

Results of a Randomized, Placebo-Controlled, Phase 3 Trial of Cebranopadol for the Treatment of Acute Pain After Abdominoplasty

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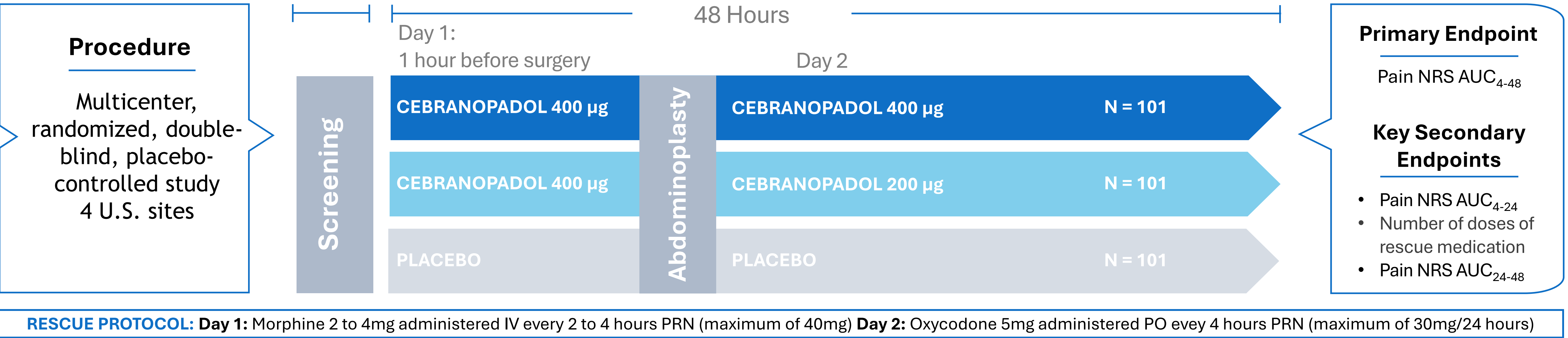
Background

Moderate to severe acute pain is a prevalent condition in the US and managing this pain, especially in the postoperative setting, remains a challenge, in part due to the limitation of existing treatment options like opioids to effectively manage pain without negative side effects, including issues of euphoria, dependence, misuse, respiratory depression and tolerability. The treatment challenges are further exacerbated by the apprehension of both clinicians and patients to use opioids. 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. This study evaluates the safety and efficacy of cebranopadol in managing acute post-operative pain following abdominoplasty.

Study Design

- The first dose of study drug was administered 1 hour prior to the abdominoplasty. The second dose of study drug was administered 24 hours (±30 minutes) after the first dose.
- The primary endpoint of Pain NRS AUC₄₋₄₈, included 2 pairwise comparisons:
 - Cebranopadol 1st 400µg; 2nd 400µg vs. placebo
 - Cebranopadol 1st 400µg; 2nd 200µg vs. placebo

