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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

Statistical Analysis Plan (SAP)

Date: 4-July-2024
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Version History

Version	Date	Description
1.0	27-Apr-2023	Initial version
2.0	12-May-2023	Same information, protocol number is corrected in the header of appendix.
3.0	04-July-2024	SAP amended based on protocol amendment Version 6.0, 12Mar2024 (Amendment #05), and findings from blinded data review.

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Introduction

1.1 STUDY OBJECTIVES

As stated in the protocol:

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.

Secondary Objective(s):
•To evaluate the onset and duration of analgesia of a fixed combination of acetaminophen/naproxen sodium.

Safety Objective(s)
• To evaluate the safety and tolerability of a fixed combination of acetaminophen/ naproxen sodium in a postoperative population.

1.2 STUDY DESIGN

As stated in the protocol:

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), a pre-study questionnaire, 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 will be assigned to one of the two treatment groups (acetaminophen [redacted]/naproxen sodium [redacted] or placebo), *with equal allocation. Both treatments will be administered as two tablets every 12 hours for 4 doses in total. 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 (between Day 7 and 10) to complete the follow-up study assessments. Efficacy assessments will include pain

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

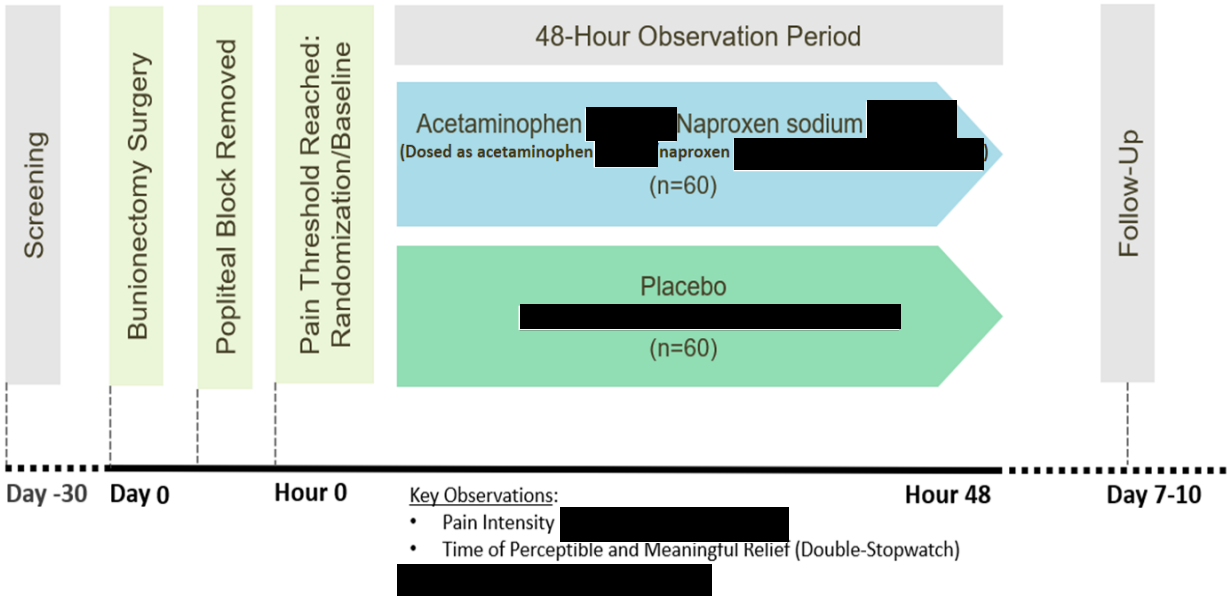
Subjects will be administered a study dose according to their randomization every 12 hours for 4 doses in total. Subjects with inadequately controlled pain symptoms may request rescue medication. Subjects should be encouraged to use rescue only when their pain is intolerable. Pain intensity assessments 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.

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.

Details of activity schedule and summary of allowable windows can be found in Appendix 1 Activity Schedule. Details regarding efficacy assessments can be found in Appendix 2 Efficacy Assessments.

Figure 1: Schematic Study Design



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2. INTERIM ANALYSES

No interim analysis is planned. Final analyses will be performed at the official database release.

3. 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 full 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).

The Safety Analysis Set will include all subjects who were randomized and received at least one dose of IP.

