**A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Analgesic Efficacy of MKN-795 Controlled-Release Oxycodeone/Acetaminophen Tablets (CR OC/APAP) in an Acute Pain Model**

**Introduction**

- Immediate-release (IR) and extended-release (ER) OC provides analgesia within an hour after administration, however, dosing every 4 to 6 hours is required to maintain analgesia over time.
- Oxycodeone, an opioid analgesic, is commonly used in combination with acetaminophen (APAP) to manage moderate to severe acute pain.

- The effects of treatment with combination therapy using opioids combined with the non-opioid acting nonopiod analgesic APAP are thought to be additive and allow for the management of pain at a lower dose of each component, potentially reducing the risk of side effects and dependence on the components.

- Formulations engineered to provide quick and sustained release may offer therapeutic benefit, as well as reduce drug burden.

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

- CR OC/APAP tablets employ a dual-layer, biphasic dissolution delivery mechanism that, when administered as a single dose (400 mg/325 mg), ensures the IR component delivers 3.75 mg of OX (45% of the total dose) and the extended-release component delivers 12.5 mg OX/325 mg APAP.

- Incorporates technology designed to provide quick and sustained release of the components in MKN-795.

- In this pivotal clinical trial, CR OC/APAP was studied in an acute pain model and was shown to be effective and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model.

- CR OC/APAP was effective and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model.

**Methods**

- Patients:
  - Randomized, double-blind, placebo-controlled trial with the combination therapy using opioids combined with the non-opioid acting nonopiod analgesic APAP are thought to be additive and allow for the management of pain at a lower dose of each component, potentially reducing the risk of side effects and dependence on the components.

- Study Design:
  - The study consisted of a screening period of 2 hours and 30 minutes before a scheduled acute postoperative pain procedure.
  - Patients randomized to one of two treatment groups for the acute postoperative pain procedure:
    - CR OC/APAP (n=166)
    - Placebo (n=163)

- Assessments:
  - Efficacy:
    - Pain intensity was rated with an 11-item numerical rating scale (0 = no pain; 10 = the worst pain imaginable).
    - Changes in pain intensity and pain relief were assessed using a 5-point scale (none, slight, moderate, marked, complete).
  - Safety:
    - Adverse events were reported during the blinded-dosing phase of the study.
    - Safety and tolerability assessments were conducted throughout the double-blind and open-label phases.
  - Other:
    - Presurgery and post-surgery assessments were conducted.

- Key results:
  - There was no difference in the primary endpoint of mean pain intensity difference (PID) over the first 48 hours.
  - However, there was a statistically significant difference in the proportion of patients achieving meaningful pain relief at 48 hours.

- Conclusions:
  - CR OC/APAP was effective and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model.

**References**


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Introduction

Immediate-release (IR) oxycodone (OC) provides analgesia within an hour after administration; however, dosing every 4 to 6 hours is required to maintain analgesia over time.

Oxycodone, an opioid analgesic, is commonly used in combination with acetaminophen (APAP) to manage moderate to severe acute pain.

The effects of treatment with combination therapy may differ compared with the commonly acting nonaddictive analgesic APAP; yet, it is thought to be at low added benefit and may allow for the management of pain at a lower dose of each component, potentially reducing the risk of gastrointestinal and respiratory adverse events.

Formulations engineered to provide quick and sustained release may offer therapeutic benefit while reducing drug burden.

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

The primary objective of the study was to evaluate the efficacy and safety of CR OC/APAP in patients with moderate to severe acute pain.

Methods

PATIENTS

Eligible patients were aged between 18 and 80 years who had reported at least moderate or severe acute pain (4.0-10.0 on an 11-point numerical rating scale) within the last 24 hours.

Study Design

The study consisted of a screening period of 2 days and 52 days before randomization to a randomized double-blind, placebo-controlled, CR OC/APAP study drug or placebo administered every 12 hours (0, 12, 24, and 36 hours; 4 total doses) for 48 hours;

The primary outcome measure was the summed pain intensity difference over the first 48 hours (SPID = [baseline pain intensity score] – [pain intensity score at time point of interest]).

