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

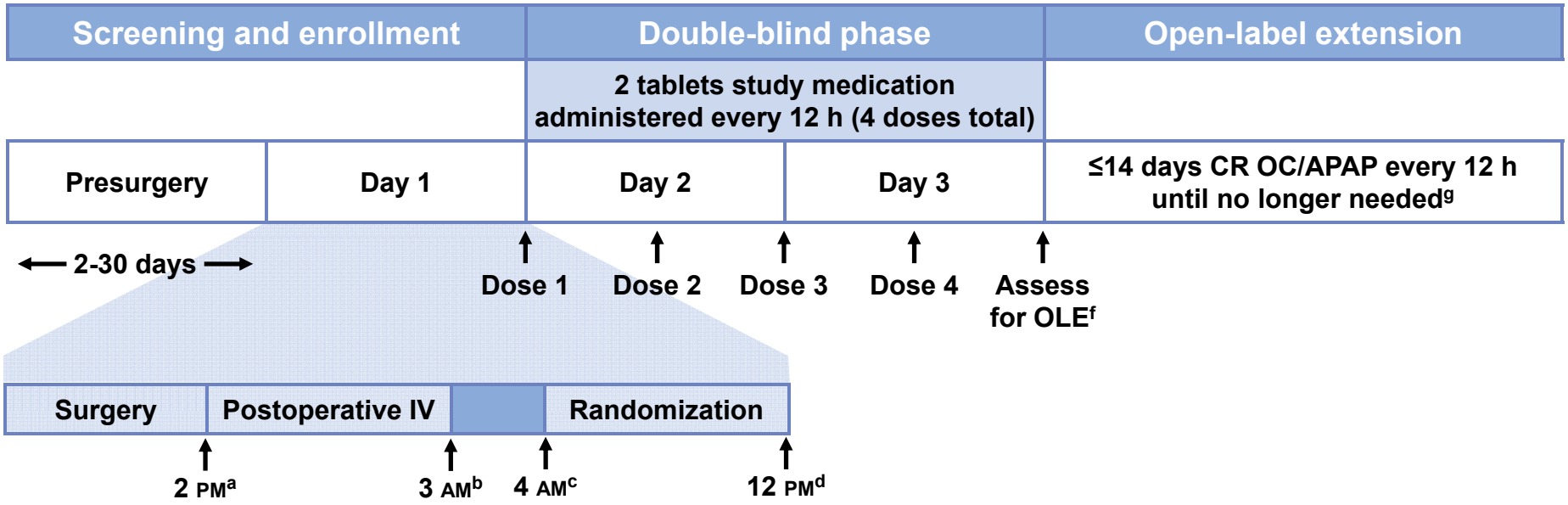
- Dose proportionality and linearity up to 30 mg/1300 mg
- After a single dose, plasma OC and APAP levels rose rapidly
  - OC plasma concentration was sustained over the 12-hour dosing interval, whereas APAP plasma concentration declined more rapidly to ~18% of the peak at 12 hours
- Steady state was 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*



[a]Surgery completed; [b]Nerve block stopped; [c]Earliest start for pain assessment and randomization; [d]Latest start for pain assessment and randomization; [e]Study medication administered within 30 minutes of randomization; [f]Patients assessed for participation in open-label extension within 48 to 52 hours of receiving first dose of study drug; [g]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).

