Document Type:	Study Protocol
Official Title:	A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Duration of Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Ibuprofen Tablets in Postsurgical Dental Pain
NCT Number:	NCT03404206
Document Date:	15-Feb-2018

1. Title page

A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Duration of Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Ibuprofen Tablets in Postsurgical Dental Pain

Test drugs:	BAY 117031 / Naproxen Sodium		
Study purpose:	Clinical efficacy		
Clinical study phase:	Phase 4	Date:	15-Feb-2018
Registration:	Not Applicable	Version no.:	3.0
IMPACT Number:	19762		
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: PPD

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

Title	A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Duration of Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Ibuprofen Tablets in Postsurgical Dental Pain
IMPACT	19762
Clinical study phase	4
Study objective(s)	To compare the duration of analgesic efficacy as determined by the time to rescue medication of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo over 24 hours in subjects experiencing moderate to severe post-impaction surgery dental pain. To compare the overall analgesic effect (SPID 0-24) of a single dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo. To compare the overall relief from pain (TOTPAR 0-24) of a single dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo.
Test drug(s) **Name of active ingredient**	Naproxen sodium tablet
Dose(s)	220 mg naproxen sodium (x2)
Route of administration	Oral
Duration of treatment	Single dose with pain/relief assessments for up to 24 hours
Reference drug(s) **Name of active ingredient**	Ibuprofen tablet
Dose(s)	200 mg ibuprofen (x2)
Route of administration	Oral
Duration of treatment	Single dose with pain/relief assessments for up to 24 hours
Reference drug(s) **Name of active ingredient**	Placebo tablet
Dose(s)	Placebo (x2)
Route of administration	Oral
Duration of treatment	Single dose with pain/relief assessments for up to 24 hours
Background treatment	not applicable
Indication	pain relief

Diagnosis and main criteria for inclusion /exclusion	Inclusion Criteria • Healthy, ambulatory, male or female volunteers 16-40 years of age; • Body mass index 18.5 to 30.0 kg/m^2 inclusive; • Scheduled to undergo surgical removal of at least 2 mandibular partial or full bony impacted third molars. Up to two maxillary third molars may be removed regardless of impaction level. Supernumerary teeth present may also be removed at the discretion of the oral surgeon; • Mandibular molars must demonstrate modified Demirjian root classification stage, **D, E, F**, G or H; • Have not taken any form of medication or herbal supplements (i.e., St. Johns Wort) within 5 days of admission (except for oral contraceptives, prophylactic antibiotics, or other routine medications to treat benign conditions, such as antibiotics to treat acne) and agree not to take any medication (other than that provided to them) throughout the study; • Female subjects of childbearing potential must be using a medically acceptable form of birth control for at least 1 month prior to screening (3 months on oral contraceptives) [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier], abstinence or in same sex relationship and have a negative pregnancy test at Screening and prior to study drug administration. Female subjects of non-childbearing potential must be amenorrheic for at least two years or have undergone surgical sterilization (i.e. tubal ligation/occlusion, hysterectomy and/or bilateral oophorectomy) • Have not consumed alcoholic beverages, or foods and beverages containing caffeine (examples; coffee, tea, chocolate, and colas) after midnight prior to surgery and agree not to consume any of these foods or beverages throughout their stay at study site • Use of only short-acting local anesthetic (e.g., mepivacaine or lidocaine) preoperatively, with a vasoconstrictor and nitrous oxide at the discretion of the Investigator; • Have moderate to severe postoperative pain on the Categorical Pain Intensity Scale (a score of at least 2 on a 4 point scale) and a score of ≥ 5 on the 0-10 pain intensity NRS within 4.5 hours postsurgery, but no later than 14:30 hours +/- 15 minutes. Exclusion Criteria • History of hypersensitivity to naproxen sodium, ibuprofen, NSAIDS, aspirin, similar pharmacological agents, local anesthetics, rescue medication or components of the investigational products; • Evidence or history of clinically significant (in the judgment of the investigator) hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years; • Relevant concomitant disease such as asthma (exercise induced asthma is permitted); • Current or past history of gastrointestinal bleeding or other bleeding disorder(s); • Acute illness or active local infection prior to surgery that can interfere with the conduct of the study in the judgment of the investigator; • Use of any OTC or prescription medications with which the administration of naproxen, acetaminophen, ibuprofen or any other NSAIDs, Hydrocodone bitartrate and acetaminophen is contraindicated or use of any medications within 5 days of surgery until discharge from the study site (except oral contraceptives, prophylactic antibiotics or medications to treat benign conditions such as antibiotics to treat acne); • Females who areplanning to become pregnant, pregnant or lactating; • Habituation to analgesic drugs including opioids (i.e., routine use of oral analgesics 5 or more times per week for greater than 3 weeks within the past 2 years); • Alcoholism or drug abuse within 2 years prior to the Screening Visit or routine consumption of 3 or more alcohol containing beverages per day. Alcohol containing beverages are defined as one beer (5%, one glass of wine (11%) and one shot hard liquor (40%); • Positive urine drug screen, alcohol breathalyser or urine cotinine test on day of surgery; • Have received any form of treatmentin the form of medication for depression in the past 6 months or any form of psychotropic agent (selective serotonin uptake inhibitors [SSRI]) within the last 6 months.

