STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Single Doses of DFN-15 in Post-Surgical Dental Pain

Protocol Number: DFN-15-CD-010

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LIST OF ABBREVIATIONS (COMMONLY USED)

Abbreviation	Definition
Adam	Analysis Data Model
AE	Adverse event
ANOVA	Analysis of variance
BMI	Body mass index
BOCF	Baseline observation carried forward
bpm	Beats per minute
CI	Confidence interval
cm	Centimeters
CRF	Case report form
CSR	Clinical study report
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EOS	End of study
HR	Heart rate
ICH	International Conference on Harmonisation
I/E	Inclusion and Exclusion (criteria for study participation)
ITT	Intent-to-treat
kg	Kilograms
LOCF	Last observation carried forward
M	Meters
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	Modified intent-to-treat
mmHg	Millimeters of mercury
NPO	Nil per Oral
NPRS	Numerical Pain Rating Scale
PI	Pain Intensity
PR	Pain Relief
PT	MedDRA Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOC	MedDRA System Organ Class
SPI	Summed Pain Intensity
SPID	Summed Pain Intensity Difference
TEAE	Treatment-emergent adverse event
TOTPAR	Total Pain Relief
WHODrug	World Health Organization Drug Dictionary
WLOCF	Windowed last observation carried forward

1.0 Purpose of the Analyses

This Statistical Analysis Plan (SAP) is being developed after review of the Dr. Reddy's Laboratories Limited, protocol number DFN-15-CD-010 Final Version 2.0 (02MAY2018), but before any analyses of the data. The SAP contains detailed information to guide the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled 'Guidance for Industry: Statistical Principles for Clinical Trials' and the most recent ICH E3 Guideline, entitled 'Guidance for Industry: Structure and Content of Clinical Study Reports' and the most recent FDA draft 'Guidance for Industry - Analgesic Indications: Developing Drug and Biological Products', dated February 2014.

This SAP describes the data sets that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified as *post hoc* in the CSR.

2.0 Protocol Summary

2.1 Study Objectives

2.1.1 Safety

To evaluate the safety of DFN-15 relative to placebo control in subjects with moderate to severe acute pain following elective bilateral lower third molar extraction, as assessed by:

- Treatment emergent adverse event (TEAE) reports,
- Laboratory test results,
- Vital signs,
- Physical examinations,
- ECG findings,
- Evaluation of wound healing.

2.1.2 Efficacy

Primary Objective

To evaluate the efficacy of DFN-15 doses relative to placebo control in subjects with predose moderate to severe acute pain following elective bilateral lower third molar extraction using the summed pain intensity difference (SPID) scores over the first 6 hours (SPID6) postdose.

Secondary Objective

To evaluate the efficacy of DFN-15 relative to placebo control postdose in subjects with predose moderate to severe acute pain following elective bilateral lower third molar extraction using:

- Total Pain Relief (TOTPAR) over 2, 4, 6 and 8 hours.
- The SPID scores over various intervals, including SPID2, SPID4 and SPID8.

- Times to perceptible and meaningful pain relief.
- Proportion of subjects reporting treatment satisfaction outcome scores of 2 (good), 3 (very good), or 4 (excellent) on a 5-point categorical scale.
- Time to administration of first dose of rescue medication.
- Percent of subjects receiving rescue medication.
- Pain intensity difference at each NPRS timepoint (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours).
- Pain relief at each NPRS timepoint (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours).
- NPRS responder analyses defined as the proportion of subjects who achieve ≥ 30% and ≥ 50% improvement in NPRS (responders).
- Peak pain relief over 8 hours and the time until peak pain relief.

2.1.3 Pharmacokinetics

Pharmacokinetic parameters will be calculated by a separate vendor for all subjects for the single oral dose taken based on the concentrations of DFN-15 (celecoxib) in plasma at predose and between 15 minutes to 8 hours postdose. Details of the PK modeling, including any criteria for inclusion/exclusion from the PK population will be described in a separate PK Analysis Plan. The calculated parameters that will be summarized in CSR appendices if available will include:

1) peak (maximum) observed plasma drug concentration (C_{max})
2) time to C_{max} (T_{max})
3) AUC from 0 to x hours after dose will also be calculated for $AUC_{0-0.25}$, $AUC_{0-0.5}$, $AUC_{0-0.75}$, AUC_{0-1}, AUC_{0-2}, AUC_{0-3}, AUC_{0-4}, AUC_{0-6} and AUC_{0-8}.

2.2 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled parallel design study, to be conducted at 1-3 centers in the United States. An adequate number of subjects will be screened to randomize approximately 120 male and female subjects, 18 to 60 years old (inclusive), who are scheduled to undergo elective bilateral lower third molar extraction. Subjects who meet all of the inclusion and none of the exclusion criteria in the protocol will be randomized in a 1:1:1:1 ratio in a double-blind fashion to receive a single oral dose of either DFN-15 62.5 mg, DFN-15 125 mg, DFN-15 250 mg or matching placebo.

The study periods include a screening period (within 28 days of the scheduled extraction of the impacted third molars), a pre-surgery period (up to 2 hours prior to procedure), surgery, baseline period (up to 6 hours post-surgery), treatment period (up to 8 hours after dosing) and a post –surgery/ treatment period between 4 and 10 days after surgery. The screening period will involve the collection of demographic information, height, weight and body mass index (BMI), urine pregnancy test (in case of women of child-bearing potential), medical and medicinal history, physical examination, dental examination, vital signs measurement (blood pressure, pulse rate, respiratory rate), clinical laboratory investigation (hematology, serology, coagulation parameters, serum chemistry and urinalysis), 12-lead ECG and a panoramic x-ray to document the impacted mandibular third molar teeth.

At screening and upon admission/Check-in (Day 1) to the clinic, prior to dental surgery, subjects will be screened for alcohol consumption and illicit drug use by alcohol breathalyzer test and urine drug screen, respectively. Subjects continuing to meet I/E criteria will proceed to undergo their planned surgery for extraction of the impacted mandibular molars on both sides. As a pre-requisite for randomization, subjects will be required to report within 6 h post-surgery (Baseline period) : a) "moderate" to "severe" baseline pain as characterized on a 4-point categorical pain intensity (PI) scale (0= none, 1= mild, 2=moderate, 3= severe), and b) a score of ≥5, on the 11-point Numerical Pain Rating Scale (NPRS) where 0 represents 'no pain' and 10 represents 'worst pain imaginable', on the provided paper diary. Eligible subjects will be randomized and will receive a single dose of the assigned study treatment (a total volume of 10 mL). The start time of dosing will be recorded as T0. Subjects will be randomized and administered the study medication within 15 minutes of meeting the post-operative inclusion criteria (baseline score).

