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CLINICAL STUDY PROTOCOL

CCSPAA005197

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Multidose Clinical Trial to Evaluate a Fixed Combination of Acetaminophen/Naproxen Sodium in Acute Postoperative Pain Following Bunionectomy

Investigational Product Name	Acetaminophen/Naproxen sodium
Protocol Number	CCSPAA005197
IND / IDE / EudraCT number	[redacted]
Phase	Phase III
Version and Date	Version 6.0 12Mar2024 (Amendment #05) Version 5.0 07Dec2023 (Amendment #04) Version 4.0 16Nov2023 (Amendment #03) Version 3.0 28Jul2023 (Amendment #02) Version 2.0 24Jul2023 (Amendment #01) Version 1.0 20Apr2023 Cumulative list with most recent first

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1. SYNOPSIS

Name and Address of the Sponsor/Company of the clinical study: Johnson & Johnson Consumer, Inc. [redacted]
Active Ingredient(s): Acetaminophen/Naproxen sodium
Title of Study: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Multidose Clinical Trial to Evaluate a Fixed Combination of Acetaminophen/Naproxen Sodium in Acute Postoperative Pain Following Bunionectomy
Countries: United States of America
Study Site(s): **Site 1001**: [redacted] **Site 1002**: [redacted] **Site 1003**: [redacted]
Principal Investigator: **Site 1001**: [redacted] **Site 1002**: [redacted] **Site 1003**: [redacted]
Phase of Development: Phase III
Objectives: **Primary:** • To evaluate the analgesic efficacy of a fixed combination of acetaminophen/naproxen sodium administered every 12 hours compared to placebo over a 48-hour period. **Secondary:** • To evaluate the onset and duration of analgesia of a fixed combination of acetaminophen/naproxen sodium. **Safety:** • To evaluate the safety and tolerability of a fixed combination of acetaminophen/naproxen sodium in a postoperative population.

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Methodology:

This will be a randomized, double-blind, parallel-group, placebo-controlled study to evaluate the analgesic efficacy and safety of the fixed combination of acetaminophen/naproxen sodium dosed every 12 hours for 48 hours.

Participants will undergo primary, unilateral, distal, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures.

Popliteal nerve catheter will be placed prior to the surgical procedure and will be removed between 5:00AM and 7:00AM the following morning. Following removal of the popliteal block, participants will be randomized to receive either study drug or placebo if their pain intensity reaches the threshold for inclusion (see Postoperative Inclusion Criteria below) before 2:00PM the day after surgery, at which point a baseline pain score will be recorded.

An adequate number of subjects will be randomized to ensure that 120 subjects complete the study. Subjects who meet the randomization criteria (see Postoperative Inclusion Criteria below) at Baseline will be assigned to one of the following two treatment groups, with equal allocation:

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

All treatments will be administered as two tablets orally every 12 hours for 4 doses in total (at 0, 12, 24 and 36 hours). In order to maintain blinding, a matched placebo that is indistinguishable from the investigational fixed combination product will be used. Rescue analgesic medication (oral oxycodone immediate release 5 mg every four hours PRN) will be available for subjects as needed for intolerable pain. Study medication will be administered on the scheduled basis regardless of use of rescue medication.

Self-reported pain intensity will be collected using a 0-10 Numerical Rating Scale (PI-NRS) immediately prior to Baseline (Hour 0 = First dose of IP). Pain intensity will be collected at 0.25, 0.5, 0.75, 1, 1.25 and 1.5 hours with a ± 5-minute window, and hourly from 2 through 12 hours with a ± 10-minute window, and every 4 hours from 12 through 48 hours with a ± 10-minute window, and immediately prior (– 10 minutes) to each administration of rescue (if applicable).

[redacted]

Time to perceptible pain relief and time to meaningful pain relief will be collected after the first dose of study treatment using two separate stopwatches.

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Time of request for rescue medication and time of administration of rescue medication will be recorded for every administration of rescue medication throughout the treatment period.

[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 Days 7 and 10 of the study.

Number of planned subjects:

An adequate number of subjects will be enrolled for 120 subjects to complete the study.

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. Participant is 16 to 65 years of age (inclusive) at the time of Screening.
2. Females have a negative urine pregnancy at Screening and on the morning of surgery.
3. Weigh 100 pounds or greater and have a body mass index (BMI) of 17.5 to 38.0 (inclusive) at Screening.
4. Scheduled to undergo primary, unilateral, distal, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures (see Surgical and Anesthetic Protocol Appendix 24.1). Subjects who have previously undergone bunionectomy on the contralateral foot will not be prohibited from enrolling in this study if performed ≥ 6 months from screening.
5. 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.
6. 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).
7. Participant agrees to the contraceptive requirements.
8. Are willing for this to be the only investigational product used during the study.
9. Have a negative urine drug screen at Screening, and on day of surgical procedure.
    a. A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary will not disqualify a subject.

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b. Drug screen results must be negative for a subject to receive study medication, a positive THC screen will only be exclusionary on Day of surgery (Day 0)

10. Have a negative alcohol screening test on day of surgical procedure.

Exclusion Criteria

Subjects will be excluded if they:

1. Are female and are pregnant, breastfeeding, or currently trying to become pregnant.
2. Are male with a pregnant partner or a partner who is currently trying to become pregnant.
3. Have a known allergy or hypersensitivity to:
    a. Naproxen or other nonsteroidal anti-inflammatory drugs, including aspirin
    b. Oxycodone or other opioids
    c. Acetaminophen
    d. Any other drug listed in the Surgical and Anesthetic Protocol or Postoperative Pain Management sections of the study protocol.
4. Have presence or a history of major medical condition that in the Investigator's opinion may jeopardize the subject's safety or well-being, or the integrity of the study, e.g.:
    a. Hepatic, renal, pancreatic, gastrointestinal, cardiovascular, cerebrovascular, or thyroid diseases
    b. History of head injury or seizures
    c. History of respiratory depression or lung problems such as but not limited to asthma or chronic obstructive pulmonary disease
    d. Psychiatric disorders (although subjects with well-controlled depression or anxiety, who are on a stable dose of medication may be allowed)
    e. Problems urinating
    f. History of blockage or narrowing of the stomach or intestines
    g. Uncontrolled hypertension indicated as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg. Blood pressure may be repeated after the subject has remained in a rested state for at least 10 minutes. The final blood pressure value will be used for eligibility.
    h. Uncontrolled diabetes, as determined by the Investigator, in the last six months
    i. Medical conditions that would interfere with normal pain perception (example diabetic neuropathy) in the opinion of the Investigator.

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5. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last two years.
6. Are not able to swallow whole large tablets or capsules.
7. Subjects will be excluded from the study for any of the following:
    a. Routine use of oral analgesics ≥ 3 times per week for a medical condition unrelated to bunion pain in the 2 months prior to surgery
    b. Opioid tolerant, i.e., the subject is currently taking or has taken a chronic opioid for pain at a dose greater than or equal to 10 mg hydrocodone per day, more than 1 out of 7 days per week, in the 2 months prior to surgery
    c. History of chronic tranquilizer use, heavy-drinking, opioid abuse, or other substance abuse, as judged by the Investigator, 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)
    d. Use of any immunosuppressive drugs, corticosteroids (except for topical corticosteroids), or injectable or oral anticoagulants (e.g., heparin, Lovenox, Xarelto, Eliquis, Pradaxa, Coumadin, Miradon) within 2 weeks prior to surgery
    e. Use of monoamine oxidase inhibitors within 2 weeks prior to surgery
    f. Use of alcohol within 24 hours prior to surgery
    g. Consumption of 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, vaping devices) < 12 hours prior to surgery
    h. Use of any other over-the-counter or prescription medications or supplements that, in the Investigator's opinion may cause participation in the study to jeopardize the subject's safety or well-being, or may jeopardize the integrity of the study, within 5 days (or longer if the Investigator deems a longer washout is warranted) prior to surgery. (Note: allowed medications should not impact pain perception and should not be a potentially interacting drug as noted in the Investigator Brochure.)
    i. Use of vitamins, dietary, and herbal supplements within 5 days before the first dose of study medication.
8. Have a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV).
9. Have participated in any interventional clinical trials withing 30 days before Screening.

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10. Are related to those persons involved directly or indirectly with the conduct of this study (i.e., Principal Investigator, sub-investigators, study coordinators, other site personnel, employees of Johnson & Johnson [J&J] subsidiaries, contractors of J&J, and the families of each).

Postoperative Inclusion Criteria

Subjects must meet the below criteria following bunionectomy surgery in order to be randomized:

10. Subject reports both of the following after discontinuation of the popliteal block and before 2:00PM on Day 1:
    a. Moderate or severe pain on a 4-point categorical pain rating scale (with categories of none, mild, moderate, or severe)
    b. A score ≥ 5 on 11-point Pain Intensity-Numerical Rating Scale (PI-NRS)
11. Subject is able to answer questions and follow commands, and appropriately participate in requisite pain evaluation assessments dictated in the protocol.
12. The surgical procedure from incision to closure was not longer than 2 hours.
13. The subject has had no evidence of respiratory insufficiency, clinically significant hypotension, bradycardia, or any other abnormality, during or following surgery that, in the Investigator's opinion, significantly increases the risks of study drug administration.
14. There were no significant deviations from the surgical protocol, anesthetic protocol, or specified analgesic regimen, that would, in the opinion of the Investigator, put the subject at risk of participation in the trial, confound the analgesic endpoints of the trial or cause concern regarding the subject's ability to participate in the trial.

Postoperative Pain Management (Surgery up to Randomization):

A continuous popliteal block infusion (0.2% ropivacaine, volume at the discretion of the Investigator) should be the first line of analgesic treatment for all subjects. If subjects require additional analgesia, the following postoperative pain management regimen is allowed:

1. Ice may be applied topically (30 min "on" and 30 min "off") as needed. Ice must be discontinued up to 30 minutes prior to block removal.
2. Ketorolac 30 mg IV may be administered for subjects requiring additional analgesia, and may be repeated Q6h PRN with the last dose administered no later than 21:00 on the day of surgery (Day 0)
3. In subjects requiring further analgesia, a 2 to 4 mg dose of morphine sulfate may be administered IV Q2h PRN up to 2 hours prior to block removal on the day after surgery (Day 1)

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4. Subjects whose pain cannot be adequately controlled utilizing the above regimen (popliteal infusion/ice/ketorolac/morphine) will be discontinued from the study and considered a screen failure.

Postoperative Pain Management/Rescue Medication (Post Randomization):

- Rescue analgesic medication (oral oxycodone immediate release 5 mg every four hours PRN) will be available for subjects as needed for intolerable pain

No additional pain management/rescue medication post randomization will be allowed. Study medication will be administered on the scheduled basis regardless of use of rescue medication.

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

- Acetaminophen [redacted] g/Naproxen Sodium [redacted] (administered as two tablets of Acetaminophen [redacted] /Naproxen Sodium [redacted]) every 12 hours to be taken orally with up to 180 mL water at ambient temperature

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

- Placebo (administered as two placebo tablets) every 12 hours to be taken orally with up to 180 mL water at ambient temperature

Duration of study per subject:

The duration of the study per subject is up to eleven days, including pre-surgery/surgery (Day 0) Post-Surgery/Baseline/Treatment/Discharge (Day 1 to Day 3) and End of Study/Follow-up (Days 7 to 10), and excluding Screening (Day -30 to Day -1).