Study design	This is a single center, randomized, stratified by baseline pain, double-blind, parallel, placebo-controlled study in subjects experiencing moderate to severe postoperative dental pain.
Methodology	Subjects desiring elective third molar surgery will be solicited to participate. Subject who consent and meet all the inclusion and exclusion criteria will be scheduled for surgical removal of impacted teeth under local anesthesia +/- light sedation with nitrous oxide/oxygen. When subjects report "moderate" to "severe" post-operative pain, they will be dosed with one of the three study treatments as determined by a predetermined randomization schedule. Pain assessments (Pain Intensity, Pain Relief, Pain Half Gone and Global Assessment) will be performed at scheduled intervals post-drug for 24 hours. For each postdose timepoint, pain intensity differences (PID) will be derived by subtracting the pain intensity at the postdose timepoint from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Time-weighted sum of pain intensity differences (SPIDs) will be calculated by multiplying the PID score at each postdose timepoint by the duration (in hours) since the preceding timepoint and then summing these values over the desired time interval. Similarly, total pain relief scores (TOTPARs), will be calculated by multiplying the pain relief score at each postdose timepoint by the duration (in hours) since the preceding timepoint and then summing these values.
Type of control	Reference product (positive control) and placebo (negative control)
Data Monitoring Committee	No
Number of subjects	385
Primary variable(s)	Time to first use of rescue medication
Time point/frame of measurement for primary variable(s)	Pain intensity and pain relief will be rated by subjects at baseline (predose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, and 24 hours postdose, and immediately prior to the use of any rescue medication.
Plan for statistical analysis	Time to first use of rescue medication will be estimated and plotted using Kaplan-Meier method and analyzed using log-rank test stratified by center and baseline pain intensity. Additional parameters calculated for SPID 0-4, SPID 0-8, SPID 0-12, SPID 0-24, SPID 6-12, TOTPAR 0-4, TOTPAR 0-8, TOTPAR 0-12, TOTPAR 0-24 and TOTPAR 6-12 analyzed using an analysis of covariance model (ANCOVA) with treatment as fixed effect and baseline pain intensity score as the covariate. A 95% of confidence interval (CI) for the treatment difference (naproxen-placebo; naproxen-ibuprofen; ibuprofen-placebo) will be calculated based on the above mentioned model.

Table of contents

List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COX	Cyclooxygenase
CRO	Clinical Research Organization
CSR	Clinical Study Report
(e)CRF	(electronic) Case Report Form
EOT	End of Trial
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NPO	nil per os
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
SAS	Statistical Analysis Software
SNR	Screening Number
SSRI	Selective Serotonin Uptake Inhibitors
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

In addition to the information provided below please also refer to the Package Insert for Aleve and Advil or any additional data supplied by the Sponsor.

Naproxen sodium and ibuprofen are nonselective cyclooxygenase (COX) inhibitors. They are propionic acid derivatives and members of a drug class s known as nonsteroidal anti-inflammatory drugs (NSAIDs). Both naproxen and ibuprofen inhibit COX-1 and COX-2 isoenzymes. COX enzymes play a key role in the inflammatory response and the production of prostaglandins. Specifically, COX-1 is expressed in the gastrointestinal epithelium, vascular endothelium and kidney, while COX-2 plays a role in induction of inflammation. COX-2 inhibition reduces prostaglandin synthesis, leading to pain relief.

In the United States, naproxen has been marketed as a prescription medication since 1976 under the brand name Naprosyn®. Its sodium salt, naproxen sodium, was first sold under the trade name Anaprox® in 1980. In 1994, the US FDA approved naproxen sodium tablets (using the brand name Aleve®), 220 mg for over-the-counter (OTC) use. Aleve is indicated for the temporary relief of minor aches and pains due to: minor pain of arthritis, muscular aches, backaches, menstrual cramps, headaches, toothaches, and the common cold. It also temporarily reduces fever. As an OTC medication, Aleve should not be taken for longer than 10 days for pain or 3 days for fever unless otherwise directed by a physician. Similarly, Advil® (a branded form of ibuprofen) has been available OTC since 1984. It carries the same indications and duration of use labeling as Aleve.

The labelled dosing interval for over-the-counter naproxen sodium is 8-12 hours due to its long elimination half-life (approximately 14 hours) and documented long duration of action.[1,2] In contrast, ibuprofen, another propionic acid nonsteroidal anti-inflammatory drug available over-the-counter, has a labeled dosing interval of 4-6 hours and a short elimination half-life, 2-4 hours.[2] These two agents have been compared in single dose dental pain studies.[3,4] The analgesic effectiveness of naproxen sodium was greater than ibuprofen at later time points in both of these 12 hour studies but the duration of the studies was relatively short and the evaluations were performed at home. The ability to assess relative differences in the later hours may have been limited by the outpatient nature of those earlier studies which used at-home diaries.

The duration of analgesia in acute pain studies is generally assessed by the time to remedication.[5] At both low OTC doses and high OTC doses, naproxen sodium showed a numerically longer duration of action compared to ibuprofen although the difference did not achieve the level of statistical significance.[3,4] However, the sample size in these two studies was not estimated based on this secondary outcome parameter.

The post-impaction dental pain model chosen for this study has been widely used in the evaluation of OTC and prescription analgesics for a number of reasons. Dental surgical procedures can be easily standardized, and the population of subjects undergoing a given procedure is usually relatively healthy and homogeneous. In addition, there is extensive data substantiating the usefulness of the dental pain model in predicting the relative efficacy of a wide range of analgesic medications. The model has been found to be very useful for comparing several measures of analgesic efficacy, including onset, peak effect, and duration

of analgesic activity. [6,7,8] Therefore, the purpose of this investigation is to use the post-impaction dental pain model to compare the duration of action of naproxen sodium to ibuprofen at over-the-counter doses.

Benefit-risk assessment

Subjects who desire to have third molar extraction will be solicited to participate in this study. Subjects who consent to participate may benefit by receiving a medical exam, dental radiographs and no-cost surgical procedures for teeth extraction. Furthermore, post-surgical subjects will be provided continual nursing care for approximately 24 hours after surgery. Potential risks of the surgical procedure include pain, dry socket, infection, swelling, bleeding, trismus, and lip or tongue numbness. Potential risks related to local anesthesia and mild sedation include paresthesia and drowsiness. Subjects who experience a treatment failure can have the option of taking a standard rescue medication commonly used for post-operative pain relief. Potential study medication benefit will be relief of postsurgical pain which is highly prevalent following extractions of wisdom teeth. Potential risks of a single dose of OTC study medication are low and described in the Drug Facts Label.

During the study, subjects will be closely monitored for evidence of adverse events. Weighing between the potential risks associated with the study, and given the ability to mitigate risks through close monitoring and routine peri-operative care, this study is considered clinically and ethically acceptable.

4. Study objectives

The primary objective of this trial is:

- To compare the duration of analgesic efficacy as determined by the time to rescue medication of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo (2 x tablets) over 24 hours in subjects experiencing moderate to severe post-impaction surgery dental pain.