4. ENDPOINTS

4.1 PRIMARY ENDPOINTS

Primary endpoint is:

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

4.2 SECONDARY ENDPOINTS

Secondary endpoints are:

- 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

4.3 [redacted]



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- [redacted]

[redacted]

5. DATA COMPUTATIONS AND HANDLING OF MISSING VALUES

5.1 Endpoints Relating to Pain Intensity, [redacted]

Pain intensity [redacted] score for each time-point is the pain intensity [redacted] score which is the closest valid score to the target time-point within ± 5 minutes for timepoints up to 90 minutes post-dose, and ± 15 minutes for the remaining timepoints, among scheduled pain assessments including pain assessments prior to rescue. In case more than one pain intensity [redacted] score are the same distance from the target time-point, the scheduled pain assessment score will be used. Only pain intensity [redacted] scores that are not within a rescue therapeutic window are considered to be valid scores.

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.

5.1.1 Imputation Methods for Pain Intensity

For subjects who use rescue medication, the last valid pain intensity score before taking that rescue medication or the baseline pain score, whichever is worse, will be carried forward from the time of rescue therapy to the subsequent time points within the [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 time points. Non-missing baseline values from all subjects will be used for imputing such missing post-baseline values. [redacted].

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

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[redacted]

5.1.2 Derivation of SPID Scores

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 timepoint/4-hour rescue therapeutic window and adding these time weighted PID scores together over the intervals from 0-12, 0-24 or 0-48 hours. Rescue medication will be accounted for by carrying forward the pain intensity just prior to that rescue medication or baseline, whichever is worse, from the current time of rescue to the current time of rescue plus the therapeutic window. Through this approach, rescue at all possible time points will be adequately accounted for. Following are examples taking into account the therapeutic window of rescue medication when deriving SPID scores:

Following are examples considering the therapeutic window of rescue medications when deriving SPID scores:

1. Suppose a subject uses 1st dose of rescue oxycodone at 11.5 hours and 2nd dose of rescue oxycodone at 17.5 hours since IP use. The SPID over 11-12, SPID over 12-16, SPID over 16-20 and SPID over 20-24 for this subject will be calculated as follows:

[redacted]

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[redacted]

2. Suppose a subject used 1st rescue medication of oxycodone at 15.5 hours since IP use. SPID over 12-16 and SPID over 16-20 for this subject is calculated as follows:

[redacted]

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5.1.4 [redacted]

[redacted]

5.2 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 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.

[redacted]

[redacted]

5.4 Time to First Use of Rescue Medication from 0-48 hours

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 from 0-48 hours, 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.

[redacted]

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[redacted]

6. SAMPLE SIZE DETERMINATION

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 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. [redacted]

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL HYPOTHESES AND DECISION RULE

For endpoints based on pain intensity (such as SPID), [redacted], Acetaminophen [redacted] / Naproxen [redacted] vs. placebo will be tested using the following hypotheses:

$H_0: \mu_1 = \mu_2$

$H_A: \mu_1 \neq \mu_2$

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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 proportions 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
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.

7.2 STATISTICAL ANALYSIS

The Global Biostatistics Department at the sponsor will be responsible for statistical analyses. For continuous distributions, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum and maximum values. Distributions of categorical variables will be summarized by presenting the number and percent of subjects in each response category.

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7.2.1 Subject Disposition

Subjects disposition will be presented using descriptive summaries overall for all screened subjects and by treatment group for all randomized subjects, respectively. Disposition summary will include screened subjects, post-surgical screen failures, subjects discontinued before randomization, randomized subjects, subjects completed the follow-up call, subjects completed the 24-hour observation period, subjects completed the 48-hour observation period, subjects discontinued after randomization and reasons for all discontinuations within the 24-hour and 48-hour observation period.

Screen Failure
Subjects who consent to participate in the study but are deemed to not qualify or the subject withdraws consent prior to the surgical procedure.

Post-Surgical Screen Failure
Subjects who qualify based on the screening visit, are admitted into the study center, and receive a surgical bunionectomy, but do not meet the postoperative criteria for enrollment or are unable to adequately control their pain using the postoperative pain management prior to randomization.

Randomized
Subjects who meet inclusion/exclusion after surgery and after the popliteal block is removed and are randomized to one of the IPs.

Full Analysis Set
Refer to Section 3. Analysis Sets for definition.