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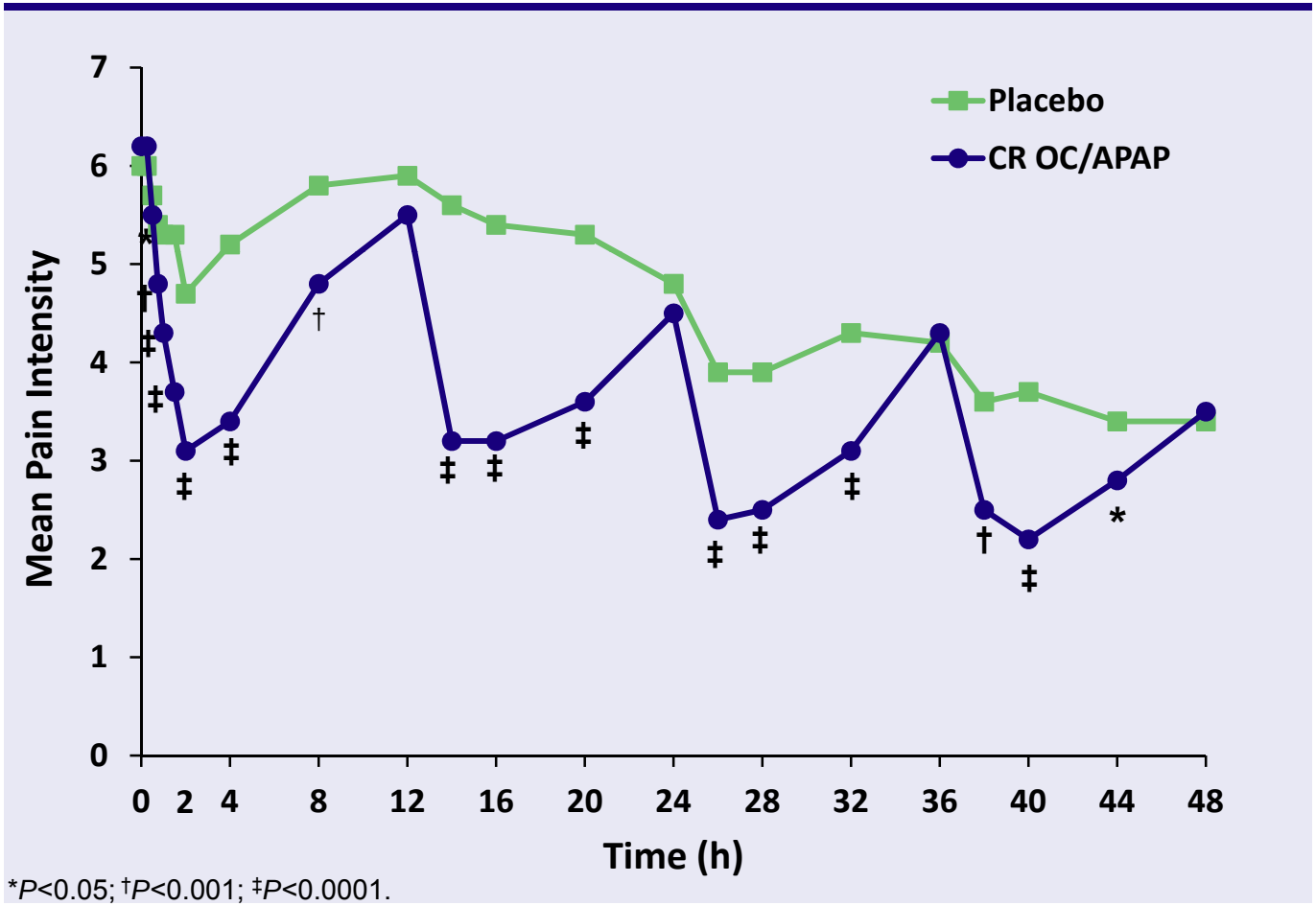
Double-Blind Efficacy
Pain Intensity Over Time

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.

