Document Type:	Study Protocol
Official Title:	A Double-Blind, Randomized, Crossover Study to Assess Menstrual Cramp Pain Associated with Primary Dysmenorrhea
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1. Title page

A Double-Blind, Randomized, Crossover Study to Assess Menstrual Cramp Pain Associated with Primary Dysmenorrhea

Test drugs:	BAY 117031 / Naproxen Sodium		
Study purpose:	Clinical efficacy		
Clinical study phase:	Phase 4	Date:	16-Apr-2018
Registration:	Not Applicable	Version no.:	2.0
IMPACT Number:	19737		
Sponsor:	Bayer HealthCare LLC, Consumer Health 100 Bayer Boulevard Whippany, NJ 07981-0915, USA		
Sponsor's medical expert:	PPD Bayer HealthCare LLC, Consumer Health		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Role: PPD
PPD

Date: .....

Signature: .....

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis - amended

Title	A Double-Blind, Randomized, Crossover Study to Assess Menstrual Cramp Pain Associated with Primary Dysmenorrhea
IMPACT	19737
Clinical study phase	4
Study objective(s)	To evaluate the analgesic efficacy of a maximum single dose of two tablets of Aleve (2 x naproxen sodium 220 mg; total dose 440 mg) as compared to two tablets of Tylenol Extra Strength (2 x acetaminophen 500 mg; total dose 1000 mg) for the treatment of menstrual cramping pain associated with primary dysmenorrhea
Test drug(s)	
Name of active ingredient	Naproxen sodium
Dose(s)	220 mg
Route of administration	Oral
Duration of treatment	12 hours
Reference drug(s)	
Name of active ingredient	Acetaminophen
Dose(s)	500 mg
Route of administration	Oral
Duration of treatment	12 hours
Background treatment	Not applicable
Indication	Primary dysmenorrhea of at least moderate severity

Diagnosis and main criteria for inclusion /exclusion	Inclusion Criteria • Ambulatory healthy female patients between 15 and 35 years of age; • Patient has a history of OTC analgesic use for treatment of primary dysmenorrhea. • Patient has a history of regular menstrual cycles that typically occurs between every 21 to 35 days; • Patient has a self-reported history of primary dysmenorrhea (onset <5 years after menarche) with at least moderate menstrual cramp pain (based on the categorical pain intensity scale) occurring during four of the past six menstrual cycles; • Patient has a self-reported history of primary dysmenorrhea with other causes of dysmenorrhea having been excluded; • Patient typically requires at least one dose of a OTC analgesic medication such as naproxen, aspirin, acetaminophen, or ibuprofen taken on at least 1 day of her menstrual cycle for the treatment of moderate or severe menstrual cramp pain, and normally experiences pain relief from these medications; • Patient is of child-bearing potential and is using one of the following methods of contraception and agrees to continue this same method for the duration of the study: - Abstinence for at least the last 60 days AND willingness to use double barrier method should the patient become sexually active during the study; - Double barrier method (condom with contraceptive foam, diaphragm with contraceptive gel); - Permanent sterilization of patient or her spouse/partner; - Oral contraceptive (must have been using the same oral contraceptive for at least three months prior to study entry and agrees to remain on the same type and method throughout the course of the study). • Patient is willing to participate in the study and return to the study site within approximately 1 week after her menstrual cycle to return the study medication, urine pregnancy test, and for review of the completed patient e-diary; • Patient is willing to abstain from alcohol consumption throughout the 12-hour Treatment Period; • Patient is willing to abstain from caffeine consumption throughout the 12-hour Treatment Period; • Patient is willing to ingest the overencapsulated tablets throughout the study. Exclusion Criteria - **amended** • Patient has a known history of allergic, idiosyncratic or serious adverse reaction, to acetaminophen, naproxen, aspirin, ibuprofen, or any other nonsteroidal anti-inflammatory drug (NSAID); • Patient has a known allergy to any of the excipients in any of the study medication products; • Patient has experienced asthma, urticaria, or allergic-type reactions after taking aspirin, acetaminophen or other NSAIDs; • Patient has significant co-existing illness, including gastrointestinal, hepatic, renal, neurologic, cardiovascular, psychiatric, endocrine, respiratory, surgical procedure or other condition that, in the Investigator's judgment, contraindicates administration of the study medication; • Patient has a current or past history of severe gastritis, gastrointestinal bleeding or ulceration; • Patient has a current or past history of one or more of the following conditions: secondary dysmenorrhea, pelvic inflammatory disease, urinary tract infection (currently acute or recurrent [defined as more than three per year]), prior history of an urinary tract infection is eligible for enrollment, adnexal masses, uterine fibroids, endometriosis, adenomyosis that in the opinion of the Investigator would impact patient safety and/or the study data; • Patient has an ongoing sexually transmitted disease (except for a history of genital herpes or Human Papillomavirus) or has abnormal vaginal discharge;

	• Patient requires prescription analgesics, narcotic, non-NSAID (i.e., defined as oral use of 5 or more times per week for greater than 3 weeks) or has routinely taken OTC medications in excess of label recommended instructions for control of dysmenorrhea symptoms; • Patient is taking mood-altering agents (e.g., antidepressants, sedatives, phenothiazines, or anti-anxiety agents). Patients who are on a stable dose for at least 3 months, and not taking this medication for dysmenorrhea or premenstrual syndrome are eligible for enrollment; • Patient does not agree to abstain from taking any analgesic and/or anti-inflammatory medication (with the exception of low dose aspirin [defined as no greater than 100 mg daily] taken for cardioprotective purposes) approximately 72 hours prior to the anticipated treatment period and throughout the dosing/assessment period. All pain and anti-inflammatory medications including supplements, topical heat or cold, and other products of topical application will be discontinued approximately 72 hours prior to the anticipated dosing for each treatment period and throughout the dosing/assessment period; • Patient does not agree to abstain from using transcutaneous electrical nerve stimulation devices that are used to treat dysmenorrhea throughout each treatment period; • Patient is taking piroxicam (Feldene®) or oral corticosteroids. Patients taking inhaled or topical corticosteroids are eligible for enrollment; • Patient is pregnant, lactating , or less than 6 months postpartum; • Patient is currently using an intra-uterine devices (IUD), or using hormonal implants (e.g., Norplant) or injections (e.g., Depo-Provera) for contraception or used within the past 6 months; • Patient is currently using an oral contraceptive for less than 3 months, has been on a unstable dose within the last 3 months or has switched from one oral contraceptive to another within the last 3 months or intends to do so in the course of the study; • Patient has a history of chronic abuse of alcohol (regularly consumes 3 or more alcoholic drinks per day), analgesics, narcotic analgesics, ergot alkaloids, tranquilizers, or opioids or other substances known to produce dependence; in the judgement of the investigator within the past 3 years; • Positive drug screen at screening and Visit 2 for illegal drug substances, or non-prescribed controlled substances; • Positive pregnancy test or breast feeding at screening and prior to dosing in each Treatment Period; • Patients with a medical disorder, condition or history such that could impair the patient's ability to participate or complete this study in the opinion of the investigator.
Study design	A multi-center, randomized, double-blind, two treatment cycle, crossover study in adolescent and adult female patients with primary dysmenorrhea of at least moderate pain. The study consists of a 21 day Screening Phase and two Treatment Periods within Treatment Phase. Qualified patients will be randomized in a 1:1 crossover fashion (A:B or B:A) to a single dose of naproxen sodium 440 mg (two tablets of 220 mg [Treatment A]) and a single dose of acetaminophen 1000 mg (two tablets of 500 mg [Treatment B])
Methodology	Total pain relief scores (TOTPAR) over 12 hours, will be calculated by multiplying the pain relief score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values
Type of control	Active (acetaminophen)
Data Monitoring Committee	No
Number of patients	200
Primary variable(s)	TOTPAR0-12
Time point/frame of measurement for primary variable(s) - amended	0-4 categorical pain relief scale at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours post-dose
Plan for statistical analysis	TOTPAR0-12 will be analyzed using analysis of variance (ANOVA) for the cross-over study design

