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STATISTICAL ANALYSIS PLAN

TITLE PAGE

A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Hydrocodone/Acetaminophen Tablets in Postsurgical Dental Pain

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DECLARATION

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

Prepared by:

Name: PPD
Designation/ Role: PPD

_____
Sign & Date (MMM DD, YYYY)

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

Reviewed by:

Name: PPD
Designation/ Role: PPD

_____
Sign & Date (MMM DD, YYYY)

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

Authorized by:

Name: PPD
PPD

_____
Sign & Date (MMM DD, YYYY)

REVISION HISTORY

Version	Date	Author	Reasons

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
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine Milligram Equivalent
NRS	Numeric Rating Scale
OTC	Over-The-Counter
PAR	Pain Relief
PI	Pain Intensity
PID	Pain Intensity Difference
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
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

Abbreviation or special term	Explanation
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This is single center, randomized, double-Blind, parallel, placebo-controlled study, stratified by baseline pain, in participants experiencing moderate to severe postoperative dental pain to compare the analgesic efficacy and safety of Naproxen Sodium tablets and Hydrocodone/Acetaminophen tablets in postsurgical dental pain.

Both naproxen sodium and Hydrocodone/Acetaminophen are widely used analgesics. However, the relative efficacy of over-the-counter dosing with naproxen sodium has not been compared to hydrocodone/acetaminophen for relief of acute pain. This assessment is important and timely as options for reducing the use of opioid analgesics in postoperative pain control are highly desired. Understanding the relative efficacy and safety of alternative analgesics can provide clinicians with important information when they select appropriate analgesics for their patients.

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 20536.

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 1.0 dated NOV 19, 2019 and CRF version 4.0 dated APR 21, 2020.

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 to compare the analgesic efficacy of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain.

The secondary objectives of the study are:

1. To compare the amount of pain relief produced by a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain.

2. To compare the time to first use of rescue medication of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain

3. To compare the duration of pain intensity at least half gone for each timepoint of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain

Other pre-specified objectives of the study are**:**
To compare the following parameters of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo in participants experiencing moderate to severe post-impaction surgery dental pain:

1. Summed Pain Intensity Difference
2. Total pain relief
3. Pain Intensity Difference (PID)
4. Proportion/percent of participants with Pain Half Gone
5. Global assessment of the investigational product

To compare the incidence of GI and Nervous system side effects produced by a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to hydrocodone/acetaminophen 10/650 mg (2 x 5/325 mg tablets) and placebo.

2.2 Study Design

This is a single center, randomized, double-blind, parallel, placebo-controlled study, stratified by baseline pain, 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 visit. Eligible participants who have undergone surgical extraction of three or four third molars, 2 of which must be mandibular partial or full bony impacted third molars will be randomized into one of three treatment groups and kept in-house and evaluated for efficacy and safety at the study center through completion of all trial procedures. For an overview on the study design study procedures see the 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**	**2-5 days after discharge**
		Check-in to study site (if needed)	Surgical teeth extraction	Categorical pain ✸ NRS pain	Stopwatch method NRS pain Pain relief Pain half gone Global assessment	Phone call or visit

✸ = randomized to either naproxen sodium 440 mg, hydrocodone/acetaminophen 10/650 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.

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 severity for randomization will then be stratified by baseline pain intensity and randomized into one of three (3) treatment groups. Participants will rate their pain severity and pain relief over the next 12 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 and in certain cases 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.

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.

The Schedule of Assessments for the study is presented below in the Table 1.

Table 1: Schedule of Assessment

Protocol Activities	Screening Visit (within 28 days prior to oral surgery)	Dosing Period *Inpatient* Day 1	End of Trial Call (2-5 days after discharge)
Written Informed Consent	x		
Inclusion/Exclusion Reviewed	x	x	
Medical/Medication History	x	x	
Physical and Oral Examination	x		
Vital Signs[a]	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	
Categorical Pain Rating Scale[b]		x	
Pain Intensity Numerical Rating Scale (NRS)[c]		x	
Categorical Pain Relief Rating Scale [c]		x	
Starting pain is at least ½ gone[c]		x	
Global Assessment of Pain Relief[d]		x	
Concomitant Medications		x	x
Adverse Events Assessed	x	x	x
Discharge from Unit the evening of Day 1		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, and 12 hours 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 and 12 hours postdose. 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 12 hours post-dose

