CO-170317095828-PACT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE- CONTROLLED, SINGLE-DOSE, EFFICACY AND SAFETY STUDY OF A [redacted] IN POSTOPERATIVE DENTAL PAIN

Study Product Name	[redacted]
Protocol Number	CO-170317095828-PACT
IND / IDE / EudraCT number	Not Applicable
Phase	3
Version and Date	FINAL 16May2017

1. SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson Consumer, Inc., McNeil Consumer Healthcare Division 7050 Camp Hill Road Fort Washington, PA 19034	
Name of Investigational Product: [redacted] Tablet [redacted]	
Name of Active Ingredient: Acetaminophen	
Title of Study: A Randomized, Double-Blind, Placebo- and Active- Controlled, Single-Dose, Efficacy and Safety Study of a [redacted] in Postoperative Dental Pain	
Study center: Jean Brown Research 1045 East 3900 South Salt Lake City, UT 84124	
Principal Investigator: [redacted]	
Study period: Estimated date first subject enrolled: July 2017 Estimated date last subject completed: May 2018	**Phase of development:** 3
Objectives: To evaluate analgesic onset, efficacy, and safety of [redacted] compared with 1000 mg acetaminophen administered as two commercial acetaminophen 500 mg caplets (ACM) and 400 mg ibuprofen administered as two commercial ibuprofen 200 mg liquid-filled capsules (IBU) in the dental pain model following third-molar extractions.	

Methodology:

This is a single-dose, randomized, double-blind, placebo- and active- controlled, parallel-group study to evaluate the analgesic onset, efficacy, and safety profile of [redacted] compared with two commercial products over a four-hour period after third-molar extractions. Subjects will undergo dental extraction of three or four third molars. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios and must not result in a trauma rating of severe on a mild, moderate, or severe scale:

- two full bony impactions
- two partial bony impactions
- one full bony impaction in combination with one partial bony impaction

Subjects who meet the randomization criteria (post-surgical pain of moderate to severe on the four-point categorical pain scale, and at least a score of 5 on the 11-point [0-10] pain intensity numerical rating scale [PI-NRS] at baseline within 4.5 hours of last stitch from dental extractions) will be assigned to one of four treatment groups.

Approximately 660 subjects will receive a single dose of either [redacted], ACM 1000 mg, IBU 400 mg, or placebo in a 4:4:2:1 allocation ratio, and will be stratified according to gender and baseline pain rating (moderate or severe). To maintain the double-blind nature of the study, an independent third party will administer study drug to blindfolded subjects. No less than approximately 30% of randomized subjects will be either male or female. In addition, no more than approximately 30% of subjects will be 17 years of age at the time of screening.

Self-reported pain intensity will be collected at baseline (time 0). Pain intensity and pain relief will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, and 4 hours (± 5 minutes) post dose as well as at the time of rescue (if applicable) and time of meaningful pain relief (if applicable). Perceptible pain relief and meaningful pain relief will be collected using two separate stopwatches. Subjects who do not experience any pain relief after dosing will be encouraged but not required to wait at least 1 hour before using rescue therapy. Subject global evaluation of the investigational product will be collected at hour 4, at the time of rescue medication, or at the time of subject withdrawal, whichever comes first, with a 0-4 categorical rating scale: (0) poor, (1) fair, (2) good, (3) very good, and (4) excellent.

Number of subjects (planned): Approximately 660 subjects
Diagnosis and main criteria for inclusion: Subjects 17 to 50 years of age who meet the inclusion and exclusion criteria, which includes surgical extraction of three or four third molars resulting in at least moderate pain and a pain intensity of ≥5 on a 0 to 10 scale, will be eligible for the study.
Investigational product, dosage and mode of administration: To maintain the double-blind nature of the study, an independent third party will administer a [redacted] tablets to blindfolded subjects depending on randomization. Subjects will swallow the dose with up to 180 mL of water at ambient temperature.
Duration of treatment: One dose, four hours

Reference treatments, dosage and mode of administration:

Depending on randomization, an independent third party will administer one of the following reference products with up to 180 ml of water at ambient temperature to blindfolded subjects:

- a single 1000-mg dose of acetaminophen as two commercial ACM 500 mg caplets,
- a single 400-mg dose of ibuprofen as two commercial IBU 200 mg liquid-filled capsules,
- a single dose of two placebo caplets

Criteria for evaluation:

Primary Efficacy Endpoint

- Time to confirmed perceptible pain relief (TCPR)

Secondary Efficacy Endpoints

- Time to meaningful pain relief (TMPR);
- Percentage of subjects with confirmed perceptible pain relief from 30 minutes to successively earlier minutes in one-minute increments ([redacted] versus PLACEBO);

Tertiary Efficacy Endpoints:

- Percentage of subjects with meaningful pain relief at 35, 40, and 45 minutes ([redacted] versus ACM)
- Percentage of subjects with confirmed perceptible relief at 15, 20, and 25 minutes
- Time weighted sum of pain intensity difference from 0 to 4 hours (SPID 0-4);
- Time weighted sum of pain relief from 0 to 4 hours (TOTPAR 0-4);
- Pain relief (PAR) and pain intensity difference (PID) scores at individual time points;
- Time to rescue analgesic (duration of relief after dosing);
- Subject Global Evaluation.

Safety:

Safety will be monitored and assessed by reviewing the collection, evaluation, and analysis of subject-reported spontaneous adverse events (AEs).

Statistical Methods:

Time to confirmed perceptible pain relief (TCPR) and time to meaningful pain relief (TMPR) will be analyzed using survival data analysis. The survival function (cumulative proportions of subjects with pain relief at each time point) and the median survival time will be estimated by the Kaplan-Meier method for each treatment. The median survival times for the active treatments will be compared using the bootstrap re-sampling method and the survival functions of the active treatments will be compared with the survival function of placebo using the Wilcoxon test. The earliest time of separation between [redacted] and placebo will be established by comparing the percentage of subjects with confirmed perceptible pain relief starting from 30 minutes to successive earlier minutes in one minute increments, until statistical significance is no longer achieved. The dichotomized response will be analyzed using logistic regression analysis.

2. STUDY FLOWCHART

Table 1: Schedule of Activities

	Screening	**Baseline (Day of Surgery)**	**Hours Post-Dose**	**Follow-Up Call**
Procedures	**Day -30 to 1**	**Day 1**	**0 to 4 hours**	**Day 6 (±1 day)**
Written informed consent and/or assent	X			
Demography	X			
Collection of age		X		
Inclusion / Exclusion assessment	X[1]	X		
Significant medical history	X[1]	X		
Vital signs[2]	X[1]	X		
Height, weight, and BMI	X			
Urine pregnancy test[3]	X[1]	X		
Urine drug screen[11]	X[1]	X		
Serology[4]	X			

	Screening	Baseline (Day of Surgery)	Hours Post-Dose	Follow-Up Call
Procedures	**Day -30 to 1**	**Day 1**	**0 to 4 hours**	**Day 6 (±1 day)**
Dental extraction surgery		X		
Categorical and Numerical Pain Intensity		X[5]		
Randomization criteria		X		
Investigational product administration		X		
Stopwatch assessments (pain relief)			X	
Pain intensity and pain relief ratings[6]			X	
Rescue therapy			X[7]	
Subject Global Evaluation			X[8]	
Prior and Concomitant Therapy	X	X	X	X
Safety monitoring	X	X[9]	X[9]	X[9]
Subject Disposition			X[10]	
Follow up interview				X

1: Only baseline assessments will be collected on the CRF
2: Blood pressure, heart rate, respiratory rate, and oral temperature
3: Women of childbearing potential
4: HIV antibody, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV)
5: Scored within 4.5 hours after last stitch from dental surgery
6: Subjects will record pain ratings on worksheets that will be entered into the CRF by designated site staff. Ratings will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, and 4 hours (± 5 minutes) post dose. If a subject requests rescue medicine, ratings will be collected before administration. Ratings will also be collected at the time of meaningful pain relief (if applicable).
7: Subjects will be encouraged to wait at least 1 hour after investigational product administration before using rescue medicine.
8: At Hour 4, at time immediately before use of rescue medication, or at the time of early termination if a subject is discontinued or withdrawn earlier than four hours after dosing.
9: Includes collection of AEs and any report of pregnancy
10: End of Study is when all 4-Hour assessments are complete or at the time of subject withdrawal
11: Minimum requirements for urine drug testing at screening and on the day of surgery include cocaine, tetrahydrocannibinol, opioids (e.g., buprenorphine, oxycodone, methadone, and morphine), benzodiazepines, and amphetamines

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation/ Term	Definition
AE	Adverse event
ACM	Acetaminophen
BMI	Body Mass Index
CRF	Case report form
EDC	Electronic data capture
EIU	Exposure in Utero
IBU	Ibuprofen
ICH GCP	International Conference on Harmonization Good Clinical Practice
IRB/IEC	Institutional Review Board/Independent Ethics Committee
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the counter
PAR	Pain relief
PI	Principle Investigator
PID	Pain intensity difference
PQC	Product Quality Complaint
PI-NRS	Pain intensity-numerical rating scale
PR-NRS	Pain relief-numerical rating scale
RSI	Reference Safety Information
SAE	Serious adverse event
SPID	Time weighted sum of pain intensity difference
TOTPAR	Time weighted total pain relief scores

4. ETHICS

4.1. Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File (Site Master File). Copies of IRB/IEC approvals should be forwarded to the Sponsor.

