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Onset of Analgesia and Efficacy of Ibuprofen Sodium in Postsurgical Dental Pain

A Randomized, Placebo-controlled Study Versus Standard Ibuprofen

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Objectives: A novel, immediate-release tablet formulation of ibuprofen (IBU) sodium dihydrate, Advil Film Coated Tablets (IBU_{Na}), has been developed that is absorbed faster than standard IBU tablets. The objective of the current study was to compare the efficacy and onset of analgesia of this new formulation with standard IBU tablets after a single dose.

Materials and Methods: Patients (N = 316) with at least moderate baseline postsurgical dental pain were randomized to 400 mg IBU_{Na}, Advil (IBU_{Adv}), Motrin (IBU_{Mot}), or placebo. Primary endpoints were time-weighted sum of pain relief (PR) and pain intensity differences over 8 hours (SPRID 0-8) and time to onset of meaningful pain relief (TMPR) measured by the double-stopwatch method.

Results: SPRID 0-8 was significantly greater for IBU_{Na} and the other active treatments versus placebo ($P < 0.001$). IBU_{Na} had a significantly earlier TMPR versus placebo, pooled IBU_{Adv}/IBU_{Mot}, and IBU_{Mot} ($P < 0.001$ for all), and a marginally faster TMPR ($P = 0.075$) versus IBU_{Adv}. Results for secondary endpoints were similar. Adverse events were comparable across treatment groups, with gastrointestinal disorders being most frequently reported. Most adverse events were mild or moderate.

Discussion: This novel formulation of IBU_{Na} provided superior overall PR compared with placebo and more rapid onset of analgesic effect compared with standard IBU tablets. Rapid PR is important in the treatment of acute pain, including dental pain, and this IBU_{Na} formulation represents a new treatment option for rapid PR.

Key Words: ibuprofen sodium dihydrate, fast-absorbed ibuprofen, dental pain, analgesia, over-the-counter

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Ibuprofen (IBU), a peripherally acting nonsteroidal anti-inflammatory drug (NSAID), is one of the most widely used nonprescription analgesic/antipyretic agents available. The labeling of current over-the-counter (OTC) IBU products directs adults and children 12 years and older to take 1 to 2 tablets (i.e. 200 to 400 mg) every 4 to 6 hours while symptoms (e.g. pain, fever) persist[1,2]; the maximum daily dose should not exceed 6 tablets (1200 mg) in 24 hours, unless directed by a doctor.

The analgesic efficacy of OTC doses of IBU has been extensively evaluated in multiple clinical trials. Studies have shown that a single 400 mg dose of the standard formulation of IBU free acid provides superior analgesic efficacy compared with acetaminophen (1000 mg) in several different clinical pain models (i.e. third molar extraction, sore throat, postpartum episiotomy pain, tension-type headache, and delayed-onset muscle soreness).[3–7] These studies also demonstrated that IBU is safe and well tolerated.

Rapid onset of action is a desirable attribute of OTC analgesics. Serum concentrations of IBU are highly correlated with the level of analgesia[8]; therefore, the more rapidly IBU is absorbed to achieve therapeutic concentrations, the earlier the onset of analgesia will occur. Considerable effort has been expended to develop faster-absorbed, and therefore faster-acting, formulations of IBU, including the development of soft gelatin capsules containing solubilized IBU (Advil® Liqui-Gels; Pfizer Consumer Healthcare, Madison, NJ) as well as salt forms of IBU (e.g. arginine, lysine, sodium). Solubilized forms of IBU have demonstrated a faster rate of absorption (reflected by a higher maximum plasma concentration [C_{max}] and a shorter time to reach maximum plasma concentration [T_{max}]) than standard IBU tablets.[9] Clinical trials have shown that a single 400 mg dose of solubilized IBU provides a faster onset of analgesia and superior overall analgesic effect compared with acetaminophen (1000 mg) in postsurgical dental pain, tension-type headache, and migraine.[10–13] In addition, studies evaluating a single 400 mg dose of IBU arginine in a model of postsurgical dental pain have demonstrated that this IBU salt formulation has a more rapid onset of action compared with standard IBU tablets.[14,15] These studies have also demonstrated a similar safety profile for faster-absorbed IBU formulations when compared with standard IBU.[10–15]