The secondary objectives of this trial are:

- To compare the overall analgesic effect (SPID 0-24) of a single dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo;
- To compare the overall relief from starting pain (TOTPAR 0-24) of a single dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo.

Other objectives of this trial are:

- To compare the efficacy of naproxen 440 mg, ibuprofen 400 mg and placebo for the following measures:
    - SPID 0-4, SPID 0-8, SPID 0-12, SPID 6-12;
    - TOTPAR 0-4, TOTPAR 0-8, TOTPAR 0-12 and TOTPAR 6-12;
    - Peak Pain Intensity;
    - Peak Pain Relief;
    - Sum of Observations with Pain Half Gone;
    - Duration of Pain Relief At Least Half Gone;
    - Total amount of time that subject reported at least a 2-point PID;
    - Global Pain Assessment.

5. Study design

Design Overview

This is a single center, randomized, double-blind, parallel, placebo-controlled study, stratified by baseline pain, in subjects experiencing moderate to severe postoperative dental pain. The study will consist of a Prescreening telephone call, a Screening Visit, a two day Treatment Period and a Post-Operative visit. Eligible subjects who have undergone surgical extraction of at least 2 mandibular partial or full bony impacted third molars will be kept in-house and evaluated for efficacy and safety at the study site overnight.

The study consists of a Screening Phase, Treatment Phase and a Follow-Up Phase. During Treatment Phase, subjects will be kept in-house at the study site for one overnight stay. Qualified subjects will then be randomized into one of two treatments. Approximately 485 subjects will be screened prior to surgery. Approximately 397 will have surgery and approximately 385 will be randomized to a specific treatment.

Screening Phase

Eligible subjects will be screened and selected up to 28 days prior to oral surgery and dosing with investigational product.

Treatment Phase

Following selection, qualified subjects will enter the Treatment Phase and be scheduled for their surgical teeth extraction. After completion of the surgical teeth extractions, subjects will remain at the study site for observation. Subjects with appropriate pain severity for randomization will then be stratified by baseline pain intensity and randomized into one of three (3) treatment groups. Subjects will rate their pain severity and pain relief over the next 24 hours. After completion of all trial procedures, subjects will be discharged from the study site.

All subjects are required to remain at the study center and complete all assessments regardless of rescue.

Follow-Up Phase

Subjects will be evaluated at a post-operative visit/call approximately 6-10 days after surgery for follow up for any adverse events or medications not known at the time of treatment.

The duration of each subject's participation will be approximately 38 days. For an overview on the study design and study procedures see Figure 1.

Figure 1 – Design Overview

	Screening Phase	Treatment Phase					Follow up Phase
Trial Days	**Day -28 to -1**	**Day 1 Presurgery**	**Day 1 Surgery**	**Day 1 Postsurgery**	**Day 1**	**Day 2**	**Days 6-10**
		Check-in to study site (if needed)	Surgical teeth extraction	Categorical pain NRS pain ✸	NRS pain Pain relief Pain half gone	NRS pain Pain relief Pain half gone Global assessment	Phone call or visit

✸ = randomized to either naproxen (440 mg), ibuprofen (400 mg), or placebo

Justification of the design

The study was designed specifically to capture and measure acute post-surgical dental pain in healthy subjects who could benefit from the administration of an OTC pain reliever. This pain model has been widely studied for OTC pain medications; however, should a subject not get sufficient pain relief from the IMP, then rescue medication approved for treating acute pain (e.g., acetaminophen plus hydrocodone, tramadol, acetaminophen, etc.) may be requested. The endpoints and study design are consistent with most recent Guidance by FDA and methods advocated by experts.[9,10]

6. Study population

The subject population will consist of healthy individuals who are status post extraction of 2 mandibular partial or full bony impactions. No more than 25% of the enrolled subjects may be less than 18 years of age.

6.1 Inclusion criteria

Those who inquire about the trial will be allowed to participate in the study if they meet the following eligibility criteria:

1. Healthy, ambulatory, male or female volunteers 16 to 40 years of age;

2. Body mass index 18.5 to 30.0 kg/m2 inclusive;

3. Scheduled to undergo surgical removal of at least 2 mandibular partial or full bony impacted third molars. Up to two maxillary third molars may be removed regardless of impaction level. Supernumerary teeth present may also be removed at the discretion of the oral surgeon;

4. Mandibular molars must demonstrate modified Demirjian root classification stage **D, E, F,** G or H; [11]

5. Have not taken any form of medication or herbal supplements (i.e., St. Johns Wort) within 5 days of admission (except for oral contraceptives, prophylactic antibiotics, multivitamin supplements, or other routine medications to treat benign conditions, such as antibiotics to treat acne) and agree not to take any medication (other than that provided to them) throughout the study;

6. Female subjects of childbearing potential must be using a medically acceptable form of birth control for at least 1 month prior to screening (3 months on oral contraceptives) [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier], abstinence or in same sex relationship and have a negative pregnancy test at Screening and prior to study drug administration. Female subjects of non-childbearing potential must be amenorrheic for at least two years or have undergone surgical sterilization (i.e. tubal ligation/occlusion, hysterectomy and/or bilateral oophorectomy);

7. Have not consumed alcoholic beverages, or foods and beverages containing caffeine (examples; coffee, tea, chocolate, and colas) after midnight prior to surgery and agree not to consume any of these foods or beverages throughout their stay at the study site;

8. Use of only short-acting local anesthetic (e.g., mepivacaine or lidocaine) preoperatively, with or without a vasoconstrictor and nitrous oxide at the discretion of the Investigator;

9. Have moderate to severe postoperative pain on the Categorical Pain Intensity Scale (a score of at least 2 on a 4 point scale) and a score of ≥ 5 on the 0-10 pain intensity NRS within 4.5 hours postsurgery, but no later than 14:30 hours +/- 15 minutes.