The only circumstance in which a protocol amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/IEC and the Sponsor in writing within 5 working days after implementation.

4.2. Ethical Conduct of the Study

The study will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice (GCP) guidelines (ICH E6) and applicable local regulatory requirements and laws.

4.3. Subject Information and Consent

Only subjects who provide informed consent will continue in the study. All parties will ensure protection of subject personal data and will not include subject names or subject initials on any forms, reports, publications, or in any other disclosures. Each subject will be assigned a study number that is used in the Case Report Form (CRF) in lieu of the subject's name. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be agreed to by the Sponsor and the IRB/IEC and must be in compliance with ICH E6, GCP, local regulatory requirements, and legal requirements.

The Principal Investigator (PI) must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use. The Investigator will retain the original of each subject's signed consent form. A copy of the signed and dated consent form will be provided to subjects.

4.4. Subject Written Assent

After the informed consent form is signed and dated by the parents or legally authorized representatives and witnessed by a member of the investigator's clinical team, written assent to participate in the study must be obtained from prospective subjects who are below the age of legal consent yet old enough to understand details of the study. During the assent process, the PI or designee will provide the minor with an assent document that explains, in concrete and age-appropriate terms, the purpose of the research, what they will be asked to do and what procedures they will undergo. The assent document will focus on the risks, benefits, and alternatives to research participation as well as the confidentiality of any information obtained as a result of their participation. The PI or designee will explain the information, give the minor a chance to ask questions and ask the minor to indicate their assent by signing the assent document. The prospective subject will do this by signing an IRB/IEC-approved assent form or designated assent section of the informed consent, depending on individual institutional regulations. A witness must also sign and date the assent form. The original signed assent form will be retained by the investigator as part of the source documents and will be available for review by the Sponsor. A copy of the signed and dated assent form will be given to the subject. Assent by the subject acknowledges willingness to participate, but does not necessarily constitute an understanding of the procedures and hazards of the study.

5. STUDY ADMINISTRATIVE STRUCTURE

Details on the administrative structure of the study (e.g., Principal Investigator (PI)/study site personnel, the Sponsor study team, and the external service providers) will be included in a study contact list. The study contact list will also include contact information for the Sponsor, Investigator(s), Monitor(s), Clinical and Bioanalytical Laboratories, and IRB/IECs, as well as the names and titles of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor. This list will be maintained in the study and site master files throughout the study for inclusion in the clinical study report.

6. INTRODUCTION

Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties, and is thought to produce analgesia by inhibiting prostaglandin synthesis centrally and elevating the pain threshold. Acetaminophen is available as an over-the-counter (OTC) analgesic and antipyretic in many global markets. In the US, TYLENOL® is commercially available in extra strength (500 mg) and regular strength (325 mg) dosage forms marketed under the Internal Analgesic, Antipyretic and Antirheumatic Drug Products for OTC Human Use Tentative Final Monograph. TYLENOL® Regular Strength 325 mg is dosed 2 dosage units every 4 to 6 hours and TYLENOL® Extra Strength 500 mg is dosed 2 dosage units every 6 hours. It is labeled for the temporary relief of minor aches and pains due to the common cold, headache, backache, toothache, premenstrual and menstrual cramps, minor pain of arthritis, muscular aches and for the temporary relief of fever.

The overall purpose of this study is to evaluate the analgesic onset, efficacy, and safety of a single dose of 1000 mg acetaminophen administered as [redacted] tablets compared with a single dose of 1000 mg acetaminophen administered as two commercial acetaminophen 500 mg caplets (ACM), a single dose of 400 mg ibuprofen administered as two commercial ibuprofen 200 mg liquid-filled capsules (IBU), and placebo over 4 hours. [redacted] The dental pain model, a validated model of acute pain widely used to study analgesic efficacy of compounds, will be used in this study [1, 2]. Reference Safety Information (RSI) for the [redacted] and ACM commercial product is the Drug Facts labeling for the ACM commercial product in the US, and the RSI for the IBU commercial product is the associated Drug Facts Label in the US.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1. STUDY OBJECTIVES

To evaluate analgesic onset, efficacy, and safety of 1000 mg acetaminophen administered as [redacted] compared with 1000 mg acetaminophen administered as two commercial acetaminophen 500 mg caplets (ACM) and 400 mg ibuprofen administered as two commercial ibuprofen 200 mg liquid-filled capsules (IBU) in the dental pain model following third-molar extractions.

7.2. STUDY ENDPOINTS

7.2.1. Primary Efficacy Endpoint

- Time to confirmed perceptible pain relief

7.2.2. Secondary Efficacy Endpoint

- Time to meaningful pain relief
- Percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments ([redacted] versus PLACEBO);

7.2.3. Tertiary Efficacy Endpoint

- Percentage of subjects with meaningful relief at 35, 40, and 45 minutes [redacted] versus ACM);
- Percentage of subjects with confirmed perceptible relief at 15, 20, and 25 minutes
- Time weighted sum of pain intensity difference from 0 to 4 hours (SPID 0-4);
- Time weighted sum of pain relief from 0 to 4 hours (TOTPAR 0-4);
- Pain relief (PAR) and pain intensity difference (PID) scores at individual time points;
- Time to rescue analgesic (duration of relief after dosing);
- Subject Global Evaluation.

7.3. Safety

Safety will be monitored and assessed by reviewing the collection, evaluation, and analysis of subject-reported spontaneous adverse events (AEs).

