A Phase 3 Multiple-Dose Efficacy and Safety Trial of a Novel Fixed-Dose Combination of Acetaminophen and Naproxen Sodium in a Postsurgical Bunionectomy Pain Model

Marsha Tharakan, MD, DDS[1]; Steven Sacavage, PharmD[2]; Daniel S. Budnitz, MD, MPH[2]; Anusha Sunkara, PhD[2]; James A. McGuire, MS[2]; Andrew Myers, MD[2]; Leslie Bloom, MS[2]; Neil Singla, MD[3]; Rajesh Mishra, MD, PhD[2]

[1]Independent Consultant, Denver, CO, USA. [2]Kenvue Brands LLC, Summit, NJ, USA; [3]Latigo Biotherapeutics, Pasadena, CA, USA

ASRA PAIN MEDICINE
25th Annual Pain Medicine Meeting
November 5-7, 2026 | Tampa, Florida
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Introduction

- Multiple health professional organizations and federal health agencies recommend non-opioid multimodal analgesia—including use of 2 or more analgesics that work through different mechanisms—for first-line management of acute pain[1-3]
- **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 been shown to provide highly effective analgesia with rapid onset and long duration in a single-dose postoperative dental pain trial[4]
- Postsurgical bunionectomy pain is a well-established pain model that has been used to assess moderate- and high-potency analgesics and support regulatory agency review and approval of many prescription analgesics, including suzetrigine, fast-acting meloxicam, and hydrocodone bitartrate/acetaminophen[2,5-8]

Objective

Phase 3 randomized, double-blind, placebo-controlled, parallel-group, **multidose trial** to evaluate analgesic efficacy and tolerability of FDC Acet650/NPX220 every 12 hours for a total of 48 hours, following Austin bunionectomy surgery (osteotomy and internal fixation)

Methods

Day 0
Adults undergoing bunionectomy surgery
Popliteal nerve block + supplemental analgesia on day of surgery

Day 1
Nerve block discontinued; pain qualification for randomization
Based on moderate/severe pain[a] + Pain Intensity Numeric Rating Scale (PI-NRS) score[b] ≥5

R
1:1

FDC Acet650/NPX220
Q12h × 48h
(Administered as 2 tablets,
Acet325/NPX110)

Placebo
Q12h × 48h

Efficacy and safety assessments
- *Primary endpoint:* Sum of pain intensity difference over 24 hours (SPID 0-24)
- *Secondary endpoints*: **SPID 0-12** and **0-48**, **time to perceptible pain relief**, **time to meaningful pain relief**, **time to first use of rescue medication**, and **proportion of participants using rescue medication 0-12 hours**
- *Key Exploratory endpoints:* pain intensity difference[c] scores at individual timepoints, proportion of participants using rescue medication 0-24 and 0-48 hours, total amount of rescue medication used 0-24 and 0-48 hours (0-12 conducted as post hoc analysis), and participant's global assessment[d] of treatment as a pain reliever at 24 and 48 hours
- *Safety:* Adverse events monitored throughout the trial

Final follow-up for adverse events (days 7-10)

[a]Measured on a 4-point categorical pain rating scale (none, mild, moderate, severe). [b]Measured on an 11-point Pain Intensity Numeric Rating Scale (0 = no pain; 10 = worst pain imaginable). [c]Pain intensity difference–based endpoints used imputation to account for use of rescue medication: last reported pain intensity score before taking rescue or at baseline, whichever was worse, carried forward from time of rescue to subsequent timepoint within the 4-hour therapeutic window of rescue (rescue medication, oxycodone, was available as needed for intolerable pain). [d]5-point scale, poor through excellent.

For participants who discontinued due to lack of efficacy or adverse events, multiple imputation of baseline observation carried forward was used.

FDC Acet650/NPX220, fixed-dose combination of acetaminophen 650 mg and naproxen sodium 220 mg; Q12h, every 12 hours; × 48h, to continue the dosing schedule for a total duration of 48 hours; R, randomization.

Results

- Participant population characteristics and baseline pain were similar between groups (**Table 1**)

Table 1. Key baseline characteristics

	FDC Acet650/NPX220	Placebo
N	72	71
Male, n (%)	12 (16.7)	13 (18.3)
Female, n (%)	60 (83.3)	58 (81.7)
Mean age, years (SD)	44.9 (11.9)	43.6 (11.5)
Baseline pain intensity		
PI-NRS	7.5 (1.5)	7.7 (1.5)
Moderate, n (%)	47 (65.3)	39 (54.9)
Severe, n (%)	25 (34.7)	32 (45.1)

FDC Acet650/NPX220, fixed-dose combination of acetaminophen 650 mg and naproxen sodium 220 mg; PI-NRS, pain intensity-numerical rating scale; SD, standard deviation.