10. Ability to understand and follow study-related instructions;

11. Be willing and able to participate in all scheduled visits, treatment plan, and trial procedures according to the clinical protocol;

12. Subject must have signed the IRB-approved Informed Consent.

6.2 Exclusion criteria

Subjects presenting with any of the following will not be included in the trial:

1. History of hypersensitivity to naproxen sodium, ibuprofen, NSAIDS, aspirin, similar pharmacological agents, local anesthetics, rescue medication or components of the investigational products;

2. Evidence or history of clinically significant (in the judgment of the investigator) hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years;

3. Relevant concomitant disease such as asthma (exercise induced asthma is permitted);

4. Current or past history of gastrointestinal bleeding or other bleeding disorder(s);

5. Acute illness or active local infection prior to surgery that can interfere with the conduct of the study in the judgment of the investigator;

6. Use of any OTC or prescription medications with which the administration of naproxen, acetaminophen, ibuprofen or any other NSAIDs, Hydrocodone bitartrate and acetaminophen), is contraindicated or use of any medications within 5 days of surgery until discharge from the study site (except oral contraceptives, prophylactic antibiotics, multivitamin supplements, or medications to treat benign conditions such as antibiotics to treat acne);

7. Females who are planning to become pregnant, pregnant or lactating;

8. Habituation to analgesic drugs including opioids (i.e., routine use of oral analgesics 5 or more times per week for greater than 3 weeks within the past 2 years);

9. Alcoholism or drug abuse within 2 years prior to the Screening Visit or routine consumption of 3 or more alcohol containing beverages per day; Alcohol containing beverages are defined as one beer (5%), one glass of wine (11%) and one shot (40%) hard liquor.

10. Positive urine drug screen, alcohol breathylyzer or urine cotinine test on day of surgery.

11. Use of Nicotine containing products within 3 days prior to presurgery to the completion of the study.

12. Have received any form of treatment in the form of medication for depression in the past 6 months or any form of psychotropic agent (including selective serotonin uptake inhibitors [SSRI]) within the last 6 months.

13. Member or first-degree relative of study staff or the Sponsor directly involved in the study;

14. Unwilling or unable to comply with all requirements outlined in the protocol;

15. Subjects with a medical disorder, condition, or history of such that could impair the subject's ability to participate or complete this trial in the opinion of the investigator;

16. Previous enrollment in this study.

6.3 Justification of selection criteria

The selection criteria are chosen to ensure that subjects with specific risks for administration of either study medication and/or subjects with conditions which may have an impact on the outcomes of the study are excluded.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

Subjects *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 subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject's pain intensity post-surgery at pre-dose does not exceed 'mild' and the NRS is <5 (see Section 16.2);
- If, in the Investigator's opinion, continuation of the study would be harmful to the subject's well-being;
-

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

- Subject experiences one or more serious adverse events;
- At the specific request of the Sponsor and in consultation with the Investigator (e.g., obvious non-compliance, safety concerns);
- Protocol violation: if the subject develops conditions which would have prevented his/her entry into the study according to the inclusion/exclusion criteria, he/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 subject is referred to as either a "*screening failure*", *"run-in failure"* or "*dropout*" as specified below:

Screening failure

A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study prior to the start of surgery is regarded as a "Screening failure".

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

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

In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Subjects who re-screen will re-sign the informed consent form, even if it was not changed after the subject's previous screening and will be assigned a new screening number.

Run-in failure

A subject who, for any reason terminates the study after surgery and prior to the start of study drug administration (e.g., not meeting pain threshold) is regarded as a "Run-in failure".

Dropout

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

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 in the subject's medical records.

The subject 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

Subjects will not be replaced.

6.5 Subject identification

Each subject is identified by the study site's unique subject identification code. After informed consent procedure every subject is given a screening number (SNR). At the time

point of randomization, subjects who meet the entry criteria will be sequentially assigned to a four-digit number in sequential order (randomization number, RNR). See Section 7.3.

7. Treatment(s)

The study center will dispense a single-dose of an assigned treatment within 4.5 hours postsurgery. The tablets and placebo will be administered in a 3:3:1 randomization ratio (naproxen sodium; ibuprofen; placebo) based on a computer-generated randomization schedule and the severity of pain experienced (moderate or severe). Subjects who characterize their pain severity as mild and have a NRS <5 will not receive treatment and will be discharged from the study site, if deemed safe by an Investigator.

7.1 Treatments to be administered

The treatments to be administered during the study are displayed in Section 7.2.

Table 1: Treatments administered

Treatment (condition)	**Dose / route**	**Amount / form**	**Frequency of administration**
Naproxen sodium 440 mg (postsurgery)	220 mg / orally	2 / tablets	single dose
Ibuprofen 400 mg (postsurgery)	200 mg / orally	2 / tablets	single dose
Placebo (postsurgery)	NA / orally	2 / tablets	single dose

7.2 Identity of study treatment

Table 2: Study treatments

Treatment	Naproxen	Ibuprofen	Placebo
Dose	two tablets	two tablets	two tablets
Pharmaceutical Form	tablet	tablet	tablet
Strength	220 mg	200 mg	not applicable
Formulation	naproxen sodium FD&C blue #2 lake hypromellose magnesium stearate microcrystalline cellulose polyethylene glycol povidone talc titanium dioxide	ibuprofen acetylated monoglycerides colloidal silicon dioxide corn starch croscarmellose sodium methylparaben microcrystalline cellulose pharmaceutical glaze pharmaceutical ink povidone pregelatinized starch propylparaben sodium benzoate sodium lauryl sulfate stearic acid sucrose synthetic iron oxide titanium dioxide white wax	dibasic calcium phosphate dihydrate magnesium stearate microcrystalline cellulose
Route of administration	orally with a full glass of water (i.e. about 8 ounces or 240 mL)	orally with a full glass of water (i.e. about 8 ounces or 240 mL)	orally with a full glass of water (i.e. about 8 ounces or 240 mL)
Batch Number	see study file	see study file	see study file
Trade Name and Manufacturer	Aleve® Bayer Bitterfeld, Germany	Advil® Pfizer Madison, NJ USA	Bayer Morristown, NJ USA

All study drugs 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 drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug 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, subjects who meet the entry criteria will be sequentially assigned to a unique number in sequential order (randomization number, RNR) according to the randomization schedule 3:3:1 (naproxen sodium: ibuprofen: placebo) prepared prior to the study.

