

Results of ALLEVIATE 1 and ALLEVIATE 2 Phase 3 trials of cebranopadol, a first-in-class, dual NOP/MOP receptor agonist for the treatment of acute pain after abdominoplasty and bunionectomy

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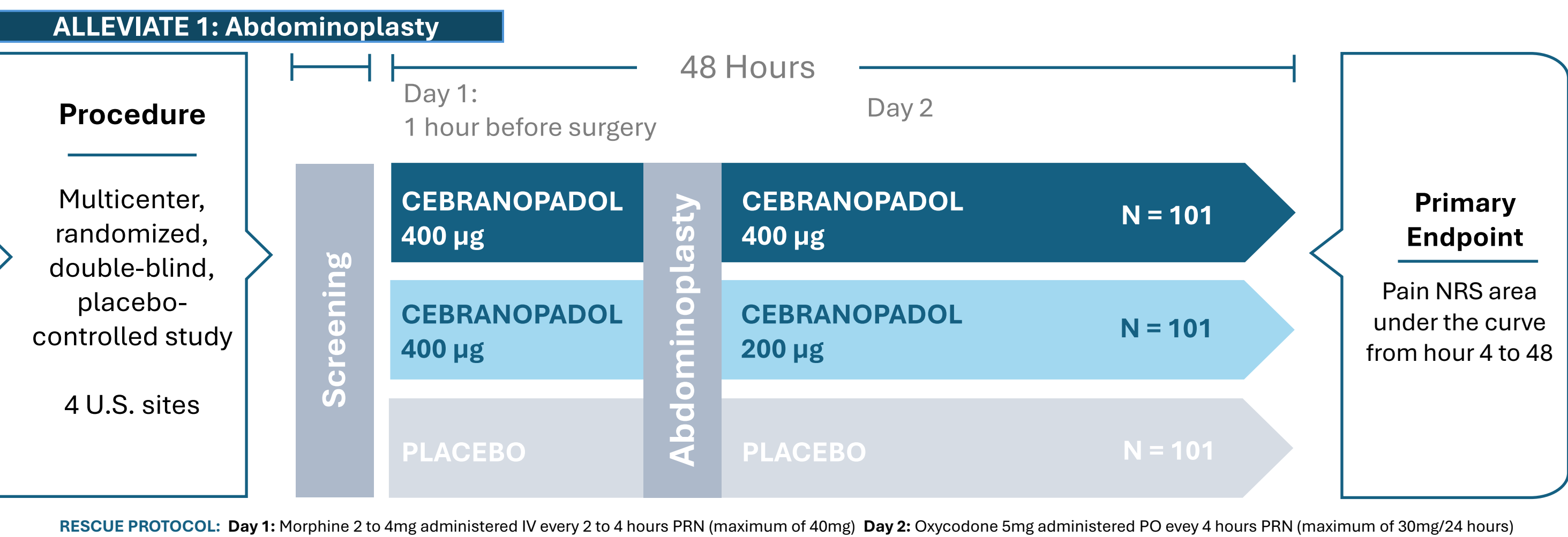
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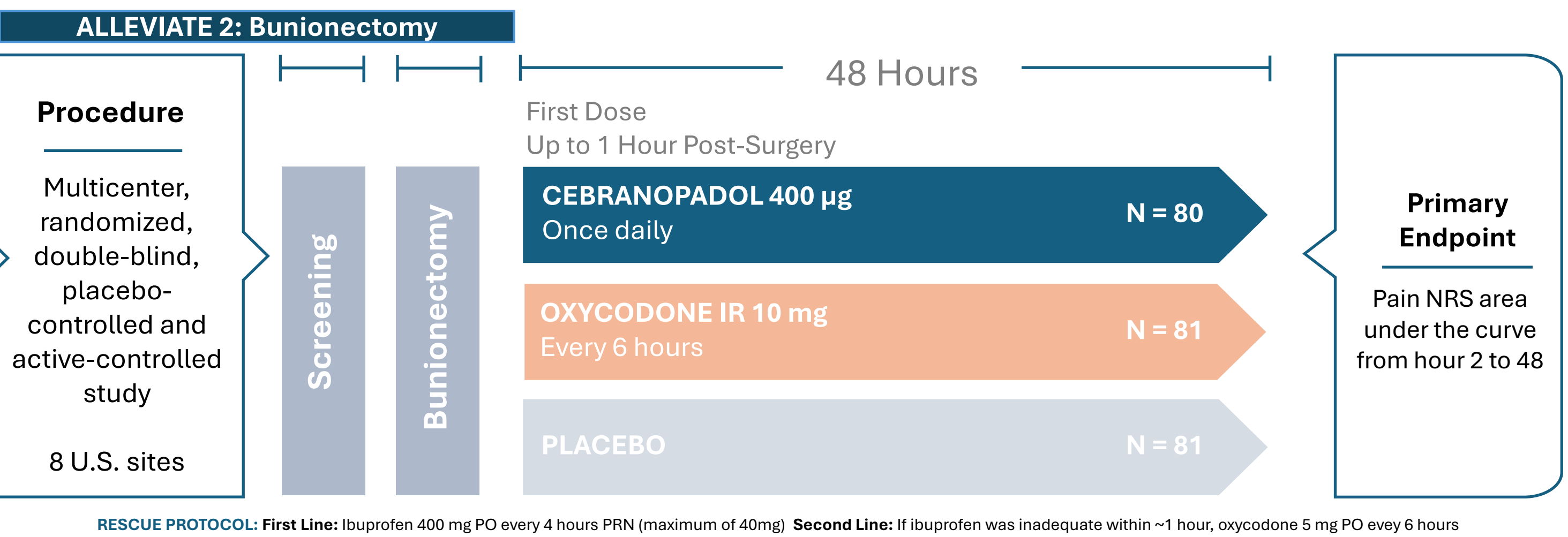
Background

