CLINICAL PROTOCOL DFN-15-CD-010

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

Study Phase:	**2**
IND #:	**138593**
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Date:	**May 2, 2018**
Version:	**2.0**

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(Print Name)

Signature: _____

Date: _____ (MM/DD/YYYY)

PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE:

(To be signed by the Principal Investigator at each Clinical Site)

By signing this, the Principal Investigator agrees to conduct the clinical study which is the subject of this protocol in accordance with the Clinical Study Agreement, this protocol including all Administrative Considerations described therein, all applicable government regulations including Part 54 of title 21 of the CFR, and the conditions of approval imposed by the reviewing Institutional Review Board.

Principal Investigator: _____

(Print Name)

Signature: _____

Date: _____ (MM/DD/YYYY)

PROTOCOL SYNOPSIS

Protocol No:	DFN-15-CD-010
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, Safety and Pharmacokinetic Study of Single Doses of DFN-15 in Post-Surgical Dental Pain.
Study Drug/ **Investigational Product:**	1. DFN-15 (celecoxib oral solution, 25 mg/mL) - Test product 2. Placebo of DFN-15 (oral solution, 0 mg/mL of celecoxib) DFN-15 and placebo will be supplied in bottles containing a deliverable volume of 4.8 mL solution. Doses of DFN-15 (62.5 mg, 125 mg and 250 mg) and placebo will be allocated on site for each subject by drawing the appropriate amounts of DFN-15 and/or placebo solutions into syringes, based on each subject randomized treatment arm. Regardless of DFN-15 dose, the total volume administered to each randomized subject will be the same (10 ml) given as a single oral dose to ensure blinding is maintained.
Country:	United States of America
Phase:	2
Primary Objective:	To assess the analgesic efficacy of DFN-15 in acute pain (post-operative pain following extraction of bilateral mandibular third molars), when administered as a single dose of 62.5 mg, 125 mg or 250 mg, as compared to placebo.
Number of Subjects:	An adequate number of subjects will be screened in order to randomize 120 subjects into the study. Subjects who discontinue study participation after randomization and prior to completing the study will not be replaced.
Trial Design:	This is a randomized, double-blind, placebo-controlled parallel design study, to be conducted at 1-3 centers in the United States. Male and female subjects, 18 to 60 years old (inclusive), who are scheduled to undergo elective bilateral lower third molar extraction will be enrolled. 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. Subjects will undergo a screening procedure (within 28 days of the scheduled extraction of the impacted third molars) that will involve

	the collection of demographic information, height, weight and body mass index (BMI), urine pregnancy test (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. As a pre-requisite for randomization, subjects will be required to report "moderate" to "severe" baseline pain on the provided paper diary within 6 h post-surgery (Baseline period) as characterized on a 4-point categorical pain intensity (PI) scale (0= none, 1= mild, 2= moderate, 3= severe), and a score of ≥5, on the 11-point Numerical Pain Rating Scale (NPRS) where 0 represents 'no pain' and 10 represents 'worst pain imaginable'. 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 patient 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: 1. Pain intensity using the 11-point Numerical Pain Rating Scale (NPRS). Followed by: 2. 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: 1. 'Patient Rating of Treatment Satisfactoriness' using a 5-point verbal rating scale (0 =poor, 1 =fair, 2 =good, 3=very good, 4 =excellent). Subjects will remain NPO (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. 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 time points 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.
Treatment:	A single dose of total volume of 10 mL of oral solution will be administered providing DFN-15 (62.5 mg, 125 mg or 250 mg) or placebo. The 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.
Study Duration:	The duration of study participation will be approximately 39 days, for randomized subjects, including a screening period of approximately 4 weeks, surgery and treatment period day (subjects will be confined within the clinical study facility for at least 8 hours post-dose) and a post-surgery/ treatment follow up visit to the research center up to 10 days post-surgery.
Study Visits:	Total number of visits to the clinical facility: 3 Visit no. 1 (Day -28 to Day -1): Screening Visit no. 2 (Day 1): Bilateral mandibular third molar extraction surgery, followed by randomization, administration of study treatment and observation in the clinical facility for 8 hours post dose. Subjects will be confined within the clinical study facility for at least 8 hours post-dose.

	No overnight stay at the research facility will be required, however if it is clinically appropriate to do so, subjects should remain at the research center until they are safe to leave. Visit no. 3 (Day 4 to Day 10): Follow-Up visit
Study Population:	Male and female subjects (approximate ratio of 1:1) who meet all of the inclusion criteria (including postoperative inclusion criteria) and none of the exclusion criteria below.
Inclusion Criteria:	1. Subjects must be scheduled to undergo elective bilateral lower (mandibular) third molar extraction under local anesthesia (as specified in the anesthetic protocol, Section 5.1.1), with mandibular third molars involving a full or partial bony impaction confirmed by radiographic evidence (panoramic x-ray). Extraction of 1 or 2 impacted or non-impacted maxillary third molars as part of the surgical procedure is permitted but not required. 2. Subjects must voluntarily provide signed, written, and dated informed consent prior to any study-specific procedures. 3. Subjects must be between 18-60 years of age, inclusive, at the time of screening. 4. Subjects must be generally healthy, ambulatory, able to understand and willing to comply with study procedures, study restrictions, assessments, and requirements per the discretion of the investigator. 5. Subjects must be deemed able to comprehend English and fully understand the informed consent form (ICF). 6. Subjects must have a body mass index (BMI) ≥19.0 to ≤35.0 kg/m^2 7. Women are eligible only if all the following apply: a. Not pregnant (women of child bearing potential must have negative urine pregnancy tests at screening and prior to surgery/ randomization) b. Not lactating c. Not planning to become pregnant during the study; d. Surgically sterile (irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal occlusion), bilateral tubal ligation, or at least two years post-menopausal; or is practicing double-barrier contraception; or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening visits. Commits to the

	use of a double-barrier, insertable, injectable, transdermal or combination oral contraceptive for the duration of the study and for 30 days after the last dose study drug administration. In addition, a female subject whose partner has had a vasectomy, or who abstains from sex, or who is involved in a same sex relationship is eligible.
Exclusion Criteria:	1. History of allergy or hypersensitivity to celecoxib and similar pharmacological agents including any NSAID (including aspirin), or to any pre- and post- operative medications used in this study, including lidocaine, oxycodone or acetaminophen, as judged by the investigator. Subjects with conditions known to be contraindications to NSAIDS (risk of thrombovascular events and renal insufficiency.) 2. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic diseases, malignancies, or any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study, including but not limited to: **a.** Any bleeding or blood coagulation disorders **b.** History of an upper GI disorder within 6 months of Screening visit (e.g. gastric or duodenal ulcers) **c.** History of gastric bypass within 6 months of screening visit **d.** Dysphagia **3.** History of migraine or frequent headaches, low back pain, or other acute or chronic pain conditions that according to the investigator's judgment could interfere with efficacy and safety evaluations as required by the protocol. **4.** Acute illness or unresolved local infection prior to surgery that can interfere with the conduct of the study, as judged by the investigator. **5.** History of previous or ongoing psychiatric disease/condition including psychosis, affective disorder, anxiety disorder, borderline state and personality disorder according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders. The following exceptions may be applied: **a.** Subjects with history of mild unipolar depression may be included if eligible otherwise, and not currently receiving SNRIs and medications referenced in Exclusion 10.

	b. Subjects with mild ADHD or mild anxiety may be included if eligible otherwise, and not currently receiving SNRIs and medications referenced in Exclusion 10. **6.** Known or suspected drug (including analgesic drugs or tranquilizers) or alcohol abuse or dependence, as defined by DSM-IV, and not in full remission, as judged by the investigator, or history of alcohol abuse or excessive intake of alcohol, defined as regular weekly intake of >15 units for men and >10 units for women. (1 unit = 25 mL spirits, 125 mL wine, 250 mL beer or lager). **7.** Any clinically significant abnormalities in clinical chemistry, hematology, coagulation parameters, or serology results at screening that in the investigator's judgment puts the subject at risk due to study participation. **8.** Any clinically significant 12-lead ECG abnormalities at screening according to the judgment of the investigator. **9.** Evidence of any clinically significant vital sign abnormality that in the investigator's opinion significantly increases the risks for study participation. **10.** Positive results on urine drug screen or alcohol breath test indicative of illicit drug (Cocaine Metabolites, Marijuana (THC), MDMA (Ecstasy), and Phencyclidine) or alcohol abuse at screening and/or prior to extraction procedure. Positive results for prescription, (Amphetamines, Barbiturates, Benzodiazepines, Methadone, Methamphetamine, Opiates, Oxycodone, and Tricyclic Antidepressants.) The following exception may apply: **a.** Over-the-counter medications (non-NSAIDs), multi-vitamins and supplements are allowable per the opinion of the investigator or sponsor (see Exclusion 13-c). **11.** Frequent use of tobacco (smoking, snuff) or other nicotine-containing products (nicotine chewing gum, nicotine plaster, or other smoking cessation therapy). Frequent use is defined as smoking or consumption/intake of nicotine products more than 2 days per week during the last 12 weeks prior to enrollment. Note: occasional smokers/users of nicotine products (<5 cigarettes per day, and maximally 2 days per week) may be included in the study, provided that they refrain from smoking and/or the use of nicotine containing products for at least 10 days before administration of investigational product and for the duration of the study (through Day 7, ±3 days). **12.** Excessive intake of caffeine-containing foods or beverages (more than 5 units or equivalent per day) within 48 hours prior to

	surgery. One caffeine unit is contained in the following items: 1 cup of coffee, 2 cans of cola, 1 glass of tea, ½ cup of energy drink (e.g., Red Bull), or 3 chocolate bars. **13.** Routinely uses pain medication, including any of the following: **a.** Any opioid medication, or combination medication, equivalent to 5 mg oral morphine per day for 3 or more days per week within 4 weeks before surgery. **b.** Nonsteroidal anti-inflammatory drugs [NSAIDs] or selective COX-2 inhibitors more than 5 times per week within 4 weeks before surgery. **c.** Cannabinoids use within 4 weeks before surgery. **14.** Currently taking any corticosteroid chronically (except for an inhaled steroid for pulmonary disease, and local topical or ophthalmic steroid) or has taken systemic corticosteroids within 4 weeks of the proposed date of surgery. 15. Currently (within 30 days prior to Screening Visit) taking central nervous system (CNS) active drugs such as hypnotics, sedatives, monoamine oxidase inhibitors, sympathomimetic amines, benzodiazepines, tricyclic antidepressants, or serotonin norepinephrine reuptake inhibitors (SNRIs), and anticonvulsants for pain. The following exception may apply: **a.** Subjects taking a stable dose of selective serotonin reuptake inhibitors (SSRIs) to treat mild depression for at least 30 days prior to screening may be included if eligible otherwise. **16.** Donated blood products/ blood loss >500 mL 30 days prior to Screening or between Screening and surgery. **17.** Member or relative of study staff or the Sponsor directly involved in the study. **18.** Previous participation in this study. **19.** Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 30 days prior to the Screening visit. Note: subjects consented and screened, but not dosed in such a study, are not excluded. **20.** Previous exposure to DFN-15 in a clinical trial.

	21. Currently receiving or have received within 7 days prior to investigational product administration in the study, any drug (s) that is metabolized by hepatic microsomal enzyme CYP 2D6. For examples of drugs that are metabolized by CYP2D6, please refer to Table 3-1 'in the FDA's development resource 'Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers' available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Post-Operative Inclusion Criteria:	1. Subjects must report "moderate" to "severe" baseline pain within 6 hours post-surgery, as characterized on a 4-point categorical pain intensity scale (0= none, 1= mild, 2= moderate, 3= severe) 2. Subjects must report a score of ≥5 on the 11-point Numerical Pain Rating Scale (NPRS) within 6 h post-surgery, where 0 represents 'No pain' and 10 represents 'worst pain imaginable' at study baseline. 3. Subject has had no evidence of any clinically significant abnormality during or following surgery that, in the judgment of the investigator, significantly increases the risks due to study participation. 4. In the judgment of the investigator, study participation would not put the subject at risk from the specified surgical procedure, anesthetic protocol, or specified analgesic regimen.
Trial Center:	JBR Clinical Research 1045 E 3900 S Salt Lake City, UT 84124 Additional 1-2 study centers may be included, if deemed necessary, during the conduct of the study.
Primary Endpoint:	Summed pain intensity difference over the first 6 hours (SPID6) between DFN-15 doses and placebo. The comparison of primary interest is DFN-15 doses vs. placebo.

