Study Protocol

Official Title of the Study

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine With or Without Aura

NCT Number:

NCT02856802

Document Date:

June 1, 2016

16. APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Clinical Study Protocol DFN-02-CD-012 version 1.0 dated 01 June 2016

CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine With or Without Aura

Protocol Number:	DFN-02-CD-012
Study Medication/ Investigational Product:	DFN-02
IND Number:	108,088
Phase:	2
Indication:	Episodic Migraine With or Without Aura in Adults
Sponsor:	Dr. Reddy's Laboratories Ltd. [redacted]
Sponsor Agent:	Dr. Reddy's Laboratories Inc. [redacted]
Protocol Date:	01 June 2016
Protocol Version:	Version 1.0

Protocol Approval Signatures

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine With or Without Aura

Protocol Number: DFN-02-CD-012

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 Conference on Harmonisation (ICH) guidelines for current Good Clinical Practice (cGCP)

Sponsor Signatory and Medical Monitor

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01 June 2016
Date

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01 JUNE 2016
Date

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Biostatistician
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Signature

01 JUNE 2016
Date

CONFIDENTIAL

1 Protocol Synopsis

Protocol Number:	DFN-02-CD-012
Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine With or Without Aura
Study Medication/ Investigational Product:	DFN-02
Country:	United States of America
Phase:	2
Objectives:	
Primary Objective:	To assess the proportion of patients who are pain-free at 2 hours postdose (first double-blind [DB1] treatment period)
Secondary Objectives	To assess the proportion of patients who are pain-free at 2 hours postdose (second double-blind [DB2] treatment period) **(Each Double-Blind [DB] Period)** • To assess the proportion of patients who are pain-free at 10, 15, 20, 30, 60, and 90 minutes postdose • To assess the proportion of patients who have pain relief at 10, 15, 20, 30, 60, 90, and 120 minutes postdose • To assess the proportion of patients with their most bothersome symptom (MBS) among nausea, photophobia, and phonophobia, absent at 10, 15, 20, 30, 60, 90, and 120 minutes postdose • To assess the proportion of patients who are free from nausea, photophobia, and phonophobia at each postdose time point • To assess time to meaningful pain relief • To assess time to pain freedom • [redacted] • To assess the proportion of patients who have sustained pain freedom at 24 hours (2 to 24 hours) postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication or additional study medication and no recurrence of headache pain within 2 to 24 hours postdose) • To assess change in functional disability score at 2 hours and 24 hours postdose • To assess the proportion of patients who use a second dose of the study medication or rescue medication after 2 hours (2 to 24 hours) postdose

- To assess treatment satisfaction at 2 hours postdose (7-point scale)
- To assess treatment satisfaction as measured by Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) at 24 hours postdose
- Tolerability as assessed by adverse events (AEs) (also overall)
- Safety as assessed by clinical laboratory tests, vital signs and electrocardiogram (ECG) (also overall)

Exploratory Objectives (Each DB Period):

- [redacted]

Number of Patients: Approximately 100 patients will be randomized. Patients who discontinue study participation prior to completing the study will not be replaced.

Study Design: This is a randomized, 2 DB treatment period dosing study, to be conducted at multiple centers in the United States. Previously diagnosed patients with a history of episodic migraine (as defined by International Classification of Headache Disorders, 3rd edition [beta version][1] [ICHD-3]), who experience an average of 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 headaches, will be randomized in a 1:1 ratio in both DB periods to receive either DFN-02 (sumatriptan nasal spray) 10 mg or a matching placebo.

There will be a screening period to evaluate whether the patient fits the migraine inclusion criteria and does not have medication overuse. Patients with at least a 12-month medical history of acute migraine will be eligible for

enrollment in the treatment period. Patients will continue to take their normal migraine medication during this screening period.

Randomized patients will be instructed to use the study medication in 1 migraine attack as soon as (and no more than within 1 hour after) experiencing moderate to severe pain (defined as headache pain rating of Grade 2 [moderate] or Grade 3 [severe] on pain severity scale of 0 to 3). Patients will return to the study site within 2 to 7 days in the DB1 treatment period and, if continuing to be eligible, will be re-randomized into a DB2 treatment period to receive either DFN-02 (sumatriptan nasal spray) 10 mg or a matching placebo to treat 1 migraine attack at any pain level. They will then return to the study site within 2 to 7 days of their second treatment for study completion assessments. Once randomized, the total duration of each patient's participation in the study would be up to 10 weeks.

After using the first dose of study medication in their migraine attack, patients will have the option to take another dose of study medication for the same attack if they experience relief but feel it is insufficient, or, if required, take rescue medication more than 2 hours after the first dose and after completing in the electronic diary (eDiary) the 2 hours postdose assessments. No more than 2 doses of study medication will be taken in a 24-hour period. Rescue medication will be decided between the Investigator and the patient.

During both treatment periods, data regarding the study medication effect on pain and symptoms and the associated impact on function and the patient's satisfaction with the study medication will be collected. Patients will record criteria in real-time in an eDiary that will include, but is not limited to, the date and time of each migraine attack, the occurrence of aura, predose pain level, date and time of study medication use, postdose pain level, symptoms and functional disability, treatment satisfaction, and date and time of rescue medication. The eDiary will be reviewed for compliance and rescue medication. Data will be entered into the electronic case report form (eCRF). After study completion or early termination, patients should be referred to their usual healthcare professional to resume pre-study standard of care, as per the Investigator discretion.

Treatment:

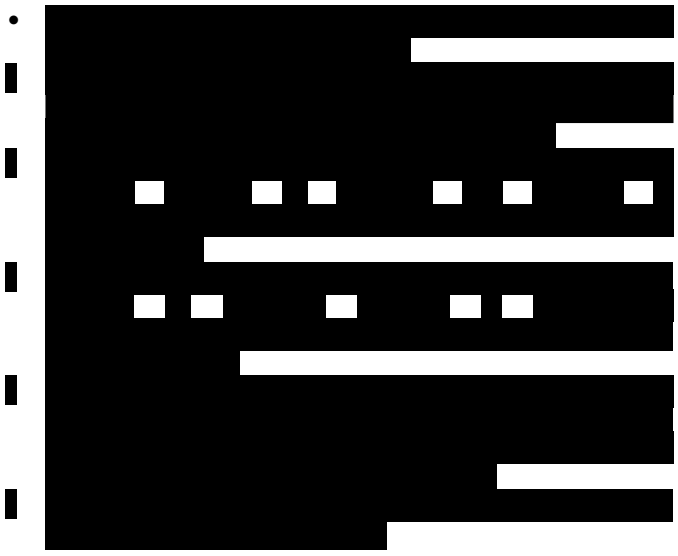
For the DB1 treatment period, all patients will be randomly assigned in a 1:1 ratio to receive either DFN-02 10 mg or a matching placebo to be used in 1 migraine attack as soon as (and no more than within 1 hour after) experiencing moderate to severe pain. Eligible patients will then be re-randomized in a 1:1 ratio into the DB2 period to receive either DFN-02 10 mg or a matching placebo to treat another migraine attack

	at any pain level. In each treated migraine attack, study medication may be repeated once (if needed), more than 2 hours after the initial dose and after completing in the eDiary the 2 hours postdose assessments.
Study Duration:	The duration of study participation will be up to approximately 13 weeks, including a screening period of approximately 3 weeks (wherein patients may be randomized earlier than 3 weeks provided 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 (each period) for patients to experience and treat migraine attacks, and 2 to 7 days for patients to return to the site after treatment. The 2 DB treatment periods combined would total up to 10 weeks.
Study Population:	Male and female patients 18 to 75 years of age, inclusive, previously diagnosed with ICHD-3 episodic migraine 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 at least 48 hours of headache-free time between migraine headaches, will be included. Migraines can be with or without aura, but the aura cannot last longer than 60 minutes. Patients with medication overuse, patients who use mini-prophylaxis for menstrual migraine, patients who have been on unstable doses of migraine prophylactic medications 30 days prior to and through screening, and patients with migralepsy will be excluded. See inclusion and exclusion criteria for additional study entry requirements.
Primary Efficacy Endpoint (DB1 period):	Proportion of patients who are pain-free at 2 hours after the first dose of study medication compared between DFN-02 and placebo (defined as a reduction from predose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0])
Secondary Endpoints:	Proportion of patients who are pain-free at 2 hours after the first dose of study medication compared between DFN-02 and placebo (any pain level) (DB2 period) **(Each DB Period):** • Proportion of patients who are pain-free at 10, 15, 20, 30, 60, and 90 minutes postdose • Proportion of patients who have pain relief at 10, 15, 20, 30, 60, 90 and 120 minutes postdose • Proportion of patients with their MBS among nausea, photophobia, and phonophobia, absent at 10, 15, 20, 30, 60, 90, and 120 minutes postdose • Proportion of patients who are free from nausea,

