Early Analgesic Efficacy of Acetaminophen 650 mg + Naproxen Sodium 220 mg in Moderate-Severe Post-surgical Pain

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Introduction

- Fast, early, effective analgesia is important in pain management. These analyses compare efficacy during the initial 6-hour treatment window following dental surgery to determine:
  - Early pain relief efficacy
  - Proportion of participants using rescue medication

  among participants with moderate or severe pain receiving Acet 650 mg + NPX 220 mg, Acet 1000 mg + NPX 440 mg, HC10/Acet650, NPX440 or Placebo [1]
- A new fixed-dose combination (FDC) of acetaminophen 650 mg and naproxen sodium 220 mg (FDC Acet650/NPX220) has been approved by the United States Food and Drug Administration

Methods

- Design: randomized, double blind, single dose, 12 hours, placebo-controlled trial
- Participants: underwent surgical removal of 3 or 4 third molars and had at least moderate pain on a 4-point categorical scale and a score ≥5 on the 11-point pain intensity numerical rating scale (PI-NRS)
- Rescue medication: tramadol 50 mg, 1-2 tablets every 6 hours; participants encouraged to wait at least 1.5 hours before rescue
- Efficacy endpoints focused on first 6 hours:
  - Time-weighted sum of pain intensity difference scores over 0-6h (SPID 0-6)
  - Pain intensity difference scores (PID) at individual time points 0-6h
  - Percentage of participants using rescue medication (RM, tramadol 50 mg) through 2h, 4h and 6h (post-hoc analyses conducted to compare rescue rates at these time points)
- Safety: adverse events (AEs) were monitored through follow-up on days 7-10

Results

- Participants were similar across treatment groups; mean age = 18.4 ± 1.5 years
- Mean baseline pain intensity (PI-NRS) similar across groups = 7.9 ± 1.1; 62.9% reported severe pain
- Acet 650 + NPX 220 and Acet 1000 + NPX 440 were superior to HC 10/Acet 650 and NPX 440 for diminishing pain intensity (SPID 0-6) and % using rescue medication through 6h; active treatments were superior to Placebo through 6h.
- No serious adverse events (AEs) or AEs leading to treatment discontinuation were reported

Discussion

- This dental impaction pain trial used surgical parameters expected to produce moderate-to-severe pain and efficacy endpoints that are well established, widely used, and recommended by the FDA and pain research collaboratives[2,3]
- Acet650+NPX220 or Acet1000+NPX440 demonstrated superior analgesic efficacy and fewer participants requested rescue medication in the initial 6h after dosing compared with HC10/Acet650 or NPX440 in participants with moderate-to-severe pain
- Limitations include that this single-dose, 12-hour study was not designed for evaluating multi-dose analgesic efficacy or long-term safety of any of the treatments. Participants were young (29% aged <18 years at surgery, range 17 – 27 years), predominantly White (90.0%) and non-Hispanic/Latino (88.3%), with a mean BMI of 24.3; potentially limiting generalizability to older patients, patients of other races/ethnicities, and patients with obesity, but prior experience with individual active ingredients is reassuring.

References

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2. Carrasco-Labra A, et al. *J Am Dent Assoc*. 2024;155(2):102-117.e9.
3. Cooper SA, et al. *Pain*. 2016;157(2):288-301.

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Key Findings & Conclusions

- Concomitantly dosed **Acet 650 + NPX 220 demonstrated early analgesic superiority in the first 6 hours after dosing compared to:**
  - **HC 10/Acet 650 (maximum labeled dose)**
  - **NPX 440**
- Fewer Acet 650 + NPX220 and fewer Acet 1000 + NPX 440 participants requested rescue medication in the first 6 hours compared with HC 10/Acet 650 or NPX 440 participants.
- Initiating treatment with Acet 650 + NPX 220 could have a dose-sparing effect for both active ingredients and provide convenient continuation with a simple 12-hour dosing regimen.
- As findings from the dental impaction pain model have been generalizable to other pain conditions, the recently approved fixed dose combination (FDC) Acet 650/NPX 220 mg (2 tablets of Acet 325/NPX 110 mg) can provide healthcare professionals and patients with a new, non-opioid, multimodal over-the-counter FDC analgesic containing low doses of acetaminophen and naproxen sodium, with simple labeled dosing instructions that maximize convenience and minimize patient confusion.

