CLINICAL STUDY PROTOCOL

AMENDMENT #2

CCSPAA002398

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE FIVE STRENGTHS OF A FIXED COMBINATION OF ACETAMINOPHEN/NAPROXEN SODIUM IN POSTOPERATIVE DENTAL PAIN

Investigational Product Name	Acetaminophen/Naproxen sodium
Protocol Number	CCSPAA002398
IND / IDE / EudraCT number	145,058
Phase	II
Version and Date	Amendment 2, Version 3, 25 November 2020 Amendment #1, Version 2 (Final), 08 October 2020 Version 1 (Final), 10 July 2020

1. SYNOPSIS

Name and Address of the Sponsor/Company of the clinical study: Johnson & Johnson Consumer, Inc. 7050 Camp Hill Road Fort Washington, PA 19034
Active Ingredient: Acetaminophen/Naproxen sodium
Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Evaluate Five Strengths of a Fixed Combination of Acetaminophen/Naproxen Sodium in Postoperative Dental Pain
Countries: United States of America
Study Site: JBR Clinical Research 650 East 4500 South, Suite 100 Salt Lake City, Utah 84107
Principal Investigator: Todd Bertoch, MD
Phase of Development: Phase II
Objectives: **Primary:** • To evaluate the relative analgesic efficacy of five strengths of a fixed combination of acetaminophen/naproxen sodium over 12 hours. **Secondary:** • To evaluate the relative analgesic duration of five strengths of a fixed combination of acetaminophen/naproxen sodium. [redacted]
Methodology: This will be a randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and safety profile of the following doses of a fixed combination of acetaminophen/naproxen sodium: • [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium

- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- Placebo

Subjects will undergo dental extraction of three or four third molars. Supernumerary teeth may also be removed. Judgment of impaction level will be made by the oral surgeon based on visual examination of the panorex x-ray. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios:

- Two full bony impactions
- Two partial bony impactions
- One full bony impaction in combination with one partial bony impaction

Post-surgery trauma assessment will be done on the day of surgery (Baseline visit). Subjects will be excluded from the study if the mandibular extraction results in a trauma rating of "severe" on a mild, moderate, or severe scale on the categorical and numerical pain intensity scale.

Approximately 300 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 the following six treatment groups, with equal allocation among the treatment groups:

- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen Sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- Placebo (administered as two placebo tablets)

All treatments will be administered as a single dose. Rescue analgesic medication (oxycodone immediate release 5 mg every four to six hours as needed for pain; not to

exceed 30 mg in 24 hours) will be available for subjects as needed.

No less than approximately 30% of randomized subjects will be either male or female. To maintain the double-blind nature of the study, an independent third party will administer study drug to blindfolded subjects.

Self-reported pain intensity will be collected using a 0-10 NRS at Baseline (Time 0). Pain intensity and pain relief will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, hourly from 2 through 12 hours, and every 4 hours from 12 through 24 hours (±5 minutes) post-dose as well as [redacted] at the time of first rescue (if applicable, before administration). [redacted]

[redacted]

After completion of all study assessments, subjects will be discharged from the study site. Subjects will be interviewed by telephone to follow-up on appropriate post-surgical medical care and changes in their health, including any emergent or existing adverse events (AEs). The interview will occur between the sixth and ninth day after the dental surgery (Days 7 to 10 of the study).

Number of planned subjects: Planned for 300 subjects to be randomized.

Diagnosis and main criteria for inclusion in the study: Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Males or females who are 17 to 50 years of age (inclusive) at the time of Screening.
2. If female and of childbearing potential have a negative urine pregnancy at Screening and at Baseline.
3. Weigh (100) pounds or greater and have a body mass index (BMI) of 17.5 to 30.4 (inclusive) at Screening.
4. 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.

5. 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) PI-NRS at Baseline within 4.5 hours of the last stitch from oral surgery.
6. Are able to comprehend and follow the requirements of the study (including pre-surgical instructions provided by the site and availability on scheduled visit dates) based upon research site personnel's assessment.
7. Provide written informed consent (for subjects who are below the age of legal consent, parent or legally authorized representative provides written informed consent and the subject provides written assent).
8. Females of childbearing potential and males agree to the contraceptive requirements.
9. Are willing for this to be the only investigational product used during the study.
10. Have a negative urine drug screen at Screening, and on day of surgical procedure.

Exclusion Criteria

Subjects will be excluded if they:

1. Are female and are pregnant, breastfeeding, or currently trying to become pregnant.
2. Are male with a pregnant partner or a partner who is currently trying to become pregnant.
3. Have extraction of mandibular third molars resulting in a trauma rating of "severe" on a mild, moderate, or severe scale.
4. Have a known allergy or hypersensitivity to naproxen or other nonsteroidal anti-inflammatory drugs, including aspirin, acetaminophen, oxycodone or other opioids.
5. Have presence or a history of major medical condition that in the Investigator's opinion may jeopardize the subject's safety or well-being (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) or the integrity of the study.
6. Have a history of a confirmed or suspected Coronavirus Disease 2019 (COVID-19) infection in the last 30 days or contact with COVID-19-infected person within

14 days prior to any site visit.

7. Have any international travel within 14 days prior to any site visit including members in the same household.
8. Have self-reported symptoms within 14 days prior to any site visit:
    - Unexplained cough, shortness/difficulty breathing, fatigue, body aches (headaches, muscle pain, stomach aches), conjunctivitis, loss of smell, loss of taste, poor appetite, nausea, vomiting, diarrhea, palpitations, or chest pain/tightness;
    - Temperature ≥37.5°C/99.5°F, within 14 days prior to any site visit or when measured upon arrival at any site visit;
    - Use of fever or pain reducers within the past three days prior to any site visit.
9. Are not able to swallow whole large tablets or capsules.
10. Routinely use oral analgesics ≥5 times per week.
11. Have a history of chronic tranquilizer use, heavy drinking, or substance abuse, as judged by the Investigator site staff, in the last five years. Heavy drinking is defined as the use of more than four standard drinks daily or more than 14 drinks a week for men, and more than three standard drinks daily or more than seven 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).
12. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last two years.
13. Used oral over-the-counter or prescription products (except contraceptive medications and those required for use during the oral surgical procedure), within five half-lives before the oral surgical procedure.
14. Used vitamins, dietary or herbal supplements within five days before the oral surgical procedure.
15. Used any immunosuppressive drugs, corticosteroids (except for topical corticosteroids), or injectable or oral anticoagulants (e.g., heparin, Lovenox, Xarelto, Eliquis, Pradaxa, Coumadin, Miradon) within two weeks of Screening.
16. Used alcohol within three days before the oral surgical procedure.
17. 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.
18. Used monoamine oxidase inhibitors within 14 days prior to surgery.

19. Have a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV).
20. Have participated in any interventional clinical trials within 30 days before Screening.
21. 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 [J&J] subsidiaries, contractors of J&J, and the families of each).

Test Products, Dosage and Mode of Administration:

- [redacted] mg Acetaminophen/[redacted] mg Naproxen Sodium (administered as two tablets of Acetaminophen/Naproxen Sodium [redacted]), to be taken orally with up to 180 mL water
- [redacted] mg Acetaminophen/[redacted] mg Naproxen Sodium (administered as two tablets of Acetaminophen/Naproxen Sodium [redacted]), to be taken orally with up to 180 mL water
- [redacted] mg Acetaminophen/[redacted] mg Naproxen Sodium (administered as two tablets of Acetaminophen/Naproxen Sodium [redacted]), to be taken orally with up to 180 mL water
- [redacted] mg Acetaminophen/[redacted] mg Naproxen Sodium (administered as two tablets of Acetaminophen/Naproxen Sodium [redacted]), to be taken orally with up to 180 mL water
- [redacted] mg Acetaminophen/[redacted] mg Naproxen Sodium (administered as two tablets of Acetaminophen/Naproxen Sodium [redacted]), to be taken orally with up to 180 mL water

Comparator Product, Dosage and Mode of Administration:

- Placebo (administered as two placebo tablets), to be taken orally with up to 180 mL water

Duration of Study per Subject: Ten days, including Baseline (Day 1 [day of surgery]) and follow-up (Days 7 to 10), and excluding Screening (Day -30 to Day 1).

