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Perrigo / Omega Pharma Manufacturing GmbH & Co.
KG
Innovation
Dr. Herr Dr. Philipp Eckert
Benzstr. 25
71083 Herrenberg

Ben.-Gruppe: USER-GROUP-2
Tel: +49 7032 922123
Mail: docdel@subito-doc.de
Fax: +49 2241 8499011

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Longer analgesic effect with naproxen sodium than ibuprofen in post-surgical dental pain: a randomized, double-blind, placebo-controlled, single-dose trial

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ORIGINAL ARTICLE

Longer analgesic effect with naproxen sodium than ibuprofen in post-surgical dental pain: a randomized, double-blind, placebo-controlled, single-dose trial

Stephen A. Cooper^a, Paul Desjardins^b, Patrick Brain^c, Alberto Paredes-Diaz^d, Emanuel Troullos^d, Robert Centofanti^e and Bob An^f

^aStephen A. Cooper, DMD, PhD, LLC, Palm Beach Gardens, FL, USA; ^bDesjardins Associates, LLC, Maplewood, NJ, USA; ^cJean Brown Research, Salt Lake City, UT, USA; ^dGlobal Medical Affairs, Bayer Consumer Health, Whippany, NJ, USA; ^eClinical Development, Bayer Consumer Health, Whippany, NJ, USA; ^fBiostatistics, Bayer Consumer Health, Whippany, NJ, USA;

ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line medications in mild-to-moderate acute pain. However, comparative data regarding the duration of analgesia for commonly-used NSAIDs at non-prescription doses is lacking. This study evaluated the time to rescue medication following a single dose of naproxen sodium (NAPSO) vs ibuprofen (IBU) and placebo in subjects with moderate-to-severe post-surgical dental pain.

Methods: This single-center, randomized, double-blind, parallel group, placebo-controlled study included healthy subjects with moderate-to-severe baseline pain (Categorical Pain Intensity Scale) who also rated their pain ≥ 5 on a 0–10 pain intensity Numerical Rating Scale following extraction of two impacted mandibular third molars. A single oral dose of NAPSO (440 mg), IBU (400 mg), or placebo was administered. The primary efficacy endpoint was the time to first rescue medication, while secondary endpoints included the sum of pain intensity difference (SPID) and total pain relief (TOTPAR) over 24 h. ClinicalTrials.gov trial registration number: NCT03404206 (EudraCT 2017-005049-67).

Results: In the per protocol population ($n = 385$; mean age = 19 years), the time to rescue medication was significantly ($p < .001$) longer with NAPSO than IBU and placebo. After treatment, the greatest separation of NAPSO from IBU occurred at 9–14 h and from placebo at 1–6 h. Fewer NAPSO subjects required rescue medication (58/166, 34.9%) compared with IBU (137/165, 83.0%) and placebo (44/54, 81.5%). SPID 0–24 h and TOTPAR 0–24 h were both greater with NAPSO than IBU or placebo.

Conclusions: The duration of pain relief after a single dose of NAPSO was significantly longer than after IBU, and significantly fewer NAPSO-treated subjects required rescue medication over a 24-h period.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line drugs in many guidelines for a variety of acute pain episodes^{1–5}. Naproxen sodium (NAPSO) and ibuprofen (IBU) are among the most commonly used NSAIDs because they lack opioid side-effects, are markedly efficacious, and have a favorable safety profile^{6–10}, complemented by their availability as non-prescription drugs. However, there are few comparative studies regarding their relative analgesic efficacy at optimal non-prescription doses. Fast and effective pain relief is important to patients, and long-lasting relief is advantageous to enhance compliance. An NSAID with a long elimination half-life, such as NAPSO (~ 10 – 15 h¹¹), has a long duration of action¹² and requires only once or twice daily dosing. In contrast, an NSAID with a shorter half-life, such as IBU (half-life ~ 1 – 2 h¹¹), has a relatively shorter duration of action that often requires more frequent dosing over a 24-h period.

The dental impaction pain model is well validated and has been used in hundreds of successful analgesic efficacy

studies¹³. The model has excellent assay sensitivity because surgical removal of impacted third molars can be easily standardized and the target population is generally young and healthy. Most importantly, the post-surgical pain is often sustained, lasting for 24 h or longer. The sensitivity of this pain model allows comparison of several measures of analgesic efficacy, including reliable estimates of onset of analgesia, peak effects, and the duration of analgesic activity of various pharmacologic interventions^{13–15}. Acute pain studies generally assess the duration of analgesia by measuring the time to re-medication¹⁶ with a rescue drug or a second dose of the same study drug.

The difference in pharmacokinetic profiles between NAPSO and IBU suggests that NAPSO should show a longer time to remedication, but direct evidence has been lacking. In two previous single-dose dental pain studies comparing NAPSO to IBU^{17,18}, the duration of analgesia of NAPSO was longer than IBU, but the difference in those studies did not reach statistical significance. However, both were 12-h outpatient studies, which may have been too short of an

CONTACT Alberto Paredes-Diaz ✉ alberto.paredes-diaz@bayer.com Bayer Consumer Health, 100 Bayer Blvd, Whippany, NJ 07981, USA

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evaluation period to fully assess their duration of analgesia. Furthermore, those studies appear to have been under-powered to detect a difference in duration of effective analgesia.

The primary purpose of our study was to use the dental impaction pain model to compare the duration of action of a single oral, non-prescription dose of NAPSO (440 mg) to IBU (400 mg) and placebo over 24 h. Secondary objectives were to compare the overall analgesic effects (Summed Pain Intensity Difference [SPID] and Total Pain Relief [TOTPAR]) over 24 h post-dosing. The study was specifically designed to assess the acute post-surgical dental pain episode in subjects who could benefit from the administration of a non-prescription, non-opioid pain reliever.

Methods

Study design

This was a single-center, randomized, double-blind, placebo-controlled study in healthy subjects experiencing moderate-to-severe post-operative dental pain following the surgical removal of two mandibular impacted third molars, and who also rated their pain intensity ≥ 5 on a 0–10 Numerical Rating Scale (NRS). We evaluated the analgesic efficacy and safety of a single dose of NAPSO (440 mg) or IBU (400 mg) and placebo over 24 h. The trial was conducted between February 12, 2018 and July 10, 2018. The study protocol was approved by IntegReview IRB (Austin, TX). The endpoints and study design were consistent with FDA Guidance and the methods advocated by experts^{13,19}. The study was conducted in accordance with the Declaration of Helsinki and in compliance with all current Good Clinical Practice guidelines. The ClinicalTrials.gov trial registration number is NCT03404206 (EudraCT 2017-005049-67).

