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Official Title:	A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Hydrocodone/Acetaminophen Tablets in Postsurgical Dental Pain
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Title Page

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Protocol Number: 20536

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Sponsor Signatory

PPD

19 Nov 2019

Date

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1. Protocol Summary

1.1 Synopsis

Naproxen sodium and Hydrocodone/Acetaminophen are two widely used analgesics for acute pain. In light of the concern with overuse of opioids, a comparison of the analgesic effectiveness of these two commercially available medications provides clinicians with important information to help them select an appropriate analgesic for their patient with acute pain.

The post-impaction dental pain model 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 participants 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 (Cooper, 2010, Cooper 1976, Kleinert, 2008). This study will use the dental pain model to examine an OTC NSAID to a commonly prescribed oral opioid combination analgesic.

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Hydrocodone/Acetaminophen Tablets in Postsurgical Dental Pain

Rationale:

Both naproxen sodium and hydrocodone/acetaminophen are widely used analgesics. However, the relative efficacy of over-the-counter naproxen sodium has not been compared to hydrocodone/acetaminophen for relief of acute pain. This is important because clinicians need to weigh the risks and benefits of available analgesic medications when selecting an appropriate analgesic to manage their patients complaints of acute pain.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the analgesic efficacy of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain.	• Sum of Pain Intensity Difference over 12 hours (SPID 0-12)
Secondary	
• To compare the amount of pain relief produced by a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain.	• Total Pain Relief over 12 hours (TOTPAR 0-12) • Total Pain Relief over 6 hours (TOTPAR 0-6) • Sum of Pain Intensity Difference over 6 hours (SPID 0-6) • Time to first use of rescue medication • Duration of Pain at Least Half Gone • Duration of Pain at Least Half Gone over first 6 hours

Overall Design:

This is a single center, randomized, double-blind, parallel, placebo-controlled study, stratified by baseline pain, in participants experiencing moderate to severe postoperative dental pain. The study will consist of a Prescreening telephone call, a Screening Visit, a one day Treatment Period and a Post-Operative visit. Eligible participants who have undergone surgical extraction of three or four third molars, 2 of which must be mandibular partial or full bony impacted third molars will be randomized into one of three treatment groups and kept in-house and evaluated for efficacy and safety at the study center through completion of all trial procedures.

Disclosure Statement: This is a parallel group treatment study with 3 arms that is participant and investigator blinded.

Intervention Model: Parallel

Primary Purpose: Treatment

Number of Arms: 3

Masking: No masking

Number of Participants:

Approximately 300 participants will be screened to achieve 220 randomly assigned to study intervention and 200 evaluable participants for an estimated total of 80 evaluable participants per active intervention group (total of 2 groups) and 40 for placebo.

Intervention Groups and Duration:

Participants will receive a single dose of study intervention of either naproxen sodium 440 mg, hydrocodone/acetaminophen 10/650 mg, or placebo with pain and pain relief assessments performed over the next 12 hours.

Data Monitoring Committee: No

1.2 Schema

Figure 1 – Design Overview

	Screening Phase	Treatment Phase				Follow up Phase
Trial Days	**Day -28 to -1**	**Day 1 Pre-surgery**	**Day 1 Surgery**	**Day 1 Post-surgery**	**Day 1**	**2-5 days after discharge**
		Check-in to study site (if needed)	Surgical teeth extraction	Categorical pain ✸ NRS pain	Stopwatch method ✸ NRS pain ✸ Pain relief ✸ Pain half gone ✸ Global assessment	Phone call or visit

✸ = randomized to either naproxen sodium 440 mg, hydrocodone/acetaminophen 10/650 mg or placebo

1.3 Schedule of Activities (SoA)

Protocol Activities	Screening Visit (within 28 days prior to oral surgery)	Dosing Period *Inpatient* Day 1	End of Trial Call (2-5 days after discharge)
Written Informed Consent	x		
Inclusion/Exclusion Reviewed	x	x	
Medical/Medication History	x	x	
Physical and Oral Examination	x		
Vital Signs[a]	x	x	
Urine for Drug Screen	x	x	
Breath or saliva alcohol test	x	x	
Dental x-ray examination	x		
Urine Pregnancy Test (if applicable)	x	x	
Admission to Unit		x	
Oral surgery (between 0530 h and 1030 h)		x	
Randomization Number Assigned		x	
Investigational Product Administration		x	
Surgical Trauma Rating		x	
Stop watch method (perceptible and meaningful relief)		x	
Categorical Pain Rating Scale[b]		x	
Pain Intensity Numerical Rating Scale (NRS)[c]		x	
Categorical Pain Relief Rating Scale [c]		x	
Starting pain is at least ½ gone[c]		x	
Global Assessment of Pain Relief [d]		x	
Concomitant Medications		x	x
Adverse Events Assessed	x	x	x
Discharge from Unit the evening of Day 1		x	

