NCT #: NCT03009019

Study ID #: DFN-15-CD-006

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine with or without Aura

Protocol: Version 2.0, 09 May 2017

[redacted]

CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura

Protocol Number:	DFN-15-CD-006
Study Drug/ Investigational Product:	DFN-15, Celecoxib Oral Solution, 120 mg (25 mg/mL)
IND Number:	125,585
Phase:	3
Indication:	Episodic Migraine With or Without Aura in Adults
Sponsor:	Dr. Reddy's Laboratories Ltd. 8-2-337, Road No. 3 Banjara Hills Hyderabad - 500034, Telangana India
Sponsor Agent:	Dr. Reddy's Laboratories Inc. 107 College Road East Princeton, NJ 08540 United States
Protocol Date:	09 May 2017
Protocol Version:	Version 1.0, dated 12 September 2016
Protocol Amendment 1:	Version 2.0, dated 09 May 2017

Protocol Amendment 1

Summary of Changes (v_1.0 to v_2.0)

The following changes were made in Amendment 1 (v_2.0) of the DFN-15-CD-006 Protocol. ***Bold, italicized*** indicates added text; ~~strikethrough~~ indicates removed text:

Section	Revision
Protocol Approval Signatures	Minor administrative changes to signatories to Protocol Amendment 1
1 Synopsis	
Co-Primary Objectives:	To assess the proportion of subjects who are free from their ***Screening*** most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose (first treated DB1 attack)
Co-Primary Endpoints (for first treated DB1 attack):	The proportion of subjects who are free from their ***Screening*** most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose compared between DFN-15 and placebo in the DB1 period.
Secondary Endpoints:	• Revised: The proportion of subjects who are free from nausea, photophobia, and phonophobia at ***15, 30, and 45 minutes and 1, 1.5***, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period • Revised: The proportion of subjects who have pain relief ~~(defined as a reduction in migraine pain from predose severe [Grade 3] or moderate [Grade 2] to mild [Grade 1], or none [Grade 0] pain, respectively)~~ at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period; added definition of headache pain relief as follows: ***Headache pain relief is defined for DB1 as a reduction from moderate or severe pain prior to dosing reduced to mild or none postdose, and for DB2 as moderate or severe pain predose reduced to mild or none postdose, or mild pain predose reduced to none postdose*** • Revised: The proportion of subjects with their ~~predose~~ ***Screening*** MBS (***and have this symptom predose***) absent at 15, 30, and 45 minutes, and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period • Revised: The proportion of subjects who have sustained pain relief at 2 to 24 hours, postdose (i.e., pain-~~free~~ ***relief*** at 2 hours

	postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose compared between DFN-15 and placebo in each DB period • Revised: Treatment satisfaction at 2 hours and 4 hours postdose as determined on a 7-point scale compared between DFN-15 and placebo in each DB period. ***DFN-15 will also be compared to the same question in the baseline PPMQ-R***
4.1 Co-Primary Objectives	• To assess the proportion of subjects who are free from their ***Screening*** most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose (first treated DB1 attack).
4.2 Secondary Objectives	• Revised: To assess the proportion of subjects who are free from nausea, photophobia, and phonophobia at ***15, 30, and 45 minutes and 1, 1.5,*** 2, 4, and 24 hours postdose • Revised: To assess the proportion of subjects with their ~~predose~~ ***Screening*** MBS absent at 15, 30, and 45 minutes and 1, 1.5, 2 (second attack), 4, and 24 hours postdose • Revised: To assess the proportion of subjects who have sustained pain relief at 2 to 24 hours, postdose (i.e., pain-~~free~~ ***relief*** at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose)
6.2 Inclusion Criteria	Modified Inclusion Criteria 2b to include ***bilateral tubal ligation*** to list of acceptable forms of contraception
6.3 Exclusion Criteria	Revised Exclusion Criteria #32: Subjects with any medical condition ***or procedure*** that in the judgment of the Investigator and/or Medical Monitor would confound the objectives of the study (e.g., clinically significant abnormal thyroid-stimulating hormone [TSH] levels, systemic lupus erythematosus, ***a history of gastric bypass surgery or other bariatric procedures***)
6.3.1 Additional Exclusion Criteria Clarification ***for SBP/DBP and QTcF***	Revised for consistency for subjects presenting with a history of uncontrolled hypertension. Revised SBP/DBP from ≥ (greater than or equal to) to **>** ***(greater than***) eg, SBP/DBP **>** 140/90 mmHg
6.3.1 Additional Exclusion Criteria Clarification ***for SBP/DBP and QTcF***	Added detailed procedures for subjects presenting at screening with ECG QTcF >450 msec. Added detailed procedures for ECG QTcF findings at Visits 2 and 3.
7.3 Storage, Packaging, and Labeling	Revised: The study drug will be shipped to a designee at each study site and must be stored in a pharmacy or locked and secured in a storage facility (between 20°C and 25°C [68°F and 77°F], USP controlled room temperature; ***excursions permitted between 15°C***

	and 30°C [59°F and 86°F]) environment, and protected against direct heat, light, and humidity.
9.2 Study Assessments	Revised Table 9-1 Schedule of Assessments as follows: Migraine history (***including MBS for the co-primary analysis***) and current treatment status
9.2.1.1 Screening (Visit 1) (Day -21 to Day -1)	Clarification that subjects were to collect at least 1 migraine episode during the screening period as follows: An eDiary will be dispensed at V1 to collect at least 1 migraine episode ***during the screening period*** and, if ***eligible***, the subject ***will be*** ~~is~~ randomized (V2) and will continue to collect migraine data through end of treatment (V4/ET). Clarification of the following Screening Visit assessment: ➢ Demographics, medical history, prior medications, and migraine history (including associated symptoms ***and MBS for the co-primary analysis***, medications taken for migraine management, satisfaction and headache pain relief with current medication)
9.2.1.4.1 Efficacy Assessments ~~Using eDiary~~	Clarification that subjects were to collect at least 1 migraine episode during the screening period. Added clarification to eDiary assessment process. Subjects will be provided with an eDiary at screening (V1) to collect at least 1 migraine attack ***during the screening period***. ***The migraine episode may be treated with medication the subject currently uses for a migraine during this period, unless otherwise instructed by the Investigator. After at least 1 migraine attack has been recorded in the eDiary, as instructed, the subject will contact the study site to schedule Visit 2 (V2). At V2 (randomization), it will be determined if subjects meet all study requirements and are eligible to continue in the study. If a subject does not meet all requirements, they must return all study equipment that was provided at the Screening Visit.*** If randomized, subjects will continue to collect migraine data (for a migraine attack treated with study drug), study drug, last food intake and fat content, and any rescue medication used to treat a migraine. Subjects will record migraine predose assessments, study drug date and time taken, and postdose efficacy data in real time in the 2 DB periods through V4/ET: Addition of the following statement: ***MBS will also be collected during Screening via Migraine History evaluation and this Screening MBS will be used for the***

	evaluation of the second co-primary endpoint.
9.2.2.5 Twelve-Lead Electrocardiogram	Clarified the following: ***With the exception of QTcF evaluation as specified in Section 6.3.1,*** the overall interpretation and determination of the clinical relevance of ECG findings will be the responsibility of the Investigator, taking into account the central reader's evaluation, and will be recorded in the subject's eCRF.
9.2.2.7 Serious Adverse Events (subsection Breaking the Blind)	Updated explanation of management of breaking the blind to conform with prior Section 8.4 Blinding.
10.2 Analysis Datasets or Populations	Added ***Screened Set*** and ***Randomized Set*** to populations to be analyzed. ***Screened Set*** ***The Screened Set will include all screened subjects. The set of analyses, including subject listings and summary tables of subject disposition, will be analyzed based on all eligible screened subjects who are databased for the study.*** ***Randomized Set*** ***Each DB treatment period will have a Randomized Set. The randomized set for DB1 will include all subjects who give informed consent and are eligible for and randomized into the DB1 treatment period. The randomized set for DB2 will include all subjects in the randomized set for DB1 who are eligible for and are re-randomized into the DB2 treatment period.*** Revised Full Analysis Set to include assessment ***for pain or symptom (among nausea, photophobia, phonophobia)*** in both DB1 and DB2 treatment periods. Revised Safety Population to include eDiary recording: The safety population will include all subjects who receive at least one dose of DB study drug during one or both treatment periods ***and have it recorded in their eDiary***. Revised Per Protocol Population to include endpoint assessments of ***observed and last observation carried forward (LOCF)*** for DB1 treatment period.
10.4.1 Co-Primary Endpoints	• The proportion of subjects who are free from their ***Screening*** MBS among nausea, photophobia, and phonophobia at 2 hours postdose compared between DFN-15 and placebo in the DB1 period.
10.4.2 Secondary	• Revised: The proportion of subjects who are free from nausea, photophobia, and phonophobia at ***15, 30, and 45 minutes and***

Endpoints	***1, 1.5***, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period • Revised: The proportion of subjects who have pain relief ~~(defined as a reduction in migraine pain from predose severe [Grade 3] or moderate [Grade 2] to mild [Grade 1], or none [Grade 0] pain, respectively)~~ at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period; added definition of headache pain relief as follows: ***Headache pain relief is defined for DB1 as a reduction from moderate or severe pain prior to dosing reduced to mild or none postdose, and for DB2 as moderate or severe pain predose reduced to mild or none postdose, or mild pain predose reduced to none postdose*** • Revised: The proportion of subjects with their ~~predose~~ ***Screening*** MBS (***and have this symptom predose***) absent at 15, 30, and 45 minutes, and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period • Revised: To assess the proportion of subjects who have sustained pain relief at 2 to 24 hours, postdose (i.e., pain-~~free~~ ***relief*** at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose compared between DFN-15 and placebo in each DB period • Revised: Treatment satisfaction at 2 hours and 4 hours postdose as determined on a 7-point scale compared between DFN-15 and placebo in each DB period. ***DFN-15 will also be compared to the same question in the baseline PPMQ-R***
10.5.1 Primary Efficacy Analysis	Modified: The first co-primary efficacy endpoint of the proportion of subjects who are free from headache pain at 2 hours after the first dose of study drug taken for a migraine attack with moderate to severe headache pain during the DB1 period, will be analyzed using Fisher's exact test. The second co-primary efficacy endpoint of the proportion of subjects who are free from their ***Screening*** MBS among nausea, photophobia, and phonophobia at 2 hours postdose during the DB1 period will be similarly analyzed using Fisher's exact test. ***A subject's MBS will be obtained at Screening via Migraine History assessment and, for the analysis of the co-primary endpoint, that symptom must be present predose but does not have to be designated as the MBS at predose.***
10.5.3 Exploratory Analysis	Revised: ~~No exploratory analysis is planned~~. ***Exploratory analyses based on predose pain level and predose MBS are planned and details will be provided in the SAP.***
10.7 Determination of	Revised the following paragraph to add term 'Screening' MBS:

Sample Size	The second co-primary endpoint is the comparison of the proportion of subjects who are free from their ***Screening*** MBS among nausea, photophobia, and phonophobia at 2 hours after the first dose of study drug. It is assumed that 28.2% of placebo and 44.7% of DFN-15 (treated) subjects will be free from their ***Screening*** MBS at 2 hours. A sample size of 480 subjects will provide 94% power to detect this assumed difference between placebo and DFN-15 at a 5% (2-sided) level of significance and with a 15% dropout rate.