Key Secondary Endpoints:	• Total Pain Relief (TOTPAR) over 2, 4, 6 and 8 hours using a 5-point categorical scale (TOTPAR2, TOTPAR4, TOTPAR6 and TOTPAR8) • Summed Pain Intensity Differences (SPID) at 2, 4 and 8 hours post-dose (SPID2, SPID4 and SPID8) • Time to perceptible and meaningful pain relief as measured by two stopwatch technique • Proportion of subjects reporting treatment satisfaction outcome as either 2 = good, 3 = very good or 4 = excellent, on the 5-point categorical scale • Time to use of rescue medication and percentage of patients using rescue medication • Pain intensity difference at each NPRS time point (15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h) • Pain relief at each time point (15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h) • Characterization of plasma pharmacokinetic profiles of DFN-15 doses in fasting conditions (using C_{max} AUC_{0-t}, $T_{max;}$ Other pharmacokinetic parameters like $AUC_{0-0.25}$, $AUC_{0-0.5}$, $AUC_{0-0.75}$, AUC_{0-1}, AUC_{0-2}, AUC_{0-3}, AUC_{0-4}, AUC_{0-6} will also be calculated)
Secondary/ Exploratory Endpoints:	Additional analyses may be performed and pre-specified in the SAP as appropriate.
Statistical and PK Methods:	The SAP will supersede the protocol in case of a discrepancy. **Sample Size:** 120 subjects will be randomized into the study in (1:1:1:1) ratio into one of 3 doses of active study medication or placebo. All safety and efficacy variables will be summarized using descriptive statistics by treatment group and time point. Descriptive statistics will include (n, arithmetic mean, standard deviation, median, minimum and maximum) for continuous variables, categorical variables will be summarized with counts and percentages. **Analysis Populations:** • Modified Intent-to-Treat (mITT) Population will include all subjects who are randomized, take the assigned dose of the study medication and complete at least one post-baseline pain assessment.

	• Safety Population will include all subjects receiving any amount of study medication. **Primary Efficacy Analysis:** SPID6 values will be analyzed using an ANCOVA (analysis of covariance) model with treatment as the main effect; the baseline pain intensity (PI) score will be added to the model as a covariate. Analgesic effect of DFN-15 at each dose level will be evaluated compared to placebo using Dunnett's test. Imputation methods for rescue use and missing data due to early termination will be specified in a statistical analysis plan (SAP) prior to database lock. **Secondary Efficacy Analyses:** Other SPID and TOTPAR endpoints will be analyzed using similar methods as the primary analysis. Time to meaningful and perceptible pain relief and time to rescue will be summarized graphically with Kaplan-Meier curves and compared across treatments using the log-rank test. Proportion of subjects reporting treatment satisfaction outcome will be summarized and treatments compared using Chi-Square techniques. **Exploratory Efficacy Analyses:** Similar analysis methods will be used for any exploratory endpoints. **Safety:** All safety parameters and changes from baseline will be summarized descriptively by treatment arm and time point. No statistical testing will be performed. **Pharmacokinetics:** Key pharmacokinetic endpoints will be C_{max}, AUC_{0-t} and T_{max}. Other pharmacokinetic parameters like $AUC_{0-0.25}$, $AUC_{0-0.5}$, $AUC_{0-0.75}$, AUC_{0-1}, AUC_{0-2}, AUC_{0-3}, AUC_{0-4}, AUC_{0-6} will also be calculated. Any other additional parameters requiring estimation will be included in the PK Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood Pressure
BPM	Beats Per Minute
ºC	Degrees Centigrade
CFR	(United States) Code of Federal Regulations
CNS	Central Nervous System
COX-2	Cyclooxygenase-2
CRF	Case report form
DBP	Diastolic Blood Pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ET	Early Termination/Early Discontinuation
ºF	Degrees Fahrenheit
GCP	Good Clinical Practice
GI	Gastro-intestinal
GMP	Good Manufacturing Practice
h/ hs	Hour / hours
HR	Heart rate
ICH	International Conference on Harmonization
I/E	Inclusion/Exclusion Criteria
IEC	Independent Ethics Committee

Abbreviation	Definition
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
LOCF	Last Observation Carried Forward
m^2	Square meters
MDMA	Ecstasy
MAOI	Monoamine oxidase inhibitors
Mg	Milligram
Min	Minute
mITT	Modified Intent to Treat
mL	Milliliter
mm Hg	millimeters of mercury
NPRS	Numerical Pain Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
µL	Micro liter
NPO	Nothing by mouth
PCP	Phencyclidine
pH	Negative log of hydrogen ion concentration
PI	Pain Intensity
PID	Pain Intensity Difference
PK	Pharmacokinetic
PO	By mouth

Abbreviation	Definition
PR	Pain Relief
Prn	As needed
Q	Every
SAR	Suspected adverse reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SPID	Summed Pain Intensity Difference
SNRI's	Serotonin norepinephrine reuptake inhibitors
SSAR	Serious suspected adverse reaction
SSRI's	Selective serotonin reuptake inhibitors
TCA	Tricyclic Antidepressants
THC	Tetrahydrocannabinol
TOTPAR	Total Pain Relief Scores
US	United States
VS	Vital signs
WHO	World Health Organization

AMENDMENT 1 - PROTOCOL CHANGES LOG

Original Protocol issued dated March 22, 2018, Final Version.

Version 2.0 dated May 2, 2018

Applicable section(s)	Description of Change(s)
Synopsis - Trial Design	Clarified that admission to the clinic (Check-in) occurs on Day 1 and is referred to as Check-in
Synopsis - Trial Design	Specified dietary conditions prior and subsequent to dosing as follows: Subjects will remain NPO (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).
Synopsis - Exclusion Criteria	Added the following exclusion requirement: Currently receiving or have received within 7 days prior to investigational product administration in the study, any drug(s) that is metabolized by hepatic microsomal enzyme CYP 2D6. For examples of drugs that are metabolized by CYP 2D6, please refer to Table 3-1 in the FDA's development resource "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Applicable section(s)	Description of Change(s)
Protocol Section 4.2 Exclusion Criteria	Added the following exclusion requirement: Currently receiving or have received within 7 days prior to investigational product administration in the study, any drug(s) that is metabolized by hepatic microsomal enzyme CYP 2D6. For examples of drugs that are metabolized by CYP 2D6, please refer to Table 3-1 in the FDA's development resource "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Protocol Section 4.5.2 Diet	Specified dietary conditions prior and subsequent to dosing as follows: Subjects will remain NPO (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).
Protocol Section 5.13 Prohibited Medications	Added the following: Currently receiving or have received within 7 days prior to investigational product administration in the study, any drug(s) that is metabolized by hepatic microsomal enzyme CYP 2D6. For examples of drugs that are metabolized by CYP 2D6, please refer to Table 3-1 in the FDA's development resource "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
Protocol Section 6.4.1 Clinical Laboratory Tests and Appendix A	Clarified that admission to the clinic (Check-in) occurs on Day 1 and is referred to as Check-in
Appendix C	Changed urinalysis testing from bile salts to bilirubin

1. INTRODUCTION

Dr. Reddy's Laboratories, Limited is developing DFN-15, a new formulation of celecoxib [p-[5-p-Tolyl-3-(Trifluoromethyl) pyrazol-1-yl] benzene sulfonamide] for the indications of: (1) acute treatment of migraine with or without aura, and (2) management of acute pain in adults. This study is designed to evaluate the efficacy, safety, tolerability and pharmacokinetic properties of dosing with three doses of DFN-15 (celecoxib; 62.5 mg, 125 mg, and 250 mg) in a postoperative pain population. A single-dose, dose ranging design using the oral surgery model will be used to provide useful data in terms of analgesic onset, single-dose duration of analgesia, and effect size of pain-time curves during an 8-hour evaluation period of postoperative pain. Plasma concentrations and calculated Pharmacokinetic parameters will be used to determine the concentration-effect relationships for efficacy and safety. Efficacy assessments will attempt to identify the time to onset of analgesia, the duration of analgesia, and magnitude of analgesic effect in comparison with placebo.

NSAIDs produce meaningful analgesia without opioid associated side effects such as sedation, nausea and vomiting[1] and they have a low risk of abuse and dependence[2]. NSAIDs, such as celecoxib, that selectively inhibit cyclooxygenase 2 (COX-2) target the prostaglandins (synthesized via COX-2) responsible for inflammation and pain while sparing the prostaglandins responsible for maintenance and protection of the gastrointestinal (GI) tract (synthesized involving COX-1)[3]. The analgesic efficacy of COX-2 selective NSAIDs is similar to nonselective NSAIDs[4] but celecoxib has reduced incidence of upper GI ulcers and bleeds and less GI upset[5,6,7,8]. Data suggests that selective COX-2 inhibitors may be safer in the immediate pre- and peri-operative periods, especially with respect to the incidences of bleeding[9,10], incisional wound hematomas, gastro-intestinal ulceration[11], and they may not impact bone fusion and wound healing[12].

DFN-15 (Celecoxib Oral solution) is a new liquid oral formulation of the selective inhibitor of the type 2 (inducible) isoform of the enzyme cyclooxygenase, celecoxib. Celecoxib is approved as an oral capsule formulation, Celebrex®, for the management of acute pain in adults. DFN-15 contains celecoxib in solution at concentration of 25 mg per mL, and is formulated using self-micro-emulsifying Drug Delivery System (SMEDDS) technology for quicker absorption. In comparative bioavailability studies in healthy subjects, Celebrex was seen to reach peak plasma concentrations at approximately 3 hours (T_{max})[13], whereas, the DFN-15 oral liquid formulation has a more rapid celecoxib absorption rate leading to a higher peak plasma concentration within one hour. Moreover, DFN-15 provides higher systemic exposure (as determined by the calculated partial AUC, AUC_{0-2h}) than Celebrex®, 400 mg in the first 2 hours after dosing (Pharmacokinetic results from studies DFN-15-CD-008, DFN-15-CD-003, as presented in DFN-15 Investigator Brochure edition 3.0). On account of the unique physico-chemical and pharmacokinetic characteristics of DFN-15, it is expected to provide a quicker onset of analgesia and better relief early on in acute pain, such as post-surgical pain.

2. STUDY OBJECTIVES

The primary objective of the study would be to evaluate the analgesic efficacy of celecoxib at three dose levels of DFN-15 (62.5 mg, 125 mg and 250 mg) in comparison to placebo and to determine the pharmacokinetics of celecoxib from different doses, in acute post-surgical dental pain.

The secondary objective of the study would be to evaluate the tolerability and safety of single doses of DFN-15 when administered to patients experiencing post-surgical dental pain.

Additional analyses may be performed and pre-specified in the SAP as appropriate.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2, randomized, double-blind, parallel group, dose-ranging placebo-controlled evaluation of the analgesic efficacy, safety, tolerability and pharmacokinetics of DFN-15 in adult subjects who experience post-operative pain after undergoing bilateral third mandibular molar extraction. The study will randomize approximately 120 subjects across 1-3 sites.

Subjects will be at least 18 years to 60 years of age and will be scheduled to undergo elective bilateral mandibular third molar extraction under local anesthesia. The mandibular third molars must involve a full or partial bony impaction confirmed by radiographic evidence (panoramic x-ray).

After signing the informed consent: demographics, medical/medicinal history, physical examination (including height, weight and BMI), dental examination, baseline clinical laboratory testing, 12-lead electrocardiogram (ECG), vital sign measurements, urine pregnancy testing (females of child bearing potential) and urine drug and alcohol screen will be completed during the screening visit.

On the day of surgery (Day 1), prior to surgery, eligibility will be confirmed through updating medical/medicinal history, 12-lead electrocardiogram (ECG), vital sign measurements, urine pregnancy testing (females of child bearing potential), urine drug and alcohol screen, and review of inclusion exclusion criteria. A patient training program will be implemented to ensure that all subjects understand the relevant scales and assessments prior to study participation. Eligible subjects will undergo bilateral mandibular third molar extractions. Subjects who experience acute postoperative pain of 'moderate' to 'severe' intensity, on a 4-point categorical pain intensity scale (0= none, 1= mild, 2= moderate, 3= severe), within 6 hours following the end of surgery, and a pain intensity ≥ 5 on an 11-point numeric pain rating scale (NPRS), will be eligible for randomization and will stay at the study center for at least approximately 8 hours after treatment initiation.

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 to receive a single oral dose of DFN-15 62.5 mg, DFN-15 125 mg, DFN-15 250 mg or placebo. The time of the study drug administration will be designated as T0.

Subjects will be domiciled at the research facility during the first 8 hours after initiation of study drug treatment. For safety and welfare of the subject, the site may choose to have subjects stay overnight at the study center. An 11-point numerical pain rating scale (NPRS) will be used to determine the intensity of pain, 0-10 where 0 is 'no pain' and 10 is 'worst imaginable pain'. NPRS

assessments will be performed at: baseline, 15, 30, and 45 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after study drug administration (T0). Also at these time points, Pain Relief (PR) will be assessed 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). Numerical pain rating scale (NPRS) and pain relief (PR) assessments will also be completed before taking any dose of rescue medication, and at time of early discontinuation (if it occurs). The time to first perceptible pain relief and time to meaningful pain relief will be determined using the 'two stop watch' method. Subjects will also complete a Patient Rating of Treatment satisfactoriness at 8 hours after treatment initiation (prior to discharge from the clinical research center), or immediately prior to the time of first rescue analgesic administration, or at time of early discontinuation. Serial vital signs and 12 lead ECG will be done as indicated in Section 6.4.