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List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COX	Cyclooxygenase
CSR	Clinical Study Report
(e)CRF	(electronic) Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-Treat
IUD	intra-uterine device
IV/WRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over-the-Counter
PID	Pain Intensity Differences
PP	Per Protocol
QA	Quality Assurance
RNR	Randomization Number
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNR	Screening Number
SOC	System Organ Class
SPID	Summed Pain Intensity Difference
SUSAR	Serious Unexpected Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TOTPAR	Total Pain Relief

3. Introduction

Background

Primary dysmenorrhea (painful menstrual cramping that occurs during menses) is a common problem experienced by women in their reproductive years. In a study to determine the prevalence of dysmenorrhea in reproductive-age women, 36% reported always or often having pain with their menstrual periods and 90% of the women reported to have some degree of dysmenorrhea.[1] This type of pain can interfere significantly with their daily activities. The pathophysiology of the condition is primarily prostaglandin driven. At the beginning of menses, prostaglandins are released and play a major role in inducing uterine contractions within the female reproductive system. These contractions lead to uterine ischemia which stimulates pain neurons resulting in pain. The severity of pain has been studied and correlated with the level of menstrual prostanglandin.[2]

Naproxen sodium is a non-selective cyclooxygenase inhibitor and ultimately inhibits prostaglandins. Aleve® (naproxen sodium) is available over-the-counter and is indicated for temporary relief of minor aches and pains due to various pain states, including menstrual cramps. Tylenol® Extra Strength (acetaminophen) is also available over-the-counter and is indicated to temporarily relieve minor aches and pains due to premenstrual and menstrual cramps.

The purpose of this study is to compare the maximum single dose of Aleve® (two tablets, equivalent to 440 mg of naproxen sodium) to the maximum single dose of Tylenol Extra Strength (two tablets, equivalent to 1000 mg of acetaminophen) in the treatment of primary dysmenorrhea.

Benefit-risk assessment

Patients with at least moderate pain due to primary dysmenorrhea who would typically take over-the-counter NSAIDs for pain relief will be enrolled in this study. The two menstrual cycle treatment design falls within established treatment guidelines. Patients who experience a treatment failure have the option of taking rescue medication for pain relief.

During the study, patients will be closely monitored for the occurrence of adverse events. Weighing between the potential risks of OTC analgesics associated with the study, and given the ability to mitigate risks through close monitoring, this study is considered clinically and ethically acceptable.

4. Study objectives

Primary

- The primary objective of this study is to evaluate the analgesic efficacy of a maximum single dose of two tablets of Aleve (2 x naproxen sodium 220 mg; total dose 440 mg) as compared to two tablets of Tylenol Extra Strength (2 x acetaminophen 500 mg; total dose 1000 mg) for the treatment of menstrual cramping pain associated with primary dysmenorrhea.

Secondary

- To evaluate the safety and tolerability of naproxen sodium and acetaminophen.

5. Study design

Design Overview

This is a multi-center, randomized, double-blind, two treatment cycle, crossover study in adolescent and adult female patients with primary dysmenorrhea. At the completion of the Screening phase, eligible patients will be randomized in a 1:1 crossover fashion (A:B or B:A) to a single dose of naproxen sodium 440 mg (two tablets of 220 mg [Treatment A]) and a single dose of acetaminophen 1000 mg (two tablets of 500 mg [Treatment B]).

The study consists of a 21 day Screening Phase and two Treatment Periods within the Treatment Phase. The study center may schedule screening testing on multiple days as needed, provided all screening tests are done within 21 days. Qualified patients will be randomized into one of two treatment sequences. Approximately 260 patients will be screened prior to the first Treatment period during the Treatment Phase. Approximately 200 patients will be randomized to a specific treatment sequence.

Screening Phase Visit 1 - (Day -21 to -1)

Eligible patients will be selected within a screening period of 21 days prior to the start of the first Treatment Period within the Treatment Phase of the study. Patients will be questioned in order to determine the severity of menstrual pain (at least moderate pain on a categorical pain intensity scale in order to be included) experienced in past menstrual cycles prior to randomization in the study.

After the successful completion of screening procedures, patients will be randomized into one of two treatment sequences. In addition, each patient will receive a treatment kit, pregnancy test kits and e-diary. The patients will receive training on the use of the e-diary in addition to instructions on how to take their assigned medication. Automatic reminders will be set up in the e-diary to instruct patients to complete the assessments as needed.

During both Treatment Periods, patients will be instructed to discontinue use of all pain medications including supplements, topical heat or cold, and other products of topical application approximately three days before the expected first day of menstruation of their menstrual cycle and throughout the dosing/assessment period.

Treatment Period 1

After completion of screening and randomization, patients will start the first of two Treatment Periods. This part of the Treatment Phase will vary from patient to patient depending on the duration of their menstrual cycle (in days) and when the menstrual cycle started with respect to randomization. Patients will be instructed to use their e-diary when they think they are *close* to approaching the first day of their menstrual cycle. Patients will discontinue the use of all pain medications including supplements, topical heat or cold, and other products of topical application approximately three days before the expected first day of menstruation and throughout the treatment/assessment period. Once the patient has reached qualifying pain, the patient will notify the site through a phone call to the study center before beginning treatment. Patients are only required to call and leave a voice message. Approval is not needed to proceed with the next steps. Patients will then perform a urine pregnancy test and will take the designated treatment only if the pregnancy test is negative and when they feel their pain is ≥5

on the NRS scale. After taking the study medication the patient will complete the pain/pain relief assessment (0-10 NRS and the 0-4 categorical pain relief scale) at the designated time intervals using the e-diary over the next 12 hour time period. At 12 hours after taking the study medication, patients will complete the Global Evaluation of the overall satisfaction with the effectiveness of the study medication. If the patient decides to take rescue medication prior to the 12 hours, the patient will be instructed to complete the Global Evaluation prior to taking the rescue medication.

If the patient does not have sufficient menstrual pain intensity, has taken prohibited medications within the specified period of 3 days, developed other confounding pain conditions, or is not able to complete all assessments for the next 12 hours, then Treatment Period 1 can be extended to the next menstrual cycle. Patients must inform study staff if they require an extension and only one extension for Treatment Period 1 is possible. If the patient does not dose the study medication within the next menstrual cycle (as part of the extension), then the patient will contact the study center immediately. The patient will proceed to Visit 2 and if eligible, the patient will proceed to Treatment Period 2.

Visit 2 (after the completion of Treatment Period 1)

Patients will return to the study center approximately one week after use of study medication. On visit 2, the patients will bring their used/unused pregnancy test kit/s, treatment kit and e-diary for review. Patients will be given the instructions for treatment period 2 if still eligible to participate in the study.

Treatment Period 2

Patients will be instructed to use their e-diary when they think they are *close* to approaching the first day of their menstrual cycle. Patients will discontinue use of all pain medications including supplements, topical heat or cold, and other products of topical application approximately three days before the expected first day of menstruation and throughout the treatment /assessment period. Once the patient has reached qualifying pain, the patient will notify the site before beginning treatment by phone call to the study center. Patients are only required to call and leave a voice message. Approval is not needed to proceed with the next steps. Patients will then perform a urine pregnancy test and take the designated treatment only if the pregnancy test is negative and when they feel their pain is ≥5 on the NRS scale. After taking the study medication, the patient will complete the pain/pain relief assessment (0-10 NRS and the 0-4 categorical pain relief scale) at the designated time intervals using the e-diary over the next 12 hour time period. At 12 hours after taking the study medication, patients will complete the Global Evaluation of the overall satisfaction with the effectiveness of the study medication. If the patient decides to take rescue medication prior to the 12 hours, the patient will be instructed to complete the Global Evaluation prior to taking the rescue medication.