Duration of Treatment: Twenty four (24) hours. Subjects will be observed at the study site for at least 24 hours after dosing with study medication, regardless of whether or not the subject rescues, vomits, or experiences other AEs.

Criteria for Efficacy Evaluation:

Primary Efficacy Endpoint:

- Time weighted sum of pain intensity difference from 0-12 hours after dosing (SPID 0-12)

Secondary Efficacy Endpoints:

- Time weighted sum of pain relief from 0 to 12 hours (TOTPAR 0-12)
- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first use of rescue analgesic (duration of relief after dosing)
- Proportion of subjects who require rescue analgesic

[redacted]

Safety Evaluation:
Safety will be monitored and assessed by reviewing the collection, evaluation, and analysis of AEs. Any causally related AEs that are unresolved upon completion of the last study visit will be followed by the study staff until the event, or its sequelae, resolvs or stabilize at a level acceptable to the medically qualified Investigator or designee, and recorded on the electronic case report form. An event that is assessed as resolved with sequelae or resolving indicates that the subject has stabilized to a level acceptable to the medically qualified Investigator or designee and has concurrence by the Sponsor.

Statistical methods:

Sample Size: The total sample size of 300 subjects (50 per treatment group) provides 90% probability that the model-based estimated SPID 0-12 for at least one of the combination doses included in the study design will be statistically significantly higher than the estimate for each corresponding monotherapy, based on one-sided α=0.01 for each comparison and a regression model accounting for acetaminophen, naproxen, and acetaminophen-by-naproxen interaction effects. Power was estimated using simulations assuming an emax dose response for the monotherapies, maximum effect sizes of 0.6 for acetaminophen and 1.4 for naproxen over the doses in this study, and an interaction index that provides for slightly less than an additive effect for each monotherapy component. Effect size is defined here as the difference between the active and placebo means divided by the standard deviation. Maximum effect sizes and assumptions regarding interaction were based on a previous proof-of-concept study and acetaminophen and naproxen monotherapy studies.

Statistical Analysis: For the primary endpoint, SPID 0-12, the dose response will be assessed by fitting a linear regression model with SPID 0-12 as the response variable, including terms for acetaminophen dose, naproxen dose, and acetaminophen by naproxen interaction. Based on this regression model, the model-based means for each strength of fixed combination and corresponding monotherapy doses will be estimated and statistically compared. Pairwise comparisons will be made using an analysis of variance (ANOVA) with baseline pain (moderate or severe) score, gender, and treatment group.

As a secondary analysis, pairwise comparisons between acetaminophen/naproxen sodium combination doses and placebo will be made using an ANOVA with baseline pain (moderate or severe) score, gender, and treatment group. This ANOVA model will also be used to analyze [redacted] SPID 6-12, [redacted] TOTPAR 0-12 [redacted]

[redacted] time to first rescue will be analyzed using survival data analysis. The survival function (cumulative proportions of subjects at each time point) and the median survival time will be estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared using the Wilcoxon test stratified by baseline pain (moderate or severe) and gender.

For proportions of subjects receiving rescue, treatment comparisons will be based on the Kaplan-Meier method with standard errors approximated using the Greenwood formula. (This method will be used for this endpoint due to the censoring that may occur between 0 and 24 hours.)

[redacted]

Except where noted otherwise, all statistical tests of hypothesis will be two-sided and employ a significance level of α=0.05.

2. ACTIVITY SCHEDULE

Table 1: Activity Schedule

	Screening	Baseline (Day of Surgery)	Hours Post-dose	Follow-up Call
Procedures	**Day -30 to 1**	**Day 1**	**0 to 24 hours**	**Days 7 - 10**
Written informed consent and/or assent	X			
Demography (including age)	X			
Inclusion and Exclusion assessment	X[1]	X[1]		
Significant medical history	X[1]	X[1]		
Vital signs[2]	X[1]	X[1]		
Physical exam (height, weight and BMI)	X			
Urine pregnancy test[3]	X[1]	X[1]		
Urine drug screen[4]	X[1]	X[1]		
Serology[5]	X			
Dental extraction surgery		X		
Post-surgery trauma assessment[6]		X		
Categorical and numerical pain intensity		X[7]		
Randomization criteria		X		
Investigational product administration		X		
[redacted]			[redacted]	
Pain intensity and pain relief ratings[8]			X	
[redacted]			[redacted]	
Rescue therapy			X	
[redacted]			[redacted]	
Prior and concomitant therapy	X	X	X	X
Safety monitoring	X	X[11]	X[11]	X[11]
Subject disposition	X[12]	X[12]	X[12]	X[12]
Follow-up interview				X

Abbreviations: AE=adverse events; BMI=body mass index; eCRF=electronic case report form; HIV=human immunodeficiency virus

Note: Admission and discharge of the subjects will occur on Day 2 (24 hours).

[1] Only Baseline assessments were collected on eCRF.

[2] Blood pressure, heart rate, respiratory rate, oral temperature.

[3] Females of childbearing potential.

[4] Minimum requirements for urine drug testing for Screening & day of surgery: cocaine, tetrahydrocannabinol, opioids (e.g., buprenorphine, oxycodone, methadone, and morphine), benzodiazepines, and amphetamines.

[5] HIV antibody, hepatitis B surface antigen (HBsAg) , hepatitis C virus antibody (anti-HCV).

[6] Subjects will be excluded from the study if the mandibular extraction results in a trauma rating of "severe" on a mild, moderate, or severe scale on the categorical and numerical pain intensity scale.

[7] Scored within 4.5 hours after last stitch from dental surgery.
[8] Pain ratings collected: 0.25, 0.5, 0.75, 1, 1.25, 1.5, hourly from 2 through 12 hours, and every 4 hours from 12 through 24 hours (±5 minutes) post-dose. If subject requests rescue medicine, ratings will be collected before administration.

[redacted]

Collection of AEs and report of pregnancy.
[12] Only collected at end of study. End of Study is at the time of follow-up call or at time of subject withdrawal.

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4. 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 or Specialist Term	Explanation
AE	Adverse Event
ANOVA	Analysis of Variance
anti-HCV	Hepatitis C Virus Antibody
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIU	Exposure in Utero
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonization
IP	Investigational Product
[redacted]	[redacted]
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	Intrauterine Device
J&J	Johnson & Johnson
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over-the-Counter
PAR	Pain Relief
PI	Principal Investigator
[redacted]	[redacted]
PI-NRS	Pain Intensity-Numerical Rating Scale
PQC	Product Quality Complaint
PR-NRS	Pain Relief-Numerical Rating Scale
SAE	Serious Adverse Event

Abbreviation or Specialist Term	Explanation
SOP	Standard Operating Procedure
SPID	Time Weighted Sum of Pain Intensity Difference
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
[redacted]	[redacted]
TOTPAR	Time Weighted Sum of Pain Relief Scores
US	United States

5. ETHICS

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

It is the responsibility of the Sponsor and Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms/assent, and other written information to be provided to subjects, e.g., advertisements and diaries if applicable, from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). All correspondence with the IRB/IEC should be retained in the Investigator File (Site Master File). Copies of IRB/IEC approvals obtained by the Investigator 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 five working days after implementation.

5.2. Ethical and Regulatory Considerations

The study will be performed in accordance with the protocol, International Council for Harmonization Good Clinical Practice guidelines (ICH GCP E6), the latest version of the Declaration of Helsinki,[5] and applicable local regulatory requirements and laws.

Before initiating the clinical study, the Sponsor should submit any required application(s) to the appropriate authority (ies) for review, acceptance, and/or and/or permission to begin the study. Any notification/submission should be dated and contain sufficient information to identify the protocol.

Amendments to the protocol that are considered as substantial, i.e., are likely to have an impact on the safety of the study subjects, to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, must be reviewed and approved by the appropriate authority(ies).