[a] vital signs (blood pressure, pulse rate, and respiration after sitting for at least 5 minutes). On Day 1, vital signs are due pre-operatively, post-surgery at 1 hour, and 12 hours after study medication dosing.
[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, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours postdose. If rescue occurs, scales/questions will be completed immediately each time rescue medication is taken
[d] assessment will be completed immediately before first rescue medication is taken or at 12 hours post-dose

2. Introduction

In addition to the information provided below, please also refer to the Aleve Drug Facts Label (DFL) and the hydrocodone/acetaminophen prescribing information for any additional data on these two analgesic products.

Naproxen sodium and hydrocodone/acetaminophen are two widely used analgesics for control of postoperative pain. Therefore, the purpose of this investigation is to use the post-impaction dental pain model to compare the analgesic efficacy of over-the-counter naproxen sodium and prescription hydrocodone/acetaminophen to assess the relative effectiveness and safety of these two analgesics.

2.1 Study Rationale

Both naproxen sodium and Hydrocodone/Acetaminophen are widely used analgesics. However, the relative efficacy of over-the-counter dosing with naproxen sodium has not been compared to hydrocodone/acetaminophen for relief of acute pain. This assessment is important and timely as options for reducing the use of opioid analgesics in postoperative pain control are highly desired. Understanding the relative efficacy and safety of alternative analgesics can provide clinicians with important information when they select appropriate analgesics for their patients.

2.2 Background

Both naproxen sodium and hydrocodone/acetaminophen are indicated for relief of acute pain. Naproxen sodium is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits production of cyclo-oxygenase (COX). 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. Naproxen sodium has a long elimination half-life, approximately 10–15 h (Brune 2007). Correspondingly, it has a long duration of action (Kiersch 1994) and requires only once or twice daily dosing. Hydrocodone/acetaminophen is a combination of an opioid analgesic and non-opioid analgesic with different mechanisms of action. Hydrocodone is a mu-receptor agonist whose site of action is principally within the central nervous system [redacted] prescribing information). Despite its long history, acetaminophen's mechanism of action is not fully understood but is believed to involve different and interrelated central pathways, including effects on prostaglandin production, and on serotonergic, opioid, nitric oxide and cannabinoid pathways (Sharma 2014). Both hydrocodone and acetaminophen have a relatively short duration and half-lives of less than 4 hours ([redacted] prescribing information).

Both naproxen sodium and hydrocodone/acetaminophen have a long marketing history. 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. Hydrocodone/acetaminophen has been marketed by prescription

under the brand name Norco®. As a prescription medication, it is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

2.3 Benefit/Risk Assessment

Participants who need to have third molar extraction will be solicited to participate in this study. Participants who consent to participate may benefit by receiving a medical exam, dental radiographs and no-cost surgical procedures for teeth extraction. Furthermore, post-surgical participants will be provided continuous nursing care for approximately 12 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. Participants 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 extraction of wisdom teeth. Potential risks of a single dose of OTC and prescription study medication are low and described in the Drug Facts Label and Prescribing Information, respectively.

During the study, participants 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.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events may be found in the naproxen sodium Investigator's Brochure, CCI prescribing information and Aleve® Drug Facts Label.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the analgesic efficacy of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain.	• Sum of Pain Intensity Difference over 12 hours (SPID 0-12)