If the patient does not have sufficient menstrual pain intensity, has taken prohibited medications within the specified period of 3 days, developed other confounding pain conditions, or is not able to complete all assessments for the next 12 hours, then Treatment Period 2 can be extended to the next menstrual cycle. Patients must inform study staff if they require an extension and only one extension for Treatment Period 2 is possible. If the patient

does not dose the study medication within the next menstrual cycle (as part of the extension), then the patient will contact the study center immediately. The patient will proceed to Visit 3.

Visit 3 End of Study (after the completion of Treatment Period 2)

Patients will return to the study center approximately one week after use of study medication. Patient will return their used/unused pregnancy test kit/s, treatment kit and e-diary for review. Upon completion of all study procedures, patients will be discharged from the clinical site and be considered completed.

The duration of each patient's participation will be approximately 77 days for 2 menstrual cycles and 133 days for 4 menstrual cycles (if it was required for evaluation using an average cycle time of 28 days). For an overview on the study design and study procedures see Figure 1.

Figure 1 – Design Overview

	Screening Phase	Treatment Phase			
Study days	**Visit 1 Screening Days -21 to -1**	**Treatment Period 1 After Screening**	**Visit 2 After Period 1**	**Treatment Period 2 After Visit 2**	**Visit 3 End of Study**
Sequence 1	Urine pregnancy test Treatment kit e-diary training & distribution Categorical pain intensity (0-3)	◈**A** Urine pregnancy test done prior to dosing NRS pain (0-10) Categorical pain relief (0-4) Global evaluation (0-4)	approx. 1 week after dosing of period 1 e-diary, pregnancy and treatment kit check	◈**B** Urine pregnancy test done prior to dosing NRS pain (0-10) Categorical pain relief (0-4) Global evaluation (0-4)	approx. 1 week after dosing of period 2 e-diary, pregnancy and treatment kit returned Patient discharged
	✱				
Sequence 2	Urine pregnancy test Treatment kit e-diary training & distribution Categorical pain intensity (0-3)	◈**B** Urine pregnancy test done prior to dosing NRS pain (0-10) Categorical pain relief (0-4) Global evaluation (0-4)	approx. 1 week after dosing of period 1 e-diary, pregnancy and treatment kit check	◈**A** Urine pregnancy test done prior to dosing NRS pain (0-10) Categorical pain relief (0-4) Global evaluation (0-4)	approx. 1 week after dosing of period 2 e-diary, pregnancy and treatment kit returned Patient discharged
		✱ = Randomization of a treatment sequence **◈ = Onset of dysmenorrhea pain**			
		A = naproxen sodium 440 mg (220 mg x 2 tablets) **B = acetaminophen 1000 mg (500 mg x 2 tablets)**			
		Note: Treatment Period 1 and 2 may each be extended by one additional menstruation cycle if the patient does not elect to take the treatment due to insufficient pain, has taken prohibited medications, developed other confounding pain conditions, or do not have adequate time for pain assessments.			

Justification of the design

The study was designed to capture menstrual pain in patients who could benefit from the administration of an OTC analgesic. OTC analgesics are commonly used to treat the pain of dysmenorrhea (3,4). The dysmenorrhea pain model has been widely studied in the approval of both prescription and OTC medications. In this study, as in all pain studies, should a patient not get sufficient pain relief from the investigational medical product (IMP), then rescue medication may be used.

6. Study population

6.1 Inclusion criteria

Patients will be allowed to participate in the study if they meet the following eligibility criteria:

1. Patient has given written informed consent to participate in the study prior to admission to the study;
2. Ambulatory healthy female patients between 15 and 35 years of age;
3. Patient has a history of OTC analgesic use for treatment of primary dysmenorrhea.
4. Patient has a history of regular menstrual cycles that typically occurs between every 21 to 35 days;
5. Patient has a self-reported history of primary dysmenorrhea (onset <5 years after menarche) with at least moderate menstrual cramp pain (based on the categorical pain intensity scale) occurring during four of the past six menstrual cycles;
6. Patient has a self-reported history of primary dysmenorrhea with other causes of dysmenorrhea having been excluded;
7. Patient typically requires at least one dose of a OTC analgesic medication such as naproxen, aspirin, acetaminophen, or ibuprofen taken on at least 1 day of her menstrual cycle for the treatment of moderate or severe menstrual cramp, and normally experiences pain relief from these medications;
8. Patient is of child-bearing potential and is using one of the following methods of contraception and agrees to continue this same method for the duration of the study:
    a. Abstinence for at least the last 60 days AND willingness to use double barrier method should the patient become sexually active during the study;
    b. Double barrier method (condom with contraceptive foam, diaphragm with contraceptive gel);
    c. Permanent sterilization of patient or her spouse/partner;
    d. Oral contraceptive (must have been using the same oral contraceptive for at least three months prior to study entry and agrees to remain on the same type and method throughout the course of the study).
9. Patient is willing to participate in the study and return to the study site within approximately 1 week after her menstrual cycle to return the study medication, urine pregnancy test, and for review of the completed patient e-diary;
10. Patient is willing to abstain from alcohol consumption throughout the 12-hour Treatment Period;
11. Patient is willing to abstain from caffeine consumption throughout the 12-hour Treatment Period;
12. Patient is willing to ingest the overencapsulated tablets throughout the study;
13. Patient is willing and able to participate in all scheduled visits, treatment plan, laboratory tests and other study procedures according to the clinical protocol.

6.2 Exclusion criteria - amended

Patients presenting with any of the following will not be included in the study:

1. Patient has a known history of allergic, idiosyncratic or serious adverse reaction, to acetaminophen, naproxen, aspirin, ibuprofen, or any other nonsteroidal anti-inflammatory drug (NSAID);
2. Patient has a known allergy to any of the excipients in any of the study medication products;
3. Patient has experienced asthma, urticaria, or allergic-type reactions after taking aspirin, acetaminophen, or other NSAIDs;
4. Patient has significant co-existing illness, including gastrointestinal, hepatic, renal, neurologic, cardiovascular, psychiatric, endocrine, respiratory, surgical procedure or other condition that, in the Investigator's judgment, contraindicates administration of the study medication;
5. Patient has a current or past history of severe gastritis, gastrointestinal bleeding or ulceration;
6. Patient has a current or past history of one or more of the following conditions: secondary dysmenorrhea, pelvic inflammatory disease, urinary tract infection (currently acute or recurrent [defined as more than three per year]), prior history of an urinary tract infection is eligible for enrollment, adnexal masses, uterine fibroids, endometriosis, adenomyosis that in the opinion of the Investigator would impact patient safety and/or the study data;
7. Patient has an ongoing sexually transmitted disease (except for a history of genital herpes or Human Papillomavirus) or has abnormal vaginal discharge;
8. Patient requires prescription analgesics, narcotic, non-NSAID (i.e., defined as oral use of 5 or more times per week for greater than 3 weeks) or has routinely taken OTC medications in excess of label recommended instructions for control of dysmenorrhea symptoms;
9. Patient is taking mood-altering agents (e.g., antidepressants, sedatives, phenothiazines, or anti-anxiety agents). Patients who are on a stable dose for at least 3 months, and not taking this medication for dysmenorrhea or premenstrual syndrome are eligible for enrollment;
10. Patient does not agree to abstain from taking any analgesic and/or anti-inflammatory medication (with the exception of low dose aspirin [defined as no greater than 100 mg daily] taken for cardioprotective purposes) approximately 72 hours prior to the anticipated treatment period and throughout the dosing/assessment period. All pain and anti-inflammatory medications including supplements, topical heat or cold, and other products of topical application will be discontinued approximately 72 hours prior to the anticipated dosing for each treatment period and throughout the dosing/assessment period;
11. Patient does not agree to abstain from using transcutaneous electrical nerve stimulation devices that are used to treat dysmenorrhea throughout each treatment period;
12. Patient is taking piroxicam (Feldene®) or oral corticosteroids. Patients taking inhaled or topical corticosteroids are eligible for enrollment;
13. Patient is pregnant, lactating, or less than 6 months postpartum;