photophobia, and phonophobia at each postdose time point
- Time to meaningful pain relief
- Time to pain freedom
- [redacted]
- Proportion of patients who have sustained pain freedom at 24 hours (2 to 24 hours) postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication or additional study medication and no recurrence of headache pain within 2 to 24 hours postdose)
- Change in functional disability score at 2 hours and 24 hours postdose
- Proportion of patients who use a second dose of the study medication or rescue medication after 2 hours (2 to 24 hours) postdose
- Treatment satisfaction at 2 hours postdose (7-point scale)
- Treatment satisfaction as measured by PPMQ-R at 24 hours postdose
- Tolerability as assessed by AEs (also overall)
- Safety as assessed by clinical laboratory tests, vital signs and ECG (also overall)

Exploratory Endpoints: (Each DB Period):

- [redacted]



Safety:

- Physical examinations, including weight and height measurement
- Serum/urine pregnancy test for female patients of childbearing potential
- Clinical laboratory evaluation, including hematology, clinical chemistry, and urinalysis
- Vital sign measurements (sitting systolic and diastolic

blood pressure, pulse rate, and body temperature)
- Recording of 12-lead ECGs
- AEs
- Concomitant medication review

2 Table of Contents

2.1 List of In-Text Figures

2.2 List of In-Text Tables

3 List of Abbreviations

5-HT	5-hydroxy-tryptamine
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CAD	coronary artery disease
cGCP	current Good Clinical Practice
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	Food and Drug Administration
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 Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition (beta version)
ID	identification
IRB	Institutional Review Board
IWRS	interactive web response system
LOCF	last observation carried forward

MAO-A	monoamine oxidase-A
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MOH	medication overuse headaches
NSAID	nonsteroidal anti-inflammatory drug
PK	pharmacokinetic
PP	per-protocol
PPMQ-R	Patient Perception of Migraine Questionnaire-Revised
PT	preferred term
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
THC	tetrahydrocannabinoids
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
V	visit
WHO-DD	World Health Organization Drug Dictionary

4 Introduction

Migraine headache is a disabling neurological disorder with clinical findings of headache, often associated with nausea, photophobia, and phonophobia. In the United States (US), about 17% of all women and 6% of all men suffer from migraine.[2]

Although the exact mechanism of migraine headache is not known, the pathophysiology is related to alteration in the neurochemical balance of the brain to trigeminal-vascular activation and release of vasoactive peptides. Radiological investigations in migraine patients are characterized by hyperexcitation of neuronal networks in the occipital lobe of the cortex, the brainstem, and the trigeminal nerve ganglion.[3,4]

Clinically, migraine with aura occurs in 5 phases: prodrome, aura, headache, resolution, and postheadache. The prodrome phase is associated with nonspecific symptoms such as fatigue, muscle pain in the neck and head, cognitive impairment, anxiety, and irritability. Auras are focal neurological changes typically of a visual or somatosensory nature, lasting less than 60 minutes. Auras are considered to occur as the result of electrical disturbances in the brain. Auras occur in approximately 15% of migraine attacks. The headache phase can be divided into mild, moderate, and severe phases. The mild phase is the period of time from headache awareness to the onset of moderate pain. [redacted] In general, the headache phase lasts 4 to 72 hours. The postheadache phase lasts up to 48 hours and is characterized with symptoms similar to those of the prodrome.[5,6]

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 severe and more resistant to treatment.[7]

Several therapies such as triptans, ergot alkaloids, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and caffeine combinations, and/or opioids are used by physicians for the treatment of acute migraine. Migraine-specific therapies, such as triptans or ergot alkaloids, have become the treatment of choice when patients respond poorly to NSAIDs or combination regimens of aspirin and caffeine. For most migraine sufferers, triptans are the drug class of choice both from efficacy and tolerability perspectives.[8]

Sumatriptan, a 5-hydroxy-tryptamine $(5\text{-HT})_{1B/1D}$ receptor agonist developed by GlaxoSmithKline, is marketed under the brand name of Imitrex®. Sumatriptan is one of the most commonly used triptans for the treatment of acute migraine headache. Oral, intranasal, and subcutaneous injectable formulations of sumatriptan are approved by the US Food and Drug Administration (FDA) and are available on the market. The relative bioavailability for Imitrex following subcutaneous administration is significantly higher compared to intranasal or oral administration.[9-11] The therapeutic response rate at 2 hours is dependent upon the mode of administration—subcutaneous 70%, oral 59%, and intranasal 61%.[12]

The onset of action with subcutaneous sumatriptan (10 minutes) is faster than with intranasal (30 to 45 minutes) or oral (45 to 60 minutes) delivery.[9,10,13,14] The intranasal route of delivery for sumatriptan can be preferable compared to the oral or subcutaneous routes due to the slow rate of absorption of the oral form and invasiveness of self-injection. However, even with sumatriptan nasal spray, the issue of a relatively slow rate of absorption and lower bioavailability remains.[9]

Dr. Reddy's has developed a nasal formulation of DFN-02 composed of sumatriptan and [redacted] a permeation enhancer. The safety and effectiveness of sumatriptan have been well established.[9,10] [redacted] is a permeation-enhancing excipient that belongs to a class of nonionic surfactants classified as alkylglycosides, which consists of alkyl chains of various lengths linked to a sugar moiety, have been studied for their ability to promote increased bioavailability of drugs via the nasal, oral, and ocular routes.[15] The mechanisms by which alkylglycosides exert their permeation-enhancing effects on the nasal epithelium in vivo are unclear. The permeation enhancement properties of [redacted] have been characterized for several therapeutic compounds in development and have been discussed in a number of journal publications[15-21] ([redacted] drug master file, reference data on file).

[redacted]

One pivotal Phase 1 study (DFP-02-CD-009)[26] and four pilot Phase 1 studies (DFP-02-CD-008,[22] 2419/11,[23] 1931/09,[24] and 2010/10[25]) have been conducted in a total of 154 healthy adult male and female volunteers at a dose range of 5 mg to 20 mg. DFN-02 was generally well-tolerated without any clinically meaningful changes in laboratory parameters or vital signs.

Overall, the pharmacokinetic (PK) data suggest that sumatriptan achieved peak plasma concentration rapidly at approximately 10 minutes following 10 mg DFP-02 intranasal spray, approximately 5 minutes sooner than that of the 4 mg and 6 mg Imitrex injections. This profile may lead to improved onset of therapeutic benefit for patients suffering from migraine headaches.

In addition, in one Phase 3 open-label clinical safety study (DFP-02-CD-010),[27] 167 patients used DFN-02 (studied as DFP-02) to treat migraine attacks for up to 6 months. Overall, 4 patients experienced 5 serious adverse events (SAEs). Three of the SAEs were treatment-emergent (one subject each; diverticulitis, pyelonephritis and menometrorrhagia), and all 5 SAEs were considered by the Investigator to be not related to study medication. No new safety results were noted; the study results are currently being summarized and will be reported in the next version of the Investigator's Brochure.

In summary, DFN-02 is being developed for the treatment of acute migraine headaches with and without aura. Nonclinical and clinical studies to date have demonstrated acceptable tolerability, as well as a favorable PK profile, to allow further characterization in terms of safety tolerability and efficacy.