For time points where several procedures are scheduled, the following sequence will be followed: 12-lead ECG, Vital signs, Pain assessments (where applicable), PK blood draw, clinical laboratory (where applicable).

Subjects with inadequately controlled pain symptoms may request 1-2 oxycodone 5 mg/ acetaminophen 325 mg q 4 h as needed as rescue analgesic medication. For subjects who require additional analgesia, additional analgesic medication may be administered per the surgeon's standard of care.

Post rescue analgesic administration, subjects will continue completing pain assessments until 8 hours after treatment initiation. However, these assessments will be disregarded in the statistical analysis.

Subjects should be encouraged to wait at least 2 hours after the first study drug administration before utilizing rescue analgesia, if possible. As much as possible, rescue analgesic medication should be administered only if pain intensity (PI) prior to rescue is ≥4 on the numerical rating scale.

A maximum of twelve 4 mL blood samples will be taken from each participant at baseline and 15, 30, and 45 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours after study drug administration for analysis of plasma celecoxib concentrations. 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 be asked to return to the study site 7 days (±3 days) post-surgery for evaluation of their safety and well-being. A review of AEs experienced post-surgery, a physical examination, 12-lead ECG, and vital signs will be repeated. Hematology, serum biochemistry, coagulation 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 that are made after discharge will be reviewed and recorded.

Efficacy assessments will include numerical pain rating scale (NPRS) for pain intensity, pain relief (PR), use of rescue medication, and Patient Rating of Treatment

satisfactoriness. Safety assessments will include monitoring of AEs and SAEs, clinical laboratory tests, ECGs, and vital sign measurements.

3.2. Rationale for Study Design and Control Groups

This study will evaluate the efficacy, tolerability, safety, and pharmacokinetic properties of a known drug substance administered via an alternative formulation/dosage form.

This study will explore the analgesic effects of dosing with DFN-15 (a solution of celecoxib) in an accepted model of postoperative pain. Third molar extraction produces generally reliable and persistent pain symptoms for a period typically lasting over 24 hours, which will allow for analysis of single dose analgesic properties. Pharmacokinetic evaluations will allow determination of exposure in patients with acute postoperative pain and examination of any exposure-response relationship for DFN-15 doses. Efficacy measures will be collected in order to gain a better knowledge of the onset of analgesic effects, as well as characterizing the duration and extent of analgesic effects following a surgical procedure. These analgesic effects will be evaluated between three potentially effective doses of DFN-15 in comparison with a placebo control.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Subjects must be scheduled to undergo elective bilateral lower (mandibular) third molar extraction under local anesthesia (as specified in the anesthetic protocol, Section 5.1.1), with mandibular third molars involving a full or partial bony impaction confirmed by radiographic evidence (panoramic x-ray). Extraction of 1 or 2 impacted or non-impacted maxillary third molars as part of the surgical procedure is permitted but not required.
2. Subjects must voluntarily provide signed, written, and dated informed consent prior to any study-specific procedures.
3. Subjects must be between 18-60 years of age, inclusive, at the time of screening.
4. Subjects must be generally healthy, ambulatory, able to understand and willing to comply with study procedures, study restrictions, assessments, and requirements per the discretion of the investigator.
5. Subjects must be deemed able to comprehend English and fully understand the informed consent form (ICF).
6. Subjects must have a body mass index (BMI) ≥19.0 to ≤35.0 kg/m2
7. Women are eligible only if all the following apply:
8. Not pregnant (women of child bearing potential must have negative urine pregnancy tests at screening and prior to surgery/ randomization;
9. Not lactating;
10. Not planning to become pregnant during the study;
11. Surgically sterile (irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal occlusion), bilateral tubal ligation, or at least two years post-menopausal; or is practicing double-barrier contraception; or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening visits. Commits to the use of a double-barrier, insertable, injectable, transdermal or combination oral contraceptive for the duration of the study and for 30 days after the last dose study drug administration. In addition, a female subject whose partner has had a vasectomy, or who abstains from sex, or who is involved in a same sex relationship is eligible.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. History of allergy or hypersensitivity to celecoxib and similar pharmacological agents including any NSAID (including aspirin), or to any pre- and post- operative medications used in this study, including lidocaine, oxycodone or acetaminophen, as judged by the investigator. Subjects with conditions known to be contraindications to NSAIDS (risk of thrombovascular events and renal insufficiency.)

2. Evidence or history of clinically significant haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, neurologic diseases, malignancies, or any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study, including but not limited to:
    a. Any bleeding or blood coagulation disorders
    b. History of an upper GI disorder within 6 months of Screening visit (e.g. gastric or duodenal ulcers)
    c. History of gastric bypass within 6 months of Screening visit
    d. Dysphagia
3. History of migraine or frequent headaches, low back pain, or other acute or chronic pain conditions that according to the investigator's judgment could interfere with efficacy and safety evaluations as required by the protocol.
4. Acute illness or unresolved local infection prior to surgery that can interfere with the conduct of the study, as judged by the investigator.
5. History of previous or ongoing psychiatric disease/condition including psychosis, affective disorder, anxiety disorder, borderline state and personality disorder according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders. The following exceptions may be applied:
    a. Subjects with history of mild unipolar depression may be included if eligible otherwise, and not currently receiving SNRIs and medications referenced in Exclusion 10.
    b. Subjects with mild ADHD or mild anxiety may be included if eligible otherwise, and not currently receiving SNRIs and medications referenced in Exclusion 10.
6. Known or suspected drug (including analgesic drugs or tranquilizers) or alcohol abuse or dependence, as defined by DSM-IV, and not in full remission, as judged by the investigator, or history of alcohol abuse or excessive intake of alcohol, defined as regular weekly intake of >15 units for men and >10 units for women. (1 unit = 25 mL spirits, 125 mL wine, 250 mL beer or lager).
7. Any clinically significant abnormalities in clinical chemistry, hematology, coagulation parameters, urinalysis or serology results at screening that in the investigator's judgment puts the subject at risk due to study participation.
8. Any clinically significant 12-lead ECG abnormalities at screening according to the judgment of the investigator.
9. Evidence of any clinically significant vital signs abnormality that in the investigator's opinion significantly increases the risks for study participation.
10. Positive results on urine drug screen or alcohol breath test indicative of illicit drug (Cocaine Metabolites, Marijuana (THC), MDMA (Ecstasy) and Phencyclidine) or alcohol abuse at screening and/or prior to extraction procedure. Positive results for prescription,

(Amphetamines, Barbiturates, Benzodiazepines, Methadone, Methamphetamine, Opiates, Oxycodone, and Tricyclic Antidepressants.) The following exception may apply:

a. Over-the-counter medications (non-NSAIDs), multi-vitamins and supplements are allowable per the opinion of the investigator or sponsor (see Exclusion 13-c).

11. Frequent use of tobacco (smoking, snuff) or other nicotine-containing products (nicotine chewing gum, nicotine plaster, or other smoking cessation therapy). Frequent use is defined as smoking or consumption/intake of nicotine products more than 2 days per week during the last 12 weeks prior to enrollment. Note: occasional smokers/users of nicotine products (<5 cigarettes per day, and maximally 2 days per week) may be included in the study, provided that they refrain from smoking and/or the use of nicotine containing products for at least 10 days before administration of investigational product and for the duration of the study (through Day 7, ±3 days).
12. Excessive intake of caffeine-containing foods or beverages (more than 5 units or equivalent per day) within 48 hours prior to surgery. One caffeine unit is contained in the following items: 1 cup of coffee, 2 cans of cola, 1 glass of tea, ½ cup of energy drink (e.g., Red Bull), or 3 chocolate bars.
13. Routinely uses pain medication, including any of the following:
    a. Any opioid medication equivalent to 5 mg oral morphine per day for 3 or more days per week within 4 weeks before surgery.
    b. Nonsteroidal anti-inflammatory drugs [NSAIDs] or selective COX-2 inhibitors more than 5 times per week within 4 weeks before surgery.
    c. Cannabinoids within 4 weeks before surgery.
14. Currently taking any corticosteroid chronically (except for an inhaled steroid for pulmonary disease, and local topical or ophthalmic steroid) or has taken systemic corticosteroids within 4 weeks of the proposed date of surgery.
15. Currently taking central nervous system (CNS) active drugs such as hypnotics, sedatives, monoamine oxidase inhibitors, sympathomimetic amines, benzodiazepines, tricyclic antidepressants, or serotonin norepinephrine reuptake inhibitors (SNRIs), and anticonvulsants for pain.
    a. Subjects taking a stable dose of selective serotonin reuptake inhibitors (SSRIs) to treat mild depression for at least 30 days prior to screening may be included if eligible otherwise.
16. Donated blood products/ blood loss >500 mL 30 days prior to Screening or between Screening and surgery.
17. Member or relative of study staff or the Sponsor directly involved in the study.
18. Previous participation in this study.
19. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 30 days prior to the Screening visit. Note: subjects consented and screened, but not dosed in such a study, are not excluded.

20. Previous exposure to DFN-15 in a clinical trial.
21. Currently receiving or have received within 7 days prior to investigational product administration in the study, any drug (s) that is metabolized by hepatic microsomal enzyme CYP 2D6. For examples of drugs that are metabolized by CYP2D6, please refer to Table 3-1 'in the FDA's development resource 'Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers' available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

4.3. Post-Operative Inclusion Criteria

1. Subjects must report "moderate" to "severe" baseline pain within 6 hours post-surgery, as characterized on a 4-point categorical pain intensity scale (0= none, 1= mild, 2= moderate, 3= severe)
2. Subjects must report a score on the 11-point Numerical Pain Rating Scale (NPRS) of ≥5 within 6 h post-surgery, where 0 represents 'No pain' and 10 represents 'worst pain imaginable' at study baseline.
3. Subject has had no evidence of any clinically significant abnormality during or following surgery that, in the judgment of the investigator, significantly increases the risks due to study participation.
4. In the judgment of the investigator, study participation would not put the subject at risk from the specified surgical procedure, anesthetic protocol, or specified analgesic regimen.

4.4. Discontinuation of Subjects

4.4.1. Procedures for Withdrawal

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).

4.4.2. Replacement of Subjects

Subjects who discontinue after randomization will not be replaced in this study.

4.5. Lifestyle Guidelines

4.5.1. Confinement

Prior to the surgical procedure (Day 1), subjects will arrive at the study clinic to prepare for the procedure and confirm eligibility to participate in the study. Following the third molar extraction procedure, subjects who achieve adequate pain intensity will be randomized and initiate dosing with study drug. Subjects may be discharged from the study clinic about 8 hours after receiving the study drug treatment. For safety and welfare of the subject, the site may choose to have subjects stay overnight. Subjects will be allowed to ambulate normally as per standard of care instructions after surgery.

4.5.2. Diet

Subjects will remain NPO (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 will 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.

5. TREATMENTS

5.1. Surgical Procedure

Study staff will verify admission and surgery schedule the day of the scheduled procedure. Subjects who continue to meet all eligibility requirements for study enrollment are eligible to receive study drug as long as the Post-Operative Inclusion Criteria are met.

5.1.1. Anesthetic Care

The subject may be administered local anesthesia with Lidocaine 2% with epinephrine with (maximum volume of 20 mL). Nitrous oxide and benzocaine gel are allowed. Sedation will not be allowed. Long acting local anesthetics (e.g. bupivacaine and ropivacaine) and steroids are also prohibited.

5.1.2. Surgery

Surgical removal of the impacted third molars will be carried out per the surgeon's standard of care practice. Two (2) mandibular third molar teeth will be extracted. The mandibular third molars must involve a full or partial bony impaction confirmed by radiographic evidence. Extraction of 1 or 2 impacted or non-impacted maxillary third molars as part of the surgical procedure is permitted but not required.

5.1.3. Post-operative Care

It is anticipated that subjects will receive study medication once subject meets the post-operative inclusion criteria. Post-surgical follow-ups will be scheduled 7 days (±3 days) post-surgery for evaluation of their safety and well-being.

5.2. Disallowed medications

- Except as indicated in the rescue analgesic regimen, any additional analgesic (morphine, ketorolac, ibuprofen, acetaminophen etc.).
- General anesthesia, long acting local anesthetics (e.g. bupivacaine, ropivacaine) or other sedative medications.

5.3. Administration of Study Medication

Study drug will be administered as follows:

1. Subject must be in an upright position before administering study drug.
2. Study drug will be administered to the subject by qualified medical staff.
3. Subjects will receive a single dose of the assigned study treatment (DFN-15 [62.5 mg, 125 mg, or 250 mg] or placebo) administered, as a total volume of 10 mL, according to the randomization number.

5.4. Identity of Study Medication

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.

