Status : Approved

CLINICAL STUDY PROTOCOL

CCSPAA005199

A Full-Factorial, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Single-Dose Efficacy and Safety Study of an Acetaminophen/Naproxen Sodium Fixed Combination, Acetaminophen, and Naproxen Sodium in Postoperative Dental Pain

Investigational Product Name	Acetaminophen/Naproxen Sodium
Protocol Number	CCSPAA005199
IND / IDE / EudraCT number	[redacted]
Phase	Phase III
Version and Date	Amendment #5; Version: 6.0, 24/JUN/2024 Amendment #4; Version: 5.0, 08/FEB/2024 Amendment #3: Version: 4.0, 05/JUN/2023 Amendment #2: Version: 3.0, 21/FEB/2023 Amendment #1: Version: 2.0, 30/JAN/2023 FINAL Date: Version 1.0, 18/JAN/2023

This document contains privileged and confidential information belonging to the Sponsor. Except as otherwise agreed to in writing, by accepting or reviewing this document, you agree to hold the information contained herein in confidence and not copy or disclose it to others (except where required by applicable law) or use it for unauthorized purposes. In the event information is disclosed to others, as required by applicable law, they must be informed that the information is privileged and confidential and may not be further disclosed by them. These restrictions on disclosures will apply equally to all future information supplied to you that is indicated as privileged and confidential. You agree that no unpublished information contained herein will be published or disclosed without the prior written approval of Sponsor. In the event of any actual or suspected breach of this obligation, Sponsor must be promptly notified.

Status : Approved

1. SYNOPSIS

Name and Address of the Sponsor/Company of the clinical study: Johnson & Johnson Consumer, Inc. (JJCI) [redacted]
Active Ingredient(s): Acetaminophen/Naproxen Sodium
Title of Study: A Full-Factorial, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Single- Dose Efficacy and Safety Study of an Acetaminophen/Naproxen Sodium Fixed Combination, Acetaminophen, and Naproxen Sodium in Postoperative Dental Pain
Countries: United States of America
Study Site: [redacted]
Principal Investigator (PI): [redacted]
Phase of Development: Phase III
Objectives: **Primary**: To evaluate the analgesic efficacy of a fixed combination of acetaminophen/naproxen sodium, compared with acetaminophen, naproxen sodium and placebo over 12 hours. **Secondary**: To evaluate the duration of analgesic effect of a fixed combination of acetaminophen/naproxen sodium. **Safety**: To evaluate the safety of a fixed combination of acetaminophen/naproxen sodium. [redacted]

Status : Approved
Version :

Methodology:

This will be a randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and safety of a fixed combination of acetaminophen/naproxen sodium, compared with acetaminophen, naproxen sodium, and 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 determined by the surgeon 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.

Approximately 440 subjects who meet the randomization criteria (post-surgical pain of moderate to severe on the fourpoint 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 randomized. No less than approximately 30% of randomized subjects will be either male or female.

To maintain the double-blind nature of the study, all tablets in the study will be over-encapsulated and placebo (an inert powder) will be encapsulated in identical opaque capsules to ensure that they are indistinguishable.

Upon randomization, subjects will be assigned to one of the following treatment groups, with 4:4:2:1 allocation:

- Acetaminophen /Naproxen Sodium
- Naproxen Sodium
- Acetaminophen
- Placebo

All treatments will be administered as a single dose.

Rescue analgesic medications include:

- First-line rescue analgesic medication (celecoxib 400 mg initial dose, which can be followed by celecoxib 200 mg 12 hours after the initial dose, if needed; not to exceed 600 mg in 24 hours) will be available for subjects as needed for intolerable pain.

Status : Approved

- Second-line rescue analgesic medication (oxycodone immediate release 5 mg every four to six hours as needed; not to exceed 30 mg in 24 hours) will be available for subjects as needed for intolerable pain only during the 12-hour therapeutic window after any dose of the first-line rescue medication. If intolerable pain occurs beyond 12 hours after the initial dose of the first-line rescue medication, then the second dose of first-line rescue medication will be administered before proceeding with any additional doses of second-line rescue medication that may be needed.

Self-reported pain intensity will be collected using a four-point categorical pain scale and a 0-10 PI-NRS at Baseline (Time 0). Pain intensity (using PI-NRS) [redacted] will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5 hours, hourly from 2 through 12 hours (±5 minutes; hour 12 inclusive), and every 4 hours from 12 through 24 hours (±7 minutes) post dose as well as [redacted] and prior to each use of rescue analgesic (if applicable). [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 440 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 16 to 50 years of age (inclusive) at the time of Screening.
2. If female and of childbearing potential have a negative urine pregnancy test 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):

Status : Approved

- 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 the oral surgical procedure.
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 14.6.4 Contraception for Females and Section 14.6.5 Contraception for Males.
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 oral 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), celecoxib (or other sulfonamides), acetaminophen, oxycodone, or other opioids.
5. Are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin).
6. 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.

Status : Approved

7. Are not able to swallow whole large tablets or capsules.
8. Routinely use oral analgesics ≥ 5 times per week.
9. 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).
10. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last two years.
11. 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.
12. Used vitamins, dietary or herbal supplements within five days before the oral surgical procedure.
13. 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 the oral surgical procedure.
14. Used alcohol within three days before the oral surgical procedure.
15. 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.
16. Used monoamine oxidase inhibitors within 14 days prior to the oral surgical procedure.
17. Have a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV).
18. Have participated in any interventional clinical trials within 30 days before Screening.
19. Are related to those persons involved directly or indirectly with the conduct of this study (i.e., PI, Sub-Investigator(s), study coordinators, other site personnel, employees of Johnson & Johnson Consumer, Inc. [JJCI] subsidiaries, contractors of JJCI, and the families of each).

Test product(s), dosage and mode of administration:

- Acetaminophen [redacted] Naproxen Sodium [redacted]

All test products are to be taken as a single dose orally with up to 180 mL of water at ambient temperature.

Status : Approved

Comparator product(s), dosage and mode of administration:

- Naproxen Sodium [redacted]
- Acetaminophen [redacted]
- Placebo [redacted]

All comparator products are to be taken as a single dose orally with up to 180 mL of water at ambient temperature.

Duration of study per subject:

Ten (10) days, including Baseline (Day 1 [day of surgery]) and follow-up (Days 7 to 10), 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 to 12 hours after dosing (SPID 0-12)

Secondary Efficacy Endpoints:

- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first request for rescue analgesic
- Proportion of subjects who request rescue analgesic during the first 12 hours

[redacted]

Status : Approved

[redacted]

Safety:

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, resolves or stabilizes 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:

The primary endpoint, SPID 0-12, will be analyzed using analysis of variance including baseline pain (moderate or severe) score, gender, and treatment group in the model. The same approach will be used for all other endpoints based on PID [redacted] scores, [redacted]

[redacted]

The proportion of subjects requesting rescue medications will be based on the Kaplan-Meier method (to account for potential censoring) with standard errors estimated by the Greenwood formula.

Status : Approved

All statistical comparisons will be performed at the 5% significance level, two-sided. For primary and secondary endpoints, statistical testing will be carried out in a fixed-sequence approach as follows:

1. The following comparisons will be tested for SPID 0-12:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted]
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

   Acetaminophen [redacted] Naproxen Sodium [redacted] will meet efficacy requirements for SPID 0-12, and testing will proceed to secondary endpoints, only if the mean for Acetaminophen [redacted] Naproxen Sodium [redacted] is statistically significantly higher than the means for Placebo, Naproxen Sodium [redacted] and Acetaminophen [redacted]

2. The following comparisons will be tested for SPID 6-12:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

   Testing will proceed to the next secondary endpoint only if the mean for Acetaminophen [redacted] Naproxen Sodium [redacted] is statistically significantly higher than the means for Acetaminophen [redacted] and Placebo. [redacted]

3. The following comparisons will be tested for Time to First Request for Rescue Analgesic:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

   Acetaminophen [redacted] Naproxen Sodium [redacted] will meet efficacy requirements for Time to First Request for Rescue Analgesic only if the distribution for Acetaminophen [redacted] Naproxen Sodium [redacted] is statistically significantly different from the distributions for Acetaminophen [redacted] and Placebo, in favor of Acetaminophen [redacted] Naproxen Sodium [redacted]

4. The following comparisons will be tested for proportion of subjects requesting rescue within 12 hours:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.