Recently, a novel formulation of IBU sodium dihydrate (Advil® Film Coated Tablets; $IBU_{Na;}$ 256 mg; equivalent to 200 mg of IBU free acid; Pfizer Consumer Healthcare) has been developed as an immediate-release

tablet. Pharmacokinetic studies have shown that this novel IBU_{Na} tablet is absorbed faster than standard IBU tablets and as fast as solubilized IBU and IBU lysine.[16] The objective of the current study was to compare the overall efficacy of a single dose of the novel IBU_{Na} tablet formulation with 2 standard IBU tablet formulations and placebo in the third molar extraction model of dental pain. It was hypothesized that IBU_{Na} would be more efficacious than placebo and would provide a faster onset of analgesia compared with standard IBU tablets.

MATERIALS AND METHODS

Patients

Otherwise healthy patients 16 to 40 years of age who underwent third molar extraction (2 or more extractions, with at least 1 molar required to be partially or fully impacted) were eligible for inclusion. Female patients could not be pregnant (as verified by a pregnancy test) or breastfeeding; a reliable method of contraception was required in females of childbearing age. Patients with significant systemic illness were excluded; the use of antipsychotics, monoamine oxidase inhibitors, and bisphosphonates was exclusionary. Medications contraindicated for use in conjunction with NSAIDs, recent analgesic or NSAID use (within 5 half-lives of the respective agent), and caffeine were not allowed. Patients reported to the study center on the morning of their surgery in a fasted state (i.e., they should not have ingested food or drink after midnight of the preceding evening).

Study Design and Treatments

This was a randomized, double-blind, 8-hour, inpatient, single-dose, placebo-controlled, parallel-group study (NCT01098747) conducted at a single center in the United States (Jean Brown Research, Salt Lake City, UT). Acceptable preoperative medications/anesthetics included topical benzocaine, short-acting parenteral mepivacaine or lidocaine (with or without a vasoconstrictor), and/or nitrous oxide. At the time of surgery, patients with findings of acute localized dental alveolar infection were excluded. Within $\sim$5 hours after surgery, patients with postoperative pain of at least moderate severity (score of ≥ 2 on a 4-point Categorical Pain Severity Rating Scale [0 = none, 1 = mild, 2 = moderate, 3 = severe]) confirmed by a pain score of at least 50 mm on a 100 mm Visual Analog Pain Severity Rating Scale (VAS-PSR) were randomized in a 2:2:2:1 ratio to receive a single oral dose of Advil Film Coated Tablets (IBU_{Na}; 2×256 mg equivalent to 400 mg IBU), Advil tablets (IBU_{Adv}; 2×200 mg equivalent to 400 mg IBU; Pfizer Consumer Healthcare), Motrin tablets (IBU_{Mot}; 2×200 mg equivalent to 400 mg IBU; McNeil Consumer Healthcare, Fort Washington, PA), or placebo with 8 ounces of water. Treatment assignment was determined by a computer-generated randomization schedule generated and maintained by Pfizer Consumer Healthcare, in which patients were stratified by sex and baseline categorical pain severity score (moderate or severe). Study medications did not all identically match; however, to maintain the double-blind design of the study, an independent third party dispensed the study drug to patients who were blindfolded at the time of study drug administration. Rescue medication (5 mg hydrocodone/500 mg acetaminophen) was offered to patients who did not experience adequate pain relief (PR) within 1 hour of dosing with study medication. The study was approved by the Sterling Institutional Review Board and was conducted in accordance with International Conference on Harmonization Good Clinical Practice standards and the guiding principles of the Declaration of Helsinki (as amended in Tokyo, Venice, and Hong Kong). All patients provided written consent before initiation of any study procedures.

