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Study ID #:	DFN-15-CD-006
Study Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine with or without Aura
SAP:	Version 3.0, 08 Nov 2017

Statistical Analysis Plan

[redacted]

Sponsor Name:	Dr. Reddy's Laboratories, Ltd.
Protocol Number and Title:	DFN-15-CD-006 A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura
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[redacted] **Project Code:**	1007753
Author:	[redacted]
SAP Version:	Amendment V3.0
SAP Version Date:	08NOV2017

Summary of Changes (Amendment V2.0 to Amendment V3.0)

Section	Revision
8.1.1 Primary Analyses of the Co-Primary Endpoints	Exclusion rule is revised to apply to both co-primary endpoints. This analysis will exclude subjects who took rescue medication prior to the data collection of the 2 hours postdose time point (inclusive; LOCF), ~~For the first co-primary efficacy endpoint, subjects who have predose pain level = mild (Grade 1) will also be excluded~~ ***as well as*** subjects who have predose pain level = mild (Grade 1) or none (Grade 0).
8.2 Secondary Endpoints and Analyses	Exclusion rule is revised: Secondary endpoint analyses will be conducted as indicated for the FAS1 and FAS2 and will exclude subjects who took rescue medication prior to the data collection of the 2 hours postdose time point (inclusive; LOCF). ***For all secondary endpoint analyses in DB1 for the FAS1, subjects who have predose pain level = mild (Grade 1) or none (Grade 0) will also be excluded. For all secondary endpoint analyses in DB2 for the FAS2, subjects who have predose pain level = none (Grade 0) will also be excluded.***

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
[redacted]	
[redacted]	09 Nov 2017 Date (dd-Mmm-yyyy)
[redacted]	09 Nov 2017 Date (dd-Mmm-yyyy)
Dr. Reddy's Laboratories, Ltd.	
[redacted] Digitally signed by [redacted] Date: 2017.11.08 10:07:14 -05'00'	
[redacted]	Date (dd-Mmm-yyyy)

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
DB	Double-Blind
DBP	Diastolic Blood Pressure
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eDiary	Electronic Diary
FAS	Full Analysis Set
GI	Gastrointestinal
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ICHD-3	International Classification of Headache Disorders, 3rd Edition (Beta Version)
ID	Identification
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward

Abbreviation	Description
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
PPMQ-R	Patient Perception of Migraine Questionnaire-Revised
PPS	Per Protocol Set
PT	Preferred Term
QC	Quality Control
QTcF	Fridericia's corrected QT
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SBP	Systolic Blood Pressure
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. Exploratory analyses not identified or defined in this SAP may also be performed to support the clinical development program.

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and are responsible for the production and quality control (QC) of all tables, listings, and figures (TLFs).

2.2. TIMINGS OF ANALYSES

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study and all relevant study data have been processed and integrated into the final locked data base.

3. STUDY OBJECTIVES

3.1. CO-PRIMARY OBJECTIVES

The co-primary objectives of this study are:

- To assess the proportion of subjects who are pain-free at 2 hours postdose (first treated double-blind [DB] treatment period [DB1] attack).

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

3.2. SECONDARY OBJECTIVES

Secondary objectives for each DB period are:

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

- To assess treatment satisfaction at 2 hours and 4 hours postdose (7-point scale)
- To assess treatment satisfaction as measured by Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) at 24 hours postdose

3.3. BRIEF DESCRIPTION

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

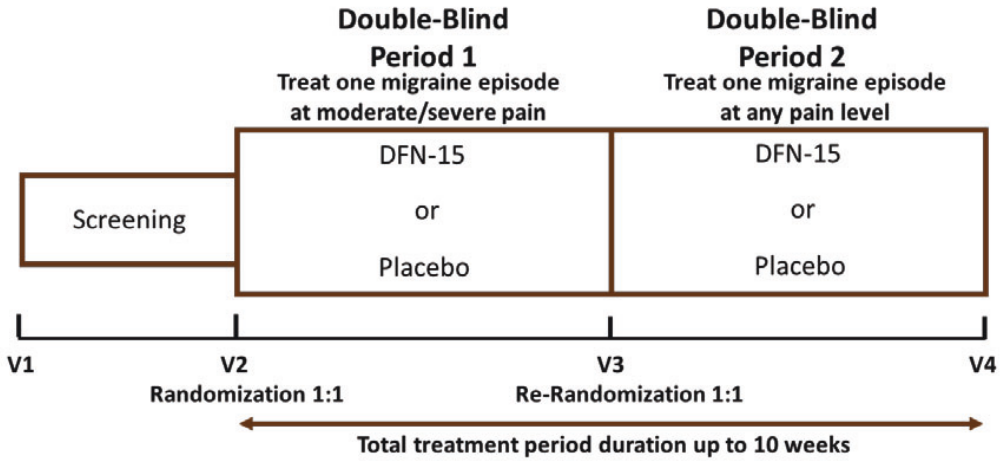
During the DB1 treatment period, subjects will treat 1 migraine attack with study drug as soon as (and no more than 1 hour after) experiencing moderate to severe pain level. If eligible, subjects will be re-randomized into the second DB treatment period (DB2) to treat another migraine attack at any pain level.

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

Subjects will record criteria in real-time in an electronic diary (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 drug use, postdose pain level, symptoms and functional disability, treatment satisfaction, last food intake and fat content, and date and time of rescue medication. The eDiary will be reviewed for compliance and rescue medication.

The overall study design is presented in Figure 1.

Figure 1 Overall Study Design



3.4. SUBJECT SELECTION

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

3.4.1. Inclusion Criteria

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

1. Able and willing to provide written informed consent
2. Male or female, 18 to 75 years of age, inclusive, at screening
   a) If female and of childbearing potential, the subject must have a negative serum pregnancy test at screening, does not plan to become pregnant during the study, and is not lactating.
   b) If female and of childbearing potential, the subject must also have a negative urine pregnancy test at all subsequent study visits after the screening visit and, unless surgically or otherwise sterile or postmenopausal for > 1 year, agrees to practice a reliable form of contraception or abstinence during the study. Acceptable forms of contraception include: bilateral tubal ligation, implants, injectables, combined oral contraceptives, an intrauterine device, a vasectomized partner, an exclusively female partner, and double-barrier methods.
   c) If male (with female partner), the subject must agree to practice a reliable form of contraception or abstinence during the study.