2.3 Determination of Sample Size

Assuming that the treatment difference of 12.3 and common standard deviation of 15.5 with respect to $SPID_{0-12}$, a total of approximately 200 subjects (80 subjects per active treatment arm and 40 in the placebo using a 2:2:1 ratio) are required to achieve at least 90% of power with the type I error of 0.05, a total of approximately 210 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 three (3) 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, labelled 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, 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 subject, treatment and visit/time point where as appropriate.

Data will be summarized by treatment group and visit/time. The total number of subjects 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 subjects (n), mean, standard deviation (SD), minimum, median, and maximum. In case of n<2, where n indicates the number of evaluable subjects at the particular time point, only n, mean, minimum and maximum will be displayed. The statistic "Missing" will also be evaluated by enumerating the number of missing entries/subjects, 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 subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects 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 lease 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). All pain at least half gone after intake of rescue medication will be imputed by "NO".

Missing data for efficacy parameter:

If subjects have missing pain data (i.e. pain intensity or pain relief scores) within the 12 hours period for the collection of pain rating data, but nonetheless complete the 12-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.

Interpolation Formula,

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

Where, 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 subjects do not complete the pain intensity assessments for the full 12 hours, then in the primary analysis, the $SPID_{0\text{-}12}$ and $TOTPAR_{0\text{-}12}$ will be calculated up to the last available timepoint, with no imputation for later timepoints.

In a sensitivity analysis, subjects 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 subjects 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 4.1.1.

If the subject's global evaluation of the study medication is missing, a value of 0 (poor) will be imputed.

For all post-dose timepoints missing values with pain at least pain half gone will be imputed by "NO".

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 & DERIVATIONS

Baseline: For all parameters, baseline will be defined as the last non-missing value before the first treatment 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.

4.1.1 Endpoint Derivations

Pain Intensity

Subjects will assess their current pain intensity using an 11-point (0: No Pain to 10: Worst possible pain) Numerical Rating Scale (NRS). Each subject 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 subject is to record pain intensity (NRS) at baseline (i.e. pre-dose). Thereafter, the subject is to record NRS pain intensity assessment at the following time points during the 12 hours period after baseline:

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

i	**Nominal T_i (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

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.

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

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.

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

$$SPID_{9-12} = \sum_{i=11}^{14} \left(T_i - T_{(i-1)}\right) * PID_i$$

$$SPID_{8-12} = \sum_{i=10}^{14} \left(T_i - T_{(i-1)}\right) * PID_i$$

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

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

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

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

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

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

The subject is to record pain relief (5-point categorical rating scale) at given time points during the 12-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.

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

$$TOTPAR_{9-12} = \sum_{i=11}^{14} \left(T_i - T_{(i-1)}\right) * PAR_i$$

$$TOTPAR_{8-12} = \sum_{i=10}^{14} \left(T_i - T_{(i-1)}\right) * PAR_i$$

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

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

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

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

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

Duration of Pain at least Half Gone
Duration of pain at least half gone will be calculated by the time between the timepoints when pain at least half gone was firstly reported and the subsequent time point when pain at least half gone was firstly reversed or the time of last assessment if pain at least half gone was retained for all subsequent time points.
If the pain at least half gone is secondly reported after the firstly reversed pain half gone and secondly reversed, then duration of pain at least half gone will be the sum of these two-time intervals. The duration will be set to 0 when no pain at least half gone was ever reported throughout the assessment period.

Time to first Perceptible Relief
Time to first perceptible relief is the time when the subject 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 subject 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 subjects 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 subjects 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.

Amount of Rescue Medication Used
To quantify opioids use, the amount of rescue medications (opioids) will be converted to a standard unit, which is Morphine Milligram Equivalent (MME) using below formula,

MME/Day = Strength per Unit * (Number of units / Day supply) * MME conversion factor

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

Cumulative percent of subjects with Pain at least half gone
Cumulative percentage of subjects with pain at least half gone will be calculated as the cumulative number of subjects with pain at least half gone at given timepoint divided by the number of subjects treated in respective treatment group.