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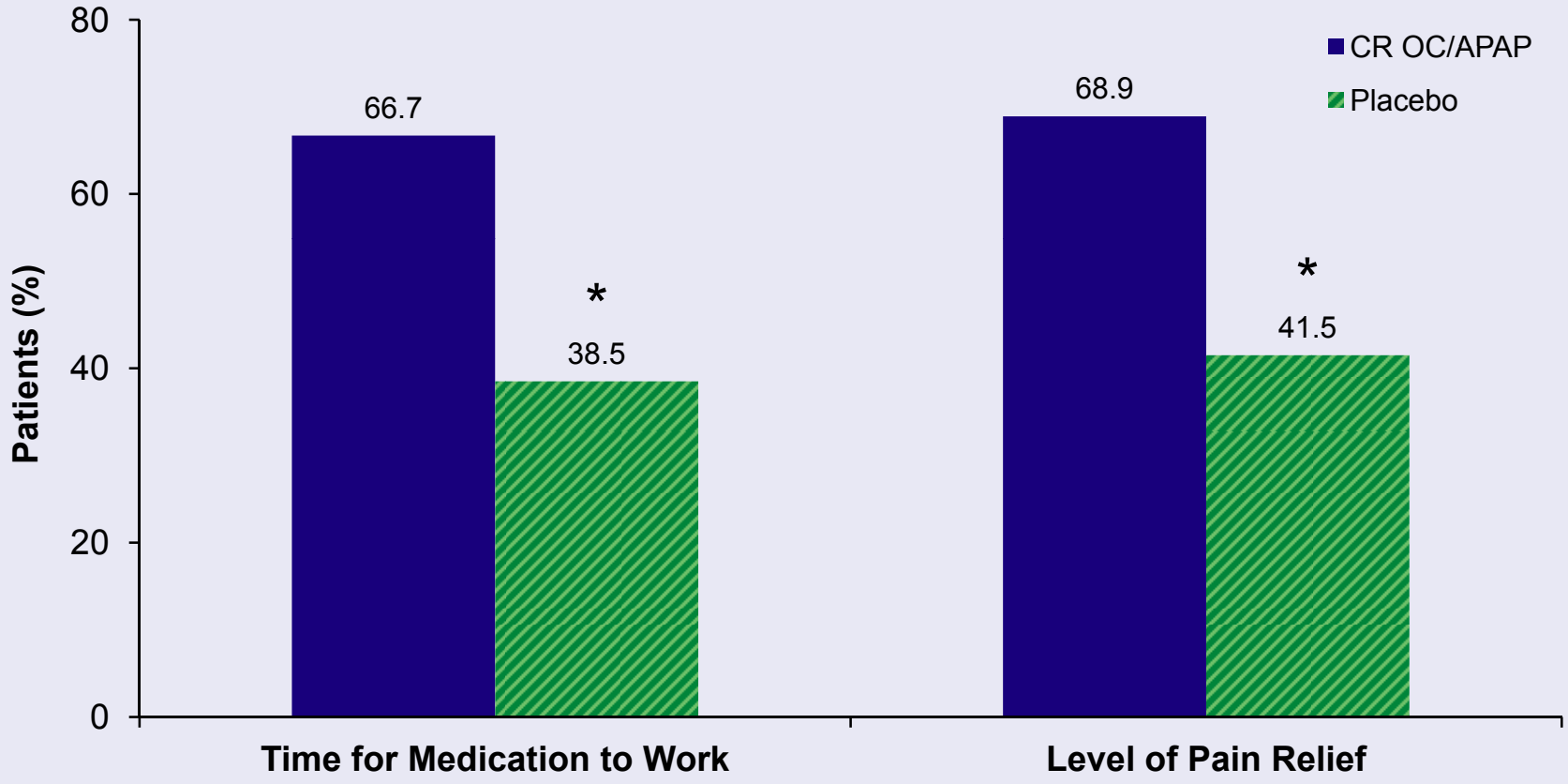
Open-Label Extension

- 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

Treatment-Emergent Adverse Events Occurring During the Open-Label Phase			
Treatment-Emergent Adverse Event, n (%)	**Prior Double-Blind CR OC/APAP (n=77)**	**Prior Double-Blind Placebo (n=69)**	**All Patients (N=146)**
Any TEAE	25 (32.5)	39 (56.5)	64 (43.8)
Nausea	8 (10.4)	18 (26.1)	26 (17.8)
Vomiting	3 (3.9)	8 (11.6)	11 (7.5)
Constipation	4 (5.2)	5 (7.2)	9 (6.2)
Somnolence	1 (1.3)	6 (8.7)	7 (4.8)
Headache	4 (5.2)	2 (2.9)	6 (4.1)
Dizziness	2 (2.6)	4 (5.8)	6 (4.1)
Peripheral edema	3 (3.9)	1 (1.4)	4 (2.7)
Pruritus	1 (1.3)	3 (4.3)	4 (2.7)
Infection	1 (1.3)	3 (4.3)	4 (2.7)

Percentage of Patients "Satisfied" or "Very Satisfied" on Items of the Global Assessment of Satisfaction at 48 Hours (end of double-blind)