3. A history of episodic migraine (per ICHD-3), who experience 2 to 8 migraine attacks per month for at least the past 12 months, with no more than 14 headache days per month, and with 48 hours of headache-free time between migraine attacks
4. Have migraine with or without aura with onset before age 50 years
5. Report usual migraine pain of 2 (moderate) or 3 (severe) on headache pain severity scale without treatment
6. Subjects who, in the opinion of the Investigator, are willing and able to:
   a. Evaluate and record pain, migraine symptoms, and study drug effectiveness information in real-time using a subject eDiary for the duration of the study;
   b. Record each instance of the use of study drug and rescue medication in real-time using a subject eDiary for the duration of the study;
   c. Comply with all other study procedures and scheduling requirements.
7. Ability to read, speak, and understand English proficiently

3.4.2. Exclusion Criteria

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

1. Minors, even if they are in the specified study age range
2. Exposure to DFN-15 prior to the study
3. Medication overuse:
   - Opioids ≥ 10 days during the 90 days prior to screening
   - Combination medications (e.g., Fiorinal®) ≥ 10 days during the 90 days prior to screening (applies only if includes opioid and/or barbiturate)
   - NSAIDs or other simple medications > 14 days a month during the 90 days prior to screening
   - Triptans or ergots ≥ 10 days a month during the 90 days prior to screening
4. Treated with onabotulinumtoxinA (Botox®) for migraine within 4 months prior to screening. (If treated for cosmetic reasons, subjects may be included.)
5. On unstable dosages of migraine prophylactic medications within 30 days prior to and through screening
6. Taking mini-prophylaxis for menstrual migraine
7. On chronic warfarin sodium or equivalent
8. Cerebrovascular events including but not limited to a history of stroke or transient ischemic attack
9. A history of migralepsy (seizure following a migraine) or a concurrent diagnosis of seizure disorder
10. Subjects who cannot differentiate between a migraine headache and tension-type or cluster headache or other types of headache
11. A history of cluster headaches
12. Subjects with the diagnosis of "probable migraine" (per ICHD-3)
13. Subjects who have intolerance to any formulation of celecoxib or sulfonamides, or who have experienced a significant AE related to any other NSAID, including

aspirin, which caused the condition of asthma, rhinitis, nasal polyps, or Samter's triad

14. Subjects for whom NSAIDs are contraindicated (e.g., gastrointestinal (GI) bleed, ulcer, history of acute renal failure)
15. Ischemic coronary artery disease including but not limited to angina pectoris, history of myocardial infarction or documented silent ischemia or coronary artery vasospasm, including Prinzmetal's angina; symptomatic peripheral vascular disease
16. A history of congenital heart disease
17. Uncontrolled hypertension or screening systolic/diastolic blood pressure (SBP/DBP) > 140/90 mmHg (the values should be confirmed to rule out a transient elevation); see protocol Section 6.3.1 for details
18. Any abnormal physiology and/or pathology that, in the opinion of the Investigator or Sponsor, would be contraindicated for study participation and would not allow the objectives of the study to be met
19. Subjects who show any clinical laboratory or electrocardiogram (ECG) abnormality that in the opinion of the Investigator or Sponsor would endanger the subject or interfere with the study conduct. If the results of the clinical laboratory or ECG are outside of normal reference range the subject may still be enrolled, but only if these findings are determined to be not clinically significant by the Investigator. This determination must be recorded in the subject's source document before enrollment.
20. Fridericia's corrected QT (QTcF) interval > 450 msec; see Section 3.4.3 for details.
21. Serum creatinine > 1.5 × the upper limit of normal (ULN)
22. Serum total bilirubin > 1.5 × ULN
23. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 × ULN
24. Subjects with uncontrolled diabetes mellitus, or a glycosylated hemoglobin (HbA1c) > 7.9%, or with diabetes mellitus requiring insulin
25. A history of alcohol or substance use disorder (including marijuana) according to the Diagnostic and Statistical Manual of Mental Disorders, Edition 5 (DSM-5) within 1 year prior to screening
26. Current treatment with antipsychotics or use of antipsychotics within 30 days prior to randomization (if used for non-psychiatric conditions, should be evaluated on a case-by-case basis with the Medical Monitor)
27. A positive urine drug screen for recreational drugs, alcohol, marijuana (whether legal or not) or for prescription drugs not explained by stated concomitant medications
    - Subjects consuming opioids for the treatment of migraine or using opioids or barbiturates temporarily for a legitimate medical cause may participate as long as they do not meet the medication overuse criteria in Exclusion Criteria #3, above.
    - Chronic use of benzodiazepines is allowed if used for legitimate medical use, as long as the regimen has been stable for at least 3 months prior to screening and is expected to remain stable throughout the study

- Chronic use of amphetamines to treat attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) and related disorders is allowed as long as the regimen has been stable for at least 3 months prior to screening and is expected to remain stable throughout the study
  Note: For the above-mentioned conditions, the site must have appropriate documentation to justify the mentioned drug use (e.g., documented medical history and a valid prescription-based dispensation)

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

3.4.3. Additional Exclusion Criteria Clarification for SBP/DBP and QTcF

Subjects 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. Subjects 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 subject has a sustained resting SBP/DBP > 140/90 mmHg at Visit 1 (V1) or V2, those subjects should be excluded. If a subject has a

sustained SBP/DBP > 140/90 mmHg at a visit after V2, those subjects should be discontinued from the study. Any subject without a known history of hypertension that presents at screening with SBP/DBP >140/90 mmHg should be excluded (if at V1 or V2) or discontinued (if at a visit after V2) if the 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 subject in a semi-reclined position in a quiet room. Subjects with persistent elevations, despite repeat assessments, should be excluded and referred to an appropriate healthcare provider for further assessment.

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

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

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

1. For QTcF between 451 msec and 460 msec (inclusive), the subject may continue in the study if the Investigator assesses the ECG as not clinically significant (NCS).
2. For QTcF > 460 msec:
    a) Instruct the subject not to take the study drug until further notice.
    b) If the Investigator has assessed the ECG as NCS, have the subject return, after Medical Monitor approval, to conduct 2 ECGs with a minimum of 5 minutes between tracings.
    c) Transmit these additional ECGs to ERT for central interpretation.
    d) If one or both ECGs again shows QTcF > 460 msec, based on the central reader, then the subject must be discontinued from the study.

3.5. DETERMINATION OF SAMPLE SIZE

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

The first co-primary endpoint is the comparison of the proportion of subjects who are pain-free at 2 hours after the first dose of study drug. It is assumed that 17.6% of

placebo and 29.2% of DFN-15 (treated) subjects will be pain-free at 2 hours. A sample size of 600 subjects will provide 88% power to detect this assumed difference between placebo and DFN-15 at a 5% (2-sided) level of significance and with a 15% dropout rate.

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

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

3.6. TREATMENT ASSIGNMENT & BLINDING

The DFN-15-CD-006 study is a randomized, 2 DB treatment period, placebo-controlled study. Eligible subjects will be randomized in a 1:1 ratio in both DB periods to receive orally either DFN-15 or matching placebo, to be used in one migraine attack. The randomization schemes for both DB periods will be generated by the biostatistics group of [redacted]. The interactive web response system (IWRS) will assign the appropriate study kit to each subject for each DB treatment period. If a subject discontinues from the study after randomization, the subject identification (ID) number and randomization number will not be reused, and the subject will not be allowed to re-enter the 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 the study. Blinding is critical to the integrity of this clinical study; however, in the event of a medical emergency for an individual subject, in which knowledge of the treatment assignment is critical to the subject's management, the blind for the subject may be broken by the Investigator (or designee) by contacting IWRS. Before unblinding, the Investigator (or designee) should have determined that the treatment information is necessary to decide the subject's immediate management, and must make every effort to contact the Medical Monitor 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 subject 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.

3.7. ADMINISTRATION OF STUDY DRUG

During the DB1 treatment period, randomized subjects will be instructed to use the study drug [either DFN-15 120 mg (25 mg/mL) or a matching placebo] 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). In the DB2 treatment period, eligible re-randomized subjects will receive study drug to treat 1 migraine attack at any pain level.