Protocol Approval Signatures

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura

Protocol Number: DFN-15-CD-006

This study will be conducted according to the Guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Brazil, 2013), the International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (cGCP)

Sponsor Signatory and Medical Monitor

[redacted]

Dr. Reddy's Laboratories Inc.
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9-MAY-2017
Date

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1 Protocol Synopsis

Protocol Number:	DFN-15-CD-006
Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura
Study Drug/ Investigational Product:	DFN-15, Celecoxib Oral Solution, 120 mg (25 mg/mL)
Country:	United States of America
Phase:	3
Co-Primary Objectives:	To assess the proportion of subjects who are pain-free at 2 hours postdose (first treated DB1 attack) To assess the proportion of subjects who are free from their Screening most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose (first treated DB1 attack)
Number of Subjects:	Approximately 600 subjects will be randomized. Subjects who discontinue study participation prior to completing the study will not be replaced.
Study Design:	This is a randomized, 2 double-blind (DB) treatment period study, to be conducted at approximately 45 centers in the United States. Male and female subjects, 18 to 75 years old (inclusive), previously diagnosed with at least 12 months' medical history prior to screening of episodic migraine (per International Classification of Headache Disorders, 3rd edition [beta version][1] [ICHD-3]), who do not have medication overuse, who experience 2 to 8 migraine attacks (with or without aura) per month, with 14 or fewer headache days per month, who can demonstrate 48 hours of headache-free time between migraine attacks, and who meet all inclusion and none of the exclusion criteria and successfully complete all screening procedures, will be randomized in a 1:1 ratio in a DB fashion to receive orally either DFN-15 or matching placebo, to be used in one migraine attack. During the first double-blind (DB1) period, 1 migraine attack will be treated with study drug as soon as (and no more than 1 hour after) experiencing moderate to severe pain level. Subjects will then return to the study site within 2 to 7 days of the first treatment and, if continuing to be eligible, will be re-randomized into a second double-blind (DB2) period to treat another attack at any pain level. They will then return to the study site within 2 to 7 days of the second treatment at the

final visit (Visit 4/early termination [V4/ET]).

Study drug should only be used to treat a new migraine attack, not a recurrence, and there should be at least 48 hours of pain and symptom freedom from a previous attack. Once randomized, the total duration of each subject's participation in the study would be up to 10 weeks from baseline.

During the treatment periods, data regarding the study drug effect and the associated impact on migraine pain, symptoms, functional disability, and subjects' satisfaction with treatment will be collected in real-time in an electronic diary (eDiary) (Section 9.2.1.4.1). After study completion or discontinuation, subjects should be referred to their usual healthcare professional to resume pre-study standard of care, as per the Investigator's discretion.

During the 2 treatment periods of the study, subjects will have an option, if required, to take rescue medication after the 2 hours postdose time point efficacy data have been recorded in the eDiary. Rescue medication will be decided between the Investigator and the subject, exclusive of study prohibited medications. Rescue medication will not be provided by the Sponsor, and its use should be managed by the subject and their Investigator.

Treatment:

For the DB1 period, all subjects will be randomly assigned in a 1:1 ratio to receive either DFN-15 or a matching placebo to be used to treat 1 migraine attack as soon as (and no more than within 1 hour after) experiencing moderate to severe pain. Eligible subjects will then be re-randomized in a 1:1 ratio into the DB2 period to receive either DFN-15 or a matching placebo to treat another migraine attack at any pain level. The migraine attacks and associated treatment and assessments are to be recorded in an eDiary.

Study Duration:

The duration of study participation will be up to approximately 13 weeks, including a screening period of approximately 3 weeks (wherein subjects may be randomized earlier if they meet inclusion/exclusion criteria and headache assessment criteria; the screening period may also be extended based on Investigator judgment and in consultation with the Medical Monitor), 2 DB treatment periods with up to 4 weeks allowed to experience and treat a migraine attack in each, and 2 to 7 days to return to the site after treatment. Once randomized, the total duration of each subject's participation in the study would be up to 10 weeks from baseline.

Study Population:

Male and female subjects, 18 to 75 years old (inclusive), previously diagnosed with at least 12 months' medical history

prior to screening of episodic migraine (per ICHD-3), who do not have medication overuse, who experience 2 to 8 migraine attacks (with or without aura) per month, with 14 or fewer headache days per month, who can demonstrate 48 hours of headache-free time between migraine attacks, and who meet all inclusion and none of the exclusion criteria and successfully complete all screening procedures, will be included.

Migraines can be with or without aura.

Subjects with medication overuse, subjects who use mini-prophylaxis for menstrual migraine, subjects who have been on unstable doses of migraine prophylactic medications within 30 days prior to and through screening, and subjects with a history of migralepsy will be excluded. See inclusion and exclusion criteria for additional study entry requirements.

Co-Primary Endpoints (for first treated DB1 attack):

- The proportion of subjects who are pain-free 2 hours postdose compared between DFN-15 and placebo in the DB1 period (defined as a reduction from predose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]).

- The proportion of subjects who are free from their Screening most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose compared between DFN-15 and placebo in the DB1 period.

Secondary Endpoints:

- The proportion of subjects with treatment-emergent adverse events (TEAEs) after study drug compared between DFN-15 and placebo.
- The proportion of subjects who are free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- Time to meaningful pain relief (defined as based on subject's perception) within 2 hours postdose compared between DFN-15 and placebo in each treated attack in each DB period.
- Time to pain freedom within 2 hours postdose compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who have pain relief at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period. Headache pain relief is defined for DB1 as a reduction from moderate or severe pain prior to dosing reduced to mild or none postdose, and for DB2 as

moderate or severe pain predose reduced to mild or none postdose, or mild pain predose reduced to none postdose.

- The proportion of subjects who are pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- The proportion of subjects with their Screening MBS (and have this symptom predose) absent at 15, 30, and 45 minutes, and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- Change in functional disability score at 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- Among those reporting cutaneous allodynia predose, the proportion of subjects who are pain-free at 2 and 4 hours postdose compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who are pain-free at 2 and 4 hours postdose whose body mass index (BMI) is < 30 vs. subjects whose BMI is ≥ 30, and whose BMI is < 25 vs. subjects whose BMI is ≥ 25 in each DB period.
- The proportion of subjects who have pain recurrence between 2 to 24 hours (i.e., pain-free at 2 hours postdose, with pain [mild, moderate, or severe] reported at 24 hours postdose) compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who have sustained pain relief at 2 to 24 hours postdose (i.e., pain-relief at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who have sustained pain freedom at 2 to 24 hours postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication, and no recurrence of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who use rescue medication after 2 hours (2 to 24 hours) postdose compared between DFN-15 and placebo in each DB period.
- Treatment satisfaction at 2 hours and 4 hours postdose as determined on a 7-point scale compared between DFN-15 and placebo in each DB period. DFN-15 will also be compared to the same question in the baseline PPMQ-R.
- Treatment satisfaction as measured by Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) at 24 hours postdose compared between DFN-15 and placebo in each DB period.

Table of Contents

1.1 List of In-Text Figures

1.2 List of In-Text Tables

2 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
cGCP	current Good Clinical Practice
COX-1, COX-2	cyclooxygenase-1, cyclooxygenase-2
DB	double-blind
DB1	first double-blind [treatment period]
DB2	second double-blind [treatment period]
DBP	diastolic blood pressure
DDM	1-O-n-dodecyl-β-D-maltopyranoside
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ET	early termination
FAS	full analysis set
FDA	United States Food and Drug Administration
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition (beta version)
ID	Identification

IRB	Institutional Review Board
IWRS	interactive web response system
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
PK	Pharmacokinetic
PP	per-protocol
PPMQ-R	Patient Perception of Migraine Questionnaire-Revised
PT	preferred term
QTcF	length of time for the electrical system of the heart to adjust to heart rate using Fridericia correction formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SNRI	serotonin norepinephrine reuptake inhibitors
SOC	system organ class
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
V	Visit
WHO-DD	World Health Organization Drug Dictionary

3 Introduction

Acute migraine is a disabling neurological disorder with clinical findings of headache, often associated with nausea and vomiting. In the United States (US), about 17% of all women and 6% of all men suffer from migraine.

Although the exact mechanism of migraine is not known, the pathophysiology involves a combination of vascular and neurologic events in the brain and cranial meninges brain leading to trigeminal-vascular activation and release of vasoactive peptides.[2] Radiologic findings in migraine patients are characterized by hyper-excitation of neuronal networks in multiple cortical regions, the brainstem, and the trigeminal nerve ganglion.[2-4]

Typical clinical characteristics of migraine headache are unilateral location, pulsating quality, moderate or severe pain, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. It is important to initiate pharmacotherapy as early as possible to abort the migraine before it becomes more resistant to treatment.

Triptans are the mainstay of acute migraine treatment.[5] A current challenge with oral and nasal triptans is a relatively slow rate of absorption with corresponding lag in onset of action resulting in slower pain relief for some migraine patients.[6] Sumatriptan subcutaneous injections have a faster onset of action, but tolerability and patient acceptance are lower than for oral triptans.[7,8] Opioids are another treatment option, but they have a high rate of adverse events (AEs) and abuse potential.[9-11] Guidelines published in 2012 by the American Society of Anesthesiology Task Force on Acute Pain Management recommend minimizing opioids and maximizing non-opioid agents in the control of acute pain.[12]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs with analgesic, antipyretic, and anti-inflammatory effects that act by inhibition of prostaglandin biosynthesis through isoenzymes, cyclooxygenase (COX)-1 and COX-2.[13] NSAIDs that selectively inhibit the COX-2 enzyme target those prostaglandins that are responsible for inflammation and pain (synthesized involving COX-2) while sparing the prostaglandins that are responsible for the maintenance and protection of the gastrointestinal (GI) tract (synthesized involving COX-1). Thus, the analgesic efficacy of NSAIDs is associated with inhibition of COX-2, whereas a majority of GI adverse effects, including bleeding and ulcers of the stomach and intestine appear to be related to the inhibition of COX-1. The use of COX-2–selective NSAIDs may provide a therapeutic advantage over non-selective NSAIDs for the acute management of migraine due to reduced incidence of upper GI ulcers and bleeds and less GI upset. Celecoxib, a selective COX-2 inhibitor, is available as an oral capsule in several dosage strengths marketed in the US by Pfizer, Inc. under the brand name Celebrex® for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, and primary dysmenorrhea.

NSAIDs can produce analgesia that is comparable with that observed with opioid administration, while sparing patients many of the opioid-associated side effects such as sedation, nausea and vomiting. The analgesic effect of celecoxib is similar to other NSAIDs.

There is no US Food and Drug Administration (FDA)-approved oral liquid formulation of celecoxib. DFN-15 is a new oral liquid formulation containing the COX-2–selective NSAID, celecoxib. It is proposed that DFN-15 will be administered to migraine patients as an oral liquid in a single dose of 120 mg. Celecoxib is the only active ingredient in the formulation.

DFN-15 or DFN-15 prototypes were investigated in 5 clinical trials that included 3 bioavailability studies (DFN-15-CD-001, DFN-15-CD-003, and DFN-15-CD-004) conducted in healthy volunteers, 1 food-effect study (DFN-15-CD-005) in healthy volunteers, and 1 proof-of-concept Phase 2, placebo-controlled, double-blind (DB), crossover study (DFN-15-CD-002) to demonstrate the tolerability, safety, and efficacy of DFN-15 for the treatment of acute migraine headaches (with or without aura). Details are provided in the DFN-15 Investigator's Brochure.[14]

The rationale for performing clinical studies with DFN-15 is to demonstrate its tolerability, safety, and efficacy for the acute relief of migraine with or without aura. The ultimate aim is to provide an alternative oral liquid NSAID for migraine patients. Dr. Reddy's Laboratories will seek an indication for DFN-15 for the acute treatment of episodic migraine with or without aura.

4 Study Objectives

4.1 Co-Primary Objectives

- To assess the proportion of subjects who are pain-free at 2 hours postdose (first treated DB1 attack).

- To assess the proportion of subjects who are free from their Screening most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose (first treated DB1 attack).

4.2 Secondary Objectives

- Safety and tolerability
- To assess the proportion of subjects who are free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1, 1.5, 2, 4 , and 24 hours postdose
- To assess time to meaningful pain relief
- To assess time to pain freedom
- To assess the proportion of subjects who have pain relief at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose
- To assess the proportion of subjects who are pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (second attack), 4, and 24 hours postdose
- To assess the proportion of subjects with their Screening MBS absent at 15, 30, and 45 minutes and 1, 1.5, 2 (second attack), 4, and 24 hours postdose
- To assess change in functional disability score at 2, 4, and 24 hours postdose
- Among those reporting cutaneous allodynia predose, the proportion who are pain-free at 2 and 4 hours postdose
- To assess the proportion of subjects who are pain-free at 2 and 4 hours postdose whose body mass index (BMI) is < 30 vs. subjects whose BMI is ≥ 30, and whose BMI is < 25 vs. subjects whose BMI is ≥ 25
- The proportion of subjects who have pain recurrence between 2 to 24 hours (i.e., pain-free at 2 hours postdose, with pain [mild, moderate, or severe] reported at 24 hours postdose)
- To assess the proportion of subjects who have sustained pain relief at 2 to 24 hours, postdose (i.e., pain-relief at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose)

- To assess the proportion of subjects who have sustained pain freedom at 2 to 24 hours postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose)
- To assess the proportion of subjects who use rescue medication after 2 hours (2 to 24 hours) postdose
- To assess treatment satisfaction at 2 hours and 4 hours postdose (7-point scale)
- To assess treatment satisfaction as measured by Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) at 24 hours postdose

5 Investigational Plan

5.1 Overall Study Design and Plan

This is a randomized, 2 DB treatment period study, to be conducted at multiple centers in the US. Male and female subjects, 18 to 75 years old (inclusive), previously diagnosed with at least 12 months' medical history prior to screening of episodic migraine (as defined by International Classification of Headache Disorders, 3rd edition [beta version][1] [ICHD-3]), who do not have medication overuse, who experience 2 to 8 migraine attacks (with or without aura) per month, with 14 or fewer headache days per month, who can demonstrate 48 hours of headache-free time between migraine attacks, and who meet all inclusion and none of the exclusion criteria and successfully complete all screening procedures, will be randomized in a 1:1 ratio in a DB fashion to receive orally either DFN-15 or matching placebo, to be used in one migraine attack.

