Statistical Analysis Plan

Official Title of the Study

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

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16.1.9 Documentation of Statistical Methods

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Note to File Removal of Analyses Associated with the Optimal Migraine Freedom Exploratory Endpoint

Note to File Listing Renumbering and Clarification of Footnote in Table, Listing and Figure Shells

Statistical Analysis Plan

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Protocol Number and Title:	DFN-02-CD-012 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10 mg) in Episodic Migraine With or Without Aura
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I confirm that I have reviewed this document and agree with the content.

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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
CAD	Coronary Artery Disease
CI	Confidence Interval
CRF	Case Report Form
DB	Double-Blind
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eDiary	Electronic Diary
FAS	Full Analysis Set
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
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
MAO-A	Monoamine Oxidase-A
MBS	Most Bothersome Symptom

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
MOH	Medication Overuse Headaches
N/A	Not Applicable
PPMQ-R	Patient Perception of Migraine Questionnaire-Revised
PPS	Per Protocol Set
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SBP	Systolic Blood Pressure
SI	Standard International System of Units
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SSRI	Selective Serotonin Reuptake Inhibitor
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

INC Research 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. PRIMARY OBJECTIVE

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

3.2. SECONDARY OBJECTIVES

A secondary objective of the study is to assess the proportion of subjects who are pain-free at 2 hours postdose during the second double-blind treatment period (DB2).

Additional secondary objectives for each DB period are:

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

3.3. EXPLORATORY OBJECTIVES

- [redacted]

- [redacted]

3.4. BRIEF DESCRIPTION

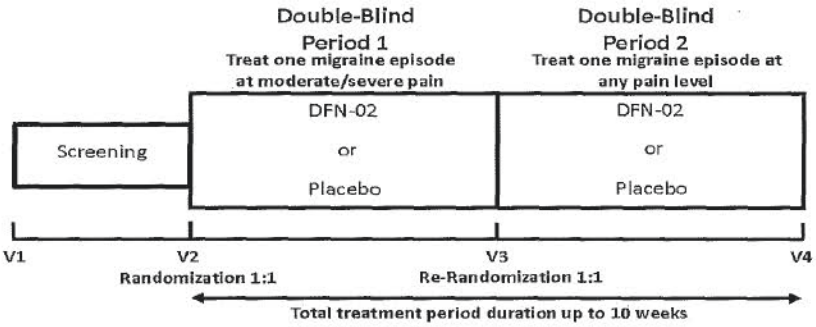
This is a randomized, 2 DB treatment period dosing study, to be conducted at multiple centers in the United States. Previously diagnosed subjects with a history of episodic migraine (as defined by International Classification of Headache Disorders, 3rd edition [beta version][1] [ICHD-3]), who experience an average of 2 to 8 migraine attacks per month for at least the past 12 months, with no more than 14 headache days per month, and with 48 hours of headache-free time between migraine headaches, will be randomized in a 1:1 ratio in both DB periods to receive either DFN-02 (sumatriptan nasal spray) 10 mg or a matching placebo. Subjects will treat 1 moderate to severe migraine attack in the DB1 treatment period and, if eligible, be re-randomized into the DB2 treatment period 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 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 medication use, postdose pain level, symptoms and functional disability, treatment satisfaction, and date and time of rescue medication. The eDiary will be reviewed for compliance and rescue medication.

The overall study design is presented in Figure 1.

Figure 1 Overall Study Design



3.5. SUBJECT SELECTION

Approximately 100 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.

3.5.1. 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
   - Note: If female and of childbearing potential (not surgically sterile or ≤ 1 year after the onset of amenorrhea due to menopause), the subject must (a) have a negative serum pregnancy test at screening and a negative urine test at Visit 2 (V2), (b) not be lactating, and (c) agree to practice a reliable form of contraception or abstinence during the study. Acceptable forms of contraception include implants, injectable contraceptives, combined oral contraceptives, an intrauterine device, a vasectomized partner, and double-barrier methods.
   - Note: If male (with female partner), the subject must agree to practice a reliable form of contraception or abstinence during the study.
3. A history of episodic migraine (as defined by ICHD-3), who experience an average of 2 to 8 migraine attacks per month for at least the past 12 months, with no more than 14 headache days per month, and with 48 hours of headache-free time between migraine headaches
4. Subjects who have migraine with or without aura. If migraine with aura, the aura cannot last longer than 60 minutes.