Study drug should only be used to treat a new migraine attack, not a recurrence, and there should be at least 48 hours of pain and symptom freedom from a previous attack.

At the end of DB1 treatment period and prior to the start of the DB2 treatment period, all used and unused study drug will need to be returned. At the end of the study, subjects will be required to return all used and unused study drug, study drug containers, and a completed eDiary.

3.8. STUDY PROCEDURES AND FLOWCHART

The duration of study participation will be up to approximately 13 weeks, including a screening period of approximately 3 weeks, 2 DB treatment periods with up to 4 weeks allowed to experience and treat a migraine attack in each, and 2 to 7 days for subjects to return to the site after treatment.

Table 1 summarizes the planned study assessments.

Table 2 summarizes the eDiary assessments.

Table 1 Schedule of Assessments

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

Vital signs (sitting SBP/DBP, pulse rate, body temperature)	X	X	X	X
Serum pregnancy test (hCG)[7]	X			
Urine pregnancy test[8,]		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis); TSH at Screening	X	X	X	X
Glycosylated hemoglobin (HbA1c)	X			X
Serology (HIV, 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 drug[9]		X	X	
Subject study drug compliance and accountability[10]			X	X
Subjects record data in the eDiary[11]	→	→	→	→
Review, confirm, and ensure proper recording of the subject eDiary entries[12]		X	X	X
Collect eDiary[13]				X

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

[1] V4 will occur up to 10 weeks after baseline (V2).
[2] Subjects who do not complete both DB periods will complete an ET visit.
[3] Subjects may be randomized earlier during this period if they meet inclusion/exclusion criteria and headache assessment criteria. The screening period may also be extended based on Investigator judgment and in consultation with the Medical Monitor.
[4] Before eDiary dispensing, initial screening should determine to the extent possible that the subject may be eligible for the study and is able, willing, and understands after being instructed how to use the eDiary; eDiary will be dispensed once if the subject is randomized and used throughout the DB periods. At V2, randomized subjects will be re instructed and re trained on the eDiary usage to ensure real time entry of predose and postdose assessments and the level of migraine pain to treat (moderate or severe for first treatment and of any pain level for the second). Thereafter, randomized subjects will be reinstructed on eDiary usage, and re trained on instructions as needed.
[5] Physical examination data will be recorded in the source at screening (V1). A complete physical examination will be performed, including examination of head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems. At other visits, symptom driven limited physical examination will be performed. Any subsequent untoward change during the study will be recorded as an AE. Suicidality risk will be determined and recorded at screening (V1) and checked at all subsequent visits. Significant suicide risk, in the opinion of the Investigator, is exclusionary at V1 and V2. A randomized subject will be discontinued if a significant suicide risk is determined at subsequent visits. At any visit, subjects who are a suicide risk should be referred to a mental health specialist. The Medical Monitor should also be notified.
[6] Weight only.
[7] Serum pregnancy test will be performed at screening (V1) for all female subjects of childbearing potential.
[8] Urine pregnancy tests will be performed at all study visits after screening for all female subjects of childbearing potential.
[9] Subjects will be instructed by the study site staff on the proper administration of study drug to ensure compliance. Written instructions for use of the study drug will be distributed to Investigator sites, and subjects should be confirmed to have, or be provided with, the instructions every time study drug is dispensed.
[10] Unused study drug returned by subjects should not be redispensed.
[11] When the subject experiences a migraine episode, they should contact the site within 1 day of treating with study drug to schedule their next visit. The eDiary will be used to record all migraine attacks treated with study drug during the study period.
[12] Screening eDiary information will be kept in the source. It is compulsory for all the subjects to check in the eDiary every day during the entire study period. If a subject does not consistently check in or does not report a migraine attack in the eDiary for 2 3 weeks, it is recommended they should be contacted by study staff to check if the subject has technical difficulties or confirm they have not experienced a migraine.
[13] Arrangements should be made by the site for a timely return of the eDiary device for subjects who screen fail.

Table 2 eDiary Assessments

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

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

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

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

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

4. ENDPOINTS

4.1. CO-PRIMARY ENDPOINTS

The co-primary endpoints of this study are:

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

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

4.2. SECONDARY ENDPOINTS

Secondary endpoints for each DB period are:

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

- The proportion of subjects who are pain-free at 2 and 4 hours postdose whose BMI is < 30 vs. subjects whose BMI is ≥ 30, and whose BMI is < 25 vs. subjects whose BMI is ≥ 25.
- The proportion of subjects who have pain recurrence between 2 to 24 hours (i.e., pain-free at 2 hours postdose, with pain [mild, moderate, or severe] reported at 24 hours postdose) compared between DFN-15 and placebo.
- The proportion of subjects who have sustained pain relief at 2 to 24 hours postdose (i.e., pain relief at 2 hours postdose, with no use of rescue medication and no worsening of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo.
- The proportion of subjects who have sustained pain freedom at 2 to 24 hours postdose (i.e., pain-free at 2 hours postdose, with no use of rescue medication, and no recurrence of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo.
- The proportion of subjects who use rescue medication after 2 hours (2 to 24 hours) postdose compared between DFN-15 and placebo.
- Treatment satisfaction at 2 hours and 4 hours postdose as determined on a 7-point scale compared between DFN-15 and placebo. DFN-15 will also be compared to same question in the Baseline PPMQ-R.
- Treatment satisfaction as measured by PPMQ-R at 24 hours postdose compared between DFN-15 and placebo.

5. ANALYSIS SETS

5.1. SCREENED SET

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

5.2. RANDOMIZED SET

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

5.3. SAFETY SET

The Safety Set (SS) will include all subjects who took at least one dose of DB study drug during one or both treatment periods, and have it recorded in their eDiary. Subjects will be analyzed according to the treatment they receive. The Safety Set 1 (SS1) will include randomized subjects who took at least one dose of DB study drug during the DB1 treatment period. The Safety Set 2 (SS2) will include subjects who were re-randomized and took at least one dose of DB study drug during the DB2 treatment period. The SS, SS1, and SS2 will be used for all analyses of safety endpoints including summaries of TEAEs, ECGs, and clinical laboratory results.

5.4. FULL ANALYSIS SET

Each DB treatment period will have a Full Analysis Set (FAS). The Full Analysis Set 1 (FAS1) will include all randomized subjects who took at least one dose of study drug during the DB1 treatment period and have at least one post-baseline efficacy time point assessment for either pain or symptom (among nausea, photophobia, phonophobia) in DB1. The Full Analysis Set 2 (FAS2) will include all re-randomized subjects who took at least one dose of study drug during the DB2 treatment period and have at least one post-baseline efficacy time point assessment for either pain or symptom (among nausea, photophobia, phonophobia). Subjects in the DB1 will be analyzed according to their randomized treatment. Subjects in the DB2 will be analyzed according to their re-randomized treatment. The FAS1 and FAS2 will be used for all analyses of efficacy endpoints.