Subject population

Subjects who sought elective third molar surgery were solicited to participate. All were healthy, ambulatory, male and non-pregnant female volunteers between 16–40 years of age, with a body mass index between 18.5–30.0 kg/m² inclusive. Individuals with a history of hypersensitivity to any NSAID, history of clinically significant disease or malignancies, current history of gastrointestinal illness, active dental infection, relevant concomitant disease such as asthma (exercise-induced asthma was permitted), positive urine drug screen, or habituation to analgesics were not eligible to participate. All subjects (or parent/guardian for subjects under 18 years old) signed the IRB-approved written informed consent. Subjects under 18 years of age signed an IRB-approved written assent form.

Subjects were scheduled to undergo surgical removal of at least two mandibular third molars that were partially or fully bony impacted under local anesthesia $\pm$ light sedation with nitrous oxide/oxygen. Mandibular molars had to demonstrate modified Demirjian root classification stage D, E, F, G, or H²⁰. In addition, the two maxillary third molars could be removed, regardless of the type of impaction. Any

supernumerary molars could be removed at the discretion of the oral surgeon. Patients fasted from midnight prior to surgery until completion of surgery, and continued fasting (apart from clear liquids) until after study drug administration. Subjects were screened prior to surgery: urine for drug abuse and cotinine, and a breathalyzer for alcohol use.

Subjects who had moderate-to-severe post-operative pain (baseline Categorical Pain Intensity Scale, where 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain) and a pain intensity NRS score (0 = no pain to 10 = worst possible pain) of ≥ 5 within 4.5 h post-surgery (but no later than 14:45 h) continued in the study and were randomized to study treatment. Subjects not meeting these criteria were withdrawn from the study.

Treatments administered

A single dose of one of the three study treatments, as determined by a pre-determined randomization schedule, was administered: oral NAPSO 220 mg $\times$ two tablets (Aleve Caplets, Bayer Healthcare LLC, Whippany, NJ, USA; total dose 440 mg), oral IBU 200 mg $\times$ two tablets (Advil Caplets, Pfizer Consumer Healthcare, Madison, NJ, USA; total dose 400 mg), or placebo $\times$ two tablets, all taken with a 8 oz glass of water. Subjects who did not achieve sufficient pain relief could request rescue medication at any time during the study, although they were encouraged to wait 90 min, if possible, to allow the investigational product to take effect. Rescue medication was acetaminophen 325 mg plus hydrocodone 5 mg, or other appropriate analgesics approved for treating acute pain, according to the discretion of the investigator. Following discharge from the research facility, analgesic medication was up to the discretion of the investigator according to standard practice. No other medication, apart from oral contraceptives, prophylactic antibiotics, multivitamin supplements, or other routine medications to treat benign conditions such as acne, was allowed throughout the study.

Randomization and blinding

A unique subject identifier number was assigned in numerical order stratified by Baseline Pain (moderate or severe) on the categorical pain scale. Stratification was used in this study to ensure that the subject's perceived pain severity (moderate or severe) was balanced across the treatment groups prior to administration of study medication. The two active study treatments and placebo were administered in a 3:3:1 randomization ratio (NAPSO: IBU: placebo) based on a computer-generated randomization schedule.

All subjects, investigators, and staff involved in pain assessment were blinded to the treatments administered, and subjects were blindfolded during drug administration to preserve blinding. The study drug was dispensed by an unblinded study team member based on the randomization schedule; that team member had no other role in the study and did not reveal the identity of the study drug to any members of the blinded study team.

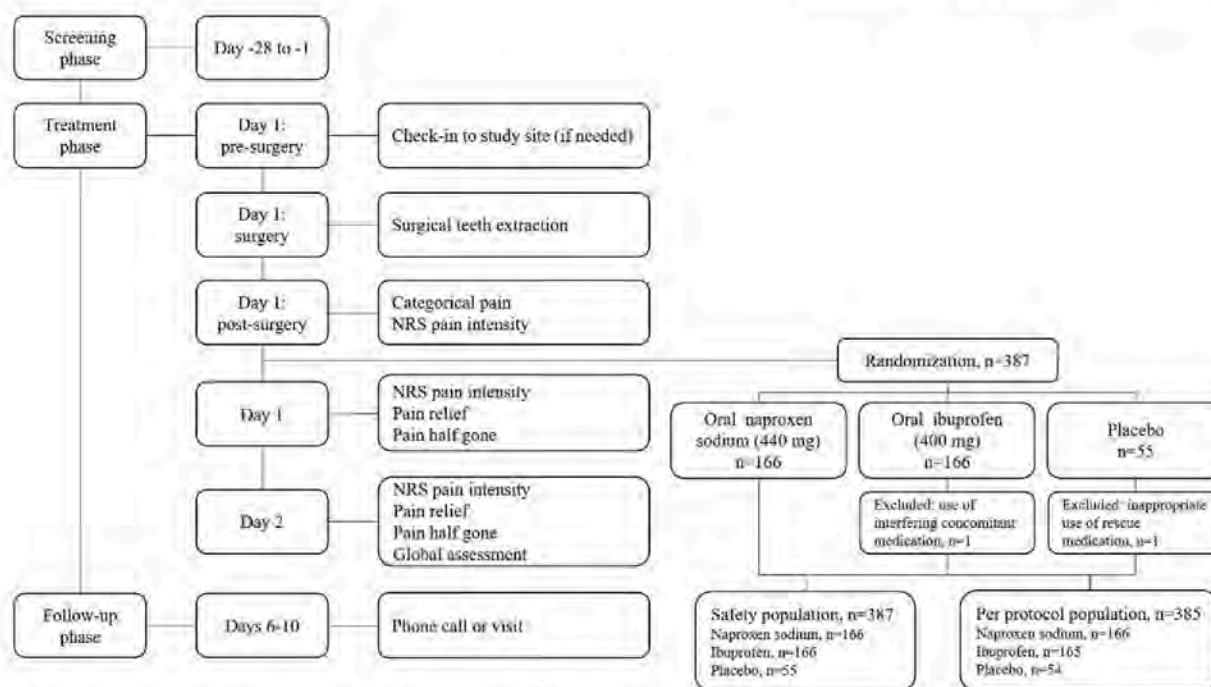


Figure 1. Study design. Pain relief assessed using the Categorical Pain Relief Rating Scale (0 = no relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). Pain intensity and pain relief were measured at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, and 24 h post-dose. Abbreviation. NRS, numerical rating scale (0 = no pain to 10 = worst possible pain).

