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Significant, long-lasting pain relief in primary dysmenorrhea with low-dose naproxen sodium compared with acetaminophen: a double-blind, randomized, single-dose, crossover study

Stephen Daniels, A. Paredes-Diaz, R. An, R. Centofanti and A. Tajaddini*

Bayer Healthcare, Consumer Health, Whippany, NJ, USA

*corresponding author: Azita Tajaddini, Bayer U.S. LLC, R&D Therapeutics Unit, Consumer Health, Global Medical Affairs Analgesics, 100 Bayer Boulevard, Whippany, NJ 07981, US; email: Azita.tajaddini@bayer.com

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Objectives. Many women experience menstrual cramps, which adversely affects quality of life. Both naproxen and acetaminophen are indicated to relieve menstrual pain. We assessed the analgesic efficacy of a single, maximum non-prescription dose of naproxen sodium compared with that of acetaminophen in the treatment of primary dysmenorrhea.

Methods. Healthy females with primary dysmenorrhea were included in our double-blind, randomized, crossover study (trial registration no. NCT03448536). When pain was moderate (≥ 5 on 0-10 numerical rating scale), subjects took a single dose of naproxen sodium (440 mg) and crossed over to acetaminophen (1000 mg) in the next cycle, or vice versa. Total pain relief over 12 h (TOTPAR0-12) was the primary outcome, while secondary outcomes included summed pain intensity differences (SPID) and TOTPAR scores throughout 12 h, and subject overall evaluation of treatment.

Results. The per protocol population ($n=189$) used naproxen sodium ($n=170$) and acetaminophen ($n=160$). TOTPAR0-12 was significantly greater with naproxen sodium than acetaminophen (least-squares (LS) mean difference 4.31; $p<0.001$), and pain intensity was significantly lower (SPID0-12 LS mean difference 9.80; $p<0.001$). Some measures of pain intensity favoring naproxen sodium became significant at earlier time points (e.g. SPID4-6 LS mean difference 1.49; $p=0.02$). After 6 h post-dose, naproxen sodium was significantly more effective than acetaminophen, maintained for 12 h (SPID6-12 LS mean difference 8.27; TOTPAR6-12 LS mean difference 3.75; both $p<0.001$). Significantly more subjects rated naproxen sodium as good-to-excellent (70.6%) versus acetaminophen (63.1%) ($p=0.002$).

Conclusions. A single, maximum non-prescription dose of naproxen sodium was more effective than acetaminophen over 12 hours.

Keywords: acetaminophen; anti-inflammatory agents, non-steroidal; dysmenorrhea; naproxen sodium.

Short title: Non-prescription naproxen sodium relieves pain in dysmenorrhea.

Background

Pain from menstrual cramps caused by uterine contractions during menstruation known as primary dysmenorrhea, is the most common gynecological disorder in women of reproductive age. Over 70% of women report some degree of dysmenorrhea during a menstrual period [1], while over one-third always or often experiences menstrual cramps [2]. The dull, throbbing or cramping that occurs can range from mild discomfort to severe pain in the lower abdomen, which can spread to the lower back or thighs [3]. The disorder is associated with nausea, vomiting, backache, disturbed sleep, fatigue and poorer mood, and is often severe enough to significantly interfere with activities of daily living [3, 4], leading to absenteeism from school or work [5]. It has been estimated that the loss of quality-adjusted life years in primary dysmenorrhea is comparable to that seen in chronic diseases such as asthma or chronic migraine [6]. Yet despite the high prevalence of primary dysmenorrhea and the substantial distress it can cause, the pain is often accepted as a normal part of the menstrual cycle; accordingly, few women seek medical treatment [4] but instead choose to treat with over-the-counter medications.

Primary dysmenorrhea occurs when the lining of the womb or endometrium is expelled from the body during menstruation. This process is modulated and augmented by prostaglandins, such as $\text{PGF}_2\alpha$ [7], which cause the myometrium to contract, leading to uterine ischemia that stimulates pain neurons and thus elicits menstrual pain [4, 8]. While many factors contribute to menstrual cramps, the severity of pain correlates with prostaglandin levels [3, 9]. Suppression of prostaglandin formation, such as $\text{PGF}_2\alpha$ [7], reduces prostaglandin secretion from the uterus, and thus decreases the frequency and vigor of uterine contractions [10]. Therefore, treatment of primary dysmenorrhea predominantly depends on drugs that inhibit prostaglandin formation, and thus attenuate the symptoms of dysmenorrhea.

Both naproxen and acetaminophen are indicated for and commonly used on a non-prescription basis to treat the pain of primary dysmenorrhea [11, 12]. Their analgesic efficacy in primary dysmenorrhea has been evaluated in previous studies [13]. NSAIDs are effective inhibitors of the cyclooxygenase (COX) enzyme, which in turn inhibits prostaglandin synthesis and thereby reduces pain [14]. In contrast, acetaminophen is a weak COX inhibitor whose exact mechanism of action is still uncertain, but may include a reduction in prostaglandin production [7, 15].