5.5. PER PROTOCOL SET

The Per Protocol Set (PPS) will include all FAS1 subjects who have at least 1 post-baseline primary endpoint assessment for both co-primary endpoints (observed and LOCF), and who have no significant protocol deviations that will impact the collection

or interpretation of the co-primary endpoint data during the DB1 treatment period. Identification of subjects in the PPS will be determined before the database lock and unblinding. Subjects in the PPS will be analyzed according to their DB1 randomized treatment.

5.6. PROTOCOL DEVIATIONS

Protocol deviations will be captured during monitoring visits or via remote monitoring. All deviations will be recorded in the [redacted] clinical trial management system and will be categorized as major or minor. Major protocol deviations will be summarized by deviation type using frequency counts. All deviations will be listed by subject.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

6.1.1. Summary Statistics

In general, descriptive statistical methods will be used to summarize the data from this study. With appropriate sample sizes, hypothesis testing can be performed for the co-primary and secondary efficacy endpoints.

The term "treatment group" refers to the applied treatment regimen during DB1 or DB2 (DFN-15 120 mg or placebo). All data collected during the study will be included in subject data listings. All subjects entered into the database will be included in subject data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data and frequencies and percentages for categorical data.

All categorical/qualitative data will be presented using absolute frequency counts and percentages. The total number of subjects in the treatment group overall (N) in the specified population will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. All percentages will be presented in parentheses with 1 decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

Unless specified otherwise, all statistical testing and confidence intervals (CIs) will be 2-sided and will be performed using a significance (alpha) level of 0.05.

6.1.2. Reporting Precision

Summary statistics will be presented to the following degree of precision:

Table 3 Reporting Precision

Statistics	Degree of Precision
Mean (of all kinds), Median, Quartiles, Confidence limit boundaries	One more decimal place than the raw data
Standard deviation, Standard error	Two more decimal places than the raw data
Minimum, Maximum	The same number of decimal places as the raw data
P-value	Rounded to 3 decimal places and formatted as 0.xxx; P-values smaller than 0.001 as '<0.001'; P-values smaller than 0.0001 as '<0.0001'
Percent	One decimal place

All fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 - 0.30, not .12 - .30).

All analyses and summaries will be produced using Statistical Analysis System (SAS®) for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA) or higher. Summaries will be presented by treatment unless otherwise specified.

6.2. KEY DEFINITIONS

6.2.1. Baseline

Unless specified otherwise, the baseline assessment will be the latest available valid measurement taken prior to the administration of the initial dose of study drug during each DB period. In the event that a migraine attack happens immediately following randomization, the assessments taken on the same day as the administration of the initial dose of study drug, but prior to the time study drug is taken, can be considered as baseline.

6.2.2. First Dose Date

The first dose date for DB1 is defined as the first dose of study drug taken after randomization in DB1. The first dose date for DB2 is defined as the first dose of DB2 study drug taken after re-randomization into DB2.

6.2.3. Study Day

If the assessment date is after the date of the first dose during each treatment period, the study day is calculated as date of assessment - date of the first dose administration + 1. If the assessment date is prior to the date of the first dose during each treatment period, the study day is calculated as date of assessment - date of the first dose administration. Study day 1 for each DB treatment period is the day during which the first dose of study drug during the first treatment period is administered.

6.2.4. Treatment Day

If the assessment date is after the date of the first dose during the current DB treatment period, the treatment day is calculated as date of assessment - date of the first dose administration during the current DB treatment period + 1. If the assessment date is prior to the date of the first dose during the current DB treatment period, the treatment day is calculated as date of assessment - date of the first dose administration during the current DB treatment period. Treatment day 1 is the day during which the first dose of study drug during the current DB treatment period is administered.

6.2.5. Treatment Emergent Adverse Events

A TEAE for DB1 is defined as an AE that started on or after the first dose of study drug (DFN-15 or placebo) in DB1 or any existing AE that worsens in severity on or after the date of the first dose of study drug in DB1 up to 5 days after the date of the last dose of study drug in DB1 or up to taking DB2 study drug, whichever occurs first.

A TEAE for DB2 is defined as an AE that started on or after the first dose of study drug (DFN-15 or placebo) in DB2 or any existing AE that worsens in severity on or after the date of the first dose of study drug in DB2, up to 5 days after the date of the last dose of study drug in DB2.

6.3. MISSING DATA

Subjects are allowed to withdraw from the study at any time. Subjects who withdraw from the study will have all data listed and, wherever relevant, included in any subject summaries. Analyses on quantitative and categorical variables will include data from subjects with non-missing values. Partial dates will be listed as recorded on the case report form (CRF). Imputation of missing or incomplete dates will only be performed for summaries of AEs and concomitant medications unless otherwise specified.

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day, and the year is present	January 1 of that year or DB period dose date if the year is the same as the year	December 31 of that year

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
	of the DB period dose date	
Missing day, but year and month are present	First day of that month or DB period dose date if the year and month are the same as the year and month of the DB period dose date	Last day of that month
Missing month, but year and day are present	Missing month imputed as January	Missing month imputed as December

6.4. VISIT WINDOWS

There will be no derivation for visit windows in terms of summary of assessments. Nominal visits as indicated in Table 1 will be used for TLFs.

6.5. POOLING OF CENTERS

There will be no pooling of centers.

6.6. SUBGROUPS

Subgroup analyses will be conducted on the co-primary efficacy endpoints and will be exploratory in nature. The following categories will be evaluated in the subgroup analyses:

- Age (18-34 years, 35-49 years, 50-64, and >=65 years)
- Gender (male and female)
- Ethnicity (Hispanic and non-Hispanic)

Subgroup analyses of efficacy are described in Section 8.3. Additional subgroup analyses based on baseline information may be performed. These analyses will be data driven, exploratory, and described in the Clinical Study Report if conducted.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be presented for the Screened Set, and will include the following:

- The number of subjects screened
- The number (%) of subjects who failed screening
- The number (%) of subjects randomized into DB1
- The number of subjects re-randomized into DB2
- The number (%) of subjects in the FAS1
- The number (%) of subjects in the FAS2
- The number (%) of subjects in the SS
- The number (%) of subjects in the SS1
- The number (%) of subjects in the SS2
- The number (%) of subjects in the PPS
- The number (%) of subjects who completed DB1
- The number (%) of subjects who completed DB2
- The number (%) of subjects who completed the study
- The number (%) of subjects who discontinued from DB1 and the primary reason for discontinuation
- The number (%) of subjects who discontinued from DB2 and the primary reason for discontinuation
- The total number (%) of subjects who discontinued from the study and the primary reason for discontinuation

The summary will be performed for the Screened Set, as well as for the DB1 and DB2 treatment periods. The denominators for the percentage calculation will be listed in the footnote of subject disposition table.. No statistical testing will be performed on these data.

Subjects' completion/discontinuation status will be listed, including subject identifier, date of completion/early discontinuation and, for those who discontinued early, the specific reason(s) for discontinuation.

The inclusion/exclusion criteria for the subjects who fail screening will be listed.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and other baseline characteristics will be summarized for the SS, SS1, and SS2 by treatment group and overall, with descriptive statistics including n, mean, standard deviation, median, minimum, and maximum for numeric variables and frequency and percentage for categorical variables. Demographics include age, gender, childbearing potential for females, ethnicity, race, height, weight, smoking history, and BMI.