Moderate to severe acute pain is a prevalent condition in the US and managing this pain, especially in the postoperative setting, remains a challenge. Existing treatments like opioids often cause side effects such as dependence, misuse, and respiratory depression, and both clinicians and patients are increasingly hesitant to use them. Cebranopadol is a first-in-class dual nociceptin/orphanin FQ peptide (NOP) and mu-opioid peptide (MOP) receptor (dual-NMR) agonist. This dual mechanism leads to potent analgesia while attenuating the negative side effects including euphoria, physical dependence, and respiratory depression of MOP agonism. These studies evaluated the safety and efficacy of cebranopadol in managing acute post-operative pain following abdominoplasty and bunionectomy.

Study Design



- The abdominoplasty study was a multicenter, randomized, double-blind, placebo-controlled study.
- Eligible participants were randomized in a 1:1:1 ratio to cebranopadol 400 µg on Days 1 and 2, cebranopadol 400 µg on Day 1 and 200 µg on Day 2 or placebo all administered once daily. The first dose was administered approximately 1 hour prior to abdominoplasty and the second dose approximately 24 hours later.



- The bunionectomy study was a multicenter, randomized, double-blind, placebo- and active-controlled parallel-group study of cebranopadol following primary unilateral bunionectomy with first metatarsal osteotomy.
- Eligible participants were randomized in a 1:1:1 ratio to a cebranopadol 400 µg, oxycodone immediate release (IR) 10 mg or placebo. Cebranopadol was administered once daily on Days 1, 2, and 3; placebo was administered at 6, 12, and 18 hours to maintain blinding. Oxycodone 10 mg and placebo were administered every 6 hours.

Key inclusion criteria:

- Non-smoking adults between 18 and 75 years of age.
- Those in the abdominoplasty study were scheduled to undergo full abdominoplasty procedure without liposuction or other collateral procedures. Those in the bunionectomy study were scheduled to undergo primary unilateral bunionectomy with first metatarsal osteotomy and internal fixation with no collateral procedures.