Per-Protocol Analysis Set
Refer to Section 3. Analysis Sets for definition.

Safety Analysis Set
Refer to Section 3. Analysis Sets for definition.

Completers for 48-hour assessments
Subjects who are randomized to one of the IPs and complete the efficacy assessments through 48 hours.

Completer
Subjects who are randomized to one of the IPs and complete the follow-up call.

7.2.2 Demographic and Baseline Characteristics

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.

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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.

Pre-study questionnaire will be summarized by treatment group.

7.2.3 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 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.

7.2.4 Protocol deviations

Major protocol deviations will be summarized by treatment group and all protocol deviations will be listed for Full Analysis Set.

7.2.5 Analysis of Primary Endpoints

1. <u>SPID 0-24</u>

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 in Table 1.

Table 1. Attributes of Primary Estimand

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 report moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11 point (0-10) PI-NRS 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)

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Intercurrent events/Missing Data Handling:	**Rescue Medication during the 24-hour evaluation period** 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. **Discontinuation due to lack of efficacy or adverse events during the 24-hour evaluation period** 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. Non-missing baseline values from all subjects will be used for imputing such missing post-baseline values. [redacted] **Discontinuation due to reasons other than lack of efficacy or adverse events or are missing time point data without withdrawal during the 24-hour evaluation period** 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.

Statistical Model

As the primary analysis, pairwise comparisons of SPID 0-24 will be made using an analysis of covariance (ANCOVA) with baseline pain numerical score, center, and treatment group. The analysis results for the imputed datasets will be combined using standard methods (Little & Rubin, 2002). The SAS procedure MIXED will be used to implement ANCOVA analysis. The SAS procedure MI will be used to generate imputed datasets and MIANALYZE will be used

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to combine analysis results. The difference of least-square means, and its 95% confidence interval and p-value will be reported. (Details for the imputation approach are provided in Section 5.1 Endpoints Relating to Pain Intensity, [redacted]).

Interaction Term of Treatment by Center

Additionally, treatment by center interaction will be evaluated for the full analysis set by performing an exploratory analysis using ANCOVA with baseline pain numerical score, center, treatment and treatment by center interaction.

Supplementary and Sensitivity Analyses

As supplementary analysis, the pairwise comparisons of SPID 0-24 will be analyzed based on the per-protocol analysis set, if the per-protocol analysis set differs from the full analysis set by at least 5% of the subjects.

As a sensitivity analysis, for subjects who withdraw the study 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 remain the same as primary analysis.

7.2.6 Analysis of Secondary Endpoints

1. **SPID 0-12**

The secondary estimand #1 is the main clinical quantity of interest relative to pain relief over 0-12 hours after dosing and is defined according to the attributes in Table 2.

Table 2. Attributes of Secondary Estimand #1

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 report moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11 point (0-10) PI-NRS 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/Missing Data Handling:	**Rescue Medication during the 12-hour evaluation period** 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.

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	Discontinuation due to lack of efficacy or adverse events during the 12-hour evaluation period For subjects who discontinue the study early due to lack of efficacy or adverse events during the 12-hour evaluation period, composite strategy 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 or are missing time point data without withdrawal 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. [redacted]
Population level Summary:	Differences in least square means of SPID 0-12 between treatment groups.

Statistical Model

SPID 0-12 will be analyzed using ANCOVA with baseline pain numerical score, center, and treatment group in the model using the same imputation methods as for the primary analysis for SPID 0-24. The difference of least-square means, and its 95% confidence interval and p-value will be reported. The SAS procedure MIXED will be used to implement ANCOVA analysis.

2. SPID 0-48

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.

Table 3. Attributes of Secondary Estimand #2

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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 report moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11 point (0-10) PI-NRS 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/Missing Data Handling:	**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 taking rescue medication or baseline pain score, whichever is worse, will be carried forward to the subsequent time points within the [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. Non-missing baseline values from all subjects will be used for imputing such missing post-baseline values. [redacted] **Discontinuation due to reasons other than lack of efficacy or adverse events or are missing time point data without withdrawal 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. [redacted]

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	[redacted]
Population level Summary:	Differences in least square means of SPID 0-48 between treatment groups.