5.3. Subject Information and Consent

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 subject number that is used in the electronic Case Report Form (eCRF) 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 upon by the Sponsor and the IRB/IEC. It must be in compliance with current regulatory requirements (e.g., ICH E6), and legal requirements, and be in a language that the subject can read and understand with compliance to the International Standard and any regional or national regulations, as appropriate.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation in the study. Subjects must consent to informing the site if they develop symptoms of Coronavirus disease 2019 (COVID-19). 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.

Prior to a subject's participation in the study, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

Only subjects who provide informed consent will be permitted to participate in the study.

5.4. 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 as required by the site's IRB/IEC or Principal Investigator (PI), or local requirements. During the Assent process, the PI or designee will provide the minor with an assent document that explains, in terms appropriate to the child's age, experience, maturity and condition, any discomfort and inconveniences the child may expect to experience if he or she agrees to participate. The subject should also be made aware of his or her rights to decline participation or to withdraw from the study at any time.

The assent document will focus on the risks, benefits and alternatives to research participation as well as confidentiality of information obtained as a result of their participation. The minor should be given an opportunity to ask questions prior to signing the approved assent form or designated assent signature line within the Informed Consent Form. An impartial 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/study files and will be available for review by the Monitor and 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 ensure a thorough understanding of the procedures, risks, and benefits of the study.

6. STUDY ADMINISTRATIVE STRUCTURE

Details on the administrative structure of the study (e.g., PI/study site personnel, the Sponsor's study team, and the external service providers) will be included in the 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/IEC(s), as well as the names and titles of the person(s) authorized to sign the protocol and the protocol amendment(s) for the Sponsor. The complete contact list will be maintained in the trial master file throughout the study for inclusion in the clinical study report.

7. INTRODUCTION

The investigational product (IP) will involve a fixed combination tablet of [redacted] acetaminophen and naproxen sodium [redacted] Currently there are no fixed combination products containing acetaminophen and naproxen sodium marketed in the United States (US).

Acetaminophen has been available in the US for over-the-counter (OTC) adult analgesic use since the 1960s. In the US, adult single-ingredient OTC acetaminophen products are indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache, for the minor pain of arthritis, for the pain of premenstrual and menstrual cramps and for the reduction of fever. Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties. Although the precise mechanism of action has not been definitively established, it is believed that acetaminophen produces its analgesic and antipyretic effects by inhibiting prostaglandin synthesis centrally and elevating the pain threshold.[2,3]

Naproxen sodium has been available in the US for OTC analgesic use since 1994. Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. In the US, [redacted] naproxen sodium is available as an OTC medication for the temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backache, menstrual cramps, headache, toothache, and the common cold, and for the temporary reduction of fever.[4] The therapeutic effects of naproxen are produced through nonselective inhibition of cyclooxygenase enzymes (COX-1 and COX-2) resulting in inhibition of prostaglandin synthesis. Naproxen sodium salt has similar therapeutic properties as comparable doses of naproxen free acid based on molecular weight, but with more rapid systemic absorption. In this respect, [redacted] naproxen sodium is approximately equivalent to [redacted] naproxen.[1]

The fixed combination of acetaminophen/naproxen sodium is not currently marketed in the United States (US).

The current study will evaluate relative efficacy of five strengths of a fixed combination of acetaminophen and naproxen sodium to help inform selection of dose(s) for further development and to evaluate the safety of a fixed combination of acetaminophen and naproxen sodium.

8. STUDY OBJECTIVES

8.1. Primary Objective

- To evaluate the relative analgesic efficacy of five strengths of a fixed combination of acetaminophen/naproxen sodium over 12 hours.

8.2. Secondary Objective

- To evaluate the relative analgesic duration of five strengths of a fixed combination of acetaminophen/naproxen sodium.

8.3. [redacted]

8.4. Primary Endpoint

- Time weighted sum of pain intensity difference from 0-12 hours after dosing (SPID 0-12).

8.5. Secondary Endpoints

- Time weighted total pain relief from 0 to 12 hours (TOTPAR 0-12).
- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first use of rescue analgesic (duration of relief after dosing)
- Proportion of subjects who require rescue analgesic

8.6. [redacted]

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan

This will be a randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and safety profile of the following doses of a fixed combination of acetaminophen/naproxen sodium (Figure 1):

- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium
- Placebo

Subjects will undergo dental extraction of three or four third molars. Supernumerary teeth may also be removed. Judgment of impaction level will be made by the oral surgeon based on visual examination of the panorex x-ray. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios:

- Two full bony impactions
- Two partial bony impactions
- One full bony impaction in combination with one partial bony impaction

Post-surgery trauma assessment will be done on the day of surgery (Baseline visit). Subjects will be excluded from the study if the mandibular extraction results in a trauma rating of "severe" on a mild, moderate, or severe scale on the categorical and numerical pain intensity scale.

Approximately 300 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 the following six treatment groups, with equal allocation among the treatment groups:

- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])

- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- Placebo (administered as two placebo tablets)

All treatments will be administered as a single dose. Rescue analgesic medication (oxycodone IR 5 mg every four to six hours as needed for pain; not to exceed 30 mg in 24 hours) will be available for subjects as needed.

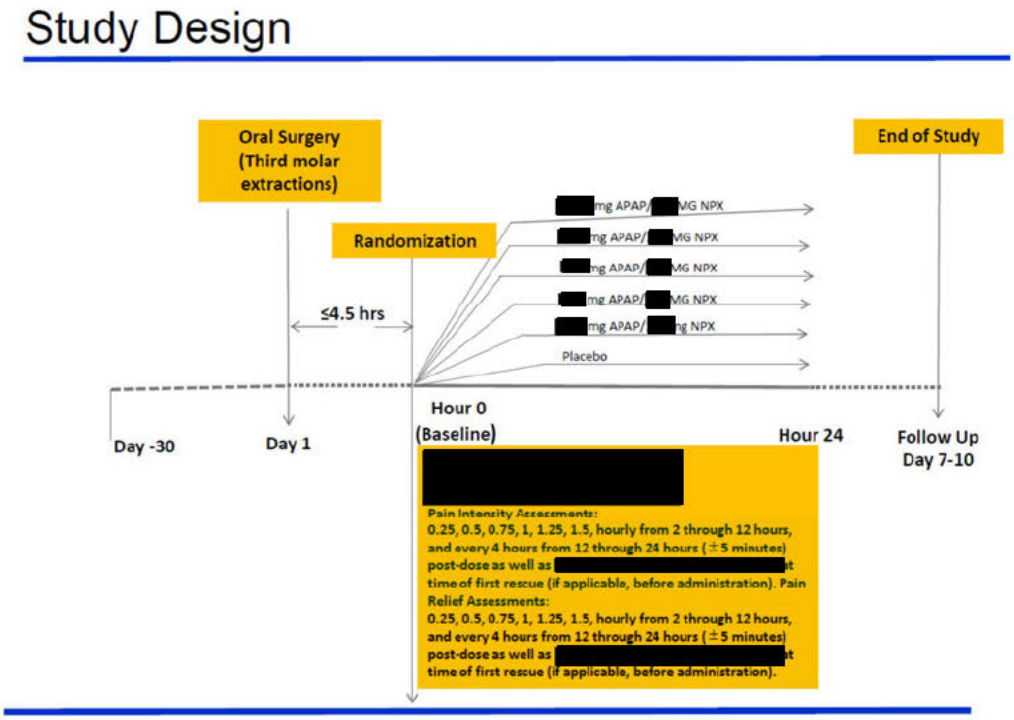
No less than approximately 30% of randomized subjects will be either male or female. To maintain the double-blind nature of the study, an independent third party will administer study drug to blindfolded subjects.

Self-reported pain intensity will be collected using a 0-10 NRS at Baseline (Time 0). Pain intensity and pain relief will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, hourly from 2 through 12 hours, and every 4 hours from 12 through 24 hours (±5 minutes) post-dose as well as [redacted] at the time of first rescue (if applicable, before administration). [redacted]

After completion of all study assessments, subjects will be discharged from the study site. 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 sixth and ninth day after the dental surgery (Days 7-10 of the study).