Subjects with 'at least a 2-point PID'
Subjects with 'at least a 2-point PID' will be calculated as $PID_i = PI_0 - PI_i$; for all i > 0.
Where, PI_0 pain intensity at baseline, PI_i is the PI score at post-dose time point i

Subjects 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'.

Subject's Global Assessment of Investigational Product
At hour 12 or immediately prior to the first dose of rescue medication (if prior to hour 12), study participants will be asked to provide a Global Assessment of investigational product after completion of the other assessments. The subject will be instructed to score his or her global evaluation of the study treatment on a 5-point categorical scale where 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.

5 PRIMARY AND SECONDARY ENDPOINTS

5.1 Primary Endpoint

- Sum of Pain Intensity Difference over 12 hours (SPID 0-12)

5.2 Secondary Endpoints

- Total Pain Relief over 12 hours (TOTPAR 0-12)
- Total Pain Relief over 6 hours (TOTPAR 0-6)
- Sum of Pain Intensity Difference over 6 hours (SPID 0-6)
- Amount of Rescue Medication Used
- Time to first use of rescue medication over 12 hours
- Duration of Pain at Least Half Gone over 12 hours
- Duration of Pain at Least Half Gone over first 6 hours

5.3 Other Pre-Specified Endpoints

- The SPID 0-4, 0-8, 6-12, 8-12, and 9-12
- TOTPAR 0-4, 0-8, 6-12, 8-12, and 9-12
- Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose
- 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 subjects who had meaningful pain relief (the second stopwatch time)
- The cumulative proportion of subjects taking rescue medication over the 12-hour period.
- Peak PID and peak pain relief
- Percent of participants with Pain Half Gone at least once over 12 hours
- Percent of participants with Pain Half Gone at each time point over 12 hours
- Proportion of participants with pain at least one-half gone at each time point
- Cumulative percent of subjects with Pain at least half gone will be plotted over time
- Cumulative percent of subjects with ‘at least a 2-point PID’ will be plotted over time
- Global Assessment of the investigational product

- Percent of subjects reporting GI and Nervous system AEs prior to use of rescue medication

6 ANALYSIS POPULATION AND TREATMENT GROUPS

6.1 Analysis Population

Randomized Population

All subject who received a randomization number, regardless of receiving study medication.

Safety Population

All subjects who are randomized and take at least one dose of investigational product. Safety measures will be analysed for all subjects in safety population.

Intent-To-Treat (ITT) Population

All subjects in the Safety Population who provide at least one pain (pain intensity/ pain relief score) assessment after the first dose of the investigational product. ITT population will be used as secondary to conduct the sensitivity analysis for the selected parameters.

Per protocol (PP) Population

PP population will include all subjects in ITT who do not have any major protocol violations and complete the 12-hour assessments. PP population will be used as the primary analysis for the efficacy 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 subject 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 440 mg	Naproxen
Hydrocodone / Acetaminophen 10/650 mg	Hydrocodone
Placebo	Placebo

7 ANALYSIS METHODS AND REPORTING DESCRIPTION

7.1 Analysis Methods

7.1.1 Disposition

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

- The number of subjects Randomized
- The number of subjects in safety population
- The number of subjects in ITT population
- The number of subjects in Per-Protocol population
- The number of subjects who completed the study
- The number of subjects who discontinued early, as well as the reason for discontinuation

Subjects' disposition status will be listed by treatment group and will include subject 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 listed.

7.1.2 Demographic 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.

7.1.3 Medical or Medication or Surgical 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 23.0. and summarized by treatment group and overall, by frequency count and percentage of subjects in each system organ class (SOC), preferred term (PT) using Safety Population.

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

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

7.1.4 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 subject in the Safety Population, prior medications will include any medication taken prior to subject'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 ATC level X class per World Health Organization Drug Dictionary (WHODRUG; Version 2019SEP01) will be summarized by treatment group and overall, for the Safety Population. The frequency count and percentage of subjects using each medication will be displayed. Subjects who taken the same medication (in terms of PT) more than once will be counted only once for that medication.

