| | |
|---|---|
| Document Type: | Statistical Analysis Plan |
| Official Title: | A Randomized, Double-Blind, Single-Dose, Parallel, Placebo-Controlled Pivotal Trial to Confirm the Efficacy of a Fixed Dose Combination Tablet of Naproxen Sodium and Caffeine to Effectively Alleviate Postsurgical Dental Pain |
| NCT Number: | NCT05485805 |
| Document Date: | 11-Mar-2024 |

# STATISTICAL ANALYSIS PLAN

## TITLE PAGE

**A Randomized, Double-Blind, Single-Dose, Parallel, Placebo-Controlled Pivotal Trial to Confirm the Efficacy of a Fixed Dose Combination Tablet of Naproxen Sodium and Caffeine to Effectively Alleviate Postsurgical Dental Pain**

**Final Version 1.0: MAR 11, 2024**

**TABLE OF CONTENTS** **PAGE**

## DECLARATION

I, the undersigned, declare that I have prepared the statistical analysis plan along with TLF mock shells and that to the best of my knowledge this document is internally consistent with protocol and scientifically rational.

Prepared by:

PPD

**Name:** PPD **PhD**
**Designation\Role:** PPD **Sign & Date (MMM DD, YYYY)**

I, the undersigned declare that I have reviewed the statistical analysis plan along with TLF mock shells and that to the best of my knowledge the document is internally consistent with protocol and scientifically rational.

Reviewed by:

PPD

**Name:** PPD **PhD**
**Designation\Role:** PPD **Sign & Date (MMM DD, YYYY)**

AUTHORIZATION: I, the undersigned, declare that I have reviewed the statistical analysis plan along with TLF mock shells and that to the best of my knowledge the document accurately reflects the protocol objectives.

Authorized by:

PPD

**Sponsor representative(s) name:** PPD **PhD**
**Designation\Role:** PPD **of Biostatistics and Data Management. Sign & Date (MMM DD, YYYY)**

## REVISION HISTORY

| Version | Date | Author | Reasons |
|---|---|---|---|
| 1.0 | 11 Mar 2024 | PPD | Based on Protocol Amendment Number-3 |

# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CM | Concomitant Medication |
| CRF | Case Report Form |
| EOS | End of Study |
| EOT | End of Trial |
| FDC | Fixed Dose Combination |
| ICH | International Conference on Harmonization |
| ITT | Intent-To-Treat |
| LS Means | Least Square Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NRS | Numeric Rating Scale |
| OTC | Over-The-Counter |
| PAR | Pain Relief |
| PI | Pain Intensity |
| PID | Pain Intensity Difference |
| PP | Per Protocol |
| PT | Preferred Term |
| SAP | Statistical Analysis Plan |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SPID | Summed Pain Intensity Difference |
| TEAE | Treatment-Emergent Adverse Event |
| TFLs | Tables, Figures, and Listings |
| TOTPAR | Total Pain Relief |
| WHODRUG | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

This is a single center, randomized, double-blind, parallel, placebo-controlled study in participants experiencing moderate to severe postoperative dental pain.

This proposed product is intended to be a tablet with a fixed dose combination of 220 mg naproxen sodium and 65 mg caffeine based on the recently completed dose ranging study. The purpose of this product is to provide temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backache, menstrual cramps, headache, and toothache for adults and children over 12 years of age.

This pivotal efficacy study is intended to examine the analgesic effect of this FDC compared to its components, naproxen sodium and caffeine to satisfy the combination rule set forth in 21CFR 330.10(a)(4)(iv).

This Statistical Analysis Plan (SAP) describes the statistical methods and data handling procedures to be followed during the final reporting and analyses of data collected for the study Protocol 22093.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol Version 4.0, dated MAR 13, 2023 and CRF Version 5.0, dated APR 14, 2023.

The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document. Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9.

# 2 STUDY DETAILS

## 2.1 Study Objectives

The primary objective of the study is:

1. To compare a single oral dose of the FDC relative to naproxen sodium 220mg, Caffeine 100 mg and placebo.

The secondary objectives of the study are:

2. To compare a single oral dose of the FDC relative to naproxen sodium 220mg, caffeine 100 mg and placebo. The assessments are made in terms of:

    - Pain intensity differences
    - Measures of pain relief
    - Duration of analgesic efficacy

- Onset of pain relief as determined by the time of perceptible relief
- Onset of pain relief as determined by the time to meaningful relief
- Overall relief from pain based on measures of pain intensity and pain relief
- Global assessment of the investigational product

3. To assess the safety and tolerability of the investigational product in terms of adverse events (AEs) and clinical parameters.

## 2.2 Study Design

This is a single center, randomized, double-blind, parallel, placebo-controlled study in participants experiencing moderate to severe postoperative dental pain. The study will consist of a Prescreening telephone call, a Screening Visit, a one day Treatment Period and a Post-Operative phone call or visit. Eligible participants who have undergone surgical extraction of three or four third molars, 2 of which were mandibular partial or full bony impacted third molars will be kept in-house and evaluated for efficacy and safety at the study site through completion of all trial procedures.

Qualified participants will then be randomized into one of five treatments. Approximately 750 participants will be screened prior to surgery. Approximately 540 will have surgery and approximately 528 will be randomized to a specific treatment. For an overview on the study design and study procedures, see figure 1 below:

**Figure 1 – Design Overview**

| | Screening Phase | Treatment Phase | | | | | Follow up Phase |
|---|---|---|---|---|---|---|---|
| **Trial Days** | **Day -28 to -1** | **Day 1 Pre-surgery** | **Day 1 Surgery** | **Day 1 Post-surgery** | **Day 1** | **Day 2** | **2-5 days after discharge** |
| | | Check-in to study site | Surgical teeth extraction | Categorical pain NRS pain | ✸ Stopwatch method NRS pain, Pain relief | Stopwatch method NRS pain Pain relief Global assessment | Phone call or visit |

✸ = randomized study intervention of:
naproxen sodium/caffeine 220/65 mg;
naproxen sodium/caffeine 2 x 220/65 mg;
naproxen sodium 220 mg;
caffeine 100 mg;
or placebo.

### Screening Phase

Eligible participants will be screened and selected up to 28 days prior to oral surgery and dosing with investigational product (study intervention).