Assessments

Mean SPID for CR OC/APAP was numerically superior beginning at the earliest time point measured (15 min); median time to pain relief was significantly shorter for CR OC/APAP compared with placebo (20.5 [11.0–30.0] vs 47.9 [22.0–92.4] minutes; P < 0.001). The time to perceptible pain relief was 9.0 minutes (95% CI: 7.3–10.6) in patients administered CR OC/APAP compared with placebo (41.9 minutes [95% CI: 33.2–50.6]; P < 0.001).

Conclusions

CR OC/APAP is effective in reducing moderate to severe acute pain in an acute pain model when compared with placebo administered every 12 hours.

Disclosures

Dr. Singla received grants as a clinical investigator from Mallinckrodt Inc. Dr. Barrett, Ms. Sisk, Dr. Young, and Dr. Giuliani received compensation for work performed in connection with this research. Dr. Singla has served as a consultant for Mallinckrodt Inc.

References


2. Smolenski DM, Hucht EE, Endo (N=329) Placebo (n=163) 80

0 20 40 60 80 100

FIGURE 2: Time to Perceptible Pain Relief

20.5 (11.0–30.0) 47.9 (22.0–92.4)
P < 0.001

FIGURE 3: Percentage of Patients Satisfied or Satisified with Inhibition of the Total Nausea and Perceptible Pain Model

P < 0.001

Table 3: Median Time to Opioid Use, Categorized by Perceptible Pain and Mean Pain

Sustained-release OC/APAP may offer therapeutic benefit while reducing drug burden.

The results support that CR OC/APAP is effective in patients with moderate to severe acute pain.

Objectives

To evaluate the efficacy and safety of CR OC/APAP in patients with moderate to severe acute pain.

Results

PATIENT POPULATION

293 patients (89.1%) completed the double-blind phase of the study. The primary outcome measure was the summed pain intensity difference over the first 48 hours.

STUDY DESIGN

The study consisted of a screening period of 2 days and 52 days before randomization to a randomized double-blind, placebo-controlled, CR OC/APAP study drug or placebo administered every 12 hours (0, 12, 24, and 36 hours; 4 total doses) for 48 hours.

Patient satisfaction was assessed using a modified version of a validated instrument to assess the level of comfort, pain relief, and confirmed perceptible pain relief compared to placebo.

The most common TEAEs reported during the blinded-dosing phase of the study are summarized in Table 1.

TABLE 1: Demographic and Baseline Characteristics of mITT Population (n=166)

Table 2: Total Nausea and Perceptible Pain (Based on CR OC/APAP Only)

Table 3: Median Time to Opioid Use, Categorized by Perceptible Pain and Mean Pain

Table 4: Summary of Treatment-Emergent Adverse Events (N=329)
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Introduction

- Immediate-release (IR) cyclohexone (OC) provides analgesia within an hour after administration; however, dosing every 4 to 6 hours is required to maintain analgesia over time.
- Oxycodeone, an opioid analgesic, is commonly used in combination with acetaminophen (APAP) to manage moderate to severe acute pain.
- The effects of treatment with combination therapy (OC/APAP) combined with the concomitantly acting noninvasive opioid analgesics (APAP) are thought to be at least additive and may allow for the management of pain at a lower dose of each component, potentially reducing the risk of (concentration-dependent) adverse events.
- Formulations engineered to provide quick and sustained release may offer therapeutic benefit as well as reduce side effects.

MKN-795 (CR OC/APAP) is a controlled-release (CR) combination OCAPAP analgesic, and is being designed to provide twice-daily analgesia within 1 hour and sustained analgesia over the 12-hour dosing interval.

- CR OCAPAP tablets employ a dual-layer enteric delivery mechanism that, when administered as a single dose (ie, 2 tablets), ensures the IR component delivers 3.75 mg CR OC/APAP and the enteric-coated component delivers 8.25 mg OC/325 mg APAP.
- Incorporates technology designed to provide sustained release of the CR component.
- In this pivotal clinical trial, CR OC/APAP was studied in an acute pain model in patients undergoing a first medical/clinical treatment.
- The burstone model is a commonly used and accepted model of acute pain used for evaluation of new analgesics.

