Efficacy and Safety of an Intravenous Acetaminophen/Ibuprofen Fixed-dose Combination After Bunionectomy: a Randomized, Double-blind, Factorial, Placebo-controlled Trial

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ABSTRACT

Purpose: Multimodal analgesia with acetaminophen and/or nonsteroidal anti-inflammatory drugs is recommended for the treatment of postoperative pain. Although oral fixed-dose combinations (FDCs) are available, parenteral administration may be clinically justified. The goal of this study was to investigate the clinical efficacy and safety of an intravenous FDC of ibuprofen and acetaminophen after bunionectomy.

Methods: This study was a prospective, randomized, double-blind, multicenter, placebo-controlled factorial clinical trial conducted at 2 clinical research centers in the United States between November 2016 and June 2017. Eligible patients (male and female subjects, aged 18−65 years, reporting pain intensity levels ≥40 mm on a 100-mm visual analog scale (VAS) after distal, first metatarsal bunionectomy) were randomized (3:3:3:2) to receive the FDC (ibuprofen 300 mg + acetaminophen 1000 mg), ibuprofen 300 mg, acetaminophen 1000 mg, or placebo (vehicle), administered as 15-minute intravenous infusions every 6 hours for 48 hours. The primary efficacy end point was the time-adjusted sum of pain intensity differences from baseline over 48 hours ($SPID_{48}$). In addition to VAS pain intensity scores, pain relief scores, time to perceptible and meaningful pain relief, the use of rescue medication, and participant's global evaluations of the study drug were recorded. Adverse events occurring during the 48-hour treatment period were included in the safety analysis.

Findings: A total of 276 participants were enrolled; most were female (82%), the mean age was 42.4 years, and the median baseline VAS was 67 mm, indicating moderate to severe pain. $SPID_{48}$ was significantly higher for the FDC (23.4 [2.5] mm) than for ibuprofen (9.5 [2.5] mm), acetaminophen (10.4 [2.5] mm), and placebo (−1.3 [3.1] mm; all, $P < 0.001$). The superior analgesic effect of the FDC was supported by a range of secondary end points, including reduced opioid usage rates (75% for FDC, 92% for ibuprofen, 93% for acetaminophen, and 96% for placebo; all, $P < 0.005$). The safety profile of the FDC was comparable to that of intravenous ibuprofen or acetaminophen alone. Three participants withdrew from the study due to adverse events: 2 in the ibuprofen group and 1 in the acetaminophen group.

Implications: The study found that repeated administration of an intravenous FDC of ibuprofen and acetaminophen provided statistically significant improvement in $SPID_{48}$ over comparable doses of either monotherapy without an increase in adverse events. ClinicalTrials.gov identifier: NCT02689063. (*Clin Ther*. 2019;41:1982−1995) © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key Words: acetaminophen, bunionectomy, combination therapy, ibuprofen, postoperative pain.

INTRODUCTION

Effective management of postoperative pain remains a significant clinical challenge. The vast majority of

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surgical patients experience pain, with 75% experiencing moderate to extreme pain in the immediate postsurgical period, and most reporting pain after discharge.[1] Multimodal analgesia with a variety of analgesics (systemic pharmacologic therapies with local, regional, and neuraxial anesthetics) is strongly recommended for the treatment of postoperative pain.[2] In terms of systemic treatments, nonopioid oral or parenteral acetaminophen and/or nonsteroidal anti-inflammatory drugs generally form the basis of treatment, in conjunction with opioids of increasing strength as required. In this time of rising concerns about the misuse of opioids, strategies to reduce opioid consumption while providing effective pain relief are of critical importance.

Ample evidence supports the superior analgesic effect of ibuprofen and acetaminophen administered together over either component alone when given orally after minor surgery.[3–5] In patients presenting to the emergency department with acute extremity pain, a single co-administered oral dose of ibuprofen and acetaminophen provides pain reduction at 2 hours equivalent to that of analgesics containing an opioid with acetaminophen.[6] However, oral administration may not be suitable in some patients due to intubation, sedation, postoperative nausea and vomiting, and reduced gastric motility. There is limited evidence regarding the effect of combining ibuprofen and acetaminophen when one or both drugs are administered parenterally; published reports suggest that co-treatment affords superior pain relief.[7,8]

To simplify multimodal analgesia and extend the therapeutic advantages of existing fixed-dose combination tablets to patients in whom parenteral administration is clinically justified, a fixed-dose combination containing ibuprofen 300 mg + acetaminophen 1000 mg in 100-mL solution for infusion has been developed (henceforth FDC). It has previously been shown that when given together by this route, there is no pharmacokinetic interaction between the 2 active ingredients.[9] We report the results of a Phase III study that aimed to investigate the clinical efficacy and safety of the FDC compared with intravenous administration of the individual constituents and placebo in 276 patients experiencing moderate to severe pain after primary, unilateral, distal, first metatarsal bunionectomy.

PATIENTS AND METHODS

Study Design

The trial design was randomized, double-blind, multicenter, placebo-controlled and factorial. The study was conducted at 2 clinical research centers in the United States (Texas and Maryland) between November 2016 and June 2017. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and received approval from MaGil IRB (Rockville, Maryland). Written informed consent was obtained before any protocol-specified procedures or assessments were completed. This trial was prospectively registered on ClinicalTrials.gov (identifier: NCT02689063).

Study Population

English-speaking male and female subjects aged 18 to 65 years classified in the American Society of Anesthesiology Physical Status Classification System as P1 (normal, healthy patients) to P2 (patients with mild systemic disease), who had undergone primary, unilateral, distal, first metatarsal bunionectomy (with osteotomy and internal fixation), and were experiencing a pain intensity rating ≥40 mm on a 100-mm visual analog scale (VAS) during the 9-hour period after discontinuation of the postsurgical anesthetic block were eligible for inclusion (see Supplemental Table I in the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008 for all inclusion and exclusion criteria). A standardized anesthetic technique was used. Subjects received midazolam and/or propofol for initial sedation and lidocaine 1% for local anesthesia. Ropivacaine 0.5% was used to establish a popliteal sciatic nerve block; a standard Mayo block with lidocaine 2% was permitted if the popliteal sciatic block was insufficient to provide adequate intraoperative anesthesia. Regional anesthesia was continued postoperatively via continuous infusion and discontinued at ~3:00 AM the day following surgery, after which patients meeting the inclusion criteria for baseline pain intensity were randomized to treatment.

Randomization and Blinding

A randomization sequence was generated by the study statistician using a computerized program before any participant enrollment. The randomization list was in permuted blocks and included stratification of study site. The statistician maintained a confidential schedule of participant numbers and drug allocation. Each site received sealed opaque unblinding envelopes for each individual in case of medical emergency. Randomization occurred at each site once participant eligibility for the study was confirmed postoperatively, with each eligible subject assigned a unique randomization number in sequential order. Double-blinding (of participants, care providers, and investigators) was achieved by the identical appearance and packaging of the investigational products (100-mL glass vials with aluminum caps, labeled with the participant's randomization number).

Interventions

Eligible subjects were randomized (3:3:3:2) to receive ibuprofen 300 mg + acetaminophen 1000 mg (FDC), ibuprofen 300 mg (IBU), acetaminophen 1000 mg (APAP), or placebo (vehicle; a clear liquid manufactured under the same conditions as the active treatments). Study medications were administered by trained study staff as 15-minute infusions into a dedicated indwelling venous cannula every 6 hours over a treatment period of 48 hours. Subjects remained at the study site for the 48-hour study period and were followed up by telephone 7 days after surgery.

Rescue medication (primary, oral oxycodone 5−10 mg; secondary, intravenous morphine sulfate 2−4 mg) was available upon request after surgery and before randomization to help control breakthrough pain if regional anesthetic infusion failed to provide adequate anesthesia. After randomization, rescue medication was available upon request. Subjects were encouraged to wait at least 1 hour after the first dose of study drug before receiving rescue medication to allow time for the study drug to exert its pharmacologic effect; however, rescue was not restricted if required. The study medication was dosed as per protocol until completion of the study, regardless of rescue usage. The use of any analgesic medications not specified in the protocol was prohibited from before surgery to the end of the 48-hour treatment period.