Subjects with inadequately controlled pain symptoms may request rescue analgesic medication. The rescue medication for this study will be 1-2 oxycodone 5 mg/acetaminophen 325 mg q 4 h PRN. Subjects will be encouraged to delay using the rescue medication if their pain is tolerable until 120 minutes post-dose of study medication. A subject who is administered rescue pain medication will continue completing pain assessments until 8 hours after treatment initiation. The use of ice packs will not be allowed in the 8-hour observation period. All randomized subjects will be provided with a paper diary to record pain assessments. A subject training program will be implemented to ensure that all subjects understand the relevant scales and assessments prior to study participation. At study medication administration, two stopwatches will be started, to measure times to 'perceptible' and 'meaningful' pain-relief. Subjects will be instructed to stop the first stopwatch when they first perceive pain relief to occur (time to perceptible relief). Subjects will be instructed to stop the second stopwatch when they first experience meaningful pain relief (time to meaningful relief). Stopwatch times of perceptible relief and meaningful relief will be recorded using exact stopwatch time displayed.

The following efficacy assessments will be completed by the subjects at 15, 30, and 45 min and at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after study medication administration, as well as within 5 minutes prior to first use of rescue medication and at early termination from the study, if it occurs. Subjects will be asked to record responses for the following assessments, in order:

- Pain intensity (PI) using the 11-point Numerical Pain Rating Scale (NPRS).
- Pain relief (PR) using a 5-point categorical scale (where 0= no pain relief, 1= little pain relief, 2= some pain relief, 3= a lot of pain relief, 4= complete pain relief).

In addition, at 8 hours post-dose or within 5 minutes prior to first use of rescue medication (whichever is earlier), subjects will be asked to record within the provided patient diary:

- 'Patient Rating of Treatment Satisfactoriness' using a 5-point verbal rating scale (0=poor,1=fair, 2 =good, 3=very good, 4=excellent).

Randomized subjects will remain NPO (nil per oral or nothing by mouth), including water, from Check-in (i.e., at least 2 hours before the administration of the dose of study medication to randomized subjects) until 2 hours post-dose, on Day 1 (study day). After 2 hours post-dose, subjects may be permitted to consume water, or gelatin snacks. Subjects are prohibited from ingesting solid foods or carbonated beverages for at least 6 hours post-dose.

Safety assessments will include 12-lead ECGs, vital sign parameters, physical exam and clinical labs. 12-lead ECGs will be performed before surgery, at baseline (before administration of the study treatment) and repeated at 1, 2, 4 and 8 hours post-dose, with a window period of ± 45 minutes for each timepoint. Vital sign parameters (sitting pulse rate, sitting or supine blood pressure and respiratory rate) will be measured and recorded before surgery, at baseline, 1, 2,

4, and 8 hours (before discharge), with a window period of ± 30 minutes for each timepoint. Vital signs may be performed concurrently with ECG if supine position is performed. Safety vital signs and ECG may be performed prior to initiation of efficacy assessments should they coincide, with priority designated toward efficacy assessment timepoints. At discharge (8 hours post-surgery) from the clinical facility, all AEs reported for the subjects will be reviewed. A physical examination, including evaluation of the incision site for hematomas, and clinical laboratory evaluation (coagulation parameters and specific hematology, serum biochemistry and urinalysis parameters) will be conducted.

All subjects will have blood drawn at specified timepoints for pharmacokinetic evaluation. Pharmacokinetic blood samples will be drawn immediately prior to dosing and at 15 min, 30 min, 45 min, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 and 8.0 hours post-dose, to estimate the concentrations of celecoxib, using a validated LC-MS/MS method. Whenever the times of PK blood sample collection coincide with the efficacy or safety assessments, the PK sample may be drawn within ± 5 minutes of the scheduled time in first hour and within ± 10 minutes of the scheduled time after the first hour, at each timepoint, immediately following the efficacy assessments. The exact clock time of sample collection will be recorded and used in the PK analysis.

Subjects will return to the research center 7 days (± 3 days) post-surgery for evaluation of their safety and well-being. Any AEs experienced post-surgery will be reviewed. A physical examination of the subject will be performed, 12-lead ECG, and vital signs parameters will be repeated. Hematology, coagulation parameters, serum biochemistry and urinalysis parameters will be repeated only if there is a clinically significant abnormality or ongoing AE(s). Any changes to the prior and concomitant medication made after discharge will be reviewed and recorded.

A subject may request to be withdrawn from study participation at any time, without disclosing the reason if chosen not to. Subject may be discontinued from the study by the Investigator or the Sponsor at any time if either determines that it is not in the subject's best interest to continue participation or due to non-compliance with the protocol. Investigator is encouraged to contact the study Medical Monitor to discuss details surrounding non-compliance. Subjects who withdraw consent to continue treatment or who are discontinued from the study before completing the protocol-specified duration of treatment should be encouraged to complete the early termination assessments and procedures outlined for 8 hours after treatment initiation. Subjects will be encouraged to agree to return to the study site 7 days (±3 days) post-surgery for evaluation of their safety and well-being. The date the subject is withdrawn and the primary reason for discontinuation will be recorded in the subject's case report form (CRF).

The protocol-defined visits are presented in the following (example) table:

Table 1 Protocol-Specified Visits and Visit Windows

Study Phase	*Visit Time*
Screening	From days -28 to -1
Day 1 Prior to Dose	Day 1 up to 6 hours post-surgery
Day 1 Post-Dose	Day 1. Assessments at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after administration of study medication
Follow-up	Day 7

2.3 Study Population

The study will consist of approximately120 male and female subjects, 18 to 60 years old (inclusive), who are scheduled to undergo elective bilateral lower third molar extraction. The full list of inclusion and exclusion criteria are mentioned in sections 4.1 and 4.2 of the protocol respectively.

2.4 Study Material and Treatment Regimens

DFN-15 is an oral solution containing 25 mg/mL of celecoxib. Each mL of DFN-15 will contain 25 mg celecoxib. DFN-15 will also contain the inactive ingredients, lauroyl polyoxylglycerides, glyceryl caprylate, caprylic/capric triglyceride, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, propyl gallate, menthol, magnasweet, sucralose, acesulfame potassium, peppermint flavor, banana flavor, bubble gum flavor, glycerol, ethanol, and water.