Status : Approved

- Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

  Acetaminophen [redacted] Naproxen Sodium [redacted] will meet efficacy requirements for proportion of subjects requesting rescue within 12 hours only if Acetaminophen [redacted] Naproxen Sodium [redacted] has a statistically significantly lower proportion than Acetaminophen [redacted] and Placebo.

The above fixed-sequence procedure will provide strong familywise error rate control at 5% for the family of comparisons including primary and secondary endpoint pairwise comparisons, with the exception of comparisons between Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted] for SPID 6-12 and rescue-related endpoints. [redacted]
The rationale for excluding these comparisons from familywise error rate control is as follows: [redacted] The proposed dosing interval of the fixed combination product is no longer than the maximum labeled interval for existing over-the-counter (OTC) naproxen sodium products. [redacted]

Status : Approved

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 to 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			
Impaction evaluation (review of panorex x-ray)		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 [redacted] ratings[8]			X	
Rescue therapy			X	
[redacted]			[redacted]	
Prior and concomitant therapy	X	X	X	X
Safety monitoring	X	X[10]	X[10]	X[10]
Subject disposition	X[11]	X[11]	X[11]	X[11]
Follow-up interview				X

Abbreviations: AE=adverse events; BMI=body mass index; eCRF=electronic case report form; HIV=human immunodeficiency virus
Note: Admission and surgery of subjects will occur on Day 1. Discharge of the subjects will occur on Day 2 (24-hours post dose).

[1] Only Baseline assessments will be collected on eCRFs.
[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).

Status : Approved

[redacted]

[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.
[7] Scored within 4.5 hours after last stitch from dental surgery.

[redacted]

[10] Collection of AEs and report of pregnancy.
[11] Only collected at end of study. End of Study is at the time of follow-up call or at time of subject early termination, which will be documented in the source documents and Subject Disposition eCRF. In addition, for randomized subjects, early discontinuation during the 0 to 24- hour post-dose period will be documented in the source documents and the 24-hour post-dose observation status eCRFs.

Status : Approved

3. TABLE OF CONTENTS

1. Synopsis 2
2. Activity schedule 11
3. Table of Contents 13
5. List of Figures 17
6. List of Abbreviations and Definitions of Terms 18
7. Ethics ….....20
7.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) 20
7.2 Ethical and Regulatory Considerations 20
7.3 Subject Information and Consent 20
7.4 Subject Written Assent 21
8. Study Administrative Structure 21
9. Introduction 22
10. Study Objectives 23
10.1 Primary Objective(s) 23
10.2 Secondary Objective(s) 23
10.3 Safety Objective(s) 23
[redacted]
11. Investigational Plan 23
11.1 Overall Study Design and Plan 23
11.2 Discussion of Study Design 26
11.3 Sponsor Discontinuation Criteria 26
12. Study Population 27
12.1 Subject Eligibility 27
12.1.1 Subject Inclusion Criteria 27
12.1.2 Subject Exclusion Criteria 27
12.1.3 Subject Withdrawal/Termination Criteria 29
13. Investigational Products 30
13.1 Treatment Administration 30
13.2 Description of Investigational Products(s) 30
13.3 Packaging and Labeling 31

Status : Approved

13.4 Preparation and Handling 31
13.5 Storage, Accountability, and Disposal 33
13.6 Randomization/Treatment Allocation 33
13.7 Blinding and Unblinding 34
13.8 Communication Plan 35
13.9 Treatment Compliance 35
13.10 Previous and Concomitant Medications 35
13.10.1 Permitted Therapies 35
13.10.2 Prohibited Therapies 36
13.11 Rescue Therapy 36
13.12 Retention of Reserve Drug Product 36
13.13 Product Quality Complaints 36
14. Study Procedures 37
14.1 Overview 37
14.2 Screening Visit 37
14.3 Study Visits (Periods) 37
14.3.1 Baseline Visit (Day of Surgery) 37
14.3.2 Post-dose Assessments (0-24 Hours) 38
14.3.3 Follow-Up Phone Call (Days 7 to 10) 39
14.4 End of Study for Subject 39
14.5 COVID-19 Pandemic Response Plan 40
14.6 Lifestyle Restrictions 40
14.6.1 Meals and Dietary Restrictions 40
14.6.2 Alcohol, Caffeine and Tobacco Restrictions 40
14.6.3 Physical Activity Requirements / Restrictions 40
14.6.4 Contraception for Females 40
14.6.5 Contraception for Males 41
15. Assessments 41
15.1 Efficacy Assessments 41
15.2 Safety Assessments 42
15.2.1 Physical Examination 42

Status : Approved

15.2.2 Vital Signs....42
15.2.3 Clinical Laboratory Tests....43
16. Adverse Event Reporting....43
16.1 Definitions....43
16.1.1 Definition of Adverse Event....43
16.1.2 Abnormal Test Findings....44
16.1.3 Definition of Serious Adverse Events (SAE) for Drugs....44
16.1.3.1 Hospitalization....45
16.2 Adverse Event Assessments....46
16.2.1 Severity Assessment....46
16.2.2 Causality Assessment....46
16.2.3 Resolution....47
16.3 Adverse Event Reporting....47
16.3.1 Time Period....47
16.3.2 Process for Reporting....48
16.3.2.1 Serious Adverse Event Reporting....48
16.3.2.2 Contacts for Serious Adverse Event Reporting....49
16.4 Suspected Unexpected Serious Adverse Reaction....49
16.5 Special Situations....49
16.5.1 Exposure In Utero....49
16.6 Withdrawal Due to Adverse Events....50
17. Statistics....51
17.1 Determination of Sample Size....51
17.2 Analysis Sets....51
17.2.1 Efficacy Analysis Sets....51
17.2.2 Safety Analysis Population....51
17.3 Baseline and Demographics....51
17.4 Previous and Concomitant Medications....52
17.5 Efficacy Analysis....52
17.5.1 Efficacy Endpoints....52
17.5.1.1 Primary Endpoint(s)....52

Status : Approved

17.5.1.2 Secondary Endpoints 52
[redacted]
17.5.2 Statistical Hypotheses 53
17.5.3 Data Computations and Handling of Missing Values....55
17.5.3.1 Endpoints Relating to Pain Intensity [redacted] 55
17.5.3.2 Time to First Request for Rescue....56
[redacted]
17.6 Analysis Methods....57
17.6.1 Analysis of Primary Endpoint....57
17.6.2 Analysis of Secondary Endpoints 59
[redacted]
17.6.4 Subgroup Analysis 63
17.7 Safety Analysis 63
17.7.1 Adverse Events 63
17.8 Interim Analysis....64
18. Study Monitoring 64
18.1 Direct access to source data/documents....65
19. Quality control and quality assurance....65
19.1 Audits and Inspections....65
20. Data Handling and Recordkeeping 65
20.1 Case Report Forms / Electronic Data Capture....65
20.2 Source Documents 66
20.3 Inspection of Records 66
20.4 Retention of Records....66
21. Publication Policy 67
22. List of References 68
23. Appendices....69
APPENDIX 1. PAIN RATING SCALES/ CATEGORICAL PAIN INTENSITY SCALE 70
[redacted]

Status : Approved

4. List of Tables

Table 1: Activity Schedule....11
Table 2: Abbreviations and Specialist Terms....18
Table 3: Investigational Product(s)....30