Subjects will be numbered according to the following scheme:

14001XXXX

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

The unique subject identifier number will be assigned in numerical order stratified by baseline 2 or 3 categorical pain level (moderate or severe) prior to dosing (see Section 16.2). Subjects who designate their baseline pain as ***moderate*** will use the lowest randomization number available with subsequent moderate randomizations using the next available lowest number. Subjects who designate their baseline pain as ***severe*** will use the highest randomization number available with subsequent severe randomizations using the next available highest randomization number. Subjects who characterize their pain severity as ***mild*** and <5 on the NRS will not receive treatment and be withdrawn from the study.

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

Subjects completing the Screening Visit, if not scheduled for surgery the same day, will return to the trial site within 28 days, and if they continue to meet inclusion/exclusion criteria postsurgery will be randomized to one of three treatment groups:

- Naproxen sodium tablets (220 mg x 2 tablets)
- Ibuprofen tablets (200 mg x 2 tablets)
- Placebo tablets (2 tablets)

Subjects will be assigned to treatment groups in accordance with the randomization schedule. The Sponsor or designee will provide a randomization schedule to the study site.

7.4 Dosage and administration

Each subject will receive a single dose randomized to naproxen (220 mg x 2 tablets), ibuprofen (200 mg x 2 tablets) or placebo (2 tablets). Subjects receive the study drug with a full glass of non-refrigerated, non-carbonated water (about 8 ounces or 240 mL). Study drug will be administered using dosing cups. Selection and preparation of the proper dose will be performed by an unblinded study team member using the provided randomization schedule (see Section 7.5.1). The Investigator or a designee will supervise the study drug administration in a manner which maintains the masking conditions (blinding of the subject).

Subjects must be NPO from midnight prior to surgery until completion of surgery. Subject will continue fasting, with the exception of clear liquids, until after study drug administration.

7.5 Blinding

7.5.1 Blinding measures

Subjects enrolled in the trial, investigators and their staff involved in protocol procedures or who are involved in data collection, data entry and data analysis will be blinded to the identity of the treatments until the database is locked. The study monitor will conduct product accountability after database lock. To preserve blinding, subjects will be blindfolded. Study drug will be dispensed by an unblinded study team member based on the randomization schedule. That team member may have no other role in the study conduct and may not reveal the study drug's identity to any members of the blinded study team.

Sponsor will supply study medication in bulk containers. Selection of the proper dose for an individual subject will be performed by an unblinded study team member using the provided randomization schedule. The unblinded study team member will withdraw the appropriate study medication from the bulk container and transfer it to a dispensing cup. The unblinded study team member will then bring the study medication to the treatment room where it will be dispensed to the subject by the unblinded study team member. The unblinded study team member should have no other responsibilities in the study.

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 trial. Randomization code-break envelopes must be securely maintained at the trial site and with the Sponsor.

In compliance with applicable regulations, in the event of a serious unexpected adverse event (SUSAR) related to the blinded treatment, the subject'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 code-break envelopes that can be used to break the blinding of the study drug. Any subject who was unblinded using the code-break envelopes must document this occurrence in the subject's medical record. The investigator must report the blind break in conjunction with a SAE within 24 hours of becoming aware of the effect as defined in Section 9.6.1. Subjects 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 investigational medicinal product (IMP) to the study site. The study center will dispense IMP according to the randomization schedule and the subject's categorical pain intensity (moderate or severe) postsurgery. IMP will be supplied to the study center in multi-dose bottles and dispensed by an unblinded member of the study team.

All study drugs will be stored at the investigational site in accordance with GCP and GMP 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 study investigational products in writing. The personnel will use the study investigational products only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

7.7 Treatment compliance

The administration of the study medication will be supervised by an unblinded member of the Investigator's team. This person will perform the oral cavity inspection after study drug administration and document that the subject receives the treatment as planned.

8. Non-study therapy

8.1 Prior and concomitant therapy

The following treatments are prohibited from screening and during the study:

- Use of any form of medication or herbal supplements within 5 days of surgery that would confound the evaluation of the study product, until discharge from the study site;
- Use of acetaminophen, naproxen, ibuprofen, aspirin, or other NSAIDs or any other pain reliever (OTC or prescription) within 5 days before surgery;
- Use of alcoholic beverages, any food or beverages containing caffeine after midnight prior to surgery and throughout the evaluation period;
- No smoking within 3 days prior to presurgery to the completion of the study.

All medications (prescription and nonprescription products, vitamin and herbal products) taken by the subject from 30 days prior to Screening to End of Trial (EOT) will be documented. The reported medications will be reviewed and evaluated by the Principal Investigator or designee to determine if they affect the subject's eligibility to participate in the study.

8.2 Post-study therapy

This study is a single dose administration after surgery and there is no additional treatment allocated. Subjects who randomize into the study will be discharged from the study center after the final (24 hour post dosing) assessments, regardless of whether rescue medication had been taken or not.

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 9.2.6 will be performed by a designated study team member as designated by the Principal Investigator.

9.2.1 Screening Period

Note: No screening procedures may be performed unless subjects have been provided an IRB-approved written informed consent which subjects have read, understood, and signed.

The Screening Period will be up to 28 days long. The following will be determined during the Screening Visit:

- Signed Informed Consent Form (ICF);
- Review inclusion and exclusion criteria;
- Subject demographics;
- Medical/surgical history including history of drug, alcohol and tobacco use;
- Medication history of all prescription, OTC products including vitamins or dietary/herbal supplements, taken during the past 30 days;
- Vital signs consisting of sitting blood pressure, respiratory rate and pulse after sitting for at least 5 minutes;
- Physical and oral examination;
- Dental x-ray examination and interpretation;
- Urine tests for illicit drugs and cotinine;
- Breath alcohol test;
- Urine pregnancy test (if applicable);
- Impaction score.

Upon satisfying the inclusion/exclusion criteria, eligible subjects will be instructed to return to the trial site within 28 days for oral surgery. Subjects will be instructed to refrain from the use of all medications (prescription, nonprescription, herbal supplements) unless in the opinion of the Investigator or Sponsor, the medication will not interfere with study procedures, data integrity, or compromise the safety of the subjects.

Subjects will be instructed not to consume alcohol, any food or beverages containing caffeine (e.g., coffee, tea, chocolate, and colas) products after midnight prior to surgery. Surgery will be scheduled between 0630 h and 1000 h (+/- 30 minutes).