In an effort to contribute to the body of evidence regarding the treatment of primary dysmenorrhea, we evaluated the analgesic efficacy of a maximum single, non-prescription dose of naproxen sodium (440 mg) compared with acetaminophen (1000 mg) in the treatment of menstrual pain associated with primary dysmenorrhea. We enrolled subjects with menstrual cramps who had at least moderate pain (2 on a categorical scale of 0-3), who would typically use over-the-counter NSAIDs for pain relief, and who could therefore benefit from a non-prescription analgesic. The primary outcome was the total pain relief (TOTPAR) score over 12 h. Secondary outcomes included summed pain intensity differences (SPID) and TOTPAR scores at various times over 12 h, the subjects' overall evaluation of treatment, and its safety and tolerability. The hypothesis was that naproxen sodium would provide greater relief of menstrual cramps over a longer period of time than acetaminophen, thus reducing the need for re-medication.

Methods

This was a multi-center, randomized, double-blind, two-treatment cycle, crossover study in healthy females with self-reported primary dysmenorrhea of moderate severity (confirmed by medical history and routine physical exam during the first visit). All eight sites were based in the US, and subjects were recruited through local advertisement and a proprietary database from the contract research organization. After a 21-day screening period (the time allotted for recruitment), eligible subjects were randomized to a maximum single non-prescription dose of either naproxen sodium (440 mg) or acetaminophen (1000 mg) when their menstrual cramps reached moderate severity, crossing over to the other treatment in the next menstrual cycle (Figure 1).

[Figure 1 near here]

Written informed consent was obtained from all subjects prior to admission in the study. Informed consent for subjects 15–17 years old was obtained from the child's parent or legal guardian using an institution review board-approved assent form and a parental/guardian informed consent form. The study adhered to Good Clinical Practice guidelines and the guiding principles detailed in the Declaration of Helsinki. Ethical approval was obtained from IntegReview IRB in Austin, Texas, USA, before the start of the study. The trial was registered on ClinicalTrials.gov, registration number NCT03448536 and EudraCT as 2017-005031-17.

Subjects

Healthy, ambulatory adolescent and adult female subjects (15–35 years old to ensure a reliable menstrual pattern) with a self-reported history of primary dysmenorrhea (onset <5 years after menarche) and at least moderate (2 on a categorical pain intensity scale, for easier recall, where 0=no pain and 3=severe pain) menstrual pain occurring during four of their past six menstrual cycles. A history of non-prescription analgesic use (e.g. naproxen sodium, aspirin, acetaminophen, or ibuprofen) for the treatment of moderate or severe menstrual pain, taken on at least one day of the menstrual cycle and which normally provided pain relief, was required. Subjects were required to have regular menstrual cycles (every 21–35 days) and be of child-bearing potential (but not pregnant, lactating, or less than 6 months postpartum), and using an appropriate method of contraception throughout the duration of the study. Key exclusion criteria included the use of prescription analgesics (i.e., oral use ≥ 5 times per week for >3 weeks) or routine use of non-prescription medications in excess of label recommended instructions for control of dysmenorrhea symptoms. Mood-altering agents (e.g., antidepressants, sedatives, phenothiazines, or anti-anxiety agents) were not allowed, unless on a stable dose for at least three months and not used specifically for dysmenorrhea or premenstrual syndrome. Additionally, piroxicam or oral corticosteroids were not allowed, except for inhaled or topical corticosteroids. Subjects were excluded if they had been using an oral contraceptive for less than 3 months, or were on an unstable dose within the last 3 months, or had switched from one oral contraceptive to another within the last 3 months or intended to do so in the course of the study. Use of an intrauterine device or hormonal implant or injection for contraception within the past 6 months was not allowed.

Procedure

Subjects were screened for up to 21 days to ensure they met all inclusion and exclusion criteria before being randomized to treatment (Figure 1). During this time, each subject received a treatment kit, pregnancy test kits, and an e-diary.

Eligible subjects were then randomized in a 1:1 crossover fashion to one of two blinded treatment sequences: 1) naproxen sodium 440 mg (2 x 220 mg tablets) for Treatment Period 1, crossing over to acetaminophen 1000 mg (2 x 500 mg caplets) for Treatment Period 2 (treatment sequence A/B); 2) acetaminophen 1000 mg (2 x 500 mg caplets) for Treatment Period 1, crossing over to naproxen sodium 440 mg (2 x 220 mg tablets) for Treatment Period 2 (treatment sequence B/A). Subjects, investigators, and staff involved in protocol procedures or data collection and analysis were blinded to the identity of the treatment sequence by over-encapsulation of the test products to ensure that they looked identical. Similar dissolution curves of over-encapsulated medications and original products were duly obtained.

Subjects self-administered the study drug (with a full glass of water) only at the onset of at least moderate menstrual pain (i.e., when they felt their pain intensity was ≥ 5 on the 0-10 numerical rating scale (NRS), and only if the pregnancy test was negative); site staff were notified prior to dosing. If the subject did not have sufficient menstrual pain intensity, had taken prohibited medications within the specified period of three days, had developed other confounding pain conditions, or was not able to complete all assessments for the next 12 h, then the Treatment Period was extended to the next menstrual cycle. Subjects were allowed a total of four menstrual cycles to complete two dosing cycles.