Statistical Model

SPID 0-48 will be analyzed using ANCOVA with baseline pain numerical score, center, and treatment group in the model using the same imputation methods as for the primary analysis for SPID 0-24. The difference of least-square means, and its 95% confidence interval and p-value will be reported. The SAS procedure MIXED will be used to implement ANCOVA analysis.

3. TCPR

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.

Table 4. Attributes of Secondary Estimand #3

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 11 point (0-10) PI-NRS 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/Missing Data Handling:	**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.
Population level Summary:	Proportion of subjects achieving TCPR will be estimated by Kaplan-Meier method.

Statistical Model

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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. The SAS procedure LIFETEST will be used to conduct Kaplan-Meier analysis and statistical testing.

4. TMPR

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.

Table 5. Attributes of Secondary Estimand #4

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 report moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11 point (0-10) PI-NRS after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Time to Meaningful Pain Relief
Intercurrent events/Missing Data Handling:	**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.
Population level Summary:	Proportion of subjects achieving TMPR will be estimated by Kaplan-Meier method.

Statistical Model

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. The SAS procedure LIFETEST will be used to conduct Kaplan-Meier analysis and statistical testing.

5. Time to First Use of Rescue medication

Secondary Estimand #5

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

Table 6. Attributes of Secondary Estimand #5

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 report moderate or severe pain on a 4-point categorical pain-rating scale (none, mild, moderate and severe) AND at ≥ 5 on 11 point (0-10) PI-NRS 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 medication
Intercurrent events/Missing Data Handling:	**No rescue and discontinue the study before 48 hours** 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. **No rescue during the 48-hour study** 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 medication estimated by Kaplan-Meier method.

Statistical Model

Time to first use for rescue medication will analyzed using Kaplan-Meier method and censored according to Section 5.3
5.4 Time to First Use of Rescue Medication. The cumulative percentage of subjects using rescue will be presented by treatment group in tabular and graphical formats. The median, Q1 and Q3 time to first use of rescue will be tabulated. The survival functions will be compared using the Wilcoxon test stratified by center. The SAS procedure LIFETEST will be used to conduct Kaplan-Meier analysis and statistical testing.

6. Proportion of subjects who use rescue medication up to 12 hours

Secondary Estimand #6

The secondary estimand #6 is the main clinical quantity of interest relative to proportion of subjects who use rescue medication during the first 12 hours and is defined according to the attributes in Table 7.

Table 7. Attributes of Secondary Estimand #6

Status : Approved

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 11 point (0-10) PI-NRS after discontinuation of popliteal block before 2 PM on Day 1, as reflected in Inclusion/Postoperative Inclusion/Exclusion criteria.
Variable:	Proportion of subjects who use rescue medication during the first 12 hours at each treatment group
Intercurrent events/Missing Data Handling:	**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

Statistical Model

Proportion of subjects using rescue medication up to 12 hours, will be estimated using the Kaplan-Meier method. The standard errors will be approximated using the Greenwood method. This method will be used for this endpoint due to the censoring that may occur at times between 0 and 12 hours. The proportion differences between Acetaminophen [redacted]/Naproxen Sodium [redacted] and placebo will be transformed by complementary log-log transformation and tested for statistical significance using Wald test stratified by center. The corresponding 95% CI of the proportion will also be tabulated. The SAS procedure LIFETEST will be used to conduct Kaplan-Meier analysis. The statistical details for stratified Wald test are in Appendix 3 Wald Test

[redacted]

Status : Approved

[redacted]

Status : Approved

[redacted]

Subgroup Analysis

The primary endpoint (SPID 0-24) will be analyzed based on the following subgroups: gender, race (white, non-white) and qualifying categorical pain (moderate, severe). Each will be analyzed using the same ANCOVA as for the analysis of primary endpoint using imputation methods defined in Data Imputations Section 5.1 Endpoints Relating to Pain Intensity, [redacted] and Section 7.2.5 Analysis of Primary Endpoints.

7.2.8 Safety analysis

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.

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.

Status : Approved

8. REFERENCES

1. 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.
2. Ratitch B, Kelly MO, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharamecutical Statistics, 2013, 12 337-347. DOI: 10.1002/pst. 1549.
3. Little R.J. & Rubin D.B. (2002). Statistical Analysis with Missing Data. New Jersey: Wiley.
4. Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med. 2007 Oct 30;26(24):4505-19. doi: 10.1002/sim.2864. PMID: 17348080.