Clinical assessments

Assessments were performed at scheduled intervals over the 24-h period post-dosing (Figure 1 and Supplementary Table 1). Pain intensity was assessed by subjects using the 0–10 NRS scale, pain relief was evaluated using the Categorical Pain Relief Rating Scale (0 = no relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, and 4 = complete relief). Whether the Baseline Pain was Half Gone was assessed as No (0) or Yes (1), while the Global Assessment of the investigational product as a pain reliever was graded on a 5-point scale (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent) at 24 h or immediately prior to the first dose of rescue medication during the 24-h evaluation period, whichever came first. Safety was assessed by spontaneous reports and observations of adverse events (AEs) using non-leading questions and any notable changes in vital signs.

Efficacy endpoints

For each post-dose time point, a Pain Intensity Difference (PID) was derived by subtracting the pain intensity at the post-dose time point from the Baseline Pain Score (NRS Baseline Score – NRS post-Baseline Score); a positive difference was indicative of improvement. Time-weighted SPIDs were calculated by multiplying the PID score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values over the desired time interval. Similarly, the Total Pain Relief Scores (TOTPARs) were calculated by multiplying the Pain Relief Score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values.

The primary efficacy endpoint was the time to first use of rescue medication. Secondary endpoints were the overall analgesic effects (SPID 0–24) and overall relief from starting pain (TOTPAR 0–24). Other endpoints included SPID and TOTPAR over hours 0–4, 0–8, 0–12, and 6–12, Peak Pain Intensity and Peak Pain Relief, Sum of Observations with Pain Half Gone, the duration of pain relief at least half gone, the proportion of subjects reporting their pain as half gone or better at each time point, and the total amount of time that a subject reported at least a 2-point PID improvement.

Statistical analysis

Assuming that 22.2% of NAPSO subjects and 35.8% of IBU subjects would not need the rescue medication by 12 h following the study drug administration, as observed in a prior study¹⁸, a total of 364 subjects (156 subjects per active treatment arm and 52 in the placebo using a 3:3:1 ratio) were required to achieve 80% of power with a type I error of 0.05. Thus, at least 385 subjects were to be randomized into the study assuming a drop-out rate of 5%.

All analyses were performed using SAS Version 9.3¹ or higher unless otherwise stated. Except where noted, all statistical tests were two-sided and performed at the 0.05 level of significance. No adjustments for multiplicity were made. Descriptive statistics were used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category were presented. For continuous parameters, descriptive statistics included *N* (number of subjects [sample size]), *n* (number of observations), mean, standard deviation (SD), median, minimum, and maximum. The primary efficacy

analysis was performed on the per protocol (PP) population (all subjects who provided at least one pain assessment after the first dose of the investigational product, who did not have any major protocol violations and were analyzed according to the treatment they actually received) and corroborated using data from the intent-to-treat (ITT) population. The PP data are presented here, as the populations for PP ($n = 385$) and ITT ($n = 387$) were virtually identical. The safety analysis was conducted on all subjects who were randomized and took the one dose of investigational product.

Primary efficacy analysis

Time (h) to first use of rescue medication during the treatment period was the primary efficacy endpoint. If a subject did not take the rescue medication during the treatment period, the subject was considered censored at the time of last assessment (24 h post-dose). Time to first use of rescue medication was estimated and plotted using Kaplan-Meier method and analyzed using a log-rank test stratified by baseline pain intensity. Kaplan-Meier 25th, 50th, and 75th percentiles, as well as minimum and maximum times observed, were determined. Log-rank tests were used to compare NAPSO to IBU, and NAPSO to placebo.

Secondary and other efficacy analyses

SPID 0–24 and TOTPAR 0–24, as well as SPID and TOTPAR at 0–4, 0–8, 0–12, and 6–12 h, were analyzed using an analysis of covariance model (ANCOVA), with treatment as fixed effect and baseline pain intensity score as the covariate. The least squares mean (LSMean) $\pm$ SD and 95% confidence intervals (CIs) for the treatment differences (NAPSO-placebo; NAPSO-IBU; and IBU-placebo) were also calculated. The cumulative proportion of subjects taking rescue medication by each time point was summarized and compared using Chi-square tests. The global assessment score was compared using the Chi-square test with modified ridit score.

Adverse events

All AEs were recorded and classified on the basis of MedDRA terminology. Treatment-emergent AEs (TEAEs) were defined as AEs with an onset on or after the date of the first study drug administration. AEs noted prior to the first study drug administration that worsened after baseline were also reported.

Missing data

The last observation carried forward (LOCF) method was used to extrapolate efficacy data that were missing beyond the last observation. Missing scheduled pain and relief scores prior to the last observation were imputed using the weighted average of adjacent evaluations. Missing AE start dates were imputed using partial date imputation rules. In all analyses, all pain intensity scores after intake of rescue medication were replaced by the baseline pain score or the score assessed immediately before taking rescue medication,

whichever was worse. All pain relief scores after intake of rescue medication were replaced by “no relief” (0).

Results

Subject population

A total of 387 subjects were randomized to treatment, 166 subjects each to NAPSO or IBU and 55 subjects to placebo (Figure 1). Four (2.4%) subjects withdrew from the NAPSO group and two (1.2%) from the IBU group (lost to follow-up or withdrawal by the subject). The PP population included 385 patients, as two subjects were excluded: one from the placebo group (use of rescue medication at or prior to 60 min after ingesting study medication) and one from the IBU group (use of interfering concomitant medication). The safety population included all 387 randomized subjects.

Demographic characteristics were comparable across the treatment groups, although there was a slightly larger proportion of males in the NAPSO group (Table 1). Overall, the mean age was 19.0 (range = 16–35) years and the mean number of teeth extracted was 3.8; all subjects had extractions of the left and right mandibular third molars and a slightly lower percentage (86.7–89.8%) had extraction of the left and right maxillary third molars. The mean (range) dental surgery duration from first incision to last suture was 13.3 (3–54) min. The mean categorical pain intensity score at baseline was 2.6; severe pain was reported in 59.0% (228/387) of subjects and moderate pain in 41.0% (159/387) of subjects. The mean NRS score at baseline was 7.5 in all three groups.