DFN-15 and matching placebo are packaged in amber-colored glass bottles containing 4.8 mL solution per bottle (120 mg) and equipped with child-resistant and tamper-evident caps.

Treatment consists of a single dose of either DFN-15 62.5 mg, DFN-15 125 mg, DFN-15 250 mg or matching placebo of total volume of 10 mL of oral solution.

The 10 mL dose will be prepared by a designated unblinded pharmacist at site, as per the randomization schedule. Designated blinded study staff will dose subjects and administer study assessments. Blinded study staff will remain blinded to the dose administered to each subject throughout the study.

2.5 Randomization

A computer-generated randomization scheme will be prepared prior to study initiation.

Subjects will be randomly assigned to treatment with DFN-15 62.5 mg, DFN-15 125 mg, DFN-15 250 mg, or placebo in a 1:1:1:1 assignment ratio according to the randomization scheme. Randomization will occur after the subject has qualifying baseline pain, other post-operative inclusion criteria are met, and all Pre-Dose Baseline assessments have been performed on Day 1. All study doses administered will be according to the treatment assignment. No stratification will be performed as part of the randomization; however, male and female subjects will be enrolled in an approximate ratio of 1:1. Subjects who discontinue after randomization will not be replaced in this study.

2.6 Sample Size Determination

The sample size of 120 subjects for this study was selected without a formal statistical calculation. However, group sizes of 30-40 per group are typically sufficient to detect a treatment effect over placebo in the dental pain model.

3.0 General Analysis and Reporting Conventions

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies are provided in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All continuous study assessments will be summarized by treatment and timepoint (as applicable) using descriptive statistics (n, mean, median, SD, minimum, and maximum). All the categorical study assessments, including responder variables, will be summarized by treatment and timepoint (as applicable) using frequency counts and percentages. Changes from baseline

for continuous outcomes will be presented as their corresponding continuous measures for post-baseline visits. Shifts from baseline for the ECG outcomes will be presented in shift tables by timepoint and treatment group. All study data will be listed by subject, treatment group, and timepoint (as applicable).

No preliminary rounding will be performed; rounding will only occur after the analysis. To round, consider the digit to the right of the last significant digit: if <5, then round down; if ≥5, then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. Minimums and maximums will be presented with the same precision as the original data.

All analyses will be performed using the SAS System® version 9.3 or higher. The domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, figures and listings. The SDTM and ADaM data sets will be provided to the sponsor along with display deliveries. The specifications for the domain data sets and analysis data sets will be provided in a separate document.

For all efficacy analyses, subjects will be analyzed according to their randomized treatment group, regardless of the actual treatment received, unless otherwise indicated. For all safety analyses, subjects will be analyzed by treatment group according to the actual product received during treatment, i.e., “as treated.”

The following conventions will be used throughout the study analysis:

- Assessment visit times are defined by time after administration of study drug.
- Time T_0 is the time of first treatment with study drug.
- Baseline value is defined as the last valid measurement prior to first treatment administration (prior to T_0).
- Pain Intensity Difference (PID) and changes from baseline are defined as post-baseline value minus baseline value.
- The date of first treatment with study drug is Day 1.
- Percentage PID and percent change from baseline is computed as:

  (post-baseline value - baseline value) × 100 / (baseline value).
- Treatment difference is computed as DFN-15 mean minus control mean. (Note: for the SPID statistics, for which the treatment goal is to reduce the score over time, improvement will be represented as a negative number.)
- SPID statistics will be computed using the trapezoid rule for computing area under the curve.
- All statistical tests will be two-tailed and at the $\alpha = 0.05$ significance level
- Duration of an AE will be computed in days or hours as the stop date/time of the event minus the start date/time plus 1. If reported as ongoing at the time of database lock, the stop date is defined as the date of the last visit or the last date of any AE for the subject in the database, whichever is later. Missing dates will be imputed as described in Section 9.2 Table 2.
- The number of days/hours in the study is computed as:

Date/time of study completion /withdrawal - the date/time of first treatment administration (Day 1) + 1.

- If duplicate values are obtained at a given timepoint (e.g., repeated vital sign measurements), the last value will be used unless it is noted that the measurement was in error for that value. Values that compromise interpretation will not be used in summaries (e.g., values that were obtained post-dose will not be summarized as pre-dose values).

4.0 Analysis Populations

4.1 Modified ITT Population

The mITT population includes all subjects who are randomized, receive study medication and have recorded at least one post dosing pain intensity (PI) score. This population will be used to summarize and analyze efficacy outcomes and treatment grouping will be based on randomized treatment.

4.2 Safety Population

The safety population includes all subjects who receive a dose of study medication (DFN-15 or placebo). This population will be used to summarize safety and demographic data, and for these summaries, treatment grouping will be based on treatment actually received.

4.3 Per-Protocol Population

The per-protocol population includes all mITT subjects who complete all pain assessments for at least 8 hours post-dose and have no major protocol deviations that impact subject safety or the interpretation of the primary analysis. Major protocol deviations excluding subjects from the Per Protocol population will be defined prior to unblinding (Section 5.2). This population will be analyzed by randomized treatment, unless otherwise indicated in the Blinded Data Review Meeting (BDRM). In the BDRM, a decision may be made to analyze the PP population as per treatment actually received in study by subjects.

4.4 Pharmacokinetic Population (PK)

The pharmacokinetic (PK) population will be determined by the PK Vendor and documented in a separate PK Analysis Plan.

5.0 Patient Summaries

5.1 Disposition of Subjects

A subject is considered randomized once the subject is assigned a treatment randomization number. If a subject is randomized but does not receive treatment, they will be included in the All Randomized population summaries, but no others.

Investigators are instructed to encourage subjects to attend all visits. If subjects are unable or unwilling to return, the reason for the subject withdrawal will be recorded. Subjects who successfully complete the 8-hour post treatment assessment period will be counted as treatment period completers regardless if they complete the study, by returning for the 7 day end of study visit, or not.

All treated/randomized subjects and the populations for which they qualify will be listed. The

number of subjects who are screened, and who fail screening or withdraw consent prior to randomization will be listed and summarized in total. Subjects who are randomized, subjects who are treated, subjects who complete the treatment period of 8 hours on study medication, subjects who complete follow-up, as well as subjects who withdraw early from the study and the reason for withdrawal will be summarized by treatment group and overall in the subject disposition summary tables, both overall and by center (if applicable). Days/Hours in study will be calculated as date/time of subject's last visit minus date/time of study drug administration plus 1. Subjects that complete any portion of a day will be counted as on study during that day.