The total study duration for an individual subject will be 10 days, including Baseline (Day 1 [day of surgery]) and follow-up (Days 7 to 10), and excluding Screening (Day -30 to Day 1).

Figure 1: Schematic Study Design



Key: APAP=acetaminophen; NPX=naproxen sodium

9.2. Discussion of Study Design

The relative efficacy of five strengths of a fixed combination of acetaminophen and naproxen sodium is being investigated to help inform selection of dose(s) for further development and to evaluate the safety of a fixed combination of acetaminophen and naproxen sodium.

9.3. 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 this investigational compound 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 eCRFs and electronic source documents completed to the greatest extent possible.

10. STUDY POPULATION

10.1. Subject Eligibility

This clinical study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. No waivers to inclusion or exclusion criteria will be permitted at point of enrollment.

10.1.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Males or females who are 17 to 50 years of age (inclusive) at the time of Screening.
2. If female and of childbearing potential have a negative urine pregnancy at Screening and at Baseline.
3. Weigh (100) pounds or greater and have a body mass index (BMI) of 17.5 to 30.4 (inclusive) at Screening.
4. 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.
5. 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) PI-NRS at Baseline within 4.5 hours of the last stitch from oral surgery.
6. Are able to comprehend and follow the requirements of the study (including pre-surgical instructions provided by the site and availability on scheduled visit dates) based upon research site personnel's assessment.
7. Provide written informed consent (for subjects who are below the age of legal consent, parent or legally authorized representative provides written informed consent and the subject provides written assent).
8. Females of childbearing potential and males agree to the contraceptive requirements as outlined in Section 12.6.4 and 12.6.5.
9. Are willing for this to be the only IP used during the study.
10. Have a negative urine drug screen at Screening, and on day of surgical procedure.

10.1.2. Subject Exclusion Criteria

Subjects will be excluded if they:

1. Are female and are pregnant, breastfeeding or currently trying to become pregnant.
2. Are male with a pregnant partner or a partner who is currently trying to become pregnant.
3. Have extraction of mandibular third molars resulting in a trauma rating of "severe" on a mild, moderate, or severe scale.
4. Have a known allergy or hypersensitivity to naproxen or other NSAIDs, including aspirin, acetaminophen, oxycodone, or other opioids.
5. Have presence or a history of major medical condition that in the Investigator's opinion may jeopardize the subject's safety or well-being (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) or the integrity of the study.
6. Have a history of a confirmed or suspected COVID-19 infection in the last 30 days or contact with COVID-19-infected person within 14 days prior to any site visit.
7. Have any international travel within 14 days prior to any site visit including members in the same household.
8. Have self-reported symptoms within 14 days prior to any site visit:
    - Unexplained cough, shortness/difficulty breathing, fatigue, body aches (headaches, muscle pain, stomach aches), conjunctivitis, loss of smell, loss of taste, poor appetite, nausea, vomiting, diarrhea, palpitations, or chest pain/tightness;
    - Temperature ≥37.5°C/99.5°F, within 14 days prior to any site visit or when measured upon arrival at any site visit;
    - Use of fever or pain reducers within the past three days any site visit.
9. Are not able to swallow whole large tablets or capsules.
10. Routine use of oral analgesics ≥5 times per week.
11. Have a history of chronic tranquilizer use, heavy drinking, or substance abuse, as judged by the Investigator site staff, in the last five years. Heavy drinking is defined as the use of more than four standard drinks daily or more than 14 drinks a week for men, and more than three standard drinks daily or more than seven 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).

12. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last two years.
13. Used oral OTC or prescription products (except contraceptive medications and those required for use during the oral surgical procedure), within five half-lives before the oral surgical procedure.
14. Used vitamins, dietary or herbal supplements within five days before the oral surgical procedure.
15. Used any immunosuppressive drugs, corticosteroids (except for topical corticosteroids), or injectable or oral anticoagulants (e.g., heparin, Lovenox, Xarelto, Eliquis, Pradaxa, Coumadin, Miradon) within two weeks of Screening.
16. Used alcohol within three days before the oral surgical procedure.
17. 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.
18. Used monoamine oxidase inhibitors within 14 days prior to surgery.
19. Have a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV).
20. Have participated in any interventional clinical trials within 30 days before Screening.
21. Are related to those persons involved directly or indirectly with the conduct of this study (i.e., PI, sub-investigators, study coordinators, other site personnel, employees of Johnson & Johnson [J&J] subsidiaries, contractors of J&J, and the families of each).

10.1.3. Subject Withdrawal/Termination 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 treatment and/or study follow-up in the event of any of the following:

- Medical reasons considered significant by the subject, Investigator and/or the Sponsor, which may include, an adverse event (AE), inter-current illness or medical reasons unrelated to the study
- Nonmedical reasons (e.g., subject request or noncompliance with the treatment procedure as determined by the Investigator, the Sponsor and/or subject)
- Pregnancy
- Non-eligibility or on-study violation of the protocol

- Administrative or other reasons (e.g., lost to follow-up, non-compliance)

Should a subject decide to withdraw from the study at any point, all efforts should be made to complete all end of study assessments (see Section 12.3.3 for details). In case of questions surrounding the circumstances that a subject needs to be withdrawn from the study (e.g., protocol deviation), the Sponsor, or the Sponsor representative should be consulted. The reason for withdrawal should be documented in the subject's source document and in the Subject Disposition eCRF.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal before considering the subject to be lost to follow-up. Such efforts should include repeated telephone calls, certified letters, and email requests. The measures taken to follow-up must be documented.

11. STUDY INTERVENTION

11.1. Treatment Administration

All study treatments will be taken orally with up to 180 mL water.

11.2. Description and Administration of Investigational Products

A description of the IPs are provided in Table 3.

Table 3: Investigational Products

Product	**APAP/NPX** [redacted]	**APAP/NPX** [redacted]	**APAP/NPX** [redacted]	**APAP/NPX** [redacted]	**APAP/NPX** [redacted]	**Placebo**
Dosage Form	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Unit Dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA
Physical Description	[redacted] tablet, debossed with double circular arrows with lightning bolt inside the circle, on one side; opposite side plain	[redacted] tablet, debossed with double circular arrows with lightning bolt inside the circle, on one side; opposite side plain	[redacted] tablet, debossed with double circular arrows with lightning bolt inside the circle, on one side; opposite side plain	[redacted] tablet, debossed with double circular arrows with lightning bolt inside the circle, on one side; opposite side plain	[redacted] tablet, debossed with double circular arrows with lightning bolt inside the circle, on one side; opposite side plain	White oval shaped tablet
Manufacturer/Brand	Johnson & Johnson Consumer Inc	Johnson & Johnson Consumer Inc	Johnson & Johnson Consumer Inc	Johnson & Johnson Consumer Inc	Johnson & Johnson Consumer Inc	Patheon Inc. Manatai, PR

Abbreviations: APAP=acetaminophen; NA=not applicable; NPX=naproxen sodium

11.3. Packaging and Labeling

Product will be provided in subject specific wallets containing two count blisters. Each subject specific wallet will be labeled with two panel Sponsor study label. The second panel will contain an unblinding panel. The unblinding panel should be removed prior to subject dispensation and stored with the site's Pharmacy (IP) binder.

11.4. Preparation, Handling and Disposal

Investigational products and placebo will be packaged in blister packs. Each pack will have a sufficient supply for the duration of the study for one subject. The Sponsor will label the blister packs for use per the standard operating procedures (SOPs). The pack will have a two panel label with a perforation between Panels I and II. Panel I will provide study-related information, instructions for use, storage conditions, and randomization number. Panel II will include a concealed scratch off sticker containing the treatment assignment for each subject. Panel II of the label should be removed at the perforation line and attached to the site's Pharmacy (IP) binder prior to dispensing the kit to the subject. The scratch off unblinding panel should not be removed from the label and the integrity of the scratch off surface should be preserved. 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.