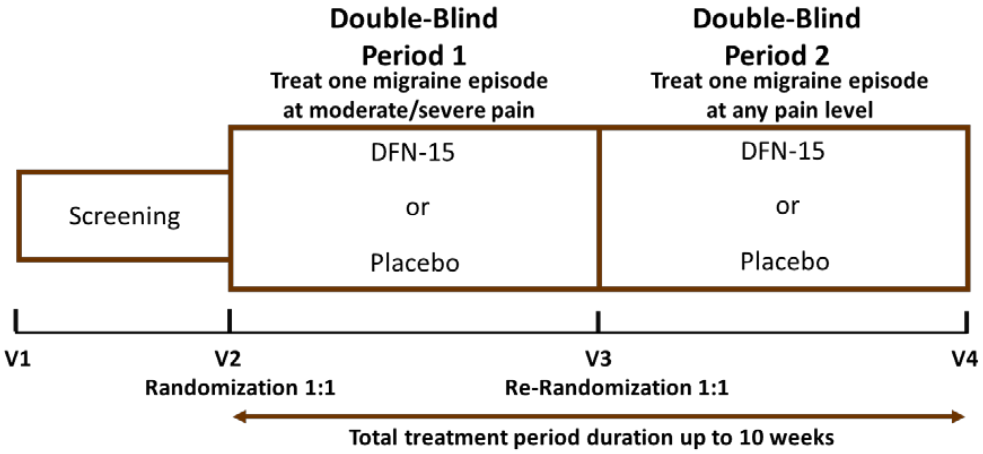
During the first double-blind (DB1) period, 1 migraine attack will be treated with study drug as soon as (and no more than 1 hour after) experiencing moderate to severe pain level. Subjects will then return to the study site within 2 to 7 days of the first treatment and, if continuing to be eligible, will be re-randomized into a second double-blind (DB2) period to treat another attack at any pain level. They will then return to the study site within 2 to 7 days of the second treatment for the final visit (Visit 4/early termination [V4/ET]). See Figure 5-1.

Study drug should only be used to treat a new migraine attack, not a recurrence, and there should be at least 48 hours of pain and symptom freedom from a previous attack. Once randomized, the total duration of each subject's participation in the study would be up to 10 weeks from baseline.

During the treatment periods, data regarding the study drug effect and the associated impact on migraine pain, symptoms, functional disability, and subjects' satisfaction with treatment will be collected in real-time in an electronic diary (eDiary) (Section 9.2.1.4.1). After study completion or discontinuation, subjects should be referred to their usual healthcare professional to resume pre-study standard of care, as per the Investigator's discretion.

During the 2 treatment periods of the study, subjects will have an option, if required, to take rescue medication after the 2 hours postdose time point efficacy data have been recorded in the eDiary. Rescue medication will be decided between the Investigator and the subject, exclusive of study prohibited medications. Rescue medication will not be provided by the Sponsor, and its use should be managed by the subject and their Investigator.

Figure 5-1 Trial Design



5.2 Discussion of Study Design

The current study design was chosen to determine the efficacy of DFN-15 for the acute treatment of episodic migraine with or without aura. A screening period will allow sufficient time for screening laboratory test results availability and verification that subjects meet the inclusion and exclusion criteria.

Subjects will be randomized in a blinded fashion to receive DFN-15 or matching placebo and self-administer when experiencing a migraine attack to determine whether DFN-15 can relieve migraine pain and symptoms and disability compared with placebo. For the first treated acute migraine attack (DB1 period), subjects will treat moderate or severe pain to meet regulatory requirements for efficacy determination; for the second attack (DB2 period), subjects will treat migraine at any pain level to determine if efficacy is achieved throughout the pain level range.

During the treatment periods, subjects will have an option, if required, to take rescue medication after the 2 hours postdose time point efficacy data has been recorded in the eDiary. Rescue medication will be decided between the Investigator and the subject to provide subject comfort while supporting clinically relevant data collection (see Section 8.5.2). Rescue medication will not be provided by the Sponsor, and its use should be managed by the subject and their Investigator.

6 Selection of Subjects and Criteria for Withdrawal

6.1 Number of Planned Subjects

Approximately 600 subjects will be randomized. Subjects who do not qualify for enrollment after the screening period will be terminated as screen failures and will be replaced. Randomized subjects who discontinue study participation before study completion will not be replaced.

6.2 Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Able and willing to provide written informed consent
2. Male or female, 18 to 75 years of age, inclusive, at screening
    a. If female and of childbearing potential, the subject must have a negative serum pregnancy test at screening, does not plan to become pregnant during the study, and is not lactating.
    b. If female and of childbearing potential, the subject must also have a negative urine pregnancy test at all subsequent study visits after the screening visit and, unless surgically or otherwise sterile or postmenopausal for > 1 year, agrees to practice a reliable form of contraception or abstinence during the study. Acceptable forms of contraception include: bilateral tubal ligation, implants, injectables, combined oral contraceptives, an intrauterine device, a vasectomized partner, an exclusively female partner, and double-barrier methods.
    c. If male (with female partner), the subject must agree to practice a reliable form of contraception or abstinence during the study.
3. A history of episodic migraine (per ICHD-3), who experience 2 to 8 migraine attacks per month for at least the past 12 months, with no more than 14 headache days per month, and with 48 hours of headache-free time between migraine attacks.
4. Have migraine with or without aura with onset before age 50 years
5. Report usual migraine pain of 2 (moderate) or 3 (severe) on headache pain severity scale without treatment.
6. Subjects who, in the opinion of the Investigator, are willing and able to:
    a. Evaluate and record pain, migraine symptoms, and study drug effectiveness information in real-time using a subject eDiary for the duration of the study;
    b. Record each instance of the use of study drug and rescue medication in real-time using a subject eDiary for the duration of the study;
    c. Comply with all other study procedures and scheduling requirements.
7. Ability to read, speak, and understand English proficiently.

6.3 Exclusion Criteria

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

1. Minors, even if they are in the specified study age range
2. Exposure to DFN-15 prior to the study
3. Medication overuse:
    - Opioids ≥ 10 days during the 90 days prior to screening
    - Combination medications (e.g., Fiorinal®) ≥ 10 days during the 90 days prior to screening (applies only if includes opioid and/or barbiturate)
    - NSAIDs or other simple medications > 14 days a month during the 90 days prior to screening
    - Triptans or ergots ≥ 10 days a month during the 90 days prior to screening
4. Treated with onabotulinumtoxin A (Botox®) for migraine within 4 months prior to screening. (If treated for cosmetic reasons, subjects may be included).
5. On unstable dosages of migraine prophylactic medications within 30 days prior to and through screening

6. Taking mini-prophylaxis for menstrual migraine
7. On chronic warfarin sodium or equivalent
8. Cerebrovascular events including but not limited to a history of stroke or transient ischemic attack
9. A history of migralepsy (seizure following a migraine) or a concurrent diagnosis of seizure disorder
10. Subjects who cannot differentiate between a migraine headache and tension-type or cluster headache or other types of headache
11. A history of cluster headaches
12. Subjects with the diagnosis of "probable migraine" (per ICHD-3)
13. Subjects who have intolerance to any formulation of celecoxib or sulfonamides, or who have experienced a significant AE related to any other NSAID, including aspirin, which caused the condition of asthma, rhinitis, nasal polyps, or Samter's triad
14. Subjects for whom NSAIDs are contraindicated (e.g., GI bleed, ulcer, history of acute renal failure)
15. Ischemic coronary artery disease including but not limited to angina pectoris, history of myocardial infarction or documented silent ischemia or coronary artery vasospasm, including Prinzmetal's angina; symptomatic peripheral vascular disease
16. A history of congenital heart disease
17. Uncontrolled hypertension or screening systolic/diastolic blood pressure (SBP/DBP) > 140/90 mmHg (the values should be confirmed to rule out a transient elevation); see Section 6.3.1 for details
18. Any abnormal physiology and/or pathology that, in the opinion of the Investigator or Sponsor, would be contraindicated for study participation and would not allow the objectives of the study to be met
19. Subjects who show any clinical laboratory or electrocardiogram (ECG) abnormality that in the opinion of the Investigator or Sponsor would endanger the subject or interfere with the study conduct. If the results of the clinical laboratory or ECG are outside of normal reference range the subject may still be enrolled, but only if these findings are determined to be not clinically significant by the Investigator. This determination must be recorded in the subject's source document before enrollment.
20. Fridericia's corrected QT (QTcF) interval > 450 msec; see Section 6.3.1 for details
21. Serum creatinine > 1.5 × the upper limit of normal (ULN)
22. Serum total bilirubin > 1.5 × ULN
23. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 × ULN
24. Subjects with uncontrolled diabetes mellitus, or a glycosylated hemoglobin (HbA1c) > 7.9%, or with diabetes mellitus requiring insulin
25. A history of alcohol or substance use disorder (including marijuana) according to the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5) within 1 year prior to screening
26. Current treatment with antipsychotics or use of antipsychotics within 30 days prior to randomization (if used for non-psychiatric conditions, should be evaluated on a case-by-case basis with the Medical Monitor)
27. A positive urine drug screen for recreational drugs, alcohol, marijuana (whether legal or not) or for prescription drugs not explained by stated concomitant medications
    - Subjects consuming opioids for the treatment of migraine or using opioids or barbiturates temporarily for a legitimate medical cause may participate as long as they do not meet the medication overuse criteria in Exclusion Criteria #3, above.

- Chronic use of benzodiazepines is allowed if used for legitimate medical use, as long as the regimen has been stable for at least 3 months prior to screening and is expected to remain stable throughout the study
- Chronic use of amphetamines to treat attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) and related disorders is allowed as long as the regimen has been stable for at least 3 months prior to screening and is expected to remain stable throughout the study

Note: For the above-mentioned conditions, the site must have appropriate documentation to justify the mentioned drug use (e.g., documented medical history and a valid prescription-based dispensation)

28. A history of or current neurological or psychiatric impairment including but not limited to psychosis, current major depression, bipolar disorder, or cognitive dysfunction that, in the opinion of the Investigator, would compromise data collection, or any subject who, in the opinion of the Investigator, is at significant risk for suicide
29. Subjects who have received treatment with an investigational drug or device within 30 days of randomization, or participated in a central nervous system clinical trial within 2 months prior to randomization
30. Subjects who have received treatment with CYP2C9 inducers or with CYP2D6 substrates with a narrow therapeutic window (i.e., thioridazine) within 7 days prior to randomization
31. Use of prohibited medications pursuant to Section 8.5.3; non-compliance with wash-out period criteria (Section 8.5.1)
32. Subjects with any medical condition or procedure that in the judgment of the Investigator and/or Medical Monitor would confound the objectives of the study (e.g., clinically significant abnormal thyroid-stimulating hormone [TSH] levels, systemic lupus erythematosus, a history of gastric bypass surgery or other bariatric procedures)
33. Subjects with positive screening test for human immunodeficiency virus [HIV], positive hepatitis B surface antigen (HBsAg), or positive hepatitis C virus [HCV] antibody
34. History of cancer within the past 5 years (except adequately treated basal cell or squamous cell skin carcinoma or in situ cervical cancer)
35. Subjects who should not be enrolled per the precautions, warnings, and contraindications section of the celecoxib product label or package insert[14]
36. Subjects who plan to donate blood, sperm, or oocytes during the study and for 30 days post last dose of study drug
37. Subjects who are employees or immediate relatives of the employees of the Sponsor, any of its affiliates or partners, or of the clinical research study site.