NRS: Numerical Rating Scale; AUC: Area under the curve



Results

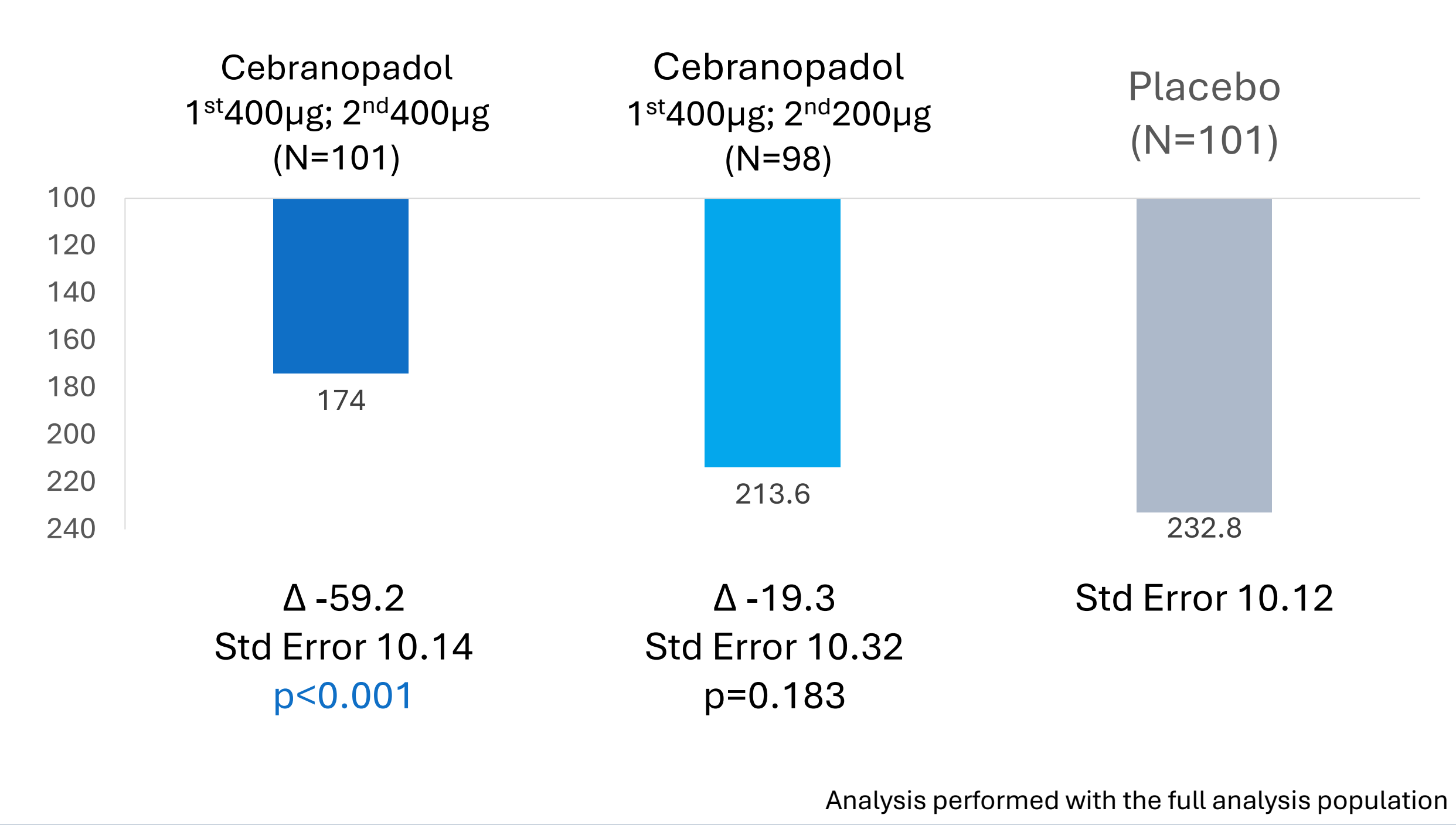
Table 1. Patient Disposition				
	Cebranopadol 1 st 400µg; 2 nd 400µg	Cebranopadol 1 st 400µg; 2 nd 200µg	Placebo	Total
Screened, n				471
Randomized, n	101	101	101	303
Full Analysis Population*, n	101	98	101	300
Completed, n	98	97	97	292
Discontinued, n	3	4	4	11
Reason for Discontinuation, n				
Adverse Event	-	2	1	3
Lost to Follow-up	-	-	2	2
Withdrawal of consent	2	-	1	3
Other	1	2	-	3

* Full analysis population included all randomized subjects who received at least one dose of the study drug and underwent the abdominoplasty procedure.

Table 2. Patient Demographics and Baseline Characteristics				
	Cebranopadol 1 st 400µg; 2 nd 400µg (N=101)	Cebranopadol 1 st 400µg; 2 nd 200µg (N=101)	Placebo (N=101)	Total (N=303)
Age (years), mean (SD)	43.6 (9.24)	43.9 (7.47)	43.5 (8.80)	43.6 (8.51)
Sex, n (%)				
Male	1 (1.0)	1 (1.0)	2 (2.0)	4 (1.3)
Female	100 (99.0)	100 (99.0)	99 (98.0)	299 (98.7)
Race				
White	66 (65.3)	74 (73.3)	79 (78.2)	219 (72.3)
Black or African American	33 (32.7)	24 (23.8)	19 (18.8)	76 (25.1)
Other	2 (2.0)	3 (3.0)	3 (3.0)	8 (2.6)
BMI (kg/m ²), mean (SD)	28.50 (3.549)	28.07 (3.452)	27.36 (3.50)	27.98 (3.521)
Duration of Surgery (minutes), mean (SD)	93.3 (32.07)	86.2 (30.76)	94.0 (30.96)	91.2 (31.7)