Methods

- **Objectives**
  - Evaluate the efficacy and safety of CR OC/APAP in patients with moderate to severe acute pain.

- **Patients**
  - For the 24-hour period before the study enrollment, each patient completed a validated pain intensity score (eg, Brief Pain Inventory). To be eligible for the study, patients must have had moderate to severe pain (scale 6-10).

- **Study Design**
  - The study was a randomized, double-blind, placebo-controlled, single-site (n=30) trial for the treatment of moderate to severe acute pain.
  - The study consisted of a 2-week treatment period of 2 tablets given within 30 minutes before a scheduled medical/clinical treatment on the first postoperative day and one tablet administered prior to each scheduled medical/clinical treatment thereafter.

- **Assessments**
  - Pain intensity scores were assessed at baseline and over 60 minutes, at each scheduled medical/clinical treatment, and at 6, 12, and 24 hours after the last administration.
  - Patients were administered a questionnaire that included a validated pain intensity score (Brief Pain Inventory). To be eligible for the study, patients must have had moderate to severe pain (scale 6-10).

- **Efficacy**
  - Pain intensity scores were assessed at baseline and over 60 minutes, at each scheduled medical/clinical treatment, and at 6, 12, and 24 hours after the last administration.

- **Primary Endpoint**
  - Global assessment of satisfaction was conducted during the study.

- **Secondary Endpoints**
  - Pain intensity scores.
  - Pain intensity associated with each pain intensity score.
  - Time to onset of pain relief.
  - Time to significant pain relief.
  - Mean SPID over 0-4, 0-12, 0-24, and 0-36 hours.

- **SAFETY AND TOLERABILITY**
  - Patients were monitored for adverse events (AEs) and deemed to be both serious and nonserious. AEs were monitored for all patients within 1 hour after administration and at 12, 24, 36, and 48 hours after the last administration.

- **Adverse Events**
  - Any TEAE that was reported during the blinded-dosing phase of the study may be associated with perceptible pain relief, meaningful pain relief, and/or meaningful pain relief with moderate to severe acute pain.

- **Patient Satisfaction**
  - The double stopwatch method was used to determine time to onset of pain relief.

- **Table 1**
  - Pain Intensity Scores Over Time Following Treatment With Placebo 4.8% 0 72.2 (12.8) 11 (7.2) 4 (2.7) 0 60 (18.2) 24 (7.3) 16.8 (9.8–23.8) 0.001

- **Table 2**
  - Pain Intensity Scores Over Time Following Treatment With Placebo 4.8% 0 72.2 (12.8) 11 (7.2) 4 (2.7) 0 60 (18.2) 24 (7.3) 16.8 (9.8–23.8) 0.001

- **Table 4**
  - Summary of Treatment-Emergent Adverse Events

- **Conclusions**
  - The CR OC/APAP was safe and effective in treating the moderate to severe acute pain in an acute pain model. CR OC/APAP administered as 2 tablets every 12 hours (4 doses total) provided significant and sustained analgesia over 48 hours.

References


Disclosures

- This study was supported by grants from Mallinckrodt Inc.

Acknowledgment

- The authors thank the study participants and all study staff for their important contributions to this study.

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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

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Objectives

- Evaluate the efficacy and safety of CR OC/APAP in patients with moderate to severe acute pain

Methods

**Patients**
- For inclusion in this trial, patients must have been determined to be medically indicated for the treatment of acute postoperative pain
- Patients must have moderate to severe acute pain (measured via VAS) at time of entry into the study
- Patients must have had their current surgical procedure completed within the first 7 days prior to beginning pain treatment
- Only patients with a VAS score of ≥50 mm were considered for enrollment
- Patients must have had trouble sleeping at least 3 consecutive nights prior to their scheduled surgery

**Study Design**
- The CR OC/APAP tablet is a delayed-release, rapid-release oxycodone and acetaminophen formulation designed to provide quick and sustained analgesia over a 12-hour dosing interval
- A randomized, double-blind, placebo-controlled, phase 3 study
- Patients were randomized to receive placebo or CR OC/APAP
- Primary endpoint: 0-12 hour TOTPAR
- Secondary endpoints: 0-24 hour TOTPAR, 0-36 hour TOTPAR, and individual pain intensity scores