14. Patient is currently using an intra-uterine devices (IUD), or using hormonal implants (e.g., Norplant) or injections (e.g., Depo-Provera) for contraception or used within the past 6 months;
15. Patient is currently using an oral contraceptive for less than 3 months, has been on a unstable dose within the last 3 months or has switched from one oral contraceptive to another within the last 3 months or intends to do so in the course of the study;
16. Patient has a history of chronic abuse of alcohol (regularly consumes 3 or more alcoholic drinks per day), analgesics, narcotic analgesics, ergot alkaloids, tranquilizers, or opioids or other substances known to produce dependence; in the judgement of the investigator within the past 3 years;
17. Positive drug screen at screening and Visit 2 for illegal drug substances, or non-prescribed controlled substances;
18. Positive pregnancy test or breast feeding at screening and prior to dosing in each Treatment Period;
19. Patients with a medical disorder, condition or history such that could impair the patient's ability to participate or complete this study in the opinion of the investigator;
20. Current participation in any other studies involving investigational or marketed products within 30 days prior to the Screening Visit;
21. Unwilling or unable to comply with all requirements outlined in the protocol;
22. Member or relative of study staff or the Sponsor directly involved in the study.

In addition to the above stated inclusion/exclusion criteria and restrictions, patient selection in this study is to be made consistent with all the warnings, precautions, and contraindications associated with the use of Aleve and Tylenol Extra Strength. The Investigator should review and be familiar with the information available on these marketed products and the information in the package label.

6.3 Justification of selection criteria

The selection criteria are chosen to ensure that patients with specific risks for administration of the study medication and/or patients with conditions which may have an impact on the safety of the patient or data integrity during their participation in the study are excluded.

6.4 Withdrawal of patients from study

6.4.1 Withdrawal

Withdrawal criteria

Patients *must* be withdrawn from the study if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.

Patients *may* be withdrawn from the study if any of the following occurs:

- Serious adverse events;
- If, in the Investigator's opinion, continuation of the study would be harmful to the patient's well-being;
- At the specific request of the Sponsor and in liaison with the Investigator (e.g., obvious non-compliance, safety concerns);
- Protocol violation: if the patient develops conditions which would have prevented her entry into the study according to the inclusion/exclusion criteria, she must be withdrawn immediately if safety is concerned; in other cases, the investigator will decide whether there is a conflict with the study objectives

Depending on the time point of withdrawal, a withdrawn patient is referred to as either a "*screening failure*" "*Inadequate pain reporter*" or "*dropout*" as specified below:

Screening failure

A patient who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study prior to randomization is regarded as a "screening failure".

Re-starting the defined set of screening procedures (re-screening) to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:

- The patient had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).

- Other situations where the patient had to withdraw consent due to "life circumstances" though they otherwise qualified. These situations will be considered on a case by case basis by the sponsor or sponsor representative in consultation with the investigator.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. In addition, for re-screening, the patient has to re-sign the informed consent form, even if it was not changed after the patient's previous screening.

Inadequate pain reporter

A patient who is successfully screened and eligible for treatment but does not meet the minimum NRS pain threshold (≥5).

Dropout

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has been randomized and administered at least one dose of study medication.

General procedures

In all cases, the reason for withdrawal must be recorded in the case report form/electronic case report form (CRF/eCRF) data collection system and progress noted in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature termination of the Study).

6.4.2 Replacement

Patients who prematurely discontinue participation after randomization will not be replaced.

6.5 Patient identification

Each patient is identified by the study site's unique patient identification code. After informed consent procedure every patient is given a screening number (SNR). At the time point of randomization, patients who meet the entry criteria will be sequentially assigned to a four-digit number in ascending order (randomization number, RNR). See Section 7.3.

7. Treatment(s)

The study center will dispense a blinded treatment sequence (A/B or B/A) after successfully completing screening procedures. The overencapsulated tablets (IMP) for each treatment sequence will be dispensed using an Interactive Voice/Web Response System (IV/WRS) to maintain a balanced stratification amongst the study centers participating in the study.

7.1 Treatments to be administered

The treatments to be administered during the study are displayed in Sections 7.2 and 7.3.

Table 1: Treatments administered

Treatment (condition)	**Dose / route**	**Amount / form**	**Frequency of administration**
A: Naproxen sodium 440 mg (menstrual pain)	220 mg / orally	2 / tablets	single dose
B: Acetaminophen 1000 mg (menstrual pain)	500 mg / orally	2 / tablets	single dose

7.2 Identity of study treatment

Table 2: Study treatments

Treatment	Treatment A	Treatment B
Dose	Naproxen sodium 440 mg/day (220 mg x 2 single dose)	Acetaminophen 1000 mg/day (500 mg x 2 single dose)
Pharmaceutical Form	over-encapsulated tablet	over-encapsulated tablet
Strength	220 mg	500 mg
Formulation	naproxen sodium FD&C blue #2 lake hypromellose magnesium stearate microcrystalline cellulose polyethylene glycol povidone talc titanium dioxide --- Swedish orange opaque DBcaps® size AA-el capsules* micro crystalline cellulose*	acetaminophen carnauba wax castor oil corn starch FD&C red #40 aluminum lake hypromellose magnesium stearate polyethylene glycol powdered cellulose, pregelatinized starch propylene glycol shellac sodium starch glycolate titanium dioxide --- Swedish orange opaque DBcaps® size AA-el capsules* micro crystalline cellulose*
Route of administration / Dosing instructions	orally with a full glass of water	orally with a full glass of water
Batch Number	available in the study file	available in the study file
Manufacturer	Bayer Bitterfeld, Germany	McNeil Consumer Healthcare Fort Washington, PA USA

*components of the over-encapsulation and filler material.

All study medications will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study medications, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study medication can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all investigational products as well as the labels will be maintained in the clinical supply file.

The source of test and reference products will be documented in the clinical supply file.

7.3 Treatment assignment

At the beginning of the first treatment period, after completion of the pre-treatment baseline procedures/assessments, patients who meet the entry criteria will be sequentially assigned to a unique number in ascending order (randomization number, RNR) according to the randomization schedule prepared prior to the study.

Patients will be numbered according to the following scheme:

14001XXXX

Whereas the "Xs" will be replaced with a four digit sequentially assigned number as each patient enters the study (e.g., first patient number will be 140011001).

Once a number has been assigned to a patient, it cannot be reassigned to another patient.

Patients entering the Treatment Phase are randomized in a 1:1 fashion into one of two blinded treatment sequences:

- Naproxen sodium 440 mg (two tablets of naproxen sodium 220 mg) for Treatment Period 1 and acetaminophen 1000 mg (two tablets of acetaminophen 500 mg) for Treatment Period 2 (treatment sequence A/B);
- Acetaminophen 1000 mg (two tablets of acetaminophen 500 mg) for Treatment Period 1 and naproxen sodium 440 mg (two tablets of naproxen sodium 220 mg) for Treatment Period 2 (treatment sequence B/A).