Results

Baseline Demographic and Disposition

- In the abdominoplasty study, 303 participants were randomized to treatment at four locations in the United States, and 292 (96.4%) completed the study.
 - Eleven participants discontinued the study for AEs (3), lost to follow-up (2), withdrawal of consent (3), and other (3).
- In the bunionectomy study, 242 participants were enrolled at 10 locations in the United States, and 236 (97.5%) completed the study.
 - One participant discontinued in the oxycodone group for hypersensitivity, which was considered a severe and serious AE.
 - No other participants discontinued or experienced a severe or serious AE.
- Across the two trials, baseline characteristics were similar among groups. More participants in the abdominoplasty study had a history of substance abuse.

Figure 1. Primary Endpoint, Pain NRS AUC₄₋₄₈ and Pain NRS AUC₂₋₄₈

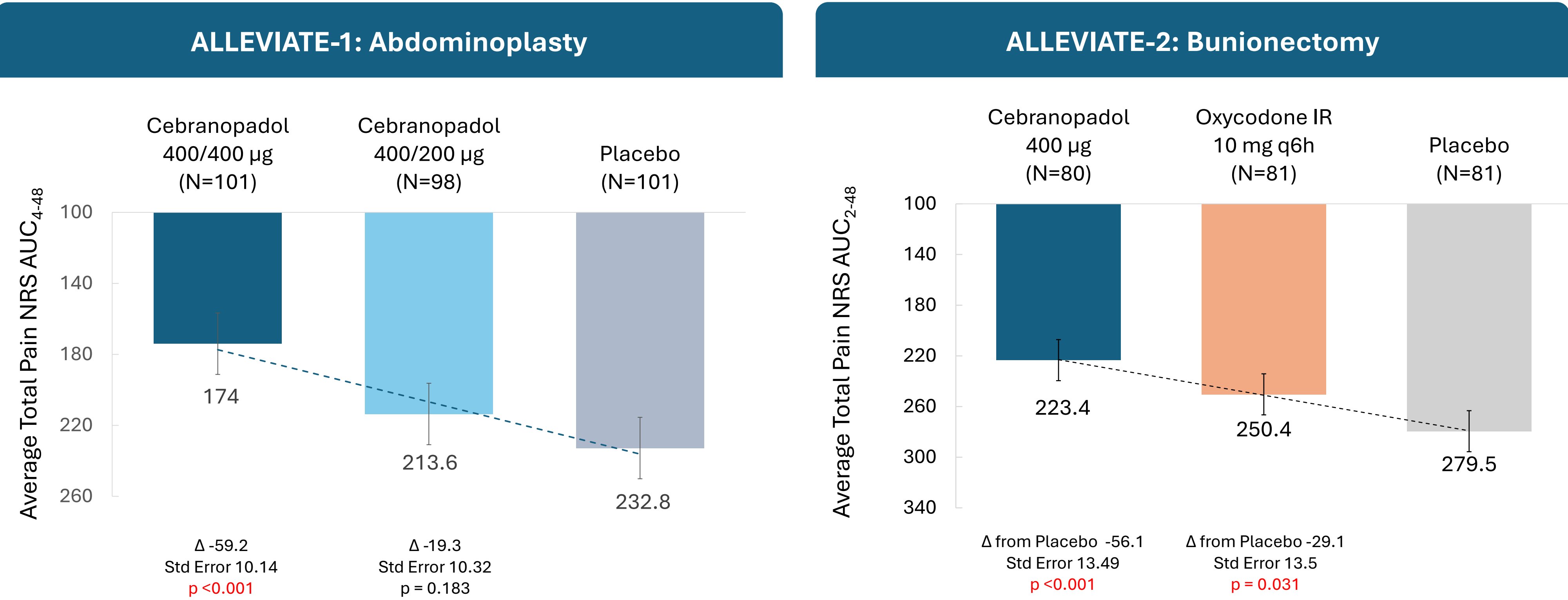


Figure 2. Mean Pain NRS Over Time

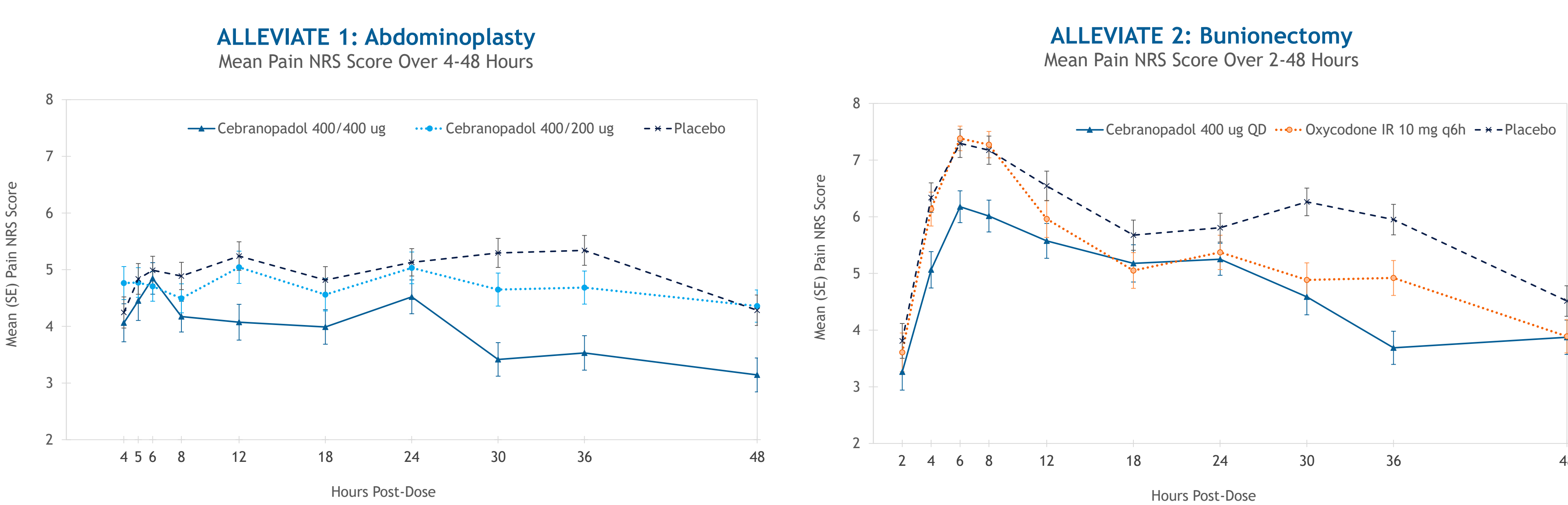
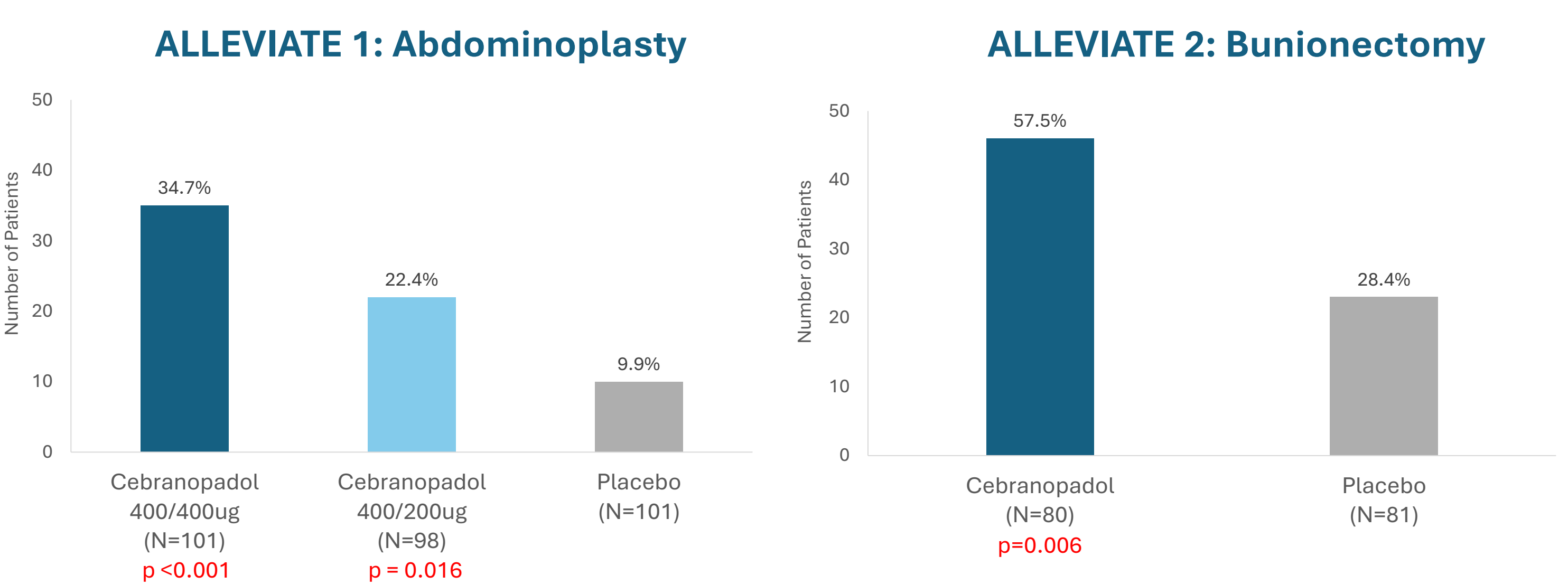