5. Subjects who, in the opinion of the Investigator, are willing and able to:
   a. Evaluate and record pain, migraine symptoms, and study medication effectiveness information in real-time using an eDiary for the duration of the study;
   b. Record each instance of the use of study medication and rescue medication in a subject eDiary in real-time for the duration of the study;
   c. Comply with all other study procedures and scheduling requirements.
- 6. Subjects who can use the nasal spray device correctly after instruction

3.5.2. 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. Medication overuse:
   - Opioids ≥ 10 days during the 90 days prior to screening
   - Combination medications (e.g., Fiorinal®) ≥ 10 days during the 90 days prior to screening (only applies if combination medication contains an opioid and/or barbiturate)
   - NSAIDs or other simple medications > 14 days a month during the 90 days prior to screening
   - Triptans or ergots ≥ 10 days a month during the 90 days prior to screening
3. Prior exposure to DFN-02 (or DFP-02)
4. Treated with onabotulinumtoxinA (Botox®) or other botulinum toxin treatment within 4 months prior to screening for migraine prophylaxis (subjects who were treated with same for cosmetic purposes may be allowed on a case-by-case basis after approval from the Medical Monitor)
5. On unstable dosages of migraine prophylactic medications within 30 days prior to and through screening
6. Taking mini-prophylaxis for menstrual migraine
7. Subjects with hemiplegic migraine, or other forms of neurologically complicated migraine
8. Subjects who have prolonged aura (i.e., more than 1 hour)
9. A history of stroke or transient ischemic attack
10. A history of migralepsy (seizure following a migraine) or a concurrent diagnosis of seizure disorder
11. Subjects who cannot differentiate between a migraine headache and tension-type or cluster headache
12. A history of more than occasional tension-type headache (based on Investigator judgment)
13. A history of cluster headaches
14. Known intolerance to sumatriptan (any formulation), or who have experienced a significant AE related to any triptan medication, including sumatriptan
15. Non-responsiveness to subcutaneous sumatriptan (≤ 6 mg dosage), in the opinion

of the Investigator

16. Prior ischemic coronary artery disease (CAD): angina pectoris, history of myocardial infarction or documented silent ischemia or coronary artery vasospasm, including Prinzmetal's angina
17. Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders
18. Uncontrolled hypertension or systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg (the values should be reconfirmed to rule out a transient fluctuation)
19. Peripheral vascular disease or ischemic bowel disease
20. Subjects using monoamine oxidase-A (MAO-A) inhibitor that cannot be completely washed out (at least 15 days)
21. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and steroids for chronic conditions, unless the dose is stable for at least 3 months prior to randomization and is not expected to change during the study
22. Known intolerance to nasal sprays
23. Subjects taking any medications or with illnesses likely to affect the physiology of the nasal mucosa (i.e., subjects with colds [upper respiratory infections], influenza, nasal septum surgery, or chronic nasal rhinitis)
24. Any abnormal nasal physiology or pathology, or any other abnormal physiology and/or pathology that, in the opinion of the Investigator, would not allow the objectives of the study to be accomplished
25. Acute sinusitis. Subjects may be rescreened 7 days after resolution of acute sinusitis infection/symptoms with no complaints of headache pain and if, in the opinion of the Investigator, it will not interfere with accomplishing the objectives of the study
26. Chronic sinusitis
27. Severe renal impairment (defined as creatinine > 1.5 × the upper limit of normal [ULN])
28. Serum total bilirubin > 1.5 × ULN
29. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 × ULN
30. Subjects with uncontrolled diabetes mellitus, or a glycosylated hemoglobin (HbA1c) > 7.9%, or with diabetes mellitus requiring insulin
31. A history of alcohol or substance abuse (including marijuana) within 1 year that would compromise data collection
32. A positive urine drug screen for recreational drugs, alcohol, marijuana (whether legal or not), or for prescription drugs not explained by stated concomitant medications:
    a. 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 headaches (MOH) criteria.
    b. Benzodiazepines are allowed if used for legitimate medical reasons.
    c. Chronic use of amphetamines to treat attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) and related disorders is

allowed as long as the regimen has been stable for at least 3 months prior to screening and is expected to remain stable throughout the study.
- Note: For the above-mentioned conditions, the site must have appropriate documentation to justify the mentioned drug use (e.g., documented medical history and a valid prescription-based dispensation)

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

3.5.3. Additional Exclusion Criteria

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 > 140 mmHg and/or DBP > 90 mmHg at Visit 1 (V1) or V2, those subjects should be excluded. Any subject without a known history of hypertension that presents at screening with SBP > 140 mmHg and/or DBP > 90 mmHg should be excluded if the BP reading is due to suspected hypertension or another pathological condition, not if due to a transient fluctuation, based on the Investigator's evaluation. If the Investigator believes the BP is falsely elevated, they should repeat the assessment 2 to 3 times with the 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.