8. INVESTIGATIONAL PLAN

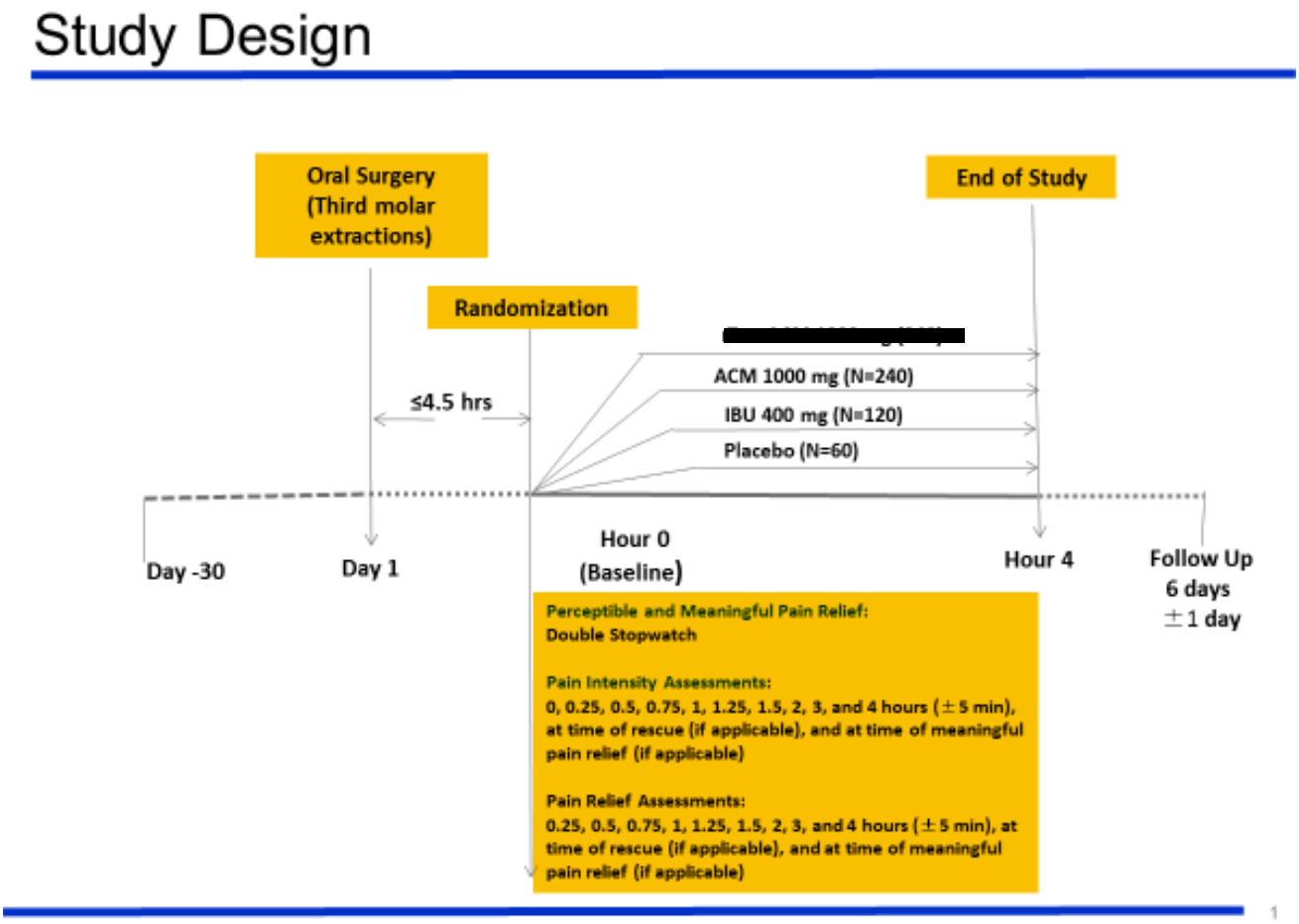
8.1. Overall Study Design and Plan

This is a single-dose, randomized, double-blind, placebo- and active- controlled, parallel-group study to evaluate the analgesic onset, efficacy, and safety profile of [redacted] compared with two commercial products over a four-hour period after third-molar extractions (Figure 1). Subjects will undergo dental extraction of three or four third molars. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios and must not result in a trauma rating of severe in a mild, moderate, or severe scale:

- two full bony impactions
- two partial bony impactions
- one full bony impaction in combination with one partial bony impaction

Subjects who meet the randomization criteria (post-surgical pain of moderate to severe on the four-point categorical pain scale, and at least a score of 5 on the 11-point [0-10] pain intensity numerical rating scale [PI-NRS] at baseline within 4.5 hours of last stitch from dental extractions) will be assigned to one of four treatment groups. Approximately 660 subjects will receive a single dose of either [redacted], ACM 1000 mg, IBU 400 mg, or placebo in a 4:4:2:1 allocation ratio, and will be stratified according to gender and baseline pain rating (moderate or severe). No less than approximately 30% of randomized subjects will be either male or female. In addition, no more than approximately 30% of subjects will be 17 years of age at the time of screening. Self-reported pain intensity will be collected at baseline (time 0). Pain intensity and pain relief will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, and 4 hours (± 5 minutes) after the dose. Perceptible pain relief and meaningful pain relief will be collected using two separate stopwatches. Subjects who do not experience any pain relief after dosing will be encouraged, but not required, to wait at least 1 hour before using rescue therapy.

Figure 1: Study Design



8.2. Selection of Study Population

The following eligibility criteria are designed to select subjects for whom study treatment is considered appropriate. All relevant medical and nonmedical conditions should be considered when deciding whether this protocol is suitable for a particular subject. No waivers to inclusion or exclusion criteria will be permitted.

8.2.1. Inclusion Criteria

Subjects are eligible for enrollment if they:

1. Are 17 to 50 years of age (inclusive) at the time of screening;

2. Weigh 100 lbs. or greater and have a body mass index (BMI) of 18 to 30 (inclusive) at screening;

3. Have undergone dental extraction of three or four third molars. Maxillary third molars may be removed regardless of impaction level. Supernumerary teeth may also be removed. The

mandibular extractions must meet one of the following scenarios (and must not result in a trauma rating of 'severe' on a mild, moderate, or severe scale):

- two full bony impactions
- two partial bony impactions
- one full bony impaction in combination with one partial bony impaction;

4. Indicate at least moderate pain on a categorical scale ranging from (0) none, (1) mild, (2) moderate, or (3) severe AND at least a score of 5 on the 11-point (0-10) pain intensity numerical rating scale (PI-NRS) at baseline within 4.5 hours of the last stitch from oral surgery;

5. Are able to comprehend and follow the requirements of the study (including availability on scheduled visit dates) based upon research site personnel's assessment;

6. Are able to provide written informed consent;

7. Females of childbearing potential and males who are sexually active must be willing to use a medically acceptable method of birth control during the study. In addition, females of childbearing potential who are sexually active must be willing to use a medically acceptable method of birth control for up to 30 days after the last dose of investigational product;

8. Are willing for this to be the only investigational product used during the study.

8.2.2. Exclusion Criteria

Subjects will be excluded if they:

1. Are female and are pregnant or breastfeeding;

2. Are male with a pregnant partner or a partner who is currently trying to become pregnant;

3. Have a known allergy to acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin as well as hypersensitivity to hydrocodone or other opioids;

4. Presence or history of major medical condition that in the investigator's opinion may jeopardize the subject's safety or well-being, or the integrity of the study (e.g. hepatic, renal, pancreatic, gastrointestinal, cardiovascular, cerebrovascular, or thyroid diseases as well as a history of head injury or seizures, history of respiratory depression or lung problems such as but not limited to asthma or chronic obstructive pulmonary disease, psychiatric disorders, problems urinating, a history of blockage or narrowing of the stomach or intestines, uncontrolled hypertension indicated as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg, or uncontrolled diabetes in the last 6 months);

5. Are not able to swallow whole large tablets or capsules;

6. Routinely use oral analgesics ≥5 times per week;

7. Have a history of chronic tranquilizer use, heavy drinking, or substance abuse in the last 5 years. Heavy drinking is defined as the use of more than 4 standard drinks daily or more than 14 drinks a week for men, and more than 3 standard drinks daily or more than 7 standard drinks in a week for women. Standard drink refers to 14 g (0.6 oz.) of pure alcohol, which is approximately 12 oz. of beer, 8 oz. of malt liquor, 5 oz. of wine, 1.5 oz. or "shot" of 80-proof distilled spirits or liquor (e.g., gin, rum, vodka, or whiskey);

8. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last 2 years;

9. Used oral OTC or prescription products (except contraceptive medications and those required for use during the oral surgical procedure), vitamins, or herbal supplements within 5 days or 5 half-lives (whichever is longer) before the oral surgical procedure;

10. Used any immunosuppressive drugs, corticosteroids (except for topical corticosteroids), or injectable or oral anticoagulants (e.g., heparin, Lovenox, Xarelto, Eliquis, Pradaxa, Coumadin, Miradon) within 2 weeks of screening;

11. Used alcohol within 3 days before the oral surgical procedure;

12. Have a positive urine drug screen, including a test for buprenorphine. However, if tested positive for amphetamine/methamphetamine due to treatment for Attention Deficit Hyperactivity Disorder, the subject will not be excluded;

13. Consumed methylxanthine-containing products (e.g., chocolate bars or chocolate beverages, coffee, tea, cola or caffeinated energy drinks), tobacco, or nicotine containing products (e.g., cigarettes, cigars, nicotine replacement therapies) < 12 hours before the oral surgical procedure;

14. Use of monoamine oxidase inhibitors within 14 days prior to surgery;

15. Has a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV);

16. Participated in any interventional clinical trials within 30 days before screening or had participated in this current trial previously;

17. Are related to those persons involved directly or indirectly with the conduct of this study (i.e., principal investigator, sub investigators, study coordinators, other site personnel, employees of Johnson & Johnson subsidiaries, contractors of Johnson & Johnson, and the families of each).

8.3. Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason without compromising their rights to receive further treatment. The investigator and/or the Sponsor may terminate a subject from investigational product and/or study follow-up in the event of any of the following:

- Serious eligibility or on-study violation of the protocol
- Medical reasons that are considered significant by the subject, investigator, or Sponsor
- AEs
- Intercurrent illness
- Medical reason unrelated to the study
- Non-medical reasons
    - Compliance problems
    - Subject withdrew consent
- Pregnancy
- Treatment was unblinded
- Administrative or other reasons

Should a subject decide to withdraw from the study after beginning Day 1 Baseline procedures, he or she will be strongly encouraged to complete all end-of-study assessments and the follow-up telephone call. In case of questions surrounding the circumstances that a subject needs to be withdrawn from the study (e.g., protocol deviation), the Sponsor or its designated representative should be consulted. The reason for withdrawal will be documented in the source document and CRF.

If a subject does not return for a scheduled visit or cannot be reached for the follow-up phone call, the staff will attempt to contact the subject at least three times by telephone, and lastly, by certified letter. The outcome for each attempt will be recorded in the source document. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

Investigational products and placebo will be supplied by the Sponsor in bulk containers in an unblinded manner. In order to maintain the double-blind status of the study, the site must adhere to the following general storage, dispensing, and dosing procedures.