Duration of Treatment:

Forty-eight (48) hours. Subjects will be observed at the study site for at least 48 hours starting after the first dose of study medication, and all safety data will be collected according to the protocol-mandated schedule, regardless of whether or not the subject receives rescue medication, vomits, experiences other adverse events (AE), or terminates from the study. Subjects will remain at the site for the full 48-hour observation period.

Criteria for Efficacy Evaluation:

Primary efficacy endpoint:

- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 24 hours (SPID 0-24)

Secondary efficacy endpoints:

- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 12 hours (SPID 0-12)
- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 48 hours (SPID 0-48)
- Time to confirmed perceptible pain relief (TCPR) as measured with the double stopwatch

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- Time to meaningful pain relief (TMPR) as measured with the double stopwatch
- Time to first use of rescue medication
- Proportion of subjects who use rescue medication during the first 12 hours

[redacted]

Safety:
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 stabilize at a level acceptable to the medically qualified Investigator or designee, and recorded on the 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 0-24, will be analyzed using analysis of covariance including baseline pain numerical score, center and treatment group in the model. The same approach will be used for all other endpoints based on PID [redacted] scores. [redacted] l.

TCPR, TMPR and Time to first use of rescue medication, [redacted] will be analyzed using survival data analysis. The survival function (cumulative proportions of subjects at each time point) and the median survival time will be estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared using the Wilcoxon test, stratifying on center.

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The proportion of subjects who use rescue medication will be based on the Kaplan-Meier method (to account for potential censoring), stratifying on center with standard errors estimated by the Greenwood formula. [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 using a fixed-sequence approach in the following order:

1. SPID 0-24
2. SPID 0-12
3. SPID 0-48
4. TCPR
5. TMPR
6. Time to First Use of Rescue Medication
7. Proportion of Subjects Who Use Rescue Medication during the first 12 hours

If, at any point in this sequence, Acetaminophen [redacted] /Naproxen sodium [redacted] is not statistically significantly better than placebo, then all further testing in the sequence will be exploratory. This above fixed-sequence procedure will provide strong familywise error rate control at 5% for the family of comparisons involving primary and secondary endpoints.

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2. ACTIVITY SCHEDULE

Table 1: Activity Schedule

	Pre-Treatment			Treatment	Discharge	End of Study/Follow up	
Clinical Study Activities	**Screening (Day -30 to Day -1)**	**Pre-surgery/ Surgery (-24hrs. to Surgery)**	**Post-Surgery: Block removal through randomization**	**0-48 hrs.** (post randomization / study drug administration)	**>48 hrs.** (post randomization / study drug administration)	**Telephone Follow-up Day 7(+ 3 days)**	**Early Termination**
Informed Consent Form Signed	X						
[redacted]	[redacted]						
Eligibility Assessment	X	X					
Postoperative Inclusion Randomization criteria			X				
Covid 19 testing (per site policy)[1]	X[1]						
Demographics (age, sex, race, and ethnicity)	X						
Medical History	X						
Previous & Concomitant Medications	X	X	X	X	X	X	X
Rescue Medications				X			
Physical Examination[2]	X[2]						
Focused Physical Examination of surgical foot[2]					X[2]		X[2]
Vital Signs (Blood Pressure, Body Temperature, Respiratory Rate and Heart Rate)[3]	X[3]	X[3]					
Preoperative ECG and Labs[4]	X[4]						
Urine Pregnancy[5]	X[5]	X[5]					
Urine drug screening[6]	X[6]	X[6]					
Alcohol screening test[7]	X[7]	X[7]					
Serology: HIV and hepatitis screening	X						
Admission to Unit		X					
Confinement		X	X	X			
Popliteal Catheter placement[8]		X[8]					
Completion of Surgery[9]		X[9]					
Popliteal Catheter Removal[10]			X[10]				
Randomization[11]			X[11]				
Subject instruction on PI-NRS, [redacted] and double stopwatch		X					
Adverse Event Assessment	X	X	X	X	X	X	X
Study Drug Administration[12]				X[12]			

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	Pre-Treatment			Treatment	Discharge	End of Study/Follow up	
Clinical Study Activities	**Screening (Day -30 to Day -1)**	**Pre-surgery/ Surgery (-24hrs. to Surgery)**	**Post-Surgery: Block removal through randomization**	**0-48 hrs.** (post randomization / study drug administration)	**>48 hrs.** (post randomization / study drug administration)	**Telephone Follow-up Day 7(+ 3 days)**	**Early Termination**
Pain Intensity Assessment (PI-NRS)[13]			X[13]	X[13]			X[13]
[redacted]				[redacted]			[redacted]
4-Point Categorical Pain Rating Scale			X				
Time to Perceptible and Meaningful Relief[14]				X[14]			
[redacted]				[redacted]			[redacted]
Evaluate for discharge procedures					X		

1. COVID testing will be performed in accordance with site policy and may be repeated, as necessary.
2. Physical examinations must be performed by a PI, Sub-Investigator, physician's assistant, or Nurse Practitioner. Prior to discharge or early termination if the patient withdraws while still in the clinic, the PI/designee will perform a focused physical examination that includes examination of the surgical foot and addressing any subject complaints. Any focused physical examination data collected during the assessment will be captured in source documents and not recorded in the EDC system, unless related to an adverse event.
3. Vital signs including supine blood pressure, heart rate, temperature and respiratory rate will be recorded at Screening and prior to surgery. All measurements should be obtained after resting (seated/reclined) for ≥ 5 minutes. Height, weight and BMI will be collected at screening only.
4. ECG and labs may be performed at the discretion of the surgical team for preoperative assessment. Preoperative labs will be performed using local laboratories. Any ECG or lab data collected during the preoperative assessment will be captured in source documents and not recorded in the EDC system.
5. The urine pregnancy test must be performed at screening and on the morning of surgery in all females on Day 0. A urine pregnancy test with a negative result must be obtained within 24 hours before undergoing surgery.
6. Urine drug screen must be negative at screening (excluding THC) and on day of surgery (including THC).
7. Alcohol screening test must be negative on the day of surgery. Any form of alcohol testing (urine, breath, saliva, etc.) is acceptable to meet the criteria.
8. Popliteal catheter placement is to be performed within 2 hours prior to scheduled surgery.
9. Surgery start time is considered time of first incision and the completion of surgery is the time of the last suture is closed, and the time will be captured in source document and eCRF.
10. Popliteal nerve catheter will be removed between 5:00AM and 7:00AM the following morning (Day 1)
11. Randomization occurs after review of postoperative inclusion randomization criteria.
12. First dose is administered Day 1, Hour 0. Additional dosing every 12 hours, for 4 doses in total (at 12, 24 and 36 hours). A ± 15-minute window is allowed for dosing after the first dose administration.
13. Resting self-reported pain intensity will be collected using a 0-10 numerical rating scale (PI-NRS) for qualification and also immediately prior to First dose of IP (Baseline, Hour 0). Pain intensity will be collected at 0.25, 0.5, 0.75, 1, 1.25 and 1.5 hours, with a ± 5-minute window, and hourly from 2 through 12 hours, with a ± 10-minute window, and every 4 hours from 12 through 48 hours, with a ± 10-minute window. If a subject uses rescue medication, pain intensity will be collected immediately prior (– 10-minute) to each administration of rescue medication.
14. Time to perceptible and meaningful relief will be assessed by a double stopwatch method after the first dose of study medication. [redacted]

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Table 2: Summary of allowable windows

Clinical Study Activity	Timepoint window applies	Allowable Window
Vital Signs	Vital Signs should be collected after the subject has rested quietly for at least 5 minutes in a supine position	
PI-NRS	0.25, 0.5, 0.75, 1, 1.25 and 1.5 hours Assessment should be collected after the subject has rested in bed at least 20 minutes	± 5 minutes
PI-NRS	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 hours Assessment should be collected after the subject has rested in bed at least 20 minutes	± 10 minutes
PI-NRS associated with rescue medication	Immediately prior to administering rescue medication	– 10 minutes
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Study Drug Administration	[redacted]	± 15 minutes
End of Study/Telephone Follow-up Visit	Day 7	+ 3 days

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Status : Approved

6. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
BMI	Body Mass Index (kg/m^2)
CRF	Case Report Form
DO	Doctor of Osteopathic Medicine
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIU	Exposure In Utero
GCP	Good Clinical Practice
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
MAR	Missing at Random
MD	Medical Doctor
MMRM	Mixed Model for Repeated Measures
NRS	Numerical Rating Scale
[redacted]	[redacted]
[redacted]	[redacted]
PI	Principal Investigator
PI-NRS	Pain Intensity-Numerical Rating Scale
PID	Pain Intensity Difference
PQC	Product Quality Complaint
[redacted]	[redacted]
SAE	Serious Adverse Event
SPID 0-12	Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0-12 hours
SPID 0-24	Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0-24 hours

Status : Approved

Abbreviation or Specialist Term	Explanation
SPID 0-48	Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0-48 hours
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCPR	Time to Confirmed Perceptible Pain Relief
THC	Tetrahydrocannabinol
TMPR	Time to Meaningful Pain Relief
[redacted]	[redacted]

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). 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 5 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/Sponsor Representative and the PI, if required by the applicable regulatory requirement(s) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission as required by the applicable regulatory requirement(s) 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). The Sponsor may amend the protocol at any time should local public health measures require.

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 Case Report Form (CRF) in lieu of the subject's name. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form 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.

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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. 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 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 investigator’s clinical team, written assent to participate in the study must be obtained from prospective subjects who are below the age of legal consent yet old enough to understand details of the study as required by the site’s IRB/IEC or 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 he or she will be asked to do and what procedures he 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/study monitor.

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.

7.5. Pharmacogenomic Sampling

Not Applicable

Status : Approved

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 Laboratory, and IRB/IEC(s). The complete contact list will be maintained in the trial master file throughout the study. An abbreviated contact list with all site relevant contact information will be maintained in the site master file.

9. INTRODUCTION

The investigational product (IP) being evaluated in this study is a fixed combination tablet of immediate release (IR) acetaminophen and naproxen sodium under development 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).

9.1. Background

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]

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.[7] The therapeutic effects of naproxen are produced through nonselective inhibition of cyclooxygenase enzymes (COX-1 and COX-2) resulting in inhibition of prostaglandin synthesis.[8] 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.[9]

The current study is a Phase 3 clinical trial being conducted as part of the development program of a novel fixed combination of acetaminophen/naproxen sodium. This study will evaluate the multiple-dose analgesic efficacy and safety of the fixed combination of acetaminophen/naproxen sodium compared with placebo when dosed at 12-hour intervals over a 48-hour observation period.

Status : Approved

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 placebo is included in the placebo ingredient list.

9.2. Rationale

This is a Phase 3 randomized, double-blind, parallel-group, placebo-controlled multi-dose clinical trial being conducted as part of the development program of a novel fixed combination of acetaminophen [redacted]/naproxen sodium [redacted] The study will evaluate the analgesic efficacy and safety of the fixed combination of acetaminophen/naproxen sodium compared with placebo dosed at 12-hour intervals over a 48-hour observation period.