Patients will be reminded to discontinue use of all pain medications including supplements, use of topical heat or cold, and other products of topical application approximately 72 hours before the patient's anticipated initiation of the first day of menstruation of their cycle in each Treatment Period. Patients will take the e-diary and treatment kit home and complete the questionnaires when they think they are *close* to approaching the first day of menstruation of their menstrual cycle.

7.4 Dosage and administration

Each patient will self-administer the treatment at the onset of dysmenorrhea during their menstrual cycle. Depending upon which treatment in the sequence, they could be either taking naproxen sodium (220 mg x 2) or acetaminophen (500 mg x 2). Patients will administer the study medication with a full glass of non-refrigerated, non-carbonated water (about 8 ounces or 240 mL). The patient will enter the dosing date and time into the e-diary at the time of study medication administration.

7.5 Blinding

7.5.1 Blinding measures

Patients enrolled in the study, investigators and their staff involved in protocol procedures or data collection analysis will be blinded to the identity of the treatment sequence. The study monitor will conduct product accountability during and after database lock. To preserve the blinding, all investigational products will be over encapsulated and prepackaged according to the randomization schedule and managed using IV/WRS.

7.5.2 Unblinding

In the case of a medical emergency, such as serious adverse events (SAE), breaking the blind may become necessary during the study. Randomization code-break envelopes are securely maintained at the study site and with the Sponsor.

In compliance with applicable regulations, in the event of a SUSAR related to the blinded treatment, the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 9.6.1.4).

7.5.3 Emergency unblinding by the investigator

The investigator will be provided with code-break envelopes that can be used to break the blinding of the study medication. Any patient who was unblinded using the code-break envelopes must have this occurrence documented in the patient's medical record. The investigator should notify the sponsor or sponsor medical monitor prior to unblinding if at all possible, unless a delay in doing so will deleteriously affect the patient's well being. The investigator must report the blind break in conjunction with a SAE as defined in Section 9.6.1. Patients that have been unblinded will not be included in the ITT or PP efficacy analysis.

The Sponsor will collect all code-break envelopes at the end of the study.

7.6 Drug logistics and accountability

The Sponsor will provide sufficient quantity of the IMP to the study site. All study centers will dispense IMP according to the randomization schedule entered in the IV/WRS.

All study medication will be stored at the investigational site in accordance with GCP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of IMP in writing. The personnel will use the IMP only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study medication must be properly documented according to the sponsor's agreed and specified procedures.

7.7 Treatment compliance

The distribution of the study medication will be supervised by a member of the Investigator's team. Patients will self-adminster IMP at their discretion and document the dosing in the e-diary system. The study center will monitor used and unused IMP for compliance. Any discrepancies between actual and expected amount of returned study medication must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

8. Non-study therapy

8.1 Prior and concomitant therapy

The following treatments are prohibited:

- Use of all pain medications and/or anti-inflammatory medications (with the exception of low dose aspirin [defined as no more than 100 mg daily] taken for cardioprotective purposes) including supplements, topical heat or cold, and other products of topical application approximately three days before the expected first day of menstruation of their menstrual cycle and throughout the dosing/assessment period.
- Use of transcutaenous electrical nerve stimulation devices that are used to treat dysmenorrhea throughout each treatment period.
- The use of mood-altering agents (antidepressants, sedatives, phenothiazines, or anti-anxiety agents). Patients who are on a stable dose for at least 3 months, and are not taking this medication for dysmenorrhea or premenstrual syndrome are eligible for enrollment.
- Piroxicam (Feldene®) and corticosteroids. However, patients taking inhaled or topical corticsteroids will be eligible for enrollment.
- Intra-uterine devices, hormonal implants (e.g., Norplant) or injections (e.g., Depo-Provera) used throughout the study or used within the past 6 months.
- Patient is currently using an oral contraceptive for less than 3 months, has been on an unstable dose within the last 3 months or has switched from one oral contraceptive to another within the last 3 months or intends to do so in the course of the study.

Patients will be asked to abstain from caffeine and alcohol throughout the 12-hour treatment period.

All medications (oral or topical) prescription and nonprescription products, supplements and herbal products, as well as topical heat or cold taken or used by the patient from 30 days prior to Screening will be documented. The reported medications will be reviewed and evaluated by the Principal Investigator or designee to determine if they affect the patient's eligibility to participate in the study.

8.2 Post-study therapy

This a blinded two period, two treatment crossover study for patients with primary dysmenorrhea and therefore no additional treatment after the second treatment period will be allocated. Patients will be discharged upon their completion of Visit 3.

9. Procedures and variables

9.1 Tabular schedule of evaluations

See flow chart in Section 16.1

Regarding protocol deviations, the processes and responsibilities defined by the Sponsor will be followed. Respective details (e.g., identification and classification of protocol deviations) are described separately.

9.2 Visit description

If not stated otherwise, the measures / actions listed in the following Sections 9.2.1 to 9.2.5 will be performed by or under the supervision of the investigator.

9.2.1 Screening phase visit 1 (Day -21 to -1)

At the Screening visit, the Principal Investigator or appropriate designee will discuss with each patient the nature of the study, its requirements and its restrictions. Written informed consent will be obtained prior to performance of any protocol-specific procedures.

The Screening Period will be up to 21 days. The following will be determined during the Screening Visit:

- Signed Informed Consent;
- Review Inclusion and Exclusion Criteria;
- Patient demographics;
- Medical History (primary dysmenorrhea is based on the patient's self-reported history)
- Medication history of all prescription and over-the-counter drugs (including topicals, herbal products, vitamins and nutritional supplements), use of topical heat or cold, and other products of topical application and investigational drugs, taken within 30 days prior to screening;
- History of drug, alcohol and tobacco use;
- Height, weight, and Body Mass Index (BMI);
- Physical examination (general routine);
- Urine drug screen;
- Urine pregnancy test;
- History of Categorical pain intensity (0-3 scale) of moderate or severe for menstrual cramp pain during four of the past six menstrual cycles;
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after at least 5 minutes in a sitting position);
- Discuss the procedure to report adverse events;
- e-diary distribution and training;
- Pregnancy test kits (2);
- Rescue medication;
- Treatment kit (randomized patients only).

The Principal Investigator or his/her designee must review all screening results before proceeding to the Treatment phase of the study. Eligible patients will receive their allotted treatment kit as per randomization, pregnancy test kits and e-diary and be trained on how to

use the e-diary, treatment and pregnancy kits prior to starting the first Treatment Period. The study center will dispense Investigational Medicinal Product (IMP or treatment kit) using the Interactive Voice / Web Response System (IV/WRS).

9.2.2 Treatment period 1

After screening, all Patients will start the first Treatment Period. The start of treatment will vary based on when the patient's last menstrual cycle occurred. Once the patient has reached qualifying pain, the patient will notify the site by a phone call to the study center and begin treatment. Patients are only required to call and leave a voice message. Approval is not needed to proceed with the next steps. The patient takes the assigned study medication when menstrual cramp pain is ≥5 in severity using the 0-10 Numerical Rating Scale (NRS) questionnaire.

"*My menstrual cramp pain at this time is …?*"

If the patient designates that her menstrual cramp pain is <5 on the NRS, has taken prohibited medications, developed other confounding pain conditions or does not have adequate time to finish 12 hours of evaluation, the patient should stop all activities and inform the study center immediately.

Patients are allowed to continue on the study and Treatment Period 1 can be extended to their next menstrual cycle. Patients must inform study staff if they require an extension and only one extension for Treatment Period 1 is possible. If the patient does not dose within the next menstrual cycle (as part of the extension), then the patient will immediately contact the study center. The patient will proceed to Visit 2 and if eligible, the patient will proceed to Treatment Period 2.