- The site will delegate a qualified third party and back-up staff member(s) who will be responsible for dispensing and administering study medication and who will have no other direct or indirect role in the execution of this study.
- The Sponsor will provide a randomization schedule directly to the qualified third party individual. The randomization schedule will be kept in a locked, secured area with access limited to only the assigned third party individual and un-blinded monitor.
- Covered dosing cups will be used by the assigned third party dispenser to transport the assigned investigational product from the designated dispensing room to the subject's room.

Detailed dosing procedures to ensure maintenance of the double-blind status of the study are provided in Section 9.7.

9.2. Description of Study Product

A description of the [redacted], acetaminophen, ibuprofen, and placebo investigational products are provided in Table 3.

Table 3: Investigational Product

Product	[redacted]	**ACM (1000 mg)**	**IBU[b] (400 mg)**	**Placebo**
Dosage Form	[redacted]	Caplet	Liquid-filled Capsule	Caplet
Route of Administration	[redacted]	Oral	Oral	Oral
Unit Dose	[redacted]	500 mg	200 mg	Not applicable
Physical Description	[redacted]	White caplet	Teal liquid- filled capsule	White caplet

Table 3: Investigational Product

Product	[redacted]	**ACM (1000 mg)**	**IBU[b] (400 mg)**	**Placebo**
Manufacturer/Brand	[redacted]	J&J Consumer Inc., McNeil Consumer Health Division/ Tylenol	Pfizer/Advil Liqui-Gel®	Catalent

[redacted]

b: Ibuprofen is solubilized as the free acid and potassium salt.

9.3. Investigational Product Packaging and Labeling

[redacted]

9.4. Investigator Unblinding

If, in the opinion of the Investigator, it is necessary to break the treatment code for safety reasons and circumstances allow, the Investigator will first contact the Designated Physician Representative or designee for consultation about breaking the study blind. If there is a medical emergency and the Investigator deems it necessary to know the subject's study treatment urgently for the subject's proper medical care, the Investigator may break the treatment code immediately, and then contact the Designated Physician Representative or designee as soon as possible afterward.

In the event of a medical emergency that necessitates breaking the code, the third-party person(nel) will be permitted to inform the Investigator what study drug the subject was given.

When the blind is broken, the Investigator will notify the Sponsor within 24 hours after determining that it is necessary to unblind the treatment assignment and document the reason and date of the unblinding. The event will also be recorded in the CRF and in the source document. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

Once the treatment is unblinded, the subject must be discontinued from the study and followed until the event is resolved. The rationale, date, time, and attempts to contact the Sponsor must be documented in the source document. The study site should take the necessary measures to maintain the treatment blind throughout the study and prevent any unintended or premature unblinding.

9.5. Method of Assigning Subjects to Treatment Groups

The randomization schedule will be generated by the Sponsor to ensure treatment blinding. The site will keep the randomization schedule in a locked, secured area with access limited to only

the assigned third-party person(nel), back-up staff member, and un-blinded monitor. After meeting the appropriate post-surgery criteria, subjects will be randomized to receive one of four treatments ([redacted] ACM 1000 mg, IBU 400 mg or placebo) in a 4:4:2:1 ratio. Subjects will be stratified by gender and baseline pain (moderate or severe). For subjects with moderate baseline pain, randomization numbers will be assigned to subjects in sequential order starting with the lowest available number within the appropriate gender stratum. Similarly for subjects with severe baseline pain intensity, subjects will be assigned in sequential order starting with the highest available number in the appropriate gender stratum.

9.6. Study Product Storage, Accountability and Disposal

The investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational product is stored in a secured area, at room temperature, 68 ºF to 77 ºF (20 ºC to 25 ºC) and in accordance with applicable regulatory requirements.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product on the Investigational Product Accountability Log supplied by the Sponsor. The log must identify the investigational product and randomization number, and account for its disposition on a subject-by-subject basis, including specific dates administered and quantities. The log must be signed by the individual who dispensed the investigational product, and copies must be provided to the Sponsor. All Investigational Product and Investigational Product Logs are kept together in a secure, double-locked location with access only allowed to the third-party person(nel), back-up staff member and un-blinded monitor. At the end of the study, the Sponsor will provide instructions regarding the disposition of any unused and exhausted investigational product. The study site must maintain accurate and adequate records including shipment receipt and return of unused investigational product shipments.

9.7. Preparation, Dispensing and Administration of Investigational Product

Investigational product preparation and dispensing will be performed on Day 1, following dental surgery. For subjects who meet the randomization criteria, an independent third party dispenser will administer one of the following study treatments with up to 180 ml of water at ambient temperature to blindfolded subjects:

- [redacted]
- a single 1000-mg dose of acetaminophen as two commercial ACM 500 mg caplets,
- a single 400-mg dose of ibuprofen as two commercial IBU 200 mg liquid-filled capsules, or
- a single dose of two placebo caplets.

Baseline pain assessments and drug administration will be completed in the subject's room. The third-party dispenser will prepare study medication for each subject in a designated dispensing room. Study medication will be dispensed at the time that the subject's pain level is determined by verbal assessment, just prior to the completion of the baseline categorical pain severity scale and the baseline 11-point [0-10] pain intensity numerical rating scale [PI-NRS]. The study coordinator will communicate the subject's pain severity and gender to the dispenser. The dispenser will assign the next available randomization number from the appropriate stratum. The dispenser will dispense the appropriate study treatment from the appropriate bulk supply containers into an individual dosing cup. The double-blind label with the same randomization number will be affixed to the dosing cup and the tear-off portion of the label will be attached to the patient's source documents. The third-party dispenser will complete the study drug dispensing record. The study drug dispensing record will remain in a secure and locked area, with access limited to the unblinded third- party dispenser, back-up staff member, and un-blinded monitor. A second individual, with no other study involvement, will witness the preparation and dispensing process. No other study personnel will be present in the designated dispensing room at the time of study drug dispensing. The dispenser will ensure the dosing cup containing the randomized study treatment is covered prior to exiting the dispensing room.

The third-party dispenser will inform the blinded study coordinator once the study drug is dispensed and is ready to be administered to the subject. Following completion of the baseline categorical pain severity scale and baseline pain intensity numerical rating scale, the study coordinator will blindfold the subject and then exit the subject's room to inform the dispenser that the pain assessments are completed and confirm that the pain severity has not changed from the verbal assessment used to determine the appropriate randomization, and that the pain intensity numerical rating scale score qualifies the subject for randomization. If the baseline categorical pain severity has changed, new study drug from the corresponding pain stratum will be prepared. The dispenser will deliver the study drug from the designated dispensing room to the subject's room in a covered dosing cup to ensure no other individual will be able to see the study drug in the bottle. No other study personnel, other than the third-party witness, will be present in the subject's room at the time of dosing.

After the entering the blindfolded subject's room and while the subject is sitting up, the dispenser will hand the dosing cup containing the study treatment to the blindfolded subject and instruct the subject to empty the contents of the dosing cup directly into their mouth and then swallow the study medication immediately with up to 180 ml of water at ambient temperature. The dispenser will inspect the subject's oral cavity to ensure that the study treatment was swallowed. The time at which the subject swallows the study medication will be recorded as Time 0. Study drug will be administered to the subject within 5 minutes of the completion of the baseline pain assessments.

If a subject vomits after dosing, the subject will not be re-dosed but will remain in the study.

9.8. Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication, query, observation, or issue related to the identity, quality, durability, reliability, safety, efficacy or performance of investigational supplies. Any PQC discovered during the initial inventory should follow the instructions provided on the receipt letter; no PQC form should be filed for issues identified when opening or unpacking a shipment. Subsequently, any observation of a PQC requires immediate notification to the Sponsor's Clinical Supply Manager via a completed PQC form and telephone call. The PI or designee should also complete, sign, and forward a copy of the PQC form to the Clinical Supply Manager.

In addition, PQC information must be included on the Investigational Product Dispensing and Accountability Log or equivalent in the comments field and completed by the third-party dispenser. The Clinical Supply Manager listed can assist you or answer questions related to this process. To aid in the initial conversation and understanding of a PQC, the site staff may be asked to photograph the issue and send it to the Clinical Supply Manager.

10. STUDY PROCEDURES

10.1. Overview

Collection of adverse events and concomitant medications will start after the study-specific informed consent document has been signed and continue until completion of the follow-up procedures. The Schedule of Activities (Table 1) summarizes dose administration and the timing and frequency of safety and efficacy procedures and measurements. In the event of abnormal safety findings during the conduct of the study, the attending physician may request additional safety evaluations, either immediately or subsequently at a frequency considered appropriate.

10.2. Screening Visit

Informed consent should be obtained from the subjects before any study related assessments are conducted.