Subjects taking multiple prior/ concomitant medication will be counted only once in summary table. If the subject is taking medication prior to study drug administration and continues the same drug after study drug administration, then such subjects 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.

7.1.5 Protocol Deviation

Protocol deviations will be identified and classified as minor or major before un-blinding. Protocol deviations occurring during the clinical trial will be summarized descriptively by treatment group and overall. A listing and summary of protocol deviations will be presented using the Safety Population.

7.1.6 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.

7.1.7 Efficacy Analysis

7.1.7.1 Primary Endpoint

The primary efficacy endpoint is the sum of pain intensity Difference over 12 hours ($SPID_{0-12}$). The treatment comparisons will be made in the following sequential order for $SPID_{0-12}$ (each at 0.05 level of significance) in order to protect overall type 1 error at 0.05:

- Naproxen sodium 440 mg versus Placebo
- Naproxen sodium 440 mg versus hydrocodone/acetaminophen 10/650 mg
- Hydrocodone/acetaminophen 10/650 mg versus Placebo

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

The primary efficacy endpoint is the summed pain intensity difference over 0 to 12 hours after Time 0 ($SPID_{0-12}$). The formula for $SPID_{0-12}$ calculation is presented in Section 4.1.1. The primary efficacy endpoint will be analysed using an analysis of covariance (ANCOVA) model, which will include $SPID_{0-12}$ as dependent variable, treatment as main effect and baseline pain intensity as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will also be presented by treatment group. PP population (without imputation) will be used as the primary analysis for this primary endpoint. ITT population (without imputation and single imputation) will be used as secondary 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 and if subjects take rescue medication.

7.1.7.2 Secondary Endpoints

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

SPID over 0 to 6 hours (SPID 0-6)

SPID 0-6 will be calculated using the formula specified in Section 4.1.1. 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 PP population (without imputation) as primary analysis. ITT 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 and if subjects take rescue medication.

Total pain relief (TOTPAR) over 0 to 12 hours (TOTPAR 0-12), over 0 to 6 hours (TOTPAR 0-6)

TOTPAR over 0-12, 0-6 hours will be calculated using the formula specified in Section 4.1.1. The differences in TOTPAR between the treatment groups and placebo will compared using an analysis of covariance (ANCOVA) model, which will include TOTPAR as the dependent variable, treatment as main effect and baseline pain intensity as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will also be presented by treatment group. PP population (without imputation) will be used as the primary analysis for $TOTPAR_{0-12}$, $TOTPAR_{0-6}$ endpoints. ITT population (without imputation and single imputation) will be used as secondary to conduct the sensitivity analysis of $TOTPAR_{0-12,}$ and $TOTPAR_{0-6}$.

In the secondary analysis, endpoints will be imputed as described in Section 3.1.1 if any pain assessments are missing and if subjects take rescue medication.

Amount of Rescue Medication Used

The amount of analgesic rescue medication (Morphine Milligram Equivalent) used through 12 hours will be summarized. Medications will be converted to tramadol equivalents using the conversion table. (MME) using the conversion table which is provided in Appendix 1. If any rescue medication is not received in (mg/ mcg) units which is given in Appendix 1, then site/sponsor will provide the data in relevant units. Results (amount of rescue medication use) will be compared using an ANOVA model which include amount of rescue medication used as dependent variable and treatment as independent variable if the assumptions of normality and heterogeneity of variance meets. If these assumptions are violated, a non-parametric Wilcoxon Rank Sum test will be used. Descriptive statistics (including n, mean, SD, median, minimum, and maximum) will also be presented by treatment group. This endpoint will be analysed using PP population as primary analysis and ITT population as secondary to conduct the sensitivity analysis.

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 4.1.1. Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity. The summary statistics (25^{th} percentile, Median, 75^{th} 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 PP population as primary analysis and ITT population as secondary to conduct the sensitivity analysis.

