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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MNK-795 (CR OC/APAP) Overview

- Controlled-release OC/APAP is being developed to manage moderate to severe acute pain that warrants treatment with an opioid analgesic.

- Designed to provide both fast onset of analgesia (<1 h) and sustained analgesia over a q12h dosing interval.

- Tablets employ a dual-layer biphasic delivery mechanism that, when administered as a single dose (ie, 2 tablets) ensures:
  - IR component delivers 3.75 mg OC/325 mg APAP
  - ER component delivers 11.25 mg OC/325 mg APAP
MNK-795 (CR OC/APAP) Pharmacokinetics

- Dose proportionality and linearity up to 30 mg/1300 mg
- After a single dose, plasma OC and APAP levels rose rapidly
  - OC plasma concentration was sustained over the 12-hour dosing interval, whereas APAP plasma concentration declined more rapidly to ~18% of the peak at 12 hours
- Steady state was achieved by day 2 (24 h)
- At steady state, CR OC/APAP (2 tablets q12h) produced comparable AUC to IR products dosed every 6 hours, with:
  - Less fluctuation in OC plasma concentrations
  - Lower trough plasma concentrations of APAP prior to subsequent dosing
MNK-795 (CR OC/APAP) Tablets

- Incorporates technology designed to provide tamper resistance and abuse deterrence
  - Relative to a comparable IR formulation, CR OC/APAP has physicochemical properties that may deter abuse
  - More difficult to crush, snort, and inject
  - When the CR OC/APAP tablet is crushed, the IR and ER layers become mixed, delaying the onset of the medication
Study Design: Acute Pain Model

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study of CR OC/APAP (7.5 mg/325 mg) in patients with moderate to severe acute pain following unilateral, first metatarsal bunionectomy
  - 48-hour primary; 14-day open label extension

<table>
<thead>
<tr>
<th>Screening and enrollment</th>
<th>Double-blind phase</th>
<th>Open-label extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presurgery</td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>2-30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Postoperative IV</td>
<td>Randomization</td>
</tr>
<tr>
<td>2 PM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 AM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 AM&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Surgery completed; <sup>b</sup>Nerve block stopped; <sup>c</sup>Earliest start for pain assessment and randomization; <sup>d</sup>Latest start for pain assessment and randomization; <sup>e</sup>Study medication administered within 30 minutes of randomization; <sup>f</sup>Patients assessed for participation in open-label extension within 48 to 52 hours of receiving first dose of study drug; <sup>g</sup>End-of-treatment evaluations performed within 3 days of receiving last dose of study drug; follow-up telephone call 7±2 days after receiving last dose of study drug (double-blind and open-label phases).
Double-Blind Efficacy
Pain Intensity Over Time

Pain Intensity Scores over 48 hours of Double-Blind Treatment with CR OC/APAP and Placebo

*P<0.05; †P<0.001; ‡P<0.0001.
Open-Label Extension

- 146 patients entered the open-label extension; 77 from prior double-blind CR OC/APAP, and 69 from prior double-blind placebo

- Instructed to take 2 tablets of CR OC/APAP (15 mg OC/650 mg APAP) q12h until no longer needed, and up to 14 days

- Safety and tolerability assessments
  - Adverse event (AE) monitoring
  - Physical examinations
  - Laboratory testing

- Global assessment of patient satisfaction
### Open-Label Extension
### Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event, n (%)</th>
<th>Prior Double-Blind CR OC/APAP (n=77)</th>
<th>Prior Double-Blind Placebo (n=69)</th>
<th>All Patients (N=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>25 (32.5)</td>
<td>39 (56.5)</td>
<td>64 (43.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (10.4)</td>
<td>18 (26.1)</td>
<td>26 (17.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3.9)</td>
<td>8 (11.6)</td>
<td>11 (7.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (5.2)</td>
<td>5 (7.2)</td>
<td>9 (6.2)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (1.3)</td>
<td>6 (8.7)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (5.2)</td>
<td>2 (2.9)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2.6)</td>
<td>4 (5.8)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3 (3.9)</td>
<td>1 (1.4)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (1.3)</td>
<td>3 (4.3)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (1.3)</td>
<td>3 (4.3)</td>
<td>4 (2.7)</td>
</tr>
</tbody>
</table>
Percentage of Patients “Satisfied” or “Very Satisfied” on Items of the Global Assessment of Satisfaction at 48 Hours (end of double-blind)