- Inclusion and exclusion criteria
- Demography
- Significant medical history – the condition, diagnosis, or surgical procedure
- History of medication and other treatments (within 30 days)
- Vital signs: resting blood pressure, heart rate, respiratory rate, oral temperature
- Height, weight and body mass index (BMI) assessment
- A serum sample will be collected to test for HIV antibody, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV)
- Urine drug screen test, including a test for buprenorphine
- Urine pregnancy test on females with childbearing potential

Subjects who meet all inclusion/exclusion criteria will be scheduled for the dental procedure within 30 days after Screening.

10.3. Baseline Visit (Day of Surgery)

The following will be re-evaluated prior to the surgical procedure, and the evaluations will be recorded in the source documents and the CRF. For data collected on both Screening and

Baseline Visits with the exception of age, only the data collected at Baseline will be recorded on the CRF.

- Inclusion and exclusion criteria
- Any changes to medical and surgical history
- Collection of age
- Any changes to prior and concomitant therapies
- Vital signs: resting blood pressure, heart rate, respiratory rate, oral temperature
- Urine drug screen test, including a test for buprenorphine
- Urine pregnancy test on females with childbearing potential

A negative urine drug screen and urine pregnancy test (for women of childbearing potential) must be obtained on the same day as the surgical procedure.

10.3.1. Randomization

After the dental procedure, subjects will be asked to rest quietly at the study center until they experience both post-surgical pain of at least moderate pain on a categorical scale ranging from (0) none to (3) severe and at least a score of 5 on the 11-point (0-10) PI-NRS within 4.5 hours of the last stitch during oral surgery. Subjects who did not meet these criteria will be considered a screen failure.

Randomization numbers will be assigned to subjects in sequential order starting with the lowest available number within the appropriate gender stratum for subjects with moderate baseline pain and starting with the highest available number in the appropriate gender stratum for subjects with severe baseline pain intensity. Randomized subjects will receive their dose of investigational product, which will be considered time 0. The administration of investigational product should occur as described in Section 9.7. Site staff will inspect the subject's oral cavity to ensure that the investigational product was swallowed.

10.3.2. Postdose Assessments

Two stopwatches labeled as perceptible and as meaningful will be used to measure "perceptible pain relief" and "meaningful pain relief", respectively. The face of each stopwatch will be covered to prevent the subject from seeing the running clock. Subjects will only be given the second stopwatch after they stop the first one.

Site personnel will instruct the subject: "I would like you to stop the first stopwatch (perceptible) when you first begin to feel any pain relieving effect whatsoever of the drug, that is, when you first feel any pain relief. This does not necessarily mean you feel completely better, although you might, but when you first feel any difference in the pain you have now. As soon as you stop the stopwatch please press your call light to notify the study coordinator. I would like you to stop the second stopwatch (meaningful) when you have meaningful pain relief, that is, when the relief from the starting pain is meaningful to you. As soon as you stop the stopwatch, please press your call light to notify the study coordinator." Upon dosing, the investigator or the designated site staff will start both stopwatches at the same time. Once the stopwatch has been stopped, the investigator or designated study staff will retrieve the stopwatch and record the time in the source documents and CRF.

Pain relief and pain intensity will be assessed using the NRS (see APPENDIX 1) at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, and 4 hours (± 5 minutes) after the dose, at the time of rescue (if applicable), and at the time of meaningful relief (if applicable).

At the end of the 4-hour assessment, at the time of rescue, or at the time of early termination if a subject is discontinued or withdrawn earlier than four hours after dosing, subjects will be asked to report their overall impression of therapy (Subject Global Evaluation) as (0) Poor, (1) Fair, (2) Good, (3) Very good, or (4) Excellent. Subjects who use rescue therapy will continue in the study and assess pain and relief through four hours.

10.3.3. End of Study

End of study is defined as completion of the 4-hour assessments or at the time of early termination if a subject is discontinued or withdrawn earlier than four hours after the dose. Subjects who rescue are to remain at the study site through the 4-hour assessments, which is their time of end of study.

10.4. Follow-Up Phone call

Subjects will be interviewed by telephone to follow up on appropriate postsurgical medical care and changes in their health, including any emergent or existing AEs. The interview will occur between the 5th -7th day after the dental surgery unless the 5th day occurs on a Friday in which case the interview period can be extended to the next business day. Three attempts should be made to contact the subject by phone. If the subject cannot be contacted by phone by the 7th day after the dental surgery or the next business day if the 5th day after dental surgery occurs on a Friday, then a certified letter should be mailed to the subject on the 7th day after the dental surgery or the next business day if the 5th day after surgery occurs on a Friday. Every effort will be made by the investigator or designated study staff to adhere to the schedule. Additional postsurgical medicines (e.g., antibiotics or analgesic prescriptions) or therapies (e.g., ice packs) that are taken after the 4-hour and Subject Global assessments will be recorded on the subject's source documents, but not in the CRF; however concomitant medications taken for an adverse event will be recorded on the CRF. Emergent or existing AEs will be recorded in both the source documents and CRF.

10.5. Life Style Guidelines

10.5.1. Meals and Dietary Restrictions

Only clear, non-caffeinated liquids may be consumed from the time of surgery until two hours following administration of the investigational product. After two hours, subjects may consume soft foods consistent with having dental surgery.

10.5.2. Alcohol, Caffeine and Tobacco Consumption / Restrictions

Use of alcoholic beverages within three days before the oral surgical procedure and during the study is prohibited. In addition, subjects must refrain from the use of any methylxanthine-containing products (e.g., chocolate bars or beverages, coffee, tea, colas, or caffeinated energy drinks) and tobacco or nicotine containing products (e.g., cigarettes, cigars, nicotine replacement therapies) within 12 hours before surgery and during the study while confined at the site.

10.5.3. Physical Activity Requirements / Restrictions

Walking at a normal pace will be permitted. Subjects will remain sitting upright or semi-reclining for dosing and at least 4 hours immediately following treatment administration, except for short durations to use the restroom.

10.5.4. Contraception for Females

Female subjects are considered not of childbearing potential if they meet at least one of the following criteria:

- Had a hysterectomy and/or bilateral oophorectomy
- Had sterilization surgery
- Are post-menopausal (i.e., amenorrheic for at least 12 months prior to the Baseline visit)

Females with childbearing potential who are sexually active must agree to continue using a medically acceptable form of birth control during the study and for 30 days after taking the investigational product.

Medically acceptable methods of birth control for this study include:

a. Established use of hormonal methods of contraception (oral, injected, implanted, patch or vaginal ring)

b. Barrier methods of contraception with spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository.

c. Intrauterine device (IUD) or intrauterine system (IUS)

d. Surgical sterilization (e.g., vasectomy that has been confirmed effective by sperm count check, tubal occlusion, hysterectomy, bilateral salpingectomy)

e. Abstinence from heterosexual intercourse: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sexually active female subjects who use hormonal contraception must have used a stable dose for 30 days before surgery. If hormonal contraception has been used for less than 30 days or if the dose has changed within the past 30 days, subjects must agree to also use a barrier method during the study and up to 30 days after taking the investigational product.

10.5.5. Contraception for Males

If a male subject is sexually active with a woman of childbearing potential and has not had a vasectomy with confirmation of azoospermia, he must either agree to use a condom with spermicidal foam/gel/film/cream during the study or must confirm that his female partner has used a medically acceptable form of birth control for at least 30 days before study drug administration and will continue to do so during the study. Medically acceptable forms of birth control for a male subject's female partner of childbearing potential include prescription oral, vaginal or transdermal contraceptives, contraceptive implants or injections, intrauterine device, diaphragm or cervical cap, with spermicide.

10.6. Prior and Concomitant Medications and Therapies

Medications that are taken from 30 days prior to surgery until study end (as defined in Section 10.3.3) will be recorded in the source documents and CRF. Medications taken between study end and the follow-up interview (except for those taken for an adverse event) will be recorded in the source documents, but not in the CRF. Medications taken between study end and the follow-up interview for an adverse event will be recorded in the source documents and CRF.

10.6.1. Permitted Therapies

Female subjects taking hormonal contraceptives will be instructed to continue before, during, and after the study as per protocol. All subjects will be permitted a short-acting local anesthetic, lidocaine with or without epinephrine, and/or nitrous oxide during dental surgery. Topical benzocaine is also allowed.

10.6.2. Prohibited Therapies

Long-acting anesthetics are prohibited during the dental surgery. Other medications prohibited before entry into the study are listed under Exclusion Criteria.

The use of any oral OTC or prescription (except contraceptive medications and those required for use during oral surgical procedure such as short-acting local anesthetics), vitamin, or herbal supplements are prohibited within 5 days or 5 half-lives (whichever is longer) before the oral surgical procedure and during the study.

