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

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

Introduction

Methods

PATIENTS

A total of 146 patients aged 18 years and older (mean ± SD: 40.6 ± 13.2 years) with moderate to severe acute pain were enrolled in a randomized, double-blind, placebo-controlled, phase 3 study of MNK-795 ER tablets, followed by an open-label extension study. Patients were randomized to receive MNK-795 ER tablets (OC/APAP ER 15 mg/650 mg) or placebo for up to 14 days. The primary endpoint was the time to first request for pain medication (≤20% of expected doses). The key secondary endpoint was the proportion of patients who experienced postdose breakthrough pain during the double-blind and open-label phases. The study included patients with a wide range of pain etiologies, such as trauma, surgery, burns, and medical conditions.

STUDY DESIGN

PATIENT POPULATION

A total of 146 patients (90 in the OC/APAP ER arm and 56 in the placebo arm) were enrolled in the study. The mean age was 40.6 years (range: 18-69 years), and the majority of patients were male (85%). The most common pain etiologies were trauma (51%), surgery (29%), and medical conditions (20%).

SafETY AND TOLERABILITY

The most frequently reported adverse events were consistent with those seen with other opioids (n=145). The most common adverse events were constipation (21%), nausea (15%), vomiting (13%), and somnolence (12%). The incidence of adverse events was comparable between the OC/APAP ER and placebo arms. The incidence of adverse events was generally low, with no unexpected safety signals observed. The most severe adverse events were observed in the placebo arm, with 2 patients experiencing grade 3 or 4 events, compared to 1 patient in the OC/APAP ER arm.

Conclusions

The results of this study demonstrate the safety and efficacy of MNK-795 ER tablets in the management of acute pain. The use of an extended-release formulation provided a more sustained release of oxycodone and acetaminophen, resulting in a lower dose and fewer adverse events compared to other formulations. The study also highlights the importance of patient education and support in the management of acute pain.

References

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Introduction

- Despite the wide range of treatment options available for acute pain, advances in the management of acute pain are warranted.
- Multimodal therapy combining oxycodone (OC) and acetaminophen (APAP) provides an 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 well as reduce the pill burden.
- MNK-795 (OC/APAP ER) is an extended-release ER) combination OC/APAP erapent, and is being explored to provide both fast onset of analgesia within 1 hour and sustained effect over 36-72 hours, similar to OxyContin®.
- OC/APAP ER tablets employ a dual-layered technology, with the inner layer delivering immediate release OC/APAP formulation and the outer layer releasing a slow-release form of OC/APAP and the ER component delivers 9.25 mg OC/325 mg APAP.
- Incorporates technology designed to provide tamper resistance and abuse deterrent.
- In this post-hoc clinical trial, OC/APAP ER was studied in an established acute pain model in patients undergoing a first- or second-generation dental intervention.

Methods

- Study Design
- Multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study of OC/APAP ER
- Screening period of between 2 and 30 days before surgery, a randomized double-blind dosing phase of 7 days, and an optional open-label treatment period of up to 14 days.
- Patientes assessed for participation in open-label extension phase of the study included completing the double-blind phase; having a pain intensity score ≤2 days (48 h) postprocedure, and an optional extension phase of up to 14 days.
- Eligibility criteria for the open-label extension phase of the study included completing the double-blind phase and having a pain intensity score ≤2 days (48 h) postprocedure.

Results

- Safety and Tolerability
- During the double-blind phase of the study, patients were randomized to receive 2 tablets of OC/APAP ER or placebo, with a median treatment duration in the placebo group of 7 days (range: 1-14 days).
- In total, 329 patients were enrolled in the study, of which 166 patients received OC/APAP ER; 163 received placebo.
- A total of 329 patients were enrolled and received treatment in the double-blind and open-label periods.
- In general, and specifically, oxycodone dose during the double-blind phase and open-label phase were not clinically significant according to the investigator.
- Any changes from baseline in the vital signs measures and laboratory parameters were not clinically significant or otherwise not adverse.

- Treatment-Emergent Adverse Events
- Summary of the occurrence of treatment-emergent adverse events (TEAEs) during the double-blind phase and open-label phase.
- A total of 105 TEAEs were reported by 47 patients (57.2%) in the OC/APAP ER group, and 67 TEAEs reported by 31 patients (48.3%) in the placebo group.
- The most common TEAEs reported were somnolence, headache, dizziness, nausea, vomiting, dyspepsia, dermatitis, acne, and pharyngitis.
- Median maximum intensity of treatment-emergent adverse events was mild (0.3) in the OC/APAP ER group and mild (0.1) in the placebo group.

- Conclusion
- Multiple-dose administration of OC/APAP ER was generally well tolerated in this 14-day open-label extension phase of a randomized, double-blind, placebo-controlled phase 3 study.
- MNK-795 (OC/APAP ER) Tablets in an Acute Pain Model
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Table 4: Patient Satisfaction

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- Multimodal therapy combining opioid (OC) and nonopioid (APAP) analgesics in an extended-release (ER) formulation is an established approach to the management 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-onset analgesia may offer therapeutic benefit as well as reduce the pill burden.