5. LIST OF FIGURES

Figure 1: Schematic Study Design....24

Status : Approved

6. 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 (kg/m^2)
COVID-19	Coronavirus Disease 2019
COX	Cyclooxygenase
CRF	Case Report Form
CRO	Contract Research Organization
DDS	Doctor of Dental Surgery
DMD	Doctor of Medicine in Dentistry
DO	Doctor of Osteopathic Medicine
DPR	Designated Physician Representative
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
IEC	Independent Ethics Committee
IP	Investigational Product
IR	Immediate Release
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IUD	Intrauterine Device
JJCI	Johnson & Johnson Consumer, Inc.
MedDRA	Medical Dictionary for Regulatory Activities
MD	Medical Doctor

Status : Approved

Abbreviation or Specialist Term	Explanation
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over the Counter
[redacted]	[redacted]
PI	Principal Investigator
PID	Pain Intensity Difference
PI-NRS	Pain Intensity - Numerical Rating Scale
PQC	Product Quality Complaint
[redacted]	[redacted]
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SMF	Site Master File
SPID	Sum of Pain Intensity Difference
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
TMF	Trial Master File
[redacted]	[redacted]
[redacted]	[redacted]
US	United States

Status : Approved

7. ETHICS

7.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Principal Investigator (PI) to obtain prospective approval of the study protocol, protocol amendments, informed consent forms, and other written information to be provided to subjects, e.g., advertisements and diaries if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File (Site Master File [SMF]). Copies of IRB/IEC approvals obtained by the PI 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 PI must notify the IRB/IEC and the Sponsor in writing within five working days after implementation.

7.2 Ethical and Regulatory Considerations

The study will be performed in accordance with the protocol, International Council on Harmonization Good Clinical Practice guidelines (ICH E6 R2), the current version of the Declaration of Helsinki[1] 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 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).

7.3 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 and any educational material must be agreed to 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 PI 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 PI, or a person designated by the PI, 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

Status : Approved

made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use. The PI will retain the original of each subject's signed consent form. A printed 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 personally signed and 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.

7.4 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 PI'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 PI, or local requirements. During the Assent process, the PI or designee will provide the minor with an assent document that explains in clear and age-appropriate terms, the purpose of the research, what her or she will be asked to do and what procedures her or she will undergo 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 the confidentiality of any information obtained as a result of their participation. The PI or designee will explain the information, give the minor a chance to ask questions and ask the minor to indicate their assent by signing/electronically accepting the assent document. The prospective subject will do this by signing an IRB/IEC-approved assent form or designated assent section of the informed consent, depending on individual institutional regulations. An impartial witness must also sign and date/electronically accept the assent form.

The original signed assent form will be retained by the PI as part of the Site Master File and will be available for review by the Sponsor.

A copy of the signed and dated assent form will be given to the subject. Assent by the subject acknowledges willingness to participate but does not necessarily ensure a thorough understanding of the procedures, risks, and benefits of the study.

8. STUDY ADMINISTRATIVE STRUCTURE

Details on the administrative structure of the study will be included in the study contact list which will include contact information for the Sponsor, PI(s), Monitor(s), Clinical and Bioanalytical Laboratories, and IRB/IEC(s). The complete contact list will be maintained in the Trial Master File (TMF) throughout the study. An abbreviated contact list with all site relevant contact information will be maintained in the SMF.

Status : Approved

9. INTRODUCTION

The investigational product (IP) will involve a fixed combination tablet of immediate release (IR) acetaminophen and naproxen sodium for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, minor pain of arthritis, and muscular aches. 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 exact mechanism of analgesic action of acetaminophen is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold.[2,3] Several mechanisms of action, responsible for analgesic activity of acetaminophen, have been proposed including central inhibition of cyclooxygenase (COX) enzymes[4] and modulation of the cannabinoid and serotonergic systems.[5,6] Acetaminophen reduces fever by blocking the formation and release of prostaglandins in the central nervous system and inhibiting the action of endogenous pyrogens at the hypothalamic thermoregulatory centers.[7,8,9]

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.[10] The therapeutic effects of naproxen are produced through nonselective inhibition of cyclooxygenase enzymes (COX-1 and COX-2) resulting in inhibition of prostaglandin synthesis.[11] 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 200 mg naproxen.[12]

The current study is the first Phase 3 pivotal clinical trial in the development program of a fixed combination of acetaminophen/naproxen sodium. This study will evaluate the analgesic efficacy and safety of the fixed combination of acetaminophen/naproxen sodium compared with acetaminophen, naproxen sodium, and placebo.

The Reference Safety Information for the IP and the relevant findings from nonclinical and clinical studies are included in the Investigator's Brochure. The Reference Safety Information for the active comparators and the placebo is included in the commercial product labels and the placebo ingredient list, respectively.

Status : Approved

10. STUDY OBJECTIVES

10.1 Primary Objective(s)

To evaluate the analgesic efficacy of a fixed combination of acetaminophen/naproxen sodium, compared with acetaminophen, naproxen sodium and placebo over 12 hours.

10.2 Secondary Objective(s)

To evaluate the duration of analgesic effect of a fixed combination of acetaminophen/naproxen sodium.

10.3 Safety Objective(s)

To evaluate the safety of a fixed combination of acetaminophen/naproxen sodium.

[redacted]

11. INVESTIGATIONAL PLAN

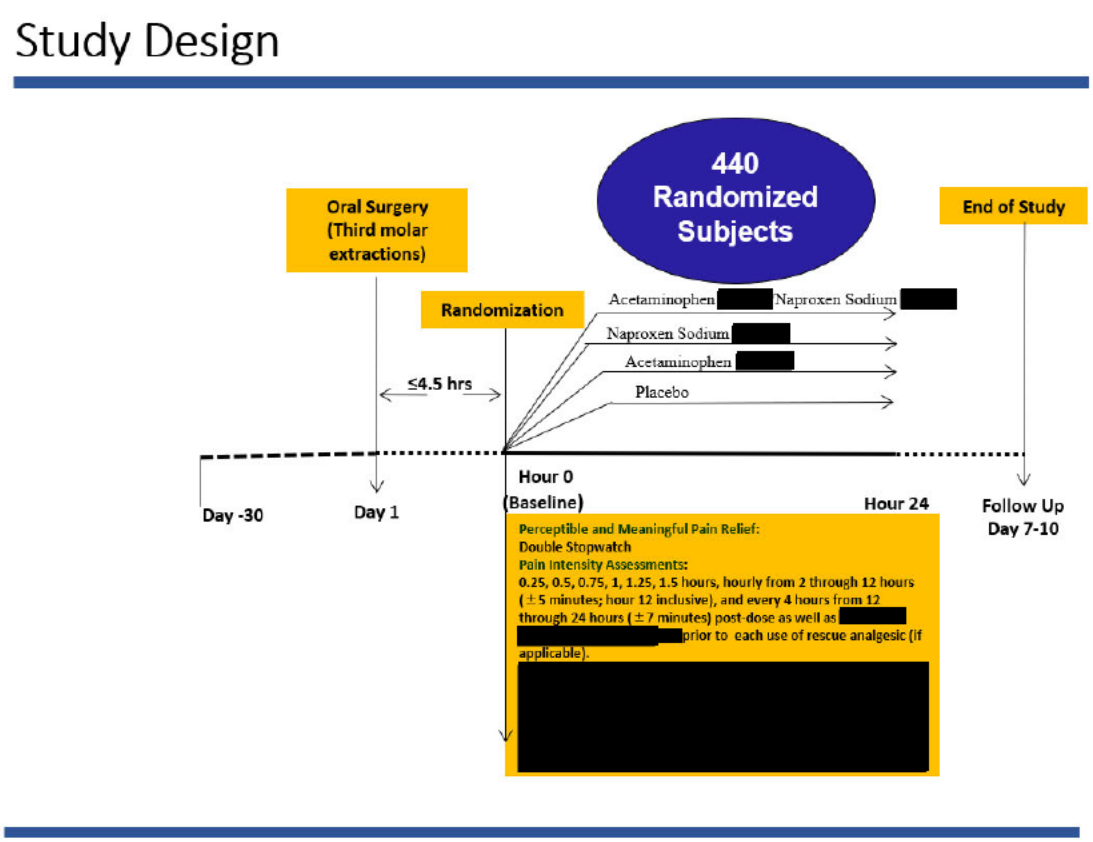
11.1 Overall Study Design and Plan

This will be a randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and safety of a fixed combination of acetaminophen/naproxen sodium, compared with acetaminophen, naproxen sodium, and placebo.