3.6. DETERMINATION OF SAMPLE SIZE

Approximately 100 subjects will be randomized for the DB1 treatment period. Subjects who discontinue participation without completing the study protocol will not be replaced.

The primary endpoint is the comparison of the proportion of subjects who are pain-free at 2 hours after the first dose of study medication. It is assumed that 15% of placebo and 42% of DFN-02 10 mg (treated) subjects will be pain-free at 2 hours. A sample size of 50 subjects in each DB1 dosing arm will provide 86% power to detect this assumed difference between placebo and DFN-02 10 mg at a 5% (2-sided) level of significance.

3.7. TREATMENT ASSIGNMENT & BLINDING

The DFN-02-CD-012 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 either DFN-02 10 mg or a matching placebo. The randomization schemes for both DB periods will be generated by the biostatistics group of INC Research. 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.

3.8. ADMINISTRATION OF STUDY MEDICATION

Randomized subjects will be instructed to use the study medication in 1 migraine attack as soon as (and no more than within 1 hour after) experiencing moderate to severe pain (defined as headache pain rating of Grade 2 [moderate] or Grade 3 [severe] on pain severity scale of 0 to 3). If the subject is not able to use study medication for the first migraine after randomization, they should be instructed to use the study medication for

the next attack. Those subjects who do not experience a migraine attack, and/or who do not treat any migraine attack with study medication or record eDiary data, will not be allowed to continue into the DB2 treatment period, and will be discontinued. In the DB2 treatment period, eligible re-randomized subjects will receive either DFN-02 10 mg or a matching placebo to treat 1 migraine attack at any pain level.

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

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

3.9. 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 (each period), 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 medication dispensed at this visit should be used to treat a migraine attack as soon as (and no more than within 1 hour after) experiencing moderate or severe pain. Treatment should be completed within 4 weeks from Baseline.	Visit is expected within 2-7 days of treating a migraine attack with study medication dispensed at V2. Study medication dispensed at this visit should be used to treat a migraine attack at any pain level.	Visit is expected within 2-7 days of treating a migraine attack with the study medication dispensed at V3. Treatment period should be completed within 10 weeks from Baseline.
Informed consent	X			
Inclusion/Exclusion criteria	X	X		
Subject eDiary instructions and dispensation[4]	X	X	X	
Adverse events review	X	X	X	X
Demographics	X			
Medical history and prior medications	X	X		

Migraine history and current treatment status	X			
Physical examination[5]	X	X	X	X
Height and weight	X			X[6]
Vital signs (pulse rate, SBP/DBP,[7] body temperature); record menses (start/stop dates)	X[7]	X[7]	X	X
Serum pregnancy test (hCG)[8, 9]	X			
Urine pregnancy test[8, 9]		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)	X	X	X	X
Glycosylated hemoglobin (HbA1c), TSH* *[screening only]	X			X
Serology (HIV, HBsAg, HCV)	X			
Urine drug test and ethanol screen	X	X	X	X
12-lead ECG	X	X	X	X
Concomitant medication review			X	X
Randomization (V2)/Re-randomization (V3)		X	X	
Dispense DB study medication[10]		X	X	

Subject compliance and study medication accountability[11]			X	X
Subjects record data in the eDiary[12]				
Review, confirm, and ensure proper recording of the subject eDiary entries[13]		X	X	X
Collect eDiary[14]				X

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

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

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

[3] Subjects may be randomized earlier than 21 days during this period if they meet inclusion/exclusion criteria and headache assessment criteria. The screening period may also be extended based on Investigator judgment and in consultation with the Medical Monitor.

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

[5] At screening (V1), complete physical examination will be performed and recorded in the source document that includes examination of head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems. At all subsequent visits, symptom-driven limited physical examination will be performed and recorded. Any subsequent untoward change during the study will be recorded as an AE.

[6] Weight only.