The Principal Investigator or his/her designee must review subject's study records before qualifying the subject for the trial.

9.2.2 Presurgery

Subjects are instructed to be nil per os (NPO) from midnight prior to surgery. If a subject had something to eat or drink after midnight, the surgeon must determine if surgery may proceed. Subjects will arrive at the unit at their assigned time and will have the following activities completed prior to dental surgery:

- Review changes in the subject's medical/medication history and inclusion/exclusion criteria since previous visit;
- Urine tests for illicit drugs and cotinine;
- Breath alcohol test;
- Vital signs (sitting blood pressure, pulse rate and respiration after sitting for 5 minutes);
- Urine pregnancy test (if applicable);
- Review pain assessment process and procedures;

9.2.2.1 Impaction Score

An Impaction Score will be used to assess each tooth based on the radiographic appearance and the intraoral examination. Each tooth will be rated from 1 to 4 using the following criteria: (1) erupted in tissue (2) soft tissue impaction (3) partial bony impaction, and (4) full bony impaction. Only subjects whose mandibular impactions are scored (3) or (4) will be eligible to participate in the study.

9.2.3 During Surgery

During surgery, subjects will be administered a short acting local anesthetic (lidocaine or mepivacaine with or without vasoconstrictor) and nitrous oxide; at the discretion of the dentist/oral surgeon. Topical anesthetics may also be used prior to the administration of the short acting local anesthetic. Long duration local anesthetics like bupivacaine are not permitted. No other perioperative analgesic or anesthetic agents are permitted. Perioperative corticosteroids are not permitted.

9.2.4 Postsurgery

During the postsurgery recovery period, subjects will rest quietly, but will be encouraged not to fall asleep. Subjects will be permitted to drink clear liquids following surgery until they have been dosed. Subject may incorporate foods according to a soft diet following dosing beginning 60 minutes after dosing. Subjects will not be allowed to eat 30 min prior to any planned assessments.

In order to qualify for randomization and continue in the trial, subjects must have 'moderate' or 'severe' postoperative pain intensity on the Categorical Pain Rating Scale **and** a score of ≥ 5 on the NRS within 4.5 hours of the last suture, but no later than 14:30 +/- 15 minutes.

Eligible subjects will be assigned a subject randomization number and investigational products will be administered according to a generated randomization schedule (see Section 7.3).

Subjects who have not met the randomization criteria within 4.5 hours from last suture by 14:30 h +/- 15 minutes will not be randomized and may be discharged from the clinic, once deemed eligible by an Investigator. Prior to being released from the clinic, discharge procedures will be reviewed with the subject. When discharged, all subjects will need to make prior arrangements for travel and should not drive themselves home.

After the baseline (pre-dose) pain intensity is determined, pain intensity, pain relief and pain half gone will be rated by subjects at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, and 24 hours (+/- 5 minutes over the first 6 hours; ±10 minutes from hours 7 through 24) postdose, and immediately prior to the use of the first dose rescue medication. If necessary, subjects will be awakened 10 minutes prior to scheduled pain assessments. The order of the pain assessments is Pain Intensity, then Pain Relief, then Pain Half Gone then query about any AEs. At hour 24 or immediately prior to the first dose of rescue medication (if required), study subjects will be asked to provide a Global Assessment of investigational product as a pain reliever after completion of the other assessments. Additionally, subjects will have vital signs taken after surgery then 1 and 24 hours postdose.

Throughout the treatment period, the subjects will be monitored for the occurrence of adverse events. Symptoms will be assessed by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as “How do you feel?” or “Are you experiencing any other effects?” All reported or observed AEs will be collected and recorded on the case report form. The information will be based on signs and symptoms reported by the subject or observed by the study personnel staff during clinical evaluation.

If a subject has any clinically significant, trial-related abnormalities at the conclusion of the treatment period, the clinical monitor (or designated representative) should be notified and the subject should be asked to remain at the trial site until such abnormalities are stabilized or resolve. If the subject is unable or unwilling to remain at the trial site, the clinical monitor (or designated representative) should be notified, and the Investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Subjects will be allowed the use of ice following the use of rescue medication. Ice will not be permitted for subjects prior to randomization until after they have been administered rescure medication (if applicable). If subject has been administered rescue, ice will be given as requested by the subject for 20 min incriments. Ice will be removed 30 min prior to the completion of any pain assessments. Upon completion of all trial procedures, subjects will be discharged from the trial site. Subjects will need to make prior arrangements for travel and should not drive themselves home.

9.2.5 Rescue Medication

If adequate pain relief was not achieved, then subjects are permitted to take rescue medication, although they will be encouraged to wait 90 minutes to allow the investigational product time to take effect. Rescue medication will be Hydrocodone 5 mg/Acetaminophen 325 mg tablets or other appropriate analgesics may be used at the discretion of the Investigator**.** Subjects will be required to complete pain assessments by rating pain intensity,

pain relief and pain half gone at each time point and global assessment immediately before the initial dose of rescue medication.

Rescue medication is also available on return of pain and the time of rescue medication will be recorded. Pain assessments will be performed immediately before the first dose of rescue medication.

- Rating of Pain Intensity (NRS);
- Rating of Pain Relief (Categorical);
- Pain Half Gone
- Global Assessment of investigational product as a pain reliever.

Subjects 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 subject or observed by the research coordinator during clinical evaluation.

9.2.6 End of Trial (EOT)

After completion of the treatment period the following additional evaluations will be performed:

- Trial sites will have the option of either contacting subjects within 5 to 9 days after surgery (by phone) or scheduling subjects for an office appointment, depending on their standard of care policies, to assess the occurrence or persistence of AEs, any medications taken, and for adequate treatment and follow up.

9.3 Population characteristics

9.3.1 Demographic

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

- Year of birth (approximate age);
- Native language;
- Reported need for third molar surgery.

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:

- Started before signing of the informed consent;
- Considered relevant for the subject'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 caffeine, smoking, drug and alcohol consumption will be collected. Surgical data (tooth number and diagnosis of each extraction, duration of surgery in minutes (first incision to last suture), identity and amount of all surgical medications, will be collected.