Concomitant administration of acetaminophen [redacted]/naproxen sodium [redacted] has recently been evaluated in a proof-of-concept study utilizing a postoperative dental pain model.[10] That study provided evidence that a single dose of acetaminophen [redacted]/naproxen sodium [redacted] can be a highly effective analgesic for postsurgical pain. In that study, the efficacy of acetaminophen [redacted]/naproxen sodium [redacted] was superior to that of hydrocodone [redacted]/acetaminophen [redacted] across multiple measures, and similar to that of naproxen sodium [redacted]. The fixed combination demonstrated strong separation from placebo for Pain Intensity Difference (PID) throughout the 12-hour observation period, and a low rate of rescue at 12 hours. Based on the results of the POC study, the Sponsor anticipates that the fixed combination will provide clinically meaningful analgesic efficacy in subjects with moderate to severe postsurgical pain when dosed at a 12-hour interval.

In contrast to the proof-of-concept study, this current study protocol utilizes a postoperative bunionectomy pain model. This model employs a standardized bunionectomy surgical procedure, generating pain with sufficient intensity and duration to enable evaluation of efficacy over multiple days.[11] The bunionectomy model has been widely utilized in previous analgesic investigations and is well-established in the literature for evaluation of efficacy and safety of analgesics for acute pain. While the bunionectomy model has been reported to have a lower standardized effect size than the dental pain model, it has the advantage of producing pain with a sufficient duration to maintain strong assay sensitivity for approximately 72 hours following the surgery.[11] This feature makes the bunionectomy model well-suited for multiple dose studies such as this one. The study procedures and anesthetic protocol have been designed to help ensure adequate pain intensity to maintain strong assay sensitivity for the duration observation period without generating a level of pain intensity that overwhelms the analgesic effects of the fixed combination product.

The Sponsor anticipates that this design will maintain a sufficient pain level after each repeated dose to allow for demonstration of treatment differences throughout the 48-hour observation period. The multiple-dose design of this study will also enable evaluation of the safety of the fixed combination when administered at the target 12-hour dosing interval through the collection, evaluation, and analysis of adverse events (AEs).

Status : Approved

10. STUDY OBJECTIVES

10.1. Primary Objective(s)

To evaluate the analgesic efficacy of a fixed combination of acetaminophen/naproxen sodium administered every 12 hours compared to placebo over a 48-hour period

10.2. Secondary Objective(s)

To evaluate the onset and duration of analgesia of a fixed combination of acetaminophen/naproxen sodium

10.3. Safety Objective(s)

To evaluate the safety and tolerability of a fixed combination of acetaminophen/naproxen sodium in a postoperative population

10.4. Primary Endpoint(s)

- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 24 hours (SPID 0-24)

10.5. Secondary Endpoint(s)

- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 12 hours (SPID 0-12)
- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 48 hours (SPID 0-48)
- Time to confirmed perceptible pain relief (TCPR) as measured with the double stopwatch
- Time to meaningful pain relief (TMPR) as measured with the double stopwatch
- Time to first use of rescue medication
- Proportion of subjects who use rescue medication during the first 12 hours

10.6. Exploratory Endpoint(s)



Status : Approved

[redacted]

11. INVESTIGATIONAL PLAN

11.1. Overall Study Design and Plan

This is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the analgesic efficacy and safety of the fixed combination of acetaminophen/naproxen sodium dosed every 12 hours for 4 doses in total.

Subjects requiring bunionectomy, age 16 to 65 years, will be screened for participation at approximately 3 study centers in the United States. Screening will occur within 30 days before study drug administration. After signing the informed consent (assent, if applicable), [redacted] medical history, physical examination, serology testing, urine drug screen, pregnancy testing (for females), and vital sign measurements will be completed during the screening visit. Preoperative 12-lead electrocardiogram (ECG) and additional laboratory assessments may also be performed at the discretion of the surgical team for the purposes of preoperative assessment.

On the day of surgery (Day 0), subjects will undergo primary, unilateral, distal, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures. Following surgery, subjects will be managed using a popliteal block until the morning of Day 1, when the block will be stopped (between 05:00 and 07:00) and subjects will be evaluated for eligibility for randomization. An adequate number of subjects will be randomized to ensure that 120 subjects complete the study.

Subjects who meet the randomization criteria at Baseline will be assigned to one of the two treatment groups, with equal allocation. Both treatments will be administered as two tablets every 12 hours for 4 doses in total (at Hour 0, 12, 24 and 36). Subjects will remain at the study center for approximately 48 hours after treatment initiation. After completion of 48 hours of evaluation, subjects may be discharged from the study center.

All treated subjects will receive an End of Study/follow-up telephone call on Day 7 to complete the follow-up study assessments.

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Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

Efficacy assessments will include pain intensity, [redacted] use of rescue medication, time to perceptible and meaningful pain relief, a [redacted]. Safety assessments will include monitoring of AEs.

The following summarizes key activities for each phase of this study: 1) Pretreatment Phase, 2) Treatment Phase, 3) Follow-up Phase.

1. **Pretreatment Phase:**
    a. Screening Period (Day -30 to Day -1): Subjects will be consented and screened
    b. Pre-Surgery/Surgery (Day 0)
        i. Pre-surgery: Subjects will be admitted to the study center and reassessed for eligibility for the study. Pre-surgery activities will be conducted.
        ii. Surgery: Eligible subjects will undergo primary, unilateral, first metatarsal Austin bunionectomy (osteotomy and internal fixation) with no additional collateral procedures. Pre/Intraoperatively, the subject will have a popliteal block placed. A standard anesthetic regimen will be followed for all subjects as outlined in the surgery and anesthesia protocol (Appendix 24.1)
        iii. Postoperative period: Following surgery, subjects will have the popliteal block maintained and will be transferred to the appropriate recovery unit. Treatments allowed during the postoperative period will include maintenance of the popliteal block, topical ice, and analgesic administration (ketorolac and/or morphine) as described (Section 13.10)
    c. Randomization Qualification (Day 1): Following discontinuation of the popliteal block and other postoperative pain management, subjects will be assessed for randomization to study treatment. Subjects will be eligible for randomization if they meet all of the postoperative inclusion criteria starting after discontinuation of the popliteal block (05:00 to 07:00), and prior to 2:00PM on Day 1 (Section 12.1.3).
2. **Treatment Phase (Hour 0 through Hour 48)**

    Once the subject meets postoperative inclusion criteria, they will be randomized in a 1:1 ratio to treatment with acetaminophen [redacted]/naproxen sodium [redacted] or placebo, administered as two tablets every 12 hours for 4 doses in total (at Hour 0, 12, 24 and 36). Subjects will be domiciled at the study center throughout the treatment phase.

    Randomization and administration of the first dose of study drug must be within 15 minutes of meeting the qualifying categorical pain rating scale and pain intensity numerical pain rating scale (PI-NRS) scores. After randomization, immediately prior to study drug administration, the baseline pain intensity assessment via NRS must be completed. Postoperative inclusion criteria will be assessed based on the qualifying NRS pain intensity assessment and not the baseline NRS.

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The time of first dose of study drug (Dose 1) will be recorded as Hour 0 from which subsequent 12-hour dosing times will be determined. Subjects will be administered a study dose according to their randomization every 12 hours for 4 doses in total.

Subjects with inadequately controlled pain symptoms may request rescue medication. Subjects should be encouraged to use rescue only when their pain is intolerable. Pain intensity assessments will be completed prior to each dose of rescue medication.

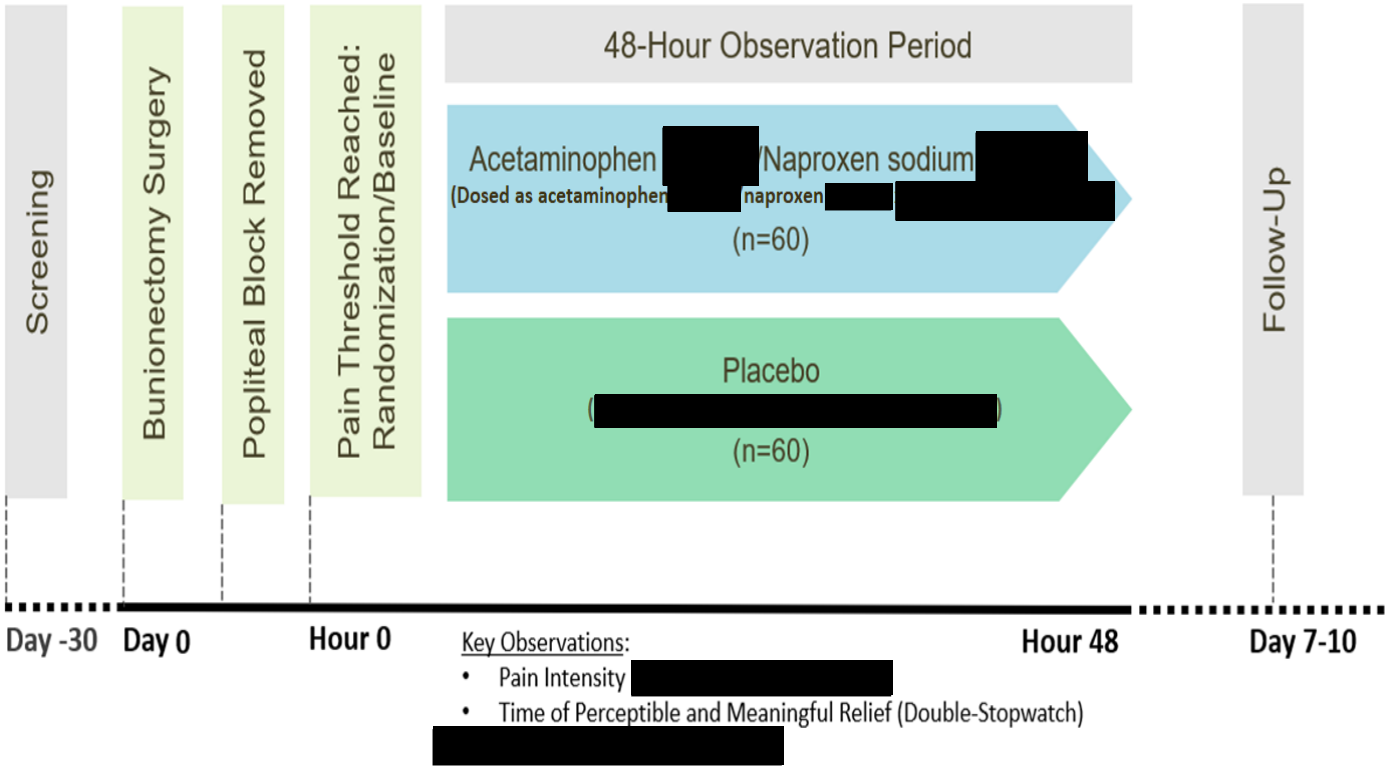
Study assessments completed during the treatment phase will include pain intensity (PI-NRS), [redacted] time to perceptible and meaningful pain relief (double stopwatch), [redacted] use of concomitant medication, and adverse event monitoring.