Objectives	Endpoints
Secondary	
• To compare the amount of pain relief produced by a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain. • To compare the time to first use of rescue medication of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain • To compare the duration of pain intensity at least half gone for each timepoint of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain	• Total Pain Relief over 12 hours (TOTPAR 0-12) • Total Pain Relief over 6 hours (TOTPAR 0-6) • Sum of Pain Intensity Difference over 6 hours (SPID 0-6) • Time to first use of rescue medication over 12 hours • Duration of Pain at Least Half Gone over 12 hours • Duration of Pain at Least Half Gone over first 6 hours
Other pre-specified	
To compare the following parameters of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain: • Summed Pain Intensity Difference • Total pain relief • Pain Intensity Difference (PID) • Proportion/percent of participants with Pain Half Gone • Global assessment of the investigational product To compare the incidence of GI and Nervous system side effects produced by a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo	• The SPID0-4, 0-8 and 8-12 • TOTPAR0-4, 0-8 and 8-12 • Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose • Time to first perceptible relief measured by a stopwatch, time to meaningful relief measured by a stopwatch, and time to first perceptible relief confirmed by meaningful relief defined as the time to perceptible pain relief (the first stopwatch time) for those subjects who had meaningful pain relief (the second stopwatch time) • The cumulative proportion of subjects taking rescue medication over the 12 hour period. • Peak PID and peak pain relief • Percent of participants with Pain Half Gone at least once over 12 hours • Percent of participants with Pain Half Gone at each time point over 12 hours • Proportion of participants with pain at least one-half gone at each time point • Cumulative percent of subjects with Pain at least half gone will be plotted over time • Cumulative percent of subjects with ‘at least a 2-point PID’ will be plotted over time • Global Assessment of the investigational product • Percent of subjects reporting GI and Nervous system AEs prior to use of rescue medication

4. Study Design

4.1 Overall Design

Design Overview

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

Qualified participants will then be randomized into one of three treatments. Approximately 300 participants will be screened prior to surgery. Approximately 220 will have surgery and approximately 200 will be randomized to a specific treatment.

Screening Phase

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

Treatment Phase

Following selection, qualified participants will enter the Treatment Phase and be scheduled for their surgical teeth extractions. After completion of the surgical teeth extractions, participants will remain at the study site for observation. Participants with appropriate pain severity for randomization will then be stratified by baseline pain intensity and randomized into one of three (3) treatment groups. Participants will rate their pain severity and pain relief over the next 12 hours. Onset of analgesia will be measured using a two stopwatch approach. The first stopwatch will be used to capture the time when any pain relief is first perceived and in certain cases the second stopwatch will be used to capture the time when pain relief becomes meaningful to the participant. After completion of all trial procedures, participants will be discharged from the study site.

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

Follow-Up Phase

Participants will be evaluated at a post-operative visit/call approximately 2-5 days after discharge for follow up for any adverse events or medications not known at the time of treatment.

The duration of each participant's participation will be approximately 37 days. For an overview on the study design and study procedures (see Figure 1).

4.2 Scientific Rationale for Study Design

The study is designed specifically to capture and measure the effectiveness and side effect profiles of naproxen sodium compared to hydrocodone/acetaminophen on acute post-surgical dental pain in healthy participants who could benefit from the administration of an analgesic medication. The molar impaction dental pain model has been widely studied with OTC and prescription pain medications; however, should a participant not get sufficient pain relief, then rescue medication approved for treating acute pain (e.g. , acetaminophen, tramadol etc.) may be requested.

The post-impaction dental pain model 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 participants undergoing a given procedure is usually relatively healthy and homogeneous. In addition, there are 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 (Cooper, 2010, Cooper 1976, Kleinert, 2008).

Time to onset will be measured using a double stopwatch method. The double-stopwatch method for measuring first perceptible relief and meaningful relief was developed using the dental pain model (Desjardins 2002). After ingesting the study medication, the participant is asked to depress a stopwatch button when first perceiving any relief (First Perceptible Relief). If and when this stopwatch is depressed, the participant is then given a second stopwatch and asked to depress the button when the relief is perceived as meaningful (Meaningful Relief). Using this method, onset to First Perceptible and Meaningful Relief can be quantified to the nearest minute. This method has been proven to be sensitive and reliable for measuring analgesic onset (Cooper 2010).

The endpoints and study design are consistent with most recent Guidance by FDA and methods advocated by experts (Cooper 2016 and Singla 2014).

4.3 Justification for Dose of Active Treatment Groups

Participants will receive a single dose of study intervention which is sufficient to provide an analgesic effect in participants who experience post-surgical dental pain.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities. Trial sites will have the option of either contacting participants within 2 to 5 days after surgery (by phone) or scheduling participants 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.