6.3.1 Additional Exclusion Criteria Clarification for SBP/DBP and QTcF

Subjects presenting with a history of hypertension that is uncontrolled during screening (i.e., SBP/DBP > 140/90 mmHg), whether on treatment or not, will be excluded. Subjects who had high or uncontrolled blood pressures in the past and are currently controlled with given therapies would be eligible for this study.

Independent of past history, if a subject has a sustained resting SBP/DBP > 140/90 mmHg at V1 or V2 they should be excluded. If a subject has a sustained SBP/DBP > 140/90 mmHg at a visit after V2, they should be discontinued from the study. Any subject **without** a known history of hypertension that presents at screening with SBP/DBP > 140/90 mmHg should be excluded (if at V1 or V2) or discontinued (if at a visit after V2) if the blood pressure reading is due to suspected hypertension or another pathological condition, not if due to a transient fluctuation, based on the Investigator's evaluation. If the Investigator believes the blood pressure is falsely

elevated, they should repeat the assessment 2 to 3 times with the subject in a semi-reclined position in a quiet room. Subjects with persistent elevations, despite repeat assessments, should be excluded and referred to an appropriate healthcare provider for further assessment.

For subjects presenting at screening with an ECG QTcF >450 msec (based on central ECG interpretation), the following procedures should be conducted:

1. Wait until all other inclusion and exclusion criteria have been satisfied.
2. If the subject otherwise appears eligible for the study, with prior Medical Monitor approval, have the subject return and conduct 2 ECGs with a minimum of 5 minutes between tracings.
3. Transmit these additional ECGs to [redacted] for central interpretation.
4. Based on the central reader interpretation, if both repeat ECGs show a QTcF ≤450 msec, the subject may continue in the study at the Investigator's discretion. If one or both repeat ECGs show QTcF >450 msec, the subject must be screen failed based on Exclusion Criteria #20.

At Visit 2 or Visit 3, additional clarification for QTcF >450 msec (based on [redacted] interpretation) is as follows:

1. For QTcF between 451 msec and 460 msec (inclusive), the subject may continue in the study if the Investigator assesses the ECG as not clinically significant (NCS).

2. For QTcF >460 msec:

    a) Instruct the subject not to take the study drug until further notice.

    b) If the Investigator has assessed the ECG as NCS, have the subject return, after Medical Monitor approval, to conduct 2 ECGs with a minimum of 5 minutes between tracings.

    c) Transmit these additional ECGs to [redacted] for central interpretation.

    d) If one or both ECGs again shows QTcF >460 msec, based on the central reader, then the subject must be discontinued from the study.

6.4 Removal of Subjects from Therapy or Assessments

Subjects are free to withdraw from the study at any time without providing any reason(s) for withdrawal and without prejudice to further treatment. If a subject is to be withdrawn from the study by the Investigator, the Investigator should first alert the Medical Monitor, if safety allows, or as soon as possible thereafter.

Subjects may be withdrawn from the study for any of the following reasons, and the date and reason(s) for withdrawal will be documented in the electronic case report form (eCRF):

1. A subject develops any significant illness, or needs to undergo any acute major surgery, during the course of the study.
2. A subject was enrolled and observed to violate any protocol requirement that may affect the outcome of the study.
3. A subject withdraws consent.
4. The Investigator deems it may not be safe or proper for the subject to continue in the study.

5. A subject is assessed by the Investigator as being a significant risk for suicide.

A subject who becomes pregnant at any time during the study must be discontinued. Subjects prematurely withdrawing from the study after entering the treatment period(s) will be encouraged to complete the early termination (V4/ET) evaluations according to this protocol.

In the event that a subject discontinues prematurely from the study due to a treatment-emergent adverse event (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a subject is withdrawn, they may not re-enter the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. At a minimum, 2 attempts by telephone contact and a certified letter should be sent. These attempts to contact must be documented in the subject's file.

The Sponsor has the right to terminate the study at any time in the event of serious adverse events (SAEs), or if special circumstances occur relating to the study drug that the Sponsor deems unfeasible to continue the study. In this event, the Investigators will be informed of the reason for study termination.

7 Investigational Products

7.1 Investigational Products Administered

DFN-15, Celecoxib Oral Solution, 120 mg (25 mg/mL) dose or placebo (undistinguishable from DFN-15) will be provided as a single dose at each DB treatment period. Details of study treatment information are provided in Table 7-1.

Table 7-1 Investigational Product Details for Study Treatments

Product Code	Preparations to be Administered	
	DFN-15	Placebo
Manufacturer	[redacted]	[redacted]
Celecoxib Dose	120 mg /4.8 mL	0 mg /4.8 mL
Route	Oral	Oral
Formulation	Solution	Solution
Celecoxib Strength	25 mg/mL	0 mg/mL

All study drug supplies (DFN-15 and placebo) will be provided by the Sponsor or Sponsor affiliates. Subjects will be instructed by the site staff on the proper administration of study drug to ensure compliance (see Section 8.6 for additional details on treatment accountability and compliance). Written instructions for use of the study drug will be distributed to Investigator

sites, and subjects should be confirmed to have or be provided with them every time study drug is dispensed. Rescue medication will not be provided by the Sponsor, and its use should be managed by the subject and their Investigator.

7.2 Identity of Investigational Products

Each mL of DFN-15 solution contains 25 mg of celecoxib. The placebo solution contains no active ingredient. Double-blinded DFN-15 and placebo are each provided as a single-dose bottle of a 4.8 mL oral solution. Subjects should shake the bottle well and drink the entire contents (4.8 mL) of the dosing bottle to ensure complete consumption of each dose.

The DFN-15 formulation and the matching placebo are manufactured for Dr. Reddy's Laboratories Ltd, by: [redacted]

The active pharmaceutical ingredient for DFN-15 is manufactured for Dr. Reddy's by: [redacted]. Manufacturing of the study drug was performed according to Good Manufacturing Practice for Medicinal Products and all relevant regulatory requirements. Additional details regarding study drug may be found in the DFN-15 Investigator's Brochure.[14]

7.3 Storage, Packaging, and Labeling

The Sponsor will supply sufficient quantities of DFN-15 oral solution and placebo to allow for completion of this study.

The study drug will be shipped to a designee at each study site and must be stored in a pharmacy or locked and secured in a storage facility (between 20°C and 25°C [68°F and 77°F], USP controlled room temperature; excursions permitted between 15°C and 30°C [59°F and 86°F]) environment, and protected against direct heat, light, and humidity. **Do not refrigerate or freeze product.** The room should be accessible only to authorized individuals. Records will be made of the receipt and dispensation of all study drug.

For the purpose of this clinical trial, DFN-15 will be packaged in amber-colored glass bottles equipped with child-resistant and tamper-evident caps. The subject will be instructed to return all used and unused study drug and all the packaging at their next visit.

The study packaging will be performed by: [redacted].

All packaging and labelling operations will be performed according to Good Manufacturing Practice for Medicinal Products and all relevant regulatory requirements.

8 Administration of Study Treatments

8.1 Method of Assigning Subjects to Treatment Groups

This study is a randomized, 2 DB treatment period, placebo-controlled study. Treatment sequences will be assigned randomly in each DB period with a 1:1 ratio to receive either DFN-15 or matching placebo (Figure 5-1).

8.1.1 Screening (Visit 1)

After written informed consent is obtained and the subject has been confirmed as qualifying to enter the screening period, the Investigator or designee will contact the designated interactive web response system (IWRS) to obtain a unique subject identification (ID) number to be used throughout the study. This subject ID number will not be reused for any other participant in the study. This unique identifier comprises the numerical order of the subjects screened and will be used to identify the subject on the eCRF.

8.1.2 Randomization (Visit 2)

Once a subject's eligibility for enrollment has been confirmed at the end of the screening period, the Investigator (or designee) should contact the IWRS centralized randomization center to receive the subject study drug kit assignment. Subjects who do not meet eligibility criteria will be registered as screen failures. It is important that the study staff reconfirm the subject's willingness to continue in the study before randomizing the subject to a treatment.

The planned treatment given to individual subjects will be determined by a randomization scheme prepared by the biostatistics group of [redacted]. For both DB periods, all subjects will receive orally DFN-15 or a matching placebo in a randomized 1:1 treatment sequencing. As detailed in Section 5.1, subjects will treat 1 migraine attack in the DB1 period and, if eligible, be re-randomized to enter into the DB2 period. The IWRS will assign the appropriate study drug kit to each subject for each treatment period. If a subject discontinues from the study after randomization, the subject ID number will not be reused, and the subject will not be allowed to re-enter the study. Subjects will be required to return unused study drug and the eDiary provided by the site.

8.2 Dose Selection

Test doses of DFN-15, Celecoxib Oral Solution, 120 mg to 240 mg (50 mg/mL) exhibited dose proportional bioavailability. The median time to peak concentration of celecoxib oral solution was faster (0.67 h) compared to Celebrex (2 h). The mean maximum concentration values and mean of partial areas under the curve (AUCs) (from $AUC_{0\text{-}0.25}$ to $AUC_{0\text{-}2.00}$) of DFN-15, Celecoxib Oral Solution 50 mg/mL were higher than Celebrex.

DFN-15, Celecoxib Oral Solution 50 mg/mL showed 60% lower maximum concentration following administration of celecoxib under fed conditions than those following administration under fasting conditions. Overall bioavailability in terms of AUC was comparable under fasting and fed conditions.

A proof-of-concept, randomized, placebo-controlled, DB, crossover study in patients with migraine headaches (with or without aura) showed an increased response with use of DFN-15, with the greatest response in the 120 mg DFN-15 treatment group, although the differences from 240 mg were not statistically significant, suggesting a ceiling effect at 120 mg.

DFN-15, Celecoxib Oral Solution 50 mg/mL was shown to be safe and well tolerated in all studies. Subsequently, DFN-15 is now being developed as a 25 mg/mL oral solution and, considering the outcome from the proof of concept study, a dose of 120 mg for the active arm was selected for the Phase 3 studies. See the DFN-15 Investigator's Brochure for additional information on the completed studies.[14]

8.3 Selection and Timing of Dose for Each Subject

At the end of the screening period, eligible subjects will be randomized to receive study drug (DFN-15 or a matching placebo) as described in Section 5.1. Information about use of study drug, predose and postdose assessments, and any rescue medication taken during the study will be recorded in the eDiary. For dosing information, see Section 7.1.

8.4 Blinding

In order to blind the study treatment, study drug kits with identical labeling appearance will be assigned unique kit numbers by IWRS and the kits will be distributed by [redacted] to the site before the start of dosing.

This is a DB study. All randomization data will be kept strictly confidential and accessible only to authorized personnel until the time of unblinding after database lock at the end of study. Blinding is critical to the integrity of this clinical study; however, in the event of a medical emergency for an individual subject, in which knowledge of the treatment assignment is critical to the subject's management, the blind for the subject may be broken by the Investigator (or designee) by contacting IWRS. Before unblinding, the Investigator (or designee) should have determined that the treatment information is necessary to decide the subject's immediate management, and must make every effort to contact the Medical Monitor before unblinding. In many cases, especially if the emergency is clearly not related to study treatment, the problem may be properly managed without unblinding by assuming that the subject is receiving active treatment. In cases of accidental unblinding or when the Medical Monitor cannot be contacted before unblinding, the Medical Monitor should be contacted as soon as possible after the breaking of the blind and every attempt to preserve the blind for all other study staff should be made.

8.5 Prior and Concomitant Therapy

Investigators should document in the eCRF all prior medications for neurological illnesses and conditions that the subject has experienced anytime in the past, and other prior medications that were taken within 12 weeks before screening. In addition, all concomitant and ongoing medications are to be documented in the eCRF. (See also Section 6.3 Exclusion Criteria and Section 8.5.3 Prohibited and Allowed Medications.)

8.5.1 Medication History

No change in any prophylactic migraine medications will be allowed during the study.

Subjects will be able to continue their prescribed medications for mild, chronic medical conditions as long as the doses of these medications have been stabilized for at least 30 days before screening and the medications are not otherwise prohibited or restricted in the protocol. See Section 8.5.3 for Prohibited and Allowed Medications.