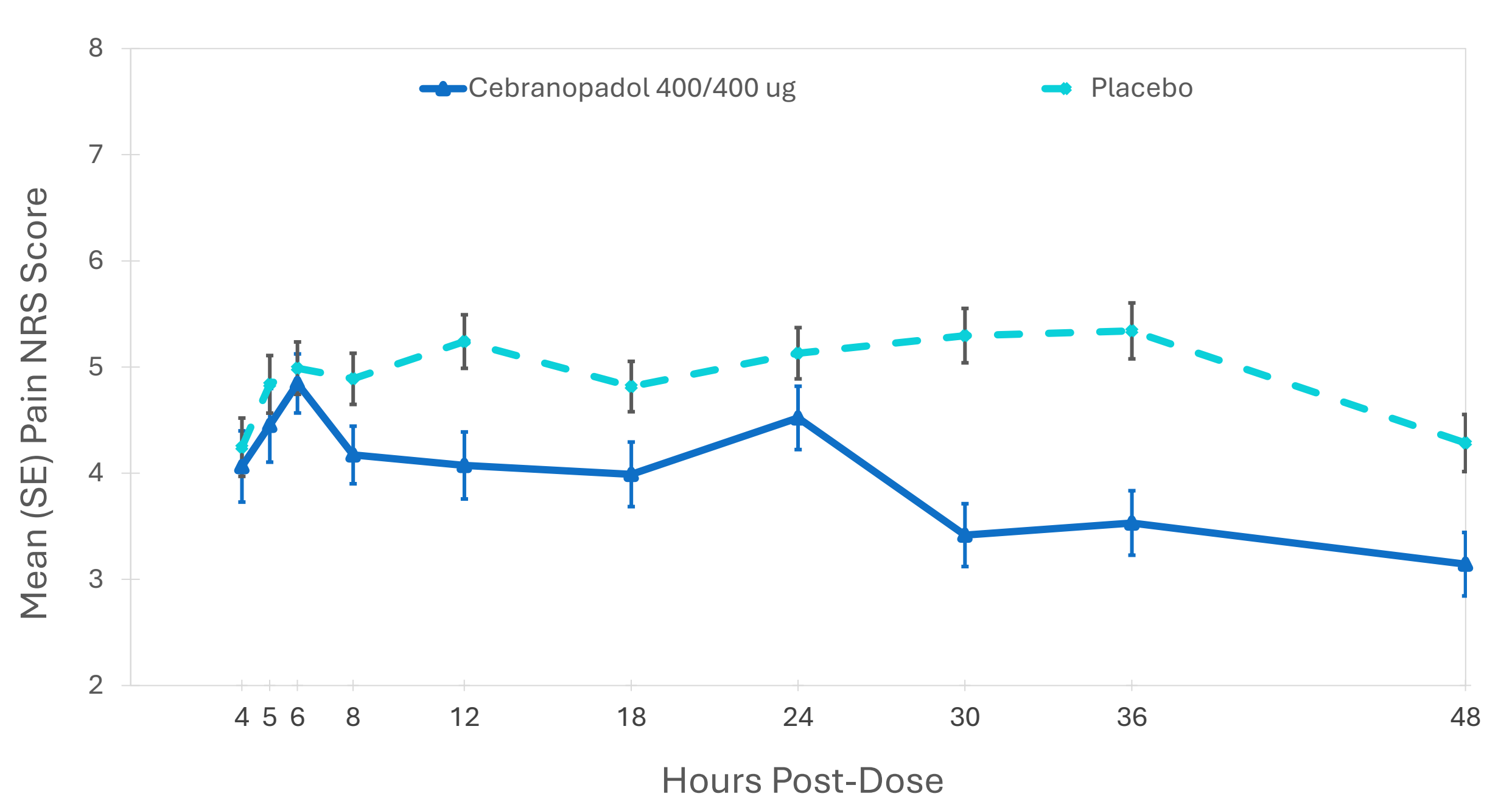
- If the primary endpoint is significant for both cebranopadol vs. placebo comparisons, the key secondary endpoints will be tested in a fixed sequence.
- Key Inclusion Criteria:**
- Non-smoking adults between 18 and 75 years of age.
 - Scheduled to undergo full abdominoplasty procedure without liposuction or other collateral procedures, using anesthesiologic and surgical procedures planned as described in this protocol.

Figure 1. Primary Endpoint, Pain NRS AUC₄₋₄₈



Cebranopadol 1st 400µg; 2nd 400µg achieved the primary endpoint of **statistically significant pain reduction** over 44 hours as compared to placebo.