Primary completion

The primary completion is defined as the date of the last visit of the last participant for the primary outcome.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The subject population will consist of healthy individuals who are status post extraction of three or four third molars, 2 of which were mandibular partial or full bony impactions.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Healthy, ambulatory, male or female volunteers 18 to 40 years of age;
2. Body mass index 18.5 to 35.0 kg/m^2 inclusive as measured by the NIH BMI Calculator;
3. Subjects will undergo surgical extraction of three or four third molars, two of which must be mandibular molars. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must have a trauma rating of mild or moderate and meet one of the following scenarios:
    - two full bony impactions
    - two partial bony impactions
    - one full bony impaction in combination with one partial bony impaction

   Supernumerary teeth present may also be removed at the discretion of the oral surgeon;
5. Have not taken any form of medication, nutritional supplements with analgesic properties (e.g. GABA, turmeric) or herbal supplements (i.e., St. John's 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: a) be using a medically acceptable form of birth control [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier]for at least 1 month prior to screening (3 months on oral contraceptives); b) abstain from sexual intercourse for at least 1 month prior to screening; or c) participate exclusively in a same sex relationship for at least 1 month prior to screening. In addition, female subjects of childbearing potential must 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;
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. Capable of giving signed informed consent as described in Section 10.1.4 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of hypersensitivity to naproxen sodium, hydrocodone/acetaminophen, 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 (including hypertension), hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years;
3. Subjects with the following medical conditions may be eligible at the discretion of the investigator: ADHD on a stable dose regimen of methylphenidate/(dextro)amphetamine for at least 6 months; subjects with hypothyroidism on a stable dose of synthetic thyroid hormone for at least 6 months;
4. 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] but excluding ADHD medications described above) within the last 6 months;
5. Relevant concomitant disease such as asthma (exercise induced asthma is permitted);
6. Current or past history of gastrointestinal ulceration, gastrointestinal bleeding or other bleeding disorder(s);
7. Acute illness or active local infection prior to surgery that can interfere with the conduct of the study in the judgment of the investigator;
8. Use of any OTC or prescription medications with which the administration of naproxen, hydrocodone/acetaminophen, acetaminophen, ibuprofen, any other NSAID, (e.g., tramadol) or if a medication is contraindicated;
9. Use of any medications within 5 days of surgery until discharge from the study site (except oral contraceptives, prophylactic antibiotics, synthetic thyroid hormones, methylphenidate or medications to treat benign conditions such as antibiotics to treat acne);

10. Females who are planning to become pregnant, pregnant or lactating;
11. 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);
12. 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;
13. Positive urine drug screen or alcohol test on day of surgery;
14. Surgeon's trauma rating of severe following surgery;
15. Use of Nicotine containing products from midnight prior to surgery until discharge from the study site or longer if so directed by the oral surgeon;
16. Member or first-degree relative of study staff or the Sponsor directly involved in the study;
17. Unwilling or unable to comply with all requirements outlined in the protocol;
18. Participants with a medical disorder, condition, or history of such that could impair the participant's ability to participate or complete this trial in the opinion of the investigator;
19. Previous enrollment in this study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.3.1 Meals and Dietary Restrictions

Participants will be instructed not to consume food that contains caffeine after midnight prior to surgery.

5.3.2 Caffeine and Alcohol

Participants will be instructed not to consume alcohol or beverages containing caffeine (e.g., coffee, tea, chocolate, and colas) products after midnight prior to surgery.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) due to scheduling surgery may be rescreened. A previous dental x-ray if taken during the original

screening visit can be used when rescreened. Rescreened participants should be assigned a new participant number.

5.5 Run-in Failures

A participant 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".

5.6 Dropouts

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

5.7 General Procedures

In all cases, the reason for withdrawal must be recorded on the screening log and in the participant's medical records.

The participant may object to the generation and processing of post-withdrawal data as specified in Section 10.1.6.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 10.1.9 (Premature termination of the Study).

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The study center will dispense a single-dose of an assigned treatment within 4.5 hours post-surgery. The tablets and placebo will be administered based on a computer-generated randomization schedule (section 6.1.1) 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 with a prescription for pain medication, if deemed safe, by an Investigator.

