Analgesic Effectiveness of a New Fixed-Dose Combination Acetaminophen/Naproxen Sodium: A Phase 3 Placebo-Controlled, Randomized, Double-Blind, Factorial Trial in Postoperative Dental Pain

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Introduction

Clinical practice guidelines often recommend a nonsteroidal anti-inflammatory drug (NSAID) or a combination of an NSAID with acetaminophen as first-line treatment of pain[1]

A new fixed-dose combination (FDC) of acetaminophen 650 mg and naproxen sodium 220 mg (FDC Acet650/NPX220), administered as 2 tablets of FDC Acet325/NPX110, has the potential to provide highly effective, non-opioid pain control with rapid onset and long duration with dose-sparing effect for both acetaminophen and naproxen sodium, and a simple dosing regimen of 2 tablets every 12 hours

Objective

Phase 3 randomized**,** double-blind **factorial trial t**o assess the efficacy, onset, and durability of analgesic effect with a **single dose** of FDC Acet650/NPX220 versus Acet650, NPX220, and placebo (PBO), and determine the contribution of each active ingredient

- Results are compared with a similarly designed Phase 2 proof-of-concept (POC) trial in the same pain model which evaluated co-administered Acet650 + NPX220, Acet1000 + NPX440, hydrocodone 10 mg/Acet650 (HC10/Acet650), NPX440, and PBO

Methods

Population

- Participants who underwent surgical removal of 3 or 4 third molars, including 2 mandibular impactions, 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)

Phase 3 Factorial Trial

- **Randomized (4:2:4:1), double-blind, placebo-controlled trial:** FDC Acet650/NPX220 (n=160), Acet650 (n=82), NPX220 (n=162), or PBO (n=43)

Phase 2 POC Trial

- Acet650 + NPX220 (n=61), Acet1000 + NPX440 (n=63), HC10/Acet650 (n=62), NPX440 (n=69), or PBO (n=35)

Endpoints: Phase 3 Factorial Trial

- **Primary**: time-weighted sum of pain intensity difference over 12 hours (SPID 0-12)
- **Secondary**: SPID 6-12, time to first request for rescue medication, and proportion requesting rescue medication
- **Key Exploratory**: pain intensity difference (PID) from baseline, pain relief (PAR), and pain intensity (PI) at individual timepoints, SPID 0-6, time-weighted sum of pain relief (TOTPAR 0-6, 0-12), time to confirmed perceptible pain relief (TCPR), time to meaningful pain relief (TMPR), and participant global assessment (PGA) of analgesic efficacy at 24 hours[a] (5-point scale, poor–excellent)

Corresponding Primary and Secondary Endpoints: Phase 2 POC Trial

- **Primary:** SPID 0-6 and SPID 0-12
- **Secondary:** TOTPAR 0-6 and 0-12 and PGA at 12 hours[a]

Rescue Medication

- **Phase 3 factorial:** celecoxib 400 mg first-line, then 200 mg every 12 hours; oxycodone 5 mg every 4-6 hours available second-line
- **Phase 2 POC:** tramadol 50 mg, 1-2 tablets every 6 hours; participants encouraged to wait ≥1.5 hours before rescue

Assessments and Analysis

- PI was recorded at specified timepoints and prior to rescue (when applicable), using the 0-10 PI-NRS
- SPID and PGA were analyzed using analysis of variance (ANOVA); rescue time, TCPR, and TMPR were analyzed using the Wilcoxon method
- Adverse events (AEs) were monitored through follow-up on days 7-10

[a]PGA was assessed at 24 hours in the Phase 3 factorial trial and at 12 hours in the Phase 2 POC trial, or at first request/use of rescue medication or early termination, whichever occurred first.