Assessments

Efficacy Assessments and Parameters

Following the initial baseline assessments for inclusion, pain severity and PR were assessed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours postdose and/or immediately before rescue medication use, if needed, using the 4-point Categorical Pain Severity Rating Scale and the 5-point Categorical Pain Relief Rating Scale (0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete), respectively. In addition, 2 stopwatches were used to indicate onset of analgesia. The first stopwatch was stopped upon the experience of "first perceptible" relief (FPR); the second stopwatch was stopped when PR was considered "meaningful." At the end of the 8-hour evaluation period, or immediately before taking rescue medication (if needed), patients provided a global evaluation of study medication using a 6-point categorical scale (0 = very poor, 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

Primary efficacy endpoints were the time-weighted sum of PR scores and pain intensity difference (PID) scores from 0 to 8 hours postdose (SPRID 0-8) for IBU_{Na} versus placebo and the time to onset of "meaningful" PR (TMPR). Secondary efficacy endpoints included time to FPR (TFPR), confirmed by TMPR. In addition, at each time point postdose (i.e. 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h), the following parameters were assessed: PR, PID, and the sum of their scores (PRID); cumulative proportion of patients achieving "meaningful," "first perceptible," and "complete" PR; and the cumulative proportion of treatment failures. Furthermore, over 2, 3, 6, and 8 hours postdosing, respective time-weighted sums of PR scores (TOTPAR 0-2, TOTPAR 0-3, TOTPAR 0-6, and TOTPAR 0-8), PID scores (SPID 0-2, SPID 0-3, SPID 0-6, and SPID 0-8), and PRID scores (SPRID 0-2, SPRID 0-3, SPRID 0-6, and SPRID 0-8) were assessed. For time-weighted SPRID 0-8, IBU_{Na} versus standard IBU comparisons were made. The duration of PR was measured by time to treatment failure (i.e. time to rescue medication use or withdrawal due to lack of efficacy). A global evaluation of study medication was also assessed.

Safety Assessments

Vital signs were recorded at baseline and at study completion or upon rescue medication use. Patients were observed for adverse events (AEs) and serious AEs. No laboratory studies were performed.

Statistical Analysis

A sample size of 90 patients in each active treatment group and 45 in the placebo group was estimated to provide at least 80% power (at the 5% significance level, 2-sided) to detect a difference of 7.5 in SPRID 0-8 between each active treatment and placebo, and to detect a hazard ratio of 1.6 for TMPR between IBU_{Na} and the standard IBU tablets. These differences were based on assumptions including a root mean square of error of 14.4 for SPRID 0-8 and that 14.7% of patients in each active group would

not achieve MPR by the end of the study; both assumptions were based on data obtained in a prior study.

Primary comparisons were based on the intent-to-treat population. The summary scores of SPID, TOTPAR, and SPRID from 0 to 2, 0 to 3, 0 to 6, and 0 to 8 hours, as well as PR, PID, and PRID scores at each postdosing time point, were analyzed by analysis of variance with terms for treatment, sex, and baseline pain severity in the model. The 95% confidence intervals for each pairwise treatment difference were computed using least squares means and SE for each pairwise difference. Confirmed TFPR, TMPR, and time to treatment failure were analyzed using the proportional hazards regression model (a type of survival analysis), with terms for treatment, sex, and baseline pain severity in the model. The 95% confidence intervals for each pairwise treatment difference were computed using log hazard ratios and its SE. The global evaluation of study medication was analyzed using modified ridit scores via Cochran Mantel Haenszel row mean score test, controlling for sex and baseline pain severity.

To protect against a type I error due to multiple comparisons and assessments, 2-sided treatment group comparisons at the 5% significance level were conducted sequentially. The first comparison was SPRID 0-8 for IBU_{Na} versus placebo; if that comparison proved significant, the following assessments were made in order: TMPR for IBU_{Na} versus placebo, followed by TMPR for IBU_{Na} versus pooled IBU_{Adv}/IBU_{Mot}. If the latter comparison was significant, then IBU_{Na} versus IBU_{Adv} and IBU_{Na} versus IBU_{Mot} were eligible for declarations of significance. Secondary efficacy parameters were tested in a manner similar to TMPR as described above. In addition to these a priori statistical analyses, a post hoc analysis evaluated time to event data using the Gehan-Wilcoxon test, which assigns higher weights to earlier events, in contrast to proportional hazards regression, which assigns equal weight to all events.