**Treatment Phase**

Following selection, qualified participants will enter the Treatment Phase and be scheduled for their surgical teeth extractions. After completion of the surgical teeth extractions, participants will remain at the study site for observation. Participants with appropriate pain requirement will be randomized into one of five (5) treatment groups receiving study intervention. Participants will rate their pain severity and pain relief over the next 24 hours. Onset of analgesia will be measured using a two-stopwatch approach. The first stopwatch will be used to capture the time when any pain relief is first perceived. The second stopwatch will be used to capture the time when pain relief becomes meaningful to the participant. After completion of all trial procedures, participants will be discharged from the study site.

All participants are required to remain at the study center and complete all relevant assessments regardless of rescue.

**Follow-Up Phase**

Participants will be evaluated at a post-operative visit/call approximately 2-5 days after discharge for follow up for any adverse events or medications not known at the time of treatment.

The duration of each participant's participation will be approximately 37 days. See study schedule of assessment, table 1 below:

**Table 1: Schedule of Assessment**

| Protocol Activities | Screening Visit (within 28 days prior to oral surgery) | Dosing Period *Inpatient* | | End of Trial Call or Visit (2-5 days after discharge) |
|---|---|---|---|---|
| | | Day 1 | Day 2 | |
| Written Informed Consent | x | | | |
| Inclusion/Exclusion Reviewed | x | x | | |
| Medical/Medication History (incl. caffeine consumption) | x | x | | |
| Physical and Oral Examination | x | | | |
| Vital Signs [a] | x | x | x | |
| Urine for Drug Screen | x | x | | |
| Breath or saliva alcohol test | x | x | | |
| Dental x-ray examination | x | | | |
| Urine Pregnancy Test (if applicable) | x | x | | |
| Admission to Unit | | x | | |
| Oral surgery (between 0530 h and 1030 h) | | x | | |
| Randomization Number Assigned | | x | | |
| Investigational Product Administration | | x | | |
| Surgical Trauma Rating | | x | | |
| Stop watch method (perceptible and meaningful relief) | | x | x | |
| Categorical Pain Rating Scale [b] | | x | x | |
| Pain Intensity Numerical Rating Scale (NRS) [c] | | x | x | |
| Categorical Pain Relief Rating Scale [c] | | x | x | |
| Global Assessment of Pain Relief [d] | | | x | |
| Concomitant Medications | | x | x | x |
| Adverse Events Assessed | x | x | x | x |
| Discharge from Unit the afternoon/evening of Day 2 | | | x | |

[a] vital signs (blood pressure, pulse rate, and respiration after sitting for at least 5 minutes). On Day 1, vital signs are due pre-operatively, post-surgery at 1 hour, 12 hours and on Day 2, 24 hours (-30 minutes pre-surgery; +30 minutes post-surgery; +/- 30 minutes from hours 1 through 24) after study medication dosing

[b] to be completed prior to dosing

[c] Pain Intensity NRS to be completed at baseline (predose), and Pain Intensity NRS and Categorical Pain Relief will be assessed 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, (16, 18, 20 if awake), 22 and 24 hours (+/-5 minutes over the first 8 hours; +/-8 minutes from hours 9 through 24) post-dose. If rescue occurs, scales/questions will be completed immediately each time rescue medication is taken

[d] assessment will be completed immediately before first rescue medication is taken or at 24 hours post-dose

## 2.3 Determination of Sample Size

Assuming that the treatment difference between the combo and naproxen alone of 6.5 and common standard deviation of 16.9 with respect to SPID0-8, a total of approximately 528 subjects (144 subjects per active treatment arm and 48 in the caffeine and placebo using a 3:3:3:1:1 ratio) are required to

achieve 90% of power with the type I error of 0.05, a total of approximately 556 subjects will be randomized into the study if a drop-out rate of 5% is assumed.

### 2.4 Randomization

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the five (5) arms of the study, according to the randomization schedule generated prior to the study by the Sponsor. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study.

### 2.5 Blinding

Participants enrolled in the trial, investigators and their staff involved in protocol procedures or who are involved in data collection, data entry and data analysis will be blinded to the identity of the treatments until the database is locked. The study monitor will conduct product accountability after database lock. To preserve blinding, participants will be blindfolded during administration of study medication. Study drug will be dispensed by an unblinded study team member based on the randomization schedule. That team member may have no other role in the study conduct and may not reveal the study drug's identity to any members of the blinded study team.

## 3 DATA ANALYSIS CONSIDERATION

The statistical analyses will be performed by Quartesian Clinical Research (now a part of Veranex Solutions), using SAS Version 9.3 or higher. All Tables, Figures and Listings (TFLs) will be produced in landscape format. In general, all data will be listed by the Participant, treatment and visit/time point where as appropriate.

Data will be summarized by treatment group and visit/time. The total number of Participants in the treatment group (N) under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise stated, descriptive statistics will include total number of Participants (n), mean, standard deviation (SD), minimum, median, and maximum. In case n=0, except n, all other summary statistics will be kept blank and when n=1, only n, minimum and maximum will be reported, and all other summary statistics will be kept blank. The statistic "Missing" will also be evaluated by enumerating the number of missing entries/Participants, if any at that visit, and presented as a summary statistic only for the resulting time points.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of Participants with a particular value of a variable or event, which should always be less than or equal to the total number of Participants in the respective treatment group [N]. Percentage will be obtained by: % = (n/N) *100. Unless otherwise stated. Proportion will be obtained by: (n/N).

For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

**Decimal Precision Convention:** The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data. Also, the least square mean, standard error and its confidence interval, least square mean differences will be presented to two more decimal places than the original data. All percentages will be expressed to one decimal place. P-value will be presented three decimal places or P-value closer to zero will be presented as <0.001 and P-value closer to one will be presented as >0.999.

All dates will be displayed in DDMMMYYYY format.

## 3.1 Handling of Missing Data

### 3.1.1 Handling of Missing Data for Efficacy Assessments

**Use of Rescue Medication:**

In all analyses, for participants who take rescue medication, all pain intensity scores after intake of rescue medication will be imputed by the worse of the baseline or the score assessed immediately before taking rescue medication. All pain relief after intake of rescue medication will be imputed by "no relief" (0).

**Missing data for efficacy parameter:**

If Participants have missing pain data (i.e., pain intensity or pain relief scores) within the 24 hours period for the collection of pain rating data, but nonetheless complete the 24-hour period, then any missing timepoints will be replaced by a time-weighted average of the previous and the next available values (i.e., a linear interpolation for missing values) of the pain data (pain intensity / pain relief score). Intermittent missing data will only be imputed using linear interpolation method and if needed round down to the nearest whole number for pain relief scores, whereas for the categorical pain intensity the value will be rounded up to the nearest whole number.