[7] At screening, subjects with a history of hypertension that is uncontrolled (i.e., SBP > 140 mmHg and/or DBP > 90 mmHg), whether on treatment or not, will be excluded. 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 > 140 mmHg and/or DBP > 90 mmHg at V1 or V2, they should be excluded. Any subject without a known history of hypertension that presents at screening with SBP > 140 mmHg and/or DBP > 90 mmHg should be excluded if the BP reading is due to suspected hypertension or another pathological condition, not if due to a transient fluctuation, based on the Investigator's evaluation. If the Investigator believes the BP is falsely elevated, they should repeat the assessment 2 to 3 times with the 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.

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

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

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

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

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

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

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

Table 2 eDiary Assessments

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

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

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

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

[3] Functional disability scale: 0 = no disability, able to function normally; 1 = performance of daily activities mildly impaired, can still do everything but with difficulty; 2 =

performance of daily activities moderately impaired, unable to do some things; 3 = performance of daily activities severely impaired, cannot do all or most things, bed rest may be necessary

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

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

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the proportion of subjects who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with moderate to severe headache pain during the DB1 treatment period (ie, headache pain rating of moderate [Grade 2] or severe [Grade 3] predose reduced to none [Grade 0] at 2 hours postdose).

4.2. SECONDARY EFFICACY ENDPOINTS

A secondary efficacy endpoint is the proportion of subjects who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with headache pain of any level during the DB2 treatment period (ie, headache pain rating of mild [Grade 1], moderate [Grade 2] or severe [Grade 3] predose reduced to none [Grade 0] at 2 hours postdose).

Secondary efficacy endpoints for each DB period are:

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

- Treatment satisfaction at 2 hours postdose
- Treatment satisfaction as measured by PPMQ-R at 24 hours postdose

4.3. EXPLORATORY ENDPOINTS

Exploratory endpoints for each DB treatment period are:

- [redacted]

4.4. SAFETY ENDPOINTS

The safety endpoints are:

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

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

5.4. FULL ANALYSIS SET

Each DB treatment period will have a Full Analysis Set (FAS). The FAS1 will include all randomized subjects who took at least one dose of study medication during the DB1 treatment period and have at least one post-baseline efficacy time point assessment in DB1. The FAS2 will include all re-randomized subjects who took at least one dose of study medication during the DB2 treatment period and have at least one post-baseline efficacy time point assessment in DB2. 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 FASs 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, and who have no significant protocol deviations that will impact the collection or interpretation of the primary endpoint data during the DB1 treatment period. Identification of 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 INC Research 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 primary and secondary efficacy endpoints.

The term "treatment group" refers to the applied treatment regimen during DB1 or DB2 (DFN-02 10 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 medication 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 medication, but prior to the time study medication 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 medication taken after randomization in DB1. The first dose date for DB2 is defined as the first dose of DB2 study medication 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 medication 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 medication 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 medication (DFN-02 or placebo) in DB1 or any existing AE that worsens in severity on or after the date of the first dose of study medication in DB1 up to 5 days after the date of the last dose of study medication in DB1 or up to taking DB2 study medication, whichever occurs first.

A TEAE for DB2 is defined as an AE that started on or after the first dose of study medication (DFN-02 or placebo) in DB2 or any existing AE that worsens in severity on or after the date of the first dose of study medication in DB2, up to 5 days after the date of the last dose of study medication 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	December 31 of that year

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
	year is the same as the year 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.

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 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 denominator for the Screened Set overall portion will be the total number of screened subjects. The denominator for the DB1 portion will be the number of subjects in the randomized set for DB1.The denominator for the DB2 portion will be the number of subjects in the randomized set for DB2. 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. All protocol deviations 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 body mass index (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 Medication Accountability

All data in the study medication accountability log will be listed, which will include the dates and kit number(s) of the medication 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 dose level 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. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.1.1. Primary Analysis of the Primary Endpoint

The primary efficacy endpoint is the proportion of subjects who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with moderate to severe headache pain during the DB1 treatment period (ie, headache pain rating of moderate [Grade 2] or severe [Grade 3] predose reduced to none [Grade 0] at 2 hours postdose). The primary efficacy endpoint will be analyzed using Fisher's exact test.

Proportions of subjects free from headache pain 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-02 10 mg 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 a second dose of study medication or rescue medication prior to the data collection of the 2 hours postdose time point (inclusive). The analysis will also be performed using the PPS.

8.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

The secondary efficacy 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 efficacy endpoint analyses will be conducted as indicated for the FAS1 and FAS2 and will exclude subjects who took a second dose of study medication or rescue medication prior to the data collection of the 2 hours postdose time point (inclusive).