3. Follow-up Phase:

After completing the study assessments through Hour 48, subjects may be discharged from the study center. Subjects will be provided with routine standard of care for pain management after discharge from the study center.

All randomized 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 Days 7 and 10 of the study.

Figure 1: Schematic Study Design



Status : Approved

11.2. Discussion of Study Design

This study will evaluate the efficacy and safety of repeated dosing with acetaminophen [redacted]/naproxen sodium [redacted], administered as two tablets of an acetaminophen [redacted]/naproxen sodium [redacted] fixed combination following bunionectomy surgery. In a previous study in the postoperative dental pain model, the efficacy of acetaminophen [redacted]/naproxen sodium [redacted] was superior to that of the hydrocodone [redacted]/acetaminophen [redacted] across multiple measures, and similar to that of naproxen sodium [redacted].[10] Based on this study and the known therapeutic profiles of single-ingredient acetaminophen and naproxen sodium, the Sponsor anticipates that this fixed combination will provide rapid analgesic effects with a 12-hour duration while maintaining a safety profile supportive of nonprescription use.

This study will further explore the efficacy and safety of dosing with acetaminophen [redacted]/naproxen sodium [redacted] on a Q12h dosing schedule, in an adequate and well controlled trial of moderate to severe pain following bunionectomy. Bunionectomy is an established hard tissue model of postoperative pain lasting in excess of 48 hours. The inclusion of a placebo control group will support the statistical analysis results of the fixed dose 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 a time period set by the Sponsor (usually two weeks). All study materials must be collected and all CRFs and electronic source documents completed to the greatest extent possible.

In the case of early termination, the Sponsor must notify the end of the study to the national competent authority and the IRB/IEC of the Member State concerned immediately and at the latest within 15 days after the study is halted, clearly explain the reasons, and describe follow–up measures, if any, taken for safety reasons.

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.

Status : Approved

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. Participant is 16 to 65 years of age (inclusive) at the time of Screening
2. Females have a negative urine pregnancy at Screening and on the morning of surgery.
3. Weight of 100 pounds or greater and have a body mass index (BMI) of 17.5 to 38.0 (inclusive) at Screening.
4. Scheduled to undergo primary, unilateral, distal, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures (see Surgical and Anesthetic Protocol Appendix 24.1). Subjects who have previously undergone bunionectomy on the contralateral foot will not be prohibited from enrolling in this study if performed ≥ 6 months.
5. 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.
6. 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).
7. Participant agrees to the contraceptive requirements.
8. Are willing for this to be the only investigational product used during the study.
9. Have a negative urine drug screen at Screening, and on day of surgical procedure.
    a. A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary will not disqualify a subject
    b. Drug screen results must be negative for a subject to receive study medication, a positive THC screen will only be exclusionary on day of surgery (Day 0)
10. Have a negative alcohol screening test on day of surgical procedure.

12.1.2. Subject Exclusion Criteria

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

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 a known allergy or hypersensitivity to:
    a. Naproxen or other nonsteroidal anti-inflammatory drugs, including aspirin
    b. Oxycodone or other opioids
    c. Acetaminophen

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d. Any other drug listed in the Surgical and Anesthetic Protocol or Postoperative Pain Management of the study protocol (Appendix 24.1)

4. Have presence or a history of major medical condition that in the Investigator's opinion may jeopardize the subject's safety or well-being, or the integrity of the study, e.g.:
    a. Hepatic, renal, pancreatic, gastrointestinal, cardiovascular, cerebrovascular, or thyroid diseases
    b. History of head injury or seizures
    c. History of respiratory depression or lung problems such as but not limited to asthma or chronic obstructive pulmonary disease,
    d. Psychiatric disorders (although subjects with well-controlled depression or anxiety, who are on a stable dose of medication may be allowed)
    e. Problems urinating
    f. History of blockage or narrowing of the stomach or intestines
    g. Uncontrolled hypertension indicated as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg. Blood pressure may be repeated after the subject has remained in a rested state for at least 10 minutes. The final blood pressure value will be used for eligibility.
    h. Uncontrolled diabetes, as determined by the Investigator, in the last six months
    i. Medical conditions that would interfere with normal pain perception (example diabetic neuropathy) in the opinion of the Investigator.
5. Have a history of endoscopically documented peptic ulcer disease or bleeding disorder in the last two years.
6. Are not able to swallow whole large tablets or capsules.
7. Subjects will be excluded from the study for any of the following:
    a. Routine use of oral analgesics ≥3 times per week for a medical condition unrelated to bunion pain in the 2 months prior to surgery.
    b. Opioid tolerant, i.e., the subject is currently taking or has taken a chronic opioid for pain at a dose greater than or equal to 10 mg hydrocodone per day, more than 1 out of 7 days per week, in the 2 months prior to surgery.
    c. History of chronic tranquilizer use, heavy drinking, opioid abuse, or other substance abuse, as judged by the Investigator, 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).

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d. Use of any immunosuppressive drugs, corticosteroids (except for topical corticosteroids), or injectable or oral anticoagulants (e.g., heparin, Lovenox, Xarelto, Eliquis, Pradaxa, Coumadin, Miradon) within 2 weeks prior to surgery

e. Use of monoamine oxidase inhibitors within 2 weeks prior to surgery.

f. Use of alcohol within 24 hours prior to surgery

g. Consumption of 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, vaping devices) <12 hours prior to surgery

h. Use of any other over-the-counter or prescription medications or supplements that, in the Investigator's opinion, may cause participation in the study to jeopardize the subject's safety or well-being, or may jeopardize the integrity of the study, within 5 days (or longer if the investigator deems a longer washout is warranted) prior to surgery. (Note: allowed medications should not impact pain perception and should not be a potentially interacting drug as noted in the Investigator Brochure.)

i. Use of vitamins, dietary, and herbal supplements within 5 days before the first dose of study medication.

8. Have a positive test for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV).
9. Have participated in any interventional clinical trials within 30 days before Screening.
10. Are related to those persons involved directly or indirectly with the conduct of this study (i.e., Principal Investigator, sub-investigators, study coordinators, other site personnel, employees of Johnson & Johnson [J&J] subsidiaries, contractors of J&J, and the families of each).

12.1.3. Postoperative Inclusion Criteria

Subjects must meet the below criteria following bunionectomy surgery in order to be randomized:

10. Subject reports both of the following after discontinuation of the popliteal block and before 2:00 PM on Day 1:
    a. Moderate or severe pain on a 4-point categorical pain rating scale (with categories of none, mild, moderate, or severe
    b. A score ≥ 5 on 11-point Pain Intensity-Numerical Pain Rating Scale (PI-NRS)
11. Subject is able to answer questions and follow commands, and appropriately participate in requisite pain evaluation assessments dictated in the protocol.
12. The surgical procedure from incision to closure was not longer than 2 hours.

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13. The subject has had no evidence of respiratory insufficiency, clinically significant hypotension, brady cardia, or any other abnormality, during or following surgery that, in the Investigator's opinion, significantly increases the risks of study drug administration.
14. There were no significant deviations from the surgical protocol, anesthetic protocol, or specified analgesic regimen, that would, in the opinion of the Investigator, put the subject at risk of participation in the trial, confound the analgesic endpoints of the trial or cause concern regarding the subject's ability to participate in the trial.

12.1.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized/enrolled in the trial. Screen failures may occur at any time after signing the informed consent through post-surgery up until randomization. Subjects that fail screen will be considered either a screen failure subject or a post-surgical screen failure subject. A screen failure subject are those subjects that consent to participate in the clinical trial but are deemed to not qualify or the subject withdraws consent prior to the surgical procedure. A post-surgical screen failure is a subject that qualified based on the screening visit and was admitted into the study center and received a surgical bunionectomy but did not meet the postoperative criteria for enrollment or unable to adequately control their pain using the postoperative pain management prior to randomization. Minimal information that will be collected includes, but is not limited to, visit date, informed consent, demography, eligibility, subject disposition (including reason for screen failure) and any adverse events or serious adverse events.

12.1.5. 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 achieving the expected pharmacological action/therapeutic benefit evidenced by statements such as or similar to "the product did not work/perform as expected," this event will be categorized 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)

Subjects who withdraw consent to continue treatment or who are discontinued from the study before completing the protocol-specified duration of treatment should be encouraged to complete the early termination assessments (Section 2). Subjects will be encouraged to participate in the Day 7 End of Study/follow-up telephone interview. In case of questions surrounding the circumstances that a

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subject needs to be withdrawn from the study (e.g., protocol deviation), the Sponsor, or the Sponsor representative should be consulted. The date the subject is withdrawn and the primary reason for discontinuation will be recorded in the subject's source document and in the Subject Disposition electronic case report form (eCRF).

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

Discontinued subjects will not be replaced in the study. However, the study will enroll an adequate number of subjects to meet the target size of 120 subjects completing the study.

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

13. INVESTIGATIONAL PRODUCTS

13.1. Treatment Administration

Investigational product will be packaged in individual blister packs containing [redacted] tablets. Each blister pack will contain either the fixed-dose combination of acetaminophen [redacted]/naproxen sodium [redacted] tablets or placebo tablets.

Investigational product will be distributed to the study site using a designated distribution center identified by the Sponsor. The Sponsor will provide the Investigator with adequate quantities of investigational product and supplies to conduct the study.

13.2. Description of Investigational Products

Table 4: Investigational Products

	Treatment A	Treatment B
Active Ingredient(s)	Acetaminophen [redacted] / Naproxen sodium [redacted]	Placebo inert material
Dosage Form	Tablet	Tablet
Unit Dose	2 tablets	2 tablets
Route of Administration	Oral	Oral
Physical Description	White film coated plain faced pillow shaped tablet	White film coated plain faced pillow shaped tablet
Manufacturer	J&J Consumer Inc [redacted]	J&J Consumer Inc [redacted]

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13.3. Packaging and Labeling

Investigational products will be supplied by the Sponsor and provided in subject specific wallets containing eight count blisters. 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 contain [redacted] tablets and be a sufficient supply for administration of [redacted] doses per subject. The Sponsor will label the wallets for use per the standard operating procedures (SOPs). 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 wallet 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 Days 1 and 2. Subjects must meet criteria for randomization (Section 12.1). For subjects who meet the randomization criteria, a delegated licensed personnel will

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administer the assigned study treatment with up to 180 mL of water at ambient temperature to subjects.

Baseline pain assessments and drug administration will be completed in the subject's room. Study medication will be dispensed at the time the 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 pharmacist assigns the appropriate randomization number from the Sponsor-provided randomization list. The delegated pharmacy personnel will take out the corresponding wallet [redacted] with the same randomization number, remove Part 2 of the label from the wallet and dispense the appropriate assigned wallet 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 delegated pharmacy personnel will complete the study drug dispensing record. The study drug dispensing record will remain in a secure and locked area.

After entering the subject's room and while the subject is sitting up, the delegated licensed personnel will dispense the scheduled two tablets 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 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 delegated licensed personnel will inspect the subject's oral cavity to ensure that the study treatment was swallowed. The time at which the subject swallows first dose of IP will be recorded as Hour 0. Study drug will be administered to the subject within 15 minutes of the completion of the qualifying baseline pain assessments.