Interpolation Formula,

$$\mathrm{y} = \frac{y_2 - y_1}{x_2 - x_1}\ (x - x_1) + y_1$$

Where, and if needed round down to the nearest whole number for pain relief scores, whereas for the categorical paint intensity the value will be rounded up to the nearest whole number.
y = missing pain data to be imputed, x = respective timepoint of y.
$y_1 and\ y_2$ = pre and post available pain score of the missing pain data.
$x_1\ and\ x_2$= respective timepoints of $y_1 and\ y_2$.

If Participants do not complete the pain intensity/pain relief assessments for the full 24 hours, then the primary analysis will be calculated up to the last available timepoint, with no imputation for later timepoints.

In a sensitivity analysis, Participants who drop out of the study early because of a related AE or lack of efficacy will have later missing timepoints imputed using a worst-observation-carried-forward (WOCF) method, in which their worst observation at baseline or any time thereafter is imputed. For Participants dropping out early for any other reason, a last-observation-carried-forward (LOCF) imputation will be used.

No imputation will be done for missing data on stopwatch assessments of perceptible and meaningful pain relief. Instead, if data are missing for those assessments, data will be censored as described in Section 4.1.

### 3.1.2 Handling of Missing Data for Safety Evaluations

To handle missing or partial AE and concomitant medication dates, the following rules will be applied.

**For Partial Start Dates:**

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
   i. If the year matches the year of the dose date, then impute the month and day of the dose date.
   ii. Otherwise, assign "January."
3. If the day is unknown, then:
   i. If the month and year match the month and year of the dose date, then impute the day of the dose date.
   ii. Otherwise, assign "01."

**For Partial End Dates:**

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pre-treatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

3. If the start date is missing but the stop date is not missing and is before the day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication is considered to be concomitant while the AE is defined by start date.

5. If the Adverse Event Relationship flag is missing, the relationship for adverse event will be imputed and will be considered as "Yes". If the Adverse Event Severity flag is missing, the severity will be imputed and will be considered as "Severe".

# 4 DEFINITIONS AND DERIVATIONS

**Baseline:** Baseline is defined as the latest non missing assessment prior to the administration of the first dose of the study drug, unless otherwise specified. If the assessment occurs on the same date as the dose administration, then the time of assessment should be compared to the time of dose administration.

**Change from Baseline**: The change from baseline values will be calculated as post-baseline value minus the baseline value.

***Change from Baseline***=*Post baseline value - Baseline value*

**Treatment Emergent Adverse Event (TEAE)**: A treatment-emergent adverse event (TEAE) is any AEs that begin or worsen after the first dose of the study drug administration in the Treatment Phase.

## 4.1 Endpoint Derivations

**Pain Intensity:**

Participants will assess their current pain intensity using an 11-point (0: No Pain to 10: Worst possible pain) Numerical Rating Scale (NRS). Each Participant will be instructed to mark the number indicating his or her current pain intensity. Below is pain scale format.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible pain |

The Participant is to record pain intensity (NRS) at baseline (i.e., pre-dose). Thereafter, the Participant is to record NRS pain intensity assessment at the following time points during the 24 hours period after baseline:

0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 and 24 hours post-dose, and immediately before each use of rescue analgesia.

| I | Nominal Ti (hours) |
|---|---|
| 0 | 0 |
| 1 | 0.5 |
| 2 | 1 |
| 3 | 1.5 |
| 4 | 2 |
| 5 | 3 |
| 6 | 4 |
| 7 | 5 |
| 8 | 6 |
| 9 | 7 |
| 10 | 8 |
| 11 | 9 |
| 12 | 10 |
| 13 | 11 |
| 14 | 12 |
| 15 | 14 |
| 16 | 16 |
| 17 | 18 |
| 18 | 20 |
| 19 | 22 |
| 20 | 24 |

**Pain Intensity Difference:**

Pain intensity difference (PID) is to be calculated by subtracting the pain intensity at the post-dose time point from the pain intensity at baseline.

$$\text{PID}_i = PI_0 - PI_i \text{ ; for all i } > 0.$$

Where, $PI_0$ pain intensity at baseline, $PI_i$ is the PI score at post-dose time point i.

**Summed Pain Intensity Difference (SPID):**

The summed pain intensity difference (SPID) is to be calculated by multiplying the PID score at each post dose time point by the duration (in hours) since the preceding time point and then summing the values over the relevant time period.

$$SPID_{0-2} = \sum_{i=1}^{4} (T_i - T_{i-1}) * PID_i$$

$$SPID_{0-4} = \sum_{i=1}^{6} (T_i - T_{i-1}) * PID_i$$

$$SPID_{0-6} = \sum_{i=1}^{8} (T_i - T_{i-1}) * PID_i$$

$$SPID_{0-8} = \sum_{i=1}^{10} (T_i - T_{i-1}) * PID_i$$

$$SPID_{6-12} = \sum_{i=8}^{14} (T_i - T_{i-1}) * PID_i$$

$$SPID_{0-12} = \sum_{i=1}^{14} (T_i - T_{i-1}) * PID_i$$

$$SPID_{12-16} = \sum_{i=14}^{16} (T_i - T_{i-1}) * PID_i$$

$$SPID_{16-20} = \sum_{i=16}^{18} (T_i - T_{i-1}) * PID_i$$

$$SPID_{12-24} = \sum_{i=14}^{20} (T_i - T_{i-1}) * PID_i$$

$$SPID_{16-24} = \sum_{i=16}^{24} (T_i - T_{i-1}) * PID_i$$

$$SPID_{0-24} = \sum_{i=1}^{20} (T_i - T_{i-1}) * PID_i$$

Where, $T_0$=0, $T_i$ is actual post-dose time, $PID_i$ is the PID score at post-dose time $T_i$ for all i > 0.

The durations between two time points will be calculated using the actual post-dose times of the pain score measurement. If the actual time is missing, then the nominal planned time will be used.

**Pain Relief:**

Participants will assess their current pain relief using a 5-point scale as 0: No relief, 1: A little relief, 2: Some Relief, 3: A Lot of Relief, 4: Complete relief (categorical scale). Each Participant will be instructed to mark the number indicating his or her current pain relief.