Duration of Pain at Least Half Gone over 12 hours and 6 hours

Duration of pain at least half gone calculation is presented in Section 4.1.1. The duration of pain at least half gone will be analysed using an analysis of covariance (ANCOVA) model, which will include duration of pain at least half gone as dependent variable, treatment as main effect and baseline pain intensity as the covariate. The least square (LS) mean, standard error (SE) and 95% confidence interval (CI) for each treatment group will be estimated. In addition, the mean (LS mean) difference between each treatment and placebo, SE, p-value and the associated 95% CI will also be computed. This endpoint will be analysed using PP population as primary analysis and ITT population as secondary to conduct the sensitivity analysis.

7.1.7.3 Other pre-specified Endpoints

Analysis of the other pre-specified endpoints will be summarized according to the variable type. The details are presented in the following sections. The analysis of all below endpoints will be performed on PP population with no imputation.

SPID 0-4, 0-8, 6-12, 8-12 and 9-12

SPID 0-4, SPID 0-8, SPID 6-12, SPID 8-12, SPID 9-12 will be calculated using formulas specified in the Section 4.1.1. 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.

TOTPAR 0-4, 0-8, 6-12, 8-12 and 9-12

TOTPAR 0-4, TOTPAR 0-8, TOTPAR 6-12, TOTPAR 8-12, TOTPAR 9-12 will be calculated using formulas specified in the Section 4.1.1. The same method that is used in secondary endpoint, Total pain relief (TOTPAR) over 0 to 12 hours will be used to assess the difference between the treatment groups in each metric.

Pain Intensity Difference (PID) and Pain Relief scores at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose

The PID at each scheduled time point will be calculated using the formula specified in Section 4.1.1. Descriptive statistics (including mean, SD, median, minimum and maximum) will also be presented by treatment groups. Pain Relief score categories will be presented in the form of counts and percentage by treatment groups and overall. Also, the pain relief score at each scheduled time point will be summarised using descriptive statistics (including mean, SD, median, minimum and maximum) by treatment groups.

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

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

Time to first perceptible pain relief, time to meaningful relief and time to first perceptible relief confirmed by meaningful relief will be estimated and plotted using Kaplan-Meier methods. The definitions and censoring rules are defined in Section 4.1.1. Median time will be compared between the treatment groups and placebo using a log-rank test stratified by baseline pain intensity. The summary statistics (25^{th} percentile, Median, 75^{th} percentile and it 95% CI) and overall K-M estimates with 95% CI will be presented by treatment groups.

Cumulative proportion of subjects taking rescue medication over the 12 hours period

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

The cumulative proportion of subjects taking rescue medication over 12 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) by treatment groups and curves over time will be plotted by treatment group.

Frequency tables will be tabulated for the number of times that the subject took rescue medication over the 12 hours period.

Subject will be counted only once in cumulative addition.

Peak PID and peak pain relief

The peak PID and peak pain relief score for each subject will be identified using the description in Section 4.1.1. The data for this endpoint will be summarised by treatment group using counts and percentage.

Percent of participants with Pain Half Gone at least once over 12 hours

Participants with pain at least half gone will be identified using the method mentioned in Section 4.1.1. The percent of participants with pain half gone at least once by 12 hours will be summarised by treatment group using count and percentage and will be analysed using chi square test to compare the proportion among the treatment groups.

Percent of participants with Pain Half Gone at each time point over 12 hours

Participants with pain half gone at each time point will be identified using the method mentioned in Section 4.1.1. The percent of participants with pain half gone at each time point over 12 hours will be summarised by treatment group using count and percentage and will be analysed using chi square test to compare the proportion among the treatment groups at each time point. The proportion of subjects with pain at least half gone at each timepoint will be plotted over time by treatment group.

Cumulative percent of subjects with Pain at least half gone

Subjects with pain at least half gone will be identified using the method mentioned in Section 4.1.1. Cumulative percent of subjects with pain at least half gone will be calculated as the cumulative number of subjects with pain at least half gone at given timepoint divided by the number of subjects treated in respective treatment group. The cumulative percent of subjects with pain at least half gone will be presented using counts and percent with timepoints (0.5, ≤1, ≤1.5, ≤2, ≤3, ≤4, ≤5, ≤6, ≤7, ≤8, ≤9, ≤10, ≤11, ≤12) by treatment groups and curves over time will be plotted by treatment group. Subject will be counted only once in cumulative addition.