Prior to dosing all patients MUST perform a urine pregnancy test and verify that the results are negative (not pregnant). Any patient who has a positive pregnancy test or is not sure of the results must contact the study center immediately. Patients with a verified positive pregnancy test will be withdrawn from the study.

Before dosing, the patient will complete a baseline (immediately before dosing) 0-10 NRS menstrual cramp pain intensity evaluation. After dosing, patients will complete the 0-10 NRS menstrual cramp pain intensity questionnaires at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours post-dose. All post-dose time point assessments have an allowable window of ± 10 minutes for the 30 and 60 minute assessments. Subsequent to the 1 hour reading, assessments from hours 2-12 will have an allowable window of ± 15 minutes.

Additionally, patients will complete menstrual cramp pain relief (0-4 pain relief scale) questionnaires at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours post-dose. All post-dose time point assessments have an allowable window of ± 10 minutes for the 30 and 60 minutes assessments. Subsequent to the 1 hour reading, assessments from hours 2-12 will have an allowable window of ± 15 minutes.

At 12 hours post-dose, patients will complete the Global Evaluation of the overall satisfaction with the effectiveness of the study medication. If the patient decides to take rescue medication prior to the 12 hours, the patient will be instructed to complete the Global Evaluation prior to

taking the rescue medication. Patients will be encouraged to complete the 12 hour Treatment Period.

If the patient dosed the study medication before the onset of menstrual flow, then flow must start within 48 hours of dosing. Patients who took study medication and did not start menstrual flow within 48 hours of dosing will not be included in the primary efficacy analysis. Patients will contact the study center to schedule their next visit (Visit 2) after the prescribed treatment period.

9.2.3 Visit 2 - amended

Patients will return to the study center approximately one week after the completion of Treatment Period 1 dosing and all assessments. The following activities will be performed:

- Review concomitant medications;
- Urine drug screen
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after at least 5 minutes in a sitting position);
- Review e-diary data for completeness;
- Review treatment kit (drug accountability);
- Review used pregnancy test kit;
- Adverse Event assessment.

9.2.4 Treatment period 2 (after the completion of visit 2)

The start of treatment for the second Treatment Period will vary based on when the patient's last menstrual cycle occurred. Once the patient has reached qualifying pain, the patient will notify the site by a phone call to the study center and begin treatment. Patients are only required to call and leave a voice message. Approval is not needed to proceed with the next steps. The patient takes the assigned study medication when menstrual cramp pain is at ≥5 in severity using the 0-10 Numerical Rating Scale (NRS) questionnaire.

"*My menstrual cramp pain at this time is …?*"

If the patient designates that her menstrual cramp pain is <5 on the NRS, has taken prohibited medications, developed other confounding pain conditions or does not have adequate time to finish 12 hours of evaluation, then the patient should stop all activities and inform the study center immediately.

Patients are allowed to continue on the study and Treatment Period 2 can be extended to their next menstrual cycle. Patients must inform study staff if they require an extension and only one extension for Treatment Period 2 is possible. If the patient does not dose within the next menstrual cycle (as part of the extension), then the patient will contact the study center immediately. The patient will proceed to Visit 3.

Prior to dosing all patients MUST perform a urine pregnancy test and verify that the results are negative (not pregnant). Any patient who has a positive pregnancy test or is not sure of the results must contact the study center immediately. Patients with a verified positive pregnancy test will be withdrawn from the study.

Before dosing, the patient will complete a baseline (immediately before dosing) 0-10 NRS menstrual cramp pain intensity evaluation. After dosing, patients will complete the 0-10 NRS menstrual cramp pain intensity questionnaires at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours post-dose. All post-dose time point assessments have an allowable window of ± 10 minutes for the 30 and 60 minute assessments. Subsequent to the 1 hour reading, assessments from hours 2-12 will have an allowable window of ± 15 minutes.

Additionally, patients will complete menstrual cramp pain relief (0-4 pain relief scale) questionnaires at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours post-dose. All post-dose time point assessments have an allowable window of ± 10 minutes for the 30 and 60 minute assessments. Subsequent to the 1 hour reading, assessments from hours 2-12 will have an allowable window of ± 15 minutes

At 12 hours post-dose, the patient will complete the Global Evaluation of her overall satisfaction with the effectiveness of the study medication. If the patient decides to take rescue medication prior to the 12 hours, the patient will be instructed to complete the Global Evaluation prior to taking the rescue medication. Patients will be encouraged to complete the 12 hour Treatment Period.

If the patient dosed study medication before the onset of menstrual flow, then flow must start within 48 hours of dosing. Patients who took study medication and did not start menstrual flow within 48 hours of dosing will not be included in the primary efficacy analysis.

Patients will contact the study center to schedule their final visit (Visit 3).

9.2.5 End of study – visit 3

Patients will return to the study center approximately one week after the completion of Treatment Period 1 dosing and all assessments. The following activities will be performed:

- Review of concomitant medications;
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after at least 5 minutes in a sitting position);
- Return and review e-diary for completeness;
- Return and review treatment kit (drug accountability);
- Return and review used/unused pregnancy test kits for signs of use;
- Adverse Event assessment.

9.2.6 Rescue medication

If adequate pain relief was not achieved, then patients are permitted to take rescue medication at their discretion, though they will be encouraged to wait for at least 2 hours after dosing of study medication prior to use of rescue. The rescue medication will be ibuprofen 400 mg and only one dose for each Treatment Period will be provided. All rescue medication taken must be documented on the patient's medical record and the CRF/e-CRF data collection system.

Patients should only use the rescue medication during the 12 hour Treatment Period.

Patients will be queried in a nonspecific fashion for any adverse events. All observed and reported AEs will be collected and recorded on the case report form. The information

recorded will be based on signs and symptoms reported by the patient or observed by the research coordinator/Investigator during clinical evaluation.

9.3 Population characteristics

9.3.1 Demographic

For basic patient assessment prior to screening, some demographic information may be collected before obtaining written informed consent:

- Year of birth (approximate age);
- Sex;
- Native language.

Collection of demographic information is subject to all applicable local regulations.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent;
- Considered relevant for the patient's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

Information on smoking, as well as drug and alcohol consumption will be collected.

9.4 Efficacy analysis

Patients may be invalid for one period but valid for another period. Therefore, invalidity for either period does not make them invalid for both. For example, if a patient did not dose in Treatment Period 1, but did dose in Treatment Period 2, then the data from Treatment Period 2 will be analyzed. The following incidences will be considered as a protocol violation and excluded from the PP analysis if any one of the following occurred during the treatment period:

- Patient vomited within 30 minutes of ingesting the study medication;
- Patient took rescue medication before the 2-hour evaluation;
- Patient does not have a baseline (predose) pain evaluation;
- Patient dosed with study medication despite having a NRS <5;
- Patient took a prohibited concomitant medication preceding or during the study Treatment Period;

- Patient did not start menstrual flow within 48 hours of dosing;
- Patient failed to continue to meet the inclusion/exclusion criteria prior to the Treatment Period;
- Patient had more than 50% evaluations that were missed during the 0 through 12-hour evaluation period in those who did not use rescue medication;
- Patient missed more than 2 evaluations from hours 6-12 in those who did not use rescue medication.

9.4.1 Primary efficacy parameter

All efficacy analyses will be based on the PP population.