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

Status : Approved

Figure 1: Schematic Study Design



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 determined by the surgeon and 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.

Status : Approved

Approximately 440 subjects who meet the randomization criteria (postsurgical 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 randomized. No less than approximately 30% of randomized subjects will be either male or female.

To maintain the double-blind nature of the study, all tablets in the study will be over-encapsulated and placebo (an inert powder) will be encapsulated in identical opaque capsules to ensure that they are indistinguishable. From this point going forward, the investigational products will be referenced as tablets.

Upon randomization, subjects will be assigned to one of the following treatment groups, with 4:4:2:1 allocation:

- Acetaminophen Naproxen Sodium
- Naproxen Sodium
- Acetaminophen
- Placebo

All treatments will be administered as a single dose.

Rescue analgesic medications include:

- First-line rescue analgesic medication (celecoxib 400 mg initial dose, which can be followed by celecoxib 200 mg 12 hours after the initial dose, if needed; not to exceed 600 mg in 24 hours) will be available for subjects as needed for intolerable pain.
- Second-line rescue analgesic medication (oxycodone immediate release 5 mg every four to six hours as needed; not to exceed 30 mg in 24 hours) will be available for subjects as needed for intolerable pain only during the 12 hour therapeutic window after any dose of the first-line rescue medication. If intolerable pain occurs beyond 12 hours after the initial dose of the first-line rescue medication, then the second dose of first-line rescue medication will be administered before proceeding with any additional doses of second-line rescue medication that may be needed.

Self-reported pain intensity will be collected using a four-point categorical pain scale and a 0-10 PI-NRS at Baseline (Time 0). Pain intensity (using PI-NRS) will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5 hours, hourly from 2 through 12 hours (±5 minutes; hour 12 inclusive), and every 4 hours from 12 through 24 hours (±7 minutes) post dose as well as prior to each use of rescue analgesic (if applicable).

Status : Approved

[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).

11.2 Discussion of Study Design

This is the first Phase 3 pivotal clinical study in the development program of a novel fixed combination of acetaminophen/naproxen sodium. The study will evaluate the analgesic efficacy and safety of the fixed combination of acetaminophen/naproxen sodium compared with acetaminophen, naproxen sodium, and placebo. This full-factorial, randomized, double-blind, placebo-controlled, parallel-group, single-dose efficacy and safety study will utilize a dental impaction pain model. This model is validated and well-established for evaluation of efficacy and safety of analgesics for acute pain.[13] This pain model employs a standardized surgical procedure (third molar extraction), generating an adequate postoperative pain level to produce low variability and high assay sensitivity.[14] These characteristics make the model appropriate not only to distinguish active treatments from placebo, but also to evaluate differential analgesic efficacy between the fixed combination and the monotherapy treatments in this study. Therefore, this study is well suited to determine whether each active monocomponent of the fixed combination of acetaminophen/naproxen sodium contributes to the analgesic efficacy of the combination, which is an important aspect of this development program. Furthermore, safety will be monitored and assessed in this study by reviewing the collection, evaluation, and analysis of AEs, which will help evaluate the safety profile of the fixed combination of acetaminophen/naproxen sodium.

11.3 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 PI. After notification, the PI must contact all participating subjects within the time period set by the Sponsor, within two weeks. All study materials must be collected and all eCRFs and source documents completed to the greatest extent possible.

Status : Approved

12. STUDY POPULATION

12.1 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.

12.1.1 Subject Inclusion Criteria

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

1. Males or females who are 16 to 50 years of age (inclusive) at the time of Screening.
2. If female and of childbearing potential have a negative urine pregnancy test 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 the oral surgical procedure.
6. Are able to comprehend and follow the requirements of the study (including presurgical 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 14.6.4 Contraception for Females and Section 14.6.5 Contraception for Males.
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 the oral surgical procedure.

12.1.2 Subject Exclusion Criteria

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

Status : Approved

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), celecoxib (or other sulfonamides), acetaminophen, oxycodone, or other opioids.
5. Are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin).
6. Have presence or a history of major medical condition that in the Investigator's opinion may jeopardize the subject's safety or wellbeing (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.
7. Are not able to swallow whole large tablets or capsules.
8. Routinely use oral analgesics ≥ 5 times per week.
9. 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).
10. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last two years.
11. Used oral over-the-counter or prescription products (except contraceptive medications and those required for use during the oral surgical procedure), within five halflives before the oral surgical procedure.
12. Used vitamins, dietary or herbal supplements within five days before the oral surgical procedure.
13. 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 the oral surgical procedure.
14. Used alcohol within three days before the oral surgical procedure.
15. Consumed methylxanthinecontaining 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.
16. Used monoamine oxidase inhibitors within 14 days prior to the oral surgical procedure.
17. Have a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV).

Status : Approved

18. Have participated in any interventional clinical trials within 30 days before Screening.
19. Are related to those persons involved directly or indirectly with the conduct of this study (i.e., PI, Sub-Investigator(s), study coordinators, other site personnel, employees of Johnson & Johnson Consumer, Inc. [JJCI] subsidiaries, contractors of JJCI, and the families of each).

12.1.3 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. If subject withdraws from the study due to the treatment not providing therapeutic benefit, and this designation is deemed reasonable by the investigator based on study observations, this event will be categorized by the Investigator or designated site staff as discontinuation due to lack of efficacy. The PI 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, PI 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 PI, 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 14.3.3 Follow-Up Phone Call (Days 7 to 10)) (if subject cannot come to the study site, a telephone call to collect information could be performed. 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. 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. In addition, for randomized subjects, early discontinuation during the 0 to 24-hour post-dose period, will be documented in the source documents and the 24-hour post-dose observation status eCRFs.

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.

Status : Approved

13. INVESTIGATIONAL PRODUCTS

13.1 Treatment Administration

For subjects who meet the randomization criteria, the research site personnel will dispense the assigned investigational product to be taken orally by the subject. All study treatments will be taken orally with up to 180 mL of water at ambient temperature.

13.2 Description of Investigational Products(s)

A description of the IPs is provided in Table 3.

Table 3: Investigational Product(s)

Product	Acetaminophen / Naproxen Sodium [redacted] Tablet	Naproxen Sodium [redacted] Tablet	Acetaminophen [redacted] Tablet	Placebo
Core Dosage Form (all tablets encapsulated)	Tablet	Tablet	Tablet	Capsule
Unit Dose	[redacted]	[redacted]	[redacted]	N/A
Route of Administration	Oral	Oral	Oral	Oral
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Status : Approved

13.3 Packaging and Labeling

Investigational products will be supplied by the Sponsor [redacted] Each subject specific wallet will be labeled with a two-part three-panel Sponsor double-blind study label. Part 1 of the label will stay affixed to the wallet. Part 2 of the label will contain an unblinding panel. Part 2 of the label should be removed along the perforation line from Part 1 prior to subject dispensation and stored with the site's Pharmacy (IP) binder.