Cumulative percent of subjects with 'at least a 2-point PID'

Subjects with 2-point PID will be identified using the method mentioned in Section 4.1.1. The 2-point PID is the subject PID which is greater than or equal to 2 at post baseline records. Cumulative percent of subjects with at least a 2-point PID will be calculated as the cumulative number of subjects with 2-point PID at given timepoint divided by the number of subjects treated in respective treatment group. The cumulative percent of subjects with 'at least a 2-point PID' will be presented using counts and percent with timepoints (0.5,≤1, ≤1.5, ≤2, ≤3, ≤4, ≤5, ≤6, ≤7, ≤8, ≤9, ≤10, ≤11, ≤12) by treatment groups and curves over time will be plotted by treatment group. Subject will be counted only once in cumulative addition.

Global Assessment of the investigational product

Global assessment of the investigational product ratings poor (0), fair (1), good (2), very good (3), excellent (4), will be tabulated using counts and percentage by treatment group and will be analysed using Cochran-Mantel-Haenszel (CMH) test with modified ridit score controlling baseline pain intensity as strata. Since this is ordinal scale rating, mean score difference will be used for treatment comparison.

7.1.8 Summary of Efficacy Endpoint Analysis Strategy

Endpoint	Statistical Method/Test	Analysis Population	Missing Data Imputation Approach	Parameters/ Variables In the Analysis	Analysis Time Point
Primary Efficacy Endpoint					
Sum of Pain Intensity Difference over 12 hours (SPID 0-12)	ANCOVA, Descriptive statistics	PP	No imputation	SPID derived from pain intensity score	12 hours
Sum of Pain Intensity Difference over 12 hours (SPID 0-12)	ANCOVA, Descriptive statistics	ITT	No imputation and Single imputation	SPID derived from pain intensity score	12 hours
Secondary Efficacy Endpoint					
Total Pain Relief over 12 hours (TOTPAR 0-12)	ANCOVA, Descriptive statistics	PP	No imputation	TOTPAR derived from pain relief score	12 hours
Total Pain Relief over 12 hours (TOTPAR 0-12)	ANCOVA, Descriptive statistics	ITT	No imputation and Single imputation	TOTPAR derived from pain relief score	12 hours
Total Pain Relief over 6 hours (TOTPAR 0-6)	ANCOVA, Descriptive statistics	PP	No imputation	TOTPAR derived from pain relief score	6 hours

Total Pain Relief over 6 hours (TOTPAR 0-6)	ANCOVA, Descriptive statistics	ITT	No imputation and Single imputation	TOTPAR derived from pain relief score	6 hours
Sum of Pain Intensity Difference over 6 hours (SPID 0-6)	ANCOVA, Descriptive statistics	PP	No imputation	SPID derived from pain intensity score	6 hours
Sum of Pain Intensity Difference over 6 hours (SPID 0-6)	ANCOVA, Descriptive statistics	ITT	No imputation and Single imputation	SPID derived from pain intensity score	6 hours
Amount of Rescue Medication Used	ANOVA, Descriptive statistics	PP, ITT	No imputation	Number of units of rescue medication used	12 hours
Time to first use of rescue medication over 12 hours	Kaplan Meier Estimation Summary and graph	PP, ITT	No imputation	Rescue medication taken (Yes/No)	12 hours
Duration of Pain at Least Half Gone over 12 hours	ANCOVA	PP, ITT	No imputation	Pain at least half gone (Yes/No)	12 hours
Duration of Pain at Least Half Gone over first 6 hours	ANCOVA	PP, ITT	No imputation	Pain at least half gone (Yes/No)	6 hours
Other Specified Endpoint					