Outcome Measures

Baseline and demographic characteristics were determined at screening; baseline pain intensity scores were obtained before the first dose of study drug. Pain intensity scores were self-reported on a 100-mm VAS at time 0, 5, 10, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, and 6 hours during the first dosing interval; immediately before and 2 hours after administering each subsequent dose; and at 48 hours/early discontinuation. Pain relief scores were reported by participants at the same time points on a 5-point ordinal rating scale (0 = no pain relief [the pain is the same, or worse, than the starting pain]; 1 = a little pain relief [the pain is less than half gone]; 2 = some pain relief [the pain is about half gone]; 3 = a lot of pain relief [the pain is more than half gone]; and 4 = complete pain relief [the pain is completely gone]). Prerescue pain intensity and pain relief assessments were also collected. Time to perceptible and meaningful pain relief were assessed by patients during the first dosing interval by using the 2-stopwatch method.[10,11] At the end of the 48-hour study period, or at the time of treatment discontinuation, patients completed a global evaluation of the study drug on a 5-point ordinal scale (1 = poor; 2 = fair; 3 = good; 4 = very good; and 5 = excellent).

All adverse events (AEs), nonserious and serious,[12] occurring during the 48-hour treatment period were included in the safety analysis. AEs were classified by the investigator in terms of severity and relation to the investigational product. For each AE, the onset, duration, frequency, outcome, action taken with the investigational drug, and any treatment received were recorded. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) were assessed at baseline (before the first dose), at the end of the first dose, before the fifth dose, and at discharge/early discontinuation.

Statistical Analysis

The primary efficacy end point was the time-adjusted sum of pain intensity differences (SPID) from baseline over 48 hours ($SPID_{48}$). Secondary efficacy end points were: SPID over 6, 12, and 24 hours; total pain relief (TOTPAR) over 6, 12, 24, and 48 hours; VAS scores, pain intensity differences from baseline (PID), and pain relief scores at each scheduled time point; peak pain relief; time to peak pain relief; time to onset of analgesia (perceptible pain relief confirmed by meaningful pain relief); time to first perceptible pain relief; time to meaningful pain relief; time to first use of rescue medication;

proportion of subjects using rescue medication; total use of rescue medication over 24 and 48 hours; and patient's global evaluation of the study drug. Post hoc analyses included response rate and time to response.

A sample size of 275 (75 in each active group, and 50 in the placebo group) was calculated to provide 80% power to detect a statistically significant difference (2-tailed $\alpha = 0.05$) of at least 10.5 mm (effect size, 0.6) in $SPID_{48}$ between the FDC and each comparator, an effect size considered clinically relevant.[5] All randomized subjects received the first dose of study medication and were included in all efficacy and safety analyses (intention-to-treat population). Subjects were analyzed according to the treatment group to which they were assigned.

PIDs were calculated from the VAS at each scheduled time point until the end of 48 hours. The time-adjusted SPID was calculated as the AUC of PID divided by the time interval from baseline to the last included assessment. Linearly interpolated VAS scores were imputed for intermittent missing assessments, including off-schedule assessments. The AUC of pain relief scores was used to calculate TOTPAR. In the event of rescue medication use, SPID and TOTPAR were calculated up to the first prerescue assessment. Peak pain relief was determined from pain relief ratings before first rescue, or until the end of the study if no rescue medication was taken. Rescue medication use was converted to oral morphine milligram equivalents (MME) by multiplying the dose of oral oxycodone by 1.5 or by 3.0 for intravenous morphine.[13,14] The response rate was the percentage of patients that experienced at least a 50% reduction in VAS score from baseline before rescue.

An ANCOVA model with baseline pain intensity as a covariate was initially tested for analysis of SPID; however, because baseline VAS scores did not have a significant effect in the model, and there was no correlation between $SPID_{48}$ and baseline pain for any treatment group, the covariate was dropped. The FDC was compared with the other treatments by using a sequential testing strategy (1, placebo; 2, acetaminophen; 3, ibuprofen); pairwise comparison was performed only if the preceding test was statistically significant ($P < 0.05$). Sensitivity analyses for $SPID_{48}$ were conducted with the first prerescue VAS score carried forward to the end of the study, with $SPID_{48}$ calculated from all VAS scores (scheduled and prerescue), and with prerescue VAS scores carried forward for 4 hours. Baseline pain was retained as a covariate in the second 2 sensitivity analyses.

An ANCOVA with baseline pain intensity as a covariate was used to compare VAS and PID at each scheduled time point. Analysis of TOTPAR, pain relief scores, peak pain relief, MME, and global evaluation of study medication was by nonparametric Kruskal–Wallis test with Mann–Whitney *U* tests. The response rate was analyzed by using the χ^2 test; rescue medication usage was analyzed by using a logistic regression model with baseline intensity as a covariate. For the time-to-event end points, log-rank tests were used, and participants who did not experience the event were censored at the end of the relevant observation period.[15] Time to perceptible, meaningful and confirmed perceptible pain relief were censored at 6 hours if rescue medication was used before stopping either stopwatch.

AEs were coded according to Medical Dictionary for Regulatory Activities terminology. The incidence of common AEs (occurring in ≥10% of participants) was compared between the FDC group and the comparators by using Fisher's 2-sided exact test.

RESULTS

Baseline Characteristics

Of the 413 subjects who were screened, 276 were eligible and were randomized to treatment (Figure 1). The demographic and baseline clinical characteristics were reasonably balanced between treatment groups (Table I), with the majority of participants being female (82%) and white (62%), with a mean (SD) age of 42.4 (12.2) years. The median (interquartile range) pain intensity score at baseline was 67 mm (57–77 mm), indicating moderate to severe pain.

Analgesic Efficacy

The primary efficacy analysis found that $SPID_{48}$ was highest in the FDC group (**mean [SE]**, 23.4 [2.5] mm), with statistically significant differences ($P < 0.001$) to all comparators (IBU, 9.5 [2.5]; APAP, 10.4 [2.5]; placebo, –1.3 [3.1]) (Table II). The finding that the FDC provided a superior reduction in pain was supported by sensitivity analyses which evaluated the impact of exclusion of VAS assessments after the first dose of rescue medication (see Supplemental Table II in the online version at doi: http://doi.org/10.1016/j.