5 Study Objectives

5.1 Primary Objective

The primary objective of the study is to assess the proportion of patients who are pain-free at 2 hours postdose (first double-blind [DB1] treatment period).

5.2 Secondary Objectives

The secondary objectives of the study are to assess the proportion of patients who are pain-free at 2 hours postdose (second double-blind [DB2] treatment period)

(Each Double-Blind [DB] Period)

- To assess the proportion of patients who are pain-free at 10, 15, 20, 30, 60, and 90 minutes postdose
- To assess the proportion of patients who have pain relief at 10, 15, 20, 30, 60, 90, and 120 minutes postdose
- To assess the proportion of patients with their most bothersome symptom (MBS) among nausea, photophobia, and phonophobia, absent at 10, 15, 20, 30, 60, 90, and 120 minutes postdose
- To assess the proportion of patients who are free from nausea, photophobia, and phonophobia at each postdose time point
- To assess time to meaningful pain relief
- To assess time to pain freedom
- [redacted]
- To assess the proportion of patients who have sustained pain freedom at 24 hours (2 to 24 hours) postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication or additional study medication and no recurrence of headache pain within 2 to 24 hours postdose)
- To assess change in functional disability score at 2 hours and 24 hours postdose
- To assess the proportion of patients who use a second dose of the study medication or rescue medication after 2 hours (2 to 24 hours) postdose
- To assess treatment satisfaction at 2 hours postdose (7-point scale)
- To assess treatment satisfaction as measured by Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) at 24 hours postdose
- Tolerability as assessed by adverse events (AEs) (also overall)
- Safety as assessed by clinical laboratory tests, vital signs, and electrocardiogram (ECG) (also overall)

5.3 Exploratory Objectives (Each DB Period)

The exploratory objectives for each treatment period include:

- [redacted]

- [redacted]

6 Investigational Plan

6.1 Overall Study Design and Plan

This is a randomized, 2 DB treatment period dosing study, to be conducted at multiple centers in the US. Previously diagnosed patients with a history of episodic migraine (as defined by International Classification of Headache Disorders, 3rd edition [beta version][1] [ICHD-3]), who experience an average of 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, will be randomized in a 1:1 ratio in both DB periods to receive either DFN-02 (sumatriptan nasal spray) 10 mg or a matching placebo.

There will be a screening period to evaluate whether the patient fits the migraine inclusion criteria pursuant to ICHD-3, and does not have medication overuse. Patients with at least a 12-month medical history of acute migraine will be eligible for enrollment in the treatment period. Patients will continue to take their normal migraine medication during this screening period.

During the screening period, the electronic diary (eDiary) will be dispensed in order for the patient to enter information for daily check-in, record at least 1 migraine attack, and rescue medication use, to determine the patient's ability to properly use the eDiary. If eligible and randomized, patients in the DB1 treatment period will be instructed to use the study medication in 1 migraine attack as soon as (and no more than within 1 hour after) experiencing moderate to severe migraine pain (defined as headache pain rating of Grade 2 [moderate] or Grade 3 [severe] on a pain severity scale of 0 to 3). If the patient is not able to use study medication for the first migraine after randomization, they should be instructed to use the study medication for the next attack. Those patients who do not experience a migraine attack, and/or who do not treat any migraine attack with study medication or record eDiary data, will not be allowed to continue into the DB2 treatment period, and will be discontinued. After treating a migraine attack with study medication, patients should be instructed to contact the site within 24 hours of the treated migraine (or the next working day) to schedule their next visit.

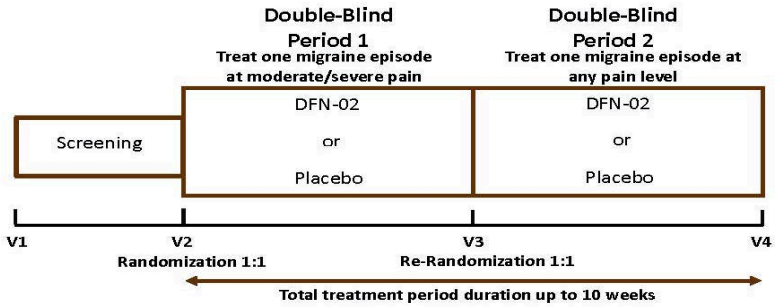
Patients will return to the study site within 2 to 7 days in the DB1 treatment period and, if continuing to be eligible, will be re-randomized into a DB2 treatment period to treat 1 migraine attack at any pain level. They will then return to the study site within 2 to 7 days of the second treatment. Once randomized, the total duration of each patient's participation in the study would be up to 10 weeks.

If after taking the first dose of study medication a patient does not experience sufficient relief, he/she may take a second dose of study medication for the same attack, or take rescue medication more than 2 hours after taking the first dose of study medication, and only after completing in the eDiary the 2 hours postdose assessment. If a patient does not experience

any relief at all from the first dose of study medication after 2 hours, he/she should not take a second dose, but may take rescue medication instead, if needed. Rescue medication will be decided between the Investigator and the patient. No more than 2 doses of study medication will be taken in a 24-hour period.

During both DB treatment periods, data regarding the migraine attack, study medication effect and the associated impact on migraine pain, symptoms, function, rescue medication, and the patient's satisfaction will be collected by the patient in real-time in an eDiary. See Section 10.2.1.4.1 for eDiary assessment criteria. The eDiary will be reviewed for compliance and rescue medication, and data will be entered into the electronic case report form (eCRF). After study completion or discontinuation, patients should be referred to their usual healthcare professional to resume pre-study standard of care, as per the Investigator discretion.

Figure 6-1 Trial Design



6.2 Discussion of Study Design

The current study design was chosen to determine the efficacy of DFN-02 for the treatment of acute migraine pain. A screening period will allow sufficient time for screening laboratory test results availability and verification that patients meet the inclusion and exclusion criteria.

Patients will be randomized in a blinded fashion to receive DFN-02 or placebo and self-administer when experiencing a migraine attack to determine whether DFN-02 can relieve migraine pain, and symptoms and disability compared with placebo. For the first treated acute migraine attack (DB1 treatment period), patients will treat moderate or severe pain to meet regulatory requirements for efficacy determination; for the second attack (DB2 period), patients will treat migraine at any pain level to determine if efficacy is achieved throughout the pain level range. Patients are allowed to use a second dose of study medication or take rescue medication more than 2 hours after taking the first dose of study medication in the attack, as described in Section 6.1 and Section 9.5.2, to optimize patient comfort while supporting clinically relevant data collection.

7 Selection of Patients and Criteria for Withdrawal

7.1 Number of Planned Patients

Approximately 100 patients will be randomized into the study. Patients who do not qualify for enrollment after the screening period will be terminated as screen failures and will be

replaced. Randomized patients who discontinue study participation prior to study completion will not be replaced.

7.2 Inclusion Criteria

Patients 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
   Note: If female and of childbearing potential (not surgically sterile or ≤ 1 year after the onset of amenorrhea due to menopause), the patient must (a) have a negative serum pregnancy test at screening and a negative urine test at V2, (b) not be lactating, and (c) agree to practice a reliable form of contraception or abstinence during the study. Acceptable forms of contraception include implants, injectable contraceptives, combined oral contraceptives, an intrauterine device, a vasectomized partner, and double-barrier methods.
   Note: If male (with female partner), the patient must agree to practice a reliable form of contraception or abstinence during the study.
3. A history of episodic migraine (as defined by ICHD-3), who experience an average of 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 headaches
4. Patients who have migraine with or without aura. If migraine with aura, the aura cannot last longer than 60 minutes.
5. Patients who, in the opinion of the Investigator, are willing and able to:
   a. Evaluate and record pain, migraine symptoms, and study medication effectiveness information in real-time using an eDiary for the duration of the study;
   b. Record each instance of the use of study medication and rescue medication in a patient eDiary in real-time for the duration of the study;
   c. Comply with all other study procedures and scheduling requirements.
6. Patients who can use the nasal spray device correctly after instruction