Changes from the Protocol:

As mentioned in Protocol Clarification Letter#3,

1. The word “at Baseline” is removed from the population definition in each of the estimands tables (from Table 1 to Table 7 in SAP) for primary and secondary endpoints mentioned in Section 17.6.1 and Section 17.6.2 of the protocol.
2. Subgroup analysis mentioned in Section 17.6.4 Subgroup Analysis of the protocol will be performed using the qualifying categorical pain (moderate, severe) instead of baseline categorical pain (moderate, severe) as described in Section 7.2.7 Subgroup Analysis of the SAP.

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APPENDIX 1 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] 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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APPENDIX 2 EFFICACY ASSESSMENTS

The following efficacy assessments will be collected.

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. 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.

3. Time to perceptible pain relief: recorded using stopwatch perceptible

4. Time to meaningful pain relief: recorded using stopwatch meaningful

5. Time to first use of rescue medication

7.

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APPENDIX 3 WALD TEST

Let $\widehat{p_{1s}}$ and $\widehat{p_{2s}}$ denote the Kaplan-Meier estimator of proportion using rescue medication in the first 12 hours for treatment group 1 and 2 and stratum s, where $s = 1,2, \dots m$. $\widehat{Var(p_{1s})}$ and $\widehat{Var(p_{2s})}$ denote the estimated standard error accordingly. n_s denote the number of subjects in stratum s for treatment group 1 and 2, and let $n = \sum_{s=1}^{m} n_s$ equals the total number of subjects for treatment group 1 and 2.

By taking complementary log-log transformation, the test statistics outperform the original test statistics (Klein 2007). Let $\hat{\phi}_{1s}$ and $\hat{\phi}_{2s}$ denote the transformation of $\hat{p}_{1s}$ and $\hat{p}_{2s}$,

$$\hat{\phi}_{1s} = log\big(-log(1-\hat{p}_{1s})\big)$$

$$\hat{\phi}_{2s} = log\big(-log(1-\hat{p}_{2s})\big)\,.$$

Therefore, using Greenwood's formula, the estimated variance of $\hat{\phi}_{1s}$ and $\hat{\phi}_{2s}$ are

$$\widehat{Var}\big(\hat{\phi}_{1s}\big) = \widehat{Var}\big[log\big(-log(1-\hat{p}_{1s})\big)\big] = [(1-\hat{p}_{1s})log(1-\hat{p}_{1s})]^{-2}\widehat{Var}[\hat{p}_{1s}]$$

$$\widehat{Var}\big(\hat{\phi}_{2s}\big) = \widehat{Var}\big[log\big(-log(1-\hat{p}_{2s})\big)\big] = [(1-\hat{p}_{2s})log(1-\hat{p}_{2s})]^{-2}\widehat{Var}[\hat{p}_{2s}].$$

The test statistics Z_s for stratum s,

$$\frac{\widehat{\phi_{1s}} - \widehat{\phi_{2s}}}{\sqrt{\widehat{Var}\big(\hat{\phi}_{1s}\big) + \widehat{Var}\big(\hat{\phi}_{2s}\big)}}$$

has a standard normal distribution under the null hypothesis.

Using the number subjects in each stratum as weighting scheme, the weighted test statistics Z,

$$\frac{\sum_{s=1}^{m} \frac{n_s}{n}\big(\hat{\phi}_{1s} - \hat{\phi}_{2s}\big)}{\sqrt{\sum_{s=1}^{m}\left(\frac{n_s}{n}\right)^2\Big(\widehat{Var}\big(\hat{\phi}_{1s}\big) + \widehat{Var}\big(\hat{\phi}_{2s}\big)\Big)}}$$

has a standard normal distribution under the null hypothesis.

Status : Approved

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Status : Approved

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Status : Approved

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Status : Approved

APPENDIX 5: SUMMARY TABLES AND FIGURES

The following tables and figures are planned for the Clinical Study Report. The numbering and titles of tables and figures in this document serves as guidance; the exact numbers and titles may be modified as appropriate.