Sample Label

Part 1	**Part 2**
This section will stay affixed on the subject wallet. **Panel I** Contains randomization number and instruction for use.	This section will be detached from Part 1, Panel I, and placed in the site's Pharmacy (IP) binder. **Panel II** Contains randomization number. **Panel III** It includes the concealed blinding laminate sticker containing the treatment assignment. The blinding laminate cover should not be removed from the label and the integrity of the blinding laminate surface should be preserved. Blinding Laminate

13.4 Preparation and Handling

IPs and placebo will be packaged in subject specific wallets. Each wallet will have a sufficient supply for administration of one dose per subject. [redacted] The wallet pack will have a two-part three-panel label with a perforation between Part 1 and Part 2. Part 1 of the label, containing Panel I, will stay affixed to the wallet. Part 1, Panel I will provide study-related information, instructions for use, storage conditions, and randomization number. Part 2 of the label, containing Panel II and Panel III, should be removed at the perforation line and placed in the site's Pharmacy (IP) binder prior to dispensing the kit to the subject. Part 2, Panel II will contain the randomization number. Part 2, Panel III will include a concealed blinding laminate sticker containing the treatment assignment for each subject. The blinding laminate cover in Panel III should not be removed from the label and the integrity of the blinding laminate surface should be preserved.

IP dispensing will be performed on Day 1, following dental surgery. Subjects must meet criteria for randomization within 4.5 hours of last stitch from dental extractions. For subjects who meet the randomization criteria, a pharmacist or study coordinator will administer one of the following study treatments with up to 180 mL of water at ambient temperature to subjects:

Status : Approved

- Acetaminophen /Naproxen Sodium
- Naproxen Sodium
- Acetaminophen
- Placebo

Baseline pain assessments and drug administration will be completed in subject's room. Study medication will be dispensed at the time that subject's pain level is determined to be eligible by the initial verbal assessment, just prior to the completion of the documented baseline categorical pain severity scale and the baseline 11-point (0-10) PI-NRS. The study coordinator will provide the pharmacist with a dosing slip reporting subject's verbal baseline pain severity and gender. The pharmacist assigns the appropriate randomization number from the Sponsor-provided randomization list. The pharmacist will take out the corresponding wallet with the same randomization number, remove Part 2 of the label from the wallet and dispense the appropriate study treatment. Part 1 of the double-blind label will stay affixed to the wallet and the tear-off portion of the label (Part 2) will be placed in the site's Pharmacy (IP) binder. The pharmacist will complete the study drug dispensing record. The study drug dispensing record will remain in a secure and locked area.

The pharmacist will inform the study coordinator once the study drug is ready to be administered to the subject. Following completion of the documented baseline categorical pain severity scale and baseline PI-NRS, the study coordinator will inform the pharmacist that the pain assessments are completed and confirm that the pain severity has not changed from the initial 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 and will not be re-used. If the severity has changed and the original treatment prepared was not administered, then pharmacy team will check the box: No, Quarantined under the Dosed column on the IP Dispensing and Accountability Log. The pharmacist will complete the quarantined log for the applicable randomization number. If the baseline categorical pain severity has changed from the initial verbal assessment and the original treatment was quarantined, subject's pain level may be determined to be eligible for randomization once more. In such case, if the subject meets criteria for re-randomization within 4.5 hours of last stitch from dental extractions, the subject will be assigned a new appropriate randomization number. The pharmacist will deliver the study drug from the designated dispensing room to the subject's room. No other study personnel, other than the pharmacist and/or study coordinator, will be present in the subject's room at the time of dosing.

After entering the subject's room and while the subject is sitting up, the pharmacist or study coordinator will empty the contents of the wallet into a dosing cup and hand the dosing cup containing the study treatment to the subject and instruct the subject to empty the contents of the

Status : Approved

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 pharmacist or study coordinator 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 5 minutes of the completion of the documented baseline pain assessments.

Subjects having received the second-line rescue medication (oxycodone immediate release 5 mg) 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 PI 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.

13.5 Storage, Accountability, and Disposal

The PI, or a designated study staff, will ensure that all IP is stored in a secured area, under recommended storage conditions [redacted] and in accordance with applicable regulatory requirements.

The PI, or assigned representative, must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP on an IP accountability log. 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 for the TMF. All IP and IP Logs are kept together in a secure, double-locked location with access only allowed to the pharmacist and back-up staff member. The study site must maintain accurate and adequate records including shipment receipt and return of unused IP shipments.

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 PI 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.

13.6 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 four treatments (Acetaminophen [redacted] Naproxen Sodium [redacted] Naproxen Sodium [redacted] Acetaminophen [redacted] and placebo) in a 4:4:2:1 ratio. Subjects will be stratified by gender and baseline pain (moderate or severe). For subjects with moderate baseline pain, randomization numbers will be assigned to subjects in sequential ascending 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 descending 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 13.4 Preparation and Handling. Site staff will inspect the subject's oral cavity to ensure that the IP was swallowed.

13.7 Blinding and Unblinding

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

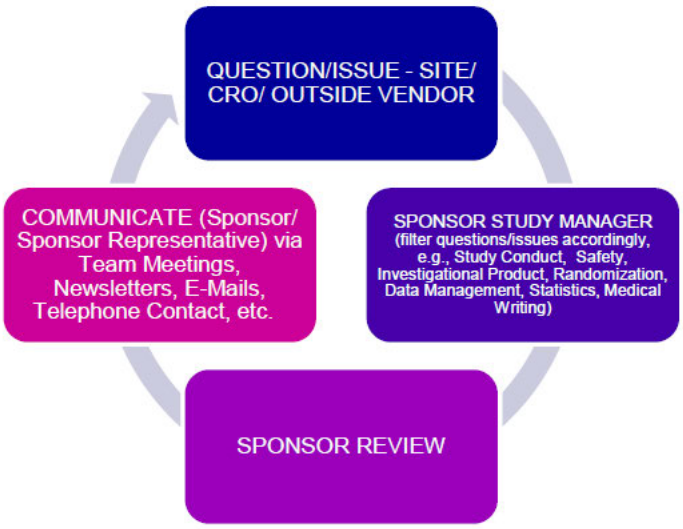
In the event of a medical emergency that necessitates breaking the code, the pharmacist will be permitted to inform the PI what study drug the subject was given.

When the blind is broken, the PI 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.

Status : Approved

13.8 Communication Plan



13.9 Treatment Compliance

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

13.10 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.

13.10.1 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.

Status : Approved

13.10.2 Prohibited Therapies

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

13.11 Rescue Therapy

Subjects are allowed to take rescue medication for intolerable pain, including:

- First-line rescue analgesic medication (celecoxib 400 mg initial dose, which can be followed by celecoxib 200 mg 12 hours after the initial dose, if needed; not to exceed 600 mg in 24 hours) will be available for subjects as needed for intolerable pain.
- Second-line rescue analgesic medication (oxycodone immediate release 5 mg every four to six hours as needed; not to exceed 30 mg in 24 hours) will be available for subjects as needed for intolerable pain only during the 12-hour therapeutic window after any dose of the first-line rescue medication. If intolerable pain occurs beyond 12 hours after the initial dose of the first-line rescue medication, then the second dose of first-line rescue medication will be administered before proceeding with any additional doses of second-line rescue medication that may be needed.

Subjects will complete global assessment immediately before the initial dose of rescue medication. Pain assessments including rating of pain intensity and pain relief will be completed prior to each use of rescue medication. Once rescue medicine has been administered, the stopwatch(s) will be collected from the subjects if they still have them. No stopwatch data will be recorded after use of rescue medication; however, subjects will continue to record pain intensity and pain relief. The time when first rescue medication was requested and administered will be recorded in the source document and eCRF. The name of the rescue medication(s) and the time when each subsequent rescue medication was administered will also be recorded in the source document and eCRF.

Subjects having received the second-line rescue medication (oxycodone immediate release 5 mg) 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.

13.12 Retention of Reserve Drug Product

Drug product reserve samples will not be retained at the clinical site for this study.

13.13 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.

Status : Approved

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.