Washout periods: Subjects should not have taken the following medications in the time period described:

- Antipsychotics: at least 30 days prior to randomization (if used for non-psychiatric conditions, should be evaluated on a case-by-case basis with the Medical Monitor)

- Investigational drug(s) or device(s): at least 30 days prior to randomization, or 2 months if associated with central nervous system
- Participated in a central nervous system clinical trial: at least 2 months prior to randomization
- CYP2C9 inducers (i.e., carbamazepine, enzalutamide, nevirapine, phenobarbital, rifampin, secobarbital, St. John's wort): within 7 days prior to randomization; if less than 7 days, the randomization visit may be rescheduled if the subject agrees to and is willing and able to follow prohibitions and restrictions per protocol
- CYP2D6 substrates with a narrow therapeutic window (i.e., thioridazine): within 7 days prior to randomization; if less than 7 days, the randomization visit may be rescheduled if the subject agrees to and is willing and able to follow prohibitions and restrictions per protocol

8.5.2 Rescue Medication

When a subject gets a migraine attack, the study drug should not be taken if the subject has treated an episodic migraine attack acutely with any other medication within the past 48 hours, or if the subject has used an analgesic for non-migraine pain acutely within the past 48 hours.

If a subject does not experience sufficient or any pain relief from the study drug, he/she may take rescue medication, if needed, after 2 hours or more after taking the study drug, and only after completing the 2 hours postdose assessments in the eDiary. The specific rescue medication will initially be decided between the Investigator and the subject before or at V2, but may be adjusted as needed during the treatment period, with the Investigator ensuring that prohibited medications (Section 8.5.3) are not assigned and consulting with the Medical Monitor, if needed. Rescue medication will not be provided by the Sponsor, and its use should be managed by the subject and their Investigator. Rescue medication related decisions should be detailed in the source documents.

Rescue medication, including NSAIDs or other migraine medications, prescription or non-prescription drugs, vitamins, herbal, and dietary supplements (including St John's Wort), should be taken as described above. Subjects should not take prohibited medications listed in Section 8.5.3 as a rescue medication.

8.5.3 Prohibited and Allowed Medications

The following medications should not be taken during the study:

- Antipsychotics (within 30 days prior to randomization; if used for non-psychiatric conditions, should be evaluated on a case-by-case basis with the Medical Monitor)
- Opioids are prohibited if used for ≥ 4 days per month
- CYP2C9 inducers (i.e., carbamazepine, enzalutamide, nevirapine, phenobarbital, rifampin, secobarbital, St. John's wort); drugs in this category must not be taken within 7 days prior to randomization and throughout the study.
- CYP2D6 substrates with a narrow therapeutic window (i.e., thioridazine); drugs in this category must not be taken within 7 days prior to randomization and throughout the study
- Celecoxib should not be taken concomitantly with study drug or used as rescue medication for study migraines
- For any questions regarding prohibited and allowed medications, consult the Medical Monitor

Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and steroids for chronic conditions are allowed during the study if the dose is stable for at least 3 months prior to randomization and is not expected to change during the study. These medications cannot be started during the study. If a subject develops a need for long-term use of one of these medications during the course of the study, the subject must be withdrawn from the trial. Short-term use of these medications during the study is prohibited.

No newly prescribed drugs should be taken by subjects during the study without agreement from the site Investigator. These drugs should not have any drug-drug interactions with the study drug or be contraindicated in the celecoxib product label or package insert.[14]

Subjects will be instructed to refrain from using illicit substances (including marijuana, even if by prescription or legal in the particular state) during the study. See also Section 6.3, Exclusion Criteria.

8.6 Treatment Compliance

Subjects will be instructed by the study site staff on the proper administration of study drug to ensure compliance. Written instructions for use of study drug will be distributed to the Investigator sites, and subjects should be confirmed to have, or be provided with, the instructions every time study drug is dispensed.

See Section 5.1 and Section 8.5.2 for details on timing of dosing with study drug and use of rescue medication.

At the end of the DB1 period (V3), subjects will be required to return all used and unused study drug from DB1 period before any study drug for the DB2 period will be dispensed.

At V4/ET, subjects will be required to return all used and unused study drug, study drug containers, and completed eDiary.

9 Study Procedures

9.1 Duration of Treatment

The duration of study participation will be up to approximately 13 weeks, including a screening period of approximately 3 weeks (wherein subjects may be randomized earlier than 3 weeks provided they meet inclusion/exclusion criteria and headache assessment criteria; the screening period may also be extended beyond 3 weeks based on Investigator judgment and in consultation with the Medical Monitor), 2 DB treatment periods with up to 4 weeks (each period) for subjects to experience and treat migraine attacks, and 2 to 7 days for subjects to return to the site after each treatment. Once randomized, the total duration of each subject's participation in the study would be up to 10 weeks from baseline. Migraine attacks and associated treatment and assessments will be recorded in an eDiary (see Section 9.2.1.4.1).

9.1.1 Data Recording Using eDiary

The eDiary will be used to record migraine attack assessment data in real-time by subjects as described in Section 5.1 and Section 9.2.1.4.1, and as shown in Table 9-2. Due to the episodic nature of the condition, it is important and compulsory for all subjects to check-in the eDiary

every day during the entire study period to ensure presence and eDiary functionality. If a subject does not check-in consistently or if he/she does not report a migraine attack in the eDiary for 2 to 3 weeks, it is recommended that they should be contacted by study staff to check if the subject has technical difficulties or confirm they have not experienced a migraine.

Investigators should train subjects on the proper use of the eDiary and document their understanding of the importance of complying with all data entry requirements and, particularly, the primary endpoints data entry (i.e., 2-hour postdose assessment).

9.2 Study Assessments

Table 9-1 summarizes the planned study assessments.

Table 9-1 Schedule of Assessments

	V1	V2	V3	V4[1]/ET[2]
	Screening	**Randomization**	**End of DB1 period – Re-randomization**	**End of DB2 period (end of study) or ET**
Assessment	**Approximately 21 days[3]**	**Baseline-Day 0** **Study drug dispensed should be used to treat a migraine attack as soon as (and no more than within 1 hour after) experiencing moderate or severe pain. Treatment should be completed within 4 weeks from Baseline.**	**Visit is expected within 2-7 days of treating a migraine attack with study drug dispensed at V2** **Study drug dispensed at this visit should be used within 4 weeks to treat a migraine attack at any pain level.**	**Visit is expected within 2-7 days of treating a migraine attack with study drug dispensed at V3** **Once randomized, the total duration of each subject's participation in the study would be up to 10 weeks from Baseline.**
Informed consent	X			
Inclusion/Exclusion criteria	X	X	X	
Subject eDiary instructions and dispensation[4]	X	X	X	
Adverse events review	X	X	X	X
Demographics	X			
Medical history and prior medications	X	X		
Migraine history (including MBS for the co-primary analysis) and current treatment status	X			
Physical examination and suicidality check[5]	X	X	X	X
Height and weight	X			X[6]
Vital signs (sitting SBP/DBP, pulse rate, body temperature)	X	X	X	X

Serum pregnancy test (hCG)[7]	X			
Urine pregnancy test[8]		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis); TSH at Screening	X	X	X	X
Glycosylated hemoglobin (HbA1c)	X			X
Serology (HIV, hepatitis B surface antigen, and hepatitis C virus antibody)	X			
Urine drug test and ethanol screen	X	X	X	X
12-lead ECG	X	X	X	X
Concomitant medication review			X	X
Randomization (V2)/ Re-randomization (V3)		X	X	
Dispense DB study drug[9]		X	X	
Subject study drug compliance and accountability[10]			X	X
Subjects record data in the eDiary[11]	→	→	→	→
Review, confirm, and ensure proper recording of the subject eDiary entries[12]		X	X	X
Collect eDiary[13]				X
Abbreviations: AE = adverse event; DB = double-blind; DBP = diastolic blood pressure; ECG = electrocardiogram; eDiary = electronic diary; ET = early termination; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; SBP = systolic blood pressure; TSH = thyroid-stimulating hormone; V = Visit				

[1] V4 will occur up to 10 weeks after Baseline (V2).

[2] Subjects who do not complete both DB periods will complete an ET visit.

[3] Subjects may be randomized earlier during this period if they meet inclusion/exclusion criteria and headache assessment criteria. The screening period may also be extended based on Investigator judgment and in consultation with the Medical Monitor.

[4] Before eDiary dispensing, initial screening should determine to the extent possible that the subject may be elig ble for the study and is able, willing, and understands after being instructed how to use the eDiary; eDiary will be dispensed once if the subject is randomized and used throughout the DB periods. At V2, randomized subjects will be instructed and re-trained on the eDiary usage to ensure real-time entry of predose and postdose assessments and the level of migraine pain to treat (moderate or severe for first treatment and of any pain level for the second). Thereafter, randomized subjects will be reinstructed on eDiary usage, and re-trained on instructions as needed.

[5] Physical examination data will be recorded in the source at screening (V1). A complete physical examination will be performed, including examination of head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems. At other visits, symptom-driven limited physical examination will be performed. Any subsequent untoward change during the study will be recorded as an AE. Suicidality risk will be determined and recorded at screening (V1) and checked at all subsequent visits. Significant suicide risk, in the opinion of the Investigator, is exclusionary at V1 and V2. A randomized subject will be discontinued if a significant suicide risk is determined at subsequent visits. At any visit, subjects who are a suicide risk should be referred to a mental health specialist. The Medical Monitor should also be notified.

[6] Weight only.

[7] Serum pregnancy test will be performed at screening (V1) for all female subjects of childbearing potential.

[8] Urine pregnancy tests will be performed at all study visits after screening for all female subjects of childbearing potential.

[9] Subjects will be instructed by the study site staff on the proper administration of study drug to ensure compliance. Written instructions for use of the study drug will be distributed to Investigator sites and subjects should be confirmed to have, or be provided with, the instructions every time study drug is dispensed.

[10] Unused study drug returned by subjects should not be redispensed.

[11] When the subject experiences a migraine episode they should contact the site within 1 day of treating with study drug to schedule their next visit. The eDiary will be used to record all migraine attacks treated with study drug during the study period.

[12] Screening eDiary information will be kept in the source. It is compulsory for all subjects to check-in the eDiary every day during the entire study period. If a subject does not consistently check-in or does not report a migraine attack in the eDiary for 2-3 weeks, it is recommended they should be contacted by study staff to check if the subject has technical difficulties or confirm they have not experienced a migraine.

[13] Arrangements should be made by the site for a timely return of the eDiary device for subjects who screen fail.

Table 9-2 eDiary Assessments

Assessment/Time	Baseline	DB1 and DB2 Treatment Period				
		Predose	Postdose			
			15, 30, 45 min	1 h and 1.5 h	2 h and 4 h	24 h
Migraine date/time and aura information, study drug, last food intake and fat content, and rescue medication taken for migraine attacks	As applicable[1]					
Time to meaningful pain relief (based on subject's perception)			As applicable up to 2 h postdose			
Time to pain freedom			As applicable up to 2 h postdose			
Pain level		X	X	X	X	X
Functional disability		X			X	X
Presence of nausea/photophobia/phonophobia/and cutaneous allodynia		X	X	X	X	X
Most bothersome symptom (selected between nausea, photophobia and phonophobia)[2]		X				
PPMQ-R	X					X
Subject treatment satisfaction					X[3]	

Abbreviations: h = hour(s); min = minutes; PPMQ-R = Patient Perception of Migraine Questionnaire-Revised

[1] End of migraine pain may occur more than 24 hours postdose.

[2] The most bothersome symptom will be collected only if more than 1 symptom is present predose; if only 1 symptom is present, it will be considered the most bothersome.

[3] Treatment satisfaction baseline for the migraine medication to be collected before randomization in the PPMQ-R.

9.2.1 Visit Procedures

9.2.1.1 Screening (Visit 1) (Day -21 to Day -1)

Written informed consent will be obtained before any study assessments are performed. Screening may take approximately 21 days before enrollment. Subjects may be randomized earlier during this period if they meet inclusion/exclusion criteria and headache assessment criteria. The screening period may also be extended based on Investigator judgment and in consultation with the Medical Monitor.