7.3 Exclusion Criteria

Patients 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. 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 (only applies if combination medication contains an 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
3. Prior exposure to DFN-02 (or DFP-02)
4. Treated with onabotulinumtoxinA (Botox®) or other botulinum toxin treatment within 4 months prior to screening for migraine prophylaxis (patients who were treated with same for cosmetic purposes may be allowed on a case-by-case basis after approval from the Medical Monitor)

5. On unstable dosages of migraine prophylactic medications within 30 days prior to and through screening
6. Taking mini-prophylaxis for menstrual migraine
7. Patients with hemiplegic migraine, or other forms of neurologically complicated migraine
8. Patients who have prolonged aura (i.e., more than 1 hour)
9. A history of stroke or transient ischemic attack
10. A history of migralepsy (seizure following a migraine) or a concurrent diagnosis of seizure disorder
11. Patients who cannot differentiate between a migraine headache and tension-type or cluster headache
12. A history of more than occasional tension-type headache (based on Investigator judgment)
13. A history of cluster headaches
14. Known intolerance to sumatriptan (any formulation), or who have experienced a significant AE related to any triptan medication, including sumatriptan
15. Non-responsiveness to subcutaneous sumatriptan (≤ 6 mg dosage), in the opinion of the Investigator
16. Prior ischemic coronary artery disease (CAD): angina pectoris, history of myocardial infarction or documented silent ischemia or coronary artery vasospasm, including Prinzmetal's angina
17. Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders
18. Uncontrolled hypertension or systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg (the values should be reconfirmed to rule out a transient fluctuation; see Section 7.3.1 for details
19. Peripheral vascular disease or ischemic bowel disease
20. Patients using monoamine oxidase-A (MAO-A) inhibitor that cannot be completely washed out (at least 15 days)
21. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and steroids for chronic conditions, unless the dose is stable for at least 3 months prior to randomization and is not expected to change during the study
22. Known intolerance to nasal sprays
23. Patients taking any medications or with illnesses likely to affect the physiology of the nasal mucosa (i.e., patients with colds [upper respiratory infections], influenza, nasal septum surgery, or chronic nasal rhinitis)
24. Any abnormal nasal physiology or pathology, or any other abnormal physiology and/or pathology that, in the opinion of the Investigator, would not allow the objectives of the study to be accomplished
25. Acute sinusitis. Patients may be rescreened 7 days after resolution of acute sinusitis infection/symptoms with no complaints of headache pain and if, in the opinion of the Investigator, it will not interfere with accomplishing the objectives of the study
26. Chronic sinusitis
27. Severe renal impairment (defined as creatinine > 1.5 × the upper limit of normal [ULN])
28. Serum total bilirubin > 1.5 × ULN
29. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 × ULN
30. Patients with uncontrolled diabetes mellitus, or a glycosylated hemoglobin (HbA1c) > 7.9%, or with diabetes mellitus requiring insulin

31. A history of alcohol or substance abuse (including marijuana) within 1 year that would compromise data collection
32. A positive urine drug screen for recreational drugs, alcohol, marijuana (whether legal or not), or for prescription drugs not explained by stated concomitant medications:
    a. Patients 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 headaches (MOH) criteria.
    b. Benzodiazepines are allowed if used for legitimate medical reasons.
    c. 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)
33. A history of or current neurological or psychiatric impairment, or cognitive dysfunction that, in the opinion of the Investigator, would compromise data collection
34. Use of antipsychotics at least 15 days prior to randomization (if used for non-psychiatric conditions, should be evaluated on a case-by-case basis with the Medical Monitor)
35. Patients who received treatment with an investigational drug or device within 30 days prior to randomization, or within 3 months if associated with central nervous system
36. Patients who participated in a central nervous system clinical trial within 3 months prior to randomization
37. Patients who test positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody serology testing
38. Patients with any other medical condition that, in the judgment of the Investigator or Medical Monitor, would confound the objectives of the study (e.g., clinically significant abnormal thyroid-stimulating hormone [TSH] levels, cancer history** [except basal cell carcinoma], systemic lupus erythematosis). ***Exceptions to be made if the Investigator believes, with Sponsor approval, that the current status will not interfere with primary objectives*
39. Patients who are employees or immediate relatives of the employees of the Sponsor, any of its affiliates or partners, or of the clinical study research site

7.3.1 Additional Exclusion Criteria

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

Independent of past history, if a patient has a sustained resting SBP > 140 mmHg and/or DBP > 90 mmHg at Visit 1 (V1) or Visit 2 (V2), those patients should be excluded. Any patient without a known history of hypertension that presents at screening with SBP > 140 mmHg and/or DBP > 90 mmHg should be excluded if the BP 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 BP is falsely elevated, they should repeat the assessment 2 to 3 times with the patient in a semi-reclined position in a quiet room. Patients with persistent elevations, despite repeat assessments, should be excluded and referred to an appropriate healthcare provider for further assessment.

7.4 Removal of Patients from Therapy or Assessments

Patients 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 patient 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.

Patients 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 eCRF:

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

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

In the event that a patient 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 patient is withdrawn, they may not re-enter the study.

Reasonable efforts will be made to contact patients 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 patient's file.

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

8 Investigational Products

8.1 Investigational Products Administered

DFN-02 and placebo (undistinguishable from DFN-02) will be provided in a single-use nasal spray device calibrated to deliver 100 µL spray. Refer to the Instructions for Use document for handling instructions and proper usage of the delivery device to administer the dose of DFN-02. Details of study treatment information are provided in Table 8-1.

Table 8-1 Investigational Product Details for Study Treatments

Product Code	Preparations to be Administered	
	DFN-02	Placebo
Manufacturer	[redacted]	[redacted]
Dose	10 mg	--
Route	Nasal	Nasal
Formulation	Nasal spray	Nasal spray
Strength	Each device contains 10 mg of sumatriptan	--

All study drug supplies (DFN-02 and placebo) will be provided by the Sponsor or Sponsor affiliates. Patients will be instructed by the site staff on the proper administration of study medication to ensure compliance (see Section 9.6 for additional details on treatment accountability and compliance). Written instructions for use of the study medication will be distributed to Investigator sites, and patients should be confirmed to have, or be provided with, them every time study medication is dispensed. Rescue medication will not be provided by the Sponsor, and its use should be managed by the patient and their Investigator.

8.2 Identity of Investigational Products

DFN-02 (sumatriptan nasal spray) is a novel formulation designed to improve relief of migraine symptoms by decreasing time to onset. DFN-02 is composed of sumatriptan and a permeation-enhancing agent, [redacted], delivered as an aqueous, intranasal solution in a metered spray.

The DFN-02 and the matching placebo intranasal spray are manufactured for Dr. Reddy's Laboratories Ltd, by: [redacted] USA.

Manufacturing of the study medication was performed according to Good Manufacturing Practice (GMP) for Medicinal Products and all relevant regulatory requirements. Additional details regarding study medication may be found in the DFN-02 Investigator's Brochure.[28]

8.3 Storage, Packaging, and Labeling

The Sponsor will supply sufficient quantities of DFN-02 10 mg nasal and placebo spray to allow for completion of this study.

The study medication 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 at a controlled, room temperature (20°C to 25°C, 68°F to 77°F) environment; excursions are permitted to 15°C to 30°C (59°F to 86°F). The room should be accessible only to authorized individuals. Records will be made of the receipt and dispensation of all study medication.

Nasal devices, individually blistered and labeled, will be joined by a perforated seal that may be subsequently separated if necessary. Nasal spray device pairs in a blister pack will then be packaged in a carton that will be labelled as well. Each pair of labels will contain a kit number, the name and address of the Sponsor Agent, and any other information required by

local regulations. The patient will be instructed to return all used and unused study medication 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 GMP for Medicinal Products and all relevant regulatory requirements.

9 Administration of Study Treatments

9.1 Method of Assigning Patients to Treatment Groups

The DFN-02-CD-012 study is a randomized, 2 DB treatment periods, placebo-controlled study. Treatment sequences will be assigned randomly in each DB period with a 1:1 ratio to receive either DFN-02 or matching placebo (Figure 6-1).