RESULTS

Demographics

Of 407 patients screened, 316 underwent oral surgery, were eligible for enrollment, and were randomized as follows: IBU_{Na} (n = 95), IBU_{Adv} (n = 86), IBU_{Mot} (n = 87), and placebo (n = 48). All patients completed the study per protocol, and there were no study discontinuations. Treatment groups were comparable with respect to baseline demographics (Table 1). Approximately equal numbers of male and female patients were enrolled (49.1% and 50.9%, respectively), the majority were white (95.3%), and the average age was 18.5 years. The mean duration of surgery was 9.4 minutes (range, 3.0 to 26.0 min) and 50.9% of patients had 4 teeth extracted. According to dental surgeon ratings, 304 (96.2%) patients experienced moderate trauma after surgery. The mean baseline pain intensity for all intent-to-treat patients on the VAS-PSR was 78.2 mm (range, 51 to 100 mm). Baseline pain severity was reported as moderate in 51.9% of patients and severe in 48.1% of patients.

Efficacy

Primary Efficacy

The mean SPRID 0-8 score was significantly greater for IBU_{Na} and the other active treatment groups compared with placebo ($P < 0.001$). The mean SPRID 0-8 scores were 29.8, 31.8, 31.6, and 5.4 for the IBU_{Na}, IBU_{Adv}, IBU_{Mot}, and placebo groups, respectively. The IBU_{Na} group reported TMPR significantly earlier (median, 42.4 min) than the placebo (median, >8 h), pooled IBU_{Adv}/IBU_{Mot} (median, 55.3 min), and IBU_{Mot} (median, 60.7 min) groups ($P < 0.001$ for all); there was a trend toward faster TMPR with IBU_{Na} compared with the IBU_{Adv} group (median, 52.0 min; $P = 0.075$; Fig. 1). On the basis of a post hoc analysis using the Gehan-Wilcoxon test, TMPR for IBU_{Na} was significantly faster than with IBU_{Adv} ($P = 0.023$). This post hoc analysis also confirmed that IBU_{Na} was superior to the pooled IBU_{Adv}/IBU_{Mot} and IBU_{Mot} groups with regard to TMPR.

Secondary Efficacy

By the end of study (8 h postdose), 95.8%, 88.4%, 94.2%, 82.8%, and 22.9% of patients had achieved meaningful PR and 54.7%, 64.2%, 69.8%, 58.6%, and 6.3% had achieved complete relief in the IBU_{Na}, pooled IBU_{Adv}/IBU_{Mot}, IBU_{Adv}, IBU_{Mot}, and placebo groups, respectively. Consistent with the results for meaningful PR, patients in the IBU_{Na} group had a significantly earlier onset of confirmed FPR (median, 16.4 min) compared with the placebo (median, >8 h), pooled IBU_{Adv}/IBU_{Mot} (median, 25.7 min), IBU_{Adv} (median, 25.1 min), and IBU_{Mot} (median, 25.8 min) groups ($P < 0.001$ for all).

For PRID scores over time, IBU_{Na} was significantly better than placebo at all time points ($P = 0.002$ at 15 min; $P < 0.001$ at all other time points; Fig. 2). IBU_{Na} was also significantly better than pooled IBU_{Adv}/IBU_{Mot} and IBU_{Mot} from 15 through 90 minutes (vs. IBU_{Adv}/IBU_{Mot}: $P < 0.01$ at 15, 30, and 60 min, $P = 0.017$ at 90 min; vs. IBU_{Mot}: $P = 0.019$ at 15 min, $P < 0.01$ at 30, 60, and 90 min). In comparison with IBU_{Adv}, IBU_{Na} had significantly better PRID scores in the first hour postdose ($P < 0.01$ at 15 and 30 min, $P < 0.05$ at 60 min). PRID scores were significantly better in the pooled IBU_{Adv}/IBU_{Mot} groups at hours 6 through 8 and at hour 6 for the IBU_{Mot} group in comparison with IBU_{Na} ($P < 0.05$ for all comparisons).

Time-weighted scores at 2 hours (SPRID 0-2, SPID 0-2, and TOTPAR 0-2) were significantly better for IBU_{Na} than for placebo ($P < 0.001$), pooled IBU_{Adv}/IBU_{Mot} ($P < 0.01$), and IBU_{Mot} ($P < 0.01$; Fig. 3). In addition, IBU_{Na} was significantly better than IBU_{Adv} for SPID 0-2 ($P < 0.05$). For the remaining time-weighted sum parameters (SPRID, SPID, and TOTPAR over 3, 6, and 8 h), IBU_{Na} was significantly better than placebo ($P < 0.001$) and comparable with the pooled and individual standard IBU groups (Fig. 3).