<table>
<thead>
<tr>
<th></th>
<th>CR OC/APAP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for Medication to Work</td>
<td>66.7</td>
<td>38.5</td>
</tr>
<tr>
<td>Level of Pain Relief</td>
<td>68.9</td>
<td>41.5</td>
</tr>
</tbody>
</table>

*P<0.001
Percentage of Patients “Satisfied” or “Very Satisfied” With CR OC/APAP After 14 Days of Open-Label Treatment

- **Ease of Administration**: 94.4%
- **Dosing Frequency**: 91.7%
- **Number of Tablets Taken**: 86.1%
- **Time for Medication to Work**: 86.1%
- **Level of Pain Relief**: 83.3%

*Day 14*
Summary

► CR OC/APAP q12h was effective and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model

► The majority of patients rated themselves as “satisfied” or “very satisfied” with every measure of treatment assessed
  ▪ Ease of administration, 94.4%
  ▪ Dosing frequency, 91.7%
  ▪ Time for medication to work, 86.1%
  ▪ Level of pain relief, 83.3%

► Multiple-dose administration of CR OC/APAP was generally well tolerated over the 14-day open-label extension
  ▪ The most frequently reported TEAEs were consistent with those seen with other opioids in general, and specifically, oxycodone
More Information on CR OC/APAP at PAINWeek

► Clinical trials
  ▪ Efficacy & safety in acute pain
    – Poster 105
  ▪ OL extension in acute pain
    – Poster 104
  ▪ OL safety study
    – Poster 70

► Pharmacokinetic studies
  ▪ Single-dose PK
    – Posters 19, 22
  ▪ Steady-state PK
    – Posters 21, 23
  ▪ Effects of food
    – Poster 20
  ▪ Dose proportionality
    – Posters 24, 25
  ▪ Half-value duration
    – Posters 87, 88

► Human abuse liability
  ▪ Subjective effects
    – Poster 69
  ▪ Relationship between PK and subjective effects
    – Poster 68
  ▪ Tamper-resistant properties
    – Poster 31
Thank You
Backup
Measures and Outcomes Assessed (DB and OLE)

► Pain Intensity as rated with 11-item NRS (double-blind phase only)
  ▪ Primary outcome was the summed pain intensity difference at 48 hours (SPID$_{48}$)
  ▪ Pain intensity differences (PID) and summed pain intensity difference (SPID) over time

► Safety and tolerability assessments during both the double-blind and open-label phases of the study
  ▪ Adverse event (AE) monitoring
  ▪ Physical examinations
  ▪ Laboratory testing

► Global assessment of patient satisfaction (48 hours and every open-label clinic visit) to assess
  ▪ Ease of administration
  ▪ Dosing frequency
  ▪ Number of tablets taken
  ▪ Time for medication to work
  ▪ Overall level of pain relief
Patient Disposition

Randomized N=329

CR OC/APAP n=164
- Blinded treatment period
  - Modified ITT: n=150
  - Blinded safety population: n=166*
    - Open-label extension n=77
    - Discontinued n=7
      - Completed open-label extension n=70
    - Blinded follow-up n=89
      - Discontinued n=10
        - Completed blinded follow-up n=89

Placebo n=165
- Blinded treatment period
  - Modified ITT: n=153
  - Blinded safety population: n=163*
    - Open-label extension n=69
    - Completed open-label extension n=59
    - Discontinued n=3
      - Completed blinded follow-up n=91

*Two patients were randomized to placebo but actually received CR OC/APAP.
## Summary of Treatment-Emergent Adverse Events Occurring in >3% of Patients