Investigational product preparation and dispensing will be performed on Day 1, following dental surgery (within 4.5 hours of last stitch from dental extractions). For subjects who meet the randomization criteria, an independent dispenser will administer one of the following study treatments with up to 180 mL of water at ambient temperature to blindfolded subjects:

- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as a two tablets of Acetaminophen/Naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as a two tablets of acetaminophen/naproxen sodium [redacted])
- [redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])
- Placebo (administered as two placebo tablets)

Baseline pain assessments and drug administration will be completed in the subject's room. The unblinded dispenser will bring the assigned blister pack to the designated dispensing room. Study medication will be dispensed at the time that the subject's pain level is

determined to be eligible by verbal assessment, just prior to the completion of the baseline categorical pain severity scale and the baseline 11-point (0-10) PI-NRS. The blinded study coordinator will communicate the subject's pain severity and gender to the unblinded team. The unblinded team (unblinded dispenser and unblinded witness) will pull the Pharmacy (IP) Binder & prepare the IP. The unblinded team assigns the appropriate randomization number from the IP Binder. The unblinded dispenser will take out a total of one blister pack (containing two tablets, per assigned treatment group), remove Panel II from the blister pack and dispense the appropriate study treatment. The double-blind label with the randomization number will be affixed to the blister packs and the tear-off portion of the label will be placed in the site's Pharmacy (IP) binder. The unblinded 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 team, back-up staff member, and unblinded 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 unblinded team will inform the blinded study coordinator once the study drug is ready to be administered to the subject. Following completion of the baseline categorical pain severity scale and baseline PI-NRS, the study coordinator will blindfold the subject and then exit the subject's room to inform the unblinded team 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 PI-NRS score qualifies the subject for randomization. If the baseline categorical pain severity has changed, randomization numbers will not be re-used and an undispensed treatment previously prepared will be quarantined. If the severity has changed and the original treatment prepared is not administered, then the unblinded team will check the box: No, Quarantined under the Dosed column on the IP Dispensing and Accountability Log. The unblinded team will complete the quarantined log for the applicable treatment group. The unblinded dispenser will deliver the study drug from the designated dispensing room to the subject's room. No other study personnel, other than the unblinded witness and dispenser, will be present in the subject's room at the time of dosing.

After entering the blindfolded subject's room and while the subject is sitting up, the dispenser will empty the contents of the blister pack into a dosing cup and 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 his/her 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 all study medication will be recorded as Time 0. Study drug will be administered to the subject within five minutes of the completion of the baseline pain assessments. Subjects that have received rescue medication will be prohibited from operating a motor vehicle when leaving the investigational site for any reason, and will be advised to avoid driving a motor vehicle within 24 hours of the last dose of rescue medication.

If a subject vomits after dosing, the subject will not be re-dosed but will remain in the study. Any post-dose emesis should be documented in source or progress notes to inform ultimate data analysis.

At the end of the study, the Sponsor will provide instructions as to disposition of any unused IP. If the Sponsor authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

11.5. Storage and Accountability

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

The Investigator, or assigned representative, must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP on the Investigational Product Accountability Log supplied by the Sponsor. The log must identify the IP 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 IP, and copies must be provided to the Sponsor. All IP and IP 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 unblinded Monitor. The study site must maintain accurate and adequate records including shipment receipt and return of unused IP shipments.

11.6. Randomization/Treatment Allocation

The randomization schedule will be generated by the Sponsor to ensure treatment blinding. After meeting the appropriate post-surgery criteria, subjects will be randomized to receive one of six treatments ([redacted] acetaminophen/[redacted] naproxen sodium, [redacted] acetaminophen/[redacted] naproxen sodium, [redacted] acetaminophen/[redacted] naproxen sodium, [redacted] acetaminophen/[redacted] naproxen sodium, [redacted] acetaminophen/[redacted] naproxen sodium, and placebo in a 1:1:1:1:1:1 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.

Randomized subjects will receive their dose of IP, which will be considered Time 0. The administration of IP should occur as described in Section 11.4. Site staff will inspect the subject's oral cavity to ensure that the IP was swallowed.

11.7. Blinding and 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 eCRF and in the source document. Any AE or serious adverse event (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.

11.8. Treatment Compliance

All subjects randomized to treatment in this study will be in compliance with treatment if they take the dose of study medication.

11.9. Previous and Concomitant Medications

Medications and other treatments that are taken from 30 days prior to Screening until the end of the 24-hour assessment period will be recorded in the source documents and eCRF.

Additional postsurgical medications (e.g., antibiotics or analgesic prescriptions) and other treatments or therapies (e.g., ice packs) that are taken after the 24-hour assessment period through the follow-up interview will be captured on the source documents, but not in the eCRF. However, concomitant medications and other treatments taken for or associated with an AE will be recorded on the eCRF and the source documents.

11.9.1. 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.

11.9.2. Prohibited Therapies

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

11.10. Rescue Therapy

If adequate pain relief is not achieved, subjects are allowed to take rescue medication. Oxycodone IR 5 mg every four to six hours as needed for pain; not to exceed 30 mg in 24 hours, may be used. Subjects will complete pain assessments by rating pain intensity, pain relief [redacted] immediately before the initial dose of rescue medication. [redacted]

11.11. 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 Study Manager via a completed PQC form and telephone call. The Study Manager will then send the completed PQC form to the Clinical Supply Manager. During the PQC process, the Study Manager can assist or answer any questions the site may have. If a photograph is required to better understand the nature of the PQC, the site should send the photograph directly to the Study Manager who will then forward it to the Clinical Supply Manager.

12. STUDY PROCEDURES

12.1. Overview

The Schedule of Activities (Section 2) 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.

12.2. Screening Visit

Informed consent/assent will 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 prior to Screening)

- Vital signs: resting blood pressure, heart rate, respiratory rate, and oral temperature
- Physical examination: height, weight and 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
- Urine pregnancy test for females with childbearing potential
- Safety monitoring

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

12.3. Study Visits (Periods)

12.3.1. 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, only the data collected at Baseline will be recorded on the eCRF.

- Inclusion and exclusion criteria
- Any changes to medical and surgical history
- Any changes to prior and concomitant therapies
- Vital signs: resting blood pressure, heart rate, respiratory rate, oral temperature
- Postsurgical trauma assessment
- Categorical and Numerical Pain Intensity
- Urine drug screen test. A negative urine drug screen must be obtained on the same day as the surgical procedure
- Urine pregnancy test on females with childbearing potential. A negative urine pregnancy test (for women of childbearing potential) must be obtained on the same day as the surgical procedure
- Investigational product administration
- Safety monitoring

12.3.2. Post-dose Assessments (0-24 Hours)

Post-dose assessments includes the following procedures (please refer to Section 13 for details):

- Randomization
- Pain intensity and pain relief ratings

- [redacted]
- Concomitant medication
- Safety monitoring and recording
- Subject disposition
- [redacted]

After the dental procedure, subjects will be asked to rest quietly at the study center until they experience both post-surgical pain of moderate to severe on a four-point categorical 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 screen failures.

[redacted]

[redacted] Pain intensity and pain relief will be assessed using the NRS (Appendix 1) at 0.25, 0.5, 0.75, 1, 1.25, 1.5, hourly from 2 through 12 hours, and every 4 hours from 12 through 24 hours (±5 minutes) post-dose as well as [redacted] at the time of first rescue (if applicable, before administration).

[redacted] Subjects who use rescue medication will continue in the study and assess pain and relief [redacted].

[redacted]

12.3.3. Follow-Up Phone Call (Days 7 to 10)

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 Days 7 to 10. At least three attempts should be made to contact the subject by phone. If the subject cannot be contacted by phone by Day 10, then a certified letter should be mailed to the subject. Every effort will be made by the Investigator or designated study staff to adhere to the schedule.

During the follow-up call, a follow-up interview will be conducted and information pertaining to safety monitoring (AEs) and concomitant medications will be collected.

12.4. End of Study for Subject

End of Study for each subject is defined as the follow-up phone call or early termination. For subjects whose participation is discontinued during this study, end of study evaluations will be completed as soon as possible after discontinuation.