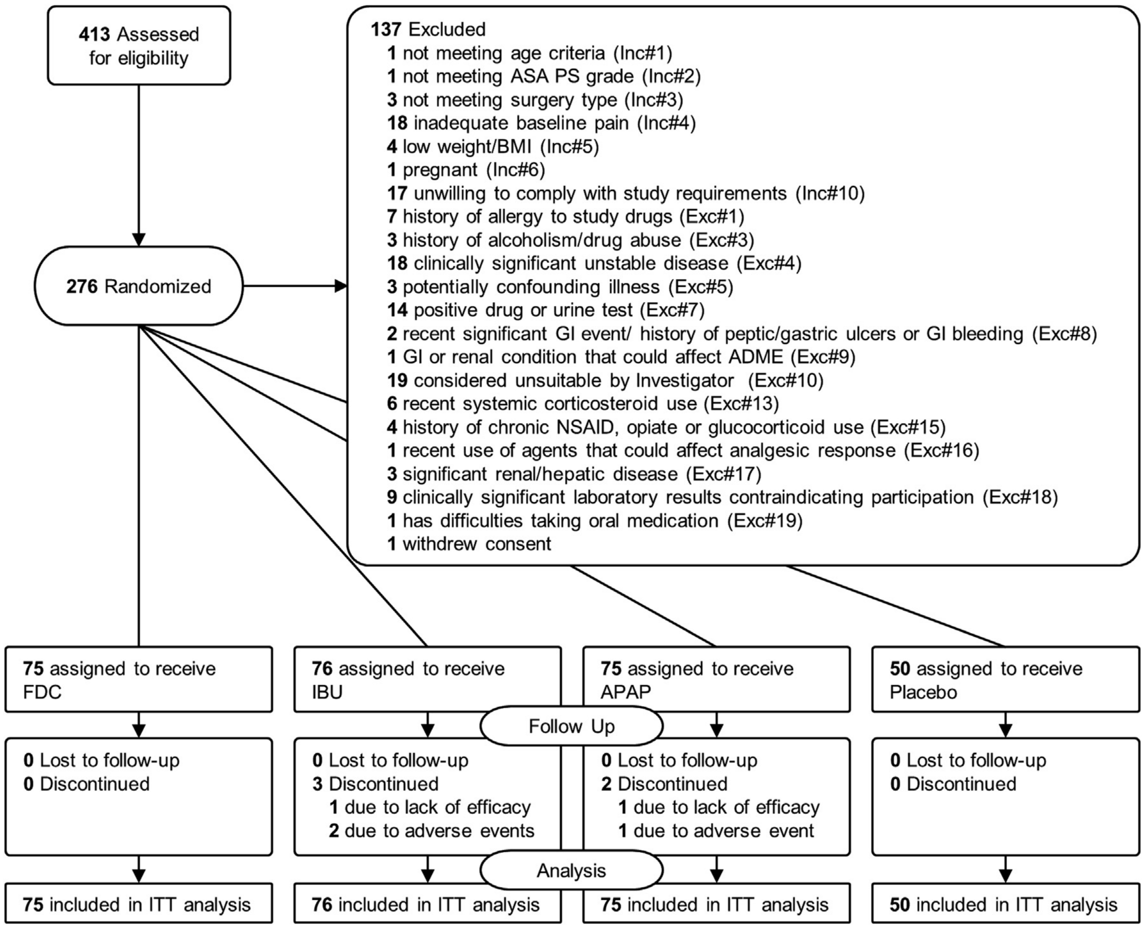

Figure 1. Flow of patients through the study. ADME = absorption, distribution, metabolism, and excretion; APAP = acetaminophen; ASA PS = American Society of Anesthesiology Physical Status; BMI = body mass index; Exc = exclusion criteria; FDC = fixed-dose combination; GI = gastrointestinal; IBU = ibuprofen; Inc = inclusion criteria; ITT = intention-to-treat; NSAID = nonsteroidal anti-inflammatory drug.

clinthera.2019.07.008). The efficacy hierarchy seen in the primary analysis was maintained in subgroup analyses according to sex, age, race, and American Society of Anesthesiology Physical Status Classification (see Supplemental Table III in the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008). Analyses of $SPID_6$, $SPID_{12}$, $SPID_{24}$, $TOTPAR_6$, $TOTPAR_{12}$, $TOTPAR_{24}$, and $TOTPAR_{48}$ support the findings of the primary end point: the FDC provided superior pain relief to each comparator over single and multiple dosing periods.

Profiles of the VAS, PID, and pain relief scores over the 48-hour study period are depicted in Supplemental Figure 1 (see the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008), Figure 2, and Supplemental Figure 2 (see the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008), respectively. Throughout the study, VAS scores were consistently lowest in the FDC group, indicative of lower pain levels, whereas PID and pain relief scores were greatest in the FDC group, indicative of greatest pain relief. A "sawtooth" pattern was observed in mean PID in the active treatments but not placebo.

Time to perceptible pain relief was shorter in the FDC group than in the APAP and placebo groups; time to meaningful pain relief and time to onset of analgesia were shorter in the FDC group than in the IBU and placebo groups. Peak pain relief was highest

Table I. Baseline and demographic characteristics of the study population.

Characteristic	FDC (n = 75)	IBU (n = 76)	APAP (n = 75)	Placebo (n = 50)
Age, y				
Mean (SD)	42.3 (11.6)	43.3 (12.3)	41.9 (12.5)	41.7 (12.7)
Range	21–65	18–63	19–65	20–65
Weight, kg				
Mean (SD)	79.2 (15.5)	75.6 (17.0)	74.2 (15.6)	79.5 (15.5)
Range	54.0–124.3	52.0–131.0	46.0–112.9	52.2–110.0
Height, cm				
Mean (SD)	166.3 (8.4)	166.3 (10.0)	166.8 (8.9)	166.7 (7.9)
Range	152.4–193.0	151.0–199.0	149.9–191.0	152.4–182.9
BMI, kg/m^2				
Mean (SD)	28.5 (4.6)	27.2 (5.1)	26.6 (5.3)	28.5 (4.8)
Range	18.7–38.8	18.0–39.8	17.1–40.0	20.8–39.3
Race, no. (%)				
White	48 (64)	39 (51)	55 (73)	29 (58)
Black or African American	23 (31)	32 (42)	17 (23)	20 (40)
Asian	3 (4)	3 (4)	2 (3)	1 (2)
Multiple	1 (1)	2 (3)	1 (1)	0
Sex, no. (%)				
Male	13 (17)	11 (15)	17 (23)	10 (20)
Female	62 (83)	65 (86)	58 (77)	40 (80)
ASA PS classification, no. (%)				
P1	44 (59)	37 (49)	47 (63)	21 (42)
P2	31 (41)	39 (51)	28 (37)	29 (58)
Surgery duration, min				
Mean (SD)	36.6 (14.5)	35.1 (12.3)	36.1 (12.8)	35.8 (12.6)
Range	18–88	16–73	16–70	15–60
Baseline VAS pain score, mm				
Median (IQR)	68 (56–81)	67.5 (61.25–76.75)	65 (55–77)	67.5 (56–76.5)
Range	41–100	40–100	41–100	42–100

APAP = acetaminophen; ASA PS = American Society of Anesthesiology Physical Status; FDC = fixed-dose combination; IBU = ibuprofen; IQR = interquartile range; VAS = visual analog scale.

in the FDC group, and time to peak pain relief was longer with the FDC than with IBU or placebo. Post hoc analysis of the response rate revealed that more FDC-treated participants achieved at least a 50% reduction in baseline pain without rescue medication than participants receiving IBU or placebo (51% vs 26% or 12%, respectively) (Table II). The time to response was shorter for the FDC compared with APAP and placebo.

The FDC delayed the time to first request for rescue medication (median time, 3.32 hours for FDC, 1.68 hours for IBU, 2.08 hours for APAP, and 1.18 hours for placebo) and resulted in a reduction in the consumption of rescue medication over 24 and 48 hours (median dose in MME over 48 hours, 30.0 mg for FDC; 43.5 mg for IBU; 45.0 mg for APAP; 67.5 mg for placebo; all, $P < 0.01$) (Table II). The majority of participants required supplementary

Table II. Results across all efficacy end points.