5.2 Major Protocol Deviations

Protocol deviation information will be captured in the CRF and in site logs by site and CRO personnel. All protocol deviations will be designated by the medical monitor(s) as major or minor prior to unblinding. A major deviation is one that may affect the outcome, analysis or interpretation of the study results. If present, major protocol deviations will be summarized and all protocol deviations will be presented in a by-subject listing.

6.0 Demographic and Other Baseline Characteristics

6.1 Demographics and Baseline Characteristics

Demographic variables include age, sex, race, and ethnicity. Baseline characteristics will include weight (kg) and BMI (kg/m^2) as well as the qualifying (baseline) NPRS and 4-point categorical pain intensity scores. Demographics and baseline characteristics will be presented in a by-subject listing and summarized overall and by treatment group for the Safety population and the mITT population, if they differ.

6.2 Medical History

Medical history, as collected at screening, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and summarized by system organ class (SOC) and preferred term (PT) in a frequency table based on the safety population. The SOC and PT will each be sorted in descending order by overall frequency. Medical histories will also be presented in a by-subject listing using the coded and verbatim history terms.

AEs that occur prior to treatment or that are related to a medical history event will be captured as medical history prior to database lock.

6.3 Prior and Concomitant Medication

Prior medications/therapies are those that stop prior to the start of the study medication administration. Any medication/therapy that stops at or after the date and time of start of treatment or those with missing stop dates are considered concomitant medication/therapy. Surgical medications/Anesthesia used during and immediately after surgery will be listed but will not be summarized.

Prior and concomitant medications are collected at screening. and updated throughout the study as needed. Prior and concomitant medications will be coded using the March 1, 2018 version of the WHODrug. Subjects who take concomitant medications will be presented in a by-subject listing of verbatim and coded terms and summarized by drug class and preferred name, overall and by treatment group, for the safety population.

A by subject listing of all prior and concomitant medications will be presented with Surgical medications/Anesthesia used during surgery identified. Additionally, a summary and by-subject listing of concomitant medications that were prescribed or modified at or after the time of

discharge on study day will also be presented.

6.4 Non-Medication Therapies and Surgery Details

Prior and concomitant non-medication therapies will be presented in a by-subject listing for each treatment group. All surgical information will appear in data listings.

7.0 Measurements of Treatment Exposure and Compliance

Because the single dose of study medication is administered at the study center by trained study personnel, compliance with study medication is not expected to be an issue. A listing of all study medication exposure (including information on any partial administrations) will be provided.

8.0 Efficacy Evaluation

8.1 Overview of Analysis Issues

8.1.1 Handling of Dropouts or Missing/Invalid Data

Subjects with missing or invalid PI NPRS data will be imputed using the following rules.

Subjects who require rescue medication will record their pain intensity (PI) NPRS, Pain Relief (PR) and Patient Rating of Treatment Satisfactoriness scores within 5 minutes prior to first use of rescue medication. These are referred to as 'pre-rescue' PI, PR, and Patient Rating of Treatment Satisfactoriness scores, respectively. Any scheduled PI or PR assessments scheduled within 4 hours after administration of rescue medication will be replaced by the pre-rescue score in the efficacy analysis. This method of replacement is referred to as the windowed Last Observation Carried Forward (wLOCF).

After any scheduled PI/PR scores within 4 hours after rescue are appropriately replaced by the pre-rescue PI/PR scores, any other scheduled PI/PR scores that are still missing intermittently and are not within 4 hours after rescue medication will be imputed using linear interpolation between adjacent observed values.

After all intermittent missing scores are imputed, any scheduled PI/PR scores missing because the subject dropped out of the study will be imputed as follows: If the subject drops out due to adverse event (AE), the PI score will be imputed using a baseline observation carried forward (BOCF) method; if the subject drops out for other reasons, the PI/PR score will be imputed using the last observation carried forward (LOCF) method. PI data with missing baseline PI score will be excluded from the analysis.

For responder endpoints, subjects that drop out will be considered as non-responders for all assessment time points after their date/time of drop out. Similarly, if a subject receives rescue medication, then the subject will be treated as a non-responder for all subsequent timepoints.

No imputation for other efficacy or safety will be performed.

8.2 Efficacy Endpoints

8.2.1 Pain Intensity Difference

Pain Intensity Difference (PID) will be calculated based on Pain Intensity (PI) scores. PI will be assessed pre-dose, immediately prior to any use of rescue, and at each post-dose timepoint (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after T0) during the study using

an 11-point NPRS where 0 equates to no pain and 10 equates to the worst pain imaginable pain.

PID will be calculated at each time point i as $PID_i = PI_i$ – PIBL (Pain intensity score at time i and Pain intensity score at Baseline). All imputation, as described in Section 8.1.1, will be performed prior to the PID calculations.

PID_i will be summarized descriptively with sample size, mean, standard deviation, median, minimum, and maximum for each treatment group. The unadjusted *p*-value from a 1-sample t-test will be presented for each post-baseline nominal timepoint. Additionally, unadjusted p-values will be shown at each post-baseline nominal timepoint comparing the mean change from baseline values for each treatment, and of all DFN-15 treatments combined, to placebo. This will be done using an ANCOVA model with treatment as the main effect and both baseline pain intensity and BMI as covariates. To supplement this analysis, group mean of pain intensity over time will be displayed graphically at the nominal timepoints. These scores will also be presented in listings.

8.2.2 Summed Pain Intensity Difference

The primary efficacy endpoint is the summed pain intensity difference over the first 6 hours ($SPID_6$) between each of the DFN-15 dose levels and placebo. $SPID_6$ is created by summing the time weighted pain intensity differences (PID) scores using the area under the PID curve methodology.

All SPID calculations will be done using the standard trapezoidal rule:

$SPIDx$ =

$$\sum_{i=0}^{x} \left(\frac{PID_i + PID_{i+1}}{2} \right) * \ (T_{i+1} - \ T_i)$$

Where: $PID_i = P_i$ – PIBL (Pain Intensity score at time i and Pain Intensity score at Baseline), (T_{i+1} – T_i) is the Time difference in minutes between time i and time i+1, and (T_{i+1} – T_i) is the Time difference in minutes between time i and time i+1.

Baseline PI will be defined as the last PI recorded prior to first dose. Time points will be selected for inclusion into specific SPID periods based on nominal time points (e.g., all scheduled assessments from Baseline to the Hour 6 assessment will be included in $SPID_6$).

