

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 pain¹

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 to 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

^aPGA 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

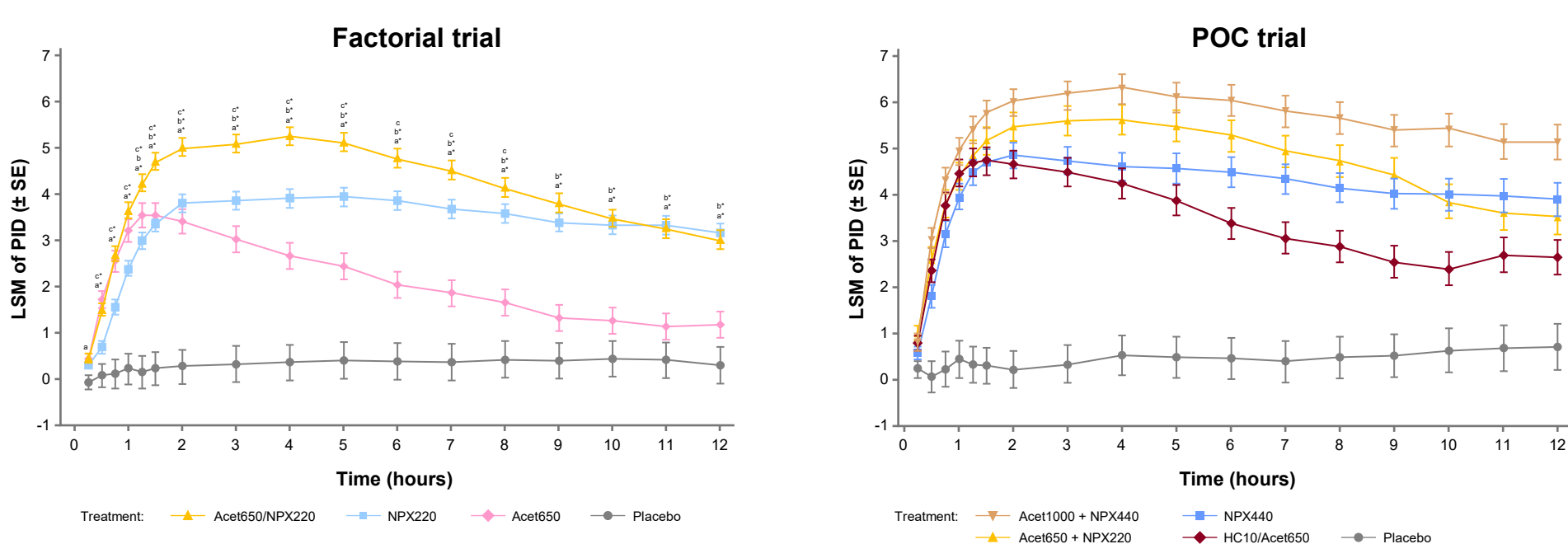
	Factorial trial				POC trial				
	FDC Acet650/NPX220	Acet650	NPX220	Placebo	Acet650 + NPX220	Acet1000 + NPX440	NPX440	HC10/Acet650	Placebo
Administered over-encapsulated	2 Acet325/NPX110 tablets	2 TYLENOL®	1 Aleve® tablet 1 PBO tablet	2 PBO tablets	2 TYLENOL® 1 Aleve® tablet 1 PBO tablet	2 TYLENOL® (Extra 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
Mean age, years (SD)	17.9 (1.8)	18.0 (1.7)	17.8 (1.9)	17.6 (1.7)	18.2 (1.3)	19.0 (2.2)	19.0 (2.4)	18.3 (1.7)	18.4 (1.5)
Female, n (%)	65 (40.6)	33 (40.2)	65 (40.1)	15 (34.9)	33 (54.1)	35 (55.6)	36 (52.2)	32 (51.6)	19 (54.3)
Mean BMI, kg/m ² (SD)	23.2 (3.0)	22.9 (3.1)	23.0 (3.1)	21.4 (2.5)	24.5 (4.3)	24.6 (4.0)	24.8 (4.8)	23.4 (3.1)	24.2 (3.3)
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}	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}	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, % ^{i,k}	46.3 ^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] ^{b,d}	27.9 [24.3, 38.9]	42.2 [35.6, 48.5]	NE [NE, NE]	20.8 [16.1, 25.7] ^d	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] ^{b,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. ^aFor 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. ^hFor 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. ⁱThe 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. ^jThe 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.