*P<0.001

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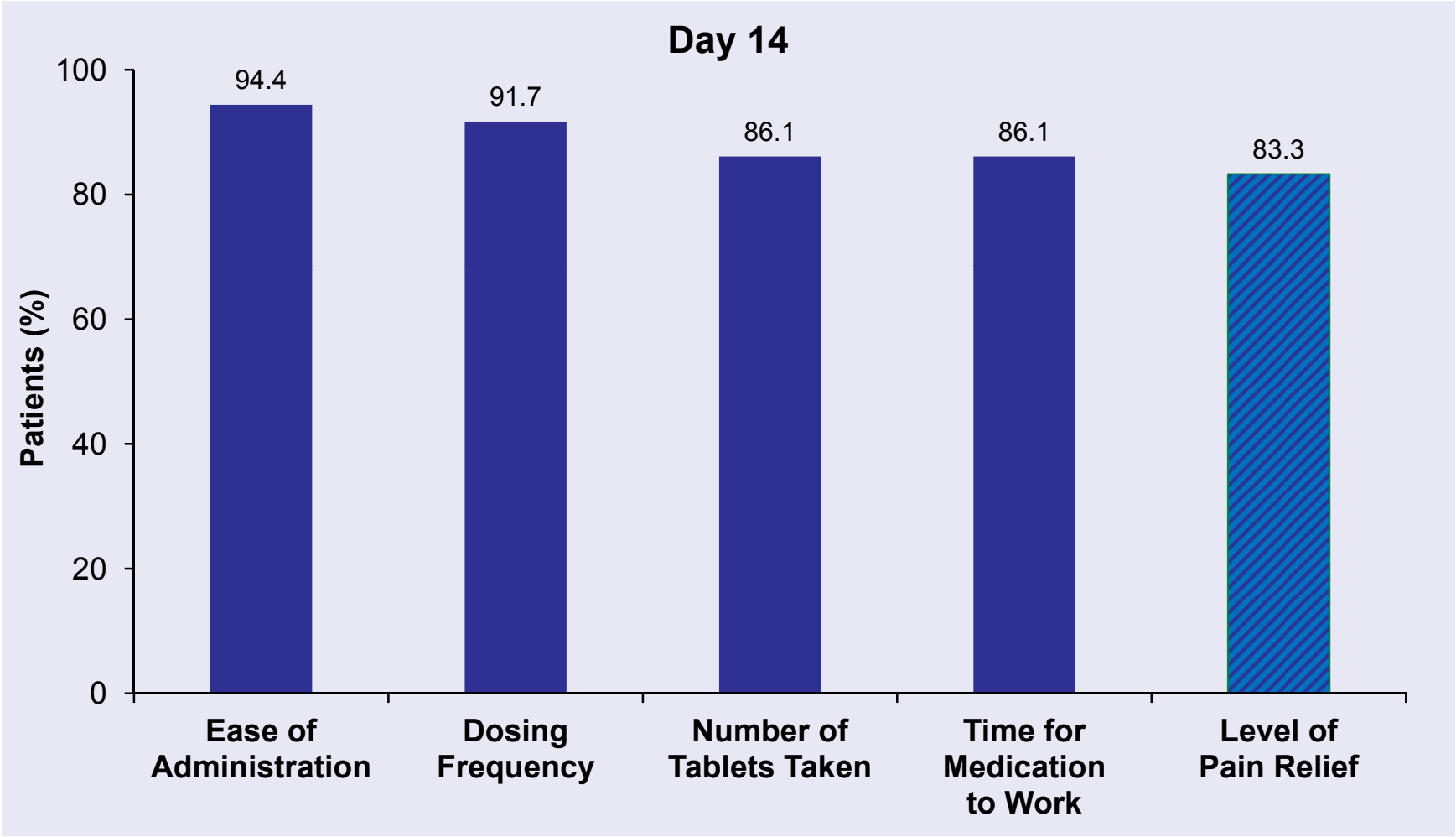
Percentage of Patients "Satisfied" or "Very Satisfied" With CR OC/APAP After 14 Days of Open-Label Treatment



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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 the14-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
- Human abuse liability
  - Subjective effects
    - Poster 69
  - Relationship between PK and subjective effects
    - Poster 68
  - Tamper-resistant properties
    - Poster 31
- 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