If adequate relief of menstrual pain was not achieved during a Treatment Period, then subjects were permitted to take rescue medication (although they were encouraged to wait at least 2 h after dosing of study medication). The rescue medication was ibuprofen 400 mg; only one dose for each Treatment Period was provided, although subjects could take their usual pain reliever afterwards if needed. Those who took rescue medication provided their last study assessment just prior to taking the rescue medication. All other pain and anti-inflammatory medications, including supplements, topical heat or cold, other products of topical application, and transcutaneous electrical nerve stimulation devices were discontinued approximately 72 h prior to the anticipated dosing for each treatment period and throughout the dosing/assessment period. The exception was low dose aspirin (≤ 100 mg daily) taken for cardioprotective purposes.

The duration of each subject's participation, using an average cycle time of 28 days, was approximately 77 days for two menstrual cycles and 133 days, for up to two extensions (four menstrual cycles) if the subject did not have sufficient menstrual pain intensity.

Assessments

All subjects used the e-diary to complete assessments for pain intensity (0-10 NRS) and pain relief (0-4 categorical pain relief scale) at baseline (pain intensity only) and for 12 h after taking the study medication (at 30 min and hourly thereafter from 1-12 h). At 12 h after taking the study medication, or immediately before first intake of rescue medication, subjects completed the global evaluation of the overall satisfaction with the effectiveness of the study medication for each dosing cycle.

The endpoint total pain relief (TOTPAR), is essentially the area under the curve of Pain Relief Score and Time. The primary endpoint TOTPAR over 12 h, was calculated by multiplying the pain relief score at each post-dose time point by the duration (h) since the preceding time point and then summing these values. Secondary endpoints included pain intensity differences (PID, derived by subtracting the NRS score at the post-dose time point from the baseline pain intensity score – a positive difference indicates improvement), summed pain intensity differences (SPID) over 0-6, 6-12, 0-12 and 6- 12 h (based on the NRS score as summation of PID), TOTPAR over 0-6 and 6-12 h, time to first use of rescue medication (h), and subject's global evaluation of treatment (performed either at 12 h post-dose or immediately after first intake of rescue medication; score based on the question, "Overall, I would rate the effectiveness of the study medication in relieving my menstrual pain as: 0=Poor, 1=Fair, 2=Good, 3=Very Good, 4=Excellent"). At each visit, adverse events (AEs) that were observed, mentioned upon questioning by study staff, or spontaneously reported by subjects were recorded. All reported AEs were collected throughout the treatment periods and coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Only treatment-emergent AEs (TEAEs) are presented here, i.e., AEs that began or worsened after the first dose of the study drug in a treatment period). Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature) and laboratory tests (urine drug screen and urine pregnancy test) were also monitored throughout the duration of the study, at every visit.

Statistical analysis

Analysis sets. Efficacy results were analyzed for both the intention-to-treat (ITT) population (i.e. all subjects randomly assigned, with at least one measure of an efficacy parameter after first dose of study drug) and the per protocol (PP) population (all subjects in the ITT population who did not have major protocol violations). Subjects who took rescue medication within 2 hour post dose were excluded from the PP. The PP population was used for the primary analysis of the efficacy parameters and the results are presented here. The ITT population was used as the sensitivity analysis. The safety population comprised all subjects who received at least one dose of study drug.

All statistical tests were two-sided and performed at the 5% level of significance, leading to 95% (two-sided) confidence intervals (CIs), unless otherwise stated. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Efficacy and safety endpoints. The primary efficacy endpoint (TOTPAR0-12) and the secondary efficacy endpoints for SPID and TOTPAR over time were analyzed using a mixed analysis of covariance (ANCOVA) model with fixed effects for baseline TOTPAR0-12, sequence, treatment, and period and included a random effect for subject within sequence for the crossover study design. The estimated treatment differences between the two treatments is also presented, together with the 2-sided 95% CIs for the difference and the p-value. Subjects who took rescue medication in the first 2 hours were excluded from the PP analysis set. Kaplan-Meier estimates of rescue medication use, and their 95% CIs, were presented over time by treatment. The PID scores were also evaluated at each post-dose time point, summarized descriptively by treatment, and plotted over time. Any missing values during the 12-h assessment period were imputed using the linear interpolation (trapezoid rule) or

extrapolation (last observation carried forward) approach, depending on availability of data surrounding the missing value. Global evaluation at 12 h post-dose or immediately before first intake of rescue medication was analyzed using the Cochran-Mantel-Haenszel (CMH) method with modified ridit scores. All AEs reported in the safety population were recorded, but only treatment-emergent AEs are displayed here.

Sample size. A total of 154 subjects would be required, assuming the treatment difference of 5.9 in TOTPAR12 with 90% power and the type I error of 0.05. Assuming a 23% drop out rate, approximately 200 subjects needed to be randomized.