9.1.1 Screening (Visit 1)

After written informed consent is obtained and the patient 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 patient identification (ID) number to be used throughout the study. This patient ID number will not be reused for any other participant in the study. This unique identifier comprises the numerical order of the patients screened and will be used to identify the patient on the eCRF.

9.1.2 Randomization (Visit 2)

Once a patient'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 patient study medication kit assignment. Patients who do not meet eligibility criteria will be registered as screen failures. It is important that the study staff reconfirm the patient's willingness to continue in the study prior to randomizing the patient to a treatment.

The planned treatment given to individual patients will be determined by a randomization scheme prepared by the biostatistics group of INC Research. For both DB periods, all patients will receive intranasal DFN-02 10 mg or a matching placebo in a randomized 1:1 treatment sequencing. As detailed in Section 6.1, patients will treat 1 migraine attack in the DB1 treatment period and, if eligible, be re-randomized to enter into the DB2 treatment period. The IWRS will assign the appropriate study medication kit to each patient for each treatment period. If a patient discontinues from the study after randomization, the patient ID number will not be reused, and the patient will not be allowed to re-enter the study. Patients will be required to return unused study medication and the eDiary provided by the site.

9.2 Selection of Doses in the Study

The human dose range of DFP-02 evaluated in the pivotal study (DFP-02-CD-009)[26] and the 4 pilot studies (DFP-02-CD-008, 2419/11, 1931/09, 2010/10), was based upon doses of the marketed intranasal formulations of Imitrex nasal spray.[22-25] The concentration of 0[redacted] was chosen based on early development work (data on file) to optimize the PK profile of sumatriptan. These studies indicated no safety, tolerability, or clinically meaningful changes in vital signs and laboratory parameters. The highest single-dose of sumatriptan in

DFN-02 for current and future clinical studies is 10 mg. The safety and tolerability of this dose was evaluated in a long-term safety study (DFP-02-CD-010)[27] that showed no new safety findings.

9.3 Selection and Timing of Dose for Each Patient

At the end of the screening period, eligible patients will be randomized to receive study medication (DFN-02 or a matching placebo) as described in Section 6.1. Information about use of study medication, predose and postdose assessments, and any rescue medication taken during the study will be recorded in the eDiary. For dosing information, see Section 8.1.

9.4 Blinding

In order to blind the study treatment, study medication kits with identical labeling appearance will be assigned unique kit numbers by IWRS and the kits will distributed by [redacted] to the site prior to 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 patient, in which knowledge of the treatment assignment is critical to the patient's management, the blind for the patient 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 patient's immediate management, and must make every effort to contact the Medical Monitor prior to 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 patient is receiving active treatment. In cases of accidental unblinding or when the Medical Monitor cannot be contacted prior to 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.

9.5 Prior and Concomitant Therapy

Investigators should document in the eCRF all prior medications for neurological illnesses and conditions that the patient has experienced anytime in the past, and other prior medications that were taken within 1 year prior to screening. In addition, all concomitant and ongoing medications are to be documented in the eCRF. (See also Section 7.3 exclusion criteria and Section 9.5.3 prohibited and allowed medications.)

9.5.1 Medication History

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

Patients 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 prior to screening and the medications are not otherwise prohibited or restricted in the protocol. See Section 9.5.3 for prohibited and allowed medications.

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

- Monoamine oxidase (MAO) inhibitors: at least 15 days prior to randomization
- Antipsychotics: at least 15 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 3 months if associated with central nervous system
- Participated in a central nervous system clinical trial: at least 3 months prior to randomization

9.5.2 Rescue Medication

If a patient does not experience sufficient relief with the first dose of the study medication, he/she may take a second dose of study medication or take rescue medication after 2 hours or more after taking the first dose of study medication and only after completing in the eDiary the 2 hours postdose assessments. If a patient does not experience any relief at all from the first dose of study medication after 2 hours, he/she should not take a second dose, but may take rescue medication instead, if needed.

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

The specific rescue medication will initially be decided mutually between the Investigator and the patient prior to or at V2, but may be adjusted as needed during the treatment period, with the Investigator ensuring that prohibited medications (as listed below) 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 patient 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. Patients should not take prohibited medications listed in Section 9.5.3 as a rescue medication.

9.5.3 Prohibited and Allowed Medications

The following medications should not be taken during the study:

- MAO inhibitors
- Triptans (except study medication) and other 5-HT1 receptor agonists
- Ergotamine or ergot-type medications
- Antipsychotics (for any reason)
- Opioids are prohibited if used for ≥ 4 days per month. Additional caution should be exercised with use of tramadol. To ensure patient safety in the study, patients should not take tramadol and triptan drugs concomitantly due to the risk of serotonin syndrome. If a patient has taken study medication, they should not take tramadol for at least 24 hours; if a patient has taken tramadol, they should not take study medication for at least 48 hours, or for at least 5 half-lives of tramadol, whichever is longer.

SSRIs, 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 patient develops a need for long-term use of one of these medications during the course of the study, the patient must be withdrawn from the trial. Short term use of these medications during the study is prohibited.

No newly prescribed drugs should be administered during the study without agreement from the site Investigator. These drugs should not have any drug-drug interactions with the study medication or be contraindicated in the Imitrex® product label or package insert.

Patients will be instructed to refrain from using illicit substances (including marijuana) during the study. Please refer to Section 7.3 for exclusion criteria.

9.6 Treatment Compliance

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

See Section 6.1 and Section 9.5.2 for details on timing of dosing with study medication and use of rescue medication.

At the end of the DB1 treatment period (V2), patients will be required to return all used and unused study medication from DB1 before any study medication for the DB2 treatment period will be dispensed.

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

10 Study Procedures

10.1 Duration of Treatment

The duration of study participation will be up to approximately 13 weeks, including a screening period of approximately 3 weeks (wherein patients 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 patients to experience and treat migraine attacks, and 2 to 7 days for patients to return to the site after treatment. The combined 2 DB treatment periods would total up to 10 weeks. Migraine attacks and associated treatment and assessments will be recorded in an eDiary (see Section 10.2.1.4.1).

10.1.1 Data Recording Using eDiary

The daily eDiary will be used to record migraine attack assessment data in real-time by patients as described in Section 6.1 and Section 10.2.1.4.1, and as shown in Table 10-2. It is compulsory for all patients to check-in the eDiary every day during the entire study period to ensure presence and functionality. If a patient 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 patient has technical difficulties or confirm they have not experienced a migraine.

Investigators should train patients 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 endpoint data entry (i.e., 2-hour postdose assessment).

10.2 Study Assessments

Table 10-1 summarizes the planned study assessments.

Table 10-1 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 medication dispensed at this visit 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 medication dispensed at V2.** **Study medication dispensed at this visit should be used to treat a migraine attack at any pain level.**	**Visit is expected within 2-7 days of treating a migraine attack with the study medication dispensed at V3.** **Treatment should be completed within 10 weeks from Baseline.**
Informed consent	X			
Inclusion/Exclusion criteria	X	X		
Patient 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 and current treatment status	X			
Physical examination[5]	X	X	X	X
Height and weight	X			X[6]
Vital signs (pulse rate, SBP/DBP,[7] body temperature); record menses (start/stop dates)	X[7]	X[7]	X	X

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Serum pregnancy test (hCG)[8, 9]	X			
Urine pregnancy test[8, 9]		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	X	X	X
Glycosylated hemoglobin (HbA1c), TSH* *[screening only]	X			X
Serology (HIV, HBsAg, HCV)	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 medication[10]		X	X	
Patient compliance and study medication accountability[11]			X	X
Patients record data in the eDiary[12]	→	→	→	→
Review, confirm, and ensure proper recording of the patient eDiary entries[13]		X	X	X
Collect eDiary[14]				X

Abbreviations: AE = adverse event; BP = blood pressure; DB = double-blind; DBP = diastolic blood pressure; ECG = electrocardiogram; eDiary = electronic diary; ET = early termination; HbA1c = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = Interactive Web Response System; SBP = systolic blood pressure; TSH = thyroid-stimulating hormone; V = Visit

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

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

[3] Patients may be randomized earlier than 21 days 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] Prior to eDiary dispensing, initial screening should determine to the extent possible that the patient may be eligible for the study and is able, willing, and understands after being instructed how to use the eDiary. The eDiary will be dispensed once, and information for at least 1 migraine attack should be entered if the patient is randomized; the eDiary should continue to be used throughout the DB periods. At V2 and V3, randomized patients will be re-instructed on the eDiary to ensure real-time entry of predose and postdose assessments and the level of migraine pain to treat Grade 2 [moderate] or Grade 3 [severe] for DB1 treatment period, and any pain level for the DB2 treatment period.