The SPID 0-4, 0-8,6-12, 8-12 and 9-12	ANCOVA, Descriptive statistics	PP	No imputation	SPID derived from pain intensity score	4,8, 6-12, 8-12 and 9-12 hours
TOTPAR 0-4, 0-8, 6-12,8-12 and 9-12	ANCOVA, Descriptive statistics	PP	No imputation	TOTPAR derived from pain relief score	4,8, 6-12, 8-12 and 9-12 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, and 12 hours post-dose	Descriptive statistics, Graph	PP	No imputation	PID derived from pain intensity score, Pain relief score	0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours
Time to first perceptible relief measured by a stopwatch	Kaplan Meier Estimation Summary and graph	PP	No imputation	Stopwatch 1	12 hours
Time to meaningful relief measured by a stopwatch	Kaplan Meier Estimation Summary and graph	PP	No imputation	Stopwatch 2	At any timepoint after first perceptible pain relief measured in 12 hours
Time to first perceptible relief confirmed by meaningful relief	Kaplan Meier Estimation Summary and graph	PP	No imputation	Stopwatch 1/ Stopwatch 2	At any time during 12 hours
The cumulative proportion of subjects	Frequency table and graph	PP	No imputation	Rescue medication taken (Yes/No)	12 hours

taking rescue medication over the 12-hour period					
Peak PID	Frequency table	PP	No imputation	Pain intensity difference	12 hours
Peak pain relief	Frequency table	PP	No imputation	Pain relief	12 hours
Percent of participants with Pain Half Gone at least once over 12 hours	Frequency table, chi square test	PP	No imputation	Pain Half Gone (Yes/No)	12 hours
Percent of participants with Pain Half Gone at each time point over 12 hours	Frequency table, chi square test and graph	PP	No imputation	Pain half gone	12 hours
Cumulative percent of subjects with Pain at least half gone will be plotted over time	Frequency table and graph	PP	No imputation	Pain at least half gone	12 hours
Cumulative percent of subjects with 'at least a 2-point PID' will be plotted over time	Frequency table and graph	PP	No imputation	Pain intensity	12 hours

Global Assessment of the investigational product	Frequency table, CMH test	PP	No imputation	Overall rating	12 hours
Percent of subjects reporting GI and Nervous system AEs prior to use of rescue medication	Frequency with percentage	Safety population	No imputation	TEAE	Start of study drug administration to EOT

7.1.9 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 subject when applicable. The safety analysis will be performed for the Safety Population.

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

Adverse Events

Adverse Events will be coded using (MedDRA version 23.0) 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 subject experiencing the same AEs and TEAEs multiple times will be counted only once for that PT. Similarly, if a subject experience multiple AEs and TEAEs (preferred terms) within the same SOC then that subject 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 Subjects who had an AE

Number of Subjects who had a Serious AEs

Number of Subjects who had a TEAEs

Number of Subjects who had a Serious TEAEs

Number of Subjects who had a TEAEs with reasonable causal relationship to the study treatment

Number of subjects with at least one treatment related serious TEAE

Number of Subjects who had a TEAEs leading to study discontinuation

Number of Subjects who had a TEAEs leading to death

Treatment-emergent Adverse Events (TEAEs)

A summary of the frequency (number and percentage of subjects) of TEAEs by treatment group and overall will be presented by SOC, PT term. Similarly, summary results will be generated for 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 subjects) 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 leading to study discontinuation will be provided.

Serious Adverse Events

SAEs will be summarized separately using frequency and percentage by SOC and PT for the Safety Population. 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 using the Safety Population.

Deaths

All TEAEs leading to death will be listed using the Safety Population.

Clinical Laboratory Data

Urine Drug Screen

Urine Drug Screen Test will be summarized by result using count and percentage by treatment groups. Listing of Urine Drug Screen will be provided.

Urine Pregnancy Test

Urine Pregnancy Test will be summarized by result using count and percentage by treatment groups. Listing of Urine Pregnancy Test will be provided.

Breath or Saliva Alcohol Test

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

Electrocardiogram (ECG)

No ECG will be performed for this study.

Vital signs:

Vital signs (systolic (mmHg) and diastolic (mmHg) blood pressure, 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 using Safety population. Vital Sign data will be listed by individual time course for each parameter.

Physical and Oral examination:
All physical and oral examination findings will be listed.

7.1.10 PK/PD Analysis

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

7.1.11 Pooled Analyses

No pooled analyses will be conducted in this trial.

7.1.12 Subgroup Analyses

There is no planned subgroup analysis; however, subgroup and exploratory analysis may be conducted as Post-hoc analysis.

7.1.13 Interim Analysis

No interim analysis will be performed.