A 6-month accelerated and 12-month real time stability data from the clinical batch meets stability specifications. The drug product for the clinical study will be continued to be supported with appropriate stability testing for the duration of any clinical study.

The DFN-15 formulation and the matching placebo are manufactured for the Reddy's Laboratories Limited by: Contract Pharmaceuticals Limited Canada, 7600 Danbro Crescent, Mississauga, ON L5N 6L6, Canada

The active pharmaceutical ingredient for DFN-15 is manufactured for Dr. Reddy's by: Hetero Drugs, Ltd., Narasapuram Village, Nakkapally Mandal, Vishakhapatnam, Andhra Pradesh, India. Manufacturing of the study drug was performed according to Good Manufacturing Practice for Medicinal Products and all relevant regulatory requirements.

5.5. Method of Assigning Subjects to Treatment Groups

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. All study doses administered will be according to the treatment assignment. Male and female subjects (approximate ratio of 1:1) who meet all of the inclusion criteria (including postoperative inclusion criteria) and none of the exclusion criteria will be stratified.

5.6. Selection of Doses

The selection of doses of DFN-15 to be evaluated in this exploratory study is based upon pharmacokinetic modelling using data from PK studies of DFN-15 in healthy subjects, and from the exposure-pain intensity response relationship that is reported for Celebrex® in acute pain.

5.7. Selection of Timing of Dose

Subjects will receive a single dose of study medication. Study drug will be administered if the subject achieves adequate pain symptoms (i.e. NPRS ≥5 out of 10 and pain of 'moderate' or 'severe' intensity on a 4-point categorical pain intensity scale) to be randomized in the study. The exact time of study drug administration start will be recorded in the subject's CRF.

5.8. Blinding and Unblinding of Study Medications

All doses administered in this study will be under double-blind conditions; both the subject and the investigator/site staff directly involved with the surgery, or efficacy/safety/PK assessments and the Sponsor personnel, will be blinded to the treatment assignment.

Each dose of study medication will be prepared by a designated unblinded pharmacist at the site, as per the randomization schedule. Each dose will consist of a total volume of 10 mL of solution administered orally. The unblinded pharmacist, who is not otherwise involved in the study, will prepare dose per the randomization schedule by pulling four bottles of either active or placebo oral solution. Pharmacist will pull solution from each of the four bottles into each of the four 2.5 mL dosing syringes, and provide the blinded dosing syringes containing the oral solution dose to the blinded staff member/s, who will administer the study medication as per Section 5.3.

The study site will be provided with individually sealed envelopes identifying the study medication each subject receives in the study. The treatment for an individual subject may be unblinded in the event of an emergency, or if the safety of a subject is at risk and the treatment plan for that subject depends on which study medication he or she received. In the event of emergent medically necessary unblinding, the blind may be broken by removing the code break envelopes provided for the assigned randomization number without breaking the code for any other subject.

Unless the subject is at immediate risk, the investigator must make diligent attempts to contact the designated Medical Monitor before unblinding the subject's data. If a subject's data are unblinded without the prior knowledge of the Medical Monitor, the investigator must notify the Medical Monitor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented.

The sealed randomization envelopes should be stored in a locked area with controlled access until required to break the blind in the event of an emergent condition in a treated subject.

5.9. Treatment Compliance and Safety

Designated study personnel will directly administer study medication with designated study personnel verifying medication administration. Time of medication administration (T0 = time of dosing) will be recorded into the CRF.

Study investigators will review the investigational brochure prepared for DFN-15 in order to be aware of the safety related events which may be anticipated with its use. A fully stocked emergency crash cart, defibrillator, oxygen, and personnel trained in emergency resuscitation will be available at the study center at all times during the confinement period.

5.10. Drug Accountability

The investigator (or designee) will sign for the study medication when received and will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The inventory of supplies at the study site may be checked at any time during the study by the unblinded monitor. The study medication must be handled and stored as described and dispensed only to those subjects formally enrolled in the study.

It is the responsibility of the Investigator (or designee) to ensure that the study drug has been correctly documented for the amount received and dispensed. A full drug

accountability log will be maintained at the study site at all times. All discrepancies must be accounted for and documented.

At the completion of the study, and after reconciliation of all delivery and usage records, any unused study medication supplied by the sponsor will be returned to the sponsor (or designee) or destroyed per written instructions from the sponsor.

5.11. Packaging, Labeling, and Storage

DFN-15 (celecoxib oral solution) and matching placebo will be contained in an amber-colored color glass bottle fitted with a child-resistant (CR) cap. The study packaging will be performed by a designated central supply management vendor. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and all relevant regulatory requirements.

Study medication should be stored in a pharmacy or locked and secured in a storage facility at the study site at temperatures between 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP controlled room temperature]. Do not refrigerate or freeze. The room should be accessible only to authorized individuals. The study medication should also be protected against direct heat, light, and humidity. A temperature log or chart should be maintained to monitor the environment at the study site.

Deviations from the storage requirements or any observed potential problems with the investigational product (i.e. breakage, cracks, leakage, mislabeling), including any actions taken, must be documented on the sponsor provided "Investigational Product Complaint Form" and reported to the sponsor.

5.12. Prior and Concomitant Medications

All medications and other treatments taken by subjects within 28 days before dosing and during the study will be recorded in the CRF. Any changes in the concomitant medications after discharge from the study, that is either prescribed or self-administered, will be documented and reviewed at the end of study visit.

5.13. Prohibited Medications

Prior to surgery, subjects should refrain from taking analgesics or anti-inflammatory agents whose duration of action will affect scheduled study evaluations. After study drug treatment, subjects must be willing to refrain from use of pharmacologic or non-pharmacologic treatments, and other forms of pain relief other than the pain relief regimen prescribed during the study.

The following medications are prohibited throughout the study:

- anticonvulsants,
- Monoamine Oxidase Inhibitors (MAOIs),
- Tricyclic Antidepressants (TCA),
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) (Serotonin selective Reuptake Inhibitors (SSRI) treatments are allowed if taken for at least 30 days before the screening period of the study at an unchanged, stable dose),

- Narcotics (other than pre-specified rescue analgesic regimen of 1-2 tablets of 5 mg oxycodone), including: hydrocodone, codeine, fentanyl, meperidine, tramadol, opioid combinations,
- Acetaminophen (other than pre-specified rescue analgesic regimen of 325 mg acetaminophen Q4H prn), and nonsteroidal anti-inflammatory agents (NSAIDS). Aspirin (acetylsalicylic acid) is prohibited unless taken for cardiac or cardiovascular prophylaxis at a dose no higher than 100 mg daily,
- Sedatives (including benzodiazepines) used as minor tranquilizers or hypnotics are not allowed unless approved by the investigator and medical monitor,
- Gabapentin or pregabalin,
- Medication or therapies that may act synergistically with the study drug e.g. barbiturates, drugs with enzyme inducing properties (CYP 2B6 inhibitors, CYP2C9 inhibitors and inducers, CYP3A4 inhibitors) e.g. rifampicin, St. John's Wort, etc.,
- Medications that are metabolized by the hepatic microsomal enzyme CYP2D6. (please refer to Table 3-1 in the FDA's development resource 'Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers' available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm, for drugs that are substrates for CYP2D6.
- General anesthetics, long-active local anesthetics (e.g. bupivacaine, ropivacaine),
- Anti-psychotic medications (e.g. neuroleptics such as haloperidol).

5.14. Concomitant Interventions and Procedures

All interventions or procedures, whether diagnostic or therapeutic, will be recorded in the CRF, along with time, date, and reason for the intervention or procedure. If an intervention or procedure is implemented to treat an AE, the event must be recorded as an AE, along with all relevant information.

Use of antibiotics may be allowed per the surgeon's standard of care practice.

Medication or therapy may be given when deemed necessary by the Investigator to treat adverse events. Such administration, however, may require discontinuation of the subject from further study participation. The administration of any additional medication must be documented in the Subject's Source Note as appropriate.

The use of concomitant medications during the study, or changes in the dose or dosing frequency of medications used prior to the study start will be documented.

Use of physical therapy for management of pain is not permitted from baseline assessment until 8 hours post-dose.

5.15. Rescue Medication

Allowed Postoperative Analgesic Regimen

1. From end of surgery until prior to T0

No analgesic concomitant medications are allowed. If subjects are inappropriate to randomize, they must be screen failed.

2. Post T0 rescue analgesic regimen (T0-T8)

   The following will comprise the post T0 supplemental analgesic medication regimen: 1-2 tablets (5 mg) oxycodone/ (325 mg) acetaminophen Q4H prn.

For subjects who require additional analgesia, additional analgesic medication may be administered per the surgeon's standard of care.

Efforts should be made to encourage the Subject to wait at least 120 minutes after initiation of study therapy (T0) before receiving post T0 supplemental analgesic medications, if possible. If subjects rescue, they will record their NPRS, PR and Patient Rating of Treatment satisfactoriness prior to receiving rescue medication.

6. STUDY PROCEDURES

Schedules of study procedures for overall study assessments and day-of-dosing assessments are provided in APPENDIX A: .

6.1. Order of Study Procedures

The order of the procedures to be performed at any scheduled time, where applicable, will be as follows:

1. Demographics, eligibility, medical history
2. 12-lead ECG
3. Vital Signs
4. 4-point PI (pre-dose timepoint only)
5. 11-point NPRS
6. PR
7. Patient Rating of Treatment satisfactoriness (8-hours post-dose timepoint only)
8. Collection of pharmacokinetic blood samples
9. Collection of clinical laboratory blood samples

Efficacy assessment windows are referenced in Sections 6.3.5 and 6.3.6. PK collection windows are referenced in Section 6.2.2. Efficacy assessments and PK samples are to be targeted for specified timepoints, with ECG completed within a window of ± 45 minutes, and vital signs should be completed within a window of ± 30 minutes prior, as illustrated in Sections 6.4.2 and 6.4.3. The actual time the study procedure is completed will be recorded.

6.2. Pharmacokinetic Assessments

6.2.1. Pharmacokinetic Groups

Pharmacokinetic samples will be collected from all randomized participants prior to and following administration of study medication. A maximum of twelve 4 mL blood samples will be taken from each participant up to 8 hours after study drug administration.

6.2.2. Sample Collection

About 4 mL whole blood will be collected in K2-EDTA/K3EDTA collection tubes.

Plasma samples will be collected within ±5 minutes of the scheduled post-dose time through 1 hour after dosing; samples collected after the first hour after dosing may be collected within ±10 minutes, immediately following the efficacy assessments. Actual times will be recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject's study records.

6.2.3. Processing, Storage, and Shipping of Pharmacokinetic Samples

Immediately after the collection of each sample, the collection tube will be gently inverted and then placed in wet ice. Within 30 minutes of withdrawal, the tubes will be

centrifuged at about 3,000 rpm for 10 minutes to separate the plasma. Two aliquots of equal volumes of plasma (the primary containing about 1 ml and the secondary containing the remaining amount) will be transferred from each sample with clean pipettes and placed in 2 polypropylene storage tubes. The storage tubes will be labeled, at minimum, with protocol number, subject number, and relative time of sample (e.g., 0.5H post dose), and biologic matrix to be analyzed (e.g., plasma). Within 60 minutes of the collection time, the storage tubes will be placed into a freezer at –20ºC or below; they will remain in the freezer until shipped.

At a time designated by the sponsor, the samples will be packed with sufficient dry ice to keep them frozen for at least 48 hours and shipped to the following address:

Investigator: Malleswar Kollu, Director Bioanalytical

Site: Sannova Analytical, Inc.

155 Pierce Street

Somerset, NJ 08873

Tel: 732-560-0066

Fax: 732-560-0266

On the day prior to shipment, clinical staff will notify (via telephone or email) the analytical laboratory of the pending shipment.

6.2.4. Bioanalytical Methodology

Plasma samples will be assayed for concentrations of using a validated method of liquid chromatography coupled with tandem mass spectrometry, at Sannova Analytical, Inc.

6.3. Demographic and Efficacy Assessment

6.3.1. Demographics

Demographics information will be collected during screening visit including age, sex, ethnicity, race, weight, height, and BMI and recorded into source and CRF as Kg/m^2.

6.3.2. Medical/Medicinal History

The Investigator or designee will document each subject's medical and medicinal history during the screening visit. Medical and medicinal history will be updated on Day 1 when the subject is admitted to the study unit, and the subject inclusion/exclusion criteria will be reviewed to confirm that they continue to meet the required study inclusion and exclusion criteria.

6.3.3. Physical Examination

The Investigator or designee will perform a physical examination (HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems) during the screening visit, 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. Body weight and height will be measured, and BMI will be calculated during the screening visit only.

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

6.3.4. Dental Examination

At the screening visit, the Investigator or designee will perform a panoramic x-ray documenting the impacted mandibular third molar teeth. An oral examination will also be performed as part of end of study assessment to ensure incision wound healing is progressing as expected.