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event, n (%)</th>
<th>CR OC/APAP (n=166)</th>
<th>Placebo (n=163)</th>
<th>All Patients (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>89 (53.6)</td>
<td>35 (21.5)</td>
<td>124 (37.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>51 (30.7)</td>
<td>9 (5.5)</td>
<td>60 (18.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (13.3)</td>
<td>2 (1.2)</td>
<td>24 (7.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (9.6)</td>
<td>8 (4.9)</td>
<td>24 (7.3)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>15 (9.0)</td>
<td>7 (4.3)</td>
<td>22 (6.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15 (9.0)</td>
<td>0</td>
<td>15 (4.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (4.2)</td>
<td>5 (3.1)</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (3.6)</td>
<td>1 (0.6)</td>
<td>7 (2.1)</td>
</tr>
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</table>
More Information on CR OC/APAP at PAINWeek

► A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Analgesic Efficacy of Controlled-Release Oxycodone/Acetaminophen Tablets (CR OC/APAP) in an Acute Pain Model, Poster 105

► 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, Poster 104

► Open-Label Safety of MNK-795, Controlled-Release Oxycodone/Acetaminophen Tablets (CR OC/APAP), in Patients with Osteoarthritis or Chronic Low Back Pain, Poster 70

► Comparison of Subjective Drug Effects of Orally Administered MNK-795 Controlled-Release Oxycodone/Acetaminophen (CR OC/APAP) Tablets Versus Immediate-Release Oxycodone/Acetaminophen Tablets in Recreational Users of Prescription Opioids, Poster 69

► Relationship Between Oxycodone Pharmacokinetics and Subjective Drug Effects Following Oral Administration of an Immediate-Release Combination of Oxycodone and Acetaminophen and MNK-795 Controlled-Release Oxycodone/Acetaminophen (CR OC/APAP) Tablets, Poster 68
More Information on CR OC/APAP at PAINWeek

► Evaluation of the Tamper-Resistant Properties of MNK-795 Controlled-Release Oxycodone/Acetaminophen (CR OC/APAP) Tablets, Poster 31

► Single-Dose Pharmacokinetics of 1 and 2 Tablets of MNK-795 Controlled-Release Oxycodone/Acetaminophen Tablets (CR OC/APAP) Compared With Immediate-Release Oxycodone and Acetaminophen, Poster 19

► Steady-State Pharmacokinetics of 1 and 2 Tablets of MNK-795, a Controlled-Release Oxycodone and Acetaminophen (CR OC/APAP) Combination, Compared With Immediate-Release Oxycodone and Acetaminophen, Poster 23

► Single-Dose Pharmacokinetics, Bioavailability, and Safety of MNK-795, a Controlled-Release Oxycodone and Acetaminophen Combination Analgesic (CR OC/APAP), Under Fed and Fasted Conditions, Poster 20

► Comparison of the Pharmacokinetic Profile of a Single Dose of MNK-795, a Controlled-Release Oxycodone and Acetaminophen Combination Tablet (CR OC/APAP) and Marketed Immediate-Release Opioids and Opioid/Acetaminophen Combination Tablets, Poster 22

► Comparison of the Pharmacokinetic Profile of MNK-795, a New Oral, Controlled-Release Formulation of Oxycodone/Acetaminophen (CR OC/APAP) Analgesic at Steady State Versus Marketed Immediate-Release Tablets, Poster 21
More Information on CR OC/APAP at PAINWeek

► Half-Value Duration Analysis for Acetaminophen After Single and Multiple Doses of Oral MNK-795 Controlled-Release Oxycodone/Acetaminophen (CR OC/APAP) Tablets, Poster 87

► Half-Value Duration Analysis for Oxycodone After Single and Multiple Doses of Oral MNK-795 Controlled-Release Oxycodone/Acetaminophen (CR OC/APAP) Tablets, Poster 88

► Dose Proportionality and Linearity of Acetaminophen After Single or Multiple Oral Doses of MNK-795 (Oxycodone/Acetaminophen) Tablets, Poster 24

► Dose Proportionality and Linearity of Oxycodone After Single or Multiple Oral Doses of MNK-795 Controlled-Release Oxycodone/Acetaminophen (CR OC/APAP) Tablets, Poster 25