Results

- Participant populations were comparable across treatment groups in both dental pain trials (**Table 1**)
- In both trials, no serious treatment-emergent adverse events (TEAEs) were reported; Acet/NPX combinations were well tolerated (**Table 1**)
- Few withdrawals before the 12-hour assessment in either trial
  - Factorial: 3 (0.7%): 1 each in Acet650 and NPX220; 1 FDC Acet650/NPX220 (mild dysphagia with the over-encapsulated drug)
  - POC: 5 (1.7%): 1 each in Acet650+NPX220, NPX440, and HC10/Acet650; 2 PBO; none in Acet1000+NPX440

Table 1. Key participant characteristics, efficacy outcomes, and AEs across both dental pain studies

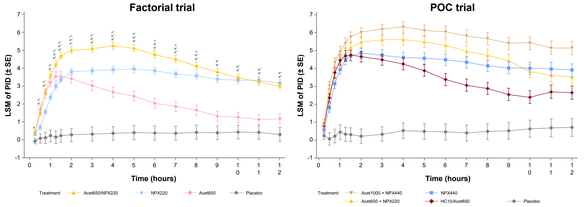
	Factorial trial				POC trial				
	FDC Acet650/NPX220	Acet650	NPX220	Placebo	Acet650 + NPX220	Acet1000 + NPX440	NPX440	HC10/Acet650	Placebo
Administered over-encapsulated	2 Acet325/NPX110 tablets	2 TYLENOL®	1 Aleve® tablet 1 PBO tablet	2 PBO tablets	2 TYLENOL® 1 Aleve® tablet 1 PBO tablet	2 TYLENOL® (Extra strength tablets) 2 Aleve® tablets	2 Aleve® tablets 2 PBO tablets	2 HC5/Acet325 tablets 2 PBO tablets	4 PBO tablets
N	160	82	162	43	61	63	69	62	35
4 molars extracted, n (%)	148 (92.5)	79 (96.3)	153 (94.4)	39 (90.7)	55 (90.2)	59 (93.7)	61 (88.4)	54 (87.1)	33 (94.3)
Baseline Pain Intensity									
PI-NRS score (0-10), mean (SD)	7.8 (1.2)	7.7 (1.1)	7.7 (1.2)	7.6 (1.2)	8.2 (1.3)	7.8 (1.3)	7.8 (1.4)	8.1 (1.3)	7.9 (1.1)
Severe (4-point categorical scale), n (%)	95 (59.4)	52 (63.4)	94 (58.0)	25 (58.1)	43 (70.5)	40 (63.5)	44 (63.8)	41 (66.1)	22 (62.9)
Efficacy									
SPID 0-12, LSM (SE)[a]	49.3 (2.1)[b,c,d]	24.0 (2.9)	40.7 (2.1)	4.1 (4.0)	55.5 (3.6)[d,e,f,g]	66.4 (3.5)[d,e,f,g]	50.1 (3.3)[d]	39.9 (3.5)[d]	5.8 (4.7)