- FDC Acet650/NPX220 provided superior pain control compared with placebo through-48 hours (**Table 2**)
- Distribution patterns of time to confirmed perceptible pain relief (TCPR) and time to meaningful pain relief (TMPR) from 0 to 12 hours for participants in the FDC Acet650/NPX220 and placebo groups were not significantly different (*P*>0.05); Median TCPR and TMPR were not estimable since <50% of participants achieved confirmed perceptible and meaningful pain relief
- Significantly fewer FDC Acet650/NPX220 participants requested rescue medication compared to placebo participants.
- When rescue medication was requested, FDC Acet650/NPX220 participants used rescue medication later and in lower amounts compared to placebo participants (**Table 2**)
- Over the 48-hour period, 4 (5.6%) of the FDC Acet650/NPX220 subjects and 14 (19.7%) of the placebo subjects discontinued the trial for lack of efficacy

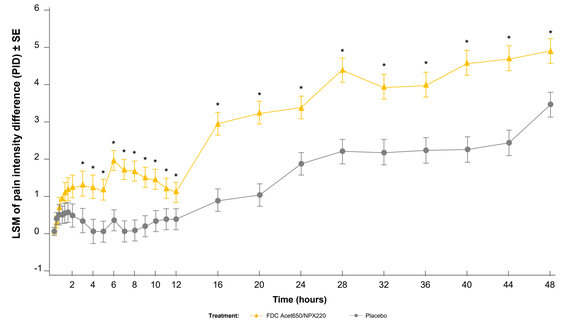
Table 2. Key efficacy endpoints

	FDC Acet650/NPX220	Placebo	*P*-value
SPID 0-12 LSM (SE)[a]	**15.2 (2.4)**	**2.6 (2.5)**	**<0.001[b]**
SPID 0-24 LSM (SE)[a]	**48.4 (5.1)**	**14.2 (5.1)**	**<0.001[b]**
SPID 0-48 LSM (SE)[a]	**151.5 (11.1)**	**68.3 (11.2)**	**<0.001[b]**
Time to first use of rescue, median (minutes) [95% CI][c]	**177.5 [105.0, 252.0]**	**98.0 [79.0, 118.0]**	**0.008[d]**
Proportion Using Rescue, %			
0-12 hours (adjusted)	**80.8 [71.0, 89.0]**	**93.4 [85.8, 97.7]**	**0.026[e]**
0-24 hours (adjusted)	82.5 [72.8, 90.3]	94.5 [87.4, 98.2]	0.026[e]
0-48 hours (adjusted)	82.5 [72.8, 90.3]	94.5 [87.4, 98.2]	0.026[e]
Total Amount of Rescue Used (Oxycodone), mean mg (SD)			
0-12 hours	7.3 (5.0)	10.5 (4.5)	<0.001[f]
0-24 hours	9.8 (7.3)	15.6 (8.2)	<0.001[f]
0-48 hours	12.8 (10.9)	21.3 (14.2)	<0.001[f]
Mean PGA score, 24 hours (SD)	2.0 (1.26)	1.1 (1.06)	<0.001[f]
Mean PGA score, 48 hours (SD)	2.5 (1.09)	1.7 (1.28)	<0.001[f]

Primary endpoints are blue and bolded. Secondary endpoints are bolded.
In order to control for multiplicity, a fixed-sequence testing procedure was used to sequentially test the primary and each secondary endpoint in the following order: 1. SPID 0-24; 2. SPID 0-12; 3. SPID 0-48; 4. TCPR; 5. TMPR; 6. Time to first use of rescue; 7. Proportion of participants who use rescue medication during the first 12 hours. If, at any point in this sequence, FDC Acet650/NPX220 was not statistically significantly better than placebo, then all further testing in the sequence was categorized as exploratory.
[a]Pain intensity differences defined as baseline pain minus postbaseline pain so that higher SPID scores = greater reductions in pain intensity. [b]*P*-value based on ANCOVA model with terms of treatment, center, and baseline numerical pain score in the model using rescue-based imputation methods (ie, the last reported pain intensity score before taking each rescue medication or baseline pain score, whichever was worse, was carried forward from the time of rescue therapy to the subsequent timepoints within the 4-hour therapeutic window of rescue (oxycodone). [c]First use of rescue occurred within initial 12 hours of treatment. [d]*P*-value based on Wilcoxon test stratified by center. [e]*P*-value based on Wald test stratified by center. [f]*P*-value based on Wilcoxon Rank Sum Test.
ANCOVA, analysis of covariance; LSM, least-squares mean; PGA, Participant Global Assessment; SD, standard deviation; SE, standard error; SPID,
time-weighted sum of pain intensity difference; TCPR, time to confirmed perceptible pain relief; TMPR, time to meaningful pain relief.