An eDiary will be dispensed at V1 to collect at least 1 migraine episode during the screening period and, if eligible, the subject will be randomized (V2) and will continue to collect migraine data through end of treatment (V4/ET). See eDiary assessments in Section 9.2.1.4.1. The following assessments will be performed at screening (V1):

- Written informed consent
- Eligibility confirmation per inclusion and exclusion criteria
- Dispense eDiary, instruct subject on use of the diary, and allow subject to demonstrate his/her ability to use the diary correctly
- Review/collection of AEs
- Demographics, medical history, prior medications, and migraine history (including associated symptoms and MBS for the co-primary analysis, medications taken for migraine management, satisfaction and headache pain relief with current medication)
- Physical examination, including weight and height measurements, and suicidality check
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature)
- Serum pregnancy test (human chorionic gonadotropin [hCG]) for female subjects of childbearing potential
- Blood draw for hematology and clinical chemistry, including HbA1c and TSH
- Urine collection for urinalysis
- Serology for HIV, HBsAg, and HCV
- Urine drug test and ethanol screen
- 12-lead ECG

9.2.1.2 Randomization (Visit 2) (Day 0)

At V2, randomized subjects will be instructed and re-trained on eDiary usage to ensure real-time entry of predose and postdose assessments and the level of migraine pain to treat moderate or severe attacks for DB1 period, and pain of any level for the DB2 period. Predose migraine assessments will be allowed to be recorded retrospectively in the event a subject did not follow the instructions.

- Continued eligibility confirmation per inclusion and exclusion criteria
- Review recordings of subject eDiary entries and confirm proper recording and compliance
- Review/collection of AEs
- Medical history and prior medications, including from eDiary entries
- Physical examination (if warranted); suicidality check
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature)
- Urine pregnancy test for female subjects of childbearing potential
- Blood draw for hematology and clinical chemistry
- Urine collection for urinalysis
- Urine drug test and ethanol screen

- 12-lead ECG
- Randomization (DB1 period)
- Dispense study drug and instructions for use
- Confirm subject completes eDiary
- Baseline PPMQ-R questionnaire

9.2.1.3 End of DB1 Period; Re-Randomization to DB2 Period (Visit 3)

At V3, randomized subjects will be reinstructed on eDiary usage to ensure real-time entry of predose and postdose assessments and the level of migraine pain to treat with study drug (at any level for the DB2 period).

- Confirm the following:
  - V3 is to be within 2 to 7 days after treatment of a migraine attack with study drug dispensed at V2 (not applicable to ET)
  - There should be at least 48 hours of pain and symptom freedom from the previously treated migraine attack
- Review recording of subject eDiary entries and confirm proper recording and compliance; retrain on instructed usage, if necessary
- Review/collection of AEs
- Physical examination (if warranted); suicidality check
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature)
- Urine pregnancy test for female subjects of childbearing potential
- Blood draw for hematology and clinical chemistry
- Urine collection for urinalysis
- Urine drug test and ethanol screen
- 12-lead ECG
- Concomitant medication review, including from eDiary entries
- Continued eligibility confirmation
- Confirm previously dispensed study drug is returned, subject compliance, and study drug accountability
- Re-randomization (DB2 period)
- Dispense study drug and instructions for use

9.2.1.4 End of DB2 Period (Visit 4); End of Treatment (or Early Termination)

- Confirm the following:
  - V4 is to be within 2 to 7 days after treatment of a migraine attack with study drug dispensed at V3 (not applicable to ET)
  - From randomization, the total duration of subject's participation in the study would be up to 10 weeks from baseline
- Review/collection of AEs
- Physical examination (if warranted); suicidality check
- Weight of subject
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature)
- Urine pregnancy test for female subjects of childbearing potential
- Blood draw for hematology and clinical chemistry, including HbA1c
- Urine collection for urinalysis
- Urine drug test and ethanol screen
- 12-lead ECG

- Concomitant medication review, including from eDiary entries
- Confirm subject compliance and study drug accountability
- Review, confirm, and ensure proper recording of eDiary entries by subject
- Collection of eDiary; empty study drug containers, and all unused study drug

9.2.1.4.1 Efficacy Assessments

Subjects will be provided with an eDiary at screening (V1) to collect at least 1 migraine attack during the screening period. The migraine episode may be treated with medication the subject currently uses for a migraine during this period, unless otherwise instructed by the Investigator. After at least 1 migraine attack has been recorded in the eDiary, as instructed, the subject will contact the study site to schedule Visit 2 (V2). At V2 (randomization), it will be determined if subjects meet all study requirements and are eligible to continue in the study. If a subject does not meet all requirements, they must return all study equipment that was provided at the Screening Visit. If randomized, subjects will continue to collect migraine data (for a migraine attack treated with study drug), study drug, last food intake and fat content, and any rescue medication used to treat a migraine. Subjects will record migraine predose assessments, study drug date and time taken, and postdose efficacy data in real time in the 2 DB periods through V4/ET:

- Level of headache pain at predose and at various time points postdose (Levels: 0 = none; 1 = mild; 2 = moderate; 3 = severe)
- Time to meaningful pain relief (based on subject's perception) and time to pain-freedom after study drug
- Migraine symptoms and MBS other than pain: nausea, photophobia, and phonophobia at predose and at various time points postdose; allodynia
- Functional disability at predose and at various time points postdose; scale: 0 = no disability, able to function normally; 1 = performance of daily activities mildly impaired, can still do everything but with difficulty; 2 = performance of daily activities moderately impaired, unable to do some things; 3 = performance of daily activities severely impaired, cannot do all or most things, bed rest may be necessary
- Treatment satisfaction (7-point scale)
- PPMQ-R

MBS will also be collected during Screening via Migraine History evaluation and this Screening MBS will be used for the evaluation of the second co-primary endpoint.

9.2.2 Safety Assessments

Safety assessments to be performed (Table 9-1) include the following:

- AEs will be collected from signing of the informed consent form (ICF) at screening (V1) until subject's completion or discontinuation from the study
- Concomitant medication review
- Physical examinations and suicidality check
- Pregnancy tests in female subjects of childbearing potential
- Measurement of vital signs (sitting SBP/DBP, pulse rate, and body temperature)
- Clinical laboratory examination (hematology, chemistry, and urinalysis)
- 12-lead ECG

Visits may be scheduled as needed for AE management. Adverse event and concomitant medication review should be performed at each unscheduled visit. Any protocol-specified safety assessment may be repeated or conducted unscheduled as necessary to ensure subject safety.

9.2.2.1 Physical Examination and Suicidality Check

A complete physical examination will be performed at screening (V1) by the Investigator, or medically qualified designee, and will include examination of the head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems. All findings will be kept in the source document. At all subsequent visits, symptom-driven limited physical examination will be performed and recorded. Any subsequent untoward change during the study will be recorded as an AE. In addition, medical history will be recorded at screening, including smoking history, if applicable.

A suicidality check will be performed at screening (V1), baseline (V2), and at all other visits. In the event a subject is evaluated to be at risk at V1 or V2, in the opinion of the Investigator, the subject will be excluded from the study. A randomized subject will be discontinued if a significant suicide risk is determined at subsequent visits. At any visit, subjects who are found to be a suicide risk will be referred to a mental health specialist. The Medical Monitor should also be notified.

9.2.2.2 Pregnancy

All female subjects of childbearing potential will be required to undergo a serum pregnancy test (hCG) at screening (V1), and a urine pregnancy test (beta hCG) at all subsequent study visits. All subjects confirmed to be pregnant at any time during the study should be immediately discontinued. Female subjects of childbearing potential will be required to use an acceptable form of birth control from screening through the end of participation in the study. Although pregnancy is not an SAE, the procedures to report pregnancies will be the same as the procedures detailed for reporting SAEs (Section 9.2.2.7). Any pregnancy that occurs in a female subject (or female partner of a male subject) during the study, or within 30 days after taking the last dose of study drug, should be reported to Dr. Reddy's Laboratories as described in Section 9.2.2.7. Pregnancies will be followed to the end, whether successful live birth or premature termination, type and date of delivery, any congenital malformations or birth defects, or any other adverse fetal or neonatal outcomes, and reported on a follow-up Pregnancy Report. Sponsor will be notified of all the above pregnancy outcomes. Pregnancy will not be considered an AE.

Male subjects (with female partner) must agree to practice a reliable form of contraception or abstinence during the study.

9.2.2.3 Clinical Laboratory Evaluation

The following clinical laboratory evaluations will be performed in accordance with assessment time points outlined in Table 9-1.

Hematology	Serum chemistry	Urine analysis (dipstick)
Hematocrit (Hct) Hemoglobin (Hb) Glycosylated hemoglobin (HbA1c) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Mean platelet volume Red blood cell (RBC) count Red cell distr bution width White blood cell (WBC) count with differential (absolute/percent basophil count, absolute/percent eosinophil count, absolute/percent lymphocyte count, absolute/percent monocyte count, absolute/percent neutrophil count)	A bumin Alanine aminotransferase (ALT) A kaline phosphatase (ALP) Aspartate aminotransferase (AST) Creatinine Creatine kinase Electrolytes (bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, sodium) Thyroid-stimulating hormone (TSH) Total bilirubin Direct bilirubin Total protein Urea nitrogen Uric acid	Color Appearance Specific gravity pH Protein Glucose Ketones Bilirubin Indicators of blood Urobilinogen Nitrite Leukocyte esterase Automated microscopic examination upon abnormal flagging
Serology tests: Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody analyses		
Urine drug and ethanol screen tests: ethanol, amphetamines, barbiturates, benzodiazepines, cocaine, opiates (including methadone), and tetrahydrocannabinoids (THC), and phencyclidine		
Pregnancy test: Serum pregnancy test will be performed on all female subjects of childbearing potential at screening visit (or at any other time during the study if needed to confirm a suspected pregnancy after a positive urine pregnancy test). A urine pregnancy test will be performed onsite at other time points for all female subjects of childbearing potential.		
Hematology (including HbA1c), clinical chemistry, and urinalysis may be repeated during the study as needed to evaluate a patient's condition. Tests not specified in the protocol may be allowed after discussion with the Sponsor's Medical Monitor or designee.		

Hematology (including HbA1c), TSH, clinical chemistry, urinalysis, urine drug test/ethanol screen, serum pregnancy tests, HIV, HBsAg, and HCV antibody analyses will be performed at the central laboratory (ACM Global Central Laboratory, 160 Elmgrove Park, Rochester, NY 14624). Reference ranges will be supplied by the central lab and will be used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

9.2.2.4 Vital Signs

Vital signs, including pulse rate, sitting SBP/DBP, and body temperature, will be collected at screening (V1) and at each study visit. Vital signs will be recorded after the subject has rested in the sitting position for 5 minutes. (See additional exclusion criteria for SBP/DBP screenings in Section 6.3.1).

Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded at screening and V4/ET, and height (without shoes) will be recorded at screening only.

Start and stop dates of last menstrual cycle for all female subjects of childbearing potential will be recorded at screening and at each study visit.

Vital sign measurements will be repeated if clinically significant per the Investigator's judgment or if machine/equipment errors occur. Out-of-range blood pressure, pulse rate, and body temperature measurements will be repeated at the Investigator's discretion. Any confirmed clinically significant vital sign measurement in the Investigator's opinion must be recorded as medical history or an AE, as applicable.

9.2.2.5 Twelve-Lead Electrocardiogram

A 12-lead resting ECG will be performed at screening (V1), and at every scheduled study visit, and will be reviewed initially by the Investigator for any immediate concerns, and then by a central reader, [redacted] At screening, the Investigator will examine the ECG tracings for signs of cardiac disease that could exclude the subject from the study. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present. [redacted] will provide ECG reports to the sites and [redacted] via a portal. With the exception of QTcF evaluation as specified in Section 6.3.1, the overall interpretation and determination of the clinical relevance of ECG findings will be the responsibility of the Investigator, taking into account the central reader's evaluation, and will be recorded in the subject's eCRF.

9.2.2.6 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a study drug and which does not necessarily have a causal relationship with this treatment. A TEAE is an AE with a start date on or after the initial dose of study drug and up to 5 days after the last dose of study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not related to the study drug. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs. **Migraine headaches will not be captured as AEs.** Migraine headaches will be captured by the subject in the eDiary provided to them.

For the purpose of the site's data collection responsibilities, any untoward event that started or worsened after the ICF was signed until the final end-of-study visit (inclusive) is to be considered an AE.

It is the responsibility of the Investigator to document all AEs that occur during the study. Adverse events will be elicited by asking the subject a non-leading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" Adverse events should be reported on the appropriate page of the eCRF.