[5] At screening (V1), complete physical examination will be performed and recorded in the source document that includes examination of head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems. 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.

[6] Weight only.

[7] At screening, patients with a history of hypertension that is uncontrolled (i.e., SBP > 140 mmHg and/or DBP > 90 mmHg), whether on treatment or not, will be excluded. Patients who had high or uncontrolled BPs in the past and are currently controlled with given therapies would be eligible for this study. Independent of past history, if a patient has a sustained resting SBP > 140 mmHg and/or DBP > 90 mmHg at V1 or V2, they should be excluded. Any patient without a known history of hypertension that presents at screening with SBP > 140 mmHg and/or DBP > 90 mmHg should be excluded if the BP 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 BP is falsely elevated, they should repeat the assessment 2 to 3 times with the patient in a semi-reclined position in a quiet room. Patients with persistent elevations, despite repeat assessments, should be excluded and referred to an appropriate healthcare provider for further assessment.

[8] Serum pregnancy test will be performed at screening (V1) for all female patients of childbearing potential (or at any other time during the study if needed to confirm a suspected pregnancy from a positive urine pregnancy test).

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

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

[11] Unused study medication, including empty study medication containers, should be returned by patients. Unused study medication should not be redispensed.

[12] When the patient experiences a migraine episode, they should contact the site within 24 hours of treating with study medication to schedule their next visit. The eDiary will be used to record all migraine attacks treated with study medication during the study period.

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

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

Table 10-2 eDiary Assessments

	Randomization	Predose Baseline	Postdose				
			10, 15, 20, 30 min	1 h	1.5 h	2 h	24 h
Migraine start and aura information, study medication, and non-study medication taken for migraine attacks dosing	As applicable[1]						
Time to meaningful pain relief			As applicable up to 2 hours postdose				
Time to pain freedom			As applicable up to 2 hours postdose				
Pain level[2]		X	X	X	X	X	X
Functional disability[3]		X				X	X
Presence of nausea/photophobia/phonophobia and [redacted]		X	X	X	X	X	X
Most bothersome symptom (selected between nausea, photophobia and phonophobia)[4]		X					
PPMQ-R	X						X
Patient treatment satisfaction (7-point scale)[5]						X	

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

[1] End of migraine pain, and non-study medication use may occur more than 24 hours postdose.

[2] Pain levels: 0 = none; 1 = mild; 2 = moderate; 3 = severe

[3] Functional disability 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

[4] 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.

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

10.2.1 Visit Procedures

10.2.1.1 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. An eDiary will be dispensed at V1 to collect at least 1 migraine episode and, if the patient is randomized (V2), to continue to collect migraine data through end of treatment (V4). See eDiary assessments in Section 10.2.1.4.1. The following assessments will be performed at the screening visit:

- Written informed consent
- Eligibility confirmation per inclusion and exclusion criteria
- Dispense eDiary, instruct patient on use of the diary, and allow patient 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, medications taken for migraine management, satisfaction and headache pain relief with current medication)
- Physical examination, including weight and height measurements
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature); record menses
- Serum pregnancy test (human chorionic gonadotropin [hCG]) for women 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

10.2.1.2 Randomization (Visit 2) (Day 0)

At V2 (and V3), randomized patients will be reinstructed on eDiary usage to ensure real-time entry of pre- and postdose assessments and the level of migraine pain to treat moderate or severe attacks for DB1 treatment period, and pain of any level for the DB2 treatment period. Predose migraine assessments will be allowed to be recorded retrospectively in the event a patient did not follow the instructions.

- Continued eligibility confirmation per inclusion and exclusion criteria
- Review recordings of patient eDiary entries and confirm proper recording and compliance; retrain if necessary
- Review/collection of AEs
- Medical history and prior medications, including from eDiary entries
- Physical examination (if warranted)
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature); record menses
- Urine pregnancy test for women 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 medication and instructions for use

- Confirm patient completes PPMQ-R questionnaire

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

- Confirm the following:
  - Visit is within 2 to 7 days of treatment of a migraine attack with study medication dispensed at V2
  - There should be at least 48 hours of pain and symptom freedom from the previously treated migraine attack
  - Treatment should be completed within 4 weeks from V2
- Review recording of patient eDiary entries and confirm proper recording and compliance; retrain if necessary
- Review/collection of AEs
- Physical examination (if warranted)
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature); record menses
- Urine pregnancy test for women 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 medication is returned, patient compliance, and study medication accountability
- Re-randomization (DB2 period)
- Dispense study medication and instructions for use

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

- Confirm the following:
  - Visit is within 2 to 7 days of treatment of a migraine attack with study medication dispensed at V3 (or ET, if applicable)
  - Treatment should be completed within 10 weeks from V2
- Review/collection of AEs
- Physical examination (if warranted)
- Weight of patient
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature); record menses
- Urine pregnancy test for women 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 patient compliance and study medication accountability
- Review, confirm, and ensure proper recording of eDiary entries by patient
- Collection of eDiary; empty study medication containers, and all unused study medication

10.2.1.4.1 eDiary Assessments

Patients will be provided with an eDiary at screening (V1) to collect at least 1 migraine episode data and, if randomized (V2), to continue to collect migraine date and time (for migraine attacks treated with study medication) and any non-study medication used to treat migraine in the study. At V2 and V3, patients will be re-instructed on the eDiary usage to ensure real-time entry of predose and postdose recordings. (Predose migraine assessments will be allowed to be recorded retrospectively in the event a patient did not follow the instructions.) All patients should be instructed to return the eDiary to the study site.

At baseline (V2), patients will complete the PPMQ-R questionnaire in the eDiary; record the migraine pain start and end (date and time) when they get the migraine; record the baseline pain level; record the functional disability scale; and record presence of symptoms and MBS (among nausea, photophobia, and phonophobia) just before taking the study medication.

At postdose, patients will record time to meaningful pain relief (based on their perception), and time to pain-free after study medication within 2 hours postdose. Patients will also record their functional disability at 2 hours and 24 hours postdose, and their pain level and presence of MBS at 10, 15, 20, 30 minutes, and at 1, 1.5, 2, and 24 hours postdose. Patients will record their treatment satisfaction at 2 hours postdose, and complete the PPMQ-R questionnaire again at 24 hours postdose. Patients will also record study medication dosing and use of rescue medication in the eDiary at applicable timings.

The following eDiary assessments will be recorded by the patient in accordance with Table 10.2.

- Migraine pain and symptoms:
  - Migraine pain start and end (date and time)
  - Level of headache pain predose and at various time points after (0 = none; 1 = mild; 2 = moderate; 3 = severe)
  - Time to meaningful pain relief (based on patient's perception) and time to pain-free after study medication
  - Migraine symptoms and MBS other than pain (nausea, photophobia, phonophobia, at predose, and at various time points, postdose)
  - [redacted]
- PPMQ-R: The PPMQ-R is a self-administered satisfaction measurement for acute migraine treatment.
- Functional disability 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).
- Overall treatment satisfaction, measured by asking questions to the patients, and the answers will be assessed on a 7-point scale (1 = very satisfied, 2 = satisfied, 3 = somewhat satisfied, 4 = neither satisfied nor dissatisfied, 5 = somewhat dissatisfied, 6 = dissatisfied, and 7 = very dissatisfied).
- Study medication and rescue use.