6.1 Study Intervention(s) Administered

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
Hydrocodone/Acetaminophen 10/650 mg (postsurgery)	5/325 mg / orally	2 / tablets	single dose
Placebo (postsurgery)	NA / orally	2 / tablets	single dose

Table 2 – Identity of study treatment

Treatment (UI number)	**Naproxen** CCI [redacted]	**Hydrocodone/Acetaminophen**	**Placebo** CCI [redacted]
Dose	two tablets	two tablets	two tablets
Pharmaceutical Form	tablet	tablet	tablet
Strength	220 mg	5/325 mg	not applicable
Formulation	naproxen sodium FD&C blue #2 lake hypromellose magnesium stearate microcrystalline cellulose polyethylene glycol povidone talc titanium dioxide	hydrocodone bitartrate acetaminophen colloidal silicon dioxide crospovidone magnesium stearate microcrystalline cellulose povidone pregelatinized starch stearic acid	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	CCI [redacted]	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.

6.1.1 Study intervention 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 2:2:1 (naproxen sodium; hydrocodone/acetaminophen; placebo) prepared prior to the study.

Subjects will be numbered according to the following scheme:

PPD

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 PPD

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 10.5). 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)
- Hydrocodone/acetaminophen tablets (5/325 mg x 2 tablets)
- Placebo tablets (2 tablets)

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

6.1.2 Participant Administration

Each participant will receive a single dose of the investigational medicinal product (IMP). Participants receive the IMP with a full glass of non-refrigerated, non-carbonated water (about 8 ounces or 240 mL). Study intervention 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 6.3). The Investigator or a designee will supervise the study intervention administration in a manner which maintains the masking conditions (blinding of the subject).

Participants should be NPO from midnight prior to surgery until completion of surgery, but, at the Investigator's discretion must meet the American Society of Anesthesiology practice

guidelines for pre-operative fasting (ASA guideline, 2017). Participants will continue fasting, with the exception of clear liquids, until after study drug administration.

6.2 Preparation/Handling/Storage/Accountability

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.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The Sponsor will provide sufficient quantity of the 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) post-surgery. 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 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.

6.3 Measures to Minimize Bias: Randomization and Blinding

On Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the three (3) arms of the study, according to the randomization schedule

generated prior to the study by the Sponsor. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study.

Participants 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, participants will be blindfolded during administration of study medication. 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 participant 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 participant by the study team member. The unblinded study team member should have no other responsibilities in the study.

6.3.1 Unblinding

In the case of a medical emergency, such as serious adverse events (SAE), breaking the blind may become necessary during the trial

In compliance with applicable regulations, in the event of a serious unexpected adverse event (SUSAR) related to the blinded treatment, the participant's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 8.3.5).

6.3.2 Emergency unblinding by the investigator

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 10.3.1. Participants who have been unblinded will not be included in the ITT or PP efficacy analysis.

6.4 Study Intervention 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 participant receives the treatment as planned.

6.5 Prior and Concomitant Therapy

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

- Use of any form of medication or herbal supplements, including GABA and turmeric, or curcumin, within 5 days of surgery that would confound the evaluation of the study product, until discharge from the study site;

- Use of acetaminophen, naproxen, hydrocodone/acetaminophen, 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;

All medications (prescription and nonprescription products, vitamin and herbal products) taken by the participant 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 participant's eligibility to participate in the study.

6.5.1 Rescue Medicine

If adequate pain relief was not achieved, then participants are permitted to take rescue medication, although they will be encouraged to wait 90 minutes to allow the investigational product time to take effect. The study site will supply the rescue medication that will be obtained locally. Rescue medication, tramadol or other appropriate analgesic may be used at the discretion of the Investigator**.** Participants 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. All active stopwatch elapsed time(s) will be stopped at the time of rescue administration and recorded on the case report form.

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.

Participants 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 participant or observed by the research coordinator during clinical evaluation.

6.6 Dose Modification

The dosing schedule cannot be modified.

6.7 Intervention after the End of the Study

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 (12 hour post dosing) assessments, regardless of whether rescue medication had been taken or not.

7. Discontinuation of Study Intervention and Participant

7.1 Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Participant Discontinuation/Withdrawal from the Study

Withdrawal criteria

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

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Participant's pain intensity post-surgery at pre-dose does not exceed 'mild' and the NRS is <5 (see Section 10.5);
- If, in the Investigator's opinion, continuation of the study would be harmful to the participant's well-being;

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

- Participant 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 participant 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.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow up.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

If not stated otherwise, the measures / actions listed in the following Sections 8.1.1 to 8.1.6 will be performed by a designated study team member as designated by the Principal Investigator.

8.1.1 Screening Period

Note: No screening procedures may be performed unless participants have been provided an IRB-approved written informed consent which participants 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;
- Participant 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 including impaction score;

  Note: The medical interpretation may occur after the screening visit provided a diagnosis of impaction is determined prior to surgery.
- Urine tests for illicit drugs;
- Breath or saliva alcohol test;
- Urine pregnancy test (if applicable).