- Sum of Total Pain Relief (TOTPAR) over 0-12 hours (TOTPAR0-12) after Time 0

9.4.2 Secondary efficacy parameters

The secondary efficacy variables include:

- Summed Pain Intensity Difference (SPID) over the 12-hour study period (SPID0-12) using 0-10 NRS
- SPID over 0-6 hours (SPID0-6)
- SPID 6-12 hours (SPID6-12)
- TOTPAR over 0-6 hours (TOTPAR0-6)
- TOTPAR 6-12 hours (TOTPAR6-12)
- Time to first intake of rescue medication
- Pain Intensity Difference (PID) scores at each evaluation
- Global Evaluation at 12 hours post-dose or immediately before first intake of rescue medication

9.4.3 Safety analysis

Safety measures will be analyzed for all patients in the safety population.

Adverse events will be collected throughout the treatment and safety follow-up periods and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Only treatment-emergent AEs will be included, i.e., AEs that begin or worsen after the first dose of the investigational products in the treatment period. The number and percent of patients who experience any event, by System Organ Class (SOC), and by Preferred Term will be displayed by treatment group. Tables will also be produced by severity and relationship to investigational product. Seriousness, severity, relationship to investigational product, duration, and outcome will also be listed.

9.5 Pharmacokinetics / pharmacodynamics

Not applicable

9.5.1 Pharmacodynamics

Not applicable

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g., physical examination findings, symptoms, diseases.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints);
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis);
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
- The admission is not associated with an AE
  (e.g., social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild: Presents with signs and symptoms easily tolerated, does not need treatment, or prolonged hospitalization and does not necessarily require stopping the drug;
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant;
- Severe: A type of adverse event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required.

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF/eCRF data collection system.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g., mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g., the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the CRF/eCRF data collection system.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the patient will be documented. The observation phase for AEs will start with signing the informed consent form and will end in general with the last visit of follow-up. After the end of follow-up there is no requirement to actively collect AEs.

In case of ongoing AEs after the last follow-up visit – especially when related to treatment with the study medication – the respective AE will be followed until resolution, if possible. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to treatment with the study medication.

The investigator has to record on the respective CRF/eCRF data collection system all adverse events occurring in the period between the signing of the informed consent and the end of the Follow-up Visit, there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study medication.

9.6.1.4 Reporting of serious adverse events and pregnancy

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient

detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF/eCRF data collection system as well as the complementary pages provided in the Investigator File must be completed for each SAE.

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to Bayer within the same timelines as a serious adverse event on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse. Send the completed SAE or pregnancy forms to:

PPD or Fax: PPD (in the USA)

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IRB

Notification of the Institutional Review Board (IRB) about all relevant events (e.g., SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform the investigational site about reported relevant events (e.g., SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the package insert for naproxen, acetaminophen and ibuprofen. If relevant new safety information is identified, the information will be integrated into an update of the safety information and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.2 Pregnancies

A patient's participation is to be terminated immediately if a pregnancy is supposed (i.e. in case her pregnancy test becomes positive).

The investigator must report to the sponsor any pregnancy occurring in a female patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE (see Section 9.6.1.4.). Send the completed pregnancy forms to:

PPD or Fax: PPD (in the USA)

9.6.3 Safety Examinations

The following safety examinations will be performed at the time points specified in the study flowchart, see Section 16.1.

- **Physical examination**

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the study site covering at least the organs of the cardiovascular, respiratory, and abdominal system.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

- **Body weight and height, BMI**

Body weight will be measured by a member of the investigator's team under the following conditions:

– Patient without shoes after having emptied her bladder

– Scale measurement units of 0.1 kg

The patient's height will be measured (without shoes) to calculate the BMI.

- **Blood pressure / heart rate**

Systolic and diastolic blood pressure and heart rate will be measured by a member of the investigator's team under the following conditions:

– Systolic blood pressure (after resting for at least 5 min in sitting position)

– Diastolic blood pressure (after resting for at least 5 min in sitting position)

– Heart rate (after resting for at least 5 min in sitting position)

– Measuring site: cuff to be placed on the right / left upper arm (if possible, the same arm will be used for all measurements in one patient); cuff location will be documented

– Method: oscillometric by an automatic or a manual measurement device

- **Laboratory examinations**

Urine samples will be collected to assess for illicit drugs at Screening (Visit 1) and Visit 2.

Table 3: Urine drug screen panel

Test Panel	Parameter
Urine Drug Screen	Methamphetamines, Amphetamines, cannabinoids, cocaine, opiates, benzodiazepines, barbiturates, Methylenedioxymethamphetamine, methadone, Oxycodone, Adulterants

- Urine pregnancy test

9.7 Other procedures and variables

Not applicable

9.8 Appropriateness of procedures / measurements

All efficacy and safety parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using SAS and the version used will be specified in the Statistical Analysis Plan (SAP) and placed on file. The SAP will contain a more comprehensive explanation than described below of the methodology used in the statistical analyses. The SAP will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

10.2 Analysis sets

Three populations will be identified in this study.

Safety Population:

All randomized patient who take at least one dose of IMP. Safety measures will be analyzed for all patients in the safety population.

Intent to Treat (ITT) Population:

All patients who are randomized and provide at least one measure of an efficacy parameter after the first dose of IMP. ITT population will be used as the sensitivity analysis for the selected parameters.

Per Protocol (PP) Population

PP population will include all patients in ITT who do not have any major protocol violations. PP population will be used as the primary analysis for the efficacy parameters.

10.3 Variables and planned statistical analyses

10.3.1 Imputation of missing values

Pain intensity differences (PID) will be derived by subtracting the pain intensity at the post-dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement.

If a patient takes rescue medication during the 12 hour assessment period, the subsequent pain intensity scores following the intake of the rescue medication will be imputed by either the baseline score (pre-dose) or the score recorded immediately prior to taking rescue medication, whichever is worse. Subsequent pain relief scores following the intake of the rescue medication will be imputed by “none relief” (0).

For those patients who are not rescued during the 12 hour assessment period, the 30 and 60 minute assessments will be considered as missing in the event that pain assessment is off-schedule by more than 10 minutes. Subsequent to the 1 hour reading values will be considered as missing in the event that the pain assessment is off-schedule by more than 15 minutes. Any missing values during 12 hour assessment period will be imputed using linear interpolation (trapezoid rule) or extrapolation (last observation carried forward) approach depending on availability of data surrounding the missing value.

10.3.2 Primary endpoint

Total pain relief scores (TOTPAR) over 12 hours, will be calculated by multiplying the pain relief score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values.

TOTPAR0-12 will be analyzed using analysis of variance (ANOVA) for the cross-over study design.

10.3.3 Secondary endpoint

The secondary efficacy variables include:

- Summed Pain Intensity Difference (SPID) over the 12-hour study period (SPID0-12) using 0-10 NRS
- SPID over 0-6 hours (SPID0-6)
- SPID 6-12 hours (SPID6-12)
- TOTPAR over 0-6 hours (TOTPAR0-6)
- TOTPAR 6-12 hours (TOTPAR6-12)

The above mentioned secondary endpoints will be analyzed similarly as the primary endpoint.

- Time to first intake of rescue medication. If a patient did not take the rescue medication during the treatment period, she will be censored at the time of last assessment. Time to first use of rescue medication will be estimated and plotted using Kaplan-Meier method and analyzed using log-rank test.
- Pain Intensity Difference (PID) scores at each evaluation. PIDs will be summarized descriptively by treatment group and plotted over time.
- Global Evaluation at 12 hours post-dose or immediately before first intake of rescue medication. This variable will be analyzed using CMH method with modified ridit score.

Safety and Tolerability

AEs will be collected from screening throughout the Treatment Phase and Follow-up Phase and will be coded using the Medical Dictionary for Regulatory Activities. Only treatment-emergent AEs will be included, i.e., AEs that begin or worsen after the first dose of the investigational medicinal product (IMP) in the Treatment Phase. The number and percent of patients who experience any event and the number of events overall, by System Organ Class,

and by Preferred Term will be displayed by treatment period and treatment group. Tables will also be produced by severity and relationship to each IMP. Seriousness, severity, relationship to each IMP duration, and outcome will also be listed.