SPID 0-6, LSM (SE)[a]	27.1 (1.0) [b,c,d]	15.6 (1.4)	20.3 (1.0)	1.8 (1.9)	30.3 (1.7)[d,e,f]	33.8 (1.6)[d,e,f]	25.6 (1.6)[d]	23.6 (1.7)[d]	2.4 (2.2)
SPID 6-12, LSM (SE)	22.2 (1.2)[b,d]	8.4 (1.6)	20.5 (1.2)	2.3 (2.2)	25.2 (2.1)[d,e]	32.7 (2.0)[d,e,f,g]	24.5 (1.9)[d]	16.3 (2.1)[d]	3.5 (2.7)
Median time to first request[h]/use[i] of rescue medication, min [95% CI]	762.0 [687.0, NE][b,d]	382.0 [320.0, 482.0]	NE [716.0, NE]	88.0 [81.0, 95.0]	NE [NE, NE][d,e,f,g]	NE [NE, NE][d,e,f,g]	NE [NE, NE][d]	NE [548.0, NE][d]	107.0 [99.0, 137.0]
Proportion requesting/using rescue medications in 12 hours, %[j,k]	46.3[b,d]	79.3	43.8	86.0	21.7	7.9	20.6	41.0	77.1
Median TCPR, min [95% CI][h]	26.1 [24.8, 30.2][c,d]	27.9 [24.3, 38.9]	42.2 [35.6, 48.5]	NE [NE, NE]	20.8 [16.1, 25.7][f]	17.0 [15.1, 21.2][d,f]	24.2 [17.1, 29.3][d]	19.4 [15.6, 24.6][d]	NE [NE, NE]
Median TMPR, min [95% CI][h]	55.5 [47.6, 63.8][c,d]	64.1 [50.6, 118.1]	97.0 [73.3, 111.3]	NE [NE, NE]	50.3 [39.3, 62.3][d]	41.2 [33.1, 53.2][d,f]	54.3 [48.5, 64.8][d]	47.7 [39.4, 63.9][d]	NE [NE, NE]
PGA of study medication as a pain reliever, LSM (SE)	2.8 (0.1)[b,c,d]	1.9 (0.1)	2.3 (0.1)	0.6 (0.2)	2.9 (0.1)[d]	3.3 (0.1)[d,e,f,g]	2.7 (0.1)[d]	2.7 (0.1)[d]	0.8 (0.2)
TOTPAR 0-12, LSM (SE)	65.4 (2.6)[b,c,d]	30.4 (3.6)	53.0 (2.6)	11.8 (5.0)	76.8 (4.3)[d,e]	90.2 (4.2)[d,e,f,g]	70.0 (4.0)[d]	57.0 (4.2)[d]	18.2 (5.6)
TOTPAR 0-6, LSM (SE)	36.2 (1.2)[b,c,d]	20.9 (1.7)	26.9 (1.2)	5.6 (2.3)	40.9 (2.0)[d,e,f]	45.1 (1.9)[d,e,f]	35.2 (1.8)[d]	32.9 (2.0)[d]	8.0 (2.6)
Safety									
Participants with ≥1 TEAE, n (%)	8 (5.0)	5 (6.1)	8 (4.9)	7 (16.3)	8 (13.1)	9 (14.3)	5 (7.2)	22 (35.5)	14 (40.0)
Nausea	2 (1.3)	2 (2.4)	4 (2.5)	1 (2.3)	2 (3.3)	3 (4.8)	2 (2.9)	20 (32.3)	9 (25.7)
Vomiting	2 (1.3)	0	1 (0.6)	2 (4.7)	4 (6.6)	6 (9.5)	2 (2.9)	9 (14.5)	7 (20.0)
Headache	0	1 (1.2)	2 (1.2)	2 (4.7)	0	0	0	1 (1.6)	4 (11.4)