Upon satisfying the inclusion/exclusion criteria, eligible participants will be instructed to return to the trial site within 28 days for oral surgery. Participants 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 participants.

Participants will be instructed not to consume alcohol, any food or beverages containing caffeine (e.g., coffee, tea, chocolate, and colas) products or use any nicotine containing products after midnight prior to surgery. Surgery will be scheduled between 0530 h and 1030 h.

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

8.1.2 Pre-surgery

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

- Review changes in the participant's medical/medication history and inclusion/exclusion criteria since previous visit;
- Urine tests for illicit drugs;
- Breath or saliva 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;

8.1.3 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 participants whose mandibular impactions are scored (3) or (4) will be eligible to participate in the study.

8.1.4 During Surgery

During surgery, participants will be administered a short acting local anesthetic (lidocaine or mepivacaine with or without vasoconstrictor) and nitrous oxide; at the discretion of the 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.

8.1.5 Surgical Trauma Score

At the completion of the procedure, the surgeon will rate the degree of surgical trauma on a of (1) mild, (2) moderate or (3) severe. Only individuals with a surgical trauma rating of mild (1) or moderate (2) will be eligible to participate in the study.

8.1.6 Postsurgery

During the post-surgery recovery period, participants will rest quietly, but will be encouraged not to fall asleep. Participants will be permitted to drink clear liquids following surgery. Participant may incorporate foods according to a soft diet following dosing beginning 60 minutes after dosing. Participants will not be allowed to eat 30 minutes prior to any planned assessments.

In order to qualify for randomization and continue in the trial, participants 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.

Eligible participants will be assigned a participant randomization number and investigational products will be administered according to a generated randomization schedule (see Section 6.1.1).

Participants who have not met the randomization criteria within 4.5 hours from last suture or 14:30 h 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 participant. When discharged, all participants 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 participants at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours (+/-5 minutes) post-dose, and immediately prior to the use of the first dose rescue medication.

Instructions will be provided for use of the two stopwatches. A double-stopwatch method will be used to record time up to 12 hours after dosing for time to "first perceptible pain relief" (stopwatch A) and time to "meaningful pain relief *determined*" (stopwatch B). When the participant is administered study medication (following mouth inspection), the Study Coordinator or designee will start two stopwatches (one designated A and one designated B). The faces of the stopwatches will be covered so that the participant remains blinded to the exact time. To determine the time when the participant begins to perceive pain relief, the participant will be given stopwatch A after dosing and will be instructed to:

"Stop the stopwatch when you first begin to feel any pain-relieving effect whatsoever of the drug. That is, when you first feel a little relief. This does not necessarily mean that you feel completely better, although you might, but when you first feel any difference in the pain that you have now."

The participant will notify the Study Coordinator as soon as this stopwatch is stopped. The elapsed time on stopwatch A will be recorded in the case report form as the time to **first perceptible pain relief**. The participant will then be asked:

"Do you consider the relief you experienced meaningful?"

This answer will be recorded by the study coordinator in the case report form. If the participant answers "Yes" to this question, then meaningful pain relief is confirmed. The time recorded in the case report form for time to **meaningful pain relief confirmed will be the <u>same time</u> recorded as first perceptible pain relief**. The participant will not be given the second stopwatch. If the participant does not consider the relief to be meaningful, (by stating No), the participant will be given a second, covered stopwatch with instructions to:

"Stop this stopwatch when you have meaningful relief, that is, when the relief from the pain is meaningful to you."

The elapsed time on stopwatch B will be recorded in the case report form as time to **meaningful pain relief determined**. Unless meaningful pain relief is achieved, the participant will always have an active stopwatch in front of them.

If the participant never experiences first perceptible pain relief, they will retain stopwatch A for the entire 12-hour evaluation period. If the participant experiences first perceptible pain relief but not any meaningful pain relief (confirmed or determined), they will retain stopwatch B for the remainder of the 12-hour evaluation period.

Participants will stay awake during the entire 12 hour assessment. The order of the pain assessments is Pain Intensity, then Pain Relief, then Pain Half Gone then query about any AEs.

At hour 12 or immediately prior to the first dose of rescue medication (if prior to hour 12), study participants will be asked to provide a Global Assessment of investigational product after completion of the other assessments. Additionally, participants will have vital signs taken after surgery then at 1 and 12 hours post-dose.