Table and Figures

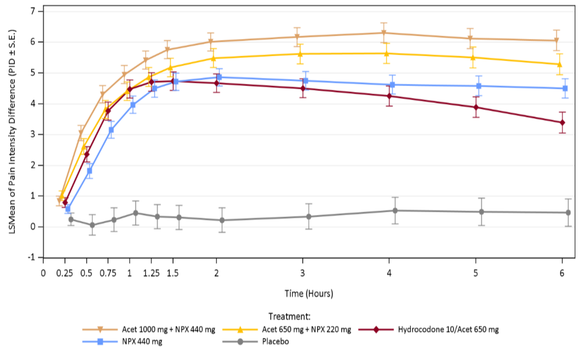
Table. Key efficacy and safety measures

	Acet650 + NPX220	Acet1000 + NPX440	NPX440	HC10/Acet 650	Placebo
	2 TYLENOL® 1 Aleve® 1 Placebo	2 TYLENOL® Extra Strength 2 Aleve®	2 Aleve® 2 Placebo	2 HC5/ Acet325 2 Placebo	4 Placebo
N	61	63	69	62	35
Efficacy					
SPID 0-6, LSM (SE)[a]	**30.3 (1.7)**[b,c,d]	**33.8 (1.6)**[b,c,d]	**25.6 (1.6)**[b]	**23.6 (1.7)**[b]	**2.4 (2.2)**
% Using rescue medication					
0–2 hours	**1.7%** [b]	**1.6%** [b]	**5.9%** [b]	**3.3%** [b]	**54.3%**
0–4 hours	**3.3%** [b]	**1.6%** [b,c,d]	**11.8%** [b]	**9.8%** [b]	**77.1%**
0–6 hours	**3.3%** [b,c,d]	**1.6%** [b,c,d]	**16.2%** [b]	**18.0%** [b]	**77.1%**
Safety					
Participants with ≥1 TEAE, n (%)	8 (13.1)	9 (14.3)	5 (7.2)	22 (35.5)	14 (40.0)
Nausea	2 (3.3)	3 (4.8)	2 (2.9)	20 (32.3)	9 (25.7)
Vomiting	4 (6.6)	6 (9.5)	2 (2.9)	9 (14.5)	7 (20.0)
Headache	0	0	0	1 (1.6)	4 (11.4)

[a]For SPID, *P*-values are based on ANOVA, with treatment, gender, and baseline categorical pain rating (moderate or severe) included in the model. [b]*P*≤0.003 vs placebo. [c]*P*≤0.05 vs HC10/Acet650. [d]*P*≤0.039 vs NPX440.

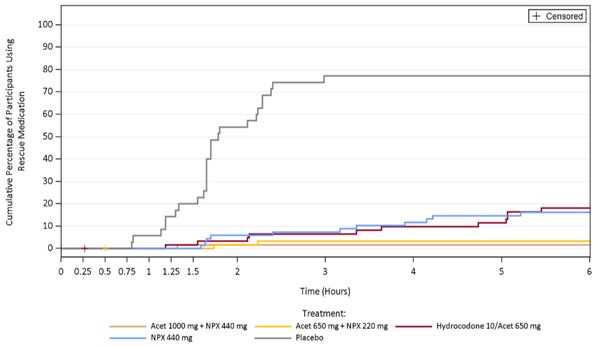
LSM, least-squares mean; SPID, time-weighted sum of pain intensity difference; TEAE, treatment-emergent adverse event

Fig 1. Mean pain intensity difference from baseline at individual timepoints



- LSMean PID (least squares mean of pain intensity difference) scores were significantly greater for Acet 650 + NPX 220 than HC 10/Acet 650 from 3-6h (p<0.05) and significantly greater for Acet 1000 + NPX 440 than HC 10/Acet 650 at 0.5 and 1.5-6h (p<0.05)
- LSMean PID scores were significantly greater for Acet 650 + NPX 220 than NPX 440 (p<0.05) at 0.25, 0.5 and 3-5h, and significantly greater for Acet 1000 + NPX 440 from 0.5-6h than NPX 440 (p<0.05).

Fig 2. Cumulative percentage of participants using rescue medication



- At 2 hours: both Acet 650 + NPX 220 and Acet 1000 + NPX 440 had numerically lower % of participants using rescue medication compared to HC 10/Acet 650 and NPX 440.
- At 4 hours: Acet 650 + NPX 220 had numerically and Acet 1000 + NPX 440 had significantly lower % using rescue medication than HC 10/Acet 650 and NPX 440.
- At 6h, both Acet 650 + NPX 220 and Acet 1000 + NPX 440 had significantly lower % of participants using rescue medication than HC 10/Acet 650 and NPX 440. All active treatment groups were superior to PBO for percentage using rescue from 0-6h.