6.3.5. Pain Intensity: 4-Point Categorical Pain Intensity (PI) and Numerical Pain Rating Scale (NPRS)

PI will be assessed using Numerical pain rating scale (NPRS) by the study subject, following training on how to perform the assessment, for their current tooth extraction pain according to an 11-point numeric pain rating scale (0 - 10) where 0 equates to 'no pain', and 10 equates to 'worst pain imaginable'. See Appendix B.1: Pain Intensity Assessment.

After surgery, when the subject is sufficiently awake to be able to follow directions, subjects will be assessed for postoperative inclusion criteria. Subjects will be eligible for randomization if pain intensity is reported as 'moderate' or 'severe' level on a 4-point categorical pain intensity (PI) rating scale (with categories of 'none', 'mild', 'moderate', or 'severe'), plus an NPRS score ≥5 (scale of 0 to 10 where 0 is 'no pain' and 10 is the 'worst pain imaginable'). The 4-point categorical rating scale for pain intensity will be completed only at baseline.

Subjects will be randomized and administered the study medication within 15 minutes of meeting the post-operative inclusion criteria (baseline score). The NPRS score completed prior to randomization will be utilized as the baseline pain intensity score.

T0 is the time of first study drug administration.

NPRS will be performed at: baseline, then 15, 30, and 45 minutes, then at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after treatment initiation (T_0). Pain intensity assessments will also be completed before taking first rescue medication dose (within 5 minutes prior to rescue dose) and/or at time of early discontinuation. All assessments should continue per protocol even after rescue is taken.

There will be a ± five (5) minute window allowed for the timing of each pain intensity assessment in the first 2 hours post T0 then a ±10-minute window for subsequent PI assessments.

As much as possible, rescue analgesic medication should be administered only if PI prior to rescue is ≥4 on the numerical pain rating scale (NPRS).

6.3.6. Pain Relief (PR)

Pain Relief (PR) will be assessed by the study subject according to a 5-point categorical scale, where (where 0= no relief, 1= little relief, 2= some relief, 3= a lot of relief, 4= complete relief). See Appendix B.2: 5-Point Categorical Pain Relief Assessment.

PR will be assessed at: 15, 30, and 45 minutes, then at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after treatment initiation (T_0). PR assessments will also be completed before taking first rescue medication dose, (within 5 minutes prior to rescue dose) and/or at time of early discontinuation.

There will be a ± five (5) minute window allowed for the timing of each PR assessment in the first 2 hours post T0 then a ±10 minute window for subsequent PR assessments.

6.3.7. Time to Perceptible Pain Relief and Time to Meaningful Pain Relief

Time to perceptible pain relief and time to meaningful pain relief will be measured using the 'two stopwatch' method. For each randomized subject, two stopwatches will be started immediately after administration of the first study dose (T0). The first stopwatch will be given to each subject with the instructions to stop the watch when they first perceive pain relief to occur ('time to perceptible relief'). Once the first watch is stopped, the second stopwatch will be given to the subject with the instructions to stop the watch when they are first experiencing meaningful pain relief ('time to meaningful relief'). The stopwatch times to perceptible and meaningful pain relief will be recorded in the subject's CRF.

6.3.8. Patient Rating of Treatment satisfactoriness

Subjects will be asked to evaluate the performance of their study medication as a pain treatment in response to the following inquiry; "Please rate how well your pain has been controlled since you received study medication? 0-poor, 1-fair, 2-good, 3-very good, or 4-excellent." See Appendix B.3: 5-Point Patient Rating of Treatment Satisfactoriness.

The assessment will be completed at 8 hours after treatment initiation, prior to discharge from the research center (before 8-hour post-dose PK and safety lab collection), or at least 5 minutes prior to first rescue analgesic dose, and/or early discontinuation.

6.4. Safety Assessments Description

6.4.1. Clinical Laboratory Tests

During the screening visit, at the 8-hour discharge or early discontinuation, subjects will have blood samples collected for routine clinical laboratory testing. Clinical laboratory testing should only be performed at the end of study visit on Day 7 if there is a clinically significant abnormality or ongoing AE(s). The hematology, coagulation profile, serum chemistry, and serology parameters, as well as urinalysis parameters that will be evaluated at each of these times is listed in APPENDIX C: PANEL OF CLINICAL LABORATORY TESTS

In addition, a urine drug screen and alcohol breath test will be conducted at the screening visit, and during admission/Check-in to the study unit on Day 1. Urine drug

screen will include urine screen for cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine (PCP), benzodiazepines, barbiturates, methadone, oxycodone, ecstasy (MDMA), and propoxyphene.

Urine pregnancy testing will be completed at the screening visit, at prior to surgery on Day 1 and at the end of study visit at Day 7.

Clinical safety laboratory test will also be collected at time of termination from the study for subjects who prematurely discontinue study participation.

6.4.2. Vital Sign Measurements

Resting vital signs (VS) will include resting blood pressure, resting pulse rate, and respiratory rate. Resting tests must be obtained after resting (seated or supine with ECG leads connected, consistently applied) for ≥ 5 minutes. Resting 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 time of early discontinuation, and at the end of study visit on Day 7 (± 3 days). Screening resting vital signs will be done in 3 determinations about 2 minutes apart to ascertain subject's true baseline heart rate and blood pressure values.

Vital signs may be checked at additional times on an *ad hoc* basis per the judgment of the Investigator or study staff. VS will have a ±30-minute window.

Actual times will be recorded for all events, and any deviation outside the specified healthy subject ranges must be clearly documented in the subject's study records. The Investigator or the Sponsor's Medical Monitor may exercise his/her judgment to terminate a subject's participation in the study due to clinically significant changes in any clinical parameter.

6.4.3. Electrocardiograms

A 12-lead ECG will be completed for all subjects 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). At the Screening Visit, the12-lead ECG will be used to exclude subjects with a clinically significant abnormal ECG. ECGs will have a ± 45 minute window.

The findings (i.e., classification as "normal", "abnormal not clinically significant" or "abnormal clinically significant will be recorded in the subject's CRF.

6.5. Assessments by Visit

6.5.1. Screening Visit

Subjects meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained to them, and they have voluntarily granted written informed consent to participate. All subjects will have a screening evaluation within 28 days before study drug administration. After informed consent is obtained, the following procedures will be performed at the screening visit for all subjects:

- Review of inclusion/exclusion criteria eligibility

- Demographics and medical/medicinal history (Section 6.3.2)
- Dental examination and panoramic x-ray (Section 6.3.4)
- Physical examination (Section 6.3.3)
- Measurement of body weight and height and calculation of BMI (Section 6.3.3)
- 12-lead ECG (Section 6.4.3)
- Measurement of resting vital signs (Section 6.4.2)
- Clinical laboratory tests (Section 6.4.1)
- Drug and alcohol screen (Section 6.4.1)
- Urine pregnancy test for women of childbearing potential (Section 6.4.1)
- Assessment and monitoring of AEs (Section 7)

6.5.2. Day 1 (Prior to surgery)

The subjects will be admitted to the study unit on the morning of the surgical procedure and the following assessments will be conducted on the day of Check-in (Day 1 prior to surgery) for all subjects:

- Medical/Medicinal history update (Section 6.3.2)
- 12-lead ECG (Section 6.4.3)
- Measurement of resting vital signs (Section 6.4.2)
- Drug and alcohol screen (Section 6.4.1)
- Urine pregnancy test (Section 6.4.1)
- Eligibility assessment. Subjects who continue to meet pre-operative eligibility criteria will undergo two mandibular third molar extractions per Section 5.1.
- Patient training program for pain assessments (Section 6.3.5)
- Assessment and monitoring of AEs (Section 7)

6.5.3. Day 1 (After surgery/Pre-dose Baseline)

The following assessments will be conducted on Day 1 after surgery prior to administration of Dose 1 (T0) for all subjects while confined at the study clinic:

- Assessment of baseline pain intensity (4-point categorical pain intensity (PI) scale and 11-point numerical pain rating scale (NPRS) (Section 6.3.5)
- 12-lead ECG (Section 6.4.3)
- Measurement of resting vital signs pre-dose (Section 6.4.2)
- Pre-dose PK sample collection (Section 6.2)
- Randomization, if subject meets I/E criteria

- Monitoring of AEs and concomitant medication (Section 7)

Dosing: Subject who meet post-operative inclusion criteria and are randomized into the study will receive the study drug per randomization assignment within 15 minutes of meeting qualifying baseline pain scores. The time of the study drug administration will be designated as T0.

6.5.4. Day 1 (Post Dose)

The following assessments will be conducted after surgery following administration of the study drug for all subjects while confined at the study clinic:

- 11-point Pain Intensity Numerical Rating Scale (NPRS) and 5-point Categorical Pain Relief Scale (PR) assessments at baseline, 15, 30, 45 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after study drug administration (T_0). (Sections 6.3.5 and 6.3.6)
- Measurement of time to pain relief via the 'two stopwatch' method (Section 6.3.7)
- Administer Patient Rating of Treatment satisfactoriness at 8 hours after study drug administration, prior to first rescue medication administration, and/or prior to early discontinuation. (Section 6.3.8)
- 12-Lead ECG at 1, 2, 4, and 8 hours after treatment initiation (Section 6.4.3)
- Measurement of resting vital signs at the following time points: at 1, 2, 4, and 8 hours after treatment initiation. (Section 6.4.2)
- A maximum of twelve 4_mL blood samples will be taken from each participant at pre-dose and at 15, 30, and 45 minutes, and at 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours following dosing (Section 6.2).
- Clinical laboratory tests at 8 hours (Section 6.4.1)
- Physical examination at 8 hours (Section 6.3.3)
- Monitoring of AEs and concomitant medication (Section 7)

Pain assessments (NPRS, PR and Patient Assessment of Treatment satisfactoriness), clinical safety lab tests, and 12-lead ECG and other procedures that are scheduled at the 8-hour post dose time point should be collected at the time of early study termination (if it should occur).

6.5.5. End of Study Visit (Day 7 ± 3 days)

The following end of study safety assessments will be conducted for all subjects during the end of study visit on Day 7.

- Physical examination (Section 6.3.3)
- 12-lead ECG (Section 6.4.3)
- Resting Vital signs (Section 6.4.2)

- Clinical laboratory tests, only if there is a clinically significant abnormality or ongoing AE(s) (Section 6.4.1)
- Urine pregnancy test for women of childbearing potential (Section 6.4.1)
- Monitoring of AEs and concomitant medications (Section 7)

Change in concomitant medications after discharge will be documented and reviewed. Clinically significant adverse events, examination or test results will be followed until appropriate resolution can be documented.

In the event of early termination (ET), every attempt should be made to have the subject return to the site to complete procedures listed within this section and in APPENDIX A: .

The efficacy measures utilized in this study are commonly used in clinical studies performed in acute postoperative pain populations. The timing of assessments is intended to evaluate the time to onset of analgesia, duration of effect and magnitude of benefit.

The selected pharmacokinetic sampling times and parameters are appropriate to support the objectives of this study. Sample times will allow evaluation of the rate and extent of absorption of the study dose, and help in establishing exposure-response analysis, if any.

Safety measures used in this study are standard for clinical trials of investigational medications.

6.6. Clinical Stopping Rules

This study will be discontinued if it is determined that there is a significant safety risk posed towards study subjects. Potential safety risks will be evaluated continuously throughout the course of enrollment in the study.

7. ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an Adverse Event (AE), Serious AE (SAE), or Serious Suspected Adverse Reaction (SSAR) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

7.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE.

Examples of an AE include the following:

- significant or unexpected worsening or exacerbation of the condition or indication under study
- exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency or intensity of the condition (e.g., abnormal physical examination finding)
- signs, symptoms, or clinical sequelae of a suspected interaction
- signs, symptoms, or clinical sequelae of a suspected overdose of the study medication or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless non-serious or serious sequelae occur)
- symptoms or behavior suggesting cognitive or psychiatric disturbance

The following examples are <u>not</u> considered AE's:

- medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen
- the disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition

All AE's, whether volunteered, elicited, or noted on physical examination, and regardless of causality or seriousness, will be assessed and recorded in the CRF beginning after administration of study medication through the final follow-up assessment (approximately 7 ± 3 days after the last study drug administration). AE's will be assessed and recorded after administration of study medication through the Day 7

visit (see Sections 7.2 and 7.3). In addition, if the investigator becomes aware of the occurrence of a SAE within 30 days of the last visit, the SAE should be reported as outlined in Section 7.7.

7.2. Definition of a Serious Adverse Event (SAE)

An SAE is defined as any event that meets the following criteria:

- It results in death or is life-threatening (i.e., presents an immediate risk of death from the event as it occurred). (This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- It results in persistent or substantial disability or incapacitation. (This criterion is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle.)
- It results in hospitalization.
- It results in prolongation of an existing hospitalization.
- It is a congenital anomaly or birth defect.
- It requires medical or surgical intervention to prevent any of the above outcomes.

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE.

Social or convenience admission to a hospital or prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE does not meet the definition of an SAE.