BMI will be calculated as follows:

$$\text{BMI } (kg/m^2) = \text{Weight } (kg)/[\text{Height}(m)^2].$$

All collected demographics and baseline characteristics will be listed.

7.3. MIGRAINE HISTORY

All migraine history data will be summarized descriptively by treatment group and overall for the SS, SS1, and SS2.

All collected migraine history data will be listed.

7.4. MEDICAL HISTORY AND CONCOMITANT DISEASES

A summary table of the number and percentage of subjects by medical history system organ class (SOC) and preferred term (PT) will be produced for subjects in the SS. Previous and concurrent diseases/conditions will be sorted alphabetically by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 19.0 or higher. For the summary tables, a subject may appear more than once if he/she has more than one medical history coded under different SOC categories. However, the subject will be counted only once in the overall category.

A separate by-subject listing for medical history data will also be provided. Surgical history including procedure, date of surgery, and reason for surgery will be listed.

7.5. MEDICATION

7.5.1. Study Drug Accountability

All data in the study drug accountability log will be listed, which will include the dates and kit number(s) of the drug dispensed and returned.

7.5.2. Prior and Concomitant Medications

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.

Summaries of medications will be presented in tabular form using the highest level ATC term as an upper classification and the preferred drug name as a lower classification level. All medications will be summarized by treatment group and overall and sorted by descending counts in the upper classification term and the lower classification term within the upper. The summary will consist of the frequency and percentage of subjects who used the medication at least once. For each subject, the medication will be counted only once within the upper classification level and only once within the lower classification level.

Medications will be considered prior if stopped before the DB1 dose date. Medications with a start or stop date on or after the DB treatment period dosing date will be considered concomitant medications. If a concomitant medication starts on or after the start time of DB1 dose administration, it is considered a concomitant medication to the study treatment in DB1, but not in DB2. If a concomitant medication starts on or after the start time of DB2 dose administration, it is considered a concomitant medication to the study treatment in DB2. All medications marked as ongoing are concomitant medications. A medication with an incomplete start/stop date will have its date imputed as described in SAP Section 6.3 solely to determine if the medication is prior or concomitant.

Summaries of prior and of concomitant medications will be presented separately in tables and will be based on the SS. Prior and concomitant medications will be listed by subject. An identifier will be included to show if a medication is prior or if it is concomitant with respect to the applicable DB treatment period.

8. EFFICACY

8.1. CO-PRIMARY EFFICACY ENDPOINTS AND ANALYSES

8.1.1. Primary Analyses of the Co-Primary Endpoints

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

The second co-primary efficacy endpoint is the proportion of subjects who are free from their Screening MBS among nausea, photophobia, and phonophobia at 2 hours postdose compared between DFN-15 and placebo in the DB1 treatment period. A subject's Screening MBS is obtained at Screening via Migraine History assessment, and for the analysis of the co-primary endpoint that Screening MBS symptom must be present at predose but it does not have to be designated as the MBS at predose.

To test for statistical significance of the co-primary efficacy endpoints, the closed sequential testing procedure will be utilized. If the first co-primary endpoint is statistically significant at a two-sided 0.05 level of significance, the second co-primary endpoint will be tested at a two-sided 0.05 level of significance. The study must show a significant statistical beneficial experimental treatment effect for both co-primary endpoints to be considered statistically successful, controlling the significance level at 0.05. Since statistical significance with both co-primary endpoints is required to declare trial success, multiplicity due to multiple primary endpoints is a non-issue.

The first co-primary efficacy endpoint will be analyzed using Fisher's exact test. Following the closed sequential procedure, the second co-primary efficacy endpoint will be analyzed using Fisher's exact test if the first co-primary endpoint is statistically significant.

The proportion of subjects who are pain-free at 2 hours postdose will be calculated as the number of subjects who are pain-free at 2 hours postdose divided by the number of subjects with non-missing assessment at 2 hours postdose. Missing primary efficacy endpoint data will be imputed using the last observation carried forward (LOCF). Results based on the LOCF data and the observed data will be displayed separately.

The number of subjects with response, the number of subjects with non-missing assessment, proportions for the DFN-15 and placebo groups, 95% exact CIs for those proportions, the odds ratio for response, and the corresponding p-value will be presented for the comparison between two treatment groups for the FAS1. This analysis will exclude subjects who took rescue medication prior to the data collection of the 2 hours postdose time point (inclusive; LOCF), as well as subjects who have predose pain level = mild (Grade 1) or none (Grade 0). The analysis will also be performed using the PPS.

If the first co-primary efficacy endpoint is statistically significant, results will be found similarly for the second co-primary efficacy endpoint.

If statistical significance ($p < 0.05$) is not achieved for either study 006 or study 007 (or both studies) co-primary endpoints, additional analyses will be conducted. Detailed information will be included in a separated Statistical Analysis Plan.

8.1.2. Sensitivity Analyses of the Co-Primary Endpoints

Besides the scenario with the observed missing data for the co-primary efficacy endpoints, two additional scenarios will be considered for each of the co-primary endpoints.

For the first co-primary endpoint, in one scenario, subjects with missing headache pain assessments at 2 hours postdose will be assigned as having a pain level of 3 (severe) at 2 hours postdose; that is, they will be assigned as having severe headache pain at 2 hours postdose. In another scenario, subjects with missing headache pain assessments at 2 hours postdose will be assigned as having a pain level of 0 (None) at 2 hours postdose; that is, they will be assigned as having headache pain freedom at 2 hours postdose.

For the second co-primary endpoint, in one scenario, subjects with a missing response for MBS status will be assigned as being free from their MBS. In another scenario, subjects with a missing response for MBS status will be assigned as not being free from their MBS.

For the first co-primary endpoint, proportions of subjects pain-free at 2 hours postdose for the DFN-15 and placebo groups, 95% exact CIs for those proportions, and the corresponding p-value from Fisher's exact test for the three scenarios will be presented. A similar analysis will be conducted for the proportion of subjects who are free from their MBS at 2 hours postdose.

8.1.3. Supplemental Analyses of the Absence of Screening MBS

Supplemental analysis will be conducted for the proportion of subjects who are free from their Screening MBS at 2 hours postdose with break down by individual symptoms (nausea, photophobia, and phonophobia) compared between DFN-15 and placebo in the DB1 treatment period.

8.2. SECONDARY ENDPOINTS AND ANALYSES

The secondary endpoints that involve proportions of subjects who have a response will be summarized by treatment group and will be analyzed using the LOCF for missing secondary efficacy endpoint data.

Secondary endpoint analyses will be conducted as indicated for the FAS1 and FAS2 and will exclude subjects who took rescue medication prior to the data collection of the 2

hours postdose time point (inclusive; LOCF). For all secondary endpoint analyses in DB1 for the FAS1, subjects who have predose pain level = mild (Grade 1) or none (Grade 0) will also be excluded. For all secondary endpoint analyses in DB2 for the FAS2, subjects who have predose pain level = none (Grade 0) will also be excluded.

8.2.1. TEAEs

The proportion of subjects who have a TEAE during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2.