Section / Table No	Title	Population / Analysis Sets
14.1 Subject Disposition, Demographics, and Baseline Information		
Table 14.1.1	Subjects Disposition and Analysis Sets	All Screened Subjects
Table 14.1.2	Subjects Disposition and Analysis Sets by Center	All Screened Subjects
Table 14.1.2.1	Screen Failures	All Screened Subjects
Table 14.1.2.2	Post-Surgical Screen Failures	All Screened Subjects
Table 14.1.3.1	Summary of Protocol Deviations	All Randomized Subjects
Table 14.1.3.2	Summary of Major Protocol Deviations	All Randomized Subjects
Table 14.1.3.3	Summary of Minor Protocol Deviations	All Randomized Subjects
Table 14.1.4.1	Demographic and Baseline Characteristics	Full Analysis Set
Table 14.1.4.2	Demographic and Baseline Characteristics by Center	Full Analysis Set
Table 14.1.4.3	Demographic and Baseline Characteristics	Per-Protocol Subjects
Table 14.1.5.1	Vital Signs Summary at Screening	All Randomized Subjects
Table 14.1.5.2	Vital Signs Summary at Pre-Surgery	All Randomized Subjects
Table 14.1.6	Previous Medications	All Randomized Subjects
Table 14.1.7.1	Concomitant Medications	All Randomized Subjects
Table 14.1.7.2	Concomitant Medications Taken By >= 5% of Subjects in One or More Treatment Groups	All Randomized Subjects
Table 14.1.8	Summary of Rescue Medications (Oxycodone 5mg)	Full Analysis Set
[redacted]	[redacted]	[redacted]
14.2 Efficacy		
Table 14.2.1.1	Time weighted Pain Intensity Difference from 0-24 hours (SPID 0-24)	Full Analysis Set
Table 14.2.1.2	Time weighted Pain Intensity Difference from 0-24 hours (SPID 0-24) – Exploratory Assessment of Treatment by Center Interaction	Full Analysis Set
Table 14.2.1.3	Time weighted Pain Intensity Difference from 0-24 hours (SPID 0-24) – Sensitivity Analysis	Full Analysis Set
Table 14.2.1.	Time weighted Pain Intensity Difference from 0-24 hours (SPID 0-24) – Per Protocol Analysis [a]	Per Protocol Analysis Set
Table 14.2.2	Time weighted Pain Intensity Difference from 0-12 hours (SPID 0-12)	Full Analysis Set
Table 14.2.3	Time weighted Pain Intensity Difference from 0-48 hours (SPID 0-48)	Full Analysis Set
Table 14.2.4	Kaplan-Meier Estimates of Time to Confirmed Perceptible Pain Relief (TCPR)	Full Analysis Set
Table 14.2.5	Kaplan-Meier Estimates of Time to Meaningful Pain Relief (TMPR)	Full Analysis Set

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Table 14.2.6	Kaplan-Meier Estimates of Time of First Use of Rescue Medication from 0-48 hours	Full Analysis Set
Table 14.2.7.1	Proportion of Subjects Using Rescue Medication from 0-12 hours	Full Analysis Set
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Table 14.2.18.1	Time weighted Pain Intensity Difference (SPID 0-24) by Gender (Female/Male)	Full Analysis Set
Table 14.2.18.2	Time weighted Pain Intensity Difference (SPID 0-24) by Race (Whites/Non-Whites)	Full Analysis Set
Table 14.2.18.3	Time weighted Pain Intensity Difference (SPID 0-24) by Qualifying Pain (Moderate/Severe)	Full Analysis Set

a. Provided if the per-protocol analysis set differs from the Full Analysis Set by at least 5% of the randomized subjects.

14.3 Safety

Section / Table No	**Title**	**Population / Analysis Sets**
Table 14.3.1.1	Summary of Adverse Events	Safety Analysis Subjects
Table 14.3.1.2	Summary of Treatment-Related Adverse Events	Safety Analysis Subjects
Table 14.3.1.3	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Subjects
Table 14.3.1.4	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Analysis Subjects