7.2.1. SAEs That Occur Before Administration of Study Medication

Before administration of study medication, only SAEs assessed by the investigator as related to study participation (e.g., related to study procedures or a change in existing therapy) will be transcribed onto the SAE reporting form and reported to the sponsor.

7.2.2. SAEs That Occur After Study Completion

If an Investigator becomes aware of an SAE or death that occurs in a subject more than 30 days after the subject receives study medication and that investigator considers the event to be related to the study medication, the investigator is obligated to report the SAE to the sponsor.

7.3. Definition of a Suspected Adverse Reaction (SAR)

A SAR is defined as any adverse event for which there is a reasonable possibility that the adverse event was caused by the study drug. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.4. Definition of a Serious Suspected Adverse Reaction (SSAR)

A SSAR is any Suspected Adverse Reaction that is determined to be serious, based on the outcomes of a SAE described in Section 7.2; i.e. death, life-threatening, causes or prolongs inpatient hospitalization, causes a persistent of significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital abnormality/birth defect.

7.5. Recording and Evaluating Adverse Events and Serious Adverse Events

It is the responsibility of the Investigator to collect all adverse events (AEs), serious and non-serious, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings e.g., "How have you felt since I last saw you?"

For randomized and enrolled patients, AEs will be captured from the time of signing of Informed Consent Form until End of Study or Early Termination. Adverse events/ Serious Adverse Events (SAEs) should be followed to resolution, stabilization, or until 30 days after the last dose of the study drug upon which patients will be referred to their primary medical provider for follow-up.

All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Subjects should be instructed to report any adverse event that they experience to the Investigator, after signing the Informed Consent. Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Pre-existing conditions will be recorded in the subject's source record and eCRF on the Medical History or appropriate page.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as adverse events.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. The Investigator will attempt to establish a diagnosis of the event on the

basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE.

Adverse event reporting will extend from signing of informed consent until End of Study visit /Early Termination visit. All AEs, regardless of the relationship to study drug, will be recorded in the subject source record and eCRF. Standard medical terminology should be used when describing AEs. The anatomical location of the AEs must be specified where applicable.

7.5.1. Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

- mild: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
- severe: an event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. *Severity* is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as *serious,* which is based on the subject's or event's outcome or on action criteria usually associated with events that pose a threat to a subject's life or functioning (see Section 7.2).

7.5.2. Assessment of Causality

The investigator is obligated to use his or her clinical judgment to assess the relationship between the study medication and the occurrence of each AE or SAE. The investigator will assess the relationship to the study medication by using the following criteria:

- **Definitely Related**: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely.
- **Probably Related**: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive.
- **Possibly Related**: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause. Dechallenge is positive.
- **Not Related**: The subject did not receive the study drug **OR** the AE has no temporal relationship to study drug **OR** the AE has a much more likely alternate

etiology **OR** the AE is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial SAE report, it is important that the investigator always make an assessment of causality for every event before transmitting the SAE reporting form and completing the AE CRF page(s). The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his or her opinion of causality in light of follow-up information and amend the SAE reporting form and AE CRF page(s) accordingly.

7.5.3. Assessment of Outcome

All SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The investigator will assess the outcome of the event by using the following terms:

- **Recovered/Resolved**: The event resolved or the subject recovered without sequelae. An event (either serious or non-serious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Recovered/Resolved with sequelae**: The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Not Recovered/Not resolved**: At the end of the study, a non-serious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown**: The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Fatal**

7.5.4. Assessment of Expectedness

For the purposes of IND safety reporting, adverse events and suspected adverse events should be assessed as being expected or unexpected. An AE or SAR is considered unexpected if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

7.6. Follow-up of Adverse Events and Serious Adverse Events

Non-serious AEs will be followed after the last scheduled study visit, until an appropriate resolution can be documented.

After the occurrence of an AE or SAE, the investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs and SAEs documented at a previous visit or contact are designated as ongoing and will be reviewed at subsequent visits or contacts.

SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. The investigator will ensure that follow-up information provided to the sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.

New or updated information will be recorded on the originally completed SAE reporting form and entered into the CRF pages, with all changes signed and dated by the investigator. The updated SAE reporting form should be resubmitted to the sponsor within the time frames outlined in Section 7.7.

7.7. Prompt Reporting of Serious Adverse Events to the Sponsor

Once the investigator determines that an event meets the protocol definition of an SAE, he or she must notify the sponsor (both Medical Monitor and Pharmacovigilance Contact) within 24 hours.

Any SAE or any outcome of death due to any cause, which occurs, during the course of this study, regardless of relationship to study medication, must be reported to the sponsor immediately (within 24 hours of site knowledge).

Complete the SAE details reporting form and forward by email or fax, in parallel, to the following sponsor and Medical Monitor contacts:

Dr. Srinivas Shenoy B., MD	Dr. Shahida Hassan, MD
Principal Scientist Clinical Development	Associate Director- Pharmacovigilance
Dr. Reddy's Laboratories, Inc.	
Fax : 908-450-1510	
Email: srinivasshenoyb@drreddys.com	**Email: SAE@drreddys.com**
Dr. John Ruckle	
Medical Monitor	
Lotus Clinical Research	
Email: MedicalMonitorDFN-15-CD-010@lotuscr.com	

Questions surrounding SAEs or other emergent medical questions should be directed to the medical hotline at 877-508-8727.

Sponsor Pharmacovigilance Contact information:

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

Dr. Reddy's Laboratories, Inc.

North American Pharmacovigilance Center

Email ID: **SAE@drreddys.com**

US Toll-Free Fax Number: +1 **877 445 3741**

Local US Fax Number: **+1 908 450 1510**

SAE Reporting Instructions:

1. All SAEs must be reported immediately (within 24 hours of becoming aware of the event). Please email the signed, scanned copy of the completed SAE form to **SAE@drreddys.com** and **MedicalMonitorDFN-15-CD-010@lotuscr.com** or fax the completed SAE form to fax number: **+1 908 450 1510**.

2. An email acknowledgement of receipt of SAE will be sent to the reporting site within one business day.

In the initial e-mail, the investigator must provide to the sponsor the following CRF pages, completed to the greatest extent possible:

- AE record
- medical history
- prior and concomitant medications

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE. Subject's full names should be redacted from any documents that are not CRFs to protect the subject's identity. The subject initials and subject numbers should be added to these documents as identifiers.

E-mail/ E-Fax transmission is the preferred method to transmit SAE information. In rare circumstances and in the absence of e-mail capacity, notification by fax is acceptable.

If the investigator does not have all information regarding an SAE, he or she must not wait to receive additional information before notifying the sponsor of the event. The form must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the sponsor by using the same procedure and timelines as for an initial report.

7.8. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 7.7, "Prompt Reporting of Serious Adverse Events to the

Sponsor." Reporting of SAEs to the Regulatory Authorities will be the responsibility of the Sponsor. Serious Unexpected Suspected Adverse Reactions (SUSARs) will be reported to the Regulatory Authorities. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that SSARs that are either unexpected or observed with increasing occurrence be reported and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

Investigator letters are prepared according to sponsor policy and are forwarded to the investigators as necessary. An investigator letter is prepared for any SAR that is attributable to study medication, serious, and unexpected. The purpose of the investigator letter is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

The investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB or IEC. It will be Investigator/CRO responsibility to report the SAE to all the participating Investigators during the study.

7.9. Precautions

If a female subject becomes pregnant during the study, study product must be discontinued immediately, the subject should immediately be withdrawn from the study and early termination study procedures must be performed. The subject must be followed through the pregnancy and delivery and up to 4 weeks after delivery for infant status.

Pregnancy occurring during a clinical investigation, although not considered a SAE, must be reported by the Investigator to Sponsor within the same timelines as a SAE (within 24 hours). The Investigator should report the event to the Sponsor immediately and complete the Pregnancy Report Form (see Section 7.7 for contact information).

The expected date of delivery or expected date of the end of the pregnancy should be included in this information. The Investigator is instructed to contact the subject every 3 months until the end of her pregnancy and report the outcome to the sponsor. The Investigator is instructed to contact the subject for 4 weeks after delivery for follow up on infant status.

Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form.

The following outcomes of pregnancy fall under the criteria for serious adverse events and should be reported as such: delivery complications, spontaneous abortion, stillbirth, death of newborn baby, congenital anomaly, and anomaly in a miscarried/stillborn fetus.

8. STATISTICAL METHODOLOGY

8.1. Determination of Sample Size

The sample size of 120 subjects for this study was selected empirically without a formal statistical assumption. However, group sizes of 30-40 per group are typically sensitive in the dental pain model to detect acute drug effects.

8.2. Study Endpoints

8.2.1. Efficacy Endpoints

The primary efficacy endpoint will be the summed pain intensity difference over the first 6 hours (SPID6) between DFN-15 doses and placebo. The comparison of primary interest is DFN-15 doses vs. placebo.

Key secondary efficacy variables will include the following:

- Total Pain Relief (TOTPAR) over 2, 4, 6 and 8 hours using a 5-point categorical scale (TOTPAR2, TOTPAR4, TOTPAR6 and TOTPAR8)
- Summed Pain Intensity Differences (SPID) at 2, 4 and 8 hours post-dose (SPID2, SPID4 and SPID8)
- Time to perceptible and meaningful pain relief as measured by two stopwatch technique
- Proportion of subjects reporting treatment satisfaction outcome as either 2 = good, 3 = very good or 4 = excellent, on the 5-point categorical scale
- Time to use of rescue medication and percentage of patients using rescue medication
- Pain intensity difference at each NPRS time point (15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h)
- Pain relief at each time point (15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h)
- Characterization of plasma pharmacokinetic profiles of DFN-15 doses in fasting conditions (using C_{max} AUC_{0-t}, $T_{max;}$ Other pharmacokinetic parameters like $AUC_{0-0.25}$, $AUC_{0-0.5}$, $AUC_{0-0.75}$, AUC_{0-1}, AUC_{0-2}, AUC_{0-3}, AUC_{0-4}, AUC_{0-6} will also be calculated)

Additional exploratory analysis will be performed and pre-specified in the Statistical Analysis Plan (SAP).

The comparison of primary interest in the study is DFN-15 250 mg dose versus placebo. The other comparisons include DFN-15 125 mg versus placebo, DFN-15 62.5 mg versus placebo and between two DFN-15 dose levels.

8.2.2. Pharmacokinetic Endpoints

Key pharmacokinetic endpoints will be C_{max}, AUC_{0-t} and T_{max}. Other pharmacokinetic parameters like $AUC_{0-0.25}$, $AUC_{0-0.5}$, $AUC_{0-0.75}$, AUC_{0-1}, AUC_{0-2}, AUC_{0-3}, AUC_{0-4}, AUC_{0-6} will also be calculated. Any other additional parameters requiring estimation will be included in the PK Analysis Plan.

8.2.3. Safety Endpoints

The safety endpoints will include the following:

1) incidence of AE's and SAEs
2) incidence of abnormal clinical laboratory tests, including routine blood chemistry and hematology, coagulation parameters and urinalysis
3) incidence of clinically significant changes in vital signs parameters
4) incidence of clinically significant abnormal ECG findings

8.3. General Considerations for Statistical Analysis

8.3.1. Analysis Datasets

Modified Intent-to-Treat (mITT) Analysis Set: The mITT set will include all subjects who receive study drug, and have recorded at least one post dosing efficacy score.

Safety Set: The safety set will include all treated subjects and will be used for safety and tolerability assessments.

Pharmacokinetic Set: The pharmacokinetic set will include all subjects who have received a dose of DFN-15 and have at least one quantifiable concentration of celecoxib in plasma.

Non-compartmental analysis as specified in a PK Analysis Plan will be used to estimate pharmacokinetic parameters and to present descriptive statistics using the Pharmacokinetic Set. Additional exposure-response analysis may be built in the full statistical analysis plan (SAP). Comparisons will be performed at the 0.05 two-sided significance level unless otherwise specified. No adjustments for multiplicity will be performed. Additional details of the analysis will be provided in the SAP and/or the clinical study report. The SAP will supersede the protocol in case of a discrepancy.

8.3.2. Procedures for Handling Missing Data

Unless indicated otherwise no imputation will be done for missing data. However, AEs with missing severity assessments will be tabulated as "severe," and AEs with missing relationship assessments will be tabulated as "related" for the purpose of analysis; and the missing data will be presented in data listing as is.

8.3.2.1. PI and PR Scores Before and After Analgesic Rescue Medication

All subjects are expected to assess their postoperative pain intensity and pain relief according to the pain intensity and pain relief schedule following the administration of study medication; those PI and PR assessments are referenced as the scheduled PIs and PRs. Subjects who require rescue analgesia are expected to report their pain intensity and pain relief within 5 minutes before taking the rescue medication; these PI and PR are referenced as the pre-rescue PI and PR. When the assessment of a scheduled PI and PR are done after the rescue medication the scheduled PI and PR scores will be replaced by the pre-rescue PI and PR scores for the purpose of efficacy analysis. This method is referenced as the Last Observation Carried Forward (LOCF). The original scheduled PI and PR scores will be displayed on data listing along with the 'imputed' PI and PR scores.