Results

Subject characteristics

The first and last patient visits occurred on 5 April and 5 September 2018, respectively. Of the 242 subjects that were screened, 201 (mean age 24.8 years) were randomized to either the naproxen sodium/acetaminophen (n=100) or acetaminophen/naproxen sodium (n=101) treatment sequence (Figure 1). A total of 185 (76.4%) subjects completed the study. In the per protocol population, 170 subjects used naproxen sodium while 160 used acetaminophen during the study period. All subjects who took at least one dose of study medication were included in the safety population (n=196). Subject demographics and baseline characteristics were comparable between the groups (Table 1).

[Table 1 near here]

Pain outcomes

Primary endpoint. Over 12 h, total pain relief was significantly greater with naproxen sodium than acetaminophen (TOTPAR0-12 LS mean difference 4.31 [95% CI 2.06, 6.56]; $p<0.001$) (Table 2).

[Table 2 near here]

Secondary outcomes. Pain intensity over 12 h was significantly lower with naproxen sodium than acetaminophen (SPID0-12 LS mean difference 9.80 [95% CI 5.75, 13.85; $p<0.001$) (Table 2), supporting the results of the primary objective. From 0–6 h after dosing, both pain intensity and total pain relief were mostly comparable between naproxen sodium and acetaminophen (SPID0-6 LS mean difference 1.52 [95% CI -0.45, 3.49], $p=0.129$; TOTPAR0-6 LS mean difference 0.56 [95% CI -0.52, 1.64], $p=0.307$). However, significant differences in pain intensity and pain relief in favor of naproxen sodium became apparent at approximately hour 6 and were maintained over 12 hours (SPID6-12 LS mean difference 8.27 [95% CI 5.76, 10.78], $p<0.001$; TOTPAR6-12 LS mean difference 3.75 [95% CI 2.34, 5.16], $p<0.001$). Additional analysis showed that some measures of pain intensity became significant favoring naproxen sodium at earlier time points, e.g. SPID4-6 LS mean difference 1.49 [95% CI 0.23, 2.75] ($p=0.02$) and PID at hour 5 LS mean difference 0.51 [95% CI 0.06, 0.95] ($p=0.026$); the LS mean difference for TOTPAR4-6 was 0.62 [95% CI -0.09, 1.34] ($p=0.087$). These findings were reflected by the mean pain intensity difference and pain relief scores at different time points (Figure 2). There was a statistically significant difference in the time to first intake of rescue medication ($p<0.001$). The proportion of subjects who used rescue medication was significantly higher in the acetaminophen group than the naproxen sodium group at 6 h (14.4%

(n=23) vs. 5.9% (n=10), respectively; $p=0.01$) and at the end of treatment at 12 h (28.0% (n=45) vs. 11.2% (n=20), respectively; $p<0.01$). Overall, a significantly higher proportion of subjects rated naproxen sodium as “good” to “excellent” (70.6%) compared to acetaminophen (63.1%) ($p=0.002$) (Table 3). The sensitivity analysis, based on the ITT population, corroborated the results observed in the PP population.

[Figure 2 near here]

[Table 3 near here]

Safety

During the study, 23 TEAEs were reported in 20 (10.2%) subjects: 12 (6.3%) subjects who used naproxen sodium and 9 (4.9%) who used acetaminophen (Table 4). All were rated as mild (n=15) or moderate (n=8) in severity by the investigator. None was serious or led to study discontinuation, and no deaths were recorded. Drug-related TEAEs occurred in six (3.1%) subjects who used naproxen sodium and two (1.1%) who used acetaminophen. With both treatments, the most frequently-recorded drug-related TEAEs were gastrointestinal disorders, reported by four (2.1%) subjects who used naproxen sodium and one (0.5%) who used acetaminophen. Nausea was recorded in two (1.0%) subjects who used naproxen sodium and one (0.5%) who used acetaminophen. There were no clinically-significant changes in vital signs with either treatment compared with baseline.

[Table 4 near here]

Discussion

The purpose of our study was to compare a maximum single, non-prescription dose of naproxen sodium (440 mg) with that of acetaminophen (1000 mg) in the treatment of primary dysmenorrhea. The results confirm our hypothesis that naproxen sodium provides greater relief of pain from menstrual cramps over a longer period of time than acetaminophen. Our primary outcome demonstrated that total pain relief with naproxen sodium was significantly higher than with acetaminophen over the 12-h study period. The study also showed that significant differences in pain intensity and pain relief, in favor of naproxen sodium, began to become apparent from 4 h after dosing and were maintained over the 12 hours of the study. Substantially fewer subjects who used naproxen sodium (n=20 compared to n=45 for acetaminophen) had a need for rescue medication during the study. Satisfaction with treatment was significantly greater with naproxen sodium than acetaminophen. Overall, both naproxen sodium and acetaminophen were safe and well tolerated.