Outcome	FDC	IBU	APAP	Placebo
	(n = 75)	(n = 76)	(n = 75)	(n = 50)
Primary end point				
$SPID_{48}$, mean (SE), mm	23.4 (2.5)	9.5 (2.5)	10.4 (2.5)	−1.3 (3.1)
Mean difference to FDC (95% CI)	—	13.9 (7.0; 20.9)	13.0 (6.0; 20.0)	24.7 (16.9; 32.5)
P[*]	—	<0.001	<0.001	<0.001
Secondary end points				
$SPID_{6}$, mean (SE), mm	20.1 (2.4)	9.0 (2.4)	10.1 (2.4)	−1.5 (2.9)
Mean difference to FDC (95% CI)	—	11.1 (4.5; 17.7)	10.0 (3.4; 16.6)	21.6 (14.2; 29.0)
P[*]	—	0.001	0.003	<0.001
$SPID_{12}$, mean (SE), mm	20.6 (2.4)	8.4 (2.4)	9.4 (2.4)	−1.7 (2.9)
Mean difference to FDC (95% CI)	—	12.2 (5.6; 18.8)	11.2 (4.6; 17.8)	22.3 (14.9; 29.7)
P[*]	—	<0.001	<0.001	<0.001
$SPID_{24}$, mean (SE), mm	22.0 (2.4)	8.6 (2.4)	9.6 (2.4)	−1.5 (3.0)
Mean difference to FDC (95% CI)	—	13.4 (6.7; 20.0)	12.4 (5.7; 19.1)	23.5 (16.0; 31.0)
P[*]	—	<0.001	<0.001	<0.001
$TOTPAR_{6}$, median (95% CI), mm	3.6 (2.3; 6.6)	1.1 (0.3; 2.2)	1.6 (0.7; 2.9)	0.0 (0; 0.5)
P[†]	—	<0.001	0.02	<0.001
$TOTPAR_{12}$, median (95% CI), mm	3.8 (2.3; 12.5)	1.1 (0.3; 2.2)	1.6 (0.7; 3.6)	0.0 (0; 0.5)
P[†]	—	<0.001	0.01	<0.001
$TOTPAR_{24}$, median (95% CI), mm	3.8 (2.3; 12.5)	1.1 (0.3; 2.2)	1.6 (0.7; 3.6)	0.0 (0; 0.5)
P[†]	—	<0.001	0.008	<0.001
$TOTPAR_{48}$, median (95% CI), mm	3.8 (2,3; 12.5)	1.1 (0.3; 2.2)	1.6 (0.7; 3.6)	0.0 (0; 0.5)
P[†]	—	<0.001	0.008	<0.001
Time to perceptible pain relief, median (95% CI), min	9.4 (6.5; 11.8)	13.8 (6.5; 24.4)	23.9 (13.5; 39.2)	— (9.9; —)
Achieved, no. (%)	63 (84)	53 (70)	54 (72)	24 (48)
P[‡]	—	0.06	0.02	<0.001
Time to meaningful pain relief, median (95% CI), min	79.2 (40.8; —)	— (296.3; —)	— (61.2; —)	— (—; —)

Table II. (*Continued*)

Outcome	FDC (n = 75)	IBU (n = 76)	APAP (n = 75)	Placebo (n = 50)
Achieved, no. (%)	45 (60)	29 (38)	37 (49)	12 (24)
P[‡]	–	0.01	0.13	<0.001
Time to onset of analgesia, median (95% CI), min	23.8 (9.8; –)	– (176.2; –)	– (25.0; –)	– (–; –)
Achieved, no. (%)	45 (60)	29 (38)	37 (49)	12 (24)
P[‡]	–	0.01	0.13	<0.001
Peak pain relief, no. (%)				
"No relief"	12 (16)	22 (29)	21 (28)	25 (50)
"A little relief"	16 (21)	17 (22)	19 (25)	13 (26)
"Some relief"	12 (16)	13 (17)	5 (7)	7 (14)
"A lot of relief"	13 (17)	20 (26)	19 (25)	2 (4)
"Complete relief"	22 (30)	4 (5)	11 (15)	3 (6)
P[†]	–	0.004	0.04	<0.001
Time to peak pain relief, median (95% CI), h	0.52 (0.25; 0.75)	0.25 (0.08; 0.50)	0.27 (0.25; 0.75)	0.08 (–; –)
P[‡]	–	0.002	0.21	<0.001
Used rescue medication, no. (%)	56 (75)	70 (92)	70 (93)	48 (96)
Odds ratio (95% CI)	–	4.13 (1.52; 11.20)	5.49 (1.89; 15.96)	9.03 (1.97; 41.47)
P[§]	–	0.005	0.002	0.005
Time to first rescue medication, median (95% CI), h	3.32 (2.53; 4.92)	1.68 (1.38; 2.20)	2.08 (1.62; 3.00)	1.18 (1.12; 2.12)
P[‡]	–	<0.001	0.006	<0.001
Rescue medication used in 24 h, median (95% CI), MME[‖]	22.5 (15; 30)	30.0 (30; 42)	42.0 (30; 45)	45.0 (45; 60)
P[†]	–	0.01	0.003	<0.001
Rescue medication used in 48 h, median (95% CI), MME	30.0 (15; 42)	43.5 (30; 60)	45.0 (30; 60)	67.5 (45; 90)
P[†]	–	0.008	0.004	<0.001

(*continued on next page*)

Table II. (*Continued*)

Outcome	FDC (n = 75)	IBU (n = 76)	APAP (n = 75)	Placebo (n = 50)
Global evaluation of study drug, no. (%)				
"Poor"	8 (11)	14 (19)	22 (30)	21 (42)
"Fair"	11 (15)	16 (21)	16 (21)	11 (22)
"Good"	14 (19)	24 (32)	16 (21)	11 (22)
"Very good"	18 (24)	14 (18)	16 (21)	6 (12)
"Excellent"	24 (32)	8 (11)	5 (7)	1 (2)
P[†]	—	0.001	<0.001	<0.001
Post hoc analyses				
Response rate,[ǁ] no. (%)	38 (51)	26 (34)	27 (36)	6 (12)
P[¶]	—	0.04	0.07	<0.001
Time to response, median (95% CI), h	3.00 (1.50; 8.00)	23.98 (3.00; 26.00)	8.00 (2.00; 38.00)	30.00 (—; —)
P[‡]	—	0.07	0.03	<0.001

APAP = acetaminophen; FDC = fixed-dose combination; IBU = ibuprofen; MME = morphine milligram equivalents; SPID = sum of pain intensity differences from baseline over 6, 12, 24, and 48 hours; TOTPAR = total pain relief over 6, 12, 24, and 48 hours.

* Fisher's least squares difference test.

† Mann—Whitney *U* test.

‡ Kplan—Meier test.

ǁ Percentage of patients experiencing ≥50% reduction in visual analog scale score from baseline, before the use of rescue medication.

§ Logistic regression with baseline pain intensity as covariate.

¶ The χ^2 test.

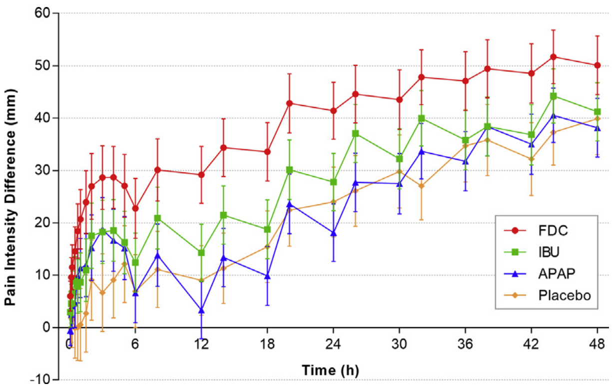

Figure 2. Mean (95% CI) pain intensity difference relative to baseline over 48 hours. APAP = acetaminophen; FDC = fixed-dose combination; IBU = ibuprofen.

analgesia; however, usage rates were lower in the FDC group (75% for FDC, 92% for IBU, 93% for APAP, and 96% for placebo; all, $P < 0.005$). The number of doses and cumulative amount of rescue medication used in each group over 24 and 48 hours are described in Supplemental Table IV (see the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008). The median number of doses of rescue medication over 48 hours was 2 for FDC, 3 for IBU and APAP, and 5 for placebo. At the end of the study, FDC-treated patients rated their study drug higher than those in the comparator arms, with 32% of FDC-treated participants rating the study drug as "excellent," compared with 11%, 7%, and 2% in the IBU, APAP, and placebo groups, respectively.

Tolerability

A total of 493 AEs were reported among 194 participants during the double-blind treatment period; none was classified as serious (Table III). There were 3 discontinuations due to AEs, 1 in the APAP group (pyrexia) and 2 in the IBU group (allergic reaction/angioedema, and burning sensation at the administration site). The most commonly reported AEs were nausea, dizziness, and vomiting

Table III. Number and frequency of adverse events (AEs). Values are given as no. (%) of patients unless otherwise indicated.