Quantitative data for blood pressure, heart rate, laboratory data, body weight, body temperature will be described by summary statistics for the original data as well as for the differences to baseline. Frequency tables will be provided for qualitative data. Laboratory data outside the reference range will be listed and highlighted with 'L' for low and 'H' for high. An additional table with all abnormal values will be presented.

Listings of individual patient data (e.g., vital signs) will be provided.

10.4 Determination of sample size

The proposed design of the study is to detect the treatment difference of 5.9 in TOTPAR12 with 90% power and a type I error of 0.05. The required sample size to meet these design criteria are 154 patients in the PP population. Assuming a 23% drop out rate, approximately 200 patients will need to be randomized.

10.5 Planned interim analyses

No interim analysis is planned for this study.

11. Data handling and quality assurance

11.1 Data recording

Data collection and storage

The data collection tool for this study will be a validated electronic data capture system to be used at the study site. Patient data necessary for analysis and reporting will be provided to the Sponsor in CDISC (Clinical Data Interchange Standards Consortium) standards.

Test results originating directly from the site (e.g., urine drug screen) will be entered into the CRF/eCRF data collection system by designated site personnel.

Analytical results generated by central laboratory / -ies

The analytical results will be provided as electronic data files using predefined data formats. Where appropriate, these data will be supplemented with data already available from the CRF/eCRF data collection system (e.g., specific time points, demographic data) before being evaluated by the responsible specialist(s). Data relevant for the clinical study report will be stored in the sponsor's validated data repository.

Source documentation

Entries made in the CRF/eCRF data collection system must be either verifiable against source documents, or have been directly entered into the CRF/eCRF data collection system, in which case the entry in the CRF/eCRF data collection system will be considered as the source data (e.g., time points of blood sampling). The site has to ensure the availability of all required documentation.

Data recorded from screening failures

Data of 'only screened patients' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the screening log:

- Demographic information (patient number; year of birth or age, sex);
- Date of informed consent;
- Reason for premature discontinuation;
- Date of last visit.

For screening failures with an SAE, the following data should be collected in the CRF/eCRF data collection system in addition to the data specified above:

- All information related to the SAE such as:
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes);
- Safety and rights of patients are being protected;
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol);
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on the CRF/eCRF data collection system as well as for data from other sources (e.g., laboratory, ECG).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

11.4 Missing data

Reasons for missing data, especially inability to perform a test, must be documented. Additional parameters for missing data are detailed in Section 10.3.1.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Study patient files will be archived according to local regulations and in accordance with the maximum period of time permitted by the study site. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g., SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity);
- If the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the study within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing;
- All affected institutions (e.g., IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law;
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction;
- In the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the Trial Master File.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IRB, head of

the study center/medical institution) must supply to the sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study patients without prior IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent/assent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. Sample patient information and informed consent/assent forms are provided as a document separate to this protocol. Patients 15 to 17 years old who cannot legally give informed consent for research participation must use an IRB-approved assent form and a Parental/Guardian informed consent form. Informed consent must first be obtained from the child's parent or legal guardian before assent may be obtained from the child.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient prior to her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB has been obtained.

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision;
- The patient's consent covers examinations as specified in the visit description described in Section 9.2.5 to be conducted after withdrawal of consent;
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan;
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the patient's oral objection may be documented in the patient's source data.

Each patient will have ample time and opportunity to ask questions.

Only if the patient agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The informed consent form and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient of changes in a timely manner and will ask the patient to confirm her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor will make the information regarding the study publicly available on the internet at www.clinicaltrials.gov as applicable to local regulations.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient numbers (SNR and RNR) will be recorded in the CRF/eCRF data collection system, and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

14. Reference list

1. Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. Obstet Gynecol. 1995;87:55-8.
2. Chan WY, Dawood MY, Fuchs F. Relief of dysmenorrhea with the prostaglandin synthetase inhibitor ibuprofen: effect on prostaglandin levels in menstrual fluid. *Am J Obstet Gynecol*. 1979;153:102.
3. Campbell MA and McGrath PJ. Use of medication by adolescents for the management of menstrual discomfort. Arch Pediatr Adolesc Med. 1997;151:905-13.
4. Ortiz MI. Primary dysmenorrhea among Mexican university students: prevalence, impact and treatment. Eur J Obstet Gynecol Reprod Biol. 2010;152:73-7.

15. Protocol amendments

15.1 Amendment 1 (16-Apr-2018)

15.1.1 Overview of changes to the study

The following sections have been modified for Amendment 1:

- Section 2 (Synopsis, Exclusion Criteria, Time point/frame of measurement for primary variable(s))
- Section 6.2 (Exclusion Criteria)
- Section 9.2.3 (Visit 2)

16. Appendices

16.1 Study Flow Chart

Table 4: Study schema

Study Procedure	Screening Phase	Treatment Phase			
	Screening Visit 1	Treatment Period 1	Visit 2	Treatment Period 2	Visit 3 End of Study
	Days -21 to -1	After Screening	After Period 1	After Visit 2	After Period 2
Signed Informed Consent	X				
Inclusion/Exclusion Criteria Review	X				
Patient Demographics	X				
Medical History	X				
Prior and Concomitant / Medication History	X		X		X
History of drug, alcohol and tobacco use	X				
Body weight, height, and BMI	X				
Physical examination (general routine)	X				
Urine drug screen	X		X		
Vital signs (incl. temperature)[a]	X		X		X
Urine pregnancy test	X	X		X	
Categorical Pain Intensity 0-3 Scale	X				
e-diary distribution/training	X				
Randomization/Kit assignment	X[b]				
IMP administration		X[c]		X[c]	
0-10 Point Pain Intensity NRS		X		X	
0-4 Categorical – pain relief		X		X	
12 hour post-dose Global Evaluation[d]		X		X	
IMP compliance			X		X
e-diary/treatment kit return/review			X		X
Adverse events		X	X	X	X

[a] Vital signs (blood pressure, respiratory rate, heart rate and body temperature after 5 minutes of rest in a sitting position).
[b] Randomization to treatment occurs only for eligible patients.
[c] Urine pregnancy test must be performed and the results must be negative (not pregnant) before dosing.
[d] If the patient decides to take rescue medication prior to the 12 hours, the patient will be instructed to complete the Global Evaluation prior to taking the rescue medication.

16.2 Subjective Assessments

Categorical Pain Intensity (at Screening Visit 1 only)

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

0-10 pain Numerical Rating Scale (NRS)
Assessed at baseline (predose), 30 minutes, 60 minutes and hourly from 2-12 hours post-dose. All post-dose time point assessments have an allowable window of ± 10 minutes for the 30 and 60 minute assessments. Subsequent to the 1 hour reading, assessments from hours 2-12 will have an allowable window of ± 15 minutes.

My menstrual cramp pain at this time is …

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Categorical Pain Relief
Assessed at 30 minutes, 60 minutes and hourly from 2-12 hours post-dose.
All post-dose time point assessments have an allowable window of ± 10 minutes for the 30 and 60 minute assessments. Subsequent to the 1 hour reading, assessments from hours 2-12 will have an allowable window of ± 15 minutes.

My relief from my starting menstrual cramp pain is…

- 0 = none
- 1 = a little
- 2 = some
- 3 = a lot
- 4 = complete

Global Evaluation
A question that rates the IMP as a pain reliever at 12 hours post-dose or immediately at the first intake of rescue medication.

Overall, I would rate the effectiveness of this study medication in relieving my menstrual cramp pain as…

- 0 = poor
- 1 = fair
- 2 = good
- 3 = very good
- 4 = excellent