Except for baseline, the actual date/times of assessments will be used in the SPID calculation whenever collected. For baseline, rather than the actual time recorded, baseline pain will be considered to be recorded at time 0(i.e., time of first dose).

All imputation, as described in Section 8.1.1, will be performed prior to the SPID calculations.

The individual SPID variables will also be presented in subject listings.

The secondary efficacy SPID outcomes ($SPID_2$, $SPID_4$, and $SPID_8$) are calculated similarly to SPID6 adjusting for the respective time periods.

All SPID endpoints will be analyzed using an ANCOVA with treatment as the main effect and both baseline pain intensity and BMI as covariates. Mean SPID values over time will be displayed graphically.

The results of the ANCOVA will be presented in summary tables with standard summary statistics as well as least square (LS) means, active dose level vs. placebo LS mean differences

(treated group – placebo), standard errors, confidence intervals (CI) and paired-comparison *p*-values with Dunnett's test.

8.2.3 Proportion of Responders

NPRS responders are defined as subjects who achieve ≥ 30% (called 30% Responders) or ≥ 50% (called 50% Responders) improvement in PI NPRS over the baseline value recorded at T0 at any time prior to first use rescue and up to 8 hours. All imputation as described in Section 8.1.1 will be performed prior to percent improvement and responder calculations. If any scheduled post-baseline NPRS score prior to rescue medication (if rescue was taken) meets or exceeds the threshold, regardless of if the subject subsequently loses their response, then the subject will be counted as an overall responder. Otherwise, the subject will be considered a non-responder. In addition, the proportion of subjects who achieve a 30%/50% improvement from baseline will also be calculated at each time point and displayed graphically.

Percent improvement = (baseline value - post-baseline value) × 100 / (baseline value)

The proportion of subjects experiencing ≥ 30% and ≥ 50% improvement in NPRS (responders) will be analyzed using chi square (CMH) test or, alternatively, a Fishers exact test if there are less than 5 subjects in any category. The testing of each dose level of DFN-15 vs. placebo will be performed separately.

Summary tables will present the by-treatment group descriptive statistics of proportions with active vs. placebo odds ratios, 95% confidence intervals and CMH chi-square or Fisher exact p-values. A cumulative proportion of responders figure will also be presented.

8.2.4 Pain Relief

Pain relief scores are captured on the 5-point pain relief scale (0= no pain relief, 1= little pain relief, 2= some pain relief, 3= a lot of pain relief, and 4= complete pain relief) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours as well as immediately prior to any rescue use. Pain relief at each postdose timepoint will be summarized descriptively for each treatment group. All imputation, as described in Section 8.1.1, will be performed prior to presentation.

PR will be summarized descriptively with sample size, mean, standard deviation, median, minimum, and maximum for each treatment group. The unadjusted *p*-value from a 1-sample t-test will be presented for each post-baseline nominal timepoint. To supplement this analysis, group mean of pain relief over time will be displayed graphically at the nominal timepoints. Pain relief scores will also be presented in listings.

8.2.5 Total Pain Relief (TOTPAR)

Total Pain Relief (TOTPAR) over 2, 4, 6, and 8 hours. Total pain relief is calculated similarly to SPID replacing the PID values with the pain relief (PR) scores on the 5-point scale where 0= no pain relief, 1= little pain relief, 2= some pain relief, 3= a lot of pain relief, and 4= complete pain relief. All imputation, as described in Section 8.1.1, will be performed prior to the TOTPAR calculations.

All TOTPAR endpoints will be analyzed using an ANCOVA with treatment as the main effect and baseline pain intensity and BMI as covariates. The results of the ANCOVA will be presented in summary tables with standard summary statistics as well as least square (LS) means, active dose level vs. placebo LS mean differences (treated group – placebo), standard errors, confidence intervals and paired-comparison *p*-values with Dunnett's test. Mean TOTPAR values over time will also be displayed graphically.

8.2.6 Peak Pain Relief

Peak pain relief is defined as the maximum post-dose score (after imputation) that a subject reaches on the 5-point pain relief scale prior to any use of rescue medication (if rescue was taken). This will be summarized with standard summary statistics (count, mean, standard deviation, median, minimum, and maximum by treatment group.

8.2.7 Time to Peak Pain Relief

Time to peak pain relief is defined as the earliest post-dose time that a subject reaches their maximum positive score on the 5-point pain relief scale prior to rescue medication (if rescue was taken). Subjects who do not record at least one positive pain relief score prior to use of rescue will be censored at 8 hours. Time to peak pain relief will be analyzed using Kaplan-Meier curves for each dose level of DFN-15 to placebo with the log-rank test. Estimated percentiles for time to peak pain relief will be tabulated by treatment group along with the number and percent of subjects censored. Additionally, a Kaplan-Meier curve will present cumulative percentages over time graphically.

8.2.8 Proportion of Subjects Satisfied with Treatment

The proportion satisfied with treatment is defined as ratio of subjects reporting treatment satisfaction scores of at least 2 on the 5-point scale (0= poor, 1= fair, 2= good, 3= very good, and 4= excellent) out of all mITT subjects. Summary tables will present the by-treatment group descriptive statistics of proportions for each active dose level vs. placebo, odds ratios, 95% confidence intervals and chi-square or Fisher exact *p*-values if chi-square test assumptions are not met. Treatment satisfaction scores will also be presented in listings. A summary of subject satisfaction scores as a continuous variable and ANCOVA analysis with treatment as the main effect and both baseline pain intensity and BMI as covariates will also be presented.

8.2.9 Time to Perceptible and Meaningful Pain Relief

Times to perceptible and meaningful pain relief will be measured using the double stopwatch method. For each randomized participant, two stopwatches will be started immediately after administration of study drug (T0). The first stopwatch will be given to the participant with the instructions to stop the watch at first perceptible pain relief (if they notice any decrease in the pain they have now). If the first watch is stopped, the second stopwatch will be given to the participant with the instructions to stop the watch if they have meaningful pain relief (pain relief that is meaningful to them). Perceptible pain relief will be summarized only for subjects that achieve meaningful pain relief (Confirmed Perceptible pain relief).

Subjects receiving rescue medication prior to stopping the stopwatch or who do not reach perceptible pain relief within 8 hours will be censored at 8 hours. Subjects will be similarly censored in calculations of meaningful pain relief.

Both time to perceptible and meaningful pain relief will be analyzed using Kaplan-Meier curves for each dose level of DFN-15 to placebo with the log-rank test. Estimated percentiles for time to perceptible/meaningful pain relief will be tabulated by treatment group along with the number and percent of subjects censored.