By study end, 26.3%, 20.2%, 23.3%, 17.2%, and 79.2% of patients in the IBU_{Na}, pooled IBU_{Adv}/IBU_{Mot}, IBU_{Adv}, IBU_{Mot}, and placebo groups, respectively, required rescue medication and were considered treatment failures. The time to treatment failure was significantly longer for IBU_{Na} and the other active treatment groups ($P < 0.001$) compared with placebo, with median times of >8 hours for each active treatment group and 1.7 hours for placebo. The time to treatment failure was not significantly different between IBU_{Na} and the pooled or individual standard IBU groups.

The global evaluation of study medication score was significantly higher for IBU_{Na} than for placebo ($P < 0.001$) and comparable with the pooled and individual standard IBU groups (Fig. 4). The percentage of patients reporting

TABLE 1. Baseline Demographics, Characteristics, and Surgery-related Parameters

	IBU_{Na} (n = 95)	IBU_{Adv} (n = 86)	IBU_{Mot} (n = 87)	Placebo (n = 48)	Total (N = 316)
Sex (n [%])					
Male	47 (49.5)	42 (48.8)	43 (49.4)	23 (47.9)	155 (49.1)
Female	48 (50.5)	44 (51.2)	44 (50.6)	25 (52.1)	161 (50.9)
Race (n [%])					
White	90 (94.7)	82 (95.3)	83 (95.4)	46 (95.8)	301 (95.3)
Black	0	0	1 (1.1)	0	1 (0.3)
Asian	0	1 (1.2)	0	1 (2.1)	2 (0.6)
Other	5 (5.3)	3 (3.5)	3 (3.4)	1 (2.1)	12 (3.8)
Age (y)					
Mean (SD)	18.6 (2.1)	18.6 (2.3)	18.4 (2.0)	18.1 (1.6)	18.5 (2.1)
Median (range)	18.0 (15-27)	18.0 (16-26)	18.0 (16-26)	18.0 (16-24)	18.0 (15-27)
Duration of procedure (min)					
Mean (SD)	9.6 (4.1)	9.5 (3.9)	9.4 (3.8)	8.9 (4.4)	9.4 (4.0)
Median (range)	9.0 (3.0-23.0)	9.0 (3.0-24.0)	10.0 (3.0-26.0)	8.0 (3.0-24.0)	9.0 (3.0-26.0)
No. teeth extracted (n [%])					
2	38 (40.0)	33 (38.4)	29 (33.3)	20 (41.7)	120 (38.0)
3	12 (12.6)	9 (10.5)	12 (13.8)	2 (4.2)	35 (11.1)
4	45 (47.4)	44 (51.2)	46 (52.9)	26 (54.2)	161 (50.9)
Baseline pain intensity (VAS) (mm)					
Mean (SD)	77.5 (11.9)	78.9 (12.2)	79.1 (12.9)	76.9 (12.5)	78.2 (12.3)
Median (range)	77.0 (54-100)	78.0 (54-100)	78.0 (51-100)	76.0 (57-100)	78.0 (51-100)
Baseline pain severity category (n [%])					
Moderate	51 (53.7)	43 (50.0)	43 (49.4)	27 (56.3)	164 (51.9)
Severe	44 (46.3)	43 (50.0)	44 (50.6)	21 (43.8)	152 (48.1)

IBU_{Adv} indicates Advil; IBU_{Mot}, Motrin; IBU_{Na}, ibuprofen sodium; VAS, Visual Analog Scale.

good, very good, or excellent global scores within each treatment was 90.6%, 86.2%, 89.5%, 82.7%, and 18.7% for the IBU_{Na}, pooled IBU_{Adv}/IBU_{Mot}, IBU_{Adv}, IBU_{Mot}, and placebo groups, respectively.