The Participant is to record pain relief (5-point categorical rating scale) at given time points during the 24-hour period and immediately before first use of rescue medication.

**Total Pain Relief (TOTPAR):**

Total pain relief (TOTPAR) is calculated by multiplying the pain relief score at each time point by the duration (in hours) since the preceding time point and then summing these over the relevant period.

$$TOTPAR_{0-2} = \sum_{i=1}^{4} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{0-4} = \sum_{i=1}^{6} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{0-6} = \sum_{i=1}^{8} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{0-8} = \sum_{i=1}^{10} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{6-12} = \sum_{i=8}^{14} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{0-12} = \sum_{i=1}^{14} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{12-16} = \sum_{i=14}^{16} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{16-20} = \sum_{i=16}^{18} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{12-24} = \sum_{i=14}^{20} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{16-24} = \sum_{i=16}^{24} (T_i - T_{i-1}) * PAR_i$$

$$TOTPAR_{0-24} = \sum_{i=1}^{20} (T_i - T_{i-1}) * PAR_i$$

Where, $T_0$=0, $T_i$ is actual post-dose time, $PAR_i$ is the Pain Relief score at post-dose time $T_i$ for all i > 0.

**Peak Pain Relief:**

Peak pain relief is the highest observed value of pain relief experienced during post-dose assessments of the study.

**Peak Pain Intensity Difference (Peak PID):**

Peak pain intensity difference is the highest observed value of pain intensity difference calculated by formula given above in this section.

**Time to first Perceptible Relief:**

Time to first perceptible relief is the time when the Participant experiences any perceptible pain relief after administration of study drug and stops the first stopwatch. If it is not stopped, time will be censored at the time of last pain relief score assessment or at the first use of rescue medication, whichever comes first.

**Time to meaningful relief:**

Time to meaningful relief is the time when the Participant experiences relief that is meaningful after the administration of study drug and stops the second stopwatch. If it is not stopped, time will be censored at the time of last pain relief score assessment or at the first use of rescue medication, whichever comes first.

**Time to first perceptible relief confirmed by meaningful relief:**

Time to first perceptible relief confirmed by meaningful relief is defined as the time to perceptible pain relief (the first stopwatch time) for those Participants who had confirmed meaningful pain relief immediately after first stopwatch and it will be time to meaningful pain relief (the second stopwatch time) for those Participants who did not confirm the meaningful relief before second stopwatch. If stopwatch is not stopped, time will be censored at the time of last pain relief score assessment or at the first use of rescue medication, whichever comes first.

**Time to the First Use of Rescue Medication:**

Time to first use of rescue medication for pain is defined as the time from first study drug administration to the first use of rescue medication. If rescue medication for pain is not taken, the time will be censored at the time of the last pain intensity score assessment.

**Time to achieve complete pain relief:**

Time to achieve complete pain relief is defined as the time from first study drug administration to the achieve complete pain relief. If complete pain relief not achieved, the time will be censored at the time of the last pain relief score assessment.

**Cumulative proportion of Participants taking rescue medication:**

The cumulative proportion of Participants taking rescue medication will be calculated as the cumulative number of Participants who taken rescue medication by a given timepoint divided by the number of Participants treated in respective treatment group.

**Participants with 'at least a 2-point PID':**

Participants with observed PID score greater than or equal to 2 at any post dose timepoints will be considered as 'at least a 2-point PID'. The same previous formula will be used to calculate the Pain intensity difference (PID).

**Participant's Global Assessment of Investigational Product:**

At hour 24 or immediately prior to the first dose of rescue medication (if prior to hour 24), study participants will be asked to provide a Global Assessment of investigational product after completion of the other assessments. The Participant will be instructed to score his or her global evaluation of the study treatment on a 5-point categorical scale.

# 5 PRIMARY, SECONDARY AND EXPLORATORY ENDPOINTS

## 5.1 Primary Endpoint

- Sum of Pain Intensity Difference over 8 hours (SPID0-8)

## 5.2 Secondary Endpoints

- Sum of pain intensity differences from 0 to 2, 4, 6, 12 and 24 hours post-dose (SPID0-2, SPID0-4, SPID0-6, SPID6-12, SPID0-12, SPID12-16, SPID16-20, SPID12-24, SPID16-24, SPID0-24)

- Total pain relief from 0 to 2, 4, 6, 8, 12 and 24 hours post-doseTOTPAR0-2, TOTPAR0-4, TOTPAR0-6, TOTPAR 6-12, TOTPAR0-8 TOTPAR0-12, TOTPAR12-16, TOTPAR16-20, TOTPAR 12-24, TOTPAR16-24 and TOTPAR0-24)

- Time to first use of rescue medication

- Time and cumulative proportion of achieving complete pain relief

- The cumulative proportion of participants taking rescue medication over the 24-hour period.

- Time to first perceptible relief measured by a stopwatch, time to meaningful relief measured by a stopwatch, and time to first perceptible relief confirmed by meaningful relief defined as the time to perceptible pain relief (the first stopwatch time) for those participants who had meaningful pain relief (the second stopwatch time)

- Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, (16, 18, 20 if awake), 22 and 24 hours post-dose

- Peak PID and peak pain relief

- Cumulative percent of participants with ‘at least a 2-point PID’ over time

- Global assessment of the investigational product

- Collect AE and clinical parameters

## 5.3 Exploratory Endpoints

- Not Applicable

# 6 ANALYSIS POPULATION AND TREATMENT GROUPS

## 6.1 Analysis Population

**Randomized Population:** All participants who received a randomization number, regardless of receiving study medication.

**Safety Population**: All participants who are randomized and take at least one dose of investigational product. Safety measures will be analyzed for all participants in the safety population.

**Intent-To-Treat (ITT) Population:**

All participants in the Safety Population. ITT population will be used as the primary analysis for the efficacy parameters.

**Per Protocol (PP) Population**: PP population will include all participants in ITT who do not have any major protocol violations and complete the 24-hour assessments. PP population will be used as secondary to conduct the sensitivity analysis for the selected parameters.

Major protocol deviations will be identified prior to database lock and may include but are not limited to significant violations of inclusion/exclusion criteria, noncompliance of the trial treatment taken, conditions such as vomiting and diarrhea or use of prohibited medications, and not following clinical trial protocol procedures. Any participant who rescues or vomits at or prior to 60 minutes after ingesting study medication will be excluded from the PP population.