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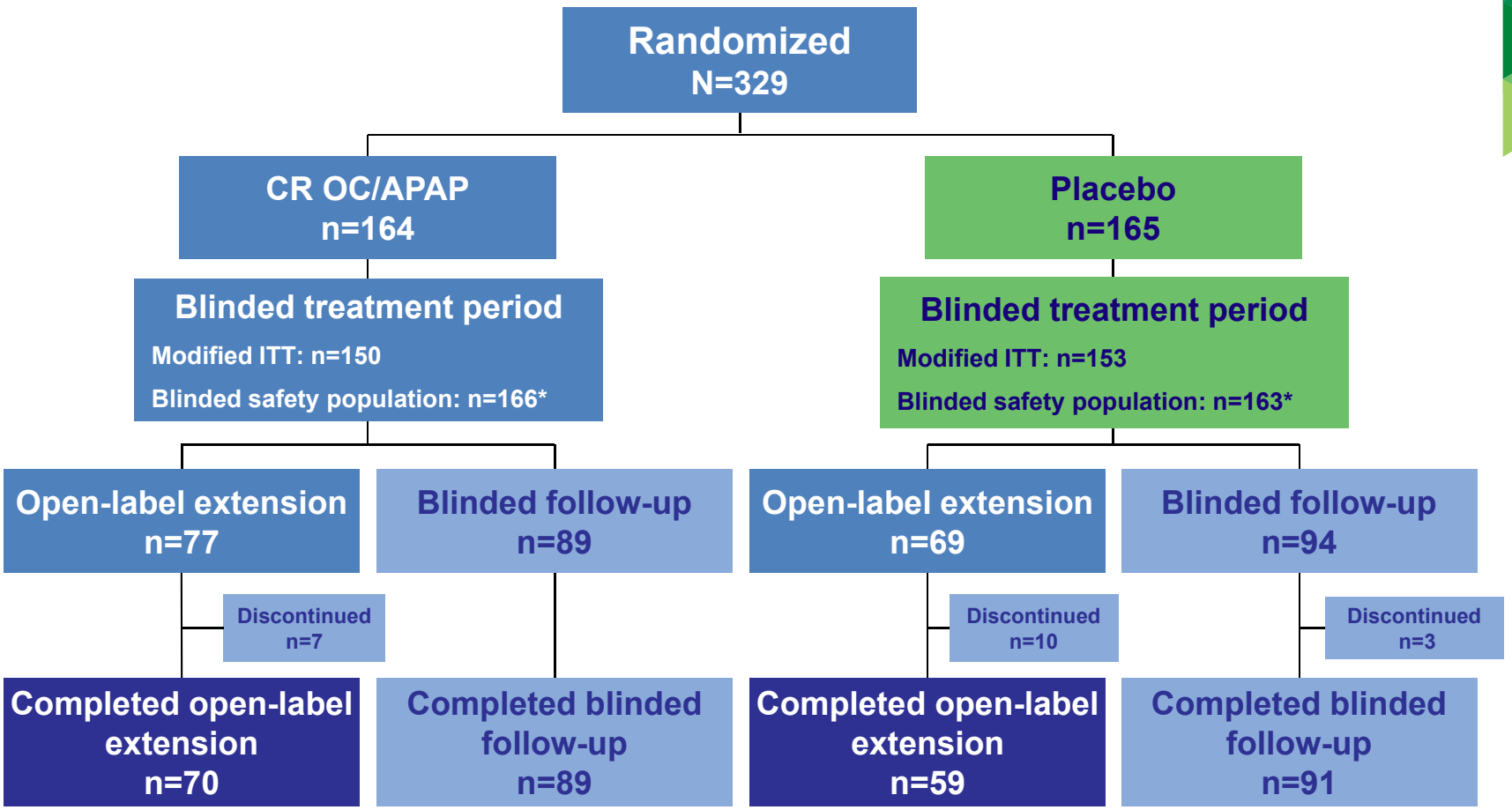
Thank You

Backup

Measures and Outcomes Assessed (DB and OLE)

- Pain Intensity as rated with 11-item NRS (double-bind 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



*Two patients were randomized to placebo but actually received CR OC/APAP.

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Double-Blind Safety
Treatment-Emergent Adverse Events

Summary of Treatment-Emergent Adverse Events Occurring in >3% of Patients			
Treatment-Emergent Adverse Event, n (%)	**CR OC/APAP (n=166)**	**Placebo (n=163)**	**All Patients (N=329)**
Any TEAE	89 (53.6)	35 (21.5)	124 (37.7)
Nausea	51 (30.7)	9 (5.5)	60 (18.2)
Dizziness	22 (13.3)	2 (1.2)	24 (7.3)
Headache	16 (9.6)	8 (4.9)	24 (7.3)
Skin and subcutaneous tissue disorders	15 (9.0)	7 (4.3)	22 (6.7)
Vomiting	15 (9.0	0	15 (4.6)
Constipation	7 (4.2)	5 (3.1)	12 (3.6)
Somnolence	6 (3.6)	1 (0.6)	7 (2.1)

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**

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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**

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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**

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