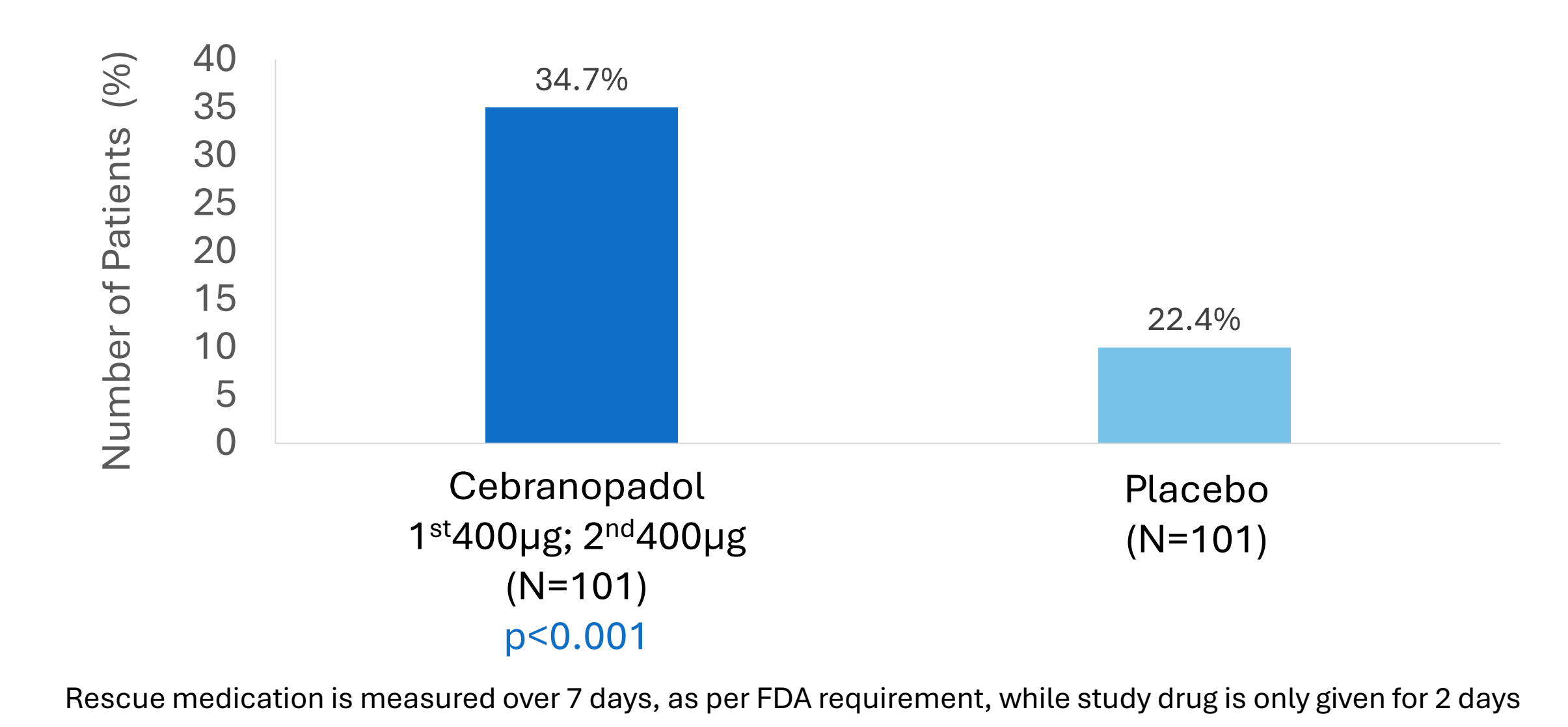
Figure 2. Mean Pain NRS Score Over 4-48 Hours



Cebranopadol 1st 400µg; 2nd 400µg exhibited an average hourly pain reduction of **1.34** over placebo

REFERENCES: Nahin RL, et al. *J Pain*. 2019;20(7):796-809. doi:10.1016/j.jpain.2019.01.003 • Dowell D, et al. *MMWR Recomm Rep*. 2022;71(3):1-95. doi:10.15585/mmwr.r7103a1 • Volkow ND, et al. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMra1507771 • Linz K, et al. *J Pharmacol Exp Ther*. 2014;349(3):535-548. doi:10.1124/jpet.114.213694 • Scholz A, et al. *Pain Physician*. 2018;21(3):E193-E206.

Figure 3. Patients Not Requiring Opioid Rescue



Statistically significantly **fewer patients** on both cebranopadol arms required opioid rescue compared to placebo

Table 3. TEAEs Experienced by >5% Patients

TEAE	Cebranopadol 1 st 400µg; 2 nd 400µg (N=101)	Cebranopadol 1 st 400µg; 2 nd 200µg (N=101)	Placebo (N=101)
Nausea*	44 (43.6%)	46 (45.5%)	48 (47.5%)
Constipation	2 (2.0%)	16 (15.8%)	13 (12.9%)
Headache	6 (5.9%)	6 (5.9%)	12 (11.9%)
Oxygen Saturation Decreased	6 (5.9%)	1 (1.0%)	3 (3.0%)
Hypertension	4 (4.0%)	4 (4.0%)	10 (9.9%)
Pruritus	7 (6.9%)	3 (3.0%)	3 (3.0%)

TEAS: treatment emergent adverse event
*Protocol included antiemetic medication administered before anesthesia for surgery and administered as nausea or vomiting occurred.

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, GI) of MOP.
- Cebranopadol 1st 400µg; 2nd 400µg achieved the primary endpoint of **statistically significant pain reduction** over 44 hours as compared to placebo.
- This trial represents the first of two registrational, Phase 3 studies highlighting cebranopadol's potential to become a **valuable new therapy for acute pain management**.