Methods
- Patients aged 18 to 75 years undergoing unilateral, first metatarsal bunionectomy who reported at least 4:00 AM and 12:00 PM on the first postoperative day.
- Study Drug: MNK-795 ER Tablets (OC/APAP ER) — 10 mg Oxydode/325 mg Acetaminophen.
- Patients were randomized to receive either OC/APAP ER (n=77) or placebo (n=69) in a 1:1 ratio in a double-blind manner.
- During the open-label dosing phase, 120 patients (82.2%) received 96% of the expected doses.
- The most frequently reported adverse events were consistent with those seen with other opioids.
- Analysis of laboratory test results, vital signs, and oxygen saturation were generally small and not clinically significant.

Results
- Safety and Tolerability:
  - No patients discontinued due to an adverse event.
  - The most frequently reported adverse events were consistent with those seen with other opioids.
- Patient Satisfaction:
  - More than 83% (of 36 patients) were "very satisfied" or "satisfied" at the 14-day follow-up.

Conclusions
- The safety and efficacy of MNK-795 ER Tablets in an acute pain model were consistent with their use in chronic pain.

References
- Apfelbaum JL, Chen C, Mehta SS, Gan TJ.
- J Clin Pharm Ther.
- Anesthesiology.
- Am J Ther.
- Anesth Analg
- J Pain Symptom Manage.
- Pain Med.
- J Pain Res.

Disclosures
- The authors report no conflicts of interest.

Acknowledgment
- The authors wish to acknowledge Dr. Bernard. M. Sisk and Dr. Young for their contributions in the design and implementation of this study.

TABLE 1: Demographics and Baseline Characteristics, Open-Label Phase Following Baseline

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>n (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC/APAP ER</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 2: Flow of Patients Through the Study

赞美和奖励在今后是否？！

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Methods

PATIENTS

1. Patients were randomized to receive a single dose of study drug in the blinded-dosing phase.
2. The open-label dosing phase was given to patients who were randomized to receive OC/APAP ER.

STUDY DESIGN

- Open-label dosing phase: patients received 42 days of open-label treatment within the 14-day study period.
- Treatment-Emergent Adverse Events (TEAEs) were evaluated in all patients who received at least one dose of study drug in the blinded-dosing phase.

PATIENT POPULATION

- A total of 329 patients were enrolled and received at least one dose of study drug in the blinded-dosing phase:
  - OC/APAP ER (n=77)
  - Placebo (n=77)
  - Patients received OC/APAP ER 180 mg daily in the blinded-dosing phase.

SAFETY AND TOLERABILITY

- Treatment-Emergent Adverse Events (TEAEs) were evaluated in all patients who received at least one dose of study drug in the blinded-dosing phase.
- Patients were monitored for adverse events throughout the open-label phase.

FIGURE 1: Study Design

FIGURE 2: Propagation of Patients, "Continue," "Drop Out," and "Definitive Drop Out"

RESULTS

- All Patients in Open-Label

TABLE 3: Descriptive and Baseline Characteristics, Open-Label Phase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OC/APAP ER (n=77)</th>
<th>Placebo (n=77)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>39.9 (12.4)</td>
<td>41.4 (14.1)</td>
<td>0.522</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>41 (53.2)</td>
<td>47 (61.0)</td>
<td>0.301</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>18 (23.4)</td>
<td>17 (22.1)</td>
<td>0.781</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>26.1 (5.3)</td>
<td>26.3 (4.8)</td>
<td>0.823</td>
</tr>
</tbody>
</table>

TABLE 4: Treatment-Emergent Adverse Events (TEAEs) in the Safety and Tolerability Assessments in the Open-Label Phase

<table>
<thead>
<tr>
<th>TEAE Category</th>
<th>OC/APAP ER (n=77)</th>
<th>Placebo (n=77)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>23 (29.9)</td>
<td>20 (26.0)</td>
<td>0.550</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (14.3)</td>
<td>14 (18.1)</td>
<td>0.527</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2.6)</td>
<td>3 (3.9)</td>
<td>0.602</td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>2 (2.6)</td>
<td>1 (1.3)</td>
<td>0.367</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (1.4)</td>
<td>3 (3.9)</td>
<td>0.343</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (1.4)</td>
<td>1 (1.3)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

FIGURE 2: Propagation of Patients, "Continue," "Drop Out," and "Definitive Drop Out"

CONCLUSIONS

- OC/APAP ER was generally well tolerated in this 14-day open-label extension phase of the study.
- More than 80% of patients were very satisfied or satisfied with every measure of treatment assessed.

REFERENCES


DISCLOSURES

- All authors have disclosed no financial relationships relevant to this article.
- The study was supported in part by Mallinckrodt Inc.

ACKNOWLEDGMENT

- The authors thank the patients who participated in this study and the participating sites.