Table 1. Adverse events experienced by >5% of Patients

	Abdominoplasty Study			Bunionectomy Study		
	Cebranopadol 400/400 mg QD N=101	Cebranopadol 400/200 mg QD N=101	Placebo N=101	Cebranopadol 400 mg QD N=80	Oxycodone IR 10 mg q6h N=81	Placebo N=81
Any TEAE	67 (66.3)	70 (69.3)	75 (74.3)	66 (82.5)	65 (80.2)	33 (40.7)
Serious TEAE	3 (3.0)	1 (1.0)	2 (2.0)	0	1 (1.2)	0
Severe TEAE	3 (3.0)	2 (2.0)	2 (2.0)	0	1 (1.2)	0
Related TEAE	34 (33.7)	36 (35.6)	43 (42.6)	57 (71.3)	57 (70.4)	15 (18.5)
Discontinuation for TEAE	1 (1.0)	1 (1.0)	2 (2.0)	0	1 (1.2)	0
Nausea	44 (43.6)	46 (45.5)	48 (47.5)	48 (60.0)	44 (54.3)	9 (11.1)
Vomiting	4 (4.0)	3 (3.0)	0	30 (37.5)	26 (32.1)	4 (4.9)
Constipation	2 (2.0)	16 (15.8)	13 (12.9)	9 (11.3)	12 (14.8)	2 (2.5)
Headache	6 (5.9)	6 (5.9)	12 (11.9)	14 (17.5)	17 (21.0)	8 (9.9)
Dizziness	2 (2.0)	3 (3.0)	2 (2.0)	19 (23.8)	15 (18.5)	1 (1.2)
Hypertension	4 (4.0)	4 (4.0)	10 (9.9)	2 (2.5)	2 (2.5)	0
Pruritus	7 (6.9)	3 (3.0)	3 (3.0)	2 (2.5)	15 (18.5)	1 (1.2)

Figure 3. Patients Who Did NOT Require Any Opioid Rescue Medication (Days 1 to 7)



Conclusions

- Cebranopadol is a **first-in-class, Dual-NMR agonist** that stimulates MOP, which delivers efficacy, and NOP, which adds efficacy and regulates addictive (dependence, abuse) and other safety effects (respiratory, pruritus, GI) of MOP.
- In both trials, cebranopadol achieved the primary endpoint of **statistically significant pain reduction** in NRS AUC and was well tolerated. In both trials, rescue medication use was significantly lower than with placebo.
- These trials represent two registrational, Phase 3 studies highlighting cebranopadol's potential to become a **valuable new therapy for acute pain management**.

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