12.5. COVID-19 Pandemic Response Plan

Regulatory authorities have recognized that the COVID-19 pandemic may impact the conduct of clinical studies of medical products. Challenges may arise, e.g., from quarantines, site closures, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the IP or adhering to protocol-mandated visits and laboratory/diagnostic testing. To accommodate these challenges and mitigate safety risks associated with COVID-19, protocol modifications will be required.

Johnson & Johnson COVID-19 guideline document entitled, "Guidelines for Resuming Clinical and Consumer Science Studies" will be shared with the Investigator for review and sign off prior to study start. Any changes to the guidelines during the conduct of the study will also require sign off by the Investigator. The signed version(s) of these guidelines will be maintained by the site and a copy will be included in the Trial Master File.

12.6. Life Style Restrictions

12.6.1. Meals and Dietary Restrictions

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

12.6.2. Alcohol, Caffeine and Tobacco 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.

12.6.3. Physical Activity Requirements/Restrictions

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

12.6.4. Contraception for Females

Female subjects with reproductive potential must agree to practice a medically acceptable form of birth control throughout the study and for 30 days following the last dose of IP, whichever is later.

Medically acceptable forms of birth control that may be used by the subject and/or his/her partner include:

- 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 IP
- Barrier methods of contraception with spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/ film/ cream/ suppository
- Intrauterine device (IUD) or intrauterine system
- Surgical sterilization (e.g., vasectomy that has been confirmed effective by sperm count check, tubal occlusion, hysterectomy, bilateral salpingectomy)
- 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

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

- Had a hysterectomy and/or bilateral oophorectomy at least six months prior to product administration
- Had sterilization surgery (e.g., hysteroscopic sterilization/tubal implants or tubal ligation) at least six months prior to Screening; tubal implants must have been confirmed effective by medical assessment as reported by the subject
- Are postmenopausal (i.e., amenorrheic for at least 12 consecutive months, without an alternative medical cause, prior medical Screening by a healthcare provider)

12.6.5. Contraception for Males

Male participants will be informed about potential risks of the study medication for embryos and fetuses.

Male subjects are instructed to practice a medically acceptable form of birth control from the first dose of study medication until at least 30 days after the last dose of study drug in order to prevent their partner from becoming pregnant. Medically acceptable forms of birth control that may be used by the subject and/or his/her partner are described in Section 12.6.4. Information about effective means of birth control (hormonal contraception, IUDs, vasectomy, sexual abstinence) will be provided, and discussed as appropriate with individual subjects.

13. ASSESSMENTS

13.1. 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, hourly from 2 through 12 hours, and every 4 hours from 12 through 24 hours (±5 minutes) post-dose as well as [redacted] the time of first rescue (if applicable, before administration). 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 as well as at time of [redacted] first rescue (if applicable, before administration).
- Pain relief: 0-10 pain relief-numerical rating scale (PR-NRS) collected at each time point as well as [redacted] at the time of first rescue (if applicable, before administration).
- [redacted]
- Time to first use of rescue medication : time when rescue medication was administered.
- [redacted]

[redacted]

13.2. 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 AE Reporting section of the protocol.

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

13.2.1. Physical Examination

Height and weight measurements will be collected at Screening and BMI will be calculated.

13.2.2. Vital Signs

Vital signs will be collected at Screening and Baseline. All vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) will be collected after at least five 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 heart 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.

13.2.3. Clinical Laboratory Tests

Females of childbearing potential will undergo a urine pregnancy atScreening visit and at Baseline. Serology will be performed at Screening for all participants and will include HIV antibody, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV). A urine drug screen will also be performed at Screening and Baseline. The minimum requirements for urine drug testing include cocaine, tetrahydrocannabinol, opioids (e.g., buprenorphine, oxycodone, methadone, and morphine), benzodiazepines, and amphetamines.

14. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting of safety information from clinical studies are crucial for the protection of subjects, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. All observed or volunteered AEs regardless of suspected causal relationship to the IP(s) will be reported as described in the following sections. For all

AEs, the Investigator or medically qualified individual (MD/DO/DMD/DDS) must pursue and obtain adequate information to make the appropriate assessments.

14.1. Reporting Period

All AEs, whether serious or non-serious, observed or spontaneously reported will be recorded on the eCRF in the AE section beginning from the time the informed consent/assent is signed and dated. Subject's participation in the clinical study begins at signing the informed consent. All AEs are recorded even if the AE occurs prior to the subject's participating in any study-related procedure and/or receiving IP. Nonserious AEs will be reported through the subject's last study visit (or termination if the subject terminates early from the study for any reason). Spontaneous reports of SAEs will be collected through and including 30 calendar days after administration of the subject's last dose or exposure to IP.

Serious adverse events require immediate notification to the Sponsor or its designated representative. Any SAE occurring any time after the reporting period (30 calendar days post IP exposure or last dose) must be promptly reported if a causal relationship to study product is suspected.

14.2. Definitions

14.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence that occurs in a subject after they have signed an informed consent for a study. The event does not need to have a suspected causal relationship with the IP. Therefore, an AE can be any unfavorable and unintended sign, symptom, disease or injury temporally associated with the subject's participation in the study. Examples of AEs include, but are not limited to:

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

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

- Overdose
- Withdrawal
- Abuse
- Drug misuse
- Drug interactions
- Medication errors

- Product dependency
- Exposure in utero
- Study related procedure

14.2.1.1. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention beyond ordering a repeat (confirmatory) test, 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 medically qualified Investigator or designee 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.

14.2.2. Definition of Serious Adverse Events (SAE) for Drugs

An AE or suspected adverse reaction is considered "serious" for a drug study if, in the view of either the medically qualified Investigator or designee (MD/DO/DMD/DDS) 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"

14.2.2.1. Hospitalization

AEs 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)
- Same day surgeries (as outpatient/same day/planned procedures)
- Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an 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.

14.3. Adverse Event Assessments

Sufficient information should be obtained for each AE to allow the Investigator or medically qualified individual to make assessments as described below.

14.3.1. Severity Assessment

The severity of AEs will be assessed by the medically qualified Investigator or designee using the following general categorical descriptors:

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

MODERATE: Sufficient discomfort is present to cause interference to some extent with the 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 the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

14.3.2. Causality Assessment

The medically qualified Investigator’s assessment of causality to IP (i.e., relationship to IP) must be provided for all AEs (serious and non-serious). The causality assessment is the determination of whether there exists a reasonable possibility that the IP 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 IP 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 IP 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.

Any AE that occurs after the informed consent has been signed, until first usage of IP, will be considered non-treatment emergent and cannot (by virtue of time of occurrence) have a causal relationship with the IP.

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

14.3.3. Resolution

The medically qualified Investigator or designee will be required to assess the outcome of the AE for IP as one of the following:

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

Any causally-related AEs that are not resolved 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 medically qualified Investigator or designee, and recorded on the eCRF. An event that is assessed as resolved with sequelae or resolving indicates that the subject has stabilized to a level acceptable to the medically qualified Investigator or designee and has concurrence by the Sponsor.

14.4. Adverse Event Reporting

14.4.1. Time Period

All AEs, whether serious or non-serious, will be collected starting from the time a subject signs and dates an informed consent until the completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Spontaneous reports of serious AEs will be collected through and including 30 calendar days after subject's last dose of IP. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study product is suspected.

If a subject develops COVID-19 during the conduct of the study, it will be considered an AE. The subject will be instructed to inform the site if diagnosed with COVID-19 during the conduct of the study.

14.4.2. Process for Reporting

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

All AEs, serious or non-serious, will be recorded on the source documents; e.g., written documentation, electronic medical records, subject diaries, or journals. Adverse events will be entered into eCRFs for screen failure subjects as well as randomized subjects. AEs should be reported using concise medical terminology on the eCRFs. Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting is required.

14.4.2.1. Serious Adverse Event Reporting

A Clinical SAE Report Form must also be completed if the event is considered to be serious. Where the same data are collected, the Clinical SAE Report Form and the AE eCRF must be completed in a consistent manner. For example, the same AE term should be used on both forms.