8.3.3. Definitions for Assessment Windows

For the purpose of data analysis, *baseline* measures for a given period will be the last measurements taken before the subject receives the study medication.

8.3.4. Derived Variables

Pain intensity scores (range from 0 to 10) should be recorded at pre-dose (Time 0; baseline) and at the defined post-dose intervals. PI data with missing baseline PI score will be excluded from the analysis.

8.3.5.1. PID and SPID

Pain intensity Difference at time t (PID_t) = $PI_0 – PI_t$, where t =15, 30, and 45 minutes, then 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours; PI_0 is baseline PI score.

Percent improvement in pain intensity at time t (% PID_t) = $100*(PI_0 – PI_t)/PI_0$

Time weighted SPID calculations will be computed by multiplying a weight factor to each pain score prior to summation. The weight factor at each time point is the time elapsed since the previous observation.

8.3.4.1. TOTPAR

Time weighted TOTPAR calculations will be computed by multiplying a weight factor to each PR prior to summation. The weight factor at each time point is the time elapsed since the previous observation.

8.4. Study Population Summaries

Population summaries will be provided for the safety analysis set included in this study.

8.4.1. Disposition

The summary tables will provide frequency counts for subject disposition (all treated subjects, subjects who completed the study, subjects who discontinued from the study, and reason for discontinuation) by treatment group and study overall.

Disposition in terms of number of subjects excluded from each analysis sets (mITT, safety and pharmacokinetic) will also be provided by treatment groups and study overall.

8.4.2. Demographics

The demographic summary will include descriptive statistics for age, sex, race, weight, height, and BMI for the overall and by treatment group.

8.4.3. Protocol Violations

All protocol violations and deviations will be identified. Tabulation may provide if data warrant.

8.4.4. Treatment Compliance

Doses of study medication will be administered by the study subjects under observation of study personnel while confined to the study site. The exact time of administration of study medication will be documented within each subject's CRF. No formal summary of treatment compliance will be produced.

8.4.5. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version 1Q2013 or higher.

8.5. Efficacy Analysis

8.5.1. SPID and PID Analyses

Time weighted SPID6 is the primary efficacy endpoint. The difference among the treatment groups for the primary endpoint, as well as the secondary endpoints of SPID2, SPID4 and SPID8 will be evaluated using analysis of variance. Model will be an ANCOVA with treatment as main effect, and baseline PI as a covariate. If multiple centers are enrolled, then center may be added as an exploratory factor and the interaction with treatment will be explored.

A sensitivity analysis will be performed to examine the interaction between the treatment and analysis center. If the interaction is considered significant at 0.10 significant level a subgroup analysis by analysis center will be performed to examine the treatment effect at each site in order to understand the nature of the interaction between the treatment and analysis center.

Analgesic effect of DFN-15 at each dose level compared to placebo will be evaluated using Dunnett's test.

PID at each time point will be summarized with descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for each treatment group; change from baseline within a group will be tested with 1-sample *t*-test. Group mean by time profile will be graphically presented for pain intensity measurements.

8.5.2. TOTPAR and Pain Relief Analyses

The difference among the treatment groups for the secondary endpoints of TOTPAR2, TOTPAR4, TOTPAR6 and TOTPAR8 will be evaluated using analysis of variance with an analysis model and sensitivity analysis similar to that specified for the primary endpoint.

Analgesic effect of DFN-15 at each dose level compared to placebo will be evaluated using Dunnett's test.

PR at each time point will be summarized with descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for each treatment group. Group mean by time profile will be graphically presented for pain relief measurements.

8.5.3. Time to Event End Points

There are 2 types of time to event endpoints in this study:

1) Time to perceptible pain relief and time to meaningful pain relief as measured by two stopwatch technique post first dose of study drug
2) Time to first dose of rescue medication post study drug dose

Time to event endpoints will be derived for each subject. Subjects without the event will be censored at time of last evaluation. Time to analgesic onset and time to rescue will be summarized graphically with Kaplan-Meier curves and compared across treatments using the log-rank test. Estimated percentiles for time to relief will be tabulated by treatment group along with number and percent subjects censored for this analysis. If center effect is significant based on the time weighted SPID6, the log-rank test for time to pain relief will be stratified by analysis center.

8.5.4. Patient Rating of Treatment satisfactoriness

Number and percent of subjects in each satisfaction category (0-poor, 1-fair, 2-good, 3-very good, or 4-excellent) will be tabulated by treatment group. The difference between the groups in global pain control will be evaluated based on proportion of subjects rated their pain control as good, very good, or excellent using Fisher's exact test.

8.5.5. Proportion of Subjects Requiring Rescue Medication

The analysis will evaluate the relative risk (DFN-15 vs. Placebo) of requiring rescue medication during the study. Proportions of subjects who used rescue medication at least once will be tabulated by treatment group; differences between each DFN-15 dose group and placebo will be assessed using the relative risk approach. Observed incidence, estimated relative risk ratio and corresponding 95% CI for the relative risk will be provided.

The number of times rescue medication used during the in-patient 8 hour evaluation phase will also be tabulated by treatment group. Incidence of rescue medication use will be summarized and analyzed with a generalized linear model using a logit link.

8.5.6. Subgroup Analyses for Efficacy

No subgroup analysis for efficacy endpoints is planned. Subgroup analyses may be performed as exploratory analyses if warranted.

8.6. Safety and Tolerability Evaluations

8.6.1. Extent of Exposure

All subjects will be expected to receive a single dose of study medication. No formal evaluation of the extent of exposure will be performed.

8.6.2. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 16 or higher) will be used to classify all AEs with respect to system organ class and preferred term.

Four types of summaries will be produced for the AE summary:

1. an overall summary of AEs: number and percentage of subjects with at least one event and number of events for each severity for all AEs, and SAEs
2. a summary table of AEs and SAEs by system organ class and preferred term and severity
3. a summary table of AEs and SAEs by system organ class and preferred term and causal relationship to the Investigational Drug

4. a summary table of AEs and SAEs by preferred terms in descending order of total incidence

AEs will be tabulated by treatment group and overall. AEs that lead to premature discontinuation from the study or to death will be listed separately via data listings.

8.6.3. Clinical Laboratory Tests

Laboratory values collected at each time point will be summarized by treatment group without formal statistical testing.

8.6.4. Vital Sign Measurements

Resting vital sign values at each time point collected will be summarized by treatment without formal statistical testing.

8.6.5. Electrocardiograms

The number and proportion of subjects with abnormal ECG findings at each time point collected will be tabulated by treatment group. A data listing will be provided for subjects with changes from normal at baseline to abnormal and clinically significant after baseline by treatment.

8.6.6. Subgroup Analyses for Safety Endpoints

No subgroup analysis is planned for safety endpoints.

8.7. Summaries of Pharmacokinetic Endpoints

Pharmacokinetic and pharmacokinetic-pharmacodynamic analyses will be conducted under a separate PK analysis plan.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before any site may initiate the study in that country.

9.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted according to GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007).

9.1.2.1. Ethics Committees

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB or IEC. The investigator agrees to allow the IRB or IEC direct access to all relevant documents. The IRB or IEC must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant documents or data needed for IRB or IEC review and approval of the study. Before investigational products can be shipped to the site, the sponsor must receive copies of the IRB or IEC approval, the approved informed consent form, and any other information that the IRB or IEC has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IRB or IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the IRB or IEC reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining IRB or IEC approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The investigator must promptly forward to the sponsor copies of the IRB or IEC approval of the amended informed consent form or other information and the approved amended informed consent form or other information. IRB or IEC approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IRB or IEC approval can be sought.

9.1.2.2. General Considerations

The ethical standards defined within GCP are intended to ensure the following:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings.
- The potential benefits of the research justify the risks.

Dr. Reddy's Laboratories Limited is the sponsor of study DFN-15-CD-010. The sponsor is responsible for all of the following:

- selecting qualified investigators
- providing investigators with the information they need to conduct the investigation properly
- ensuring proper monitoring of the investigation
- ensuring that appropriate regulatory agencies and all participating investigators are properly informed of significant new information regarding AEs or risks associated with DFN-15.

9.1.3. Informed Consent

The investigator will be provided with a sample informed consent form for this study. Investigators are encouraged to use the sample form; however, they may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final informed consent form must be accepted by the sponsor and approved by the IRB or IEC. Investigators must provide the sponsor with an unsigned copy of the final informed consent form before and after it is approved by the IRB or IEC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the informed consent form, the investigator will be provided with a revised informed consent form. The IRB or IEC must provide written approval of any revisions to the informed consent form in advance of its use.

Investigators must provide subjects with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, and possible risks.

All information in the informed consent form should be provided in a language (whether written or spoken) that is as nontechnical as practical and that is understandable to the subjects.

Before written informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject (or his or her legally authorized representative).

Before a subject undergoes procedures specific to the protocol, the informed consent form must be signed and dated by the subject (or his or her legally authorized representative) and any other signatories as required by the IRB or IEC.

After all required signatures have been obtained, a copy of the informed consent form should be provided to the subject, and the original must be kept on file at the site and made available for review by the sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

9.1.4. Investigator Reporting Requirements

The investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records (first point of entry, either hard copy or electronic), which may include progress notes, medication administration records, operation reports, laboratory reports, discharge summaries, and so on.

A complete description of the investigator's responsibilities is presented in APPENDIX D: .

9.2. Study Monitoring

The sponsor is responsible for ensuring the proper conduct of the study with regard to subject protection, ethics, protocol adherence, site procedures, and integrity of the data. At regular intervals during the study, the investigator will be provided with study monitors and will contact the study site via visits to the site, telephone calls, and letters in order to review study progress and CRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data.

9.3. Quality Assurance

The sponsor, a regulatory authority, or an IRB representative may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to examine systematically and independently all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the sponsor immediately if contacted by a regulatory agency about an inspection at their site.

9.4. Study and Site Closure

If the sponsor, investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that the study site should be closed, this action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study

- submission of knowingly false information from the research facility to the sponsor, study monitor, or regulatory agencies
- failure of the investigator to comply with GCP (e.g., ICH guidelines, regulatory agency guidelines)
- insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- evidence from the blinded data of sufficient technical problems with the study that one could believe with a high degree of certainty that subjects are being exposed to the investigational drug without a realistic expectation of evaluable data
- a decision on the part of the sponsor to suspend or discontinue testing evaluation or development of the product
- failure of the investigator to enroll subjects into the study at an acceptable rate.

9.5. Records Retention

9.5.1. Health Insurance Portability and Accountability Act of 1996

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act and in a form satisfactory to the sponsor.

9.5.2. Financial Disclosure

Financial disclosure is required for this study.

9.5.3. Access to Original Records

Regulatory authorities expect that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 9.1.4) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard-copy and electronic records.

9.5.4. Archiving of Study-Related Documents

Records related to this clinical study must be retained either for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will notify the investigator as to when these documents no longer need to be retained for this use.

9.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, the sponsor will provide the major findings of the study to the investigators.

In addition, details of the study treatment assignment will be provided to the investigators to enable them to review the data to determine the outcome of the study for their subjects.

The sponsor may list and summarize the results from coded samples by subject number in the clinical study report. In this event, the investigator and study staff would have access to the research results and would be able to link the results to a particular subject. The investigator and study staff would be directed to hold this information confidentially.

9.7. Information Disclosure and Inventions

9.7.1. Ownership

All information provided by the sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Dr. Reddy's.

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of Dr. Reddy's and are hereby assigned to Dr. Reddy's.

If a written contract is executed between Dr. Reddy's and the study site for the conduct of the study and that contract includes ownership provisions inconsistent with this statement that contract's ownership provisions shall apply rather than this statement.

9.7.2. Confidentiality

All information provided by Dr. Reddy's and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the investigator or site staff, 2) information that must be disclosed in confidence to an IEC or IRB solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study subject, or 4) study results that may be published as described in Section 9.7.3. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement, that contract's confidentiality provisions shall apply rather than this statement.

9.7.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by Dr. Reddy's. Thereafter, any secondary publications will reference the original publication(s). If no multicenter publication is submitted for publication within 18 months of study database

hard lock, then the site shall be free to disclose its own results, subject to sponsor rights under Section 9.7.1.

Before submitting material for publication, presentation, or use for instructional purposes, or before otherwise disclosing the study results generated by the site (collectively, a "publication"), the investigator shall provide Dr. Reddy's with a copy of the proposed publication and allow Dr. Reddy's a period of at least 90 days to review the proposed publication. Proposed publications shall not include either Dr. Reddy's confidential information (other than the study results) or the personal data (such as name or initials) of any subject.

At Dr. Reddy's request, the submission or other disclosure of a proposed publication will be delayed a further 90 days to allow Dr. Reddy's to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed publication.