Variable	FDC (n = 75)	IBU (n = 76)	APAP (n = 75)	Placebo (n = 50)
No. of AEs reported	142	131	112	108
Discontinuations due to AEs	0	2 (3)	1 (1)	0
Participants with ≥1 AE	52 (69)	58 (76)	45 (60)	39 (78)
Participants with ≥1 drug-related AE*	34 (45)	35 (46)	22 (29)	23 (46)
Participants with ≥1 severe AE	3 (4)	4 (5)	6 (8)	1 (2)
AEs affecting ≥5% of participants				
Nausea	22 (29)	26 (34)	25 (33)	16 (32)
Dizziness	13 (17)	7 (9)	7 (9)	8 (16)
Vomiting	16 (21)	5 (7)	11 (15)	1 (2)
Headache	4 (5)	5 (7)	5 (7)	10 (20)
Somnolence	5 (7)	6 (8)	6 (8)	3 (6)
Infusion site pain	10 (13)	7 (9)	0	1 (2)
Constipation	4 (5)	4 (5)	4 (5)	4 (8)
Infusion site extravasation	2 (3)	5 (7)	2 (3)	7 (14)
Pruritus	5 (7)	4 (5)	3 (4)	2 (4)

APAP = acetaminophen; FDC = fixed-dose combination; IBU = ibuprofen.
* Classified as possibly, probably, or definitely related to the study drug. This does not include AEs classified as nonrelated or unlikely to be related.

(≥10% of study population). The incidence of common AEs was largely comparable between the FDC group and the other active treatment groups. There was no difference in the rate of nausea or dizziness between the FDC group and the comparators ($P > 0.05$). The incidence of vomiting was significantly different between the FDC and IBU ($P = 0.001$), and placebo ($P = 0.001$) but not APAP ($P = 0.396$). There were no clinically significant changes from baseline in vital signs (see Supplemental Table V in the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008).

DISCUSSION

The bunionectomy pain model is a sensitive assay for studying analgesics due to the consistent moderate to severe pain experienced over the first 72 postoperative hours.[16] The present study found that administration of an intravenous FDC containing ibuprofen and acetaminophen provided superior pain relief and reduced the consumption of opioid analgesics compared with either drug alone over 48 hours in the early postoperative period after first metatarsal bunionectomy.

The primary efficacy end point ($SPID_{48}$) showed that the FDC offered the greatest reduction in pain over the 48-hour study period compared with the individual constituents and placebo. The negative mean $SPID_{48}$ in the placebo group is consistent with a lack of analgesic efficacy. Sensitivity analyses showed that the high use of rescue medication in the study did not invalidate the primary analysis. Due to the high usage rates of rescue medication in all comparator groups, carrying forward the first prerescue VAS score to the end of the study resulted in negative mean $SPID_{48}$ values, indicating no pain relief (Sensitivity Analysis 1). Sensitivity Analysis 2 revealed that despite higher use of opioids by patients receiving APAP, IBU, and placebo, the overall efficacy of these treatments never reached that of the FDC. Disregarding the analgesic effect of rescue (as in Sensitivity Analysis 3) further supported the statistically significant effect of the FDC over 48 hours.

The superior analgesic effect of the FDC was also observed during a single dosing interval ($SPID_6$ and $TOTPAR_6$) and at most scheduled time points (Figure 2; see Supplemental Figure 1 and Supplemental Figure 2 in the online version at doi: http://doi.org/10.1016/j.clinthera.2019.07.008). The FDC achieved faster perceptible pain relief compared with APAP and placebo, and faster confirmed perceptible pain relief and meaningful pain relief compared with IBU and placebo, suggesting that the initial perceptible pain relief is attributable to the ibuprofen component of the FDC.

Consistent with the high levels of postoperative pain after bunionectomy, the majority of patients in the present study took rescue medication. The FDC reduced the percentage of patients requiring supplementary opioids, reduced the amount of opioids used, and delayed the first request for rescue medication. Complete pain relief without rescue was achieved by 30% of patients in the FDC group, compared with 5% with IBU, 15% with APAP, and 6% with placebo. The FDC group had the highest and fastest response rate, with 51% of patients halving their baseline pain scores without rescue. Collectively, these results indicate that by combining ibuprofen and acetaminophen, the FDC has an important opioid-sparing effect while improving overall analgesia.

The findings of the time to peak pain relief are not intuitive. Although the peak pain relief achieved by the FDC was greater than that of the comparators, the time to peak pain relief was longest in the FDC group and shortest in the placebo group. As peak pain relief was defined as the greatest prerescue pain relief score, the less effective the study drug, the sooner rescue medication was required, and the less time over which the pain-relieving effect of the medication could accumulate. Because the FDC had the most patients achieving "complete relief," and the fewest patients requiring rescue medication, the longer time to peak pain relief supports a superior analgesic effect and indicates that the FDC continues to provide more pain relief after the peak pain relief of either monocomponent has been reached.

The superior analgesic efficacy of the FDC over monotherapy in the present study is consistent with published literature for oral combination therapy.[3–5] Few studies have investigated co-administration of intravenous forms of one or both of these active ingredients. One small single-center, open-label study indicated that compared with ibuprofen alone, co-treatment with intravenous ibuprofen 800 mg and intravenous acetaminophen 1000 mg over 5 days after total knee or hip arthroplasty decreased opioid consumption in the immediate postoperative period and reduced pain scores on the third day; however, differences in baseline pain levels were not accounted for in the analysis.[7] Another small single-center, double-blinded study found that the addition of intravenous ibuprofen 800 mg to oral acetaminophen 1000 mg in patients undergoing transsphenoidal surgery reduced pain scores and opioid consumption over a 48-hour period.[8] Multimodal analgesia with intravenous acetaminophen and other nonsteroidal anti-inflammatory drugs (ketoprofen, diclofenac, and parecoxib) is supported by a number of studies.[17–19]

The safety profile of the FDC was broadly comparable to either active agent alone. The incidence of vomiting was not significantly different between the FDC and APAP groups, suggesting it may be attributable to the acetaminophen component.

As with any study, the present study has strengths and limitations. The factorial study design showed that both active ingredients contribute to the analgesic effect of the FDC. Baseline characteristics, including pain intensity scores, were broadly comparable between treatment groups. Small imbalances were observed in sex and race distributions; however, subgroup analyses revealed that despite small sample sizes in certain subgroups, the analgesic superiority of the FDC was observed across demographic groups. The study was double-blinded, conducted at 2 sites, and utilized standardized anesthesia. The results of the study are generalizable to typical patients undergoing bunionectomy surgery. However, several types of patients were excluded from the study, including patients with significant unstable illness, patients using drugs or alcohol, and patients with other contraindications; thus, study results may not be relevant to these patients. Not all patients undergoing bunionectomy require parenteral pain relief over 48 hours, and therefore transition to an oral formulation of the combination product may be appropriate under some conditions. Future studies could determine opioid consumption after discharge with such a regimen. The high rate of use of rescue medication indicates that for many patients with postoperative pain, especially moderate to severe pain, the FDC may be best used as an adjunct to opioids.

CONCLUSIONS

As has been observed in studies with an oral formulation of the FDC, parenteral co-administration of ibuprofen and acetaminophen provides a statistically significant analgesic effect compared with either individual drug or placebo over multiple doses. This effect was obtained more rapidly than either drug alone, was achieved with less opioid consumption, and did not come at the expense of tolerability. The FDC offers a simplified strategy to provide multimodal analgesia to patients in whom an intravenous route of administration is clinically justified.

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Dr. Daniels was responsible for the study design, protocol development, study conduct, and reviewing the manuscript. Dr. Playne was responsible for data interpretation and drafting the manuscript. Ms. Stanescu was responsible for project supervision, study design, protocol development, data interpretation, and reviewing the manuscript. Ms. Zhang was responsible for protocol development and drafting the manuscript. Dr. Gottlieb was responsible for study conduct and reviewing the manuscript. Dr. Atkinson was responsible for study design, protocol development, data interpretation, and reviewing the manuscript.

DISCLOSURES

Dr. Daniels was the Principal Investigator of the clinical site in Austin, Texas (Optimal Research LLC). Dr. Playne is an employee of AFT Pharmaceuticals Ltd. Ms. Stanescu is an employee and shareholder of AFT Pharmaceuticals Ltd. Ms. Zhang is an employee and shareholder of AFT Pharmaceuticals Ltd. Dr. Gottlieb was the Principal

Investigator of the clinical site in Pasadena, Maryland (Chesapeake Research Group). Dr. Atkinson has patents relevant to the work, and is the majority owner and Managing Director of AFT Pharmaceuticals Ltd. Dr. Atkinson has a patent 2005260243 issued, a patent 552181 issued, a patent 1781277 issued, a patent 2570474 issued, and a patent 13/857802 pending. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The sponsor was responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

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eTable 1. Inclusion/Exclusion criteria for the study.