Primary endpoint

Analysis of the primary efficacy endpoint, time to first use of rescue medication in the PP population, demonstrated a statistically significant and clinically relevant superiority of NAPSO over IBU and placebo ($p < .001$) (Table 2 and Figure 2). Fewer than 50% of subjects in the NAPSO group needed rescue medication during the 24-h follow-up period; in contrast, the time taken before 50% of subjects had used rescue medication (i.e., the 50th percentile) was 10.5 h in the IBU group and 2.5 h in the placebo group (Table 2). The NAPSO group displayed a clear and significant separation from the IBU group from ~9 h after treatment ($p < .05$) through to the end of the 24-h period (Figure 2). The proportion of patients who did not use rescue medication and were censored at the time of last assessment (Table 2) was significantly higher in the NAPSO group (108/166, 65.1%) compared with placebo (10/54, 18.5%) and IBU (28/165, 17.0%) ($p < .001$, respectively). At ~6 h after treatment, the proportion of subjects taking rescue medication rose noticeably in the IBU group, but only slightly in the NAPSO group (Figure 2). The same results were observed for the ITT population.

Secondary endpoints

The reduction in pain intensity over 24 h (SPID0-24) was significantly greater with NAPSO (LSMean 83.30) than with

Table 1. Subject demographics and characteristics (per protocol population).

	Placebo (n = 54)	Ibuprofen (400 mg) (n = 165)	Naproxen sodium (440 mg) (n = 166)	Overall (n = 385)
Age (years), mean $\pm$ SD (range)	19.0 $\pm$ 2.93 (16–27)	19.0 $\pm$ 2.61 (16–35)	19.0 $\pm$ 2.96 (16–32)	19.0 $\pm$ 2.80 (16–35)
Sex, n (%)				
Male	25 (46.3)	77 (46.7)	89 (53.6)	191 (49.6)
Female	29 (53.7)	88 (53.3)	77 (46.4)	194 (50.4)
Weight (kg), mean $\pm$ SD (range)	67.2 $\pm$ 10.51 (43.5–92.5)	68.1 $\pm$ 10.61 (46.3–95.9)	68.0 $\pm$ 11.61 (45.4–112.9)	67.9 $\pm$ 11.01 (43.5–112.9)
Body mass index (kg/m ²), mean $\pm$ SD (range)	23.5 $\pm$ 2.94 (18.7–29.7)	23.8 $\pm$ 2.77 (18.5–29.9)	23.6 $\pm$ 2.91 (18.5–29.9)	23.7 $\pm$ 2.85 (18.5–29.9)
Ethnicity, n (%)				
Hispanic or Latino	9 (16.7)	25 (15.2)	23 (13.9)	57 (14.8)
Not Hispanic or Latino	45 (83.3)	140 (84.8)	143 (86.1)	328 (85.2)
Race				
White	47 (87.0)	147 (89.1)	148 (89.2)	342 (88.8)
Black or African American	1 (1.9)	4 (2.4)	2 (1.2)	7 (1.8)
American Indian or Alaska Native	2 (3.7)	4 (2.4)	3 (1.8)	9 (2.3)
Asian	1 (1.9)	2 (1.2)	1 (0.6)	4 (1.0)
Native Hawaiian or other Pacific Islander	1 (1.9)	3 (1.8)	1 (0.6)	5 (1.3)
Other	2 (3.7)	5 (3.0)	11 (6.6)	18 (4.7)
Number of teeth extracted, mean $\pm$ SD (range)	3.8 $\pm$ 0.60 (2–4)	3.8 $\pm$ 0.64 (2–6) ^a	3.8 $\pm$ 0.54 (2–4)	3.8 $\pm$ 0.59 (2–6)
Duration of surgery (min), mean $\pm$ SD (range)	13.9 $\pm$ 7.34 (5–35)	13.6 $\pm$ 6.48 (3–50)	12.8 $\pm$ 7.27 (4–54)	13.3 $\pm$ 6.95 (3–54)
Baseline pain intensity score, n (%)				
Moderate pain (2)	23 (42.6)	66 (40.0)	69 (41.6)	158 (41.0)
Severe pain (3)	31 (57.4)	99 (60.0)	97 (58.4)	227 (59.0)
Mean $\pm$ SD (range)	2.6 $\pm$ 0.50 (2–3)	2.6 $\pm$ 0.49 (2–3)	2.6 $\pm$ 0.49 (2–3)	2.6 $\pm$ 0.49 (2–3)
Baseline NRS score, mean $\pm$ SD (range)	7.5 $\pm$ 1.27 (5–10)	7.5 $\pm$ 1.10 (5–10)	7.5 $\pm$ 1.04 (5–10)	—

^aOne subject had four third molars and two supernumerary teeth extracted.

Abbreviations. NRS, numerical rating scale; SD, standard deviation.

Table 2. Primary efficacy endpoint: Kaplan-Meier estimates for time to rescue medication (per protocol population).

	Placebo (n = 54)	Ibuprofen (n = 165)	Naproxen sodium (n = 166)
Number of subjects who took rescue medication, n (%)	44 (81.5)	137 (83.0)	58 (34.9)
Number of subjects censored (i.e. no rescue medication was required during the study), n (%)	10 (18.5)	28 (17.0)	108 (65.1)
Time to achieving event (h)			
Minimum ^a	1.18	1.22	1.22
25th percentile ^b	2.12	8.27	11.02
50th percentile ^b	2.53	10.53	NE
75th percentile ^b	12.10	14.12	NE
Maximum ^a	21.75	18.28	22.17
p-value ^c	<.001	<.001	

^aObserved time to event;

^bEstimated using Kaplan-Meier methods;

^cp-values are from log-rank tests stratified by baseline pain intensity comparing the treatment to naproxen sodium.

Note: Percentages are based on the number of subjects in the per protocol population for each treatment group.

Abbreviation. NE, not estimable.

either IBU (48.57) or placebo (9.87) ($p < .05$, respectively; Table 3). Total Pain Relief over 24 h (TOTPAR0-24) was also significantly greater with NAPSO (LSMean 47.16) vs IBU (28.95) or placebo (13.44) ($p < .05$, respectively; Table 3). The treatment differences compared with placebo for SPID0-24 and TOTPAR0-24 were approximately twice as large with NAPSO (–73.43 and –33.72, respectively) compared with IBU (–34.73 and –18.21, respectively).