8.2.2. Freedom from Nausea, Photophobia, and Phonophobia Postdose

The proportion of subjects who are free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose during each DB treatment period will be summarized by symptom, treatment group, and time point for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups. Subjects who report a symptom predose and report the status of the symptom at the particular postdose time point will be analyzed.

8.2.3. Time to Pain Relief and Pain Freedom Postdose

The following two secondary efficacy endpoints are captured in the subject eDiary separately from the scheduled time points, and are self-initiated based on the actual time of a subject's perception of pain relief and pain freedom (if they occur) within the first 2 hours postdose. Descriptive statistics for the two endpoints will be provided by treatment group for the FAS1 and FAS2. Additionally, the two endpoints will be summarized and graphically presented by treatment group for the FAS1 and FAS2 using Kaplan-Meier survival estimation. Comparisons between treatment groups will be performed using the log-rank test.

8.2.3.1. Time to Meaningful Headache Pain Relief Postdose

Time to meaningful headache pain relief is defined as the time in minutes from the time a subject takes study drug until the time a subject indicates meaningful pain relief in the eDiary within 2 hours postdose. The time to meaningful headache pain relief postdose will be summarized and analyzed using Kaplan-Meier survival estimation for the FAS1 and FAS2. The corresponding p-values from a log-rank test will be computed for the comparison between treatment groups.

8.2.3.2. Time to Headache Pain Freedom Postdose

Time to headache pain freedom is defined as the time in minutes from the time a subject takes study drug until the time a subject indicates pain freedom in the eDiary within 2 hours postdose. The time to headache pain freedom postdose will be summarized and analyzed using Kaplan-Meier survival estimation for the FAS1 and FAS2.

The corresponding p-values from a log-rank test will be computed for the comparison between treatment groups.

8.2.4. Headache Pain Relief Postdose

The proportion of subjects who have pain relief at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose will be summarized by treatment group and time point for the FAS1 and FAS2. For DB1, headache pain relief is defined as a reduction in migraine pain from predose severe or moderate to mild or none postdose. For DB2, headache pain relief is defined as moderate or severe pain predose reduced to mild or none postdose, or mild pain predose reduced to none postdose. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups. Subjects who report a headache predose and rate the headache pain level at the particular postdose time point will be analyzed.

8.2.5. Headache Pain Freedom Postdose

The proportion of subjects who are pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.6. Absence of MBS Postdose

The proportion of subjects with their Screening MBS among nausea, photophobia and phonophobia absent at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose during each DB treatment period will be summarized by treatment group and time point for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups. Subjects who report an MBS at Screening among nausea, photophobia and phonophobia (those with only one of the three symptoms reported will have that symptom designated as MBS by default), and have this symptom present at predose and report the status of their symptoms at the particular postdose time point will be analyzed.

Absence of Screening MBS will be analyzed similarly at all postdose timepoints for both treatment periods.

8.2.7. Change in Functional Disability Score Postdose

The values of the functional disability scale are: 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.

The change in functional disability score from baseline to 2, 4, and 24 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from the Wilcoxon rank-sum test will be computed for the comparison between treatment groups. P-values from the Wilcoxon signed-rank test will be computed for the change from baseline within each treatment group.

The following levels of change from baseline in functional disability score will be compared between DFN-15 and placebo in each DB period: 3 point change, 2 point change, 1 point change, 0 point change, -1 point change, -2 point change, and -3 point change. The proportion of subjects with those levels of change from baseline during each DB treatment period will be summarized by treatment group and time point for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups for each category.

8.2.8. Headache Pain Freedom Among Subjects with Cutaneous Allodynia

The proportion of subjects who are pain-free at 2 and 4 hours postdose during each DB treatment period among those subjects reporting cutaneous allodynia prior to dosing will be summarized by treatment group and time point for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.9. Headache Pain Freedom Among BMI Categories

The proportion of subjects who are pain-free at 2 and 4 hours postdose whose BMI is < 30 vs. subjects whose BMI is ≥ 30 during each DB treatment period will be summarized by treatment group and time point for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups. The same summary will be conducted for subjects whose BMI is < 25 vs. subjects whose BMI is ≥ 25.

8.2.10. Headache Pain Recurrence Postdose

The proportion of subjects who have pain recurrence between 2 to 24 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. Pain recurrence between 2 to 24 hours is defined as pain-free at 2 hours postdose, with pain (mild, moderate, or severe) reported at 24 hours postdose. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.11. Sustained Headache Pain Relief Postdose

The proportion of subjects who have sustained pain relief at 2 to 24 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. Sustained pain relief at 2 to 24 hours is defined as pain relief at 2 hours

postdose, with no use of rescue medication and no worsening of headache pain within 2 to 24 hours postdose. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.12. Sustained Headache Pain Freedom Postdose

The proportion of subjects who have sustained pain freedom at 2 to 24 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. Sustained pain freedom at 2 to 24 hours is defined as pain-free at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.13. Use of Rescue Medication Postdose

The proportion of subjects who use rescue medication at 2 to 24 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.14. Subject-Rated Treatment Satisfaction Postdose

The possible values of the subject treatment satisfaction scale are: 1 = very satisfied; 2 = satisfied; 3 = somewhat satisfied; 4 = neither satisfied nor dissatisfied; 5 = somewhat dissatisfied; 6 = dissatisfied; 7 = very dissatisfied.

Subject-rated treatment satisfaction based on a 7-point scale at 2 and 4 hours postdose during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from the Wilcoxon rank-sum test will be computed for the comparison between treatment groups.

The subject-rated treatment satisfaction score at 2 and 4 hours postdose and the baseline PPMQ-R response for the same question will be compared for the DFN-15 group only. The corresponding p-value from the Wilcoxon rank-sum test will be computed for this comparison.

The difference between the subject-rated treatment satisfaction score at 2 and 4 hours postdose and the baseline PPMQ-R response for the same question will be summarized by treatment group for the FAS1 and FAS2. P-values from the Wilcoxon rank-sum test will be computed for the comparison between overall treatment satisfaction score at 2 and 4 hours postdose and baseline PPMQ-R response for the DFN-15 group only. P-values from the Wilcoxon signed-rank test will be computed for the difference between baseline PPMQ-R and post baseline for DFN-15 group only.

Additionally, the subject-rated treatment satisfaction scores at 2 and 4 hours postdose will be categorized to report "satisfied" versus "neither/dissatisfied";

"satisfied/neither" versus "dissatisfied"; and "satisfied" versus "neither", and "dissatisfied". The "satisfied" category consists of scores 1-3, and the "neither/dissatisfied" category consists of scores 4-7. The "satisfied/neither" group consists of scores 1-4, and the "dissatisfied" group consists of scores 5-7. The "neither" group consists of the score 4. Proportions of subjects in the "satisfied" versus "neither/dissatisfied", the "satisfied/neither" versus "dissatisfied", and the "satisfied" versus the "neither" and "dissatisfied" categories will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.15. Subject-Rated Treatment Satisfaction at 24 Hours Postdose – PPMQ-R

The PPMQ-R consists of 29 questions that assess a subject's satisfaction with migraine medication in terms of the following subscales: efficacy (11 questions), function (4 questions), ease of use (2 questions) and cost (2 questions), as well as the degree to which side effects were tolerated (tolerability; 10 questions).