The results of our study provide much-needed robust evidence that both naproxen sodium and acetaminophen are effective in the treatment of primary dysmenorrhea, but that pain relief is greater and lasts longer with naproxen sodium – as may be expected, considering the longer elimination half-life of naproxen sodium (10–15 h [16] versus 1–3 hours for acetaminophen [17]). One single dose of naproxen sodium is sufficient to relieve pain throughout a 12-h period. A strength of our study is its crossover design, which minimizes interindividual differences as every subject served as their own control [18]. To ensure comparable baseline pain intensity across different menstrual cycles, participants took their assigned study drug only if moderate pain intensity was reached during their menstrual cycles. Care was taken to avoid any possible carryover effect, with a long washout period between

use of the study drugs (at least one menstrual cycle). A study that evaluates the analgesic effects of each drug over the entire period of dysmenorrhea may be useful, to further elucidate any advantages of either drug. However, this suggestion may pose a great limitation for acetaminophen on its daily dosing. As per label instructions in the US, immediate-release acetaminophen can be taken only every 6 hours up to three times (1000 mg) during 24 hours, leaving the patient with no coverage of pain relief for entire 6 hours. Thus, an objective comparison between naproxen sodium and acetaminophen would be not achievable.

Our study results confirm those of a previous pooled analysis of five studies in primary dysmenorrhea, which found that naproxen sodium provided greater pain relief than acetaminophen and placebo 30 minutes after administration, and acetaminophen, ibuprofen and placebo after 6 hours [13]. The pooled analysis also showed that naproxen sodium was well tolerated throughout the duration of the studies. The comparative extent and duration of analgesic effect of naproxen sodium and acetaminophen has been also evaluated in another validated pain model. A study using the dental pain model showed the statistical superiority of naproxen sodium over acetaminophen ($p < 0.01$) in terms of several measures of pain, including peak pain intensity difference and pain relief from 2 hours after dosing [19]. Similarly, this study showed the duration of analgesic effect with naproxen to be significantly longer than acetaminophen (median 9.9 h vs. 3.1 h, respectively; $p < 0.001$) [19]. The pooled analysis also showed that naproxen sodium was well tolerated throughout the duration of the studies.

Conclusions

In the treatment of primary dysmenorrhea – a disorder that is known to affect the majority of menstruating women at some point – the analgesic efficacy of a maximum single, non-prescription dose of naproxen sodium (440 mg) is sufficient to effectively relieve menstrual pain for up to 12 h compared with a maximum single dose of acetaminophen (1000 mg). Additional analysis showed that significant differences in pain intensity in favor of naproxen sodium are apparent from around 4–6 hours, before the recommended re-dosing time for acetaminophen (6 hours). Thus, non-prescription naproxen sodium is an effective alternative to acetaminophen in the management of pain due to primary dysmenorrhea.

Transparency

Declaration of funding

This study was sponsored by Bayer Healthcare.

Declaration of financial/other relationships

Azita Tajaddini, Alberto Paredes-Diaz, Bob An, and Robert Centofanti are employed by Bayer Healthcare. Stephen Daniels was a consultant for Bayer during the design phase of the study.

Author contributions

Azita Tajaddini contributed to the implementation, analysis, and interpretation of the study, as well as drafting and revision of the manuscript and approval for publishing. Alberto Paredes-Diaz, and Bob An contributed to the concept, design, implementation, analysis, and interpretation of the study, as well as drafting and revision of the manuscript and approval for publishing. Robert Centofanti has contributed to implementation of the study as well as drafting and revision of the manuscript and approval for publishing. Stephen Daniels contributed to the concept, design, and interpretation of the study, as well as revision of the manuscript and approval for publishing. 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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Tables

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

	Naproxen sodium– acetaminophen (N=95), n (%)	Acetaminophen– naproxen sodium (N=94), n (%)	Total (N=189), n (%)
Age, mean ± SD (range)	24.8±5.58 (16-35)	24.9±5.74 (15-35)	24.8±5.64 (15-35)
Race, n (%)			
White	65 (68.4)	66 (70.2)	131 (69.3)
Black or African American	23 (24.2)	23 (24.5)	46 (24.3)
Asian	6 (6.3)	2 (2.1)	8 (4.2)
American Indian/Alaska native	1 (1.1)	0	1 (0.5)
Native Hawaiian/other pacific islander	0	1 (1.1)	1 (0.5)
Multiple	0	2 (2.1)	2 (1.1)
Height (cm), mean ± SD	164.94 ± 7.097	163.92 ± 6.358	164.43 ± 6.741
Weight (kg), mean ± SD	74.41 ± 21.330	78.86 ± 22.957	76.63 ± 22.208
Method of birth control, n (%)			
Abstinence and double barrier method	34 (35.8)	32 (34.0)	66 (34.9)
Double barrier method	26 (27.4)	30 (31.9)	56 (29.6)
Permanent sterilization	9 (9.5)	7 (7.4)	16 (8.5)
Oral contraceptive	26 (27.4)	25 (26.6)	51 (27.0)
Baseline pain intensity, mean ± SD (range) †	7.3 ± 1.46 (5-10)	7.3 ± 1.46 (5-10)	

* Based on initial groups after randomization; † based on total number of subjects treated with the individual drugs (naproxen sodium, n=170; acetaminophen, n=160). SD, standard deviation.