Other efficacy variables

The time-weighted summaries of the SPID and TOTPAR scores were significantly greater ($p < 0.05$, respectively, based on the 95% CI) with NAPSO than IBU over the intervals 0–12 and 6–12 h (Table 3). Comparable time-weighted summaries

of the SPID and TOTPAR scores were observed over the intervals 0–4 and 0–8 h.

Individual PID and Pain Relief scores by time point (Figure 3) revealed a rapid onset of analgesic effect that was similar between the two active treatments until ~7 h. Beginning at ~6 h, the analgesic effect started to decline in the IBU group and was essentially comparable with placebo by 14 h. In contrast, the analgesic effect of the NAPSO group was maintained throughout the 24-h period (Figure 3). The mean Peak PID and Pain Relief scores (LS means $\pm$ SD) were similar between NAPSO (5.6 $\pm$ 1.93 and 3.0 $\pm$ 0.90, respectively) and IBU (5.7 $\pm$ 1.93 and 3.1 $\pm$ 0.90), and were more than twice as high as those obtained with placebo (2.0 $\pm$ 1.93 and 1.2 $\pm$ 0.90). However, the median total time of subjects reporting at least a 2-point improvement for PID was

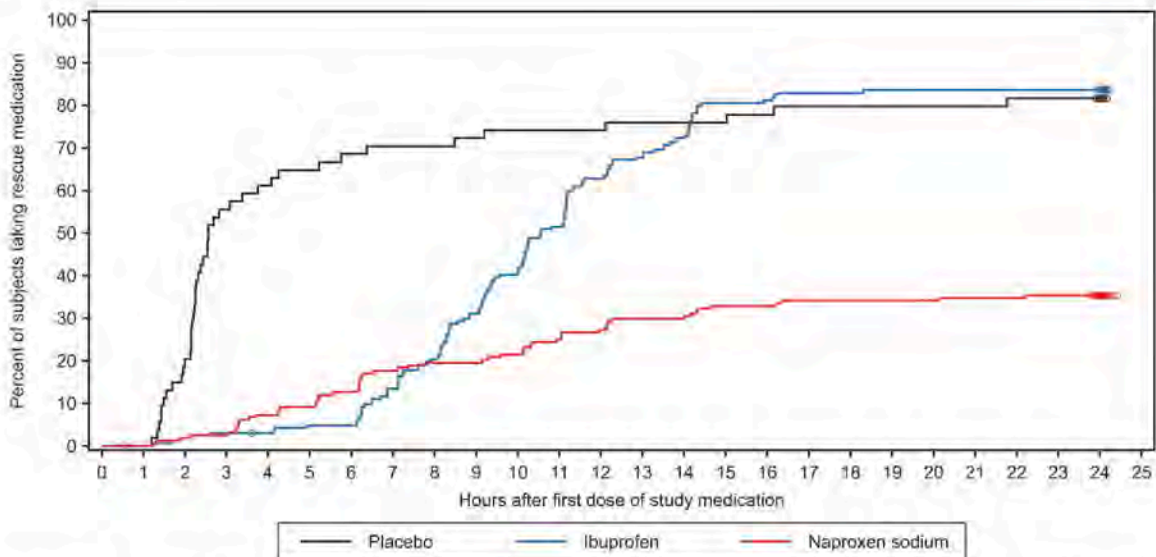


Figure 2. Primary efficacy endpoint: Kaplan-Meier estimates for time to rescue medication (per protocol population). Treatments administered were either oral naproxen sodium (220 mg $\times$ two tablets, total dose 440 mg; $n = 166$), oral ibuprofen (200 mg $\times$ two tablets, total dose 400 mg; $n = 165$), or placebo ($n = 54$).

Table 3. Secondary efficacy endpoints: SPIDs and TOTPAR scores at 24 h (per protocol population).

	Placebo ($n = 54$)	Ibuprofen ($n = 165$)	Naproxen sodium ($n = 166$)
Secondary endpoints			
SPID 0–24			
LS Mean $\pm$ SD	9.87 $\pm$ 50.58	48.57 $\pm$ 50.58 [^]	83.30 $\pm$ 50.58*
TOTPAR 0–24			
LS Mean $\pm$ SD	13.44 $\pm$ 24.59	28.95 $\pm$ 24.59 [^]	47.16 $\pm$ 24.59*
Other endpoints			
SPID (LS Mean $\pm$ SD)			
SPID 0–4	2.03 $\pm$ 7.06	17.12 $\pm$ 7.06 [^]	16.31 $\pm$ 7.06 [^]
SPID 0–8	4.01 $\pm$ 15.46	32.86 $\pm$ 15.46 [^]	32.39 $\pm$ 15.46 [^]
SPID 0–12	5.57 $\pm$ 24.18	40.24 $\pm$ 24.18 [^]	46.08 $\pm$ 24.18*
SPID 6–12	2.42 $\pm$ 14.82	14.10 $\pm$ 14.82 [^]	21.31 $\pm$ 14.82*
TOTPAR (LS Mean $\pm$ SD)			
TOTPAR 0–4	2.48 $\pm$ 3.24	9.58 $\pm$ 3.24 [^]	9.10 $\pm$ 3.24 [^]
TOTPAR 0–8	5.02 $\pm$ 7.18	18.40 $\pm$ 7.18 [^]	18.08 $\pm$ 7.18 [^]
TOTPAR 0–12	7.23 $\pm$ 11.49	23.03 $\pm$ 11.49 [^]	25.91 $\pm$ 11.49*
TOTPAR 6–12	3.40 $\pm$ 7.33	8.44 $\pm$ 7.33 [^]	12.11 $\pm$ 7.33*
Peak PID (LS Mean $\pm$ SD)	2.0 (1.93)	5.7 (1.93) [^]	5.6 (1.93) [^]
Peak Pain Relief (LS Mean $\pm$ SD)	1.2 (0.90)	3.1 (0.90) [^]	3.0 (0.90) [^]
Pain Half Gone			
At least once in 24 h (%)	33.3	94.5 [^]	89.2 [^]
Duration (hours) (LS Mean $\pm$ SD)	4.06 (7.68)	8.68 (7.68) [^]	14.05 (7.68)*
At Least a 2-Point PID			
Total time (hours) (LS Mean $\pm$ SD)	5.02 (7.53)	10.79 (7.53) [^]	16.65 (7.53)*
Global Assessment (Mean $\pm$ SD)	0.8 (1.15)	2.7 (0.94) [#]	2.7 (1.05) [#]

LS Means are from an analysis of covariance with treatment as fixed effect and baseline pain intensity score as the covariate.