In addition, three global items measuring subject satisfaction in terms of medication effectiveness, side effects and overall satisfaction are included. Items that evaluate treatment satisfaction are scored on a seven-point Likert-type scale from 1 (very satisfied) to 7 (very dissatisfied); whereas items that evaluate tolerability of side effects (i.e. bothersomeness of side effects) are scored on a five-point Likert-type scale from 1 (not at all) to 5 (extremely). For this study, the two items that comprise the cost subscale will not be used since subjects will not pay for the study drug; therefore, 27 questions and three global items will be used.

Each subscale score and the total score will be transformed to range from 0 to 100 with higher scores indicating better satisfaction or tolerability. Subscale scores and Total scores (except the Total Raw core) are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100.[2] The individual three Global items will not be transformed. The total score consists of the average of the efficacy, function, and ease of use subscale scores.[3] If a response is missing, the particular subscale or global item will be considered non-evaluable. If a subscale or global item is deemed non-evaluable, or missing, the corresponding total score will also be considered non-evaluable and assigned as missing.

The scores at 24 hours postdose for each subscale score, each global item score, the total score, and the total raw score will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from the Wilcoxon rank-sum test will be computed for the comparison between treatment groups.

The change from baseline to 24 hours for each subscale score, each global item score, the total score, and the total raw score will also be analyzed using the Wilcoxon signed-rank test. Baseline scores for each subscale score, each global item score, the total score, and the total raw score will be summarized by treatment group, and will be

compared to 24 hours postdose scores for the DFN-15 group only. The corresponding p-value from the Wilcoxon rank-sum test will be computed for these comparisons.

8.3. EXPLORATORY ANALYSES

Exploratory analysis will be conducted for the proportion of subjects who are pain-free 2 hours postdose compared between DFN-15 and placebo in the DB1 treatment period with different predose pain grades (Moderate [Grade 2] or Severe [Grade 3]), respectively. The proportion of subjects who are pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours postdose will also be compared between DFN-15 and placebo: during DB1 treatment period, predose severity = Moderate or Severe; during DB2 treatment period, predose severity = Mild, Moderate or Severe. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups.

Exploratory analysis will also be conducted for the proportion of subjects with their predose MBS among nausea, photophobia and phonophobia absent at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose during each DB treatment period. The corresponding p-values from Fisher's exact test will be computed for the comparison between treatment groups for the FAS1 and FAS2. A subject's predose MBS is obtained from eDiary.

8.4. SUBGROUP ANALYSES

Exploratory subgroup analyses on the co-primary endpoints will be conducted using the following baseline categories for the FAS1:

- Age (18-34 years, 35-49 years, 50-64 and >=65 years)
- Gender (male and female)
- Ethnicity (Hispanic and non-Hispanic)

For each subgroup, the odds ratio for response and the 95% CI for the odds ratio for each of the co-primary endpoints will be calculated using the treatment group, the subgroup variable, and the treatment-by-subgroup interaction term as covariates in the logistic regression model. Since the results of these subgroup analyses are exploratory, future studies can examine the treatment effect among the subgroup covariates that have a significant treatment-by-subgroup interaction term.

9. SAFETY

The SS, SS1, SS2, FAS1, and FAS2 will be used for safety analyses. Safety will be assessed on the basis of AE reports, clinical laboratory data, ECG parameters, physical examinations, extent of exposure and compliance with study drug use, rescue medication use, concomitant medication use, and vital signs.

9.1. EXTENT OF EXPOSURE AND COMPLIANCE WITH STUDY DRUG

In this trial, subjects are considered compliant if they treat a migraine attack with study drug. Study drug exposure will be summarized by treatment group and overall for the SS, SS1, and SS2. By definition of the SS1 and SS2, each subject in those cohorts is considered compliant.

During the DB1 treatment period, subjects are expected to administer one dose of study drug within 1 hour of experiencing moderate or severe migraine pain. During the DB2 treatment period, subjects are expected to take a single dose of study drug to treat another attack at any pain level.

The following will be presented for the SS, SS1, and SS2:

- The total number of study drug doses
- The number of days since randomization in DB1
- Number (%) of subjects who took at least one dose of study drug

The following will be presented for the SS and SS2:

- The number of days between the first dosing dates of DB1 and DB2

All study drug dosing information will be listed. For subjects who enter the DB2 period, the number of days between the first dosing dates of the DB1 and DB2 periods will also be listed.

9.2. RESCUE MEDICATIONS

Rescue medications are defined as medications taken to treat a migraine attack (in addition to the study drug) 2-24 hours after taking the study drug. Rescue medications taken during the study will either be reported in the eCRF based on entries in the subject eDiary, or will be reported outside of the eDiary. All rescue 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.

Summaries of rescue medications will be presented for the SS, SS1, and SS2 in tabular

form using the highest level ATC term as an upper classification and the preferred drug name as a lower classification level. All medications will be summarized by treatment group and overall and sorted by descending counts in the upper classification term and the lower classification term within the upper. For each subject, the medication will be counted only once within the upper classification level and only once within the lower classification level.

The number of rescue medication doses taken will be summarized by treatment group and overall for the SS, SS1, and SS2.

Separate listings will be provided for rescue medications taken during each DB treatment period.

9.3. ADVERSE EVENTS

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0 or higher). Migraine headaches will not be captured as AEs. Migraine headaches will be captured by the subject in the eDiary provided to them, and the information will be entered into the appropriate eCRF page.

All AEs will be listed by subject. The following listings of AEs will be provided:

- All AEs
- Study-drug related AEs
- Serious adverse events (SAEs)
- AEs leading to death
- Adverse events leading to study-drug termination

Only TEAEs will be included in summary tables. Summaries for AEs will be presented for the SS, SS1, and SS2. An overall summary table of TEAEs will be produced for the following categories:

- Any TEAE
- Study-drug related TEAEs
- Serious TEAEs
- TEAEs leading to study-drug termination
- TEAEs leading to death

All TEAEs will be classified by system organ class (SOC) and preferred term (PT). Frequency count and the number of unique subjects of a TEAE will be tabulated by treatment(s) received. For the number of unique subjects reporting, if a subject reported more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT.

The following summaries of TEAEs will also be provided:

- TEAEs by SOC and PT
- Study-drug related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs by maximum severity (mild, moderate, severe or missing) by SOC and PT
- TEAEs by strongest causality relationship (not related, possibly related, probably related, definitely related or missing) by SOC and PT

For TEAEs presented by relationship to study treatment(s), the strongest relationship to study treatment(s) during the study will be presented for each subject if coded to the same SOC or PT. For TEAEs presented by severity, the worst severity during the study will be presented for each subject if coded to the same SOC or PT. TEAEs with missing causality will be counted as related. TEAEs with missing severity will be counted as severe. The same will be true in the individual summaries.