Inclusion Criteria

1. Is male or female $\geq$ 18 and $\leq$ 65 years of age.
2. Is classified by the anesthesiologist as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System.
3. Has undergone primary, unilateral, distal, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures.
4. Experiences a pain intensity rating of $\geq$ 40 mm on a 100-mm Visual Analogue Scale (VAS) during the 9-hour period after discontinuation of the anesthetic block.
5. Has a body weight $\geq$ 45 kg and a body mass index (BMI) $\leq$ 40 kg/m^2.
6. If female, has negative pregnancy test results at screening (urine) and on the day of surgery prior to surgery (urine).
7. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following medically acceptable methods of birth control:
   - ➢ Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before study drug administration.
   - ➢ Total abstinence from sexual intercourse since the last menses before study drug administration through completion of final study visit.
   - ➢ Intrauterine device (IUD).
   - ➢ Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream).
8. Is able to provide written informed consent to participate in the study and able to understand the procedures and study requirements.
9. Must voluntarily sign and date an informed consent form (ICF) that is approved by an Institutional Review Board (IRB) before the conduct of any study procedure.
10. Is willing and able to comply with study requirements (including diet, alcohol, and smoking restrictions), complete the pain evaluations, remain at the study site for approximately 72 hours, and will be followed up with a phone call at 7 ± 2 days after surgery.

Exclusion Criteria

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, opioids, or any nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen); history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to sulfa (including sulfonamide) medicines, ingredients of the study drug, or any other drugs used in the study including anesthetics and antibiotics that may be required on the day of surgery.
2. Has experienced any surgical complications or other issues that, in the opinion of the investigator, could compromise the safety of the subject if he or she continues into randomized treatment period or could confound the results of the study.
3. Has known or suspected history of alcoholism or drug abuse or misuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with study drug.
4. Has any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the investigator, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.

eTable 1. (*Continued*)

5. Has any ongoing condition, other than a condition associated with the current primary, unilateral, first metatarsal bunionectomy that could generate levels of pain sufficient to confound the results of the study (eg, gout, severe osteoarthritis of the target joint or extremity).
6. Has a history or current diagnosis of a significant psychiatric disorder that, in the opinion of the investigator, would affect the subject's ability to comply with the study requirements.
7. Has tested positive either on the urine drug screen or on the alcohol breathalyzer test. Subjects who test positive at Screening only and can produce a prescription for the medication from their physician may be considered for study enrolment at the discretion of the investigator.
8. Has a history of a clinically significant (investigator opinion) gastrointestinal (GI) event within 6 months before Screening or has any history of peptic or gastric ulcers or GI bleeding.
9. Has a surgical or medical condition of the GI or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance.
10. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure [IB] for IV Maxigesic®), to be an unsuitable candidate to receive the study drug.
11. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer within 5 years before Screening (excluding treated squamous or basal cell carcinoma of the skin).
12. Is currently receiving anticoagulants (eg, heparin or warfarin).
13. Has received a course of systemic corticosteroids (either oral or parenteral) within 3 months before Screening (inhaled nasal steroids and regional/limited area application of topical corticosteroids (investigator discretion) are allowed).
14. Has received or will require any analgesic medication within 5 half-lives (or, if half-life is unknown, within 48 hours) before surgery.
15. Has a history of chronic use (defined as daily use for > 2 weeks) of NSAIDs, opiates, or glucocorticoids (except inhaled nasal steroids and regional/limited topical corticosteroids), for any condition within 6 months before study drug administration. Aspirin at a daily dose of $\leq$ 325 mg is allowed for cardiovascular prophylaxis if the subject has been on a stable dose regimen for $\geq$ 30 days before Screening and has not experienced any relevant medical problem.
16. Has been treated with agents that could affect the analgesic response (such as central alpha agents [clonidine and tizanidine], neuroleptic agents, and other antipsychotic agents) within 2 weeks before dosing with study drug.
17. Has a significant renal or hepatic disease, as indicated by clinical laboratory assessment (results $\geq$ 3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], or creatinine $\geq$ 1.5 times the ULN).
18. Has any clinically significant laboratory finding at Screening that, in the opinion of the investigator, contraindicates study participation.
19. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.
20. Previously participated in another clinical study of Maxigesic® IV or received any investigational drug or device or investigational therapy within 30 days before Screening.

eTable 2. Results of the sensitivity analyses of the primary efficacy endpoint.

Outcome	FDC	IBU	APAP	Placebo
	N=75	N=76	N=75	N=50
Primary Endpoint				
$SPID_{48}$, mean (SE), mm	23.4 (2.5)	9.5 (2.5)	10.4 (2.5)	−1.3 (3.1)
Mean Difference to FDC (95% CI)	–	*13.9 (7.0;20.9)*	*13.0 (6.0;20.0)*	*24.7 (16.9;32.5)*
P-value	–	*<0.001*	*<0.001*	*<0.001*
Sensitivity Analysis 1: First Pre-Rescue Observation Carried Forward to the End of the Study				
$SPID_{48}$, mean (SE), mm	14.1 (2.5)	−1.9 (2.5)	−2.8 (2.5)	−10.9 (3.1)
Mean Difference to FDC (95% CI)	–	*15.9 (8.9;22.9)*	*16.9 (9.8;23.9)*	*24.9 (17.1;32.8)*
P-value	–	*<0.001*	*<0.001*	*<0.001*
Sensitivity Analysis 2: All VAS Scores, Scheduled and Pre-Rescue				
$SPID_{48}$, mean (SE), mm	38.7 (2.2)	27.2 (2.2)	21.5 (2.2)	20.8 (2.7)
Mean Difference to FDC (95% CI)	–	*11.5 (5.5;17.5)*	*17.1 (11.1;23.2)*	*17.8 (11.1;24.6)*
P-value	–	*<0.001*	*<0.001*	*<0.001*
Sensitivity Analysis 3: Pre-Rescue Observation Carried Forward for 4 Hours				
$SPID_{48}$, mean (SE), mm	35.0 (2.2)	22.1 (2.2)	17.2 (2.2)	15.1 (2.7)
Mean Difference to FDC (95% CI)	–	*12.9 (6.7;19.1)*	*17.8 (11.6;24.1)*	*19.9 (12.9;26.8)*
P-value	–	*<0.001*	*<0.001*	*<0.001*

eTable 3. Subgroup analyses of the primary efficacy endpoint (gender, age, race, ASA PS Classification).

Outcome	FDC	IBU	APAP	Placebo
	N=75	N=76	N=75	N=50
Primary Endpoint				
$SPID_{48}$, mean (SE), mm	23.4 (2.5)	9.5 (2.5)	10.4 (2.5)	−1.3 (3.1)
Mean Difference to FDC (95% CI)	–	*13.9 (7.0;20.9)*	*13.0 (6.0;20.0)*	*24.7 (16.9;32.5)*
P-value	–	*<0.001*	*<0.001*	*<0.001*
By Gender				
Male				
N	13	11	17	10
$SPID_{48}$, mean (SE), mm	15.8 (5.3)	5.8 (5.7)	5.4 (4.6)	−5.1 (6.0)
Mean Difference to FDC (95% CI)	–	10.0 (−5.7;25.6)	10.4 (−3.7;24.4)	20.8 (4.8;36.9)
P-value	–	*0.21*	*0.14*	*0.01*
Female				
N	62	65	58	40
$SPID_{48}$, mean (SE), mm	25.0 (2.8)	10.1 (2.8)	11.9 (2.9)	−0.4 (3.5)
Mean Difference to FDC (95% CI)	–	14.9 (7.1;22.7)	13.1 (5.1;21.1)	25.4 (16.5;34.3)
P-value	–	*<0.001*	*0.001*	*<0.001*
By Age				
< 40 Years				
N	33	27	34	26
$SPID_{48}$, mean (SE), mm	20.5 (3.6)	6.2 (3.9)	7.4 (3.5)	−0.5 (4.0)

eTable 3. (*Continued*)