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Table 14.3.1.5	Summary of Treatment-Related Adverse Events By System Organ Class and Preferred Term	Safety Analysis Subjects
Table 14.3.1.6	Summary of Treatment-Related Adverse Events By System Organ Class, Preferred Term and Severity	Safety Analysis Subjects
Table 14.3.1.7	Most Commonly Reported (>=5% of Subjects in One or More Treatment Groups) Treatment-Emergent Adverse Events	Safety Analysis Subjects
Table 14.3.1.8	Most Commonly Reported (>=5% of Subjects in One or More Treatment Groups) Treatment-Related Adverse Events	Safety Analysis Subjects
Table 14.3.1.8	Summary of Treatment-Related Adverse Events By System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects
Table 14.3.1.9	Summary of Treatment-Emergent Adverse Events by Demographic Characteristics	Safety Analysis Subjects
Table 14.3.1.10	Summary of Subject Discontinuation from Study Due to Adverse Events By System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects
Table 14.3.1.11	Summary of Serious Adverse Events By System Organ Class and referred Term	Safety Analysis Subjects
Table 14.3.2.1	Listing of Deaths	Safety Analysis Subjects
Table 14.3.2.2	Listing of Serious Adverse Events	Safety Analysis Subjects

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FIGURES:

Figure 14.2.1.1	SPID 0-24 by Treatment	Full Analysis Set
Figure 14.2.2	SPID 0-12 by Treatment	Full Analysis Set
Figure 14.2.3	SPID 0-48 by Treatment	Full Analysis Set
Figure 14.2.1.2	SPID 0-12, 0-24 and 0-48 by Treatment	Full Analysis Set
Figure 14.2.4.1	Kaplan-Meier Estimates of Time to Confirmed Perceptible Pain Relief (TCPR) from 0-12 hours	Full Analysis Set
Figure 14.2.4.2	Kaplan-Meier Estimates of Time to Confirmed Perceptible Pain Relief (TCPR) from 0-3 hours	Full Analysis Set
Figure 14.2.5.1	Kaplan-Meier Estimates of the Time to Meaningful Pain Relief (TMPR) from 0-12 hours	Full Analysis Set
Figure 14.2.5.1	Kaplan-Meier Estimates of the Time to Meaningful Pain Relief (TMPR) from 0-3 hours	Full Analysis Set
Figure 14.2.6	Kaplan-Meier Estimates of the Time to First Use of Rescue Medication from 0-48 hours	Full Analysis Set
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

[redacted]

Status : Approved

APPENDIX 6: DATA LISTINGS

The following listings are planned for Clinical Study Report. The numbering and titles of data listings in this document serve as guidance; the exact numbers and titles may be modified as appropriate.

Listing No.	Title	Population
16. 1.7	Randomization Schedule	All Randomized
16.2.1.1	Subject Disposition	All Screened
16.2.1.2	Analysis Sets	All Screened
16.2.1.3	Discontinued Subjects	All Screened
16.2.1.4	Follow-up Interview	All Screened
16.2.2	Subjects with Protocol Deviations	All Randomized
16.2.3	Subjects Excluded from Per Protocol Population	All Randomized
16.2.4.1	Demographic and Baseline Characteristics	All Screened
16.2.4.2	Significant Medical History	All Screened
16.2.4.3	Previous and Concomitant Medications	All Screened
16.2.4.4	Non-Drug Therapy/Procedure	All Screened
16.2.4.5	Time of Popliteal Catheter Placement/Removal, Time of Surgery, Qualifying and Baseline Pain Assessments	All Randomized
16.2.5	Dosing Time of Study Medication	All Randomized
16.2.6.1.1	Pain Intensity Assessments	All Randomized
16.2.6.1.2	Time Weighted Sum of Pain Intensity Difference from 0 to 12, 0-24 and 0-48 hours (SPID 0-12, 0-24, 0-48)	All Randomized
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
16.2.6.3	Pain Intensity Assessments Out of Assessment Window and Imputed Values	All Randomized
[redacted]	[redacted]	[redacted]
16.2.6.5	Pain Intensity [redacted] Prior to Rescue	All Randomized
16.2.6.6	Time to Request/Use of Rescue Medication	All Randomized
16.2.6.7	Time to Confirmed Perceptible Pain Relief and Time to Meaningful Pain Relief	All Randomized
[redacted]	[redacted]	[redacted]
16.2.7.1	Subjects with Treatment-Emergent Adverse Events	All Screened
16.2.7.2	Subjects with Non-Treatment-Emergent Adverse Events	All Screened
16.2.7.3	Subjects with Adverse Events that Resulted in Subject Discontinuation From Study	All Screened
16.2.7.4	MedDRA Preferred Terms for Adverse Events	All Screened
16.2.8.1	Laboratory Tests	All Screened
16.2.8.2	Vital Signs	All Screened
16.2.9	Special Situations	All Screened