Safety

Overall, 68 AEs were reported by 40 patients during the study: 10 (10.5%), 12 (14.0%), 10 (11.5%), and 8 (16.7%) in the IBU_{Na}, IBU_{Adv}, IBU_{Mot}, and placebo groups, respectively (Table 2). The incidence of AEs was similar across treatment groups. Nausea and vomiting were the most frequently reported AEs. All AEs were determined by the investigator to be unrelated to study drug except 1 event of moderate nausea in a patient in the placebo group. All AEs were mild or moderate except 4 severe events in the IBU_{Adv} group that were considered unrelated to study drug (chest discomfort, dyspnea, nausea, and vomiting; n = 1 each). No deaths, serious AEs, clinically meaningful vital sign changes, or other clinically important AEs occurred during the study. No patient discontinued because of an AE.

DISCUSSION

Considerable research into the development of faster-absorbed IBU formulations has been conducted for a

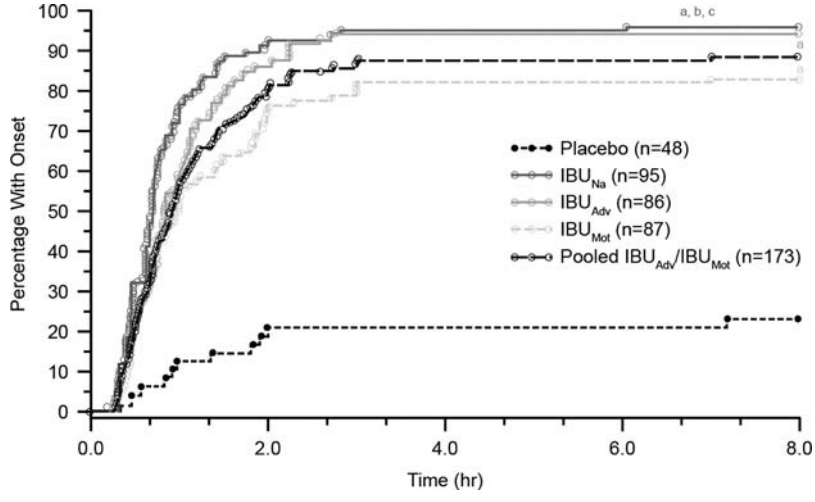

FIGURE 1. Time to meaningful pain relief. Per protocol, the comparisons of pooled IBU_{Adv}/IBU_{Mot} versus placebo and IBU_{Adv} versus IBU_{Mot} were not performed. [a]$P \leq 0.001$ versus placebo. [b]$P \leq 0.001$ versus pooled IBU_{Adv}/IBU_{Mot}. [c]$P \leq 0.001$ versus IBU_{Mot}. IBU_{Adv} indicates Advil; IBU_{Mot}, Motrin; IBU_{Na}, Advil Film Coated Tablets.