*Statistically significant at $p < .05$ compared to both ibuprofen and placebo.

[^]Statistically significant at $p < .05$ compared to placebo.

[#]Statistically significant at $p < .001$ compared to placebo based on a Chi-square test using the modified ridit score option.

Abbreviations. CI, confidence interval; LS, least squares; SD, standard deviation; SPID, sum of pain intensity differences; TOTPAR, total pain relief.

substantially longer for NAPSO (22.79 h than IBU (9.07 h) or placebo (0.00 h).

Overall, the proportion of subjects reporting that their Baseline Pain was Half Gone at least once by 24 h post-dose was comparable for NAPSO (148/166, 89.2%) and IBU (156/165, 94.5%), both being much higher than for placebo (18/54, 33.3%), whereas the median total time of subjects reporting that their Baseline Pain was Half Gone was longer for NAPSO (17.64 h) than IBU (6.98 h) or placebo (0.00 h) ($p < 0.05$). The proportion of subjects reporting that their

Baseline Pain was Half Gone at each observation over the 24-h period was similar for approximately the first 6 h post-dose in the NAPSO (e.g., 34/166, 20.5% at 0.5 h; 120/166, 72.3% at 6 h) and IBU groups (51/165, 30.9% at 0.5 h; 115/165, 69.7% at 6 h), and both were greater than in the placebo group (1/54, 1.9% at 0.5 h; 11/54, 20.4% at 6 h) (Figure 4). After 6 h, the proportion of subjects reporting that their Baseline Pain was Half Gone substantially decreased in the IBU group (range = 13.3–61.8%, 22/165–102/165), and was comparable with placebo from 14 h (14.5% vs 18.5%,

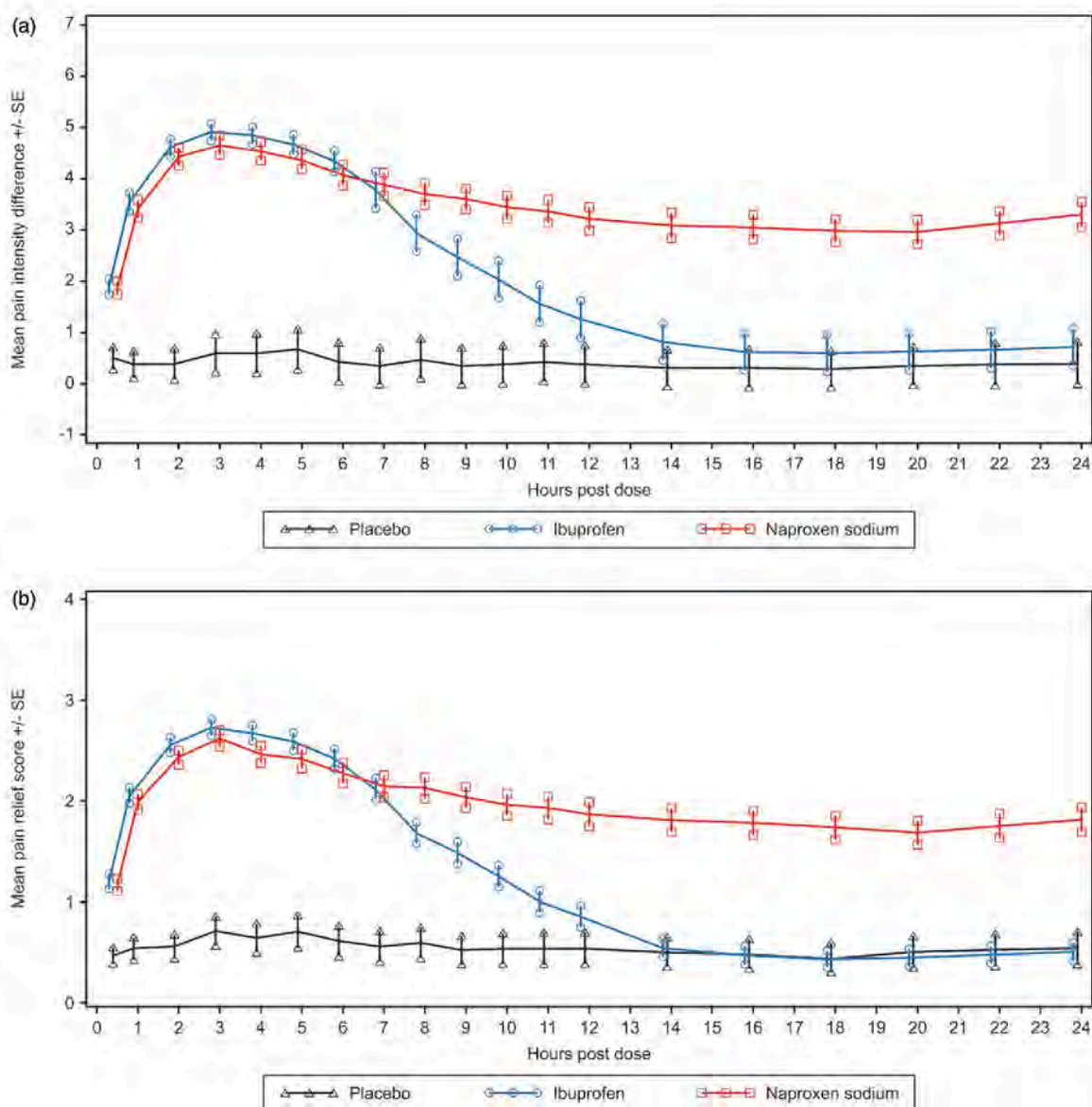


Figure 3. Mean pain intensity differences (a) and mean pain relief scores (b) over 24 h (per protocol population). Pain intensity differences (based on the Numerical Rating Scale, 0 = no pain to 10 = worst possible pain) were calculated as baseline score – post-baseline score. Total Pain Relief was assessed using the Categorical Pain Relief Rating Scale (0 = no relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, and 4 = complete relief). Treatments administered were either oral naproxen sodium (220 mg $\times$ two tablets, total dose 440 mg; n = 166), oral ibuprofen (200 mg $\times$ two tablets, total dose 400 mg; n = 165), or placebo (n = 54).

24/165 vs 10/54, respectively) onwards, while only a small decrease was observed for NAPSO (range = 51.2–66.9%; 85/166–111/166) from 7–24 h post-dose (Figure 4).