## 6.2 Treatment Groups

The below table includes the treatment labeling for all Tables, Listings and Figures (wherever as appropriate):

| Treatment | Treatment Label for TLF |
|---|---|
| Naproxen sodium/caffeine 220/65 mg | Group 1 |
| Naproxen sodium/caffeine 2 x 220/65 mg | Group 2 |
| Naproxen sodium 220 mg | Group 3 |
| Caffeine 100 mg | Group 4 |
| Placebo | Placebo |
| Overall | Overall |

# 7 ANALYSES METHODS AND REPORTING DESCRIPTIONS

## 7.1 Participant Disposition

Participant disposition will be summarized using frequency count and percentage by treatment group and overall, for the randomized Participants:

- Number of Participants in the Randomized Population
- Number of Participants in the safety Population
- Number of Participants in the ITT Population
- Number of Participants in the Per-Protocol Population
- Number of Participants who Completed the Study
- Number of Participants who discontinued early from the study, as well as the reason for study discontinuation

Participants' disposition status will be listed by treatment group and will include Participant number, study completion status, Date of completion or discontinuation, and for those who discontinued early, specific reason for discontinuation (if reason of discontinuation is "Lost to follow-up" then "Date of last contact:" will be displayed.)

## 7.2 Demography and Baseline Characteristics

Demographic and baseline characteristics (including age, gender, race, ethnicity, childbearing potential, method of contraception, weight, height, BMI) will be summarized by treatment group and for the overall using descriptive statistics (n, mean, SD, median, minimum, and maximum) for Safety and ITT population. Demographic and baseline data will also be listed for safety population.

Dental X-ray examination, Surgical Trauma Rating and social history will be listed separately for safety population.

## 7.3 Medical History

A complete medical history, including a complete review of all current and past diseases will be done on screening visit. Medical history term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. and summarized by treatment group and overall, by frequency count and percentage of Participants in each system organ class (SOC), preferred term (PT) using Safety Population.

Participants will be counted only once at the preferred term (PT), only once at the system organ class (SOC), and only once at Participant level for the counting of total number of Participants with a medical history term. Counts will be presented in descending frequency unless otherwise specified.

Listings of medical history events for Participants in the Safety Population will be provided.

## 7.4 Prior and Concomitant Medications

Any medication other than study drug, either prescription drug or over the counter (OTC) will be treated as concomitant medication.

Prior Medications

For a Participant in the Safety Population, prior medications will include any medication taken prior to Participant's first dose of Study Medication.

Concomitant Medications

Concomitant medications are defined as prescribed medications and over the counter (OTC) preparations, including herbal preparations and vitamins, other than Study medication taken during the treatment phase.

Prior and concomitant medication will be categorized by preferred Term and anatomical-therapeutic-chemical (ATC) classification (highest level available) per World Health Organization Drug Dictionary (WHODRUG B3 March 01, 2022) will be summarized by treatment group and overall, for the Safety Population.

The frequency count and percentage of Participants using each medication will be displayed. Participants who taken the same medication (in terms of PT) more than once will be counted only once for that medication.

Participants taking multiple prior / concomitant medication will be counted only once in summary table. If the Participant is taking medication prior to study drug administration and continues the same drug after study drug administration, then such Participants will be summarized in both prior and concomitant medication summary tables.

All prior and concomitant medications will be presented in a listing for the Safety Population.

## 7.5 Protocol Deviation

Protocol deviations will be identified and classified as minor or major before un-blinding. Protocol deviation categories will be summarized using frequency count and percentage by treatment group.

A listing and summary of protocol deviations will be presented using the Safety Population.

## 7.6 Study Drug Exposure and Treatment Compliance

A summary table of study drug administration will be provided. Table will be presented using counts and percentages of Number of units administered by treatment groups.

A listing of study drug exposure (administration/dispensation) will be provided.

## 7.7 Efficacy Analysis

### 7.7.1 Primary Endpoint

The primary efficacy endpoint is the sum of change in pain intensity from 0 to 8 hours (SPID0-8). The treatment comparisons will be made in the following sequential order for SPID0-8 (each at 0.05 level of significance) in order to protect overall type 1 error at 0.05:

- Naproxen sodium/caffeine 220/65 mg versus Naproxen sodium 220 mg
- Naproxen sodium/caffeine 440/130 mg versus Naproxen sodium 220 mg
- Naproxen sodium/caffeine 220/65 mg versus Naproxen sodium/caffeine 440/130 mg

Once a comparison is statistically non-significant, the subsequent comparisons will be technically ineligible to be declared significant. However, all pairwise comparisons will be presented to provide a complete picture.

The primary efficacy endpoint is the summed pain intensity difference over 0 to 8 hours after Time 0 (SPID0-8). The formula for SPID0-8 calculation is presented in Section 4.1. The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model, which will include SPID0-8 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate.

The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) of LS mean for each treatment group will be reported.

In addition, the least square mean difference, SE, 95% Confidence interval of LS mean difference and p-value for all pairwise treatment group (include placebo) comparisons will be reported. Descriptive statistics (n, mean, SD, median, minimum, and maximum) for SPID0-8 will also be presented by treatment group.

ITT population (without imputation) will be used as the primary analysis for this primary endpoint while PP population (without imputation and single imputation) will be used as secondary analysis to conduct the sensitivity analysis.

In the primary analysis, endpoint will be imputed as described in Section 3.1.1, if any pain assessments are missing or Participant takes rescue medication.

### 7.7.2 Secondary Endpoint(s)

Analysis of the secondary endpoints will be summarized according to the variable type. The details are presented in the following sections.

**SPID from 0 to 2, 4, 6, 12 and 24 hours post-dose (SPID0-2, SPID0-4, SPID0-6, SPID6-12, SPID0-12, SPID12-16, SPID16-20, SPID12-24, SPID16-24 and SPID0-24)**

SPID0-2, SPID0-4, SPID0-6, SPID6-12, SPID0-12, SPID12-16, SPID16-20, SPID12-24, SPID16-24, SPID0-24 will be calculated using the formula specified in Section 4.1. The same method that is used for the analysis of the primary endpoint will be used to assess the difference between the treatment groups in each metric.

This endpoint will be analysed using ITT population (without imputation) as primary analysis while PP population (without imputation and single imputation) will be used as secondary to conduct the sensitivity analysis.