If a written contract is executed for the conduct of the study and that contract includes publication provisions inconsistent with this statement, that contract's publication provisions shall apply rather than this statement.

9.7.4. Data Management

The investigator (or designee) will enter subject data by using the FDA Code 21 Part 11 compliant electronic CRF defined by clinical data management and will be performed in accordance with applicable standards and data-cleaning procedures. Database freeze will occur when data management quality-control procedures are completed.

In addition, validated laboratory data will be transmitted electronically from the clinical laboratory to Dr. Reddy's or its designee.

The investigator or designee must record all required data using the previously specified data collection method defined per CRF guidelines; an explanation must be documented for any critical data points. The investigator must sign and date a declaration in the CRF attesting that he or she is responsible for the quality of all data recorded and that the data represent a complete and accurate record of each subject's participation in the study.

Medical coding will use MedDRA version 21.0 or higher for concomitant diseases and AEs, and WHO-DD version March 2018 or later for medications.

9.7.5. Data Security

Access to the data will be strictly controlled.

9.8. Subject Tracking

Drug accountability logs, a subject identification log (to be retained by the Investigator only), and a subject enrollment log will be used to track subject participation in the study.

10. REFERENCES

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11. APPENDIX A: OVERVIEW OF STUDY SCHEDULE

Assessments	**Screening**	**Day 1**			**Day 1 Treatment Period (0H = time of dosing)**													**Dis-charge**	**EOS**
	Day -28 to Day -1	**Check-in / Prior to Surgery**	**Surgery**	**Pre-Dose Baseline**	**0H**	**15 min**	**30 min**	**45 min**	**1H**	**1.5H**	**2H**	**2.5H**	**3H**	**4H**	**5H**	**6H**	**7H**	**8H**	**Day 4 to Day 10**
Informed consent	X																		
Assess I/E eligibility	X	X [a]		X [b]															
Medical/ medicinal history	X	X																	
Demographics/ Weight, height, BMI	X																		
Vital signs [c]	X	X		X					X		X			X				X	X
Physical examination	X																	X	X
Clinical laboratory evaluation (Hematology, Coagulation, Serology, Serum, Urinalysis) [d]	X																	X	X [e]

Assessments	**Screening**	**Day 1**			**Day 1 Treatment Period (0H = time of dosing)**													**Dis-charge**	**EOS**
	Day -28 to Day -1	**Check-in / Prior to Surgery**	**Surgery**	**Pre-Dose Baseline**	**0H**	**15 min**	**30 min**	**45 min**	**1H**	**1.5H**	**2H**	**2.5H**	**3H**	**4H**	**5H**	**6H**	**7H**	**8H**	**Day 4 to Day 10**
Dental examination, including radiologic studies (if applicable)	X																		
Urine pregnancy test (Women of child bearing potential) [f]	X	X																	X
Urine drug screen [g]	X	X																	
Alcohol screen [g]	X	X																	
HIV, hepatitis B&C screen	X																		
12-L ECG [h]	X	X		X					X		X			X				X	X
Third molar extraction			X																
Patient training program (pain assessments)		X																	
4-Point Categorical				X [i]															

Assessments	**Screening**	**Day 1**			**Day 1 Treatment Period (0H = time of dosing)**													**Dis-charge**	**EOS**
	Day -28 to Day -1	**Check-in / Prior to Surgery**	**Surgery**	**Pre-Dose Baseline**	**0H**	**15 min**	**30 min**	**45 min**	**1H**	**1.5H**	**2H**	**2.5H**	**3H**	**4H**	**5H**	**6H**	**7H**	**8H**	**Day 4 to Day 10**
Pain Intensity Scale (PI)																			
11-point Pain Intensity Numerical Rating Scale (NPRS) [j]				X [i]		X	X	X	X	X	X		X	X	X	X	X	X	
5-point Categorical Pain Relief Scale (PR) [k]						X	X	X	X	X	X		X	X	X	X	X	X	
5-point Patient Rating of Treatment satisfactoriness assessment [l]																		X	
Randomization / Study drug administration					X														
PK blood sampling [m]				X [n]		X	X	X	X	X	X	X	X	X		X		X	
Two stopwatch technique for perceptible and meaningful pain relief [o]					X														

Assessments	Screening	Day 1			Day 1 Treatment Period (0H = time of dosing)													Dis-charge	EOS
	Day -28 to Day -1	Check-in / Prior to Surgery	Surgery	Pre-Dose Baseline	0H	15 min	30 min	45 min	1H	1.5H	2H	2.5H	3H	4H	5H	6H	7H	8H	Day 4 to Day 10
AE assessment	←																		→
Record rescue medication use					←													→	
AE monitoring					←														→
Record concomitant medications	←																	→	

a) Assess updates since screening and evaluate for continued eligibility.
b) Subject will be randomized if all I/E criteria are met, including post-operative inclusion criteria.
c) Vitals include systolic and diastolic (seated) blood pressure, pulse rate and respiratory rate, seated or supine. To be completed prior to early withdrawal, prior to pain assessments, when applicable.
d) Clinical laboratory evaluations will be performed according to the schedule in Appendix C. Any of the above laboratory parameters (or any additional laboratory parameter not part of the clinical lab evaluation) may be assessed unscheduled based on the discretion of the investigator during the study, and may be assessed during the study after consultation with the study Medical Monitor, unless needed in emergency to ensure the safety of the subject; in such a case, Medical Monitor should be notified as soon as possible.
e) Day 7, End of study follow-up safety lab draws are to be performed only if there is a clinically significant abnormality or ongoing AE(s).
f) Urine pregnancy test will be performed for all female subjects of child-bearing potential at Screening, Prior to Surgery and Randomization and at End of Study.
g) Urine screen for common drugs of abuse and alcohol breathalyzer test will be performed for all subjects at screening, and prior to admission for surgery (Check-in).
h) For timepoints where ECG coincides with vital signs collection, ECG must be conducted first or concurrently with vital signs. Should pain assessments and PK/ safety lab samples also coincide, ECG and vitals must precede applicable pain assessments, then PK and safety lab draws are to follow pain assessments; see item (l). To be completed prior to early withdrawal, when applicable.
i) Pre-dose assessments only; determines randomization if "moderate" to "severe" baseline pain outcome (PI) and NPRS score ≥5.
j) In addition to the stated assessment schedule, pain intensity will be assessed by the patient using the 11-point NPRS immediately within ±5 minutes of provision of rescue medication. Assessment will also be completed prior to early withdrawal.
k) In addition to the stated pain relief assessment schedule, pain relief will be assessed by the patient using a 5-point categorical pain relief (PR) scale immediately before provision of rescue medication. Assessment will also be completed prior to early withdrawal.
l) Patient Rating of Treatment satisfactoriness' assessment will be completed at 8 hours after treatment initiation, or at time of first provision of rescue medication, whichever is earlier. Assessment will also be completed prior to early withdrawal.
m) Whenever the time of a PK blood sample collection coincides with efficacy assessments, the PK sample will be drawn after the efficacy assessments are taken. Any PK sample within the first hour post-dose (including the sample taken at 1-hour post-dose) may be drawn ±5 minutes within the scheduled time. Any PK sample after the 1st hour post-dose may be drawn ±10 minutes within the scheduled time. The exact clock time of sample collection will be recorded and used in the PK analysis. To be completed prior to early withdrawal, after pain assessments, when applicable.

n) Pharmacokinetic (PK) blood samples drawn during treatment period, Hour 0, will be drawn immediately prior to dosing.
o) All randomized subjects will be provided with two stopwatches at time of study medication administration. 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).

12. APPENDIX B: STUDY-SPECIFIC INFORMATION

12.1. Appendix B.1: Pain Intensity Assessment

4-Point Categorical Pain Intensity Scale Assessment (PI)

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

☐ **None**

☐ **Mild**

☐ **Moderate**

☐ **Severe**

Assessment of Pain Intensity- 11-Point Numerical Pain Rating Scale (NPRS)

On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes your pain NOW.

☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10
No Pain										***worst pain*** **imaginable**

12.2. Appendix B.2: 5-Point Categorical Pain Relief Assessment (PR)

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

- ☐ **None - No Pain Relief**
- ☐ **A Little Pain Relief**
- ☐ **Some Pain Relief**
- ☐ **A Lot of Pain Relief**
- ☐ **Complete Pain Relief**

12.3. Appendix B.3: 5-Point Patient Rating of Treatment Satisfactoriness

The following question will be answered by the subject 8 hours after study treatment initiation, or prior to first rescue analgesic dose, or prior to early discontinuation:

"Overall, please rate how well your pain has been controlled since you received study medication?"

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

13. APPENDIX C: PANEL OF CLINICAL LABORATORY TESTS

Name of Clinical Laboratory Test	Screening	Discharge	End of Study
Hematology			
Total RBC count	√	√	√ *
Hematocrit			
Hemoglobin			
Total Leukocyte count			
Differential Leucocyte count (absolute counts and percentages of Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes and Band forms)			
Total Platelet Count			
Coagulation Parameters			
Prothrombin Time (PT)	√	√	√ *
Activated Plasma Thromboplastin Time (Aptt)			
INR			
Serum Bio-chemistry			
Total Protein	√	√	√ *
Albumin			

Globulin			
A/G ratio			
Serum Electrolytes (Na+, K+, Cl-, HCO_3-)			
Blood Urea Nitrogen			
Serum Creatinine			
Total Bilirubin			
Direct Bilirubin			
ALT			
AST			
Alkaline Phosphatase			
Random/Fasting Blood Glucose			
Total Cholesterol			
Triglycerides			
Serology			
Anti-HIV 1 and 2 Ab titre	√		
HBsAg titre			
Anti-HCV antibody titre			
Urinalysis			
Color and Appearance			

pH	√	√	√ *
Specific Gravity			
Blood			
Proteins			
Glucose			
Nitrites			
Leukocyte Esterase			
Bilirubin			
Urobilinogen			
Microscopy			

***** Day 7, End of study follow-up safety lab draws are to be performed only if there is a clinically significant abnormality or ongoing AE(s). Urine pregnancy tests are to be performed at Day 7, end of study follow-up visit for all female subjects.

14. APPENDIX D: INVESTIGATOR OBLIGATIONS

As an investigator, you are responsible for ensuring that the study is conducted according to the protocol, the signed Statement of Investigator, and all applicable regulations.

Debarment

Individuals ineligible to conduct or be involved with clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Dr. Reddy's. You are required to disclose immediately to the sponsor, in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by FDA under this antifraud law or if any proceeding for debarment is pending or is (to the best of your knowledge) threatened.

Institutional Review Board

You are required to obtain initial and continuing review and approval by an IRB or IEC that complies with the requirements specified in 21 CFR Part 56. Before initiating the trial, you must have written approval from the IRB or IEC for the protocol, informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects. You must submit the Investigator's Brochure and any updates to the IRB or IEC for review. The IRB or IEC must also provide written approval of any amendments to the protocol that affect the conduct of the study and any changes to the informed consent form in advance of use. If the duration of the study is longer than 1 year, re-approval by the IRB or IEC must be obtained on a yearly basis (or at more frequent intervals if required by the IRB or IEC). All IRB or IEC approvals must be forwarded to the sponsor.

You must provide reports of all SAEs from your site to the IRB or IEC. You are also responsible for providing the IRB or IEC with Safety Reports of any SAEs from any other study conducted with the study medication. The latter will be provided to you by the sponsor.

Confidentiality and Safety of Subjects

You are responsible for protecting the rights, safety, and welfare of subjects under your care and for the control of the drug(s) under investigation.

You are responsible for keeping a record of all screened subjects, including full names and last known addresses. All subjects will be identified on the CRFs by initials and subject numbers. Demographic information including date of birth, sex, race and ethnicity will also be recorded on the CRFs. Confidentiality of subject data will be maintained in accordance with local laws.

In addition to your responsibilities for reporting AEs identified during the course of a subject's participation in the study, you must also report any SAEs that occur within 30 days after the last dose of study medication (regardless of relationship to study medication) and any serious adverse drug reactions (SAEs for which you consider that

there is a reasonable possibility that the study medication caused the response) that you become aware of at any time (even if the event occurs more than 30 days after the subject's last exposure to study medication). This obligation is in addition to any protocol-specified requirement for reporting AEs occurring after the last dose of study medication. Please refer to Sections 7.7 and 7.8 of this protocol for contact information and SAE reporting requirements.

Study-Related Records

You are required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

You are required to make all study documentation promptly available for inspection, review, or audit at your study site upon request by the sponsor, its representatives, or any appropriate regulatory agencies.

Accountability of the Investigational Product

You or your designee (i.e., the pharmacist) is responsible for accountability of the investigational product at the site. You or your designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and the return to the sponsor or alternative disposition of any unused product. These records must include dates; quantities; batch, serial, or lot numbers; and expiration dates (if applicable).

You should ensure that the investigational product is used only in accordance with the protocol.