Assessment of Severity

Each AE will be assigned a category by the Investigator as follows:

Mild	An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Not Related	The event is clearly due to extraneous causes (e.g., diseases, environment), which should be specified if known; or the event is most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study drug.
Possibly Related	The event is temporally related to study drug use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.
Probably Related	The event is temporally related to study drug use and is consistent with known effects of the study drug and/or improves upon withdrawal of the study drug.
Definitely Related	The event follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response pattern to the study drug and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy and either occurs immediately following study drug administration or improves on stopping the medication or there is a positive reaction at the application site.

Action Taken

The Investigator will report the action taken in the appropriate section of the eCRF, as follows:

- Dose not changed
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

Follow-up of Adverse Events

The Investigator should follow up on subjects with AEs until the events are resolved or until, in the opinion of the Investigator, the events have stabilized or are determined to be chronic. Details of AE resolution must be documented in the eCRF. Subjects who have ongoing AEs at the time of study completion or ET should be followed up for 30 days after receiving the last dose of study drug or until the events resolve, are stabilized, or determined to be chronic, whichever occurs first.

Documentation and Reporting of Adverse Events

Adverse events will be reported and documented in accordance with the procedures outlined in this section. Adverse events will be reported from the time of informed consent through V4/ET and documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])
- Name and contact details of reporter

9.2.2.7 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose:

- Results in death.
- Is life-threatening. An AE is life-threatening if the subject is at immediate risk of death from the event as it occurs (i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF.
- Results in persistent or significant disability/incapacity. An AE is incapacitating or disabling if it results in a substantial or permanent disruption of the subject's ability to carry out normal life functions.
- Is a congenital anomaly/birth defect.

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above (i.e., any event that the Investigator regards as serious that did not strictly meet the criteria above but that may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would

suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the study drug).

Reporting of Serious Adverse Events

Subjects should report all SAEs that occur during the clinical study, or within 30 days of receiving the last dose of study drug, to the Investigator. It is the responsibility of the Investigator to follow the procedures described below, whether or not the SAE is considered to be related to the study drug.

At the first occurrence of an SAE, the Investigator should complete an SAE report and notify the Sponsor within 24 hours of occurrence of the SAE. An SAE report consists of the SAE form, the concomitant medication form, and any available supporting documentation (e.g., hospital discharge summary). A copy of the SAE form must be emailed **within 24 hours** to the attention of [redacted] at:

Dr. Reddy's Laboratories Inc.
Fax: [redacted]
Email: [redacted]

The Investigator should not wait to receive additional information to fully document the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of sufficient clinical concern to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of study drug administration and linked by the Investigator to this study, should be reported to the study Medical Monitor and the Sponsor.

The Sponsor and/or [redacted] will promptly notify all relevant parties of findings that could adversely affect the safety of subjects, influence subjects' desire to continue in the study, impact the conduct of the study, or alter the Institutional Review Board (IRB) approval of the study. In addition, [redacted], on behalf of the Sponsor, will expedite the reporting to all concerned Investigators and to the IRB (where required) of all adverse reactions that are both serious and unexpected. The Sponsor will expedite the reporting of all adverse reactions that are both serious and unexpected and for which there is a reasonable possibility of their being caused by the study drug, to the regulatory authorities as soon as possible but in no case later than 15 calendar days after becoming aware of their occurrence through an IND Safety Report 21 CFR 320.31(d)(3).

If the AE is fatal or life-threatening, and with reasonable possibility of its being related to the study drug, the Sponsor must also notify the FDA as soon as possible, but in no case later than 7 calendar days after becoming aware of its occurrence, by telephone or fax pursuant to 21 CFR 320.31(d)(3).

If the subject took one or more suspect medicinal product(s) other than the study drug, the relevant manufacturer(s) of this medicinal product(s) will be informed about the SAE by the Sponsor if the Investigator assesses there is a reasonable possibility the concomitant drug caused the SAE. The Investigator must provide their causality assessment for any concomitant medication taken by the subject.

Follow-up of Adverse Events

All follow-up reports will be subject to the same reporting timelines as the Initial Reports. Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., subject discharge summary or autopsy reports), should be faxed or emailed to the Sponsor.

The Sponsor must be notified within 5 days if any subject is withdrawn or discontinued study drug use due to an AE.

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AEs have resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, until the subject has died, or until 30 days after the last dose of the study drug upon which subjects will be referred to their primary medical provider for follow-up.

Unblinding Instructions

Breaking the Blind

The blind should be broken for all SAE IND safety reports that are judged to be expedited reports for submission to FDA.

The unblinding procedures and follow-up will be performed in accordance with the protocol and the Sponsor's standard operating procedures (SOPs).

Blinding is critical to the integrity of this clinical study; however, in the event of a medical emergency for an individual subject, in which knowledge of the treatment assignment is critical to the subject's management, the blind for the subject may be broken by the Investigator (or designee) by contacting IWRS. Before unblinding, the Investigator (or designee) should have determined that the treatment information is necessary to decide the subject's immediate management, and must make every effort to contact the Medical Monitor before unblinding. In many cases, especially if the emergency is clearly not related to study treatment, the problem may be properly managed without unblinding by assuming that the subject is receiving active treatment. In cases of accidental unblinding or when the Medical Monitor cannot be contacted before unblinding, the Medical Monitor should be contacted as soon as possible after the breaking of the blind and every attempt to preserve the blind for all other study staff should be made.

If the blind is broken, the date, time, and reason must be recorded in the subject's source record, eCRF, and any associated AE report.

If an Investigator, site personnel performing assessments, or subject is unblinded, the unblinding incident and unblinded subject must be listed as a major protocol deviation.

A subject for whom the blind is broken will discontinue study drug and be scheduled for a safety follow-up visit and then discontinued from the study. The subject will be encouraged to stay in the study until the AE is resolved or stabilized.

For all SAEs observed in the study considered to be drug related, a suspected unexpected serious adverse reaction (SUSAR) will be reported by the Sponsor to the FDA as an unblinded IND Safety Report. All Investigators and the IRB will receive blinded reports. However, on the request of the IRB, the Sponsor will send unblinded reports directly to the IRB.

Laboratory and Vital Signs Variables

Vital signs and laboratory abnormalities should be reported as AEs if they are considered to be clinically significant, as per the Investigator's judgment. If an abnormal laboratory value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE, and the associated abnormal laboratory result should be considered additional information.

Pregnancy

Although pregnancy is not an SAE, the procedures to report pregnancies will be the same as the procedures detailed above for reporting SAEs.

Female subjects should not be pregnant when entering the study and must not become pregnant during the study; see Section 9.2.2.2 for additional details. Following administration of study drug, any known cases of pregnancy in female subjects or male subjects who impregnate their female partners will be reported to the Sponsor within 24 hours of occurrence. All female subjects will be withdrawn from the study and administration of study drug will be stopped. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

Overdose

Overdose is not anticipated in this study as sites will provide randomized subjects with only 1 dose of study drug per visit.

The Investigator must notify the Sponsor of any occurrence of overdose with study drug within 24 hours of becoming aware of the overdose. In the event an overdose leads to an SAE, it will be reported to the regulatory board, and medical management will be done by the Investigator on a case-by-case basis.

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

No overdoses of celecoxib were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (> 97%), dialysis is unlikely to be useful in overdose.

Subjects should be managed with symptomatic and supportive care following an NSAID overdosage; there are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within 4 hours of ingestion or in subjects with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For further details, refer to the full celecoxib package insert.[14]

9.2.2.8 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of a study drug at any dose that is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized study drug or approved prescribing information/summary of product characteristics for an authorized product).

All SUSARs will be subject to expedited reporting. The Sponsor and/or [redacted] shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and the IRB within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the FDA and the IRB within 15 days after knowledge by the Sponsor of such cases. The Investigator should follow up on each SUSAR until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Post-study SUSARs that occur within 30 days after the subject has completed the clinical study must be reported by the Investigator to the Sponsor.

Warnings and Precautions

The following warnings and precautions have been issued for celecoxib:

Do not use this product if you had an allergic reaction (including asthma), urticaria, or other allergic-type reactions after taking celecoxib, aspirin, or other NSAID, or right before or after coronary artery bypass graft (CABG) surgery. Use caution if you have a history of ulcers or other stomach problems, kidney or liver disease, anemia, aspirin-sensitive asthma, high blood pressure, congestive heart failure or other heart or circulation problems. This medicine may cause the following problems: serious liver problem; bleeding in your stomach or intestines; and increased risk for a heart attack or stroke. For further details, refer to the full celecoxib package insert.[14]

9.2.3 Appropriateness of Measurements

All efficacy and safety assessments used in this study are widely used and generally considered reliable and accurate.

10 Statistical Methods

The statistical analysis methods planned for this study are described below. Additional details will be provided in the Statistical Analysis Plan (SAP), which will be finalized before database lock and unblinding of the data.

In general, descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the co-primary and all secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term "treatment group" refers to treatment assignment: DFN-15 or placebo. All data collected during the study will be included in subject data listings. Unless otherwise noted, the data will be sorted first by treatment assignment, subject number, and then by date within each subject number.

All statistical analyses are described in Section 10.6. Unless specified otherwise, all statistical testing and confidence intervals will be 2-sided and will be performed using a significance (alpha) level of 0.05.

All statistical analyses will be conducted with the SAS® software package version 9.3 or higher.

10.1 Statistical Analysis Plan

A SAP will be created and approved before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

A blinded data review will be conducted before unblinding of subject's treatment assignment at database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

10.2 Analysis Datasets or Populations

Screened Set

The Screened Set will include all screened subjects. The set of analyses, including subject listings and summary tables of subject disposition, will be analyzed based on all eligible screened subjects who are databased for the study.

Randomized Set

Each DB treatment period will have a Randomized Set. The randomized set for DB1 will include all subjects who give informed consent and are eligible for and randomized into the DB1 treatment period. The randomized set for DB2 will include all subjects in the randomized set for DB1 who are eligible for and are re-randomized into the DB2 treatment period.

Full Analysis Set

Each DB treatment period will have a full analysis set (FAS), which will include all randomized subjects who during the treatment period took at least one dose of study drug and have at least

1 post-baseline efficacy assessment for either pain or symptom (among nausea, photophobia, phonophobia). Subjects in DB1 will be analyzed according to their randomized treatment. Subjects in DB2 will be analyzed according to their re-randomized treatment. The FAS will be used for all analyses of efficacy endpoints.

Safety Population

The safety population will include all subjects who receive at least one dose of DB study drug during one or both treatment periods and have it recorded in their eDiary. Each DB treatment period will have a safety population which will include all subjects who were randomized in the DB treatment period and who received at least one dose of DB study drug during the treatment period.

Additional information is included in the SAP. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

Per-Protocol Population

The per-protocol (PP) population will include all DB1 FAS subjects who have at least 1 post-baseline endpoint assessment for both co-primary endpoints (observed and last observation carried forward [LOCF]), and who have no significant protocol deviations that will impact the collection or interpretation of the co-primary endpoints data during the DB1 period. Identification of all subjects in the PP population will be determined before the database lock and unblinding.

10.3 Demographic and Other Baseline Characteristics

Subject disposition and demographics will be presented and described in the SAP.

Demographics and baseline characteristics will be summarized descriptively, and all collected demographics and baseline characteristics data will be listed.

10.4 Efficacy Endpoints

10.4.1 Co-Primary Endpoints (for first treated DB1 attack only)

- The proportion of subjects who are pain-free 2 hours postdose compared between DFN-15 and placebo in the DB1 period (defined as a reduction from predose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]).
- The proportion of subjects who are free from their Screening MBS among nausea, photophobia, and phonophobia at 2 hours postdose compared between DFN-15 and placebo in the DB1 period.

10.4.2 Secondary Endpoints:

- The proportion of subjects with TEAEs after study drug compared between DFN-15 and placebo.
- The proportion of subjects who are free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1,1.5, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- Time to meaningful pain relief (defined as based on subject's perception) within 2 hours postdose compared between DFN-15 and placebo in each treated attack in each DB period.