Visits may be scheduled as needed for AE management. Adverse event and concomitant medication review should be performed at each unscheduled visit.

10.2.2 Efficacy Assessments

All efficacy data will be collected in the eDiary. The efficacy assessments are shown in Section 10.2.1.4.1 and Section 11.4.

The primary efficacy endpoint is the proportion of patients who are pain-free (defined as a reduction from predose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]) at 2 hours after the first dose of study medication compared between DFN-02 and placebo.

Secondary and exploratory efficacy endpoints are listed in Section 11.4.2 and Section 11.4.3, respectively.

10.2.3 Safety Assessments

Safety assessments, performed according to the schedule of assessments, include the following:

- Physical examination
- Serum/urine pregnancy test in female patients of childbearing potential
- Clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis)
- Vital signs measurement (sitting SBP/DBP, pulse rate, and body temperature)
- Recording of 12-lead ECGs
- AEs
- Concomitant medication review (including confirmation and recording of medications entered into the eDiary in the eCRF)

Any protocol-specified safety assessment may be repeated or conducted unscheduled as necessary to ensure patient safety.

10.2.3.1 Physical Examination

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.

10.2.3.2 Pregnancy

All female patients 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 patients confirmed to be pregnant at any time during the study should be immediately discontinued. Patients 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 10.2.3.7). Any pregnancy that occurs in a female patient (or female partner of a male patient) during the study, or within 30 days after taking the last dose of study medication, should be reported to Dr. Reddy's Laboratories as described in Section 10.2.3.7. Pregnancies will be followed to the end of the pregnancy, whether successful live birth or premature termination, type and date of delivery, any congenital

malformations or birth defects or any other adverse fetal or neo-natal 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 patients (with female partner) must agree to practice a reliable form of contraception or abstinence during the study.

10.2.3.3 Clinical Laboratory Evaluation

The following clinical laboratory evaluations will be performed in accordance with assessment time points outlined in Table 10-1.

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 distribution 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)	Albumin Alanine aminotransferase (ALT) Alkaline 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 patients 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 patients 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, laboratory, urine drug test/ethanol screen, serum pregnancy tests, HIV, HBsAg, and HCV antibody analyses will be performed at a central laboratory. Reference ranges will be supplied by Eurofins Central Laboratory and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

10.2.3.4 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 patient has rested in the sitting position for 5 minutes. (See additional exclusion criteria for SBP/DBP screenings in Section 7.3.1 and assessments in Table 10-1).

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 females 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.

10.2.3.5 Twelve-Lead Electrocardiogram

A 12-lead resting ECG will be performed at screening (V1), and at every study visit. Each ECG will be reviewed by the Investigator. Tracings will be printed, signed, and dated by the Investigator and kept in the patient's file. The overall interpretation and determination of the clinical relevance of ECG findings will be the responsibility of the Investigator and will be recorded in the patient's eCRF.

10.2.3.6 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study patient administered a study medication 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 medication and up to 5 days after the last dose of study medication. 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 medication, whether or not related to the study medication. 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 patient 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 informed consent form (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 patient 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 patient, 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 medication. 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 patient's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study medication.
Possibly Related	The event is temporally related to study medication 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 medication use and is consistent with known effects of the study medication and/or improves upon withdrawal of the study medication.
Definitely Related	The event follows a reasonable temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and could not have been produced by other factors such as the patient's clinical state, therapeutic intervention, or concomitant therapy and either occurs immediately following study medication 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 patients 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. Patients 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 medication 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]).

10.2.3.7 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 patient 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 patient'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 patient 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 medication).

Reporting of Serious Adverse Events

Patients should report all SAEs that occur during the clinical study, or within 30 days of receiving the last dose of study medication, 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 medication.

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 Dr. [redacted] at:

Dr. Reddy's Laboratories Inc.
[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 medication administration and linked by the Investigator to this study, should be reported to the study Medical Monitor.

The Sponsor and/or INC Research will promptly notify all relevant parties of findings that could adversely affect the safety of patients, influence patients' 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, INC Research, 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 medication, 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 medication, 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 patient took one or more suspect medicinal product(s) other than the study medication, 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 patient.

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., patient discharge summary or autopsy reports), should be faxed or emailed to the Sponsor.

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

All AEs experienced by a patient, 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 patient is lost to follow-up, until the patient has died, or until 30 days after the last dose of the study medication upon which patients 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).

The blind should not be broken at the study site level except in a medical emergency (where knowledge of the study medication received would affect the treatment of the emergency). For a medical emergency, the blind must only be broken following discussion on a case-by-case basis, at the discretion of the Investigator/treating physician/Sponsor.

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

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

A patient for whom the blind is broken will discontinue study medication and be scheduled for a safety follow-up visit and then discontinued from the study. The patient 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 patients should not be pregnant when entering the study and must not become pregnant during the study; please see Section 10.2.3.2 for additional details. Following

administration of study medication, any known cases of pregnancy in female patients or male patients who impregnate their female partners will be reported to the Sponsor within 24 hours of occurrence. All female patients will be withdrawn from the study and administration of study medication 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 patient 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

The Investigator must notify the Sponsor of any occurrence of overdose with study medication within 24 hours of becoming aware of the overdose. More than 4 doses within 2 hours will be considered as an overdose for this study. 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.

No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed after intravenous administration of Imitrex® Injection. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, and paralysis. The elimination half-life of sumatriptan is about 2 hours, therefore, monitoring of patients after overdose should continue for at least 10 hours or while symptoms or signs persist. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.[11]

10.2.3.8 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 medication at any dose that is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized study medication or summary of product characteristics for an authorized product).

All SUSARs will be subject to expedited reporting. The Sponsor and/or INC Research 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 patient 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 sumatriptan:

Sumatriptan should not be given to patients with documented ischemic or vasospastic CAD. It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of CAD and ischemic myocardial disease or other significant underlying cardiovascular disease. If, during the cardiovascular evaluation, the patient's medical history or ECG investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered. For further details, please refer to the full Imitrex product insert.

10.2.4 Appropriateness of Measurements

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

11 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 primary and all secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of patients (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-02 10 mg or placebo. All data collected during the study will be included in patient data listings. Unless otherwise noted, the data will be sorted first by treatment assignment, patient number, and then by date within each patient number.

All statistical analyses are described in Section 11.6. 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.

11.1 Statistical Analysis Plan

A SAP will be created and approved prior to 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 prior to unblinding of patient's treatment assignment at database lock. This review will assess the accuracy and completeness

of the study database, patient evaluability, and appropriateness of the planned statistical methods.

11.2 Analysis Datasets or Populations

Full Analysis Set

Each DB treatment period will have a full analysis set (FAS), which will include all randomized patients who during the treatment period took at least one dose of study medication, have at least one post-baseline efficacy time point assessment during the 2 hours postdose, and did not use a second dose of study medication or rescue medication prior to the data collection of the 2 hours postdose time point (inclusive).

Safety Population

The safety population will include all patients who receive at least one dose of DB study medication during both treatment periods.

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 patients who have at least 1 post-baseline primary endpoint assessment, who have no significant protocol deviations that will impact the collection or interpretation of the primary endpoint data during the DB1 treatment period. Identification of all patients in the PP population will be determined before the database lock and unblinding.

11.3 Demographic and Other Baseline Characteristics

Patient disposition will be presented for each treatment group, as applicable, and overall. They may include, but are not limited to, the following:

- The number of patients screened
- The number of patients who failed screening
- The number of patients randomized at baseline and the number of patients re-randomized at V3
- The number (%) of patients in the FAS population
- The number (%) of patients in the Safety population
- The number (%) of patients in the PP population
- The number (%) of patients who completed the study
- The number (%) of patients who discontinued from the study and the primary reason for discontinuation

Demographics and baseline characteristics will be summarized descriptively for the FAS population by treatment group and overall. They may include, but are not limited to, the following variables:

- Demographics (age, age group, gender, ethnicity, race, height, weight, body mass index)
- Baseline disease characteristics (i.e., migraine subtype and current treatment status, glycosylated hemoglobin (HbA1c), serology [HIV/HBsAg/HCV antibody])
- Medical history and medication history
- Physical examination at screening

All collected demographics and baseline characteristics data will be listed.