Table 2. Least squares mean values and differences for primary and secondary outcomes (per protocol population).

	Naproxen sodium (N=170)	Acetaminophen (N=160)	Statistical significance, p
Primary outcome			
TOTPAR0-12			
LS mean $\pm$ SE (95% CI)	29.18 $\pm$ 1.003	24.87 $\pm$ 1.029	
Difference of LS means (95% CI) ^a	(27.20, 31.16)	(22.84, 26.91)	
		4.31 (2.06, 6.56)	<0.001
Secondary outcomes			
SPID0-12 ^b			
LS mean $\pm$ SE (95% CI)	53.62 $\pm$ 1.931	43.82 $\pm$ 1.977	
Difference of LS means (95% CI) ^a	(49.80, 57.44)	(39.91, 47.73)	
		9.80 (5.75, 13.85)	<0.001
SPID0-6 ^b			
LS mean $\pm$ SE (95% CI)	23.47 $\pm$ 0.902	21.94 $\pm$ 0.925	
Difference of LS means (95% CI) ^a	(21.68, 25.25)	(20.11, 23.77)	
		1.52 (-0.45, 3.49)	NS
SPID4-6 ^b			
LS mean $\pm$ SE (95% CI)	14.77 $\pm$ 0.559	13.28 $\pm$ 0.573	
Differences of LS means (95% CI)	(13.66, 15.87)	(12.15, 14.41)	
		1.49 (0.23, 2.75)	0.02
SPID6-12 ^b			
LS mean $\pm$ SE (95% CI)	30.15 $\pm$ 1.252	21.88 $\pm$ 1.280	
Difference of LS means (95% CI) ^a	(27.68, 32.63)	(19.35, 24.41)	
		8.27 (5.76, 10.78)	<0.001
TOTPAR0-6 ^b			
LS mean $\pm$ SE (95% CI)	13.46 $\pm$ 0.451	12.90 $\pm$ 0.463	
Difference of LS means (95% CI) ^a	(12.57, 14.35)	(11.99, 13.82)	
		0.56 (-0.52, 1.64)	NS
TOTPAR4-6 ^b			
LS mean $\pm$ SE (95% CI)	7.94 $\pm$ 0.297 (7.35,	7.31 $\pm$ 0.305 (6.71,	
Differences of LS means (95% CI)	8.52)	7.91)	
		0.62 (-0.09, 1.34)	NS
TOTPAR6-12 ^b			
LS mean $\pm$ SE (95% CI)	15.72 $\pm$ 0.661	11.97 $\pm$ 0.677	
Difference of LS means (95% CI) ^a	(14.41, 17.02)	(10.63, 13.30)	
		3.75 (2.34, 5.16) *	<0.001

^a Based on mixed ANCOVA model; the difference of LS means was from the ANCOVA model; the p-value was from an F-statistic, where the null hypothesis was no difference among the adjusted population means. ^b Full model-adjusted. ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; NRS, numerical rating scale; NS, not significant;

SE, standard error; SPID, summed pain intensity difference; TOTPAR = total pain relief scores.

Table 3. Global evaluation scores (per-protocol population).

	Naproxen sodium (N=170), n (%)	Acetaminophen (N=160), n (%)
Poor	10 (6.4)	13 (8.3)
Fair	26 (16.7)	42 (26.9)
Good	25 (16.0)	38 (24.4)
Very good	60 (38.5)	38 (24.4)
Excellent	35 (22.4)	25 (16.0)

p=0.002 in favor of naproxen sodium, obtained from Cochran-Mantel-Haenszel test with modified ridit scores. Global evaluation performed either at 12 h post-dose or immediately at the first intake of rescue medication. Global evaluation score based on the question, 'Overall, I would rate the effectiveness of the study medication in relieving my menstrual pain as: 0=Poor, 1=Fair, 2=Good, 3=Very Good, 4=Excellent'.