Outcome	*FDC*	*IBU*	*APAP*	*Placebo*
	N=75	*N=76*	*N=75*	*N=50*
Mean Difference to FDC (95% CI)	—	14.3 (3.8;24.8)	13.1 (3.2;23.0)	21.0 (10.4;31.6)
P-value	—	*0.008*	*0.01*	*<0.001*
> ***40 Years***				
N	42	49	41	24
$SPID_{48}$, mean (SE), mm	25.7 (3.5)	11.4 (3.2)	13.0 (3.5)	−2.2 (4.6)
Mean Difference to FDC (95% CI)	—	14.4 (5.0;23.8)	12.8 (3.0;22.6)	27.9 (16.5;39.3)
P-value	—	*0.003*	*0.01*	*<0.001*
By Race				
White				
N	48	39	55	29
$SPID_{48}$, mean (SE), mm	23.8 (2.8)	8.6 (3.2)	10.4 (2.7)	−4.0 (3.7)
Mean Difference to FDC (95% CI)	—	15.2 (6.9;23.6)	13.4 (5.7;21.1)	27.8 (18.6;36.9)
P-value	—	*<0.001*	*<0.001*	*<0.001*
Non-White				
N	27	37	20	21
$SPID_{48}$, mean (SE), mm	22.7 (4.8)	10.5 (4.1)	10.5 (5.6)	2.4 (5.4)
Mean Difference to FDC (95% CI)	—	12.2 (−0.3;24.7)	12.3 (−2.3;26.8)	20.3 (6.0;34.7)
P-value	—	*0.06*	*0.10*	*0.006*
By ASA PS Classification				
P1				
N	44	37	47	21
$SPID_{48}$, mean (SE), mm	23.5 (3.8)	10.9 (3.8)	10.2 (2.9)	−0.3 (3.1)
Mean Difference to FDC (95% CI)	—	12.6 (3.0;22.1)	13.3 (4.3;22.3)	23.7 (12.4;35.1)
P-value	—	0.01	0.004	<0.001
P2				
N	31	39	28	29
$SPID_{48}$, mean (SE), mm	23.3 (4.6)	8.2 (3.4)	10.9 (4.6)	−2.1 (2.9)
Mean Difference to FDC (95% CI)	—	15.2 (4.7;25.7)	12.5 (1.1;23.8)	25.4 (14.1;36.7)
P-value	—	0.005	0.03	<0.001

eTable 4. Rescue Medication Use.

Outcome	FDC N=75	IBU N=76	APAP N=75	Placebo N=50
Number of Doses of Oxycodone Used in 24 hours				
0, n (%)	*20 (27)*	*6 (8)*	*6 (8)*	*2 (4)*
1, n (%)	*16 (21)*	*14 (18)*	*13 (17)*	*7 (14)*
>1, n (%)	*39 (52)*	*56 (74)*	*56 (75)*	*41 (82)*
Median (Range)	*2.0 (0–6)*	*2.0 (0–5)*	*3.0 (0–6)*	*3.0 (0–6)*
Amount of Oxycodone Used in 24 hours				
Median (IQR), mg	*15.0 (30.0)*	*20.0 (20.0)*	*20.0 (20.0)*	*30.0 (20.0)*
Range	*0–60*	*0–50*	*0–60*	*0–60*
Number of Doses of Morphine Used in 24 hours				
0, n (%)	*64 (85)*	*59 (78)*	*60 (80)*	*34 (68)*
1, n (%)	*6 (8)*	*10 (13)*	*6 (8)*	*8 (16)*
>1, n (%)	*5 (7)*	*7 (9)*	*9 (12)*	*8 (16)*
Median (Range)	*0.0 (0–3)*	*0.0 (0–4)*	*0.0 (0–6)*	*0.0 (0–6)*
Amount of Morphine Used in 24 hours				
Median (IQR), mg	*0.0 (0.0)*	*0.0 (0.0)*	*0.0 (0.0)*	*0.0 (2.0)*
Range	*0–12*	*0–12*	*0–20*	*0–12*
Number of Doses of Any Rescue Used in 24 hours				
0, n (%)	*20 (27)*	*6 (8)*	*6 (8)*	*2 (4)*
1, n (%)	*15 (20)*	*13 (17)*	*12 (16)*	*6 (12)*
>1, n (%)	*40 (53)*	*57 (75)*	*57 (76)*	*42 (84)*
Median (Range)	*2.0 (0–7)*	*2.5 (0–8)*	*3.0 (0–11)*	*3.0 (0–10)*
Number of Doses of Oxycodone Used in 48 hours				
0, n (%)	*19 (25)*	*6 (8)*	*5 (7)*	*2 (4)*
1, n (%)	*14 (19)*	*13 (17)*	*9 (12)*	*4 (8)*
>1, n (%)	*42 (56)*	*57 (75)*	*61 (81)*	*44 (88)*
Median (Range)	*2.0 (0–7)*	*3.0 (0–10)*	*3.0 (0–10)*	*4.5 (0–10)*
Amount of Oxycodone Used in 48 hours				
Median (IQR), mg	*20.0 (40.0)*	*25.0 (37.5)*	*30.0 (25.0)*	*41.0 (40.0)*
Range	*0–70*	*0–80*	*0–90*	*0–100*
Number of Doses of Morphine Used in 48 hours				
0, n (%)	*64 (85)*	*58 (76)*	*60 (80)*	*34 (68)*
1, n (%)	*6 (8)*	*11 (15)*	*6 (8)*	*8 (16)*
>1, n (%)	*5 (7)*	*7 (9)*	*9 (12)*	*8 (16)*
Median (Range)	*0.0 (0–3)*	*0.0 (0–7)*	*0.0 (0–7)*	*0.0 (0–7)*
Amount of Morphine Used in 48 hours				
Median (IQR), mg	*0.0 (0.0)*	*0.0 (0.0)*	*0.0 (0.0)*	*0.0 (2.0)*
Range	*0–12*	*0–28*	*0–28*	*0–14*
Number of Doses of Any Rescue Used in 48 hours				
0, n (%)	*19 (25)*	*6 (8)*	*5 (7)*	*2 (4)*
1, n (%)	*13 (17)*	*12 (16)*	*9 (12)*	*4 (8)*
>1, n (%)	*43 (57)*	*58 (76)*	*61 (81)*	*44 (88)*
Median (Range)	*2.0 (0–9)*	*3.0 (0–14)*	*3.0 (0–17)*	*5.0 (0–16)*

eTable 5. Vital Signs over the course of the study.