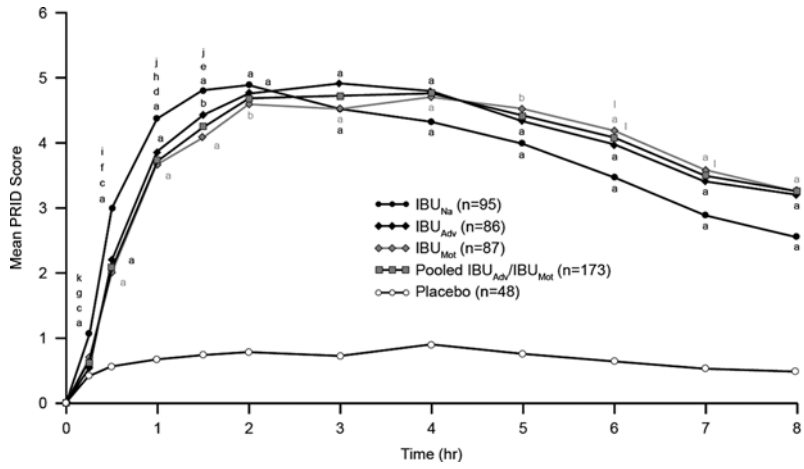

FIGURE 2. Pain relief rating combined with pain intensity difference (PRID) scores over time. Per protocol, the comparisons of pooled IBU_{Adv}/IBU_{Mot} versus placebo and IBU_{Adv} versus IBU_{Mot} were not performed. [a]$P \leq 0.001$ versus placebo. [b]$P \leq 0.01$ versus placebo. [c]$P \leq 0.001$ versus pooled IBU_{Adv}/IBU_{Mot}. [d]$P \leq 0.01$ versus pooled IBU_{Adv}/IBU_{Mot}. [e]$P \leq 0.05$ versus pooled IBU_{Adv}/IBU_{Mot}. [f]$P \leq 0.001$ versus IBU_{Adv}. [g]$P \leq 0.01$ versus IBU_{Adv}. [h]$P \leq 0.05$ versus IBU_{Adv}. [i]$P \leq 0.001$ versus IBU_{Mot}. [j]$P \leq 0.01$ versus IBU_{Mot}. [k]$P \leq 0.05$ versus IBU_{Mot}. [l]$P \leq 0.05$ versus IBU_{Na}. IBU_{Adv} indicates Advil; IBU_{Mot}, Motrin; IBU_{Na}, Advil Film Coated Tablets; PRID, sum of pain intensity difference and pain relief rating.

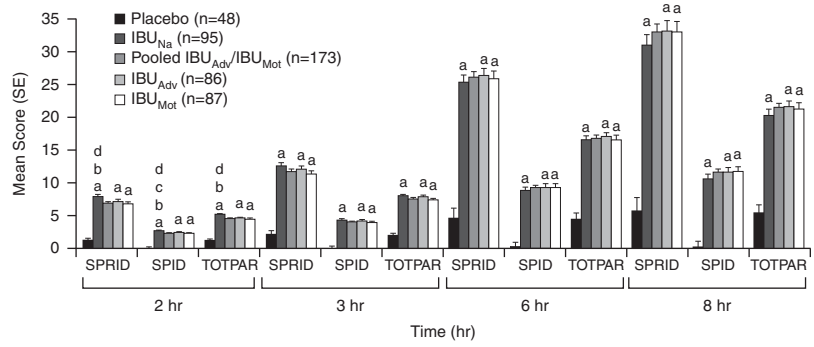

FIGURE 3. Two-, 3-, 6-, and 8-hour summary efficacy measures. Per protocol, the comparisons of pooled IBU_{Adv}/IBU_{Mot} versus placebo and IBU_{Adv} versus IBU_{Mot} were not performed. [a]$P \leq 0.001$ versus placebo. [b]$P \leq 0.01$ versus pooled IBU_{Adv}/IBU_{Mot}. [c]$P \leq 0.05$ versus IBU_{Adv}. [d]$P \leq 0.01$ versus IBU_{Mot}. IBU_{Adv} indicates Advil; IBU_{Mot}, Motrin; IBU_{Na}, Advil Film Coated Tablets: ibuprofen sodium; SPID, time-weighted sum of pain intensity difference; SPRID, time-weighted sum of pain relief and pain intensity difference; TOTPAR, time-weighted sum of pain relief.

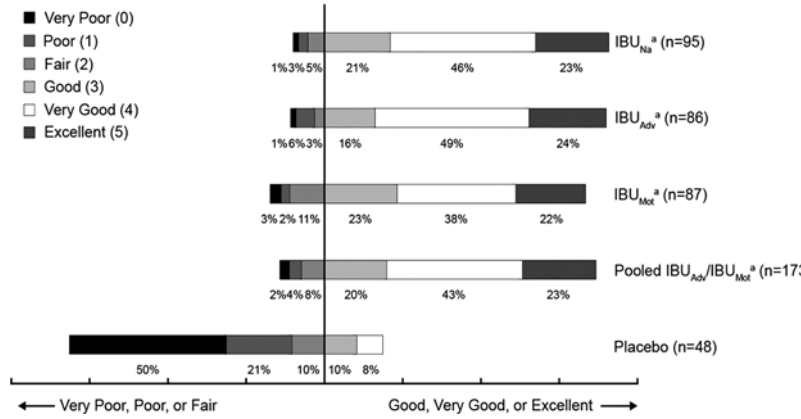

FIGURE 4. Global evaluation of study treatment. [a]$P \leq 0.001$ versus placebo. IBU_{Adv} indicates Advil; IBU_{Mot}, Motrin; IBU_{Na}, Advil Film Coated Tablets: ibuprofen sodium.