In the secondary analysis, endpoint will be imputed as described in Section 3.1.1, if any pain assessments are missing or Participant takes rescue medication.

**Total pain relief from 0 to 2, 4, 6, 8, 12 and 24 hours post-dose (TOTPAR0-2, TOTPAR0-4, TOTPAR0-6, TOTPAR 6-12, TOTPAR0-8 TOTPAR0-12, TOTPAR12-16, TOTPAR16-20, TOTPAR 12-24, TOTPAR16-24 and TOTPAR0- 24)**

TOTPAR0-2, TOTPAR0-4, TOTPAR0-6, TOTPAR 6-12, TOTPAR0-8 TOTPAR0-12, TOTPAR12-16, TOTPAR16-20, TOTPAR 12-24, TOTPAR16-24 and TOTPAR0- 24 will be calculated using the formula specified in Section 4.1. These secondary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model, which will include TOTPAR as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) of LS mean for each treatment group will be reported.
In addition, the least square mean difference, SE, 95% Confidence interval of LS mean difference and p-value for all pairwise treatment group (include placebo) comparisons will be reported. Descriptive statistics (including n, mean, SD, median, minimum, and maximum) for TOTPAR will also be presented by treatment group.

ITT population (without imputation) will be used as the primary analysis for this endpoint while PP population (without imputation and single imputation) will be used as secondary to conduct the sensitivity analysis.

In the secondary analysis, endpoints will be imputed as described in Section 3.1.1, if any pain assessments are missing or Participant takes rescue medication.

**Time to First Use of Rescue Medication**

Time to first use of rescue medication will be estimated and plotted using Kaplan-Meier method. Censoring will be applied as described in Section 4.1. Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity (Categorical pain intensity), pair wise comparison will be made using Tukey-Kramer method and adjusted P-value will be reported. The summary statistics (25th percentile, Median, 75th percentile and it 95% CI) and

K-M estimates of overall time to first use of rescue medication with 95% CI will be presented by treatment groups.

This endpoint will be analysed using ITT population as primary analysis and PP population as secondary to conduct the sensitivity analysis.

**Cumulative proportion of participants taking rescue medication over the 24-hour period**

Cumulative proportion of Participants taking rescue medication will be calculated as the cumulative number of Participants who takes rescue medication at given timepoint and percentage will be calculated by cumulative number of Participants who takes rescue medication at given timepoint divided by the number of Participants treated in respective treatment group.

The cumulative proportion of Participants taking rescue medication over 24-hours period will be presented using counts and proportion with timepoints (0.5, ≤1, ≤1.5, ≤2, ≤3, ≤4, ≤5, ≤6, ≤7, ≤8, ≤9, ≤10, ≤11, ≤12, ≤14, ≤16, ≤18, ≤20, ≤22 and ≤24 hours post-dose) by treatment groups and also curves over time will also be plotted by treatment group. The analysis will be performed for the ITT Population.

Participant will be counted only once in cumulative addition.

**Time to achieve complete pain relief**

Time to achieve complete pain relief will be analyzed similarly as for the time to first use of rescue medication.

It will estimate and plotted using Kaplan-Meier method. Censoring will be applied as described in Section 4.1. Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity (Categorical pain intensity), pair wise comparison will be made using Tukey-Kramer method and adjusted P-value will be reported. The summary statistics (25th percentile, Median, 75th percentile and it 95% CI) and K-M estimates of overall time to achieve complete pain relief with 95% CI will be presented by treatment groups.

This endpoint will be analysed using ITT population as primary analysis and PP population as secondary to conduct the sensitivity analysis.

**Cumulative percent of participants achieving complete pain relief**

Cumulative percentage of Participants achieving complete pain relief will be calculated as the cumulative number of Participants achieving complete pain relief at given timepoint divided by the number of Participants treated in respective treatment group.

The cumulative percentage of Participants achieving complete pain relief will be presented using frequency counts and percentage with timepoints (0.5, ≤1, ≤1.5, ≤2, ≤3, ≤4, ≤5, ≤6, ≤7, ≤8, ≤9, ≤10,

≤11, ≤12, ≤14, ≤16, ≤18, ≤20, ≤22 and ≤24 hours post-dose) by treatment groups and curves over time will be plotted by treatment group. Participant will be counted only once in cumulative addition. This analysis will be performed for ITT Population.

**Time to first perceptible relief, time to meaningful relief, time to first perceptible relief confirmed by meaningful relief**

Time to first perceptible relief measured by a stopwatch, time to meaningful relief measured by a stopwatch, and time to first perceptible relief confirmed by meaningful relief defined as the time to perceptible pain relief (the first stopwatch time) for those participants who had meaningful pain relief (the second stopwatch time) will be estimated and plotted using Kaplan-Meier methods.

The definitions and censoring rules are defined in Section 4.1. Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity (Categorical pain intensity), pair wise comparison will be made using Tukey-Kramer method and adjusted P-value will be reported. The summary statistics (25th percentile, Median, 75th percentile and it 95% CI) and overall K-M estimates with 95% CI will be presented by treatment groups. The analysis will be performed for the ITT Population.

**Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, (16, 18, 20 if awake), 22 and 24 hours post-dose**

The PID at each scheduled time point will be calculated using the formula specified in Section 4.1. Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented by treatment groups.

Pain Relief score categories will be presented in the form of frequency counts and percentage by treatment groups and overall. Also, the pain relief score at each scheduled time point will be summarised using descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment groups. The analysis will be performed for the ITT Population.

A graphical illustration of the time effect curve (Time versus Mean PID / Mean pain relief score) will be presented.

**Analysis of Peak Pain Intensity Difference (Peak PID)**

The peak PID for each Participant will be identified using the description given in Section 4.1.

The Peak Pain Intensity Difference over the entire study (Peak PID0-24) will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum) and analyzed using an analysis of covariance (ANCOVA) model, which includes Peak PID0-24 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) of LS mean will be reported for each treatment group. In addition, the least square mean difference, SE, 95%

Confidence interval of LS mean difference and p-value for all pairwise treatment group (include placebo) comparisons will be reported. The analysis will be performed for the ITT Population.

**Analysis of Peak Pain Relief**

The peak pain relief for each Participant will be identified using the description given in Section 4.1.