Throughout the treatment period, the participants will be monitored for the occurrence of adverse events. Symptoms will be assessed by spontaneous reporting of AEs and by asking the participants 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 participant or observed by the study personnel staff during clinical evaluation.

If a participant 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 participant should be asked to remain at the trial site until such abnormalities are stabilized or resolve. If the participant 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.

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

8.2 Safety Assessments

Safety measures will be analyzed for all participants 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 participants 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.

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

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 10.3.1).

8.2.2 Vital Signs

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 participant); cuff location will be documented
- Method: oscillometric by automatic measurement device

8.2.3 Clinical Safety Laboratory Assessments

Urine samples will be collected by a member of the investigator's team, for time points and parameters see Section 1.3.

8.2.4 Other Procedures and Variables

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

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Section 10.3.2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Expected Adverse Events

For this study, the applicable reference document is the most current version of the package insert for naproxen and prescribing information for Hydrocodone/Acetaminophen. 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.

8.3.3 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.5 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. Send the SAE CRF pages and complementary forms to:

PPD or Fax: PPD (in the USA)

8.3.6 Pregnancy

A participant'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 participant 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. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

For a pregnancy in the partner of a male study participant, all efforts will be made to obtain similar information on course and outcome, participant 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 a SAE (see Section 8.3.5). Send the completed pregnancy forms to:

PPD or Fax: PPD (in the USA)

8.4 Treatment of Overdose

For this study, any dose of study intervention greater than single dose study intervention within a 12-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

- Contact the Medical Monitor immediately;
- Closely monitor the participant for any AE/SAE;
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic biomarker parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not performed in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical 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.

9.1 Statistical Hypotheses

The primary efficacy endpoint is the sum of change in pain intensity from 0 to 12 hours ($SPID_{0-12}$). The treatment comparisons will be made in the following sequential order for $SPID_{0-12}$ (each at 0.05 level of significance) in order to protect overall type 1 error at 0.05:

- Naproxen sodium 440 mg versus Placebo
- Naproxen sodium 440 mg versus hydrocodone/acetaminophen 10/650 mg
- Hydrocodone/acetaminophen 10/650 mg versus Placebo

Once a comparison is statistically non-significant, the subsequent comparisons will be technically ineligible to be declared significant. However, all comparisons will be presented to provide a complete picture.

9.2 Sample Size Determination

Assuming that the treatment difference of 12.3 and common standard deviation of 15.5 with respect to $SPID_{0-12}$, a total of approximately 200 subjects (80 subjects per active treatment arm and 40 in the placebo using a 2:2:1 ratio) are required to achieve at least 90% of power with the type I error of 0.05, a total of approximately 210 subjects will be randomized into the study if a drop-out rate of 5% is assumed.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety	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 secondary to conduct 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 and complete the 12 hour assessments. 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 PP population.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy Analyses

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

Similarly, Total Pain Relief Scores (TOTPARs), will be calculated by multiplying the pain relief score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values.

In all analyses, for participants who take rescue medication, all pain intensity scores after intake of rescue medication will be imputed 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 imputed by "no relief" (0). All pain at least half gone after intake of rescue medication will be imputed by "NO".

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy analyses population will be based on the PP population. Sum of Pain Intensity Difference over 12 hours: **$SPID_{0-12}$** 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.
Secondary	Total Pain Relief over 12 hours: **$TOTPAR_{0-12}$** will be analyzed similarly as for the primary endpoint. Total Pain Relief over 6 hours: TOTPAR0-6 will be analyzed similarly as for the primary endpoint. Sum of Pain Intensity Difference over 12 hours: SPID0-6 will be analyzed similarly as for the primary endpoint. **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 baseline pain intensity. **Duration of Pain at Least Half Gone** and **Duration of Pain Half Gone over the first 6 hours** will be calculated by the time between the time point when pain at least half gone was firstly reported and the subsequent time point when pain at least half gone was firstly reversed or the time of last assessment if pain at least half gone was retained for all subsequent time points. The duration will be set to 0 when no pain at least half gone was ever reported throughout the assessment period. This endpoint will be analyzed similarly as for the primary endpoint.