9.4 Efficacy Analysis

For each postdose timepoint, Pain Intensity Differences (PID) will be derived by subtracting the pain intensity at the postdose timepoint from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Time-weighted sum of pain intensity differences (SPIDs) will be calculated for 4, 8, 12, 6-12, and 24 hours by multiplying the PID score at each postdose timepoint by the duration (in hours) since the preceding timepoint and then summing these values over 4, 8, 12, 6-12, and 24 hours, respectively. Similarly, total pain relief scores (TOTPARs), will be calculated by multiplying the pain relief score at each postdose timepoint by the duration (in hours) since the preceding timepoint and then summing these values.

In all analyses, for subjects who take rescue medication, all pain intensity scores after intake of rescue medication will be replaced by the worse of the baseline or the score assessed immediately before taking rescue medication. All pain relief after intake of rescue medication will be replaced by "no relief" (0).

A complete list of primary, secondary and other efficacy parameters can be found in Section 10.3.

9.4.1 Safety Analysis

Safety measures will be analyzed for all subjects 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 subjects 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 subject 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 subject 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 subject 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 or dentist/oral surgeon, 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 subject 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): Subject'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 subject may have.

- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject 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 subject'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
- 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 subject 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 drug.

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. For clarity it might be useful to state that a pregnancy is to be captured as an SAE

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 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 subject'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 study subject 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 a pregnancy in the partner of a male study subject, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

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 qualified medical staff (e.g., a physician, oral surgeon, nurse practitioner or physician assistant) at the study site covering at least the organs of the head/neck, cardiovascular, and respiratory systems.

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:

– Subject without shoes after having emptied his / her bladder

– Physician (column) scale, measurement units 0.1 kg

The subject'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 subject); cuff location will be documented

– Method: oscillometric by automatic measurement device

- **Laboratory examinations**

Urine samples will be collected by a member of the investigator's team, for time points and parameters see Section 16.1 in the appendix.

9.7 Other procedures and variables

Eligible subjects will undergo an oral examination and a dental x-ray (radiograph) exam to confirm that impacted third molar teeth are present.

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 statistical analysis software (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 trial.

Safety Population

All subjects who are randomized and take at least one dose of investigational product. Safety measures will be analyzed for all subjects in the safety population.

Intent-To-Treat (ITT)

All subjects in the Safety Population who provide at least one pain assessment after the first dose of the investigational product. ITT population will be used as the sensitivity analysis for the selected parameters.

Per Protocol (PP) Population

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

Major protocol deviations will be identified prior to database lock and may include but are not limited to significant violations of inclusion/exclusion criteria, noncompliance of the trial treatment taken, conditions such as vomiting and diarrhea or use of prohibited medications, and not following clinical trial protocol procedures. Any subject who rescues or vomits at or prior to 60 minutes after ingesting study medication will be excluded from the Per Protocol analysis.

10.3 Efficacy Analysis

For each postdose timepoint, Pain Intensity Differences (PID) will be derived by subtracting the pain intensity at the postdose timepoint from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Time-weighted Sum of Pain Intensity Differences (SPIDs) will be calculated for 4, 8, 12, 6-12 and 24 hours by multiplying the PID score at each postdose timepoint by the duration (in hours) since the preceding timepoint and then summing these values over 4, 8, 12, 6-12 and 24 hours, respectively. Similarly, Total Pain Relief Scores (TOTPARs), will be calculated by multiplying the pain relief score at each postdose timepoint by the duration (in hours) since the preceding timepoint and then summing these values.

In all analyses, for subjects who take rescue medication, all pain intensity scores after intake of rescue medication will be replaced by the worse of the baseline or the score assessed immediately before taking rescue medication. All pain relief after intake of rescue medication will be replaced by "no relief" (0).

10.3.1 Primary Efficacy Parameter

The primary efficacy analyses population will be based on the PP population.

The primary efficacy parameter is defined as:

- Time to first use of rescue medication. If a subject did not take the rescue medication during the treatment period, (s)he 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 stratified by center and baseline pain intensity.

10.3.2 Secondary Efficacy Parameters

The secondary efficacy variables include:

- SPID 0-24 and TOTPAR 0-24 will be analyzed using an analysis of covariance model (ANCOVA) with treatment as fixed effect and baseline pain intensity score as the covariate. A 95% of confidence interval (CI) for the treatment differences will be calculated based on the above mentioned model.

10.3.3 Other Efficacy Parameters

- The SPID 0-4, 0-8, 0-12, 6-12 will be analyzed using the same methodology as for SPID 0-24.
- TOTPAR 0-4, 0-8, 0-12, and TOTPAR 6-12 will be analyzed using the same methodology as for SPID 0-24.
- Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 and 24 hours postdose. Descriptive statistics for each timepoint and graphical illustrations of the time effect curves will be presented.
- The cumulative proportion taking rescue medication by timepoint will be analyzed using Chi-square tests and time-effect curves will be generated. Frequency tables will be generated for the number of times the subject took rescue medication over the 24 hour period by treatment group.

- Percent of subjects with Pain Half Gone (Yes / No question) by 24 hours will be summarized descriptively by treatment group.
- The proportion of subjects with pain at least one-half gone at each time point will be summarized descriptively and plotted over time by treatment group;
- Duration of time that subjects reported their pain was at least half gone;
- Total amount of time that subject reported at least a 2-point PID;
- Global Assessment of the investigational product as a pain reliever. This variable will be analyzed using CMH method with modified ridit score. The proportion of subjects in each surgery will also be presented.

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 subjects 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, 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 subject data (e.g., vital signs) will be provided.

10.4 Determination of sample size

The objective of this study is to establish superiority of naproxen sodium 440 mg over 24 hours compared to ibuprofen 400 mg over 24 hours with respect to the time to rescue medication.

CCI [redacted] A total of 385 subjects will be randomized into the study if a drop-out rate of 5% is assumed.

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. Subject data necessary for analysis and reporting will be provided to the Sponsor in CDISC (Clinical Data Interchange Standards Consortium) standards.

Interface to local laboratory

Laboratory test results will be received as electronic data files from the local laboratory. They will be transferred to the clinical study database at the study site. For easy access and tracking by the investigator, the results will be additionally provided in printed form. 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 subjects' 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 (subject 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 subjects 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).

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.