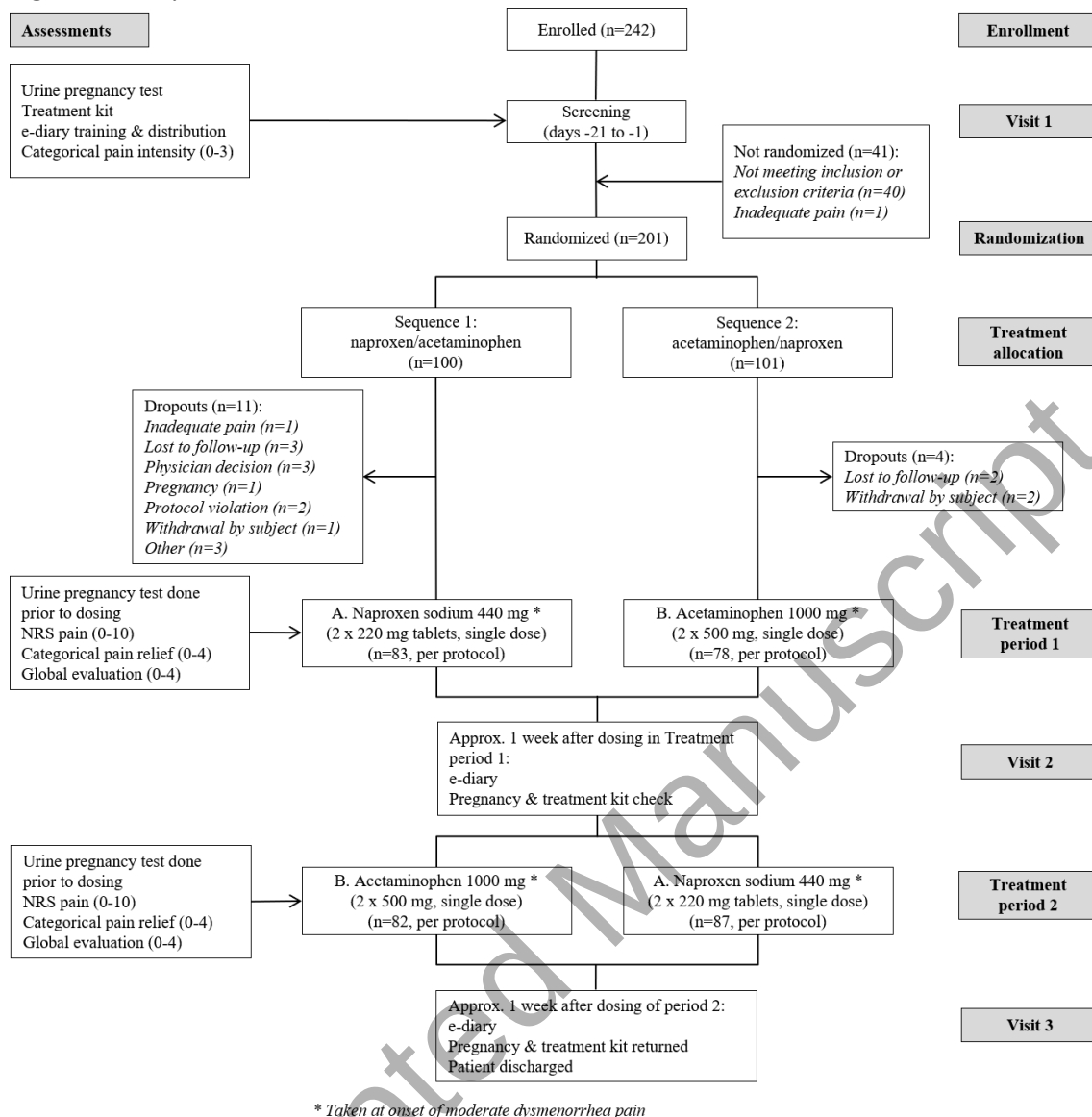
Table 4. Summary of treatment-emergent adverse events (safety population).

	Naproxen sodium (N=192), n (%)	Acetaminophen (N=185), n (%)	Total (N=196), n (%)
Total number of TEAEs	14	9	23
Number of subjects with at least one TEAE	12 (6.3)	9 (4.9)	20 (10.2)
Infections and infestations	4 (2.1)	3 (1.6)	7 (3.6)
Pharyngitis streptococcal	1 (0.5)	2 (1.1)	3 (1.5)
Upper respiratory tract infection	3 (1.6)	0	3 (1.5)
Urinary tract infection	0	1 (0.5)	1 (0.5)
Gastrointestinal disorders	4 (2.1)	1 (0.5)	5 (2.6)
Nausea	2 (1.0)	1 (0.5)	3 (1.5)
Gastritis	1 (0.5)	0	1 (0.5)
Vomiting	1 (0.5)	0	1 (0.5)
Injury, poisoning and procedural complications	1 (0.5)	1 (0.5)	2 (1.0)
Facial bones fracture	1 (0.5)	0	1 (0.5)
Laceration	1 (0.5)	0	1 (0.5)
Nail avulsion	0	1 (0.5)	1 (0.5)
Eye disorders	1 (0.5)	1 (0.5)	1 (0.5)
Eye pruritus	1 (0.5)	1 (0.5)	1 (0.5)
Investigations	1 (0.5)	0	1 (0.5)
Blood pressure increased	1 (0.5)	0	1 (0.5)
Metabolism and nutrition disorders	0	1 (0.5)	1 (0.5)
Vitamin D deficiency	0	1 (0.5)	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (0.5)	0	1 (0.5)
Back pain	1 (0.5)	0	1 (0.5)
Nervous system disorders	1 (0.5)	0	1 (0.5)
Dizziness	1 (0.5)	0	1 (0.5)
Psychiatric disorders	0	1 (0.5)	1 (0.5)
Attention deficit/hyperactivity disorder	0	1 (0.5)	1 (0.5)
Reproductive system and breast disorders	0	1 (0.5)	1 (0.5)
Amenorrhea	0	1 (0.5)	1 (0.5)

The total number of AEs counted all TEAEs for subjects. At each level of subject summarization, a subject was counted once if the subject reported one or more events. Adverse events were coded using MedDRA version 21.0. A TEAE was an AE with worsening or a start date occurring on or after the date of the first dose of study drug for that period. AE, adverse event; TEAE, treatment-emergent adverse event.