Other pre-specified	The SPID0-4, 0-8 and 8-12 will be analyzed using the same methodology as for $SPID_{0-12}$. TOTPAR0-4, 0-8 and 8-12 will be analyzed using the same methodology as for $SPID_{0-12}$. Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose. Descriptive statistics for each time point and graphical illustrations of the time effect curves will be presented. Time to first perceptible relief measured by a stopwatch, time to meaningful relief measured by a stopwatch, and time to first perceptible relief confirmed by meaningful relief defined as the time to perceptible pain relief (the first stopwatch time) for those subjects who had meaningful pain relief (the second stopwatch time) will be analyzed similarly as for the time to first use of rescue medication. The cumulative proportion of subjects taking rescue medication over time will be analyzed using Chi-square tests and curves over time will be plotted. Frequency tables will be tabulated for the number of times that the subject took rescue medication over the 12 hour period. Peak PID and peak pain relief will be analyzed descriptively. Percent of participants with Pain Half Gone at least once by 12 hours will be analyzed using Chi-square tests. Percent of participants with Pain Half Gone at each time point over 12 hours will be analyzed using Chi-square tests. The proportion of participants with pain at least one-half gone at each time point will be summarized descriptively and plotted over time by treatment group. Cumulative percent of subjects with Pain at least half gone will be plotted over time and will be analyzed using Chi-square tests. Cumulative percent of subjects with ‘at least a 2-point PID’ will be plotted over time and will be analyzed using Chi-square tests. Global Assessment of the investigational product will be analyzed using CMH method with modified ridit score. Percent of subjects reporting GI and Nervous system Adverse Events prior to use of rescue medication.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Secondary	AEs 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 change from 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.

9.5 Interim Analyses

No interim analysis will be performed.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Funding

This study will be funded by its sponsor.

10.1.4 Informed Consent Process

All relevant information on the study will be summarized in an integrated participant information sheet and informed consent form provided by the sponsor or the study center. Sample participant information and informed consent/assent forms are provided as a document separate to this protocol.

Based on this participant information sheet, the investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

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

- Each participant has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision;
- The participant's consent covers EOT examinations as specified in the visit description described in Section 7.2 to be conducted after withdrawal of consent;
- The participant's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan;
- Participant-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 participant 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 participant's oral objection may be documented in the participant's source data.

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

Only if the participant 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 participant will receive a copy of the signed and dated form.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or participant´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 participants will be revised whenever important new information becomes available that may be relevant to the participant's consent, or there is an amendment to the protocol that necessitates a change to the content of the participant information and / or the written informed consent form. The investigator will inform the participant of changes in a timely manner and will ask the participant 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.

Participants who are rescreened are required to sign a new ICF.

10.1.5 Data Protection and Confidentiality

Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from national or international regulatory authorities.

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

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

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

10.1.6 Dissemination of Clinical Study 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.

10.1.7 Data Handling and Quality Assurance

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

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.

Reasons for missing data, especially inability to perform a test, must be documented.

All participant data relating to the study, except operative medications will be recorded on a CRF/eCRF data collection system unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the monitoring plan or applicable monitoring SOP.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years (US), 25 years (Canada) after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.10 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 IEC(s)/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.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

Urine samples will be collected by a member of the investigator's team, for time points and parameters see Section 1.3. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Possible answers are "yes" or "no"
- An assessment of "no" would include:
    - The existence of a highly likely alternative explanation, e.g., mechanical bleeding at surgical site.

or

- Non-plausibility, e.g., the participant 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.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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"

Action taken with study intervention

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

Other specific treatment(s) of adverse event

- None
- Remedial drug therapy
- Other

Outcome of adverse event

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via Paper CRF/Complementary pages
• Email or facsimile transmission of the SAE paper CRF as well as the complementary pages provided is the preferred method to transmit this information to the Bayer's Pharmacovigilance department (see Section 8.3.5). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF and complementary pages within the designated reporting time frames.

10.4 Appendix 4: Contraceptive Guidance

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

1. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement [insert threshold if required (>40 IU/L or mIU/mL) or remove to allow for flexibility with different local thresholds for defining postmenopausal state] is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, after obtaining the signed informed consent from both parents, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 Appendix 5: Participant 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.

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

Finish the statement: " ***What is your overall rating of the study medication you received?***" by checking the appropriate box.

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

10.6 Appendix 6: 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
SoA	Schedule of Activities
SOC	System Organ Class
SPID	Summed Pain Intensity Difference
SUSAR	Serious Unexpected Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TOTPAR	Total Pain Relief

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