7.1.14 Changes to Analyses Specified in Protocol

1. As per the Agency's (FDA) recommendation, the amount of rescue medication and its use over time are added to the SAP and will be reported in the CSR

2. As per the sponsor requirement below exploratory endpoints are added to the SAP
   a. SPID 6-12 and SPID 9-12
   b. TOTPAR 6-12 and TOTPAR 9-12

8 REFERENCE

1. E9 Statistical Principles for Clinical Trials, ICH Guideline, Federal Register, 1997
2. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996
3. Study Protocol 20536 version 1.0, 19 NOV 2019
4. Ratitich, B. and O'Kelly, M. (2011), "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures" PharmaSUG. Available at https://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf

9 APPENDIX

Appendix 1: Opioid Oral Morphine Milligram Equivalent (MME) Conversion factors[1,2]

Type of Opioid (strength units)	MME Conversion Factor
Buprenorphine film/tablet[3] (mg)	30
Buprenorphine patch[4] (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche[5] (mcg)	0.13
Fentanyl film or oral spray[6] (mcg)	0.18
Fentanyl nasal spray[7] (mcg)	0.16
Fentanyl patch[8] (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone[9] (mg)	3
>0, <= 20	4
>20, <=40	8
>40, <=60	10
>60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol [10] (mg)	0.4
Tramadol (mg)	0.1

1 The MME conversion factor is intended only for analytic purposes where prescription data is used to calculate daily MME. It is to be used in the formula: Strength per Unit X (Number of Units/ Days Supply) X MME conversion factor = MME/Day. This value does not constitute clinical guidance or recommendations for converting patients from one form of opioid analgesic to another. Please consult the manufacturer's full prescribing information for such guidance. Use of this file for the purposes of any clinical decision-making warrants caution.

2National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2016

version. Atlanta, GA: Centers for Disease Control and Prevention; 2016. Available at https://www.cdc.gov/drugoverdose/media/. For more information, send an email to Mbohm@cdc.gov.

3 Buprenorphine formulations with a FDA approved indication for Medication Assisted Treatment (MAT) are excluded from Medicare's Overutilization Monitoring System's opioid overutilization reporting.

4The MME conversion factor for buprenorphine patches is based on the assumption that one milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 5 ug/hr buprenorphine patch X 24 hrs = 120 ug/day buprenorphine = 0.12 mg/day = 9 mg/day oral MME. In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8.

However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 X 7 = 12.6). In this example, MME/day for four 5 μg/hr buprenorphine patches dispensed for use over 28 days would work out as follows: Example: 5 ug/hr buprenorphine patch X (4 patches/28 days) X 12.6 = 9 MME/day. Please note that because this allowance has been made based on the typical dosage of one buprenorphine patch per 7 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for buprenorphine patches= # of patches x 7.

5 The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given tablet or lozenge/troche.

6 The MME conversion factor for fentanyl film and oral spray is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.

7 The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.

8 The MME conversion factor for fentanyl patches is based on the assumption that one milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24 hour day. Example: 25 ug/hr fentanyl patch X 24 hrs = 600 ug/day fentanyl = 60 mg/day oral morphine milligram equivalent.

In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4.

However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 X 3 = 7.2). In this example, MME/day for ten 25 μg/hr fentanyl patches dispensed for use over 30 days would work out as follows:

Example: 25 ug/hr fentanyl patch X (10 patches/30 days) X 7.2 = 60 MME/day. Please note that because this allowance has been made based on the typical dosage of one fentanyl patch per 3 days, you should first change

all Days Supply in your prescription data to follow this standard, i.e., Days Supply for fentanyl patches= # of patches X 3.

9 The CDC MME conversion factor to calculate morphine milligram equivalents is 3. CMS uses this conversion factor when analyzing Medicare population opioid use. CMS uses the graduated methadone MME conversion factors to calculate MME within the Overutilization Monitoring System (OMS) for identifying and reporting potential opioid overutilizers. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

10 Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. Oral MMEs are based on degree of mu-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists

We can get the above information at the below given link:

https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf

Appendix 2: Tables, Figures and Listings

Note: Since Mock TLFs is the running document; Hence some of the Tables Listings and figures presented in the below TOC may undergo changes may not reflect the same.

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