- FDC Acet650/NPX220 showed greater pain intensity difference (PID) than placebo, with statistically significant differences at each individual timepoint from 3 through 48 hours (**Figure 1**)
- Greater proportions of FDC Acet650/NPX220 participants rated their pain control good, very good, or excellent compared with placebo participants at 24 hours (68.1% vs 34.7%, *P*<0.001) and at 48 hours (82.4% vs 50.0%, *P*<0.001) (**Figure 2**)

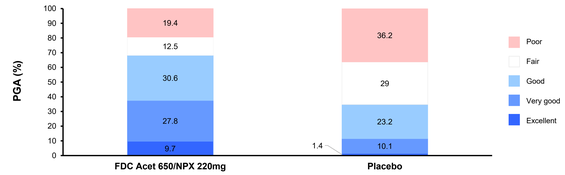
Figure 1. Mean pain intensity difference (PID) from baseline at individual timepoints



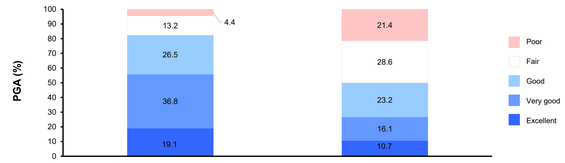
PID defined as baseline pain minus postbaseline pain. Higher scores indicate greater reductions in pain intensity.
*FDC Acet650/NPX220 statistically better than placebo (*P*≤0.05).
FDC Acet650/NPX220, fixed-dose combination acetaminophen 650 mg/naproxen sodium 220 mg; LSM, least-squares mean; SE, standard error.

Figure 2. Participant global assessment (PGA)[a] of efficacy of pain control rating overall impression of trial medication at: a) 0-24 hours and b) 0-48 hours

a) At 0-24 hours



b) At 0-48 hours



[a]Analyzed with a mixed model for repeated measures analysis.
FDC Acet650/NPX220, fixed-dose combination acetaminophen 650 mg/naproxen sodium 220 mg.

Conclusions

- FDC Acet650/NPX220, with low total daily doses of acetaminophen and naproxen sodium, provided effective analgesia throughout 48 hours in a model typically used to test prescription analgesics.
- Participants who received Acet650/NPX220 used 40% less opioid rescue medication over 48 hours compared to placebo participants.
- AEs in both FDC Acet650/NPX220 and placebo participants were similar in nature and severity; a greater proportion of placebo participants reported AEs.

- FDC Acet650/NPX220 was well tolerated, and no serious adverse events (AEs) were reported (**Table 3**)

Table 3. Adverse events reported

	FDC Acet650/NPX220	Placebo
Participants with ≥1 TEAE, n (%)	12 (16.7)	23 (32.4)
TEAEs reported by ≥3% of participants in either treatment group, n (%)		
Nausea	3 (4.2)	5 (7.0)
Constipation	4 (5.6)	3 (4.2)
Vomiting	1 (1.4)	3 (4.2)
Headache	3 (4.2)	9 (12.7)

FDC Acet650/NPX220, fixed-dose combination of acetaminophen 650 mg and naproxen sodium 220 mg; TEAE, treatment-emergent adverse event.

Discussion

- This trial was conducted based on current guidelines and recommended methodologies[2,8,9] and includes robust methods, endpoints, and analyses. Statistical methods allowed the effect of rescue medication to be appropriately accounted for and for appropriate pain intensity scores to be included in the analysis
- While some aspects of methodology can vary across bunionectomy studies, the efficacy and rescue rates for FDC Acet650/NPX220 reported in this trial are comparable to those reported in recent, similarly designed bunionectomy trials
  - The least-squares mean SPID 0-48 difference between FDC Acet650/NPX220 and placebo observed (+83.2) was numerically greater than the difference reported for suzetrigine (+29.3),[5] hydrocodone bitartrate/acetaminophen (MNK-155) (+42.4),[6] celecoxib-tramadol co-crystal (CTC) (+64.6),[9] similar to a fast-acting (FA) meloxicam (MR-107A-02) (+82.7)[10]
  - Reduction in participant use of rescue medication at 48 hours relative to placebo for FDC Acet650/NPX220 (-12.0%) was similar to the reductions for CTC (-12.7%),[9] MNK-155 (-12.0%),[6] and FA meloxicam (-13.8%).[10] There was no reduction in use of rescue medication relative to placebo found for suzetrigine[5]
- Differences in stopwatch-based onset results between the dental pain model and bunionectomy model have been previously reported and suggest the greater level of pain experienced following bunionectomy surgery results in a smaller effect size compared to the dental model[7,11]

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Disclosures and Funding

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation: **M. Tharakan, S. Sacavage, D.S. Budnitz, A. Sunkara, J.A. McGuire, A. Myers, L. Bloom, N. Singla,** and **R. Mishra** are employees of or consultants to Kenvue Brands LLC.

Acknowledgements: We would like to thank 4 Learning Group LLC and Syneos Health for their editorial contributions. This trial was sponsored by Kenvue Brands LLC.