Primary endpoints are shown in blue bold; secondary endpoints are shown in green bold. [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*<0.001 vs Acet650. [c]*P*≤0.003 vs NPX220. [d]*P*≤0.003 vs placebo. [e]*P*≤0.004 vs HC10/Acet650. [f]*P*≤0.039 vs NPX440. [g]*P*≤0.037 vs Acet650 + NPX220. [h]For TCPR, TMPR, time to complete pain relief, and time to rescue, median survival time was estimated using the Kaplan-Meier method; *P*-values were based on the Wilcoxon test stratified by baseline pain severity (moderate or severe) and gender. [i]Factorial-trial *P*-values were based on the Wilcoxon test stratified by baseline pain severity (moderate or severe) and gender. [j]The factorial trial evaluated the proportion requesting rescue medication; *P*-values were based on exact conditional logistic regression stratified by sex and categorical baseline pain intensity. [k]The POC trial evaluated the proportion using rescue medication; Median survival time estimated by Kaplan-Meier method; survival curves compared (p-values) using Wilcoxon test.

Acet, acetaminophen; AE, adverse event; ANOVA, analysis of variance; BMI, body mass index; LSM, least-squares mean; NE, not estimable because fewer than 50% experienced the event; NPX, naproxen sodium; PBO, placebo; PGA, Participant Global Assessment; PI-NRS, pain intensity numerical rating scale; POC, proof of concept; SD, standard deviation; SE, standard error; SPID, time-weighted sum of pain intensity difference; TCPR, time to confirmed perceptible pain relief; TEAE, treatment-emergent adverse event; TMPR, time to meaningful pain relief; TOTPAR, total pain relief.

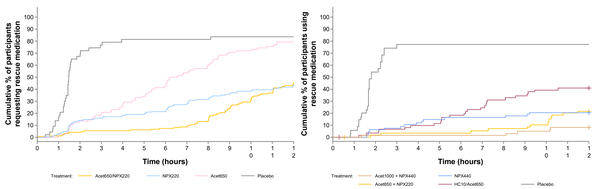
- FDC Acet 650/NPX220 provided superior pain control than Acet650, NPX220, and PBO, with faster analgesic onset than NPX220 (**Figure 1** and **Table 1**)
- Median time before requesting rescue medication was significantly longer with FDC Acet650/NPX220 than with Acet650 and PBO, but not longer than NPX220 (**Figure 2** and **Table 1**)

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



[a]*P*<0.05 vs placebo; [c]*P*<0.001 vs placebo; [b]*P*<0.05 vs Acet650; [d]*P*<0.001 vs Acet650; [e]*P*<0.05 vs NPX220; [f]*P*<0.001 vs NPX220.
Acet, acetaminophen; LSM, least-squares mean; NPX, naproxen sodium; PID, pain intensity difference; POC, proof of concept; SE, standard error.

Figure 2. Cumulative percentage of participants requesting/using rescue medication



Acet, acetaminophen; HC, hydrocodone; NPX, naproxen sodium; POC, proof of concept; SE, standard error.

Conclusions

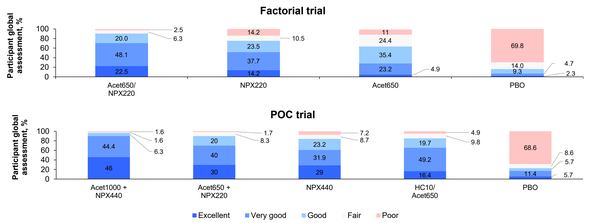
In the Phase 3 factorial trial, **FDC Acet650/NPX220 provided rapid-onset, sustained, highly efficacious 12-hour pain relief, with faster analgesic onset than NPX220 alone, longer pain relief than Acet650 alone, and greater analgesic efficacy than either individual component over 12 hours**

This second trial in a similar pain population confirms the magnitude of analgesic effect observed in the POC trial for concomitantly **dosed Acet650+NPX220, which was superior over 0-6 and 0-12 hours versus the maximum recommended dose of HC10/Acet650**, and superior over 0-6 hours versus NPX440, with half the NSAID dose and low acetaminophen doses (650 mg/dose; 1300 mg/day if administered every 12 hours)

As findings from the dental impaction pain model have been generalizable to other pain conditions, FDC Acet650/NPX220 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

- Pain control was rated good, very good, or excellent by ≥90% of Acet650/NPX220 participants in both studies **(Figure 3)**

Figure 3. Participant global assessment (PGA) of trial medication



Acet, acetaminophen; HC, hydrocodone; NPX, naproxen sodium; PGA, Participant Global Assessment; POC, proof of concept.

Discussion

- These dental impaction pain trials 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]
- These two trials (Factorial and POC) showed consistent results for overall efficacy, onset, and PGA with the combined use of Acet650 and NPX220
- Rescue medication options and parameters differed between the two trials, which may limit cross-study comparison for this endpoint
- The single-dose, 12-hour study was not designed for evaluating multi-dose analgesic efficacy or long-term safety of any of the treatments
- Participants in the Factorial trial were young (49% aged <18 years at surgery), predominantly White (94.4%) and non-Hispanic/Latino (85.5%), with a mean BMI of 22.9; potentially limiting generalizability to older patients, patients of other races/ethnicities, and patients with obesity

References

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