14. STUDY PROCEDURES

14.1 Overview

The Activity Schedule (Table 1: Activity Schedule) 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.

14.2 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 (Screening only)
- 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 will be completed for the presence of cocaine, tetrahydrocannabinol, opioids, benzodiazepines, and amphetamines
- 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 oral surgical procedure within 30 days after Screening.

14.3 Study Visits (Periods)

14.3.1 Baseline Visit (Day of Surgery)

The following will be evaluated on the day of surgery prior to investigational product administration, and the evaluations will be recorded in the source documents and the eCRF. For data collected on both Screening and Baseline Visits, only the data collected at Baseline will be recorded on the eCRF.

Status : Approved

- 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
- Impaction evaluation (review of panorex x-ray)
- Dental extraction surgery
- 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 oral 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 oral surgical procedure
- Randomization
- Investigational product administration
- Safety monitoring

14.3.2 Post-dose Assessments (0-24 Hours)

Post-dose assessments include the following procedures (please refer to Section 15. Assessments for details):

- [redacted]
- Pain intensity [redacted] ratings
- Rescue Therapy
- Concomitant medication
- Safety monitoring and recording
- Subject disposition
- [redacted]

After the oral surgical procedure, subjects will rest quietly at the study center until they experience both postsurgical 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]

Status : Approved

[redacted]

Pain intensity [redacted] will be assessed using the NRS (Appendix 1. PAIN RATING SCALES/ CATEGORICAL PAIN INTENSITY SCALE) at 0.25, 0.5, 0.75, 1, 1.25, 1.5 hours, hourly from 2 through 12 hours (±5 minutes; hour 12 inclusive), and every 4 hours from 12 through 24 hours (±7 minutes) post-dose as well as [redacted] prior to each use of rescue analgesic (if applicable).

[redacted] Subjects who use rescue medication will continue in the study and assess pain [redacted] through 24 hours [redacted].

14.3.3 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. All subjects that are randomized are encouraged to complete the follow-up interview. The interview will occur between the sixth and ninth day after the dental surgery (Days 7 to 10 of the study). 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 PI 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.

14.4 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.

Status : Approved

14.5 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 may be required.

14.6 Lifestyle Restrictions

14.6.1 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.

14.6.2 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.

14.6.3 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 their assigned subject room under observation following treatment administration, except for short durations to use the restroom.

14.6.4 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. Females must have used such birth control for at least one month prior to the Screening visit.

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 Screening visit. 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

Status : Approved

- 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 6 months prior to product administration
- Had sterilization surgery (e.g., hysteroscopic sterilization/tubal implants or tubal ligation) at least 6 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)

14.6.5 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 14.6.4 Contraception for Females. Information about effective means of birth control (hormonal contraception, IUDs, vasectomy, sexual abstinence) will be provided, and discussed as appropriate with individual subjects.

15. ASSESSMENTS

15.1 Efficacy Assessments

The PI or designated study staff will ensure the subjects complete the pain intensity [redacted] assessments at 0.25, 0.5, 0.75, 1, 1.25, 1.5 hours, hourly from 2 through 12 hours (±5 minutes; hour 12 inclusive), and every 4 hours from 12 through 24 hours (±7 minutes) post-dose as well as [redacted] prior to each use of rescue analgesic (if applicable). Subjects will record their pain intensity [redacted] directly onto the respective source worksheet. Evaluations will include the following parameters:

- Pain intensity

Status : Approved

- 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 meaningful pain relief and prior to each use of rescue analgesic (if applicable).

- [redacted]
- Time to first request for rescue medication; time when first rescue medication was requested
- [redacted]

15.2 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 PI 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 PI believes the condition worsened or was aggravated following study drug therapy.

15.2.1 Physical Examination

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

15.2.2 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 PI to confirm that the subject is medically suitable for study participation.

Status : Approved

15.2.3 Clinical Laboratory Tests

Females of childbearing potential will undergo a urine pregnancy test at Screening 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.

16. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting of safety information from clinical studies are crucial for the protection of subjects, PIs, 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 PI or medically qualified individual (MD/DO/DMD/DDS) must pursue and obtain adequate information to make the appropriate assessments.

16.1 Definitions

16.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence that occurs in a subject after he/she has 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, and
- Progression/worsening of underlying disease.

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

- Overdose,
- Withdrawal,
- Abuse,
- Drug misuse,
- Drug interactions,

Status : Approved

- Medication errors,
- Product dependency,
- Exposure *in utero*, and
- Study related oral surgical procedure

16.1.2 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 PI 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.

16.1.3 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 PI 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

Status : Approved

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.'

16.1.3.1 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.

Status : Approved

- 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.

16.2 Adverse Event Assessments

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

16.2.1 Severity Assessment

The severity of AEs will be assessed by the PI or medically qualified 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.

16.2.2 Causality Assessment

The medically qualified PI’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).

Status : Approved

- 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 PI determines an AE is associated with study oral surgical procedure, the PI must record this suspected causal relationship in the source documents.

16.2.3 Resolution

The PI or medically qualified 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, or
- 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 stabilized at a level acceptable to the medically qualified PI 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 PI or designee and has concurrence by the Sponsor.

16.3 Adverse Event Reporting

16.3.1 Time Period

All AEs, whether serious or non-serious, observed or spontaneously reported will be recorded on the eCRF and in the AE section starting from the time a subject signs and dates the informed consent and until the completion of the subject's last study-related procedure, which may include contact for follow-up of safety. 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). SAEs require immediate notification to the Sponsor or its designated representative. In addition, spontaneous reports of serious AEs will be collected through and including 30 calendar days after subject's last study procedure. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to study product is suspected.

Status : Approved

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.

16.3.2 Process for Reporting

The PI 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, any subjects who discontinue prior to randomization 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.

16.3.2.1 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 PI's site and the SAE documented on the source document. Within 24 hours of the PI 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 PI'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 PI'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 PI is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, the PI 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.

Status : Approved

16.3.2.2 Contacts for Serious Adverse Event Reporting

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

Appropriate SAE forms will be provided to the study site at the initiation of the study.

16.4 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 PI (or Sponsor) must report to the IRB/IEC as required and in accordance with the Sponsor's SOPs for safety reporting.

16.5 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 and Electronic Data Capture (EDC) system. Examples include:



16.5.1 Exposure In Utero

1. An *exposure in utero* (EIU) occurs if: A woman is exposed to the IP at any time between her last menses prior to conception through the delivery of the baby.

Status : Approved

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 PI 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 PI 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 PI 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 PI assesses as possibly related to EIU to the IP.

16.6 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 in Section 16.3 Adverse Event Reporting.

Status : Approved

17. 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.

17.1 Determination of Sample Size

The total sample size of 440 subjects (160 for Acetaminophen/Naproxen Sodium Fixed Combination, 160 for Naproxen Sodium, 80 for Acetaminophen, and 40 for Placebo) is based on, for SPID 0-12, a population standard deviation of 28. [redacted]

The assumed population standard deviation is based on previous studies using the same clinical model and study site, and the assumed differences between treatment means were based on extrapolation from a previous dose-ranging study.

17.2 Analysis Sets

17.2.1 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 analysis set by at least 5% of the subjects. The per-protocol analysis set will include all randomized subjects excluding subjects who vomited within 60 minutes after dosing, and those with major protocol deviations (The final per-protocol analysis set will be determined before unblinding).

17.2.2 Safety Analysis Population

The Safety Analysis Set will include all subjects who were randomized and took IP.

17.3 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.

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.

Status : Approved

17.4 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.