A smaller proportion of subjects from the NAPSO (range = 1.8–19.3%; 3/166–32/166) and IBU (range = 1.8–20.0%, 3/165–33/165) groups required rescue medication from 2–8 h post-dose compared with the placebo group (range = 20.4–70.4%; 11/54–38/54) (Figure 5). However, the cumulative proportion of subjects taking rescue medication rose noticeably from 6 h in the IBU group. From 9 h through 24 h, the hourly cumulative percentages were lower in the NAPSO group (range = 19.3–34.9%, 32/166–58/166) compared to the IBU group (range = 30.3–83.0%, 50/165–137/165) (Figure 5).

The percentage of subjects who rated their treatment as a good, very good, or excellent pain reliever was similar in the

NAPSO (144/163; 88.3%) and IBU (147/165; 89.1%) groups, both higher than in the placebo group (14/53; 26.4%; most rated placebo as poor or fair). It should be noted that the timing of these global evaluations differed between subjects, as they were performed before taking the first dose of rescue medication.

Safety

All three treatments were well tolerated, and the proportion of TEAEs in the active treatment groups was comparable. The proportion of subjects who reported at least one TEAE was lowest in the NAPSO group (26/166, 15.7%), followed by the IBU (31/166, 18.7%) and placebo (16/55, 29.1%) groups; no TEAE was considered related to the study drug (Supplementary Table 2). The most frequently-reported

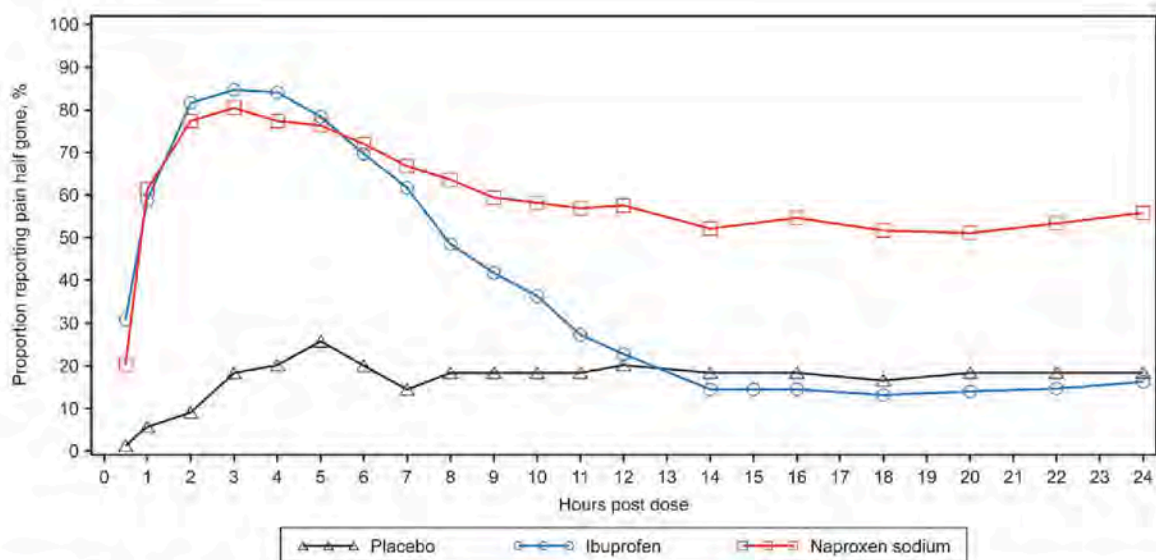


Figure 4. Proportion of subjects reporting pain half gone over 24 h (per protocol population). Response at each time point includes only subjects who have not taken a rescue medication at or prior to that time point. Treatments administered were either oral naproxen sodium (220 mg $\times$ two tablets, total dose 440 mg; $n = 166$), oral ibuprofen (200 mg $\times$ two tablets, total dose 400 mg; $n = 165$), or placebo ($n = 54$).

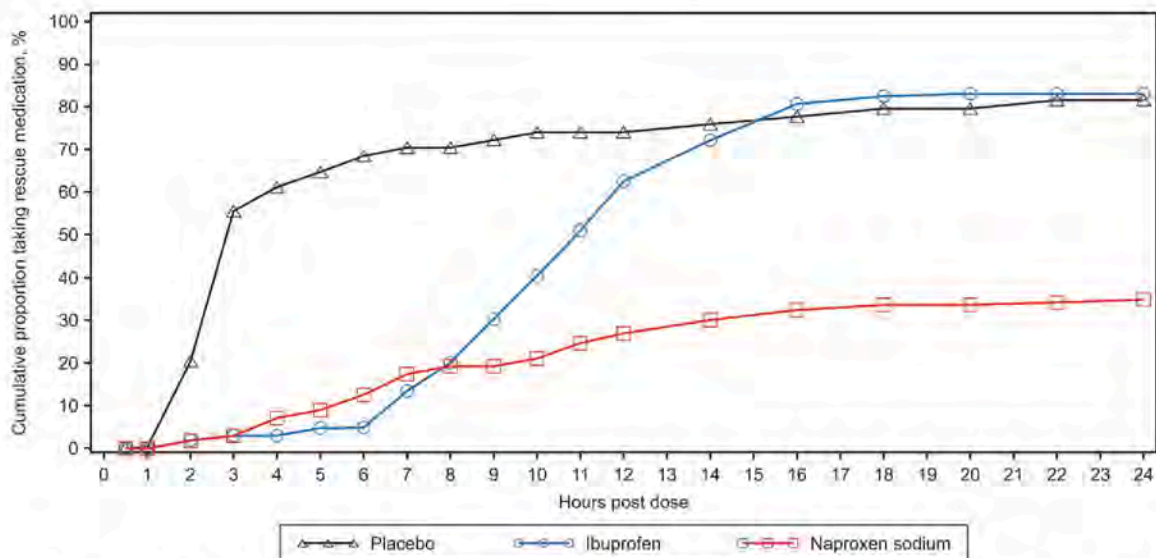


Figure 5. Cumulative proportion of subjects taking rescue medication over 24 h (per protocol population). Treatments administered were either oral naproxen sodium (220 mg $\times$ two tablets, total dose 440 mg; $n = 166$), oral ibuprofen (200 mg $\times$ two tablets, total dose 400 mg; $n = 165$), or placebo ($n = 54$).