11.4 Efficacy Endpoints

11.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

Proportion of patients who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with moderate to severe headache pain during the DB1 treatment period
Note: Freedom from headache pain is defined as a reduction from predose moderate (Grade 2) or severe (Grade 3) pain to none (Grade 0).

11.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

Proportion of patients who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with headache pain of any level during the DB2 treatment period
Note: Freedom from headache pain is defined as a reduction from predose mild (Grade 1), or moderate (Grade 2), or severe (Grade 3) pain to none (Grade 0).

(Each DB Period)

- Proportion of patients who are pain-free at 10, 15, 20, 30, 60, and 90 minutes after the first dose of study medication
- Proportion of patients who have pain relief at 10, 15, 20, 30, 60, 90, and 120 minutes postdose defined for DB1 as a reduction from predose moderate or severe pain to mild or none postdose, and for DB2 as pre-dose mild, moderate, or severe pain reduced to mild or none postdose)
- Proportion of patients with their MBS among nausea, photophobia, and phonophobia, absent at 10, 15, 20, 30, 60, 90, and 120 minutes postdose after the first dose of study medication taken for a migraine attack
- Proportion of patients who are free from nausea, photophobia, and phonophobia at each postdose time point after the first dose of study medication taken for a migraine attack
- Time to meaningful pain relief
- Time to pain freedom
- [redacted]
- Proportion of patients who have sustained pain freedom at 24 hours (2 to 24 hours) after the first dose of study medication taken for a migraine attack
  Note: Sustained pain freedom at 24 hours is defined as pain free at 2 hours postdose, with no use of rescue medication or additional study medication and no recurrence of headache pain within 2 to 24 hours postdose
- Change in functional disability score at 2 hours and 24 hours after the first dose of study medication taken for a migraine attack
- Proportion of patients who use a second dose of the study medication or rescue medication after 2 hours (2 to 24 hours) postdose
- Treatment satisfaction at 2 hours postdose
- Treatment satisfaction as measured by PPMQ-R at 24 hours postdose

11.4.3 Exploratory Endpoints

The exploratory endpoints for each DB treatment period include:

- [redacted]

11.5 Safety Endpoints

The safety endpoints include:

- Tolerability as assessed by AEs for each treatment period and overall
- Safety as assessed by clinical laboratory tests, vital signs, and ECG for each treatment period and overall.

11.6 Methods of Analysis

11.6.1 Primary Efficacy Analysis

Efficacy analysis for primary, secondary, and exploratory endpoints will be based on the FAS population.

The primary efficacy endpoint, the proportion of patients who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with moderate to severe headache pain during the DB1 treatment period, will be analyzed using Fisher's exact test. The response rate will be calculated as the number of patients who are pain-free at 2 hours postdose divided by the number of patients with non-missing assessment at 2 hours postdose. The number of patients with non-missing assessment, the number of patients with response, the response rate, and the p-value for comparing DFN-02 10 mg versus placebo will be presented.

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

Additional sensitivity analyses and data handling rules for missing data of the primary endpoint will be documented in detail in the SAP.

11.6.2 Secondary Efficacy Analysis

The secondary endpoints for proportion of patients who are free from headache pain, for proportion of patients with their MBS absent, for proportion of patients who are free from nausea, photophobia, and phonophobia, for proportion of patients who have pain relief, for proportion of patients who have sustained pain freedom, and for proportion of patients who use a second dose of the study medication or rescue medication, will be analyzed using Fisher's exact test similarly to the described analysis for the primary endpoint.

The secondary endpoints for time to meaningful pain relief and time to pain freedom will be analyzed using Kaplan-Meier product-limit method.

The secondary endpoints for the change in functional disability score at 2 hours and 24 hours after the first dose of study medication will be analyzed using Wilcoxon signed-rank test. The secondary endpoints for treatment satisfaction at 2 hours postdose as measured on the 7-point scale, and at 24 hours postdose as measured by the PPMQ-R, will be analyzed using the Wilcoxon rank-sum test.

11.6.3 Exploratory Efficacy Analysis

[redacted]

11.6.4 Subgroup Analysis

Subgroup analyses of the efficacy data will be performed as needed and details to be documented in the SAP. All subgroup analyses will be exploratory.

11.6.5 Additional Efficacy Analyses

Additional efficacy analyses will be performed on the PP population. Further statistical details and possible other analyses will be provided in the SAP.

11.6.6 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 medication and up to 5 days after the last dose of study medication. Only TEAEs will be included in summary tables. Migraine headaches will not be captured as AEs. Migraine headaches will be captured by the patient 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 patient reported more than one AE that was coded to the same SOC or PT, the patient will be counted only once for that specific SOC or PT.

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

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

All AEs will also be presented in a by-patient 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 medication, inclusive. Medications will be considered as prior if stopped before the date of first dose of study medication during the DB1 treatment 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). All ECG data, clinical laboratory data, vital signs, physical examinations, study medication use, and concomitant medication use will also be presented in by-patient data listings.

11.7 Interim Analyses

No interim analysis is planned.

11.8 Determination of Sample Size

One hundred patients will be randomized for the DB1 treatment period. Patients who discontinue participation without completing the study protocol will not be replaced.

The primary endpoint is the comparison of the proportion of patients who are pain-free at 2 hours after the first dose of study medication. It is assumed that 15% of placebo and 42% of DFN-02 (treated) patients will be pain-free at 2 hours. A sample size of 50 patients in each DB1 dosing arm will provide 81% power to detect this assumed difference between placebo and DFN-02 at a 5% (2-sided) level of significance.

12 Quality Assurance and Quality Control

12.1.1 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, INC Research, or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.1.2 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 patient who signs an ICF.

In accordance with cGCP and International Conference on 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 patient 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 medication 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 patient 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 INC Research clinical trial management system and will be categorized as major or minor prior to data analysis.

12.1.3 Data Management and Coding

INC Research will be responsible for activities associated with the data management of this study. This will include setting up a relevant database (Medidata RAVE) 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 INC Research.

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.

13 Records and Supplies

13.1 Drug Accountability

Upon receipt of the study medication, the Investigator (or designee) will conduct an inventory of the supplies and verify that study medication 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 medication 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 INC Research, will be maintained at the study site at all times. The study monitor will arrange regular collection of used and unused study medication returned by the patient. The study monitor will also perform an inventory of study medication at the close-out visit to the study site. All discrepancies must be accounted for and documented.

13.2 Financing and Insurance

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

14 Ethics

14.1 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 medication 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 patients and/or other procedures. INC Research 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 prior to 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 patients 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 patients or the conduct of the study. INC Research 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.

14.2 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.[29-31]

14.3 Patient Information and Consent

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

The Investigator or sub-Investigator will inform the patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient 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 patient will be given time to consider the study, if this is required, or if the patient requests more time. Patients will be required to sign and date the ICF. Patients 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, INC Research personnel, or third parties authorized by Dr. Reddy's Laboratories. Patients will be given a signed copy of the ICF for their records.

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

14.4 Patient 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)[32] and applicable local laws and/or regulations on personal data protection.

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

15 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 medication. 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 patient 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 medication 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 prior to the date of submission for publication. If the Sponsor determines that the proposed publication contains patentable patient 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 patients and/or who provided significant input on study design and/or interpretation on study results.

16 References

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17 Investigator Signature Page

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine With or Without Aura

Protocol Number: DFN-02-CD-012

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 Ltd./Dr. Reddy's Laboratories Inc. and of the IRB. I will submit the protocol modifications or any ICF modifications to Dr. Reddy's Laboratories Inc. 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 patients' state of health will be regarded as confidential. All attempts will be made to ensure that no patients' names will be disclosed. All patients 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 patient before disclosure of patient information to a third party.

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

_____ _____
Investigator Signature Date

_____
Printed Name

_____
Institution