8.2.10 Time to Administration of First Dose of Rescue Medication

Time to first administration of rescue medication is the date/time of the earliest rescue medication use minus the date/time of T_0. If the subject receives no rescue medication, then the value will be censored at 8 hours.

This will be analyzed using Kaplan-Meier curves for each dose level of DFN-15 to placebo with

the log-rank test. Estimated percentiles for time to first use of rescue will be tabulated by treatment group along with the number and percent of subjects censored.

8.2.11 Proportion of Subjects Receiving Rescue Medication

The proportion of subjects receiving rescue medication uses the number of subjects receiving rescue medication at any time as the numerator and the number of subjects in the mITT population as the denominator.

Summary tables will present the by-treatment group descriptive statistics of proportions with active vs. placebo odds ratios, 95% confidence intervals and CMH chi-square and Fisher exact *p*-values. The proportion of subjects receiving their first dose of rescue at each timepoint will be presented graphically.

8.3 General Analysis Methods

SPID and TOPAR endpoints will use Dunnett's test to account for multiplicity within each of those endpoints. All other *p*-values are presented without adjustment for multiplicity. The mITT population will be primary population used for all efficacy analyses. The PP population will be used as a supplemental analysis for SPID, TOTPAR, PID by timepoint, PR by timepoint, and peak pain relief.

In all cases, the null hypothesis being tested is that the means of the two treatment groups are equal, and the alternative is that the means are not equal:

- H_0: there is no treatment difference
- H_A: there is a treatment difference

If more than 1 center is used, then center effect will be added to the SPID6 ANCOVA model to investigate the impact. If the center effect is significant at the 0.05 level, then center will be added to the log-rank test for time to meaningful and perceptible pain relief analyses. Additionally, treatment-center interactions will be tested in the ANCOVA analysis of the SPID6 endpoint. If this interaction is significant at the 0.10 level, then the interaction term will be included in a sensitivity analysis.

8.4 Exploratory Analysis

Exploratory analyses may be performed to describe other results of interest from the study. Any such analyses will either be documented in a subsequent version of this SAP or in a *post hoc* SAP.

8.5 Examination of Subgroups

The primary endpoint (SPID6) will be analyzed by subgroup for gender (male or female), qualifying pain intensity category (2=moderate or 3=severe on 4-point scale), and BMI (<30 or ≥30).

9.0 Safety Evaluation

9.1 Overview of Safety Analysis Methods

All safety outcomes will be summarized using the safety population. Safety outcomes include:

- Incidence of treatment-emergent AEs (TEAEs)
- Changes from baseline in clinical laboratory test results

- Changes from baseline in vital sign measurements
- Changes from baseline in physical examinations.
- Changes from baseline in ECG findings,
- Evaluation of surgical wound healing.

9.2 Adverse Events

Treatment-emergent AEs are defined as AEs that start or worsen in severity after the first exposure to study medication through the Day 7 visit. Verbatim terms used by investigators to identify AEs in the CRFs will be mapped to the appropriate preferred (PT) and system organ class (SOC) using a standardized coding dictionary (MedDRA Version 21.0 or higher). All coding will be reviewed prior to database lock. All recorded AEs will be listed, but only TEAEs will be summarized.

In addition to a listing of all TEAEs, separate listings of subjects with SAEs and listings of subjects with severe, treatment related, and AEs leading to premature discontinuation will be provided.

An overall summary will be prepared giving for each treatment group, all DFN-15 groups combined and overall of both the number of events and the number of subjects with TEAEs, SAEs, TEAEs by severity, TEAEs by relationship to treatment, and TEAEs leading to premature discontinuation.

The incidence of TEAEs will be summarized for each treatment group by SOC and PT within SOC (sorted in descending order by overall frequency). These summaries will be given in separate tables for the following categories of TEAEs:

- All TEAEs
- TEAEs leading to premature discontinuation
- SAEs

Also summarized will be TEAEs by maximum severity and by maximum relatedness to treatment. Adverse events will be deemed treatment related if they were recorded as probably, possibly, or definitely related.

If a given subject experiences a TEAE that maps to the same PT more than once, the subject will be counted once for the PT at its greatest severity (i.e., mild, moderate, or severe) and causality (i.e., attribution to study medication).

Duration of an AE will be computed in days (or in hours when duration of the AE is less than 1 day) as the stop date/time of the event minus the start date/time plus 1. If reported as ongoing at the time of database lock, the stop date/time is defined as the date/time of the last visit or the last date/time of any AE for the subject in the database, whichever is later. If an AE is considered resolved, but the stop date is missing, the last day of the month will be imputed if the month and year are available. If only the year is available, and the year is the same as the year of the last visit, the stop date will be the latest of the last visit date or latest AE for the subject in the database. If the year of the AE is prior to the year of the last treatment, the end day and month will be set to 31 December.

For missing or partial start dates, it is most conservative to impute them as temporally related to the first dose of study medication. The following chart will be used to impute start date:

Table 2 Table of Adverse Event Start/End Date/Time Imputation Rules

Missing Portion	*Prior to Treatment*	*Same as Treatment Start Date*	*After Treatment Start Date*
Day	Month and Year < Month and Year of first treatment: Start Day = first day of the month Stop Day = last day of the month	*Month and Year = Month and Year of first treatment:* Start Day = Day of first treatment Stop Day= last day of the month	*Month and Year > Month and Year of First Treatment:* Start Day = first day of the month Stop Day= last day of the month
Day and Month Define Day as above, then:	*Year < Year of first treatment:* Start Month = July Stop Month = Dec	*Year = Year of first treatment:* Start Month = Month of first treatment Stop Month = Dec	*Year > Year of first treatment:* Month = January Stop Month = Dec
Day, Month, and Year	To be conservative, completely missing start dates will be set to the date of first treatment, completely missing end dates will be set to the date of last contact.		
Time	Missing start times will be imputed as 00:01 (or the start time of the first dose administration if AE occurred on the date of first dose administration) Missing stop times will be imputed as 23:59		

After following these imputation rules, if the start date is imputed as a date after the end date, the start date will be set to the end date to provide a positive duration for the AE.

Missing assessments for AE study medication relationship, or severity will be analyzed as related, severe, and associated, respectively. No other imputation is planned for safety data unless otherwise specified below.