TEAEs were nausea, vomiting, and headache; these were most often reported after treatment with placebo (20.0%, 12.7%, and 12.7% (11/55, 7/55, and 7/55), respectively) and less often after treatment with NAPSO (5.4%, 0.6%, and 1.8% (9/166, 1/166, and 3/166), respectively) and IBU (10.2%, 4.2%, and 3.6% (17/166, 7/166, and 6/166) (Supplementary Table 3). In the NAPSO group, the only TEAE with a rate $>2\%$ above placebo was alveolar osteitis (2.4% vs 0%, 4/166 vs 0/166, respectively), which was not considered to be related to the study drug; there were no such TEAEs in the IBU group. One subject in the NAPSO group experienced a serious AE (severe appendicitis), which was not related to treatment or to protocol-required procedures. There were no deaths during the study, and no withdrawals were attributable to AEs.

Discussion

Our randomized, double-blind, placebo-controlled trial in subjects experiencing moderate-to-severe dental impaction surgery pain has demonstrated the superiority of a maximum single, non-prescription dose of NAPSO over IBU and placebo for both overall efficacy and a significantly longer time to rescue medication ($p < .001$), with a clear difference between NAPSO and IBU after 9 h. The apparent onset and peak effect of NAPSO was equivalent to IBU, but NAPSO maintained a significantly longer duration of analgesia throughout the 24-h study period in a majority of subjects. This is consistent with the human pharmacokinetics of both drugs. In contrast, the mean pain intensity differences and mean pain relief scores in the IBU group began to decline after 6 h until both

variables were comparable to placebo at ~14 h and thereafter. Accordingly, the proportion of subjects who had sustained pain relief and did not require rescue medication during the 24-h study period was almost 4-times higher in the NAPSO group compared with the IBU and placebo groups (65.1% vs 17% and 18.5%, respectively). Two other efficacy variables from this study support the conclusion that naproxen's analgesic effect is substantially longer in duration than IBU. NAPSO-treated subjects experienced a longer period during which they reported their baseline pain "Half Gone". In addition, the NRS pain intensity differences showed "at least a 2-point improvement" for a substantially longer period in the NAPSO subjects compared to subjects treated with IBU or placebo. These outcome variables represent clinically meaningful degrees of pain reduction for extended periods with NAPSO compared to the other treatments.

These study results represent clinically meaningful benefits to patients and point to the value of having a long-acting, highly effective, and safe analgesic to treat acute pain medications. Our results are important for two reasons. First, because there is currently little head-to-head evidence regarding the duration of analgesic effect of commonly-used NSAIDs. Previous direct comparison of NAPSO and IBU in post-operative dental pain could only show a slightly longer duration of action with NAPSO that did not reach statistical significance^{17,18}. Both were single-dose, randomized, parallel, single-center studies. One study¹⁷ compared naproxen sodium 220 mg, ibuprofen 200 mg, and placebo in subjects who had at least moderate pain after surgical removal of three or four third molars. The other study¹⁸ compared naproxen sodium 440 mg, ibuprofen 400 mg, and placebo in subjects who had at least moderate pain after surgical removal of one or two bony impacted third molars. However, both of these earlier studies had shorter (12 h) observation periods, and after 2 h the evaluations were performed by subjects at home using at-home paper diaries, which could have limited the ability to assess relative differences in later hours, e.g. subjects falling asleep. The design of our in-patient study is different in that subjects were under close observation by trained nursing staff throughout a 24-h period, including an overnight period where patients were awakened prior to each scheduled pain assessment. Second, our study has clearly demonstrated the substantial effectiveness of NSAIDs in treating an acute pain condition that is too often treated unnecessarily with opioid analgesics. Supporting our results, evidence from systematic reviews shows that NSAIDs offer a better balance of delivering powerful pain relief while minimizing acute adverse events compared to oral opioid analgesics²¹. Indeed, the American Dental Association recommends that dentists should consider NSAIDs as the first-line therapy for acute pain management².

The study has some limitations. Our study was focused on the duration of effect of a single dose of medication for treating an acute episode of post-extraction dental pain. While the study is extremely useful for examining duration of effect, it is not intended to assess efficacy or tolerability after multiple doses of medication. Also, the adverse event assessment reported on the occurrence of events following administration of study medication regardless of rescue medication use. These rescue medications (hydrocodone/acetaminophen and

tramadol) have their own associated side effects. The frequencies reported in our trial reflect the overall adverse event experience resulting from both the assigned study medication and any rescue medication provided to the subjects. Further, all pain intensity scores after intake of rescue medication were replaced by the baseline pain score or the score assessed immediately before taking rescue medication, whichever was worse, which could have affected the SPID results. Finally, this single-dose study was conducted at a specialized research center in a young healthy population, which may not completely generalize to a broader consumer population.

The improved methods used in our study have enabled us to establish that a single, non-prescription dose of NAPSO can provide significantly greater and longer-lasting pain relief over a 24-h period compared with IBU. The reduced need for rescue medication with NAPSO should enhance patient compliance and convenience. Safety assessments did not raise any unexpected findings, and there was no significant difference in the safety profile of non-prescription doses of NAPSO and IBU compared with placebo, confirming previous findings that over-the-counter NAPSO has a good safety profile^{22,23}.

Conclusions

Evaluation of a single dose of two commonly-used NSAIDs over a 24-h period indicates that analgesic effectiveness lasts significantly longer with NAPSO 440 mg than with IBU 400 mg in post-surgical dental pain. Although the NSAIDs had similar analgesic efficacy over the first 6–7 h and a similar peak level of analgesia, pain relief was sustained for a longer time with NAPSO than IBU, and substantially fewer NAPSO patients required any rescue medication. Both NAPSO 440 mg and IBU 400 mg were safe and well tolerated.

Note

1. SAS Institute Inc., Cary, NC, USA.

Transparency section

Declaration of funding

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Author contributions

All authors were involved in the research plan, analysis and interpretation of the data, drafting of the manuscript and revising it critically for intellectual content, and final approval of the version to be published. All authors are accountable for all aspects of the work.

Declarations of financial/other relationships

Alberto Paredes-Diaz, Emanuel Troullos, Robert Centofanti, and Bob An are employees of Bayer Consumer Health, Stephen A. Cooper and Paul Desjardins are consultants to Bayer Healthcare, and Patrick Brain is employed by JBR Clinical Research. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work but have no other relevant financial relationships to disclose.

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