If an SAE occurs, the Sponsor or designee must be notified by telephone, email or fax immediately upon awareness of the event by the Investigator's site and the SAE documented on the source document. Within 24 hours of the Investigator site's awareness of the event, the study site must send the Sponsor the Clinical SAE Report Form (via a secure e-mail or fax). This timeframe also applies to additional new information (follow-up) on previously reported SAEs as well as to the initial and follow-up reporting of Exposure In Utero (EIU) cases. In the rare event that the Investigator's site does not become aware of the occurrence of an SAE immediately (e.g., in a telephone contact, in a subject diary or journal, or 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 date and time of the study site's first awareness of the AE in the Subject's file.

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 AE eCRF. 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.

14.4.2.2. Contacts for Serious Adverse Event Reporting

Study Contacts for reporting can be found on the Study Contact List kept in the Site Master File.

All nonserious AEs are to be reported on the AE eCRFs and will be submitted to the Sponsor.

14.5. Suspected Unexpected Serious Adverse Reaction

If the Sponsor judges an SAE to be a Suspected Unexpected Serious Adverse Reaction (SUSAR), the Sponsor will report it to the Regulatory Authority(ies) and the Investigator (or Sponsor) must report to the IRB/IEC as required and in accordance with the Sponsor's SOPs for safety reporting.

14.6. Special Situations

Special Situations are safety events that may not meet the definition of an AE; however, from a policy perspective, they are treated in the same manner as AE and recorded in the source document. Examples include:

- Pregnancy exposure (maternal and paternal) to a J&J product, see next section.
- Off-label use of a J&J product. *Note: Off-label use of a product without an associated AE should be collected only when it is specifically and voluntarily brought to the attention of the company in an unsolicited manner by a reporter (e.g., Patient or Health Care Professional), or data obtained from databases where off-label use may be systematically collected (e.g., reimbursement database in US), and in accordance with local procedure in compliance with local laws and regulations.*
- Overdose of a J&J product.
- Exposure to a J&J product from breastfeeding.
- Suspected abuse/misuse of a J&J product.
- Inadvertent, accidental exposure, or occupational exposure to a J&J product.
- For marketed products, any failure of expected pharmacological/therapeutic action (i.e., lack of effect) of a J&J product. Lack of effect/Lack of efficacy defined as any failure that a product did not achieve expected pharmacological action/therapeutic benefit when used in accordance with the Reference Safety Information or equivalent. In the context of complaint intake, lack of effect shall be reported if there is specific evidence that the reporter did not think the product

achieved expected pharmacological action/therapeutic benefit evidenced by statements such as or similar to "the product did not work/perform as expected".

- Medication error involving a J&J product (with or without subject exposure to the J&J product, e.g., product name confusion).
- Unexpected therapeutic or clinical benefit from use of a J&J product.

14.6.1. Exposure In Utero

An exposure in utero (EIU) occurs if:

1. A woman is exposed to the IP 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 IP via semen from the male partner who is taking/using the IP at the time of conception, thereby possibly exposing the fetus to the product.

If an EIU occurs, the Investigator or designee should inform the Sponsor immediately. This must be done irrespective of whether an AE has occurred. The site must complete a Pregnancy Notification and Update Form and send it securely 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). This reporting requirements include environmental exposure to the IP 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). If a male participant informs about a partner's pregnancy, the site must obtain consent to follow that pregnancy.

Follow-up should be conducted to obtain pregnancy outcome information on all EIU reports. The Investigator will follow the pregnancy until completion or until the pregnancy terminated (i.e., induced abortion) and then notify the Sponsor of the outcome. The Investigator will provide any updated information as a follow-up using the Pregnancy Notification and Update Form, and will report the outcome on the End of Pregnancy Collection Form. 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, an SAE case is created with the event of ectopic pregnancy.

The medically qualified Investigator or designee (MD/DO/DMD/DDS) should follow the procedures for reporting SAEs if the outcome of the pregnancy meets the criteria for immediate classification as an 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 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 EIU to the IP.

14.7. Withdrawal Due to Adverse Events

When a subject withdraws due to AEs, whether serious or not the AEs must be reported in accordance with the reporting requirements defined below.

15. 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.

15.1. Determination of Sample Size

The total sample size of 300 subjects (50 per treatment group) provides 90% probability that the model-based estimated SPID 0-12 for at least one of the combination doses included in the study design will be statistically significantly higher than the estimate for each corresponding monotherapy, based on one-sided α=0.01 for each comparison and a regression model accounting for acetaminophen, naproxen, and acetaminophen-by-naproxen interaction effects. Power was estimated using simulations assuming an E_{max} dose response for the monotherapies, maximum effect sizes of 0.6 for acetaminophen and 1.4 for naproxen over the doses in this study, and an interaction index that provides for slightly less than an additive effect for each monotherapy component. Effect size is defined here as the difference between the active and placebo means divided by the standard deviation. Maximum effect sizes and assumptions regarding interaction were based on a previous proof-of-concept study and acetaminophen and naproxen monotherapy studies.

15.2. Analysis Sets

15.2.1. Efficacy Analysis Sets

The primary efficacy analyses will be based on the Intent-to-Treat analysis set, which will include all randomized subjects. As a secondary analysis, the primary endpoint will be analyzed based on the per-protocol analysis set, if the per-protocol analysis set differs from the Intent-to-Treat analusisset by at least 5% of the subjects. The final per-protocol analysis set will be determined before unblinding.

15.2.2. Safety Analysis Population

The Safety Analysis Set will include all subjects who are randomized and take IP.

15.3. 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.

15.4. 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 and up through the 24-hour assessment period. In addition, those medications taken after the 24-hour assessment period through the follow-up interview for an AE will be considered concomitant medications. Medications taken after the 24-hour assessment through the follow-up call that were not taken for an AE will not be collected on the eCRF 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.

15.5. Efficacy Analysis

15.5.1. Efficacy Endpoints

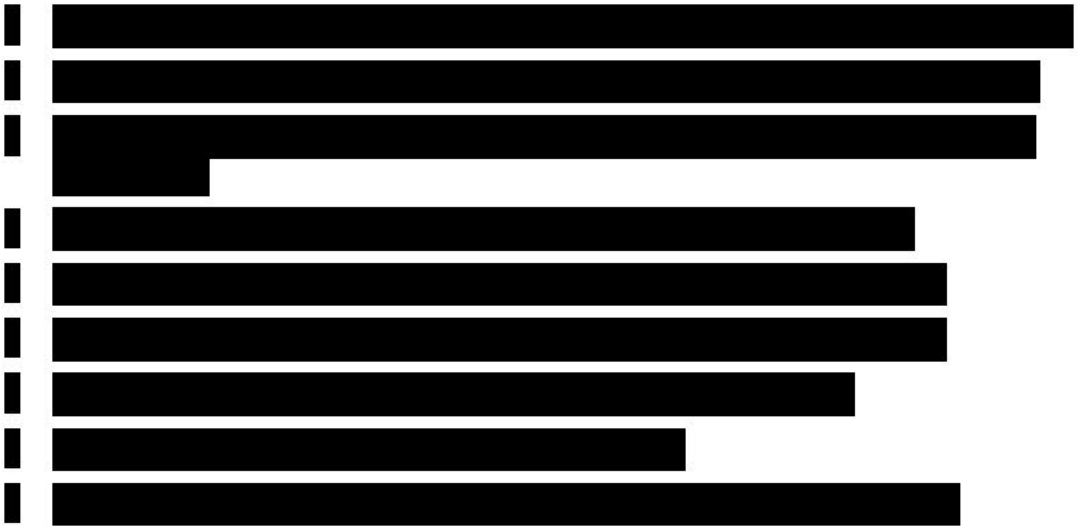
15.5.1.1. Primary Efficacy Endpoint

- Time weighted sum of pain intensity difference from 0-12 hours after dosing (SPID 0-12)

15.5.1.2. Secondary Efficacy Endpoints

- Time weighted sum of pain relief from 0 to 12 hours (TOTPAR 0-12)
- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first use of rescue analgesic (duration of relief after dosing)
- Proportion of subjects who required rescue analgesic

15.5.1.3. [redacted]



15.5.2. Statistical Hypotheses

For the primary endpoint, SPID 0-12, each strength of the fixed combination will be compared with the corresponding monotherapy doses by fitting the following regression model to the observed data:

$\mu_{xy} = f(x,y) = \alpha + \beta_1 x + \beta_2 y + \beta_3 xy$

where:

x = (continuous) acetaminophen dose

y = (continuous) naproxen dose

μ_{xy} = SPID 0-12 as a function of acetaminophen dose x and naproxen dose y

α = intercept

β_1 = slope term associated with acetaminophen dose

β_2 = slope term associated with naproxen dose

β_3 = interaction slope term

Comparisons based on this model will test the following hypothesis for each tested strength of the fixed combination:

$H_{0:}: \mu_{xy} = \max(\mu_{x0}, \mu_{0y})$

$H_{1:}: \mu_{xy} > \max(\mu_{x0}, \mu_{0y})$

Each comparison of fixed combination with monotherapy will be tested at α=0.01, one-sided, in order to control the familywise error rate at approximately 10%, one-sided.