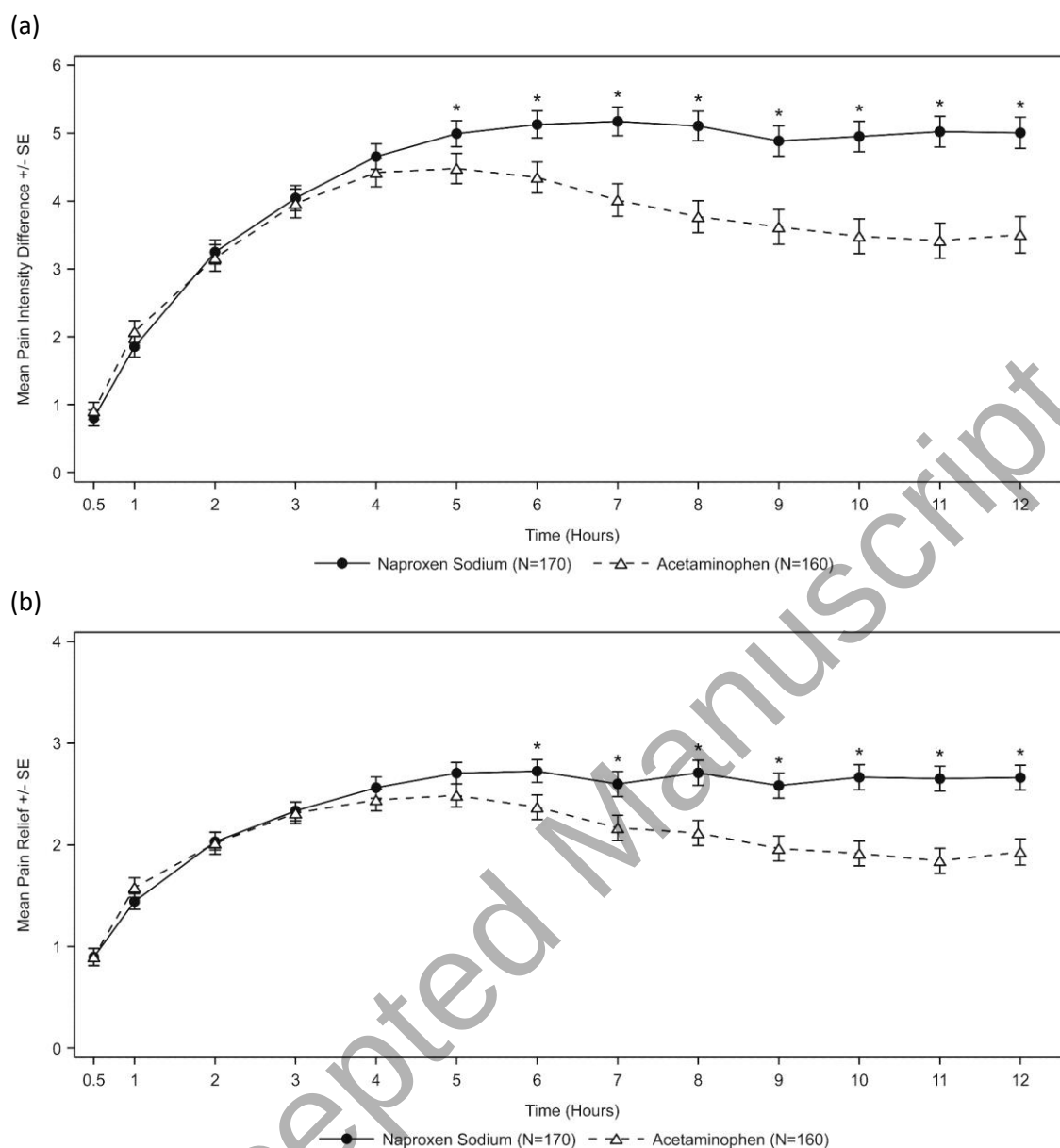
Figures

Figure 1. Study flow chart.



Treatment periods 1 and 2 were extended by one additional menstruation cycle if the subject did not elect to take the treatment due to insufficient pain, had taken prohibited medications, had developed other confounding pain conditions, or did not have adequate time for pain assessments.

Figure 2. Average pain intensity difference (a) and pain relief (b) scores over time by treatment (per-protocol population).



* $p < 0.05$. Pain intensity difference scores based on a numerical rating scale (NRS) of 0-10; pain relief scores based on nominal scoring 0=None, 1=A little, 2=Some, 3=A lot, 4=Complete; scores are derived by subtracting the post-baseline NRS score at each evaluation from the baseline score. SE, standard error; SPID, Sum of Pain Intensity Difference.