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.

13.5. Storage, Accountability and Disposal

The PI, or a designated study staff, will ensure that all investigational products are stored in a secured area, under recommended storage conditions at room temperature, 68ºF to 77ºF (20ºC to 25ºC), 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 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 pharmacy personnel and back-up staff members. 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.

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13.6. Randomization/Treatment Allocation

The randomization schedule will be generated by the Sponsor to ensure treatment blinding. After meeting the postoperative inclusion criteria, subjects will be randomized to receive one of two treatments (Acetaminophen [redacted]/Naproxen Sodium [redacted] or placebo) in a 1:1 ratio. The randomization will be stratified by center.

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.

When the blind is broken by defacing the unblinding laminate contained on Part II of the investigational product label, the PI will notify the Sponsor within 24 hours after determining that it was 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.

13.8. Treatment Compliance

Study treatments will be administered and supervised by the clinical site personnel. Any discrepancies from the IP administration instructions should be considered as protocol deviations.

13.9. Previous and Concomitant Medications

Medications or non-drug therapies used 30 days before the Screening visit and during the study will be recorded in the source document (e.g., subject medical chart, medical records, subject journal or diaries) and CRF.

Any medications taken from screening until after discharge/completion of the study will be documented as concomitant medications. Female subjects who are taking oral contraceptives will continue to take their prescribed medication daily.

Subjects who have taken any of the following medications within the specified timeframe will be excluded from the study. The following medications will not be permitted during the study period.

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- Vitamins, dietary, and herbal supplements are to be discontinued at least 5 days before the first dose of study medication,
- Routine use of oral analgesics (≥ 3 times per week for a medical condition unrelated to bunion pain in the 2 months prior to surgery),
- Chronic opioid medications (equivalent to ≥ 10 mg hydrocodone per day, more than 1 out of 7 days per week, in the 2 months prior to surgery),
- Chronic tranquilizer use, immunosuppressive drugs, corticosteroids (except for topical corticosteroids), or injectable or oral anticoagulants (e.g., heparin, Lovenox, Xarelto, Eliquis, Pradaxa, Coumadin, Miradon) within 2 weeks prior to surgery,
- Monoamine oxidase inhibitors within 2 weeks prior to surgery,
- Use of any other over-the-counter or prescription medications or supplements that, in the Investigator's opinion, may cause participation in the study to jeopardize the subject's safety or well-being, or may jeopardize the integrity of the study, within 5 days (or longer if the investigator deems a longer washout is warranted) prior to surgery. (Note: allowed medications should not impact pain perception and should not be a potentially interacting drug as noted in the Investigator Brochure.)

However, the PI should approve medication that may be required due to unexpected illness during the study. The usage must be reported to the Sponsor and recorded on the CRF. All subjects will be questioned about concomitant medications throughout the study. All concomitant medications taken during the study must be recorded with indication, daily dose, and start, stop times and dates of administration. Other analgesic agents are not permitted post-randomization in the study except for rescue medication as described in Section 13.11. Non-pharmacological approaches should be utilized, if at all possible, for AEs that require pain control e.g., headaches, backaches. If the AE cannot be adequately managed without additional analgesic medication, the subject will be discontinued for the AE and discontinuation procedures will apply. Concomitant medications and other treatments taken for or associated with an AE will be recorded on the eCRF and the source documents. However, additional postsurgical medications (e.g., antibiotics or analgesic prescriptions) and other treatments or therapies (e.g., ice packs) that are taken after the 48-hour assessment period through the follow-up interview will be captured on the source documents, but not in the eCRF.

13.10. Postoperative Pain Management (Prior to Randomization)

A continuous popliteal block infusion (0.2% ropivacaine, volume at the discretion of the Investigator) should be the first line of analgesic treatment for all subjects. If subjects require additional analgesia, the following postoperative pain management regimen is allowed:

1. Ice may be applied topically (30 min "on" and 30 min "off") as needed. Ice must be discontinued up to 30 minutes prior to block removal of the nerve block.
2. Ketorolac 30 mg IV may be administered for subjects requiring additional analgesia, and may be repeated Q6h PRN with the last dose administered no later than 21:00 on the day of surgery (Day 0)

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3. In subjects requiring further analgesia, a 2 to 4 mg dose of morphine sulfate may be administered IV Q2h PRN up to 2 hours prior to block removal on the day after surgery (Day 1)
4. Subjects whose pain cannot be adequately controlled utilizing the above regimen (popliteal infusion/ice/ketorolac/morphine) will be discontinued from the study and considered a screen failure.

13.11. Rescue Therapy (Post Randomization)

Rescue medication will be supplied by the study site.

Study investigators will review the investigational brochure prepared for acetaminophen/naproxen sodium in order to be aware of the safety related events which may be anticipated with its use. A fully stocked emergency crash cart, oxygen, and personnel trained in emergency resuscitation will be available at the study center at all times during the confinement period.

Rescue analgesic medication will be available for subjects with inadequately controlled pain symptoms following the first dose of study treatment (Hour 0) through Hour 48 of the treatment phase. Subjects will be encouraged to rescue only if they are experiencing intolerable pain. The approved rescue regiment will be oral oxycodone immediate release 5 mg every four hours as needed. Pain assessment will be completed prior to all rescue doses (Section 15.1.1 and 15.1.3).

If rescue therapy is provided to the subject, the date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. No other analgesic agents are permitted. Study medication will be administered on the scheduled basis regardless of use of rescue medication.

If a subject is not able to tolerate the allowed rescue medication, they should be discontinued from further efficacy assessment. Pain intensity score [redacted] should be obtained prior to discontinuation but not thereafter. These subjects should remain in the study center for the full 48-hour observation period, have their pain managed per standard of care medications, and continue all safety assessments.

Rescue medication at the study center should be stored in a locked area with restricted access, according to the study center's standard operating procedures.

13.12. Retention of Reserve Drug Product

Drug product reserve samples will not be retained at the clinical site for this study, as the US Food and Drug Administration (FDA)'s retention requirements do not apply because this study is not evaluating pharmacokinetics or bioequivalence/bioavailability.

13.13. Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability or safety of a product, including its labeling, delivery system or packaging integrity. This does not include effectiveness, preference, or performance measures, which will be reviewed in aggregate at appropriate intervals.

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Any PQC discovered during the initial inventory of study supplies should follow the instructions provided on the shipment receipt; 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 SM and the Clinical Supply Manager. The PI or designee should complete, sign and forward a copy of the PQC form, via an agreed upon secure exchange, to the Study Manager or designee.

In addition, the PQC must be included on the Investigational Product Dispensing and Accountability Log or equivalent in the comments field. The Study Manager or designee may assist the site staff with any questions related to this process. To aid in the initial conversation and understanding of a PQC, the site staff may be asked to photograph the issue and send it to the SM or designee.

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14. STUDY PROCEDURES

14.1. Overview

The Activity Schedule (Section 2) summarizes dose administration and the timing and frequency of safety and efficacy procedures and measurements. In the event of abnormal safety findings during the conduct of the study, the attending physician may request additional safety evaluations, either immediately or subsequently at a frequency considered appropriate.

After the subject has completed their participation in the study, the subject should follow up with their surgeon/medical doctor for standard postoperative care.

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

14.2. Screening Visit

Subjects will be screened within 30 calendar days before the study treatment to confirm that they meet the subject selection criteria for the study. The PI (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with Subject Information and Consent (Section 7.3). Once a subject has provided written informed consent, they will be assigned a screening number.

The following procedures will be performed:

- [redacted]
- Review of inclusion and exclusion criteria
- COVID-19 testing, per site policy
- Demographics (age, sex, race, and ethnicity)
- Medical History
- Previous and concomitant medications
- Physical examination (including height, weight and BMI calculation)
- Vital signs (blood pressure, body temperature, respiratory rate and heart rate)
- Urine pregnancy test for all female subjects
- Urine drug screening
- Alcohol screening test
- Clinical laboratory tests for HIV antibodies, hepatitis B surface antigen, hepatitis C antibody)
- Assessment of AEs

Preoperative ECG and labs may be performed at the discretion of the surgical team for preoperative assessment. Preoperative labs will be performed using local laboratories. Any ECG or lab data

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collected during the preoperative assessment will be captured in source documents and not recorded in the EDC system.

14.3. Study Visits (Periods)

To prepare for study participation, subjects will be instructed on the use of Lifestyle Guidelines and Concomitant Medications seen in Section 14.6. Subjects who satisfy the screening inclusion and exclusion criteria, the postoperative inclusion randomization criteria, and who agree to the conditions of the study will be eligible to enter study treatment. There is one treatment period in total that subjects should attend.

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

14.3.1. Pre-Treatment: Pre-Surgery/Surgery Day 0

Eligible subjects will report to the clinical unit as scheduled on Day 0, and will have the following assessments performed:

- Review of inclusion and exclusion criteria for continued enrollment
- Previous and Concomitant Medication
- Vital signs (blood pressure, respiratory rate, heart rate, and body temperature)
- Urine pregnancy test for all female subjects
- Urine screening drugs of abuse
- Alcohol screening test
- Subject instruction on PI-NRS, [redacted] and the double stopwatch
- Assessment of AEs

For subjects who continue to meet eligibility criteria will have a popliteal catheter placed and will undergo primary unilateral, first metatarsal Austin bunionectomy on Day 0.

14.3.2. Post-Surgery/Baseline Day 1 (pre-treatment)

The following assessments will be conducted on the day after surgery, after removal of popliteal catheter and prior to administration of Dose 1 (Hour 0) for all subjects while confined at the study center:

- Assessment of qualifying pain intensity (categorical pain scale and NRS)
- Randomization, if subject meets postoperative inclusion criteria (Section 12.1.3)
- Baseline pain intensity assessment immediately prior to first study dose
- Assessment of AEs

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

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14.3.3. Treatment (0-48 hours): Post-Surgery Day 1 - 3

The following assessments will be conducted during the treatment phase on Days 1-3 (0-48 hours) beginning with administration of the first study dose (Dose 1; Hour 0) for all subjects while confined at the study center:

- Study drug administration per randomization assignment within 15 minutes of meeting qualifying pain scores
- Measurement of time to pain relief after the first dose via the double-stopwatch method
- Pain intensity assessment
- [redacted]
- [redacted]
- Monitoring of AEs and concomitant medication, including rescue medication
- Assessment of AEs

Treatment-related AE will be followed until stabilization or resolution.

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

14.3.4. Discharge: Post-Surgery Day 3 (after 48 hours post-first study dose)

The following assessments will be conducted after the subject has completed the 48-hour observation period to evaluate the subject for discharge:

- Monitoring of AEs and concomitant medication, including rescue medication
- Focused physical examination (Hour 48 prior to discharge) of surgical foot
- Assessment of AEs

Treatment-related AE will be followed until stabilization or resolution.