The Peak Pain relief over the entire study (Peak Pain Relief 0-24) will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum) and analyzed using an analysis of covariance (ANCOVA) model, which includes Peak Pain Relief 0-24 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) of LS mean will be reported for each treatment group. In addition, the least square mean difference, SE, 95% Confidence interval of LS mean difference and p-value for all pairwise treatment group (include placebo) comparisons will be reported. The analysis will be performed for the ITT Population.

**Cumulative percent of participants with 'at least a 2-point PID' over time**

Participants with 2-point PID will be identified using the method mentioned in Section 4.1. The 2-point PID is the Participant PID which is greater than or equal to 2 at post baseline records.

Cumulative percentage of Participants with at least a 2-point PID will be calculated as the cumulative number of Participants with 2-point PID at given timepoint divided by the number of Participants treated in respective treatment group.

The cumulative percentage of Participants with 'at least a 2-point PID' will be presented using frequency counts and percentage with timepoints (0.5, ≤1, ≤1.5, ≤2, ≤3, ≤4, ≤5, ≤6, ≤7, ≤8, ≤9, ≤10, ≤11, ≤12, ≤14, ≤16, ≤18, ≤20, ≤22 and ≤24 hours post-dose) by treatment groups and curves over time will be plotted by treatment group. Participant will be counted only once in cumulative addition. This analysis will be performed for ITT Population.

**Global Assessment of the investigational product**

Global assessment of the investigational product ratings poor (0), fair (1), good (2), very good (3), and excellent (4) will be tabulated using frequency counts and percentage by treatment group. The p-value for the pair-wise treatment comparison will be calculated using Cochran-Mantel-Haenszel (CMH) test with modified ridit score controlling baseline pain intensity as strata, based on the proportion of subjects who have responded "Very Good" or "Excellent" that are grouped together.

This analysis will be performed for ITT Population.

### 7.7.3 Summary of Efficacy Endpoint(s) Analysis Strategy

| Endpoint | Statistical Method / Test | Analysis Population | Missing Data Imputation Approach | Parameters / Variables in the analysis (Stat. test/Model) | Analysis Time point |
|---|---|---|---|---|---|
| **Primary Endpoint** | | | | | |
| Sum of Pain Intensity Difference over 8 hours (SPID 0-8) | ANCOVA, Descriptive statistics | ITT | No imputation | Statistical Model: SPID0-8 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate | 8 hours |
| Sum of Pain Intensity Difference over 8 hours (SPID 0-8) | ANCOVA, Descriptive statistics | PP | No imputation and Single imputation | Same as Above | 8 hours |
| **Secondary Efficacy Endpoint** | | | | | |
| Sum of Pain Intensity Difference (SPID) from 0 to 2, 4, 6, 12 and 24 hours post-dose | ANCOVA, Descriptive statistics | ITT | No imputation | Statistical Models: SPID from 0 to 2, 4, 6, 12 and 24 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate | SPID 0-2, 0-4, 0-6, 6-12, 0-12, 12-16, 16-20, 12-24, 16-24 and 0-24 hours |
| Sum of Pain Intensity Difference (SPID) from 0 to 2, 4, 6, 12 and 24 hours post-dose | ANCOVA, Descriptive statistics | PP | No imputation and Single imputation | Same as Above | SPID 0-2, 0-4, 0-6, 6-12, 0-12, 12-16, 16-20, 12-24, 16-24 and 0-24 hours |
| Total pain relief from 0 to 2, 4, 6, 8, 12 and 24 hours post-dose | ANCOVA, Descriptive statistics | ITT | No imputation | Statistical Models: TOTPAR from 0 to 2, 4, 6, 12 and 24 as dependent variable, | TOTPAR 0-2, 0-4, 0-6, 6-12, 0-8 0-12, 12-16, 16-20, |

| Endpoint | Statistical Method / Test | Analysis Population | Missing Data Imputation Approach | Parameters / Variables in the analysis (Stat. test/Model) | Analysis Time point |
|---|---|---|---|---|---|
| | | | | treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate | 12-24, 16-24 and 0- 24 hours |
| Total pain relief from 0 to 2, 4, 6, 8, 12 and 24 hours post-dose | ANCOVA, Descriptive statistics | PP | No imputation and Single imputation | Same as Above | TOTPAR 0-2, 0-4, 0-6, 6-12, 0-8 0-12, 12-16, 16-20, 12-24, 16-24 and 0- 24 hours |
| Time to first use of rescue medication over 24 hours | Kaplan Meier Estimation Summary and graph | PP, ITT | No imputation | Statistical test: Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity (Categorical pain intensity), pair wise comparison will be made using Tukey-Kramer method (Rescue medication taken (Yes/No)) | 24 hours |
| Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, (16, 18, 20 if awake), 22 and 24 hours post-dose | Descriptive statistics, Graph | ITT | No imputation | Descriptive Statistics for PID derived from pain intensity score, Pain relief score | 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, (16, 18, 20 if awake), 22 and 24 hours post-dose |

| Endpoint | Statistical Method / Test | Analysis Population | Missing Data Imputation Approach | Parameters / Variables in the analysis (Stat. test/Model) | Analysis Time point |
|---|---|---|---|---|---|
| Time to first perceptible relief measured by a stopwatch | Kaplan Meier Estimation Summary and graph | ITT | No imputation | Statistical test: Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity (Categorical pain intensity), pair wise comparison will be made using Tukey-Kramer method (Stopwatch 1) | 24 hours |
| Time to meaningful relief measured by a stopwatch | Kaplan Meier Estimation Summary and graph | ITT | No imputation | Same as above model will be used. (Stopwatch 2) | At any timepoint after first perceptible pain relief measured in 24 hours |
| Time to first perceptible relief confirmed by meaningful relief | Kaplan Meier Estimation Summary and graph | ITT | No imputation | Same as above model will be used. (Stopwatch 1/ Stopwatch 2) | At any time for 24 hours |
| The cumulative proportion of Participants taking rescue medication over the 12-hour period | Frequency table and graph | ITT | No imputation | Descriptive Statistics for Rescue medication taken (Yes/No) | 24 hours |
| Peak PID | ANCOVA, Descriptive statistics | ITT | No imputation | Statistical Model: Peak PID0-24 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating | 24 hours |

| Endpoint | Statistical Method / Test | Analysis Population | Missing Data Imputation Approach | Parameters / Variables in the analysis (Stat. test/Model) | Analysis Time point |
|---|---|---|---|---|---|
| | | | | Score) as the covariate | |
| Peak pain relief | ANCOVA, Descriptive statistics | ITT | No imputation | Statistical Model: Peak Pain Relief 0-24 as dependent variable, treatment as main effect and baseline pain intensity (Numerical Rating Score) as the covariate | 24 hours |
| Cumulative percent of Participants with 'at least a 2-point PID' will be plotted over time | Frequency table and graph | ITT | No imputation | Descriptive Statistics for Pain intensity | 24 hours |
| Global Assessment of the investigational product | Frequency table, CMH test | ITT | No imputation | Descriptive Statistics for Overall rating | 24 hours |

### 7.8 Safety Analysis

All safety assessments, including AEs, treatment-emergent adverse events (TEAEs), clinical laboratory test results, vital signs and physical & oral examinations will be tabulated and listed by Participant when applicable. All the safety analysis will be performed using the Safety Population.