9.3 Deaths, Serious Adverse events, and Other Significant Adverse Events

A serious adverse event (SAE) is defined as an event that may constitute a significant medical hazard or side effect, regardless of the investigator or sponsor's opinion about its relationship to study material. Serious events include, but may not be limited to, any event that:

- Is fatal

- Is life-threatening (places the subject at immediate risk of death while the event is occurring)
- Requires inpatient hospitalization or prolongs hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Significant untoward medical events that may not be life-threatening or result in death or hospitalization, or events that require intervention to prevent one of the outcomes listed above or that result in urgent investigation, may be considered serious. Elective hospitalizations for conditions that existed before administration of study material are not to be considered SAEs. Serious adverse events and deaths will be listed and summarized separately for the safety population.

9.4 Clinical Laboratory Evaluation

Clinical laboratory samples will be collected at screening, Day 1 at the time of discharge, and EOS (as applicable). For continuous laboratory parameters, the observed values and changes from baseline will be summarized at each scheduled visit, overall and for each treatment group. For categorical laboratory parameters, frequency counts and percentages of subjects in each category will be provided.

Laboratory test results will be displayed in by-subject listings, and values outside of the normal reference range will be flagged.

9.5 Vital Signs, Physical Measurements, and Physical Examinations

9.5.1 Vital Signs and Physical Measurements

Vital signs will be collected at screening, Day 1 prior to surgery, at pre-dose baseline, and then at 1, 2, 4 and 8 hours after the administration of study medication, or at the time of early discontinuation, and at the end of study visit on Day 7 (± 3 days).

Observed values and changes from baseline will be summarized using mean and change-from-baseline descriptive statistics, overall and for each treatment group, for the following measurements: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/minute), and respiratory rate (breaths/minute).

Body weight and height will be measured, and BMI will be calculated during the screening visit only. These values will be summarized along with other baseline characteristics. Vital signs will be displayed in a by-subject listing.

9.5.2 Physical Examinations

Physical examinations are performed at screening, after completion of the 8-hour post-dose efficacy and safety assessments (prior to discharge), and at the end of study visit on Day 7 (± 3 days).

Findings are recorded as normal or abnormal. Physical exam results will be displayed in a by-subject listing.

9.6 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at screening, Day 1 prior to surgery, at pre-dose baseline, and at 1, 2, 4, and 8 hours after treatment initiation or at time of early discontinuation, as well as at the end of study visit on Day 7 (± 3 days).

The findings (i.e., classification as “normal,” “abnormal not clinically significant,” or “abnormal clinically significant”) will be recorded in the subject’s eCRF. Shifts of results from pre-dose baseline to later visits will be summarized in shift tables. ECG results will be displayed in a by-subject listing.

9.7 Surgical Wound Healing Evaluation

An oral examination will be performed as part of the end of study assessment to ensure incision wound healing is progressing as expected. If an adverse event is identified through this examination, it reported in the adverse event summaries. Individual data will be displayed in a by-subject listing.

10.0 Pharmacokinetic Evaluation

All subjects will be enrolled to the pharmacokinetic cohort. Following the single dose of study medication, up to 10 blood samples will be collected from each subject. These will be collected pre-dose and at the following timepoints: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hours post dose.

Subjects who receive placebo will not be included in the PK analysis.

Additional PK analyses not described in this SAP (e.g. population PK) may be performed and will be described in a separate PK Analysis Plan.

10.1 Plasma Concentration

Mean plasma concentrations of DFN-15 at each sampling timepoint will be summarized in a separate PK Report according to the analysis as defined in the PK SAP and presented as an appendix to the CSR. Concentrations will be summarized by dose and nominal sampling time with descriptive statistics. Individual plasma concentrations will be presented in by-subject listings.

Mean concentrations (+SD) versus time plots will be presented.

10.2 PK Parameters Derivation

PK Parameters will be derived by a separate pharmacokineticist under a separate analysis plan. The PK Analysis plan will detail the analysis methodology and intended parameters/summaries.

Following completion of the PK analysis, the celecoxib concentrations and PK parameters (for individual subject and descriptive statistics for the treatment groups) will be summarized in a separate PK Report according to the PK analysis set as defined in the PK SAP and presented as an appendix to the CSR.

11.0 Other Analyses

Any additional analyses conducted will be considered exploratory and identified as *post hoc* in the CSR.

12.0 Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

13.0 Changes to the Analyses Planned in the Protocol

Any deviations from the statistical plan will be described and a justification given in the CSR.

14.0 References

None

15.0 Appendices

15.1 Tables for Final Study Report

Number	Title	Analysis Population
Study Population		
14.1.1	Summary of Subject Disposition	All Subjects
14.1.2.1	Summary of Demographic and Baseline Characteristics	mITT Population
14.1.2.2	Summary of Demographic and Baseline Characteristics (if applicable)	Safety Population
14.1.3	Summary of Medical History	Safety Population
14.1.4	Summary of Concomitant Medications by Drug Class and Medication	Safety Population
14.1.5	Summary of Concomitant Medications by Drug Class and Medication after Discharge	Safety Population
Efficacy		
14.2.1.1	Primary Endpoint: Analysis of Summed Pain Intensity Difference from T0 to T6 (SPID6)	mITT Population
14.2.1.2	Analysis of Summed Pain Intensity Difference from T0 to T6 (SPID6)	PP Population
14.2.1.3	Analysis of Summed Pain Intensity Difference from T0 to T6 (SPID6) by Gender	mITT Population
14.2.1.4	Analysis of Summed Pain Intensity Difference from T0 to T6 (SPID6) by Qualifying Pain Intensity	mITT Population
14.2.1.5	Analysis of Summed Pain Intensity Difference from T0 to T6 (SPID6) by BMI Category	mITT Population
14.2.1.6	Analysis of Summed Pain Intensity Difference from T0 to Other Timepoints (SPID2, SPID4, SPID8)	mITT Population
14.2.1.7	Analysis of Summed Pain Intensity Difference from T0 to Other Timepoints (SPID2, SPID4, SPID8)	PP Population
14.2.2	Summary of Pain Intensity and Pain Intensity Difference by Timepoint	mITT Population
14.2.3	Summary of Pain Intensity and Pain Intensity Difference by Timepoint	PP Population
14.2.4	Analysis of Proportion of 30% and 50% Responders (NPRS)	mITT Population