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

14.3.5. End of Study/Follow-up, Day 7 Telephone Interview

The following procedures will be conducted for all subjects during the End of Study/Follow-up Telephone Interview:

- Assessment of concomitant medications
- Assessment of AEs

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

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14.3.6. Early Termination

Subjects who discontinue participation, or who are discontinued, prior to completing study participating will be asked to complete Early Termination procedures, including:

- Assessment of concomitant medications, including rescue medication
- Focused physical examination of surgical foot
- Assessment for AEs
- Pain intensity assessment
- [redacted]
- [redacted]
- Follow up call on Day 7

14.4. End of Study for Subject

End of Study for each subject is defined as the telephone follow up visit on Day 7. For subjects whose participation is discontinued during the course of this study, end of study procedures will be completed as soon as possible after discontinuation. The following end of study procedures include:

- Assessment of concomitant medications, including rescue medication
- Assessment for AEs

In addition to the above, early termination subjects should also include the following:

- Focused physical examination of surgical foot
- Pain intensity assessment
- [redacted]
- [redacted]

Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

14.5. Blood Volume Collected

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula (stylet catheter that requires no flushing), which will be placed in the forearm vein of the subject.

14.6. Lifestyle Restrictions

14.6.1. Meals and Dietary Restrictions

While confined at the study center, subjects will receive a standardized daily diet.

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14.6.2. Alcohol, Caffeine and Tobacco Restrictions

Subjects must not consume any methylxanthine containing products (i.e., chocolate bars or chocolate beverages, coffee, tea, cola or caffeinated energy drinks), tobacco, or nicotine containing products (e.g., cigarettes, cigars, nicotine replacement therapies, vaping devices) < 12 hours prior to surgery and until discharge from the study center. Subjects may not use alcohol within 24 hours prior to surgery. Subjects with a positive alcohol screening test will only be exclusionary on day of surgery.

14.6.3. Physical Activity Requirements / Restrictions

Prior to the surgical procedure (Day 0), subjects will arrive at the study center in sufficient time to prepare for the procedure and confirm eligibility to participate in the study. Following the bunionectomy procedure, subjects who achieve adequate pain intensity will be randomized and initiate dosing with study drug on the day after surgery (Day 1). Subjects may be discharged from the study center on Day 3, approximately 48 hours after receiving the first study drug dose.

While confined at the study center following surgery, subjects will be required to remain resting in bed at least 20 minutes prior to any pain intensity assessment. Subjects will maintain the surgical foot elevated at all times while confined after surgery, other than for brief period of ambulation to the bathroom as allowed per protocol and investigator's discretion. Subjects will be allowed to ambulate according to standard postoperative care instructions after discharge.

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 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
- Intrauterine device (IUD) or intrauterine system
- Surgical sterilization (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or male partner has had vasectomy that has been confirmed effective by sperm count check)
- 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.

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Female subjects are not considered of reproductive 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., amenorrhoeic for at least 12 consecutive months, without an alternative medical cause, prior screening)

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 prevent their partner from becoming pregnant from the first dose of study medication until at least 30 days after the last dose of study drug. Information about effective means of birth control (hormonal contraception, intrauterine devices, vasectomy, sexual abstinence) will be provided, and discussed as appropriate with individual subjects. Vasectomy performed at least six months prior to the first study drug administration is considered an effective means of birth control.

Male subjects must agree to the contraceptive requirements outlined in the previous Section 14.6.4.

15. ASSESSMENTS

15.1. Efficacy Assessments

15.1.1. Pain Intensity

The pain intensity will be assessed by the study subject for their current pain according to an 11-point numerical pain rating scale (PI-NRS; 0-10) where 0 equates to no pain, and 10 equates to the worst pain imaginable. See Appendix 24.3. Prior to randomization (Postoperative Inclusion Criteria; Section 12.1.3), pain intensity will also be assessed using a 4-point scale with categories of none, mild, moderate, and severe, for qualification of randomization in the study only.

The PI or designated study staff will ensure the subjects complete the pain intensity during the treatment phase at the following time points: Immediately prior to administration of the first dose (Hour 0), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 hours after administration of the first dose, and in the event of early discontinuation. If a subject receives rescue medication, pain intensity will be collected immediately prior to the administration of the rescue medication. Subjects will record their pain intensity directly onto the respective source worksheet.

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Please refer to Table 2: Summary of allowable windows for the summary of allowable windows for all visits and procedures.

15.1.2. Time to Perceptible and Meaningful Pain Relief

Time to perceptible pain relief and time to meaningful pain relief will be measured using the double-stopwatch method. For each randomized subject, two stopwatches will be started immediately after administration of the first study dose (Hour 0).

The first stopwatch will be given to each subject with the instructions to stop the watch when they first perceive pain relief to occur (time to perceptible relief). Once the first watch is stopped, the second stopwatch will be given to the subject with the instructions to stop the watch when they are first experiencing meaningful pain relief (time to meaningful relief).

In the event that a subject receives rescue analgesia or 12 hours has elapsed (Hour 12), prior to stopping one or both stopwatches, the remaining stopwatch(s) should be removed from the subject and recorded as being not achieved.

The stopwatch time to perceptible and meaningful pain relief will be recorded in the subject's source document and eCRF.

15.1.3. [redacted]

[redacted]

15.1.4. [redacted]

[redacted]

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15.2. Safety Assessments

Safety will be monitored and assessed by reviewing results from reported/observed AEs. Normal consequences of bunionectomy surgery (e.g., pain swelling, redness) are not considered AEs unless the Investigator believes the condition worsened or was aggravated following study drug therapy. AEs will be followed by the PI as specified in Section 16, Adverse Event Reporting.

15.2.1. Physical Examination

A physical examination will be conducted by an appropriately qualified member of site staff (PI, Sub-Investigator, physician's assistant, or Nurse Practitioner) and should include general appearance, skin, eyes, head and neck including lymph nodes, chest, cardiovascular and respiratory, abdomen, and extremities during the screening visit.

The Investigator may perform a physical examination (the extent of which is determined by the Investigator) at any time during the study if indicated by change in a subject's medical history or condition.

A focused physical examination will be conducted by an appropriately qualified members of the site staff and should include examination of the surgical foot and addressing any subject complaints at Hour 48 prior to discharge (Day 3) and in the event of early discontinuation. Any focused physical examination data collected during the assessment will be captured in source documents and not recorded in the EDC system, unless related to an adverse event.

15.3. List Other Assessments in the Schedule of Activities

15.3.1. [redacted]

15.3.2. Preoperative ECG and Laboratory Assessment

Preoperative ECG and clinical labs may be performed at the discretion of the surgical team for preoperative assessment. Preoperative labs will be performed using local laboratories. Any ECG and lab data collected during the preoperative assessment will be captured in source documents and not recorded in the EDC system.

15.3.3. Vital Signs

All vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be collected following at least 5 minutes of rest in a supine 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.

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During the screening visit only, body weight and height will be measured, and BMI will be calculated.

Resting vital signs will be collected at screening and on Day 0 prior to surgery.

Actual times will be recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject study records.

15.3.4. Clinical Laboratory Tests

The below clinical laboratory assessments will be performed during the screening visit. The PI must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the CRF. Potential laboratory events should be confirmed by repeat of clinical laboratories, if deemed necessary by the PI.

Subjects will have blood and urine samples collected to assess eligibility for the study as follows:

- Serology: HIV, and hepatitis B and C will be tested during screening
- Urine drug screen (UDS) and alcohol screening test will take place at the screening visit, and during admission to the study unit on Day 0 prior to surgery. Urine drug screen will include screening of (at minimum): cocaine, tetrahydrocannabinol (THC), opiates, amphetamines, methamphetamines, phencyclidine (PCP), benzodiazepines, barbiturates, methadone, and oxycodone.
    - A positive drug screen for a known prescribed concomitant medication that is not otherwise exclusionary will not disqualify a subject. A positive alcohol screening test is not otherwise exclusionary at screening.
    - Drug and alcohol screen results must be negative for a subject to receive study medication, a positive THC and alcohol screening test will only be exclusionary on day of surgery (Day 0).
- Urine pregnancy testing at the screening visit and during admission to the study unit on Day 0 prior to surgery for females

Clinical laboratory tests from screening should have no clinically significant findings, as judged by the PI, in order for a subject to be eligible for enrollment.

Preoperative clinical labs may be performed at the discretion of the surgical team for preoperative assessment. If deemed necessary, preoperative labs should be performed using local laboratories. Any lab data collected during the preoperative assessment will be captured in source documents and not recorded in the EDC system.

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

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reported as described in the following sections. For all AEs, the PI or medically qualified individual (Medical Doctor [MD]/Doctor of Osteopathic Medicine [DO]) 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,
- Medication errors,
- Product dependency,
- Exposure *in utero*, and
- Study related procedure

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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 investigator or designee or the Sponsor.

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

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 investigator or designee (MD/DO) or the Sponsor, it results in any of the following outcomes:

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

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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.

- 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.

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16.2.1. Severity Assessment

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

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

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

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

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

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).
- 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 investigational product, 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 procedures, the PI must record this suspected causal relationship in the source documents.

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16.2.3. Resolution

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

- Resolved,
- Not Resolved,
- Fatal,
- Resolved with sequelae,
- Resolving, 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 CRF. 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 CRF 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 or investigational device. 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.

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. AEs will be entered into the CRF for screen failure subjects as well as randomized subjects. AEs should be reported using concise medical terminology on the CRFs. Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting is required.

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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 CRF 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, a 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 CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings (if available) and death certificate should be collected if permission is obtained from the subject's family. For a hospitalization, a copy of the hospital discharge summary should be requested. If obtained, these documents (with subject's personal identifiers redacted) should be submitted as soon as possible to the Sponsor or its designated representative.

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

16.3.2.2. Contacts for Serious Adverse Event Reporting

Sponsor contact information for SAE/Pregnancy/PQC reporting will be specified in the Study Contact List provided by the Sponsor before study initiation. The Study Contact List should be kept in the SMF and Sponsor TMF. In case the contact information needs to be updated for any reason, a new version of the Study Contact List will be provided by the Sponsor during 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 standard operating procedures for safety reporting.

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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. Examples include:

- [redacted]

16.5.1. Exposure In Utero

An *exposure in utero* (EIU) occurs if:

1. A woman is exposed to the IP at any time between her last menses prior to conception through the delivery of the baby.
2. There is a possibility of intrauterine exposure to IP via semen from the male partner who is taking/using the IP at the time of conception, thereby possibly exposing the fetus to the product.

If an EIU occurs, the 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

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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 investigator or designee (MD/DO) 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.

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.

17.1. Determination of Sample Size

A sample size of 60 completed subjects per group provides greater than 90% power to detect a standardized effect size (SES) of 0.95 comparing non-steroidal anti-inflammatory drugs (NSAID) vs. placebo group, based on a two-sided test at the 0.05 significance level, where standardized effect size is defined as the difference between population treatment means divided by the within-treatment

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population standard deviation. The assumed SES of 0.95 was estimated as follows: based on a previous dental pain study [redacted], the estimated mean difference for SPID 0-12 between acetaminophen [redacted]/naproxen [redacted] vs placebo, subtracting one-standard error was 43.83, and the estimated within-treatment standard deviation was 27.48, resulting in estimated SES of 1.59. Based on Singla[11], it is reasonable to assume that SES for a bunionectomy study is approximately 0.6 times the SES for dental pain study (0.95=1.59*0.6). Provided that the SES for SPID 0-24 is at least approximately 0.63 times the SES for SPID 0-12 (i.e., the SES for SPID 0-24 is at least 0.63*0.95=0.60), the sample size of 60 completed subjects per group is sufficient for 90% power.