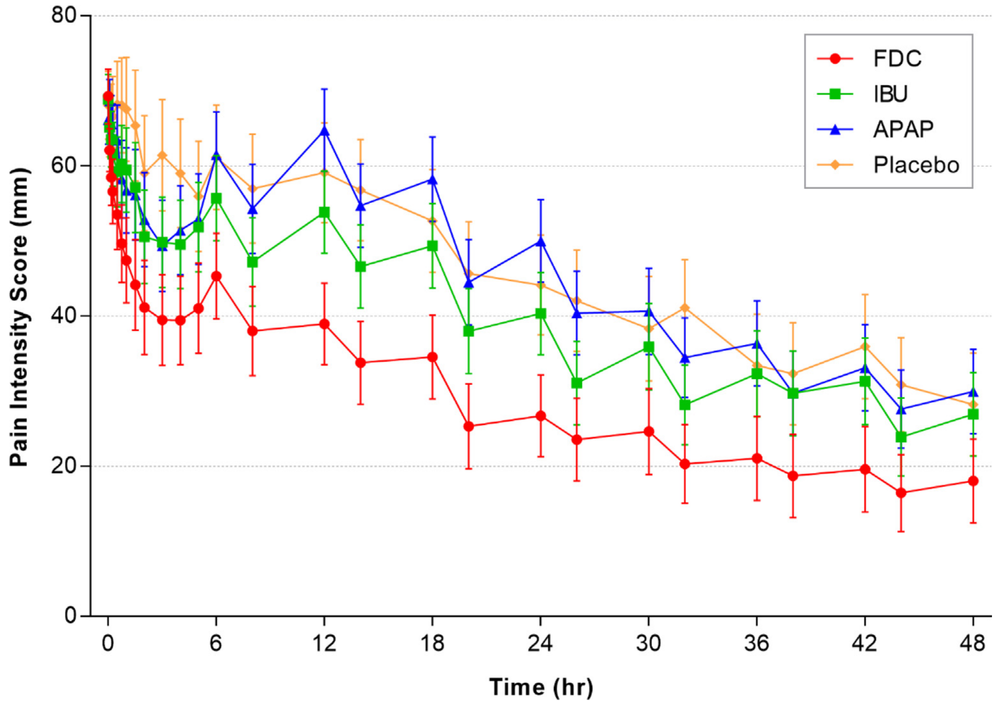
	FDC N=75	IBU N=76[1]	APAP N=75[2]	Placebo N=50
Systolic Blood Pressure (mmHg)				
Baseline				
< 90, n (%)	2 (3)	0 (0)	1 (1)	0 (0)
> 120, n (%)	25 (33)	25 (33)	25 (33)	18 (36)
End of First Dose Infusion				
< 90, n (%)	2 (3)	0 (0)	1 (1)	0 (0)
> 120, n (%)	24 (32)	27 (36)	21 (28)	21 (42)
Prior to Fifth Dose				
< 90, n (%)	3 (4)	1 (1)	0 (0)	0 (0)
> 120, n (%)	13 (17)	16 (22)	21 (28)	16 (32)
At Discharge/Early Termination				
< 90, n (%)	0 (0)	2 (3)	0 (0)	1 (2)
> 120, n (%)	23 (31)	29 (38)	25 (33)	13 (26)
Diastolic Blood Pressure (mmHg)				
Baseline				
< 60, n (%)	4 (5)	3 (4)	6 (8)	4 (8)
> 80, n (%)	15 (20)	15 (20)	15 (20)	9 (18)
End of First Dose Infusion				
< 60, n (%)	10 (13)	3 (4)	10 (13)	5 (10)
> 80, n (%)	11 (15)	17 (22)	14 (19)	13 (26)
Prior to Fifth Dose				
< 60, n (%)	15 (20)	9 (12)	4 (5)	3 (6)
> 80, n (%)	8 (11)	7 (9)	12 (16)	10 (20)
At Discharge/Early Termination				
< 60, n (%)	11 (15)	10 (13)	1 (1)	1 (2)
> 80, n (%)	14 (19)	13 (17)	16 (21)	6 (12)
Heart Rate (beats/min)				
Baseline				
< 60, n (%)	3 (4)	5 (7)	5 (7)	1 (2)
> 100, n (%)	2 (3)	1 (1)	2 (3)	1 (2)
End of First Dose Infusion				
< 60, n (%)	4 (5)	8 (11)	6 (8)	0 (0)
> 100, n (%)	1 (1)	0 (0)	0 (0)	0 (0)
Prior to Fifth Dose				
< 60, n (%)	11 (15)	6 (8)	8 (11)	1 (2)
> 100, n (%)	0 (0)	2 (3)	0 (0)	1 (2)
At Discharge/Early Termination				
< 60, n (%)	10 (13)	7 (9)	5 (7)	0 (0)
> 100, n (%)	0 (0)	0 (0)	1 (1)	0 (0)

(*continued on next page*)

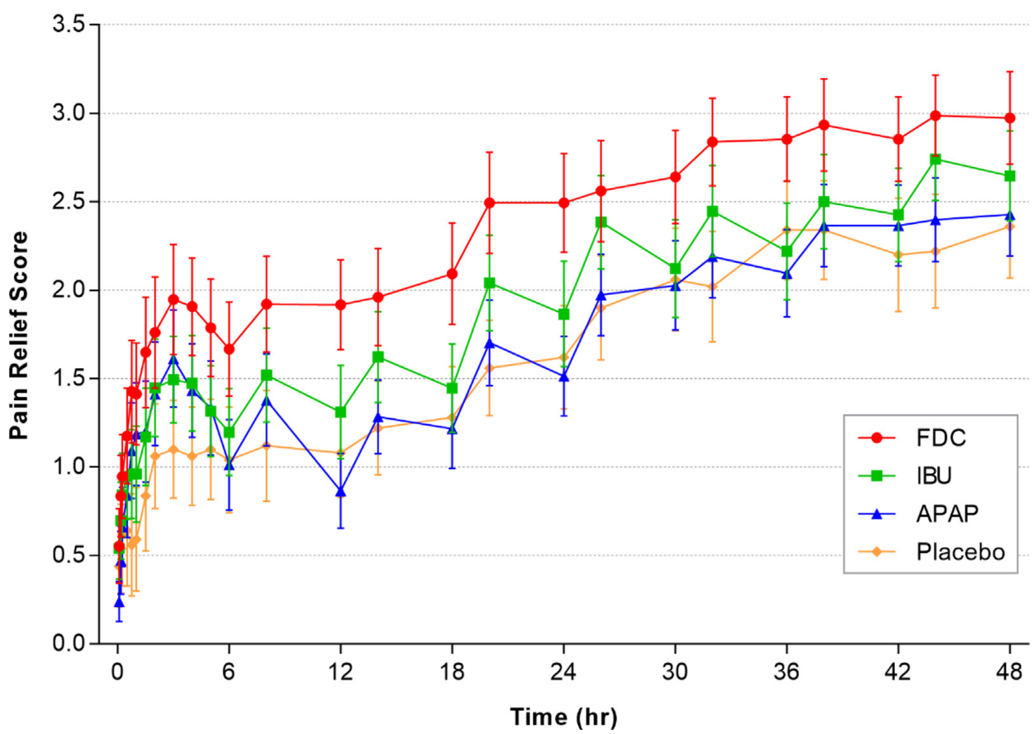
eTable 5. (*Continued*)

	FDC N=75	IBU N=76[1]	APAP N=75[2]	Placebo N=50
Respiratory Rate (breaths/min)				
Baseline				
< 12, n (%)	0 (0)	1 (1)	1 (1)	0 (0)
> 18, n (%)	17 (23)	10 (13)	12 (16)	12 (24)
End of First Dose Infusion				
< 12, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
> 18, n (%)	16 (21)	11 (14)	14 (19)	12 (24)
Prior to Fifth Dose				
< 12, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
> 18, n (%)	6 (8)	8 (11)	3 (4)	6 (12)
At Discharge/Early Termination				
< 12, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
> 18, n (%)	6 (8)	6 (8)	4 (5)	3 (6)
Temperature (°C)				
Baseline				
< 36.5, n (%)	6 (8)	6 (8)	4 (5)	4 (8)
> 37.3, n (%)	8 (11)	17 (22)	4 (5)	6 (12)
End of First Dose Infusion				
< 36.5, n (%)	3 (4)	6 (8)	8 (11)	3 (6)
> 37.3, n (%)	5 (7)	14 (18)	6 (8)	5 (10)
Prior to Fifth Dose				
< 36.5, n (%)	18 (24)	9 (12)	14 (19)	4 (8)
> 37.3, n (%)	3 (4)	4 (5)	3 (4)	6 (12)
At Discharge/Early Termination				
< 36.5, n (%)	6 (8)	6 (8)	4 (5)	4 (8)
> 37.3, n (%)	8 (11)	17 (22)	4 (5)	6 (12)

[1] At Pre-Dose 5, N=74; For Respiratory Rate at End of First Infusion, N=75
[2] At Pre-Dose 5, N=74; For Temperature at Pre-Dose 5, N=73



eFigure 1. Mean (± 95% CI) pain intensity scores over 48 hours.



eFigure 2. Mean (± 95% CI) pain relief scores over 48 hours.