- Time to pain freedom within 2 hours postdose compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who have pain relief at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period. Headache pain relief is defined for DB1 as a reduction from moderate or severe pain prior to dosing reduced to mild or none postdose, and for DB2 as moderate or severe pain predose reduced to mild or none postdose, or mild pain predose reduced to none postdose
- The proportion of subjects who are pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- The proportion of subjects with their Screening MBS (and have this symptom predose) absent at 15, 30, and 45 minutes, and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- Change in functional disability score at 2, 4, and 24 hours postdose compared between DFN-15 and placebo in each DB period.
- Among those reporting cutaneous allodynia predose, the proportion of subjects who are pain-free at 2 and 4 hours postdose compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who are pain-free at 2 and 4 hours postdose whose BMI is < 30 vs. subjects whose BMI is ≥ 30, and whose BMI is < 25 vs. subjects whose BMI is ≥ 25 in each DB period.
- The proportion of subjects who have pain recurrence between 2 to 24 hours (i.e., pain-free at 2 hours postdose, with pain [mild, moderate, or severe] reported at 24 hours postdose) compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who have sustained pain relief at 2 to 24 hours postdose (i.e., pain-relief at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who have sustained pain freedom at 2 to 24 hours postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication, and no recurrence of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo in each DB period.
- The proportion of subjects who use rescue medication after 2 hours (2 to 24 hours) postdose compared between DFN-15 and placebo in each DB period.
- Treatment satisfaction at 2 hours and 4 hours postdose as determined on a 7-point scale compared between DFN-15 and placebo in each DB period. DFN-15 will also be compared to the same question in the baseline PPMQ-R.
- Treatment satisfaction as measured by PPMQ-R at 24 hours postdose compared between DFN-15 and placebo in each DB period.

10.5 Methods of Analysis

10.5.1 Primary Efficacy Analysis

Efficacy analyses for the co-primary and secondary endpoints will be based on the FAS population.

The first co-primary efficacy endpoint of the proportion of subjects who are free from headache pain at 2 hours after the first dose of study drug taken for a migraine attack with moderate to severe headache pain during the DB1 period, will be analyzed using Fisher's exact test. The

second co-primary efficacy endpoint of the proportion of subjects who are free from their Screening MBS among nausea, photophobia, and phonophobia at 2 hours postdose during the DB1 period will be similarly analyzed using Fisher's exact test. A subject's MBS will be obtained at Screening via Migraine History assessment and, for the analysis of the co-primary endpoint, that symptom must be present predose but does not have to be designated as the MBS at predose.

Analyses will be performed using the last observation carried forward (LOCF) and observed data in the FAS population and PP population.

10.5.2 Secondary Endpoint Analysis

The analysis and presentation of the secondary efficacy endpoints will be described in the SAP.

10.5.3 Exploratory Analysis

Exploratory analyses based on predose pain level and predose MBS are planned and details will be provided in the SAP.

10.5.4 Subgroup Analysis

Subgroup analyses will be performed as needed, and details will be documented in the SAP.

10.5.5 Additional Efficacy Analyses

Other possible analyses and further statistical details, if applicable, will be provided in the SAP.

10.5.6 Safety Analysis

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher. A TEAE is an AE with a start date on or after the initial dose of study drug and up to 5 days after the last dose of study drug. Only TEAEs will be included in summary tables. Migraine headaches will not be captured as AEs. Migraine headaches will be captured by the subject in the eDiary provided to them at screening. The information will then be entered into the appropriate eCRF page.

The incidence of all TEAEs will be tabulated by treatment received. These TEAEs will be classified by system organ class (SOC) and preferred term (PT). For incidence reporting, if a subject reported more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT.

An overview of AEs, which includes subject incidence of TEAEs, headache or migraine-related TEAEs, study drug-related TEAEs, and SAEs, will be presented. The subject incidence of TEAEs, headache- or migraine-related TEAEs, study drug-related TEAEs, and SAEs will be summarized by SOC and PT.

Treatment-emergent adverse events will also be summarized in a table by severity. For TEAEs presented by severity, the worst severity during the study will be presented for each subject, SOC, and PT.

Treatment-emergent adverse events will also be summarized in a table by relationship to study drug. For TEAEs presented by relationship to study drug, the strongest relationship to study drug during the study will be presented for each subject, SOC, and PT.

All AEs will also be presented in a by-subject data listing.

All prior and concomitant medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD), version March 2016 or later. Medications will be considered concomitant if they were taken at any time between the date of first dose and the date of last dose of study drug, inclusive. Medications will be considered as prior if stopped before the date of first dose of study drug during the DB1 period.

Prior and concomitant medications will be summarized in separate tables by ATC level 2 and preferred drug name for the safety population.

One combined listing will be provided for prior and concomitant medications. An identifier will be provided to show if a medication is prior or concomitant.

Electrocardiograms, clinical laboratory data, and vital signs measurements will be summarized by treatment group and time point along with the change from baseline (V2). During the DB period, V2 will be considered as baseline, (i.e., the visit occurring just before treatment). If a subject misses a V2 assessment but has a V1 assessment, V1 will be considered as baseline. All ECG data, clinical laboratory data, vital signs, physical examinations, study drug use, and concomitant medication use will also be presented in by-subject data listings.

10.6 Interim Analyses

No interim analysis is planned.

10.7 Determination of Sample Size

Approximately 600 subjects will be randomized for the DB1 period. Subjects who discontinue participation without completing the study protocol will not be replaced.

The first co-primary endpoint is the comparison of the proportion of subjects who are pain-free at 2 hours after the first dose of study drug. It is assumed that 17.6% of placebo and 29.2% of DFN-15 (treated) subjects will be pain-free at 2 hours. A sample size of 600 subjects will provide 88% power to detect this assumed difference between placebo and DFN-15 at a 5% (2-sided) level of significance and with a 15% dropout rate.

The second co-primary endpoint is the comparison of the proportion of subjects who are free from their Screening MBS among nausea, photophobia, and phonophobia at 2 hours after the first dose of study drug. It is assumed that 28.2% of placebo and 44.7% of DFN-15 (treated) subjects will be free from their Screening MBS at 2 hours. A sample size of 480 subjects will provide 94% power to detect this assumed difference between placebo and DFN-15 at a 5% (2-sided) level of significance and with a 15% dropout rate.

Since the sample size for the first co-primary endpoint is larger than that of the second co-primary endpoint, the larger sample size will be used for the study.

11 Quality Assurance and Quality Control

11.1.1 Audit and Inspection

The study site and study documentation may be subject to quality assurance audit during the course of the study by the Sponsor, [redacted], or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.1.2 Monitoring

Source documents for this study include the eDiary and study files stored at the site. Electronic CRF data collection must be completed for each subject who signs an ICF.

In accordance with cGCP and International Council for Harmonisation (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

The following will be reviewed, at a minimum, at these visits:

- Compliance with the protocol
- Consent procedure
- Source documents
- AE procedures
- Storage and accountability of study drug materials

The monitoring visits also provide the Sponsor with the opportunity to ensure the Investigator's obligations and all applicable ICH or health authority regulation requirements are being fulfilled.

The Investigator must permit the Medical Monitor, the IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs. All efforts to protect subject confidentiality will be upheld.

An electronic medical record may be the source document; however, the study site must provide a SOP that demonstrates the electronic medical record system is compliant with applicable regulations and details the review and approval of data entries by the principal Investigator.

Protocol deviations identified by the site or the study monitor should be reported to the IRB according to the IRB's reporting guidelines. All deviations will be recorded in the [redacted] clinical trial management system and will be categorized as major or minor before data analysis.

11.1.3 Data Management and Coding

[redacted] will be responsible for activities associated with the data management of this study. This will include setting up a relevant database [redacted] and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of [redacted].

Study site staff will enter data directly into the electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study site. Any changes to the data entered into the EDC system will be recorded in the EDC audit trail, which is compliant with FDA Code of Federal Regulations 21 Part 11.

Data entered into the eCRF will be validated as defined in the data validation plan. External data checks will be programmed where appropriate (e.g., for laboratory data, ECGs) as well as for cross table checking between eCRFs (e.g., AE and concomitant medication forms).

Medical coding will use MedDRA version 19.0 or higher for concomitant diseases and AEs, and WHO-DD version March 2016 or later for medications.

Missing or inconsistent data will be queried electronically in the EDC system to the Investigator for clarification. Subsequent modifications to the database will be documented.

12 Records and Supplies

12.1 Drug Accountability

Upon receipt of the study drug, the Investigator (or designee) 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 Investigator will retain a copy of this receipt at the study site and provide the original receipt to the study monitor, to be stored in the trial master file. The inventory of supplies at the study site may be checked at any time during the study by the monitor.

It is the responsibility of the Investigator (or designee) to ensure that the study drug has been correctly documented for the amount received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log, provided by [redacted], will be maintained at the study site at all times. The study monitor will arrange regular collection of used and unused study drug returned by the subject. The study monitor will also perform an inventory of study drug at the close-out visit to the study site. All discrepancies must be accounted for and documented.

12.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement.

13 Ethics

13.1 Institutional Review Board

Before initiation of the study at the study site, the protocol, all protocol amendments, the ICF, screenshots of eDiary assessments, and any other relevant study documentation will be submitted to the IRB. Written approval of the study and all relevant study information must be obtained before the study site can be initiated or the study drug released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained, in particular, for changes to the study such as modification of the protocol, the ICF, the written information provided to subjects and/or other procedures. [redacted] will submit relevant study documentation to the central IRB on behalf of the study sites.

In the event that a study site uses a local IRB, it is the responsibility of the site Investigator to obtain written approval of the study and all relevant study information before the initiation of study activities. Extensions or renewals of local IRB approval or approvals of changes to the ICF or other written information provided to subjects will be the responsibility of the site Investigator.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. [redacted] will submit written summaries of the study status to the IRB annually or more frequently if requested by the IRB. On completion of the study, the Sponsor (or designee) will notify the IRB that the study has ended.

13.2 Ethical Conduct of the Study

This study will be conducted according to the Guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Brazil, 2013) and the ICH guidelines for cGCP as well as the demands of national drug and data protection laws and other applicable regulatory requirements.[15-17]

13.3 Subject Information and Consent

The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study. The written consent must be given by the subject after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

The Investigator or sub-Investigator will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points he or she does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given time to consider the study, if this is required, or if the subject requests more time. Subjects will be required to sign and date the ICF. Subjects should be able to read and write; the use of a legally authorized representative is prohibited in this study. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IRB, Dr. Reddy's Laboratories, [redacted] personnel, or third parties authorized by Dr. Reddy's Laboratories. Subjects will be given a signed copy of the ICF for their records.

It should be emphasized to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

13.4 Subject Confidentiality

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the American Health Insurance Portability and Accountability Act of 1996 (HIPAA)[18] and applicable local laws and/or regulations on personal data protection.

Monitors, auditors, and other authorized agents of the Sponsor or [redacted], the IRB approving this research as well as that of any applicable regulatory agency, will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study, or in publications, the subjects' identity will remain confidential.

14 Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the study drug. It is the responsibility of the Sponsor to inform the study site of when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, medical practice, or federal law. The Investigator shall not publish any articles or make any presentations relating to the study drug or referring to data or materials generated as part of the services provided under this agreement, without the prior written consent from the Sponsor; such consent shall not be unreasonably withheld.

Publication review process: The Investigator shall submit to the Sponsor for its review a copy of any proposed publication resulting from the study at least 30 days before the date of submission for publication. If the Sponsor determines that the proposed publication contains patentable subject matter which requires protection, the Sponsor may require the delay of publication for a further period of time not to exceed 180 days for the purpose of filing patent applications.

If the Sponsor publishes the results of the study, the Investigators invited to be co-authors of the manuscript or abstract will be those who randomized the largest number of valid subjects and/or who provided significant input on study design and/or interpretation on study results.

15 References

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15. World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA General Assembly, Seoul, October 2008.

16. International Council for Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. CPMP/ICH/135/35. 09 May 1997.

17. Title 21 of the Code of Federal Regulations. Food and Drug Administration.

18. US Department of Health and Human Services. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 (P.L.104-191) [HIPAA]. http://aspe.hhs.gov/admnsimp/pl104191.htm. Effective 21 August 1996.

16 Investigator Signature Page

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura

Protocol Number: DFN-15-CD-006

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, cGCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining prior approval of Dr. Reddy's Laboratories and of the IRB. I will submit the protocol modifications or any ICF modifications to Dr. Reddy's Laboratories and the IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. All attempts will be made to ensure that no subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, and source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Dr. Reddy's Laboratories to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____
Investigator Signature Date

_____
Printed Name

_____
Institution