17.5 Efficacy Analysis

17.5.1 Efficacy Endpoints

17.5.1.1 Primary Endpoint(s)

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

17.5.1.2 Secondary Endpoints

- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first request for rescue analgesic
- Proportion of subjects who request rescue analgesic during the first 12 hours



Status : Approved

[redacted]

17.5.2 Statistical Hypotheses

For endpoints based on pain intensity (such as SPID), [redacted] Acetaminophen [redacted] / Naproxen [redacted] will be compared with each of the other three treatments by testing the following hypotheses:

H_0:$\mu_1 = \mu_2$

H_A:$\mu_1 \neq \mu_2$

where μ_1 is the population mean for Acetaminophen [redacted] / Naproxen [redacted] and $\mu_2$is the population mean for Placebo, Acetaminophen [redacted] or Naproxen [redacted]

For time-to-event endpoints (time to first request for rescue analgesic [redacted]), Acetaminophen [redacted] / Naproxen [redacted] will be compared with each of the other three treatments 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 Acetaminophen [redacted] / Naproxen [redacted] and $S_2(t)$ is the survival function for Placebo, Acetaminophen [redacted] or Naproxen [redacted]

For the proportion of subjects requesting rescue Acetaminophen [redacted] / Naproxen [redacted] will be compared with each of the other three treatments by testing the following hypotheses:

H_0: $\pi_1 = \pi_2$
H_A: $\pi_1 \neq \pi_2$

where π_1 is the population proportions for Acetaminophen [redacted] / Naproxen [redacted] and π_2 is the population proportion for Placebo, Acetaminophen [redacted] or Naproxen [redacted]

All statistical comparisons will be performed at the 5% significance level, two-sided. For primary and secondary endpoints, statistical testing will be carried out in a fixed-sequence approach as follows:

1. The following comparisons will be tested for SPID 0-12:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.

Status : Approved

- Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted]
- Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Acetaminophen [redacted] Naproxen Sodium [redacted] will meet efficacy requirements for SPID 0-12, and testing will proceed to secondary endpoints, only if the mean for Acetaminophen [redacted] Naproxen Sodium [redacted] is statistically significantly higher than the means for Placebo, Naproxen Sodium [redacted] and Acetaminophen [redacted]

2. The following comparisons will be tested for SPID 6-12:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Testing will proceed to the next secondary endpoint only if the mean for Acetaminophen [redacted] Naproxen Sodium [redacted] is statistically significantly higher than the means for Placebo, and Acetaminophen 650. [redacted]

3. The following comparisons will be tested for Time to First Request for Rescue Analgesic:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Acetaminophen [redacted] Naproxen Sodium [redacted] will meet efficacy requirements for Time to First request for Rescue Analgesic only if the distribution for Acetaminophen [redacted] Naproxen Sodium [redacted] is statistically significantly different from the distributions for Acetaminophen [redacted] and Placebo, in favor of Acetaminophen [redacted] Naproxen Sodium [redacted]

4. The following comparisons will be tested for proportion of subjects requesting rescue within 12 hours:
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Acetaminophen [redacted] Naproxen Sodium [redacted] will meet efficacy requirements for proportion of subjects requesting rescue within 12 hours only if Acetaminophen [redacted] Naproxen Sodium [redacted] has a statistically significantly lower proportion than Acetaminophen [redacted] and Placebo.

The above fixed-sequence procedure will provide strong familywise error rate control at 5% for the family of comparisons including primary and secondary endpoint pairwise comparisons, with the exception of comparisons between Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted] for SPID 6-12 and rescue-related endpoints. [redacted]

Status : Approved

[redacted]

17.5.3 Data Computations and Handling of Missing Values

17.5.3.1 Endpoints Relating to Pain Intensity [redacted]

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

Pain intensity [redacted] 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.

Imputation for Pain Intensity: For subjects who use rescue medications, the last reported pain intensity score before taking first rescue medication will be carried forward from the time of each rescue medication to the subsequent time points within the therapeutic window for each rescue medication respectively. [redacted] For subjects who discontinue the treatment due to lack of efficacy or adverse event during the 24-hour period, multiple imputation of the last reported pain score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach will be used for subsequent time-points. [redacted] For subjects who withdraw from the study due to reasons other than lack of efficacy or adverse event during the 24-hour period, or are missing data without withdrawal from the study, multiple imputation method will be used for such missing time-points, under the Missing at Random assumption. [redacted]

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 0-6, 0-12, 4-12, 6-12 or 0-24 hours.

[redacted]

Status : Approved

[redacted]

17.5.3.2 Time to First Request for Rescue

Time to first request for rescue medication will be measured as the elapsed time from when IP was given until the time rescue medication was first requested. For request for rescue medication, subjects who discontinue the treatment due to Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, will be considered as having requested rescue, and their time of rescue request is the time of discontinuation. Subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, and do not discontinue the treatment due to lack of efficacy or adverse event, will be censored at the time of study withdrawal. Subjects who do not request rescue medication during the 24-hour study period, do not discontinue the treatment due to Lack of Efficacy or Adverse Event, and do not withdraw from the study before 24 hours, will have their time to first request for rescue set to 24 hours and will be censored at 24 hours.

[redacted]

Status : Approved

[redacted]

17.6 Analysis Methods

17.6.1 Analysis of Primary Endpoint

SPID 0-12

For the primary endpoint, SPID 0-12, pairwise comparisons will be made using single analysis of variance (ANOVA) with baseline pain (moderate or severe) score, gender, and treatment group (with 4 treatment groups as 4 levels) as factors, using imputation methods defined in Section 17.5.3 Data Computations and Handling of Missing Values.

Primary Estimand

The primary estimand is the main clinical quantity of interest relative to pain relief over 0-12 hours after dosing and is defined according to the attributes below.

Treatments being Compared:	The following comparisons will be tested for SPID 0-12: Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo. Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Naproxen Sodium 220 Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Time weighted sum of pain intensity difference from 0-12 hours after dosing (SPID 0-12)
Intercurrent events:	Rescue Medication during the 12-hour evaluation period For subjects who use rescue medication during the 12-hour evaluation period, the composite variable strategy will be used. The last reported pain intensity score before taking first rescue medication will be carried forward from the time of each rescue medication to the subsequent time points within the therapeutic window for each rescue medication, respectively.

Status : Approved

	[redacted] <u>Treatment discontinuation due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period</u> For subjects who discontinue the treatment due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period, the composite variable strategy will be used. To account for uncertainty, multiple imputation of the last reported pain score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach will be used for subsequent time-points. [redacted]
Missing data handling:	For subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event during the 12-hour evaluation period, or are missing data without withdrawal from the study, to account for uncertainty, a regression based multiple imputation method will be used for such missing time-points, under the Missing at Random assumption. [redacted]
Population level summary:	Differences in least square means of SPID 0-12 between treatment groups.

Sensitivity Analyses for SPID 0-12

As one of the sensitivity analyses for SPID 0-12, for subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event during the 12-hour evaluation period, the multiple imputation of worst observation carrying forward approach (the same method used for treatment discontinuation due to Lack of Efficacy or Adverse Event) will be used for subsequent missing time-points.

Status : Approved

More details will be provided in the statistical analysis plan.

17.6.2 Analysis of Secondary Endpoints

SPID 6-12

SPID 6-12 will also be analyzed using single ANOVA with baseline pain (moderate or severe), gender, and treatment group (with 4 treatment groups as 4 levels) as factors, using imputation methods defined in Data Imputations Section 17.5.3 Data Computations and Handling of Missing Values.

Secondary Estimand #1

The secondary estimand #1 is the main clinical quantity of interest relative to pain relief over 6-12 hours after dosing and is defined according to the attributes below.

Treatment being compared:	Treatment Comparisons include following: Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Time weighted sum of pain intensity difference from 6-12 hours after dosing (SPID 6-12)
Intercurrent events:	<u>Rescue Medication during the 12-hour evaluation period</u> For subjects who use rescue medication during the 12-hour evaluation period, the composite variable strategy will be used. The last reported pain intensity score before taking first rescue medication will be carried forward from the time of each rescue medication to the subsequent time points within the therapeutic window for each rescue medication, respectively. [redacted] <u>Treatment discontinuation due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period</u> For subjects who discontinue the treatment due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period, the composite variable strategy will be used.