The following variables will be evaluated to assess the safety of the investigational products:

- Adverse Events
- Clinical Laboratory Data
- Vital sign measurements
- Physical Examination

## Adverse Events

Adverse Events will be coded using (MedDRA version 25.0) AE coding system for purpose of summary tables. For each treatment group, adverse events will be summarized with frequency count and percentage by MedDRA SOC and PT.

A Participant experiencing the same AEs and TEAEs multiple times will be counted only once for that PT. Similarly, if a Participant experience multiple AEs and TEAEs (preferred terms) within the same SOC then that Participant will be counted only once for that SOC. When summarizing by severity, only event with highest severity will be counted. All AEs will be listed in chronological order of the events occurred.

An overview of AE summary will be presented by treatment group. It will include:

- Number of Participants who had an AE
- Number of Participants who had a Serious AEs
- Number of Participants who had a TEAEs
- Number of Participants who had a Serious TEAEs
- Number of Participants who had a TEAEs by highest severity
    - Mild
    - Moderate
    - Severe
- Number of Participants who had a TEAEs with reasonable causal relationship to the study treatment
- Number of Participants with at least one treatment related serious TEAE
- Number of Participants who had a TEAEs leading to study discontinuation
- Number of Participants who had a TEAEs leading to death

### *Treatment-emergent Adverse Events (TEAEs)*

- A summary of the frequency (number and percentage of Participants) of TEAEs by treatment group and overall will be presented by SOC and PT term.
- A summary of the frequency (number and percentage of Participants) of TEAEs by treatment group and overall will be presented by SOC, PT, and severity (mild, moderate, severe).
- A summary of the frequency (number and percentage of Participants) of TEAEs by treatment group will be presented by SOC, PT and "reasonable causal relationship" to the study treatment is recorded as "Yes" and "No".
- Summary of TEAE by treatment groups Leading to Study Discontinuation will be presented by SOC, PT.

A listing of TEAE and a listing of TEAE leading to study discontinuation will be provided.

***Serious Adverse Events***

SAEs will be summarized by treatment group separately using frequency and percentage by SOC and PT. All SAEs recorded on the CRF will be listed.

***Adverse Events Leading to Study Drug Discontinuation***

All TEAEs leading to study drug discontinuation will be listed.

***Deaths***

All TEAEs leading to death will be listed.

**Clinical Laboratory Data:**

***Urine Drug Screen***

Urine Drug Screen Test will be summarized by result using frequency count and percentage by treatment groups. A separate listing of Urine Drug Screen will be provided.

***Urine Pregnancy Test***

Urine Pregnancy Test will be summarized by result using frequency count and percentage by treatment groups. A separate listing will be provided.

***Breath or Saliva Alcohol Test***

Breath or Saliva Alcohol Test will be summarized by the sample type and result using frequency count and percentage by treatment groups. Listing of Breath or Saliva Alcohol test will be provided.

**Vital signs:**

Vital signs (systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths/minute)), observed and change from baseline values will be summarized at each timepoint using the descriptive statistics (n, Mean, SD, Median, Minimum, Maximum) by treatment group. For triplicate assessments of Systolic and diastolic blood pressure (mmHg) and heart rate (bpm), average of triplicate assessments will be reported in summaries.

Listing of vital signs will also be reported.

**Physical and Oral examination:**

All physical and oral examination findings will be listed.

### 7.9 PK/PD Analysis

No PK/PD analyses will be conducted in this trial.

### 7.10 Pooled Analyses

No pooled analyses will be conducted in this trial.

### 7.11 Subgroup Analyses

No Subgroup analyses will be conducted in this trial.

### 7.12 Interim Analysis

No Interim analyses will be conducted in this trial.

### 7.13 Changes to Analyses Specified in Protocol

No changes have been made to analyses specified in protocol.

## 8 REFERENCE

- E9 Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1997.
- Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.
- Study Protocol 22093 version 4.0, MAR 13, 2023.
- eCRF Version and Date: Final 5.0 and APR 14, 2023.

# 9 APPENDIX

## 9.1 Participant Assessments

### 9.1.1 Categorical Pain Intensity Scale (Predose)

Finish the statement: **"My pain at this time is"** by checking the appropriate box.

- No Pain (0)
- Mild Pain (1)
- Moderate Pain (2)
- Severe Pain (3)

### 9.1.2 Numerical Rating Scale (pre-dose and post-dose)

Circle a number to indicate level of pain (from 0 to 10) below to indicate the severity of the pain you are experiencing at this time.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible pain |

### 9.1.3 Categorical Pain Relief Rating Scale (post-dose)

Finish the statement: **"My relief from my starting pain is"** by checking the appropriate box.

- No Relief (0)
- A Little Relief (1)
- Some Relief (2)
- A Lot of Relief (3)
- Complete Relief (4)

### 9.1.4 Global Assessment of Pain (post-dose)

Finish the statement: "***What is your overall rating of the study medication you received?***" by checking the appropriate box.

- Poor (0)
- Fair (1)
- Good (2)
- Very Good (3)
- Excellent (4)

## ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Veranex- Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

### Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

### Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

### Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

### All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

**How to contact Veranex- Part 11:**

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: PPD

**To advise Veranex- Part 11 of your new email address**

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at PPD and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

**To request paper copies from Veranex- Part 11**

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to PPD and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

**To withdraw your consent with Veranex- Part 11**

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to PPD and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

**Required hardware and software**

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

**Acknowledging your access and consent to receive and sign documents electronically**

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Veranex- Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Veranex- Part 11 during the course of your relationship with Veranex- Part 11.