Number	Title	Analysis Population
14.2.5.1	Summary of Pain Relief by Timepoint	mITT Population
14.2.5.2	Summary of Pain Relief by Timepoint	PP Population
14.2.5.3	Analysis of Total Pain Relief (TOTPARx)	mITT Population
14.2.5.4	Analysis of Total Pain Relief (TOTPARx)	PP Population
14.2.6.1	Summary of Peak Pain Relief	mITT Population
14.2.6.2	Summary of Peak Pain Relief	PP Population
14.2.7.1	Analysis of Time to Peak Pain Relief	mITT Population
14.2.7.2	Analysis of Time to Peak Pain Relief	PP Population
14.2.8.1	Proportion of Subjects Satisfied with Treatment	mITT Population
14.2.8.2	Analysis of Subject Treatment Satisfaction	mITT Population
14.2.9	Analysis of Time to Perceptible Pain Relief	mITT Population
14.2.10	Analysis of Time to Meaningful Pain Relief	mITT Population
14.2.11	Analysis of Time to First Use of Rescue Medication	mITT Population
14.2.12	Proportion of Subjects Receiving Rescue Medication	mITT Population
Safety		
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events (TEAEs)	Safety Population
14.3.1.2	Summary of TEAEs by System Organ Class (SOC), and Preferred Term (PT)	Safety Population
14.3.1.3	Summary of TEAEs Leading to Study Discontinuation by SOC and PT	Safety Population
14.3.1.4	Summary of Serious TEAEs by SOC and PT	Safety Population
14.3.1.5	Summary of TEAEs by SOC, PT, and Maximum Severity	Safety Population
14.3.1.6	Summary of TEAEs by SOC, PT, and Maximum Relationship to Treatment	Safety Population
14.3.2.1	Summary of Chemistry Results and Change from Baseline by Time Point	Safety Population
14.3.2.2	Summary of Hematology Results and Change from Baseline by Time Point	Safety Population
14.3.2.3	Summary of Coagulation Results and Change from Baseline by Time Point	Safety Population

Number	Title	Analysis Population
14.3.2.4	Summary of Continuous Urinalysis Results and Change from Baseline by Time Point	Safety Population
14.3.2.5	Summary of Categorical Urinalysis Results by Time Point	Safety Population
14.3.3	Summary of Vital Signs and Change from Baseline by Time Point	Safety Population
14.3.4	12-Lead ECG Shift Table	Safety Population

15.2 Figures for Final Study Report

Number	Title	Analysis Population
14.2.1.1	Mean Pain Intensity by Timepoint Using NPRS (Imputed Data)	mITT Population
14.2.1.2	Mean SPID by Timepoint (Imputed Data)	mITT Population
14.2.2.1	Mean Pain Relief by Timepoint (Imputed Data)	mITT Population
14.2.2.2	Mean TOTPAR by Timepoint (Imputed Data)	mITT Population
14.2.3.1	Proportion of Responders (>30%/>50%) at each Timepoint	mITT Population
14.2.3.2	Cumulative Proportion of Responders Analysis at each Timepoint	mITT Population
14.2.4	Kaplan-Meier Curve for Time to Peak Pain Relief	mITT Population
14.2.5	Mean Subject Rating of Satisfactoriness by Timepoint	mITT Population
14.2.6	Kaplan-Meier Curve for Time to Confirmed Perceptible Pain Relief	mITT Population
14.2.7	Kaplan-Meier Curve for Time to Meaningful Pain Relief	mITT Population
14.2.8	Kaplan-Meier Curve for Time to First Dose of Rescue Medication	mITT Population

15.3 Listing for Final Study Report

Number	Title	Analysis Population
16.1.1.1	Randomization and Population Inclusion	All Screened Subjects
16.2.1.2	Screen Failures and Subjects Not Receiving Treatment	All Screened Subjects
16.2.1.3	Subject Completion/Early Termination	All Randomized Subjects
16.2.1.4	Protocol Deviations	All Randomized Subjects
16.2.2	Demographics and Baseline Characteristics	All Randomized Subjects
16.2.3	Medical History	All Randomized Subjects
16.2.4	Dental History	All Randomized Subjects
16.2.5	Prior and Concomitant Medications	All Randomized Subjects
16.2.6	Non-Medication Therapy	All Randomized Subjects
16.2.7	Surgery Procedure and Anesthesia	All Randomized Subjects
16.2.8	Post-Operative Pre-Randomization Pain Intensity Assessments	All Randomized Subjects

Number	Title	Analysis Population
16.2.9	Study Drug Administration	All Randomized Subjects
16.2.10.1	NPRS Pain Intensity Assessments and Summed Pain Intensity Differences (SPIDs)	mITT Population
16.2.10.2	Pain Relief Assessments and Total Pain Relief (TOTPAR)	mITT Population
16.2.10.3	Time to Perceptible and Meaningful Pain Relief	mITT Population
16.2.10.4	Patient Ratings of Treatment Satisfactoriness	mITT Population
16.2.10.5	Rescue Medication Administration	mITT Population
16.2.11.1	All Adverse Events	Safety Population
16.2.11.2	Serious Adverse Events	Safety Population
16.2.11.3	Adverse Events Leading to Study Discontinuation	Safety Population
16.2.12.1	Chemistry Laboratory Results	Safety Population
16.2.12.2	Hematology Laboratory Results	Safety Population
16.2.12.3	Urinalysis Laboratory Results	Safety Population
16.2.12.4	Coagulation Laboratory Results	Safety Population
16.2.13.1	Vital Signs	Safety Population
16.2.13.2	Physical Examinations	Safety Population
16.2.13.3	ECG Exam Assessments	Safety Population
16.2.13.4	Serology and Pregnancy Laboratory Results	Safety Population
16.2.13.5	Alcohol and Urine Drug Screens	All Randomized Subjects

16.0 Document History

Version #	Summary of Changes	Section Changed	Date
1.0	• Initial document released	NA	13-Aug-2018
2.0	• Version 2.0 released • 8.2.1 Added analysis of treatment effect at each post-baseline timepoint for Pain Intensity Difference (Tables 14.2.2, 14.2.3) • 8.2.2 Added Mean SPID by Timepoint (Figure 14.2.1.2) • 8.2.5 Added Mean TOTPAR by Timepoint (Figure 14.2.2.2)	8.2.1, 8.2.2, 8.2.5, 8.2.8, 14.0, 15.1, 15.2, 15.3	08-Oct-2018

Version #	Summary of Changes	Section Changed	Date
	• 8.2.8 Added descriptive analysis of Subject Treatment Satisfaction as a continuous variable and ANCOVA Analysis of the same (Table 14.2.8.2) • 10.2 Clarified location and presentation of PK data in study report • Added Table 14.3.2.5 Summary of Categorical Urinalysis Results by Timepoint • References were removed. • Minor formatting updates made throughout the document.		