Status : Approved

	To account for uncertainty, multiple imputation of the last reported pain score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach will be used for subsequent time-points. [redacted]
Missing data handling:	For subjects who withdraw from study due to reasons other than Lack of Efficacy or Adverse Event during the 12-hour evaluation period, or are missing data without withdrawal from the study, to account for uncertainty a regression based multiple imputation method will be used for such missing time-points, under the Missing at Random assumption. [redacted]
Population level summary:	Differences in least square means of SPID 6-12 between treatment groups.

Time to First Request for Rescue

Kaplan-Meier estimates of cumulative percentage of subjects requesting rescue 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 request for rescue 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.

Secondary Estimand #2

The secondary estimand #2 is the main clinical quantity of interest relative to Time to first request for rescue analgesic and is defined according to the attributes below.

Treatment being compared:	Treatment Comparisons include following: Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo

Status : Approved

	Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Time to first request for rescue analgesic.
Intercurrent events:	Treatment discontinuation due to Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication A composite variable strategy will be used, and subjects will be considered as having requested rescue, and their time of rescue request is the time of treatment discontinuation.
Missing data handling:	For subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, and do not discontinue the treatment due to Lack of Efficacy or Adverse Event, subjects will be censored at the time of study withdrawal, considering a non-informative censoring. For subjects who do not request rescue medication during the 24-hour study period, do not discontinue the treatment due to Lack of Efficacy or Adverse Event, and do not withdraw from the study before 24 hours, subjects will be censored at the time of 24 hours, considering a non-informative censoring. [redacted]
Population level Summary:	Proportion of subjects who request rescue analgesic estimated by Kaplan-Meier method.

Proportion of subjects who request rescue analgesic up to 12 hours

The proportion of subjects requesting rescue medication through 12 hours will be estimated using the Kaplan-Meier method, and standard errors will be approximated using the Greenwood method. The complementary log-log transformed proportion differences between fixed combination and placebo/ Acetaminophen will be tested for statistical significance using Wald test stratified by

Status : Approved

baseline pain (moderate or severe) and gender. This method will be used for this endpoint due to the censoring that may occur at times between 0 and 12 hours.

Further details will be provided in the Statistical Analysis Plan.

Secondary Estimand #3

The secondary estimand #3 is the main clinical quantity of interest relative to Proportion of subjects who request rescue analgesic during the first 12 hours and is defined according to the attributes below.

Treatment being compared:	Treatment Comparisons include following: Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Placebo Acetaminophen [redacted] Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Proportion of subjects who request rescue analgesic during the first 12 hours at each treatment group
Intercurrent events:	Treatment discontinuation due to Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication A composite variable strategy will be used, and subjects will be considered as having event, and their event time is the time of treatment discontinuation due to Lack of Efficacy or Adverse Event.
Missing data handling:	For subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, and do not discontinue the treatment due to Lack of Efficacy or Adverse Event, subjects will be censored at the time of study withdrawal, considering a non-informative censoring. For subjects who do not request rescue medication during the 24-hour study period, do not discontinue the treatment due to Lack of Efficacy or Adverse Event, and do not withdraw from the study before 24 hours, subjects will be censored at the time of 24 hours, considering a non-informative censoring. [redacted]

Status : Approved

	[redacted]
Population level Summary:	Proportion of subjects who request for rescue analgesic during the first 12 hours

[redacted]

17.6.4 Subgroup Analysis

The 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 17.5.3 Data Computations and Handling of Missing Values.

17.7 Safety Analysis

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

17.7.1 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.

Status : Approved

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.

17.8 Interim Analysis

Not applicable.

18. STUDY MONITORING

Before an investigational site can enter a subject into the study, a representative of JJCI may visit the investigational study site to:

- Determine the adequacy and capabilities 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 JJCI or its representatives. These responsibilities will be documented in a Clinical Study Agreement between JJCI and the Investigator(s).

During the study, a Monitor from JJCI or representative will have regular contacts with the investigational site for monitoring on-site and other contacts, 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

Status : Approved

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 JJCI. The PI 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 JJCI 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 PI or other staff needs information or study-related direction.

18.1 Direct access to source data/documents

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

19. 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 19.1 Audits and Inspections for more details regarding the audit process.

19.1 Audits and Inspections

Authorized representatives of JJCI, 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 JJCI 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 PI 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.

20. DATA HANDLING AND RECORDKEEPING

20.1 Case Report Forms / Electronic Data Capture

As used in this protocol, the term Case Report Form (CRF)/ electronic Case Report Form (eCRF) should be understood to refer to the Electronic Data Capture (EDC) system.

Status : Approved

All data will be collected on source documents first and then recorded in an EDC system. The EDC system is the database where pertinent study data are collected such as informed consent, visit date, demography, subject randomization, efficacy assessments, AEs, Special Situations, 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.

For all subjects, including screen failures and any subjects who discontinue prior to randomization, data will be recorded on source documents first. For randomized subjects, screen failures, and subjects who discontinue prior to randomization, the relevant data will then be recorded in an EDC system. For all screen failures and any subjects who discontinue prior to randomization, data collected in the EDC system will include, but is not limited to, informed consent, visit date, demography, eligibility, subject disposition, and AEs.

It is the PI's responsibility to ensure completion, review and approval of all information captured in the EDC system. The subject's data in the EDC system must be electronically signed by the PI. These signatures serve to attest that the information contained in the EDC system is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Subject site-specific source documents are the PI'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 system 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 and kept at the clinical site.

20.2 Source Documents

The PI/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).

20.3 Inspection of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the PI 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.

20.4 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. The retention period is two years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or per local requirements if longer than two years, or if not approved

Status : Approved

two years following the discontinuance of the test article for investigation. If it becomes necessary for JJCI or the Regulatory Authority to review any documentation relating to the study, the PI must permit access to such records.

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

21. PUBLICATION POLICY

Publication of study results by the PI 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.

Status : Approved

22. LIST OF REFERENCES

1. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191-2194.

2. Guzman F, Braun C, Lim RKS, et al. Narcotic and non-narcotic analgesics which block visceral pain evoked by intra-arterial injection of bradykinin and other analgesic agents. Arch Intern Pharmacodyn Ther 1964;149:571-588.

3. Lim RKS, Guzman F, Rodgers DW, et al. Site of action of narcotic and non-narcotic analgesics determined by blocking bradykinin-evoked visceral pain. Arch Intern Pharmacodyn 1964;152:25-58.

4. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther. 2006;79(1):9-19.

5. Pickering G, Loriot MA, Libert F, Eschalier A, Beaune P, Dubray C. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther. 2006;79(4):371-378.

6. Mallet C, Daulhac L, Bonnefont J, et al. Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. Pain. 2008;139(1):190-200.

7. Koch-Weser J. Drug therapy; acetaminophen. N Engl J Med 1976;295:1297-1300.

8. Milton AS. Modern views on the pathogenesis of fever and the mode of action of antipyretic drugs. J Pharm Pharmacol 1976;28:393-399.

9. Ameer B, Greenblatt DJ. Acetaminophen. Ann Intern Med 1977;87:202-209.

10. Product Monograph for Aleve (Naproxen Sodium Tablets USP/Liquid Gels/Capsules 220 mg). Bayer Inc. Consumer Care. Revised 8 January 2015

11. Todd PA, Clissold SP. Naproxen. A reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. Drugs. 1990;40(1):91-137.

12. Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. Clin Pharmacokinet. 1997;32:268-293.

13. Cooper SA, Desjardins PJ. The value of the dental impaction pain model in drug development. Methods Mol Biol. 2010;617:175-190.

14. Cooper SA, Desjardins PJ, Turk DC, et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain. 2016;157(2):288-301.

Status : Approved

23. APPENDICES

Status : Approved

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

Status : Approved