**Efficacy Measures**
- **Primary endpoint:** 0-12 hour TOTPAR (time to perceptible, meaningful, and confirmed pain relief is defined as a VAS score of ≤20 mm for 3 consecutive hours)
- **Secondary endpoints:** 0-24 hour TOTPAR, 0-36 hour TOTPAR, and individual pain intensity scores

**Safety and Tolerability**
- Adverse events were assessed at follow-up, and any significant measures were followed-up as medically indicated
- Patients were observed for the first 48 hours; and the time to perceptible, meaningful, and confirmed pain relief

**Results**

**Patient Population**
- CR OC/APAP (n=150)
- Placebo (n=153)
- 293 patients (89.1%) completed the double-blind phase of the study
- **Primary Efficacy Endpoint:**
  - **Time to Perceptible, Meaningful, and Confirmed Pain Relief (TOTPAR):**
    - CR OC/APAP: 13.2 hours (95% CI: 12.0, 14.3)
    - Placebo: 16.5 hours (95% CI: 15.4, 17.7)
    - **P-value:** 0.0001

**Adverse Events**
- incidence rates within each treatment group
- **Table 1**

**Conclusions**

- CR OC/APAP was efficacious in patients treated for the management of moderate to severe acute pain in an acute postoperative pain model
- Patients treated with CR OC/APAP experienced a superior analgesic profile compared to placebo
- CR OC/APAP provided quick and sustained analgesia over the 12-hour dosing interval
- This study supports CR OC/APAP in acute pain management and provides a new treatment option for patients with acute postoperative pain

**References**

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

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Introduction

Immediate-release (IR) oxycodeone (OC) provides analgesia within an hour after administration; however, dosing every 4 to 6 hours is required to maintain analgesia over time.

Oxycodone, an opioid analgesic, is commonly used in combination with acetaminophen (APAP) to manage moderate to severe acute pain.

The effects of treatment with combination therapy vs. oxycodone combined with the clinically active non-narcotic analgesic APAP are thought to be at least additive and may allow for the management of pain at a lower dose of each component, potentially reducing the risk of withdrawal and dependence.

Conclusions

CR OC/APAP was effective in the primary endpoint of the treatment of moderate to severe acute pain in an acute pain model; this is the first study to demonstrate the analgesic efficacy and safety of CR OC/APAP for the treatment of moderate to severe acute pain. The study found that CR OC/APAP administered as 2 tablets every 12 hours provided significant and sustained analgesia over the 48-hour dosing interval.

The results support that CR OC/APAP is effective for patients with moderate to severe acute pain.

The most common TEAEs reported during the blinded-dosing phase of the study are summarized in Table 2. The results support that CR OC/APAP is effective for patients with moderate to severe acute pain.

Refrain from any reference material that is not in the public domain. For more information, please refer to the Mallinckrodt website.

Safely and tolerability: Patients were monitored for the occurrence of treatment-emergent adverse events (TEAEs). The results support that CR OC/APAP is effective for patients with moderate to severe acute pain.

References


Disclosures

This study was supported by Mallinckrodt Inc., Hazelwood, MO.
Objectives

Evaluate the efficacy and safety of CR OC/APAP in patients with moderate to severe acute pain.

Methods

PATIENTS

Eligible patients were adults 18 years of age or older, with moderate to severe acute pain, as defined below, that included pain score of 40% or greater of the total visual analog pain score within 48 hours of receiving first dose of study drug; however, 

ASSESSMENTS

The primary efficacy measure for the study was the CR OC/APAP analgesic, and is being designed to provide robust proof of analgesia within 1 hour after administration; however, 

SAFETY AND TOLERABILITY

As expected for this class of medication, a greater percentage of patients receiving CR OC/APAP reported nausea (30.7% vs 5.5%), dizziness (13.3% vs 1.2%), headache (9.6% vs 4.9%), skin and subcutaneous disorders (9.0% vs 4.3%), vomiting (9.0% vs 0%), and somnolence (3.6% vs 0.6%)

Conclusions

The results support that CR OC/APAP is effective for patients with moderate to severe acute pain.

References