TABLE 2. Treatment-Emergent Adverse Events With an Incidence Rate of ≥2%

	Patients (n [%])			
TEAE	**IBU_{Na} (n = 95)**	**IBU_{Adv} (n = 86)**	**IBU_{Mot} (n = 87)**	**Placebo (n = 48)**
Nausea	7 (7.4)	6 (7.0)	3 (3.4)	5 (10.4)
Vomiting	2 (2.1)	3 (3.5)	2 (2.3)	2 (4.2)
Headache	1 (1.1)	4 (4.7)	3 (3.4)	1 (2.1)
Dizziness	1 (1.1)	3 (3.5)	3 (3.4)	1 (2.1)
Feeling hot	1 (1.1)	0	2 (2.3)	2 (4.2)
Ear pain	0	0	0	1 (2.1)
Lymphadenopathy	0	0	0	1 (2.1)
Hypotension	0	0	2 (2.3)	0
Pain in extremity	0	0	0	1 (2.1)

IBU_{Adv} indicates Advil; IBU_{Mot}, Motrin; IBU_{Na}, ibuprofen sodium; TEAE, treatment-emergent adverse event.

potentially more rapid onset of action, which is desirable in an OTC analgesic. Subsequently, a novel, immediate-release tablet formulation containing 256 mg of IBU_{Na} (equivalent to 200 mg of IBU free acid) was identified. In this study, IBU_{Na} was statistically superior to placebo for all analgesic efficacy parameters evaluated. In addition, IBU_{Na} was superior to pooled IBU_{Adv}/IBU_{Mot} and to IBU_{Mot} for the onset of analgesic effect. Furthermore, IBU_{Na} was comparable with both IBU_{Adv} and IBU_{Mot} for duration of action and in the global evaluation of PR. Treatment with IBU_{Na} was well tolerated, and AEs were mostly mild in severity and similar across treatment groups.

Median TMPR for IBU_{Na} was approximately 13 minutes faster than for pooled IBU_{Adv}/IBU_{Mot} (42.4 vs. 55.3 min; $P < 0.001$). IBU_{Na} was also significantly faster (by almost 20 min) than IBU_{Mot} (42.4 vs. 60.7 min; $P < 0.001$) and trended faster (by 10 min) than IBU_{Adv} (42.4 vs. 52.0 min; $P = 0.075$). A post hoc analysis that assigned more value to earlier events found the difference between IBU_{Na} and IBU_{Adv} to be statistically significant ($P = 0.023$). The faster onset of action seen with the novel IBU_{Na} formulation described herein is likely due to the faster dissolution of the salt formulation and more rapid availability of IBU for absorption.

This study was conducted in relatively young patients (average age, 18.5 y). However, it is expected that these results would be generalizable to older populations, as a previous study demonstrated that the pharmacokinetics of IBU are only minimally influenced by age.[17]

Although greater efficacy was observed at later time points with standard IBU formulations compared with IBU_{Na} as measured by PRID, IBU_{Na} provided greater analgesic benefit at earlier time points. It should be noted, however, that the duration of analgesia for the standard and sodium dihydrate formulations of IBU were similar as measured by time to rescue medication use, which was >8 hours for all active treatments.

The efficacy and safety results obtained from this trial evaluating a newly developed IBU sodium salt formulation are similar to those from other trials evaluating other IBU_{Na} formulations in postsurgical dental pain.[18,19] In a trial evaluating IBU_{Na} (256 mg sodium salt; n = 198) and 200 mg standard IBU (n = 198) in patients with moderate to severe pain following third molar extraction, median time to substantial PR was 14 minutes faster in the IBU_{Na} group ($P < 0.001$).[19] In addition, the reduction in pain intensity was noted 10 minutes faster in the IBU_{Na} group than in the standard IBU group (5 vs. 15 min, respectively; $P < 0.01$). In a trial evaluating a higher IBU_{Na} dose (equivalent to 400 mg standard IBU; N = 144) in the third molar extraction dental pain model, TFPR was faster in the IBU_{Na} group compared with the standard IBU group (24.6 vs. 30.5 min; $P = 0.004$).[18] Taken together, these trials suggest that IBU_{Na} provides more rapid clinically meaningful PR compared with standard IBU.

In conclusion, the current study demonstrated that a novel IBU_{Na} tablet provided superior overall PR compared with placebo and a more rapid onset of analgesic effect compared with standard IBU tablets. This novel formulation of IBU_{Na} represents a new treatment option for rapid relief of acute pain.

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