuliani, MD
Luton Clinical Research LLC, Pasadena, CA, USA; Mallinckrodt Inc., Hazelwood, MO, USA

Introduction
Despite the wide range of treatment options available for acute pain, advances in the management of acute pain are needed.

Multimodal therapy combining oxycodone (OC) and acetaminophen (APAP) is a well-established approach to the treatment of acute pain.

Combining agents with different mechanisms of action may offer additive effects, while allowing for the management of pain at a lower dose of each component, potentially reducing the risk of concentration-dependent adverse events.

In addition, formulations engineered to provide quick and sustained release may offer therapeutic benefit as each component, potentially reducing the risk of concentration-dependent adverse events as well as reduce the pill burden.

MNK-795 (CR OC/APAP) is a controlled-release (CR) combination OC/APAP analgesic, and is being designed to provide both fast onset of analgesia within 1 hour and sustained release over the 12-hour dosing interval.

CR OC/APAP tablets employ a dual-layer bipartisan, delivery-liability technology, when administered as a single dose (2 tablets), ensures the IR component delivers 2 tablets of CR OC/APAP every 12 hours (4 doses total) until no longer needed.

In this pivotal clinical trial, CR OC/APAP was studied in an open-label extension phase of a randomized, double-blind, placebo-controlled, phase 3 study.

Objectives
Evaluate the safety of the administration of multiple doses of CR OC/APAP in patients with moderate to severe acute pain in an open extension phase of a randomized, double-blind, placebo controlled, phase 3 study.

Methods

PATIENTS

Enrollment: 156 patients were randomized to receive CR OC/APAP, 155 patients completed the study (2 lost to follow-up).

STUDY DESIGN

In this pivotal clinical trial, CR OC/APAP was studied in an open-label extension phase of a randomized, double-blind, placebo-controlled, phase 3 study.

Screening and enrollment
Double-blind phase
Open-label extension

ASSESSMENTS DURING THE OPEN-LABEL EXTENSION

Assessment performed during the open-label extension phase

SAFETY AND TOLERABILITY

At least 1 patient was assessed for each parameter.

Table 1: Demographic and Baseline Characteristics, Open-Label Safety Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Race, n (%)</th>
<th>Age, Mean (SD)</th>
<th>Body temperature, °C</th>
<th>Respiratory rate, breaths/min</th>
<th>Heart rate, bpm</th>
<th>Oxygen saturation, %</th>
<th>Systolic blood pressure, mm Hg</th>
<th>Diastolic blood pressure, mm Hg</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Mean (SD)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native Hawaiian or Other Pacific Islander, n (%)</td>
<td>27 (16.6)</td>
<td>49.8 (14.0)</td>
<td>36.8 (0.9)</td>
<td>19.4 (1.7)</td>
<td>74.0 (6.0)</td>
<td>98.1 (1.7)</td>
<td>122.0 (10.0)</td>
<td>66.0 (9.0)</td>
<td>12.0 (1.2)</td>
<td>1.0 (0.2)</td>
<td>0 (0.0)</td>
<td>10 (0.0)</td>
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<tr>
<td>White, n (%)</td>
<td>100 (61.9)</td>
<td>49.8 (15.0)</td>
<td>36.8 (0.9)</td>
<td>19.0 (1.5)</td>
<td>74.0 (6.0)</td>
<td>98.1 (1.7)</td>
<td>122.0 (10.0)</td>
<td>66.0 (9.0)</td>
<td>12.0 (1.2)</td>
<td>1.0 (0.2)</td>
<td>0 (0.0)</td>
<td>10 (0.0)</td>
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</tr>
<tr>
<td>Black, n (%)</td>
<td>19 (11.5)</td>
<td>49.3 (17.0)</td>
<td>36.8 (0.9)</td>
<td>19.9 (1.5)</td>
<td>74.0 (6.0)</td>
<td>98.1 (1.7)</td>
<td>122.0 (10.0)</td>
<td>66.0 (9.0)</td>
<td>12.0 (1.2)</td>
<td>1.0 (0.2)</td>
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</tbody>
</table>

Table 2: Adverse Events Occurring During the Study and at Follow-Up

<table>
<thead>
<tr>
<th>Event</th>
<th>CR OC/APAP</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.8%</td>
<td>0.3%</td>
<td>0.82</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.4%</td>
<td>0.3%</td>
<td>0.22</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.1%</td>
<td>0.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.65</td>
</tr>
<tr>
<td>Headache</td>
<td>0.1%</td>
<td>0.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.1%</td>
<td>0.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Conclusions

In this open-label extension phase of the study, patients were discharged with instructions to take 2 tablets of CR OC/APAP every 12 hours until no longer needed.

More than 80% of patients were very satisfied or satisfied with every measure of treatment assessed, with scores ranging from 7 to 10 on a 10-point scale.

Patients assessed for participation in the open-label extension phase of the study entered the open-label phase of the study, with 129 patients (88.4%) completing the 200-day follow-up.

Conclusion: CR OC/APAP was safe and efficacious in this randomized, double-blind, placebo-controlled, phase 3 study.

References

Disclosures
This clinical trial was sponsored by Mallinckrodt Inc. Drs. Singla and Kostenbader have received grant support and/or honoraria from Mallinckrodt Inc. Dr. Giuliani is employed by Mallinckrodt Inc.