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 subject 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 trial 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 subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject'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 subject 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 subjects 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 IEC/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 trial subjects 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 Subject information and consent/assent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. Sample subject information and informed consent/assent forms are provided as a document separate to this protocol. Subjects 16 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 subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject prior to his/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 subject will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision;
- The subject's consent covers EOT examinations as specified in the visit description described in Section 9.2.6 to be conducted after withdrawal of consent;
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan;
- Subject-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 subject 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 subject's oral objection may be documented in the subject's source data.

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

Only if the subject 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 subject 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 subject'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 subject´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 subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/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 subjects / 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 subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject numbers (SNR and RNR) will be recorded in the CRF/eCRF data collection system, and if the subject 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 subjects 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 subject's identity will remain confidential.

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

14. Reference list

1. Grosser T, Smyth E, FitzGerald GA. Anti-inflammatory, Antipyretic, and Analgesic Agents; Pharmacotherapy of Gout. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e* New York, NY: McGraw-Hill; 2011. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1613&sectionid=102161048. Accessed July 16, 2017.

2. Kiersch TA, Halladay SC, and Hormel PC. A Single-Dose, Double-Blind Comparison of Naproxen Sodium, Acetaminophen, and Placebo in Postoperative Dental Pain. *Clin Ther* 1994;16(3):394-404

3. Kiersch TA, Halladay SC, and Koschik M. A Double-Blind, Randomized Study of Naproxen Sodium, Ibuprofen, and Placebo in Postoperative Dental Pain. *Clin Ther* 1993;15(5):845-54.

4. Fricke JR, Halladay SC, and Francisco CA. Efficacy and Safety of Naproxen Sodium and Ibuprofen for Pain Relief After Oral Surgery. *Curr Ther Res* 1993;54(6):619-27.

5. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry Analgesic Indications: Developing Drug and Biological Products. February 2014 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf Accessed July 16, 2017.

6. Cooper SA and Desjardins PJ. The value of the dental impaction pain model in drug development. *Methods Mol Biol*, Szallasi A, Ed. Humana Press 617: 175 – 190, 2010.

7. Cooper SA, Beaver WT. A model to evaluate mild analgesics in oral surgery outpatients. *Clin Pharmacol Ther* 1976;20:241–50.

8. Kleinert R, Lange C, Steup A, Black P, Goldberg J, Desjardins P. Single dose analgesic efficacy of tapentadol in postsurgical dental pain: the results of a randomized, double-blind, placebo-controlled study. *Anesth Analg*. 2008;107:2048-55.

9. Cooper SA, Desjardins PJ, Turk DC, et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. *Pain* 2016;157:288-301.

10. Singla NK, Desjardins PJ, Chang PD. A comparison of the clinical and experimental characteristics of four acute surgical pain models: dental extraction, bunionectomy, joint replacement, and soft tissue surgery. *Pain*. 2014;155:441-56.

11. Jung YH, Cho BH. Radiographic evaluation of third molar development in 6- to 24-year-olds. *Imaging Science in Dentistry* 2014; 44: 185-91.

15. Protocol amendments

Amendment 1 (dated 25-Jan-2018) is attached to the front of this protocol.

16. Appendices

16.1 Study Flow Chart

Table 3: Study schema

Protocol Activities	Screening Visit (within 28 days prior to oral surgery)	Dosing Period *Inpatient*		End of Trial Call (2-5 days after discharge)
		Day 1	Day 2	
Written Informed Consent	x			
Inclusion/Exclusion Reviewed	x	x		
Medical/Medication History	x	x		
Physical and Oral Examination	x			
Vital Signs[a]	x	x	x	
Urine for Drug Screen and Cotinine test	x	x		
Breath alcohol test	x	x		
Dental x-ray examination	x			
Urine Pregnancy Test (if applicable)	x	x		
Admission to Unit		x		
Oral surgery (between 0630 h and 1000 h (+/- 30 minutes)		x		
Randomization Number Assigned		x		
Investigational Product Administration		x		
Categorical Pain Rating Scale [b]		x		
Pain Intensity Numerical Rating Scale (NRS) [c]		x	x	
Categorical Pain Relief Rating Scale [c]		x	x	
Starting pain is at least ½ gone[c]		x	x	
Global Assessment of Pain Relief [d]			x	
Concomitant Medications		x	x	x
Adverse Events Assessed	x	x	x	x
Discharge from Unit morning of Day 2			x	

[a] vital signs (blood pressure, pulse rate, and respiration after sitting for at least 5 minutes). On Day 1, vital signs are due post-surgery and 1 hour after study medication dose. On Day 2, vital signs are due at 24 hours post-dose.
[b] to be completed prior to dosing
[c] Pain Intensity NRS to be completed at baseline (predose), and Pain Intensity NRS and Categorical Pain Relief will be assessed 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 and 24 hours postdose. If rescue occurs, scales/questions (except pain ½ gone) will be completed immediately each time rescue medication is taken
[d] assessment will be completed immediately before first rescue medication is taken or at 24 hours post-dose

16.2 Subjective Assessments

Categorical Pain Intensity Scale (predose)

Finish the statement: **"My pain at this time is"** by checking the appropriate box.

- □ No Pain (0)
- □ Mild Pain (1)
- □ Moderate Pain (2)
- □ Severe Pain (3)

Numerical Rating Scale (predose and post-dose)

Circle a number to indicate level of pain (from 0 to 10) below to indicate the severity of the pain you are experiencing at this time.

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

Categorical Pain Relief Rating Scale (post-dose)

Finish the statement: **" My relief from my starting pain is""** by checking the appropriate box.

- ☐ No Relief (0)
- ☐ A Little Relief (1)
- ☐ Some Relief (2)
- ☐ A Lot of Relief (3)
- ☐ Complete Relief (4)

Half Way Pain Relief (post-dose)

Finish the statement: **"Is your starting pain at least ½ gone?"** by checking the appropriate box.

☐ No (0)
☐ Yes (1)

Global Assessment of Pain (post-dose)

How would you rate the study medication you received as a pain-reliever?

☐ Poor (0)
☐ Fair (1)
☐ Good (2)
☐ Very Good (3)
☐ Excellent (4)