10.7. Rescue Medicine

Subjects will be encouraged, but not required, to wait at least 1 hour after investigational product dosing before using the rescue medicine, hydrocodone bitartrate 7.5 mg / ibuprofen 200 mg tablets, if the severity of the subject's pain increases to an intolerable level. Hydrocodone bitartrate 7.5 mg / ibuprofen 200 mg tablets will be used according to its product labeling. Use of rescue medicine will be recorded in the source document and CRF. Once rescue medicine has been administered, the stopwatch(s) will be collected from the subject. No stopwatch data will be recorded after use of rescue medication; however, subjects will continue to record pain intensity and pain relief.

11. ASSESSMENTS

11.1. Efficacy Assessments

The investigator or designated study staff will ensure the subjects complete the pain intensity and pain relief assessments at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, and 4 hours (± 5 minutes) after dosing. Subjects will record their pain intensity and pain relief directly onto the respective source worksheet. Evaluations will include the following parameters:

- Pain intensity
    - Four-point categorical scale collected at baseline: (0) no pain; (1) mild pain; (2) moderate pain; (3) severe pain
    - 0-10 PI-NRS collected at baseline and at each time point (including at time of rescue and at time of meaningful relief)
- Pain relief– 0-10 PR-NRS collected at each time point (including at time of rescue and at time of meaningful relief)
- Time to perceptible pain relief – recorded using stopwatch perceptible
- Time to confirmed perceptible pain relief is defined as the time to perceptible pain relief, provided that the subject subsequently stopped the second stopwatch indicating meaningful pain relief.
- Time to meaningful pain relief – recorded using stopwatch meaningful
- Time to rescue – time when rescue therapy was administered
- Subject global evaluation – subject's overall impression of the investigational product at hour 4, at time of rescue, or at the time of early termination if a subject is discontinued or withdrawn earlier than four hours after dosing:

  (0) poor (1) fair (2) good (3) very good (4) excellent

11.2. Safety Assessments

Safety will be monitored via AE reporting. If an AE is reported, the subject will be asked to elaborate on the nature of the event. The investigator or designated study staff will evaluate and record according to the Adverse Event Reporting section of the protocol.

Normal consequences of dental surgery (e.g., dry-socket, pain, swelling, bruising) are not considered AEs unless the investigator believes the condition worsened or was aggravated following study drug therapy.

11.3. Vital Signs

Vital signs will be collected at screening and baseline. All vital signs (blood pressure, pulse, respiratory rate, and oral body temperature) will be collected after at least 5 minutes of rest in a supine or semi -reclining position in a quiet setting without distractions (e.g., television, cell phones). Systolic and diastolic blood pressure and pulse rate measurements will be assessed with a completely automated device, consisting of an inflatable cuff and an oscillatory detection system. All values will be registered on an automated recorder so that measurements are observer independent. Manual techniques will be used only if an automated device has malfunctioned. Respiratory rate will be measured over at least 30 seconds. Oral body temperature will be measured using a Sponsor-approved standard method. Abnormal vital signs collected at screening and baseline will be assessed by the medically qualified investigator to confirm that the subject is medically suitable for study participation.

12. ADVERSE EVENT REPORTING

12.1. Introduction

All observed or volunteered AEs regardless of treatment group, device group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections. For all AEs, the Investigator or medically qualified individual (MD/DO/Dentist) must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a Serious Adverse Event (SAE) requiring immediate notification (within 24 hours) to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator or medically qualified individual (MD/DO/Dentist) to try to determine causality.

The Investigator / site is required to assess causality. For AEs with a suspected causal relationship to the investigational product, follow-up by the Investigator or medically qualified individual (MD/DO/Dentist) is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and the Sponsor concurs with that assessment.

12.2. Reporting Period

All AEs, whether serious or non-serious will be recorded on the CRF in the AE section beginning from the time the informed consent is signed and dated. Informed consent is considered the point at which the subject is participating in the clinical study and all events are captured even if it is prior to undergoing any study-related procedure and/or receiving investigational product or investigational device. Non-serious -AEs will be reported through the subject's last study visit (or termination if the subject terminates early from the study for any reason). Serious AEs will be reported through and including 30 calendar days after administration of the subject's last dose or exposure to investigational product. Serious AEs require immediate notification to the Sponsor or its designated representative. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study product is suspected.

12.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation whether or not a subject is administered the investigational product or medical device. The event does not need to have a suspected causal relationship with the investigational product or device. An AE can therefore be any unfavorable and unintended sign, symptom, disease, or injury temporally associated with the use of an investigational product or device, whether or not related to the investigational product or device. Examples of - AEs include but are not limited to:

- Abnormal test findings,

- Clinically important symptoms and signs,
- Changes in physical examination findings,
- Hypersensitivity, and
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Investigational product overdose,
- Investigational product withdrawal,
- Investigational product abuse,
- Investigational product misuse,
- Investigational product interactions,
- Medication errors,
- Investigational product dependency
- Exposure in utero, and
- Study related procedure

12.4 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AEs are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a discontinuation from the study, significant additional concomitant treatment, or other therapy, and/or
- Test result is considered to be an AE by the Investigator or the Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

12.5. Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" for a drug study if, in the view of either the Investigator (physician/dentist) or the Sponsor, it results in any of the following outcomes:

- Results in death,
- Is life-threatening (immediate risk of death),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly/birth defect,
- Is considered medically significant (medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed above). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an Emergency Room or at home, blood dyscrasia, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignancy), or,
- Is a suspected transmission of any infectious agent via a medical product (medically significant) and should be reported as an SAE in the category 'Other medically important conditions'.

12.6 Hospitalization

Adverse events reported from clinical studies associated with hospitalization or prolonging hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Hospitalization does not include the following:

- Rehabilitation facilities,

- Hospice facilities,
- Respite care (e.g., caregiver relief),
- Skilled nursing facilities,
- Nursing homes,
- Emergency room visits (unless the reason for the emergency room visit meets one of the other outcomes in the definition of serious), and/or
- Same day surgeries (as outpatient/same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality),
- Social admission (e.g., subject has no place to sleep),
- Administrative admission (e.g., for yearly physical exam),
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol),
- Optional admission not associated with a precipitating clinical AE (e.g., or elective cosmetic surgery),

Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

12.7. Resolution

The Investigator will be required to assess the outcome of the AE for investigational product (drug or device) as one of the following:

- Resolved,

- Not Resolved,
- Fatal,
- Resolved with sequelae,
- Resolving, or
- Unknown

Any causally-related AEs unresolved upon completion of the last study visit will be followed up by the study staff until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and recorded on the CRF. An event that is assessed as resolved with sequelae or resolving indicates that the subject has stabilized to a level acceptable to the Investigator and has concurrence by the Sponsor.

12.8. Severity Assessment

The severity of AEs will be assessed by the Investigator or medically qualified individual (MD/DO/Dentist) using the following general categorical descriptors:

MILD: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with subject's usual function or normal everyday activities

MODERATE: Sufficient discomfort is present to cause interference to some extent with subject's usual function or normal everyday activity

SEVERE: Extreme distress, causing significant impairment of functioning or incapacitation; interferes significantly with subject's usual function; prevents normal everyday activities

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

12.9. Causality Assessment

The Investigator's or medically qualified individual (MD/DO/Dentist) assessment of causality for investigational product (i.e., relationship to investigational product) must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE.

- Not Related - An AE that is not related to the use of the drug

- Doubtful - An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship to investigational product is unlikely.

- Possible - An AE that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship to investigational product cannot be excluded.

- Probable - An AE that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge) and an alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

- Very Likely - An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge) for a causal relationship to the drug.

If the Investigator determines a SAE is associated with study procedures, the Investigator must record this suspected causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

12.10. Exposure In Utero

For investigational products within clinical studies and for marketed products, an exposure *in utero* (EIU) occurs if:

1. a woman is exposed to the investigational product at any time between her last menses prior to conception through the delivery of the baby.

2. There is a possibility of intrauterine exposure to drug via semen from the male partner who is taking the investigational product at the time of conception, thereby possibly exposing the fetus to the product.

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's participation, the Investigator must report the pregnancy to the Sponsor on a Pregnancy Notification Form (to be provided by the Sponsor when applicable). In addition, the Investigator must submit information regarding environmental exposure to a Sponsor product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Pregnancy Notification Form. This must be done irrespective of whether an AE has occurred and notification must occur within 24 hours of awareness of the pregnancy. Initial notification via telephone to the Sponsor's study team contact must occur immediately upon the Investigator site's awareness of the pregnancy. The Pregnancy Notification Form must then be sent to the Sponsor within 24 hours of the site's

awareness. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports. The Investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The Investigator will provide this information as a follow-up to the initial Drug Exposure during Pregnancy Collection Form A and/or End of Pregnancy Collection Form B (provided by the Sponsor when applicable). The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a SAE case is created with the event of ectopic pregnancy.