9.4. LABORATORY EVALUATIONS

Abnormal-clinically significant lab results for clinical laboratory categories including hematology, clinical chemistry, serology, TSH, urinalysis, as well as results for urine drug screens and serum and urine pregnancy tests will be recorded on the eCRF. Parameters will be standardized according to the International System of Units (SI) prior to summarization. Baseline and post-baseline assessments, as well as the change from baseline, will be summarized for hematology, clinical chemistry, and urinalysis using descriptive statistics. The overall clinical significance and shift from baseline to end of study assessments will be provided in a summary table for hematology, clinical chemistry, and urinalysis. Summaries for laboratory evaluations will be presented for the SS, SS1, and SS2. Separate listings will be produced for each laboratory test group (hematology, clinical chemistry, serology/TSH, urinalysis, urine drug screens, and serum and urine pregnancy tests).

9.5. VITAL SIGNS

Vital signs measurements will include sitting blood pressure (mmHg), pulse rate (bpm), oral temperature (Celsius), and menses details. Baseline and post-baseline assessments,

as well as the change from baseline, will be summarized for the SS, SS1, and SS2 for SBP, DBP, pulse rate, and oral temperature using descriptive statistics.

All vital signs data will be listed.

9.6. TWELVE-LEAD ECG

Twelve-lead ECGs will be performed at screening and at every study visit. The overall ECG interpretation and shift from baseline to end of study assessments, as well as the change from baseline, will be summarized for the SS, SS1, and SS2.

All ECG findings collected in the CRF will be listed.

9.7. PHYSICAL EXAMINATION

Abnormal physical examination findings will be listed.

9.8. SUICIDALITY CHECK

Suicidality check findings collected in the CRF will be listed.

10. INTERIM ANALYSES

No interim analyses are planned for this study.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The following are analyses that are not present in the current version of the protocol (V 2.0, 09MAY2017).

- Section 3.2: The modification of this below secondary objective:
  - To assess the proportion of subjects who have sustained pain relief at 2 to 24 hours postdose (i.e., pain relief at 2 hours postdose, with no use of rescue medication and no worsening of headache pain within 2 to 24 hours postdose).
- Section 4.2: The modification of this below secondary endpoint:
  - The proportion of subjects who have sustained pain relief at 2 to 24 hours postdose (i.e., pain relief at 2 hours postdose, with no use of rescue medication and no worsening of headache pain within 2 to 24 hours postdose) compared between DFN-15 and placebo.
- Section 5.3: The modification of Safety Analysis Set definition:
  - The Safety Set (SS) will include all subjects who took at least one dose of DB study drug during one or both treatment periods, and have it recorded in their eDiary. Subjects will be analyzed according to the treatment they receive. The Safety Set 1 (SS1) will include randomized subjects who took at least one dose of DB study drug during the DB1 treatment period. The Safety Set 2 (SS2) will include subjects who were re-randomized and took at least one dose of DB study drug during the DB2 treatment period. The SS, SS1, and SS2 will be used for all analyses of safety endpoints including summaries of TEAEs, ECGs, and clinical laboratory results.
- Section 5.4: The modification of Full Analysis Set definition:
  - Each DB treatment period will have a Full Analysis Set (FAS). The Full Analysis Set 1 (FAS1) will include all randomized subjects who took at least one dose of study drug during the DB1 treatment period and have at least one post-baseline efficacy time point assessment for either pain or symptom (among nausea, photophobia, phonophobia) in DB1. The Full Analysis Set 2 (FAS2) will include all re-randomized subjects who took at least one dose of study drug during the DB2 treatment period and have at least one post-baseline efficacy time point assessment for either pain or symptom (among nausea, photophobia, phonophobia). Subjects in the DB1 will be analyzed according to their randomized treatment. Subjects in the DB2 will be analyzed according to their re-randomized treatment. The FAS1 and FAS2 will be used for all analyses of efficacy endpoints
- Section 8.1.1: The modification of the co-primary efficacy endpoint analyses:

- To test for statistical significance of the co-primary efficacy endpoints, the closed sequential testing procedure will be utilized. If the first co-primary endpoint is statistically significant at a two-sided 0.05 level of significance, the second co-primary endpoint will be tested at a two-sided 0.05 level of significance. The study must show a significant statistical beneficial experimental treatment effect for both co-primary endpoints to be considered statistically successful, controlling the significance level at 0.05. Since statistical significance with both co-primary endpoints is required to declare trial success, multiplicity due to multiple primary endpoints is a non-issue.

- The first co-primary efficacy endpoint will be analyzed using Fisher's exact test. Following the closed sequential procedure, the second co-primary efficacy endpoint will be analyzed using Fisher's exact test if the first co-primary endpoint is statistically significant.

- The number of subjects with response, the number of subjects with non-missing assessment, proportions for the DFN-15 and placebo groups, 95% exact CIs for those proportions, the odds ratio for response, and the corresponding p-value will be presented for the comparison between two treatment groups for the FAS1. This analysis will exclude subjects who took rescue medication prior to the data collection of the 2 hours postdose time point (inclusive), as well as subjects who have predose pain level = mild (Grade 1) or none (Grade 0).

- If the first co-primary efficacy endpoint is statistically significant, results will be found similarly for the second co-primary efficacy endpoint.

12. REFERENCE LIST

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
2. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City cardiomyopathy questionnaire: a new health status measure for heart failure. Journal of the American College of Cardiology. 2000:35(5): 1245-55.
3. Kimel M, Hsieh R, McCormack J, Burch SP, Revicki DA. Validation of the revised patient perception of migraine questionnaire (PPMQ-R): measuring satisfaction with acute migraine treatment in clinical trials. Cephalalgia. 2008:28:510-23.

13. PROGRAMMING CONSIDERATIONS

The following conventions are recommended approaches for programming and for TLFs.

All TLFs and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA) or higher. Computer-generated TLFs will adhere to the following specifications.

The layout of the tables should be as consistent as possible, taking into account indentation and spacing, and consistency should be maintained within capitalization of words in the main title and row and column headers. Common row titles should be checked and the titles should be of a standard layout specifying the table number, title and analysis set. Table development should also take into account programming efficiency.

13.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TLFs will follow International Conference of Harmonization (ICH) E3 guidance.

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:
  Sponsor Name: Dr. Reddy's Laboratories, Ltd.
  Protocol: DFN-15-CD-006 (1007753)
- All output should have Page n of N at the top right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table). The following header should appear at the top right of each page:
  Page n of N
  Status: Draft/Final (Data Extraction Date: DDMMMYYYY)

- The date output was generated should appear along with the program name as a footer on each page, as follows:
  Program: M:\...\xxx.sas
  Date/Time of Generation: DDMMYYYY; Data Source: Listing xxx

13.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
FAS Analysis Set

13.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable).

P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can

be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.

- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

14. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted] Standard Operation Procedure (SOP) 03.010 and 03.013 provide an overview of the development of such SAS programs.

[redacted] SOP 03.009 describes the QC procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

For all data sets, tables and listings generated by SAS, [redacted] Biostatistics will create SAS codes independently, and then use SAS PROC COMPARE procedure to perform 100% electronic comparison for all numerical and character values. In addition, the Lead Biostatistician, Lead Programmer and Senior Statistical Reviewer will review all TLFs for consistency and accuracy.

15. INDEX OF TABLES

Index of tables can be found in table shells.

16. INDEX OF FIGURES

Index of figures can be found in figure shells.

17. INDEX OF LISTINGS

Index of listings can be found in listing shells.