17.2. Analysis Sets

17.2.1. Efficacy Analysis Sets

The primary efficacy analyses will be based on full analysis set including all randomized subjects who received at least one dose of investigational product (IP). 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 be the full analysis set 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 received at least one dose of 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 screening and pre-surgery will be summarized (number of subjects, mean, standard deviation, median, minimum and maximum) by treatment group.

[redacted]

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 48-hour assessment period. In addition, those medications taken after the 48-hour assessment period through the follow-up interview for an AE will be considered concomitant medications. Medications taken after the 48-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

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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 Score on 11-Point Numerical Scale from 0 to 24 hours (SPID 0-24)

17.5.1.2. Secondary Endpoints

- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 12 hours (SPID 0-12)
- Time-weighted Sum of Pain Intensity Difference Score on 11-Point Numerical Scale from 0 to 48 hours (SPID 0-48)
- Time to confirmed perceptible pain relief (TCPR) as measured with the double stopwatch
- Time to meaningful pain relief (TMPR) as measured with the double stopwatch
- Time to first use of rescue medication
- Proportion of subjects who use rescue medication during the first 12 hours

17.5.1.3. [redacted]

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[redacted]

17.5.2. Statistical Hypotheses

For endpoints based on pain intensity (such as SPID), [redacted], Acetaminophen [redacted] / Naproxen [redacted] vs. placebo will be tested using 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 μ_2 is the population mean for Placebo.

For time-to-event endpoints (TCPR, TMPR and time to first use of rescue medication), Acetaminophen [redacted] / Naproxen [redacted] vs. placebo will be tested using 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.

For the proportion of subjects who use rescue, Acetaminophen [redacted] / Naproxen [redacted] vs. placebo will be tested using the following hypotheses:

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

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

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

1. SPID 0-24
2. SPID 0-12
3. SPID 0-48
4. TCPR
5. TMPR
6. Time to First Use of Rescue Medication

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7. Proportion of Subjects who use Rescue Medication During the First 12 Hours

If, at any point in this sequence, Acetaminophen [redacted] / Naproxen sodium [redacted] is not statistically significantly better than placebo, then all further testing in the sequence will be exploratory. This above fixed-sequence procedure will provide strong familywise error rate control at 5% for the family of comparisons involving primary and secondary endpoints.

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.

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 0-12, 0-24 or 0-48 hours. [redacted]. 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.

For subjects who use rescue medication, the last reported pain intensity score before taking rescue medication or baseline pain score, whichever is worse, will be carried forward to the subsequent time points within [redacted] therapeutic window of rescue (oxycodone). For subjects who discontinue the study early due to lack of efficacy or adverse events, multiple imputation of baseline observation carried forward approach will be used for imputing the subsequent missing time points. For subjects who discontinue the study early due to reasons other than lack of efficacy or adverse events, or missing visit data without withdrawal, multiple imputation will be used under the assumption of Missing at Random (MAR).

[redacted] For subjects who discontinue the study early due to reasons other than lack of efficacy or adverse events, or missing visit data without withdrawal, multiple imputation will be used under the assumption of Missing at Random (MAR).

[redacted]

17.5.3.2. Time to Confirmed Perceptible (TCPR) and Meaningful Pain Relief (TMPR)

Time to confirmed perceptible pain relief is defined as the time (in minutes) to perceptible pain relief as indicated on the first stopwatch, provided that the subject also stopped the second stopwatch indicating meaningful pain relief. Time to perceptible pain relief is defined as the time (in minutes) to perceptible pain relief as indicated on the first stopwatch, irrespective of whether the subject

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stopped the second stopwatch. Time to meaningful pain relief is defined as the time (in minutes) to meaningful pain relief as indicated on the second stopwatch.

For each of these time to relief variables, subjects who do not have relief by 12 hours, who take rescue medication before having relief during the first 12 hours, or who discontinue before having relief will have time to relief set to 12 hours and be censored at 12 hours.

17.5.3.3. [redacted]

17.5.3.4. Time to First Use of Rescue Medication

Time to first use of rescue medication will be measured as the elapsed time from when IP was given until the time rescue medication was first given. For first use of rescue medication, subjects who discontinue from the study before 48 hours, but do not use rescue medication, will be censored at the time of discontinuation. Subjects who do not use rescue medication during the 48-hour study period, and do not discontinue from the study before 48 hours, will have their time to first use of rescue set to 48 hours and will be censored at 48 hours.

17.5.3.5. [redacted]

17.6. Analysis Methods

17.6.1. Analysis of Primary Endpoint

1. SPID 0-24

For the primary endpoint, SPID 0-24, pairwise comparisons will be made using an analysis of co-variance (ANCOVA) with baseline pain numerical score, center, and treatment group using imputation methods defined in Section 17.5.3.

Primary Estimand

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The primary estimand is the main clinical quantity of interest relative to pain intensity over 0-24 hours after dosing and is defined according to the attributes below.

Treatments Being Compared:	The following comparisons will be tested for SPID 0-24: Acetaminophen [redacted] /Naproxen Sodium [redacted] vs. Placebo.
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11point (010) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Time weighted sum of pain intensity difference on the 11-Point Numerical Scale from 0-24 hours after dosing (SPID 0-24)
Intercurrent events:	<u>Rescue Medication during the 24-hour evaluation period</u> For subjects who use rescue medication during the 24-hour evaluation period, composite strategy will be used. The last reported pain score before taking rescue medication or baseline pain score, whichever is worse, will be carried forward to the subsequent time points within the [redacted] therapeutic window. <u>Discontinuation due to lack of efficacy or adverse events during the 24-hour evaluation period</u> For subjects who discontinue the study early due to lack of efficacy or adverse events during the 24-hour evaluation period, composite strategy will be used; baseline values will be used for imputing the subsequent missing time points. To account for uncertainty, multiple imputation of baseline observation carried forward will be used. <u>Discontinuation due to reasons other than lack of efficacy or adverse events during the 24-hour evaluation period</u> For subjects who discontinue the study early due to reasons other than lack of efficacy or adverse events during the 24-hour evaluation period, a hypothetical strategy will be used. [redacted]
Population level Summary	Differences in least square means between treatment groups.

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As a sensitivity analysis, for subjects who discontinue due to lack of efficacy or adverse events, a single imputation approach will be used, carrying forward individual subject baseline pain intensity to the remaining time points. For all other intercurrent events, imputation methods will be the same as for the primary analysis.

More details will be provided in the statistical analysis plan.

17.6.2. Analysis of Secondary Endpoints

SPID 0-12

SPID 0-12 will also be analyzed using an ANCOVA with baseline pain numerical pain score, center, and treatment group in the model using imputation methods defined in Data Imputations Section 17.5.3.

Secondary Estimand#1

The secondary estimand #1 is the main clinical quantity of interest relative to pain intensity over 0-12 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
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11point (010) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Time weighted sum of pain intensity difference on 11-Point Numerical Scale from 0-12 hours after dosing (SPID 0-12).
Intercurrent events:	<u>Rescue Medication during the 12-hour evaluation period</u> For subjects who use rescue medication during the 12-hour evaluation period, composite strategy will be used. The last reported pain score before taking rescue medication or baseline pain score, whichever is worse, will be carried forward to the subsequent time points within the [redacted] therapeutic window. <u>Discontinuation due to lack of efficacy or adverse events during the 12-hour evaluation period</u> For subjects who discontinue the study early due to lack of efficacy or adverse events during the 12-hour evaluation period, composite strategy

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	will be used; baseline values will be used for imputing the subsequent missing time points. [redacted] Discontinuation due to reasons other than lack of efficacy or adverse events during the 12-hour evaluation period For subjects who discontinue the study early due to reasons other than lack of efficacy or adverse events during the 12-hour evaluation period, a hypothetical strategy will be used. To account for uncertainty, multiple imputation will be used for the subsequent missing time points via a regression-based model under the assumption of MAR.
Population level Summary:	Differences in least square means of SPID 0-12 between treatment groups.

SPID 0-48

SPID 0-48 will also be analyzed using an ANCOVA with baseline pain numerical score, center and treatment group in the model using imputation methods defined in Data Imputations Section 17.5.3.

Secondary Estimand #2

The secondary estimand #2 is the main clinical quantity of interest relative to pain intensity over 0-48 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
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11point (010) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Time weighted sum of pain intensity difference on 11-Point Numerical Scale from 0-48 hours after dosing (SPID 0-48).
Intercurrent events:	Rescue Medication during the 48-hour evaluation period For subjects who use rescue medication during the 48-hour evaluation period, composite strategy will be used. The last reported pain score before

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	taking rescue medication or baseline pain score, whichever is worse, will be carried forward to the subsequent time points within [redacted] therapeutic window. Discontinuation due to lack of efficacy or adverse events during the 48-hour evaluation period For subjects who discontinue the study early due to lack of efficacy or adverse events during the 48-hour evaluation period, composite strategy will be used; baseline values will be used for imputing the subsequent missing time points. To account for uncertainty, multiple imputation of baseline observation carried forward will be used. Discontinuation due to reasons other than lack of efficacy or adverse events during the 48-hour evaluation period For subjects who discontinue the study early due to reasons other than lack of efficacy or adverse events during the 48-hour evaluation period, a hypothetical strategy will be used. To account for uncertainty, multiple imputation will be used for the subsequent missing time points via a regression-based model under the assumption of MAR.
Population level Summary:	Differences in least square means of SPID 0-48 between treatment groups.

TCPR

Time to confirmed perceptible pain relief will be analyzed using survival data analysis. The survival function (cumulative proportions of subjects at each time point) and the median survival time will be estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared using the Wilcoxon test, stratifying on center.

Secondary Estimand #3

The secondary estimand #3 is the main clinical quantity of interest relative to time to confirmed perceptible pain relief and is defined according to the attributes below.

Treatment being compared:	Treatment Comparisons include following: Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥

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	5 on 11point (0-10) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Time to Confirmed Perceptible Pain Relief
Intercurrent events:	Use rescue or Discontinue before having relief For subjects who use rescue or discontinue before having relief, composite strategy will be used: time to relief will be set to 12 hours and be censored at 12 hours. No relief (and No rescue) by 12 hours For subjects who do not have relief and not received rescue by 12 hours, hypothetical strategy will be used: time to relief will be set to 12 hours and censored at 12 hours. Considering a non-informative censoring, subjects will be censored at the time of 12 hours.
Population level Summary:	Proportion of subjects achieving TCPR will be estimated by Kaplan-Meier method.

TMPR

Time to meaningful pain relief will be analyzed using survival data analysis. The survival function (cumulative proportions of subjects at each time point) and the median survival time will be estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared using the Wilcoxon test, stratifying on center.

Secondary Estimand #4

The secondary estimand #4 is the main clinical quantity of interest relative to time to meaningful pain relief and is defined according to the attributes below.

Treatment being compared:	Treatment Comparisons include following: Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11point (0-10) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.