For endpoints based on pain intensity (such as SPID), endpoints based on pain relief (such as TOTPAR), [redacted] each strength of the fixed combination will be compared with placebo by testing the following hypotheses:

$H_0: \eta_1 = \eta_2$
$H_1: \eta_1 \neq \eta_2$

where η_1 is the population mean for the strength of the fixed combination and η_2 is the population mean for placebo.

For time-to-event endpoints (time to first use of rescue analgesic [redacted]), each fixed combination will be compared with placebo by testing the following hypotheses:

$H_0 : S_1(t) = S_2(t)$ (all t)
$H_A : S_1(t) \neq S_2(t)$ (at least some t)

where S_1(t) is the survival function for the fixed combination and S_2(t) is the survival function for placebo.

Each pairwise comparison with placebo will be performed at α=0.05, two-sided.

15.5.3. Data Computations and Handling of Missing Values

15.5.3.1. Endpoints Relating to Pain Intensity and Pain Relief

The 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.

The SPID scores will be derived by first multiplying each PID score by the time from the previous time point, and adding these time-weighted PID scores together over the intervals from [redacted] 0-12, 6-12 [redacted] hours. The 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 before taking rescue medication 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.

15.5.3.2. Time to First Rescue

Time to first use of rescue medication will be measured as the elapsed time from when the IP was given until the time, rescue medication was first given. Subjects who discontinue from the study before 24 hours, but do not use rescue medication, will be censored at the time of discontinuation. Subjects who do not use rescue medication during the 24-hour study period will have their time to first rescue set to 24 hours and be censored at 24 hours.

15.5.3.3. [redacted]

15.5.3.4. [redacted]

15.6. Analysis Methods

15.6.1. Analysis of Primary Endpoint

SPID 0-12

For the primary endpoint, SPID 0-12, the dose response will be assessed by fitting a linear regression model with SPID 0-12 as the response variable, including terms for acetaminophen dose, naproxen dose, and acetaminophen by naproxen interaction, as further described in Section 15.5.2. Based on this regression model, the model-based means for each strength of fixed combination and corresponding monotherapy doses will be estimated and statistically compared. Pairwise comparisons will be made using an analysis of variance (ANOVA) with baseline pain (moderate or severe) score, gender, and treatment group. Analyses for SPID 0-12 will use imputation methods defined in Data Imputations Section 15.5.3.

15.6.2. Analysis of Secondary Endpoints

SPID 6-12 and TOTPAR 0-12

Each of these endpoints will be analyzed using an ANOVA with baseline pain (moderate or severe), gender, and treatment group in the model using imputation methods defined in Data Imputations Section 15.5.3. Missing data will not be imputed for subject global evaluation.

Time to First Rescue

Kaplan-Meier estimates of cumulative percentage of subjects rescuing will be presented by treatment group in tabular and graphical formats. The survival function (cumulative proportions of subjects at each time point) and the median time to first rescue will be

estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared between fixed combinations and placebo using the Wilcoxon test stratified by baseline pain (moderate or severe) and gender.

Proportion of subjects who required rescue analgesic

The proportion of subjects requiring rescue medication through 24 hours will be estimated using the Kaplan-Meier method, and standard errors will be approximated using the Greenwood method. This method will be used for this endpoint due to the censoring that may occur at times between 0 and 24 hours. The analysis will be adjusted for baseline pain (moderate or severe) and gender by obtaining the Kaplan-Meier estimates and Greenwood approximation within each stratum and then combining across strata. Further details will be provided in the Statistical Analysis Plan.

15.6.3. [redacted]

[redacted]

15.6.4. Subgroup Analysis

Primary endpoint (SPID 0-12) 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). Each will be analyzed with an ANOVA with treatment group in the model using imputation methods defined in Data Imputations Section 15.5.3.

15.6.5. [redacted]

15.7. Safety Analysis

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

15.7.1. 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 Medical Dictionary for Regulatory Activities (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 AEs (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 AEs 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.

15.7.2. Vital Signs

Vital signs (temperature, respiratory rate, heart rate, and blood pressure) collected at Baseline will be summarized (number of subjects, mean, standard deviation, median, minimum and maximum) by treatment group.

15.8. Interim Analysis

Not applicable.

16. STUDY MONITORING

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

- Determine the adequacy of the facilities

- Discuss with the Investigator(s) and other personnel their responsibilities the site's responsibility with regard to protocol adherence as well as the study and monitoring responsibilities of J&J or its representatives. These responsibilities will be documented in a Clinical Study Agreement between J&J and the Investigator.

During the study, a Monitor from J&J 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 rights and well-being of subjects are taken care of
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that IP 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 source documents, e.g., written medical records, electronic medical records at the hospital or practice, subject diaries/journals 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 J&J. The Investigator should not deviate from the protocol except if specified by the Sponsor or within the protocol.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to J&J and those SAEs that met criteria for reporting to Regulatory Authority/Competent Authority and/or IRB/IEC, as applicable, have been forwarded to the required authorities. The Monitor will be available between visits if the Investigator(s) or other staff needs information or study-related direction.

16.1. Direct access to source data/documents

The Sponsor should ensure that it is specified in the protocol or other written agreement that the Investigator(s)/institution(s) shall permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

17. QUALITY CONTROL AND QUALITY ASSURANCE

The clinical study will be executed and reported following GCPs, all applicable regulatory requirements and applicable SOPs, including quality control of documents. Deviations will be analyzed and documented. To ensure compliance, the Sponsor may conduct one or several quality assurance audit(s). Please see Section 17.1 for more details regarding the audit process.

17.1. Audits and Inspections

Authorized representatives of J&J, a regulatory/competent authority, an IRB/IEC representative may visit the site to perform audits or inspections, including source data verification. The purpose of a J&J 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, GCP guidelines of the ICH E6, and any applicable regulatory requirements. The Investigator should notify the Sponsor (e.g., Study Manager, Monitor) listed within the protocol or other contacts provided immediately if contacted by a regulatory agency about an inspection.

18. DATA HANDLING AND RECORDKEEPING

18.1. Case Report Forms/Electronic Data Capture

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, AEs, and subject disposition. EDC eCRFs 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, review and approval of 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 eCRF must be supported by source documents.

18.2. Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site’s study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

18.3. Inspection of Records

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., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition.

18.4. Retention of Records

The PI must maintain all documentation relating to the study according to ICH/GCP guidelines or as specified in the Clinical Study Agreement for a period of two years after the last marketing application approval or per local requirements if longer than two years, or if not approved two years following the discontinuance of the test article for investigation. If it becomes necessary for J&J or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

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, e.g., another Investigator. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

19. 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.

20. LIST OF REFERENCES

1. Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. Clin Pharmacokinet. 1997;32:268-293.
2. Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet. 1982;7:93-107.
3. Paracetamol. In: Sweetman S, ed. Martindale - The Complete Drug Reference. London, UK: The Pharmaceutical Press. 37th ed. 2011:76-79.
4. [redacted]
5. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191-2194.

21. 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. [redacted]

[redacted]

APPENDIX 3A. [redacted]

[redacted]

APPENDIX 3B. [redacted]

[redacted]