The Investigator should follow the procedures for reporting SAEs if the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]). In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an End of Pregnancy Collection Form B can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre- abortion test findings are suggestive of a congenital anomaly.

Additional pregnancy outcomes that are classified as SAEs and should be reported as such include:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth, without regard to causality.
- Any infant death after 1 month that the Investigator assesses as possibly related to in utero exposure to the investigational product.

12.10.1. Withdrawal Due to Adverse Events

When a subject withdraws due to a SAE, the SAEs must be reported in accordance with the reporting requirements defined below.

12.10.2. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

12.10.3. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for a SAE. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

All AEs will be reported on the AE page(s) of the CRF. A Clinical Serious Adverse Event (SAE) Report Form must also be completed if the event is considered to be serious. It should be noted that this Clinical SAE Report Form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

12.10.3.1. Serious Adverse Event Reporting Requirements

If a SAE occurs, the Sponsor is to be initially notified by telephone immediately upon awareness of the event by the Investigator's site. Within 24 hours of the Investigator site's awareness of the event, the study site must send the Sponsor the Clinical SAE Report Form. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EIU cases. In the rare event that the Investigator's site does not become aware of the occurrence of a SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the Investigator's site is to report the event immediately after learning of it as described and document the time of the study site's first awareness of the adverse event.

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings (if available) and death certificate should be collected if permission is obtained from the subject's family. For a hospitalization, a copy of the hospital discharge summary should be requested. If obtained, these documents (with subject's personal identifiers redacted) should be submitted as soon as possible to the Sponsor or its designated representative.

Appropriate SAE forms will be provided to the study site at the initiation of the study. Upon notification of an SAE at the study site, the Investigator or designated study site staff should call and speak to their Sponsor's study manager contact immediately to initially notify them of the SAE.

Within 24 hours of awareness of the event, the Investigator or designated study site staff:

- complete the Clinical SAE Report Form ([provided by the Sponsor] with as much information as possible, however at a minimum, the subject identification number, name of product, SAE, and name of reporter are required);

- ensures the Investigator signs the Clinical SAE Report Form **prior to** sending to the Sponsor;

- scans and emails (via secure email) the Clinical SAE Report Form to the Sponsor contacts.

The Sponsor contact information is maintained in the table below:

Table 4: Sponsor Contact Information

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

All nonserious adverse events are to be reported on the adverse event CRFs and will be submitted to the Sponsor.

13. STATISTICS

The Sponsor will be responsible for the statistical analysis of study data. Detailed methodology for the statistical analysis of the data will be documented in a Statistical Analysis Plan finalized and approved prior to database lock and release of randomization codes.

13.1. Sample Size Determination

A simulation [3] was conducted based on the two previous dental pain studies [redacted] to evaluate the sample size and power within different effect size ranges. Based on the simulation results, the time to confirmed perceptible pain relief (TCPR) is identified as the primary efficacy endpoint, and the primary interest is to compare the median survival times in TCPR between [redacted] and ACM. Based on the assumption that the median survival time of [redacted] will be faster than that of ACM within the range of 5.0 – 5.5 minutes, a sample size of n=240 for the [redacted] and ACM groups will provide 90% power. If the median survival time in TCPR of [redacted] is assumed to be faster than that of IBU within the range of 6.0 – 6.5 minutes, the sample size of n=240 for the [redacted] group and n=120 for the IBU group will provide greater than 90% power.

Based on the above, it is recommended that the eligible subjects will be randomly assigned in a ratio of 4:4:2:1, with 240, 240, 120, and 60 subjects being assigned to [redacted], ACM, IBU and placebo for a total of 660 subjects.

13.2. Analysis Sets

13.2.1. Efficacy Analysis Sets

The primary analysis set for the efficacy analyses will include all subjects who are randomized. The per protocol set will exclude subjects who took rescue medication within 60 minutes after dosing, vomited within 60 minutes after dosing, and those with major protocol deviations. The final per-protocol set will be determined before unblinding.

13.2.2. Safety Analysis Population

The Safety Set will include all subjects who are randomized and take investigational product.

13.2.3. Subject Disposition and Protocol Violations

Subject disposition will be summarized by treatment group. The number of subjects with protocol violations will be summarized in a table by treatment and violation as well as in a listing by subject.

13.3. Baseline and Demographics

Baseline and demographic characteristics will be presented by treatment group for each analysis set. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median and range (min, max). For categorical variables, the number and percent of subjects in each response category will be presented.

13.4. Previous and Concomitant Medications

Previous and concomitant medications will be coded. Previous medications will be those that were discontinued before the surgery day. Concomitant medications will be those continued through, or started on, the surgery day. In addition, those medications taken between study end and the follow-up interview for an adverse event will be considered concomitant medications. Medications taken after End of Study (see Section 10.3.3) and up to the follow-up call that were not taken for an adverse event will not be collected on the CRF or summarized. Previous medications and concomitant medications will be summarized by treatment in separate tables. Number and percentage of subjects receiving each coded medication will be presented by treatment. Additionally, concomitant medications taken by greater than or equal to 5% of subjects in at least one treatment group will be presented.

13.5. Efficacy Analysis

Primary efficacy endpoint

- Time to confirmed perceptible pain relief

Secondary efficacy endpoints

- Time to meaningful pain relief;
- Percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments ([redacted] versus placebo)

Tertiary efficacy endpoints

- Percentage of subjects with meaningful pain relief at 35, 40, and 45 minutes ([redacted] versus ACM);
- Percentage of subjects with confirmed perceptible relief at 15, 20, and 25 minutes;
- Time weighted sum of pain intensity difference from 0 to 4 hours (SPID 0-4);
- Time weighted sum of pain relief from 0 to 4 hours (TOTPAR 0-4);
- Pain relief (PAR) and pain intensity difference (PID) scores at individual time points;
- Time to rescue analgesic (duration of relief after dosing);

- Subject Global Evaluation.

13.6. Statistical Hypotheses and Treatment Comparisons

The primary hypothesis is

$$H_0 : M_1 = M_2 \quad \text{vs} \quad H_A : M_1 \neq M_2$$

where M_1 and M_2 are the median survival times of [redacted] and ACM in TCPR, respectively.

Besides the primary hypothesis, the median survival times in TCPR between [redacted] and IBU will be compared. The median survival times in TMPR will be compared between [redacted] vs ACM and between [redacted] vs IBU.

The survival functions of the active treatments will be compared with the survival function of placebo.

To control the family-wise Type I error rate at 0.05 for primary and secondary endpoints, the fixed sequence testing with fallback method will be used [4]. Table 5 presents the order of the tests and the assigned α values for each ordered test. The comparison of [redacted] to IBU in TMPR is not included in the fixed testing sequence. Testing will commence with an assigned alpha = 0.049 and an alpha value of 0.001 will be reserved for the comparison of [redacted] and placebo on the percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments.

Table 5: Order of Tests and Assigned Alpha Values

	Pre-Assigned α-value	**α-value available if previous test positive**	**α-value available if previous test(s) negative**
TCPR [redacted] vs PLACEBO	0.049	---	---
TMPR [redacted] vs PLACEBO	None	0.049	None
TCPR [redacted] vs ACM	None	0.049	None
TCPR [redacted] vs IBU	None	0.049	None
TMPR [redacted] vs ACM	None	0.049	None

Table 5: Order of Tests and Assigned Alpha Values

	Pre-Assigned α-value	α-value available if previous test positive	α-value available if previous test(s) negative
Percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments [redacted] vs PLACEBO)	0.001	0.05	0.001

13.7. Data Computations and Data Imputations

13.7.1. Time to Confirmed Perceptible and Meaningful Pain Relief

The time to meaningful pain relief is defined as the time (in minutes) elapsed from dosing until the subject stopped the second stopwatch. Time to confirmed perceptible pain relief is defined as the time (in minutes) to perceptible pain relief as indicated on the first stopwatch, provided that the subject also stopped the second stopwatch indicating meaningful pain relief.

For these relief variables, subjects who do not have relief by 4 hours, who take rescue medication before having relief, or who discontinue before having relief will have their time of relief set to 4 hours and be censored at 4 hours.

13.7.2. Endpoints Relating to Pain Intensity and Pain Relief

The pain intensity difference (PID) at each time point will be derived by subtracting the pain intensity from the baseline pain intensity. A higher value is indicative of a greater improvement.

Time-weighted sum of the pain intensity difference scores (SPID) will be derived by first multiplying each PID score by the time from the previous time point, and adding them together for each scheduled time point from 0-4 hours. Time-weighted total pain relief (TOTPAR) for each specified interval will be similarly derived.