Status : Approved

Variable:	Time to Meaningful Pain Relief
Intercurrent events:	Use rescue or Discontinue before having relief For subjects who use rescue or discontinue before having relief, composite strategy will be used: time to relief will be set to 12 hours and be censored at 12 hours. No relief (and No rescue) by 12 hours For subjects who do not have relief and not received rescue by 12 hours, hypothetical strategy will be used: time to relief will be set to 12 hours and censored at 12 hours. Considering a non-informative censoring, subjects will be censored at the time of 12 hours.
Population level Summary:	Proportion of subjects achieving TMPR will be estimated by Kaplan-Meier method.

Time to First Use of Rescue Medication

Kaplan-Meier estimates of cumulative percentage of subjects using 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 use of rescue will be estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared using the Wilcoxon test, stratifying on center.

Secondary Estimand #5

The secondary estimand #5 is the main clinical quantity of interest relative to Time to first use of rescue analgesic and is defined according to the attributes below.

Treatment being compared:	Treatment Comparisons include following: Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11point (0-10) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Time to first use of rescue analgesic.

Status : Approved

Intercurrent events:	<u>No rescue and discontinue the study before 48 hours</u> Discontinue from the study before 48 hours, but do not use rescue medication. A hypothetical strategy will be used. Considering a non-informative censoring, subjects will be censored at the time of discontinuation. <u>No rescue during the 48-hour study</u> Do not use rescue medication during the 48-hour study period. A hypothetical strategy will be used. Considering a non-informative censoring, subjects will be censored at the time of 48 hours.
Population level Summary:	Proportion of subjects who use rescue analgesic estimated by Kaplan-Meier method.

Proportion of subjects who use rescue medication up to 12 hours

The proportion of subjects using rescue medication through 12 hours will be estimated using the Kaplan-Meier method, stratifying on center with standard errors estimated by Greenwood method. The log-log transformed proportion differences between Acetaminophen [redacted]/Naproxen Sodium [redacted] and placebo will be tested for statistical significance using Wald test stratified by center. 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 #6

The secondary estimand #6 is the main clinical quantity of interest relative to Proportion of subjects who use 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
Population:	Subjects who are 16 to 65 years of age (inclusive) undergoing primary, unilateral, distal, first metatarsal bunionectomy surgery with no additional collateral procedures and reports moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11point (0-10) PINRS at Baseline after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.

Status : Approved

Variable:	Proportion of subjects who use rescue analgesic during the first 12 hours at each treatment group
Intercurrent events:	Discontinue from the study before 12 hours, but do not use rescue medication A hypothetical strategy will be used. Considering a non-informative censoring, subjects will be censored at the time of discontinuation. Do not use rescue medication during the 12-hour study period. A hypothetical strategy will be used. Considering a non-informative censoring, subjects will be censored at the time of 12 hours.
Population level Summary:	Proportion of subjects who use rescue medication during the first 12 hours

17.6.3. Analysis of Exploratory Endpoints

[redacted]

Status : Approved

[redacted]



17.6.4. Subgroup Analysis

The primary endpoint (SPID 0-24) will be analyzed based on the following subgroups: gender, race (white, non-white) and baseline categorical pain (moderate, severe). Each will be analyzed with an ANCOVA with treatment group in the model using imputation methods defined in Data Imputations Section 17.5.3.

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.

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: gender and race.

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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 J&J will visit the investigational study site to determine the adequacy and capabilities of the facilities.

During the study, a monitor from J&J or representative will have regular contacts with the investigational sites. At these monitoring on-site visits and other contacts, the monitor will provide information to support the PI and the site staff. In addition, the monitor will confirm that the investigational team is adhering to the protocol, that data are being accurately recorded and that IP is stored appropriately and that accountability checks are performed. Any protocol deviation will be reported to the Sponsor.

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 for more details regarding the audit process.

19.1. Audits and Inspections

Authorized representatives of J&J, a regulatory/competent authority, an IRB/IEC representative may visit the site to perform audits or inspections, including source data verification. The purpose of a J&J audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH E6, and any applicable regulatory requirements. The PI should notify the Sponsor (e.g., Study Manager, Monitor)

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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. 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 Visit Date, Demography, Informed Consent, Eligibility, Disposition and Adverse Events.

All data will be collected on source documents first and then recorded in an Electronic Data Capture (EDC) system. The EDC system is the database where pertinent study data are collected such as demography, subject randomization, efficacy assessments, AEs, 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.

It is the PI's responsibility to ensure completion, review and approval of all information captured in the EDC. The subject's data in the EDC system must be electronically signed by the 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 must match those charts. All final data recorded in EDC system will be copied into files and kept by the Sponsor. A copy of these files will also be kept at the clinical site. All data provided in the CRF must be supported by source 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).

Status : Approved

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., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, 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 two years following the discontinuance of the test article for investigation. If it becomes necessary for [redacted] 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. DEFINITION OF END OF STUDY

Not Applicable

22. 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

23. LIST OF REFERENCES

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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 twoprostaglandin H2 synthases. Clin Pharmacol Ther. 2006;79(1):9-19.
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10. Johnson and Johnson Consumers Clinical Study Report CCSPAA001068: A Randomized, Double-blind, Placebo- and Active- Controlled, Proof of Concept Study to Evaluate Two Strengths of Concomitantly Dosed Naproxen Sodium with Acetaminophen, Compared with Naproxen Sodium, Hydrocodone/Acetaminophen and Placebo in Postoperative Dental Pain. 2019
11. Singla NK, Desjardins PJ, Chang PD. A comparison of the clinical and experimental characteristics of four acute surgical pain models: dental extraction, bunionectomy, joint replacement, and soft tissue surgery. *Pain*. 2014;155(3):441-456. doi:10.1016/j.pain.2013.09.002

Status : Approved

24. APPENDICES

24.1. Surgical and Anesthetic Protocol

Subjects will undergo primary, unilateral, first metatarsal Austin bunionectomy. The surgical procedure should be limited to a maximum duration of 120 minutes with a target duration of ≤ 90 minutes. Start time of surgery will be defined as the time of first incision and the end of surgery will be defined as completion of the last suture.

The surgery will be performed under regional anesthesia via a popliteal sciatic nerve block (0.5% ropivacaine, volume at the discretion of the Investigator) and a local Mayo block using short-acting 2% lidocaine without epinephrine, with intravenous propofol for sedation.

Propofol induction (dose per discretion of anesthesiologist) will be given as an initial bolus followed by a continuous infusion of up to 250 µg/kg/min intraoperative sedation.

A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered to reduce vein irritation at the infusion site.

Intraoperatively, all subjects will be given 50 µg of fentanyl IV around the time of induction with propofol.

Once sedated, a Mayo block of the first metatarsal will be induced using 2% lidocaine without epinephrine, administered volume can range from 5-20 mL.

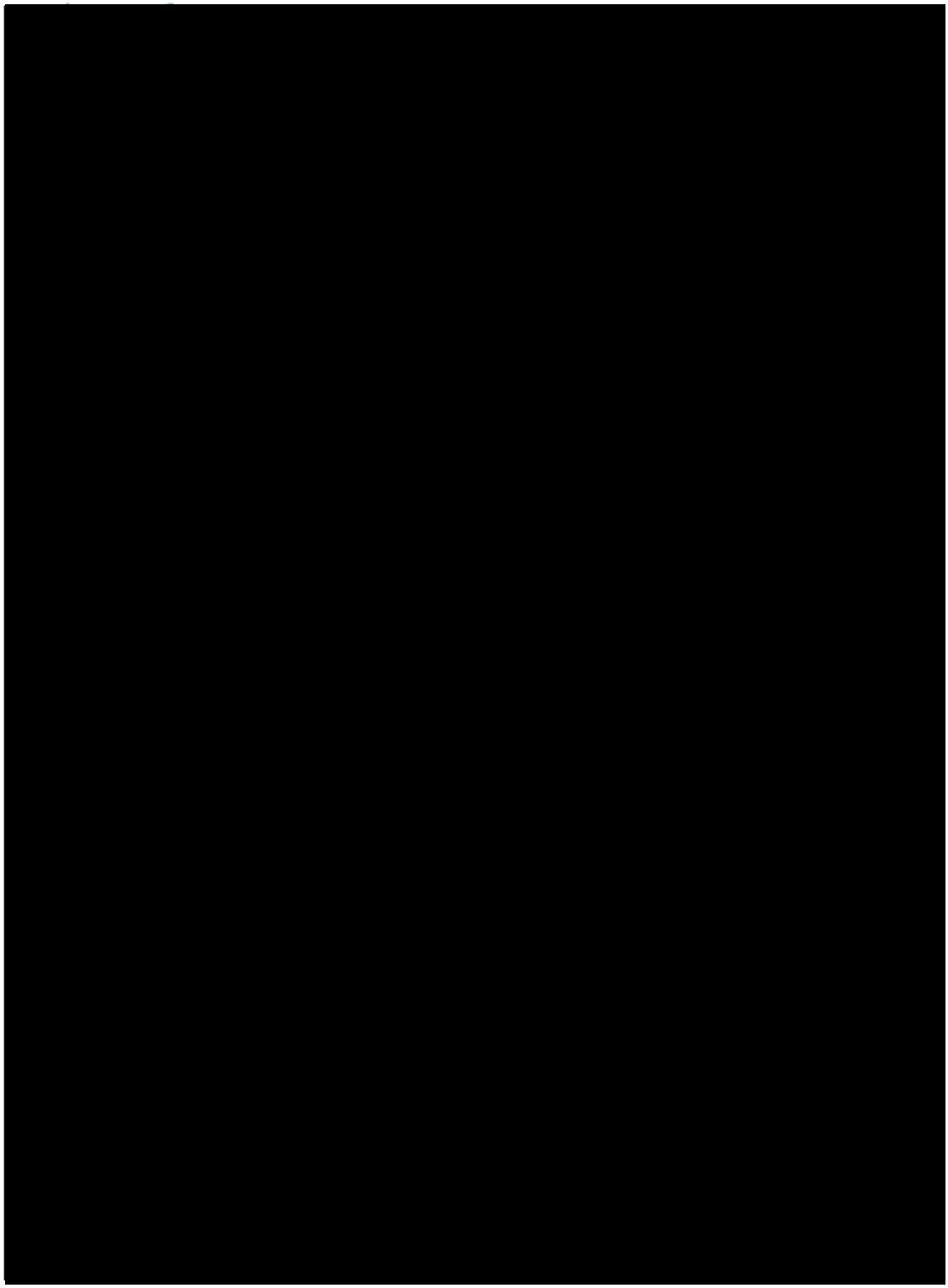
Midazolam (up to 2 mg IV) may be administered preoperatively for anxiolysis.

A ankle tourniquet will be applied to achieve hemostasis. Propofol infusion may be discontinued prior to the last suture, thus anesthesia end time may be prior to surgery end time.

Ondansetron IV is permitted for post-operative nausea and vomiting prophylaxis on Day 0.

Status : Approved

24.2. [redacted]



Status : Approved

[redacted]

Status : Approved

[redacted]

Status : Approved

24.3. Pain Intensity Numerical Rating Scale (PI-NRS)

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 Worst pain imaginable

24.4. [redacted]

24.5. [redacted]