CONFLICT OF INTEREST

- Dr. Singla received grants as a clinical investigator from Mallinckrodt Inc. Dr. Barrett, Ms. Sisk, and Dr. Young have nothing to disclose.

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

- Multimodal therapy combining opioid (OC) and nonopioid therapy (APAP) is an established approach to the management 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 well as reduce the pill burden.

- MNK-795 (OC/APAP ER) is an extended-release (ER) combination OC/APAP capsule, and is being studied to provide both fast onset of analgesia within 1 hour and sustained analgesia over the 36-hour dosing interval.

- OC/APAP ER tablets employ a dual-layer technology, with the ER capsule (one 325 mg oxycodone and 500 mg acetaminophen) as a single dose (1 capsule), ensures the immediate-release (IR) formulation provides effective analgesia during the first 2 hours, while the ER component delivers 9.25 mg oxycodone and 25 mg acetaminophen.
- Incorporated technology designed to provide tamper resistance and abuse deterrence.

In this post-hoc clinical trial, OC/APAP ER was studied in an extended-release acute pain model (patients undergoing a first metatarsal osteotomy procedure) to evaluate its pharmacokinetics, clinical efficacy, and safety in the treatment of moderate to severe pain.

Methods

PATIENTS

- In a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study of OC/APAP ER, 146 patients (N=146) were treated with OC/APAP ER 10/500 mg IR, 325/500 mg IR, or placebo in the double-blind dosing phase and at every clinic visit for the open-label extension phase of the study.
- Patients aged 18 to 75 years undergoing unilateral, first metatarsal bunionectomy who reported at least moderate or severe pain intensity and numeric rating scale score of ≥4 on day 1 were eligible for the study.
- Onset of pain was defined as the time for first administration of study drug; and follow-up telephone call 7 days after receiving the first dose of study drug; and agreeing to participate in the open-label extension phase of the study no later than 52 hours after receiving the first dose of study drug; and signing an open-label extension consent form prior to surgery; and agreeing to participate in the open-label extension phase of the study.
- Patients were excluded if they had a history of drug or alcohol abuse or dependence; had a history of drug- or alcohol-related criminal activity; or were pregnant or breastfeeding.
- The most frequently reported adverse events were primarily gastrointestinal related (nausea, vomiting, diarrhea).

STUDY DESIGN

- Placebo-controlled, phase 3 study. The double-blind dosing phase and at every clinic visit for the open-label extension phase of the study.
- Screening period of between 2 and 30 days before surgery, a randomized double-blind dosing phase of 4-6 days (48 h) postprocedure, and an optional 2 days (48 h) postprocedure, and an optional 2 days after receiving last dose of study drug (double-blind and open-label phases).
- The most frequently reported adverse events were primarily gastrointestinal related (nausea, vomiting, diarrhea).

SAFETY AND TOLERABILITY

- Safety and tolerability were evaluated up to 14 days, with clinic visits at days 7 and 14 (Figure 1).
- By Day 14, very few patients required pain medications (n=36); therefore, data from n=145 completing day 7 are shown here.

<table>
<thead>
<tr>
<th>Table 2: Descriptive and Baseline Characteristics, Open-Label Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
</tr>
<tr>
<td>Race, n (%): n (%)</td>
</tr>
<tr>
<td>Native American or Pacific Islander or Hispanic</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
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<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
</tr>
<tr>
<td>History of chronic pain</td>
</tr>
<tr>
<td>Preoperative medication use</td>
</tr>
<tr>
<td>Concurrent opioid use</td>
</tr>
<tr>
<td>Concurrent nonopioid use</td>
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<table>
<thead>
<tr>
<th>Table 3: Vital Sign Measurements and Changes From Baseline, Open-Label Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
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</thead>
<tbody>
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<td>Characteristic</td>
</tr>
<tr>
<td>Pruritus 1 (1.3) 3 (4.3) 4 (2.7)</td>
</tr>
<tr>
<td>Peripheral edema 3 (3.9) 1 (1.4) 4 (2.7)</td>
</tr>
<tr>
<td>Dizziness 2 (2.6) 4 (5.8) 6 (4.1)</td>
</tr>
<tr>
<td>Headache 4 (5.2) 2 (2.9) 6 (4.1)</td>
</tr>
<tr>
<td>Constipation 4 (5.2) 5 (7.2) 9 (6.2)</td>
</tr>
<tr>
<td>Vomiting 3 (3.9) 8 (11.6) 11 (7.5)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Table 5: Patient Satisfaction (N=145)</th>
</tr>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Patient satisfaction, median (range)</td>
</tr>
</tbody>
</table>

Conclusions

OC/APAP ER is an important addition to the armamentarium for patients with moderate to severe pain.

References


Disclosures

This study was funded by Mallinckrodt Pharmaceuticals. Dr. Sinta, Dr. Barrett, Dr. Sisk, and Dr. Young are employees of Mallinckrodt Pharmaceuticals. Dr. Barrett, Dr. Sisk, and Dr. Young have no financial disclosures to report.

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