Pain intensity and pain relief ratings provided at times differing from the intended times by more than ± 5 minutes for the scores up to 90 minutes post-dose, and by more than ± 15 minutes for the remaining measurements will be estimated by linear interpolation. For subjects who use rescue medication, the last reported pain score or baseline pain score, whichever is worse, will be carried forward to the remaining time points; pain relief scores after rescue medication will be set to zero. For subjects who discontinue the study early, the same imputation approach will be used.

13.8. Analysis Methods

13.8.1. Time to Confirmed Perceptible and Meaningful Relief

Time to confirmed perceptible pain relief (TCPR) and time to meaningful pain relief (TMPR) will be analyzed using survival data analysis. The survival function (cumulative proportions of subjects with pain relief at each time point) and the median survival time will be estimated by the Kaplan-Meier method for each treatment. The median survival times for the active treatments will be compared using the bootstrap re-sampling method, and the survival functions of the active treatments will be compared with the survival function of placebo using the Wilcoxon test. The median survival time is chosen as an endpoint for evaluating the effect of time to onset, and the bootstrap method is an appropriate method for comparing the median survival time when the survival functions are non-proportional.

13.8.2. Earliest Statistically Significant Separation of [redacted] and Placebo on Percentage of Subjects with Confirmed Perceptible Relief

The earliest time of separation between [redacted] and placebo will be established by comparing the percentage of subjects with confirmed perceptible pain relief starting from 30 minutes to successive earlier minutes in one minute increments, until statistical significance is no longer achieved. The dichotomized response will be analyzed using logistic regression analysis.

13.8.3. Percentage of Subjects with Meaningful Pain Relief at 35, 40, and 45 minutes

The percentage of subjects with meaningful pain relief at 35, 40 and 45 minutes will be analyzed using logistic regression analysis and compared between [redacted] and ACM at each time point.

13.8.4. Percentage of Subjects with Confirmed Perceptible Pain Relief at 15, 20, and 25 minutes

The percentage of subjects with confirmed perceptible pain relief at 15, 20 and 25 minutes will be analyzed using logistic regression analysis at each time point.

13.8.5. SPID0-4 and TOTPAR0-4

SPID0-4 and TOTPAR0-4 will each be analyzed with an analysis of variance with baseline pain (moderate or severe) score and treatment group in the model using imputation methods defined in Data Imputations Section 13.7.2.

13.8.6. PID and PAR at each Time

PID and PAR will be analyzed at each time point with an analysis of variance with baseline pain score (moderate or severe) and treatment group in the model.

13.8.7. Time to Rescue

Time to first use of rescue medication will be measured as the elapsed time from when the investigational product was given until the time rescue medication was first given. Subjects who discontinue from the study before 4 hours, but do not use rescue medication, will be censored at the time of discontinuation. Subjects who do not use rescue medication during the 4-hour study period will have their time to rescue set to 4 hours and be censored at.4 hours. Kaplan-Meier estimates of cumulative percentage of subjects rescuing will be presented by treatment group in tabular and graphical formats. The survival functions will be compared between the treatment groups using the Wilcoxon test.

13.8.8. Subject Global Evaluation

Subject Global Evaluation will be analyzed using an analysis of variance with treatment and categorical baseline pain as factors. Missing data will not be imputed for this variable. Pairwise comparisons specified in Section 13.6 will be analyzed.

13.8.9. Subgroup Analyses

Time to confirmed perceptible relief and time to meaningful relief will be analyzed based on the following subgroups: age group (<18 years, ≥18 years), gender, race (white, non-white) and baseline categorical pain (moderate, severe). The survival function and the median survival time will be estimated by the Kaplan-Meier method within each subgroup.

13.9. Safety Analysis

The safety analysis will be based on the safety analysis set.

13.9.1. Adverse Events

Treatment-emergent AEs are those with a start date and time at or after the time of study drug administration. All summaries described below are for treatment-emergent AEs except where noted. Non treatment-emergent AEs will be provided in a listing.

The number and percentage of subjects experiencing AEs will be tabulated by treatment, system organ class and preferred term using the MedDRA coding dictionary. The number and percentage of subjects experiencing treatment-related AEs will also be presented by system organ class and preferred term. Treatment-related AEs will include events marked as being at least possibly related to study treatment. The number and percentage of subjects with AEs will be presented by severity. Subjects will be counted only once for each system organ class and preferred term by selecting the most severe event. The number of subjects with the most commonly reported adverse events (those reported by 5% or more in any one treatment group) will be summarized by treatment, system organ class and preferred term. The number of subjects with adverse events will also be summarized by demographic characteristics: age group (<18 years, ≥18 years), gender, and race.

The number and percentage of subjects experiencing SAEs or who discontinued the study due to an AE will be presented by system organ class and preferred term. These displays will include all AEs, not just treatment-emergent AEs.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The sponsor should ensure that it is specified in the protocol or written agreement that the investigator(s)/institutions(s) will permit study related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing access to the source data/documents.

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Johnson & Johnson will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other site personnel their responsibilities with regard to protocol adherence as well as the study and monitoring responsibilities of Johnson & Johnson or its representatives. These responsibilities will be documented in a Clinical Study Agreement between Johnson & Johnson and the investigator. During the study, a monitor from Johnson & Johnson or representative will have regular contacts with the investigational site, for the following:
- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report all protocol deviations not previously sent to Johnson & Johnson.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Johnson & Johnson and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or study-related direction.

14.2. Audits and Inspections

Authorized representatives of Johnson & Johnson, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Johnson & Johnson audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP and any applicable regulatory requirements. The investigator should contact their study contacts immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval of the protocol and all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained in the Site Master File by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to oversee the progress of a clinical trial, and to ensure that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures, ICH/GCP, and the applicable regulatory requirement(s).

The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow the Sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.

In the event that the study site is notified of a regulatory inspection, the Sponsor must be notified immediately.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

16. DATA HANDLING AND RECORDKEEPING

16.1. Case Report Forms/ Electronic Data Record

All data will be collected on source documents first and then recorded in an Electronic Data Capture (EDC) system. The EDC system is the database where pertinent study data are collected such as demography, subject randomization, efficacy assessments, adverse events, and subject disposition. EDC CRFs should be completed for each included subject. The completed pages of the EDC system are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

It is the Investigator's responsibility to ensure completion and to review and approve all information captured in the EDC. The subject's data in the EDC system must be electronically signed by the Investigator. These signatures serve to attest that the information contained in the EDC system is true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Subject source documents are the Investigator's/physician's subject records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts. All final data recorded in EDC system will be copied into files and kept by the Sponsor. A copy of these files will also be kept at the clinical site. All data provided in the CRF must be supported by source document. For this study, the Sponsor will provide specific worksheets (NRS scales/Subject Global Evaluation) to serve as source document tools to collect pain intensity, pain relief, and global evaluation.

16.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE report forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

17. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the

sponsor. In addition, the sponsor retains the right to discontinue development of the [redacted] 500 mg at any time.

If a study is prematurely terminated or discontinued, the sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects within two weeks. All study materials must be collected and all CRFs completed to the greatest extent possible.

18. PUBLICATION POLICY

Publication of study results by the investigator is discussed in the Clinical Study Agreement, as appropriate. Results from this study may be published in the form of oral or written presentations at scientific meetings or as one or more peer-reviewed journal articles. In these cases, no information on individual subjects will be revealed.

19. LIST OF REFERENCES

1. Averbuch M, Katzper M. Baseline pain and response to analgesic medications in the postsurgery dental pain model. J Clin Pharmacol 2000;40:133-137.

2. Cooper SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. In: Max M, Portenoy R, Laska E, eds. Advances in pain research and therapy. Vol 18. New York, NY: Raven Press, Ltd., 1991:117-24.

3. Data on file for “Simulation based sample size and power for dental 3 study”, McNeil Consumer Healthcare, Fort Washington, PA, 2017.

4. Wiens, BL. A fixed sequence Bonferroni procedure for testing multiple endpoints. Pharmaceutical Statistics 2003; 2:211-215.

20. APPENDICES

APPENDIX 1: PAIN RATING SCALES/ CATEGORICAL PAIN INTENSITY SCALE

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)

0-10 PAIN INTENSITY - NUMERICAL RATING SCALE (PI-NRS)

Circle the number that best represents your pain.

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

0-10 PAIN RELIEF – NUMERICAL RATING SCALE (PR-NRS)

Circle the number that shows your amount of pain relief.

No relief 0 1 2 3 4 5 6 7 8 9 10 Complete relief

APPENDIX 2: SUBJECT GLOBAL EVALUATION

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

Poor (0)

Fair (1)

Good (2)

Very Good (3)

Excellent (4)