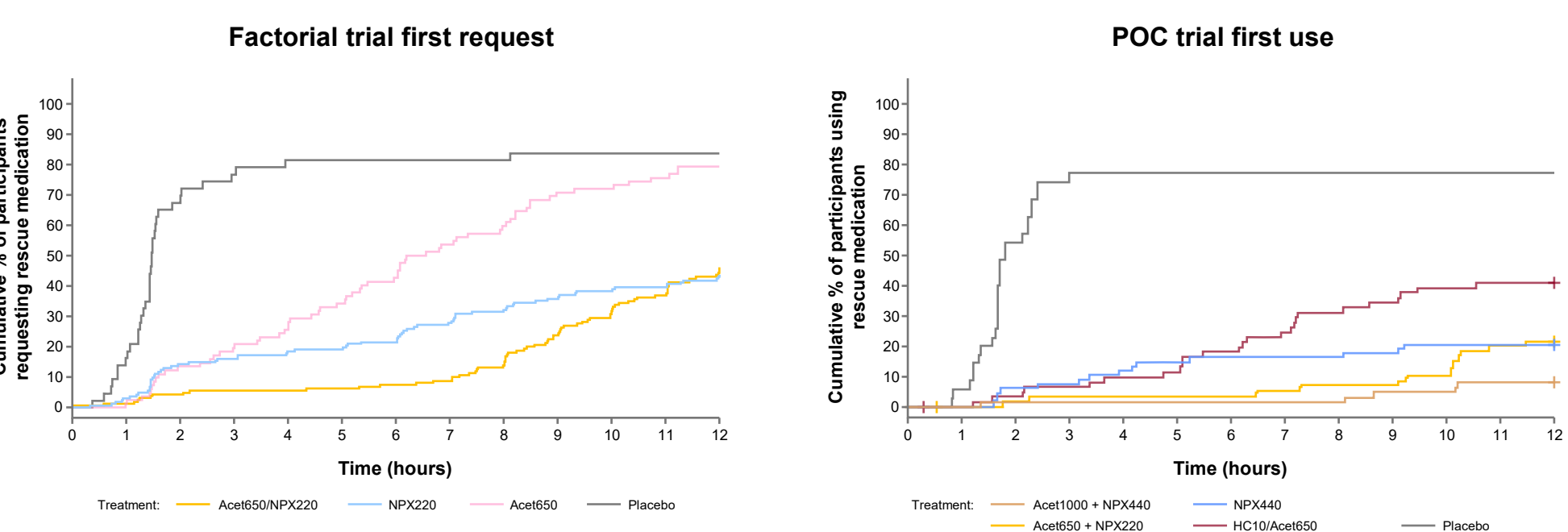
- FDC Acet 650/NPX220 provided superior pain control than Acet650, NPX220, and PBO, with faster analgesic onset than NPX220 (**Figure 1** and **Table 1**)
- Median time before requesting rescue medication was significantly longer with FDC Acet650/NPX220 than with Acet650 and PBO, but not longer than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

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



^a*P*<0.05 vs placebo; ^b*P*<0.001 vs placebo; ^c*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



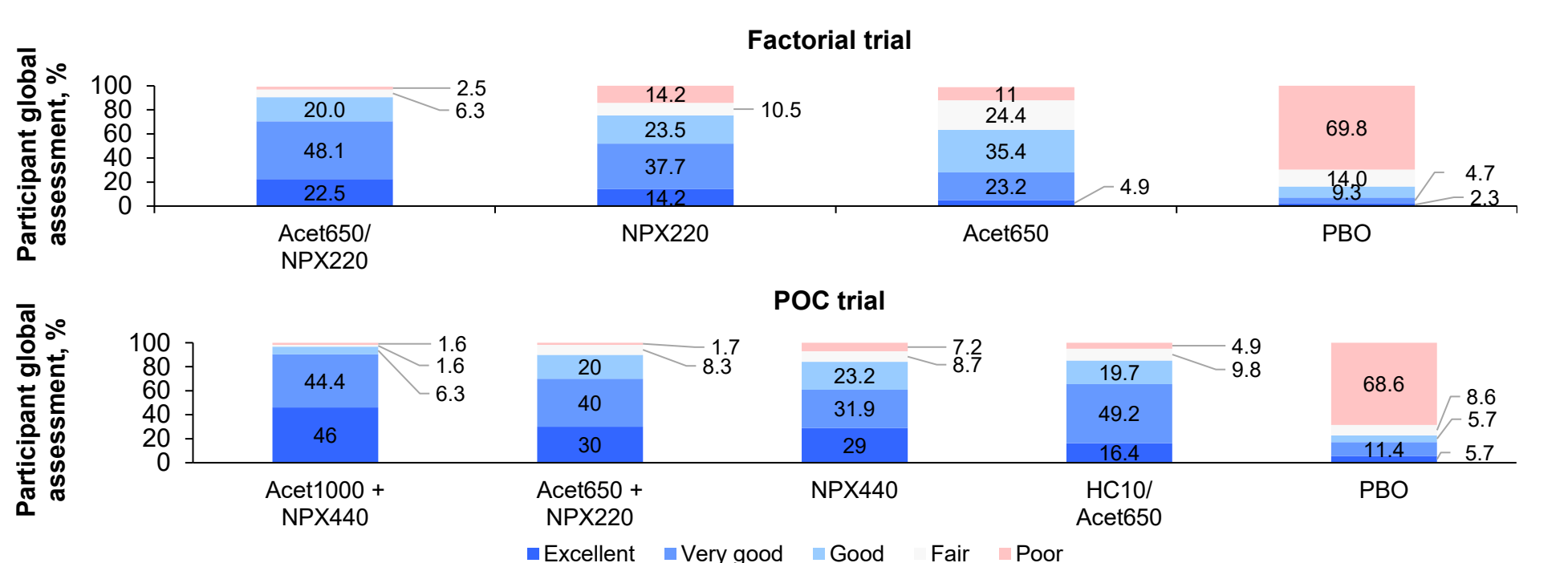
Acet, acetaminophen; HC, hydrocodone; NPX, naproxen sodium; POC, proof of concept; SE, standard error.

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

1. Carrasco-Labra A, et al. *J Am Dent Assoc.* 2024;155(2):102-117.
2. Cooper SA, et al. *Pain.* 2016;157(2):288-301.
3. U.S. Food and Drug Administration. Development of Non-Opioid Analgesics for Acute Pain: Draft Guidance. 2026. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-non-opioid-analgesics-acute-pain>.

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