8.2.1. Headache Pain Freedom at 2 Hours Postdose During DB2 Period

The proportion of subjects who are free from headache pain at 2 hours after the first dose of study medication taken for a migraine attack with headache pain of any level during the DB2 treatment period will be summarized by treatment group for the FAS2 (ie, headache pain rating of mild [Grade 1], moderate [Grade 2] or severe [Grade 3] predose reduced to none [Grade 0] at 2 hours postdose). The 95% exact CIs for those proportions, the odds ratio for response, and corresponding p-value from Fisher's exact test will be computed for the comparison between treatment groups.

8.2.2. Headache Pain Freedom Postdose

The proportion of subjects who are free from headache pain at 10, 15, 20, 30, 60, and 90 minutes after the first dose of study medication 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.

8.2.3. Headache Pain Relief Postdose

The proportion of subjects who have pain relief at 10, 15, 20, 30, 60, 90, and 120 minutes after the first dose of study medication will be summarized by treatment group and time point for the FAS1 and FAS2. 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 before dosing reduced to mild or none postdose, or mild pain before dosing 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 pre-dose and rate the headache pain level at the particular postdose time point will be analyzed.

8.2.4. Absence of MBS Postdose

The proportion of subjects with their MBS among nausea, photophobia and phonophobia absent at 10, 15, 20, 30, 60, 90, and 120 minutes after the first dose of study medication taken for a migraine attack 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 a MBS pre-dose and report the status of the MBS at the particular postdose time point will be analyzed.

8.2.5. Freedom from Nausea, Photophobia, and Phonophobia Postdose

The proportion of subjects who are free from nausea, photophobia, and phonophobia at 10, 15, 20, 30, 60, 90, 120 minutes and 24 hours after the first dose of study medication taken for a migraine attack 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 pre-dose and report the status of the symptom at the particular postdose time point will be analyzed.

8.2.6. 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.

8.2.6.1. 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 medication 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.

8.2.6.2. 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 medication 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.

8.2.8. Sustained Headache Pain Freedom at 24 Hours

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

8.2.9. 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 hours and 24 hours after the first dose of study medication taken for a migraine attack during each DB treatment period will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from the Wilcoxon signed-rank test will be computed for the comparison between treatment groups.

The following levels of change from baseline in functional disability score will be compared between DFN-02 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.

8.2.10. Use of Second Study Medication Dose or Rescue Medication Postdose

The proportion of subjects who use a second dose of study medication or 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.

8.2.11. Subject-Rated Treatment Satisfaction at 2 Hours 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 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 hours postdose and the baseline PPMQ-R response for the same question will be compared for the DFN-02 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 hours postdose and the baseline PPMQ-R response for the same question will be summarized by treatment group for the FAS1 and FAS2. The corresponding p-values from the Wilcoxon signed-rank test will be computed for the comparison between treatment groups.

Additionally, the subject-rated treatment satisfaction scores will be categorized to report "satisfied" versus "neither/dissatisfied" as well as "satisfied/neither" versus "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. Proportions of subjects in the "satisfied" versus "neither/dissatisfied", and the "satisfied/neither" versus "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.

8.2.12. 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 medication; 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. Scale scores 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 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. The total score at 24 hours postdose and the total score at baseline will be compared for the DFN-02 group only. A similar comparison for the total raw scores for the DFN-02 group will be performed. The corresponding p-value from the Wilcoxon rank-sum test will be computed for those two comparisons.

8.3. EXPLORATORY EFFICACY ENDPOINTS AND ANALYSES

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, study medication use, concomitant medication use, and vital signs.

9.1. EXTENT OF EXPOSURE AND COMPLIANCE WITH STUDY MEDICATION

In this trial, subjects are considered compliant if they treat a migraine attack with study medication. Study medication exposure will be summarized by treatment group and overall for the SS, FAS1, and FAS2. By definition of the FAS1 and FAS2, each subject in those cohorts is considered compliant.

Subjects are expected to administer one dose of study medication within 1 hour of experiencing moderate or severe migraine pain. If after 2 hours a subject does not experience sufficient relief, the subject may take a second dose of study medication for the same migraine attack. Two nasal sprays will be dispensed to each subject for each DB treatment period.

The following will be presented for the SS, FAS1, and FAS2:

- The total number of study medication doses
- The number of days since randomization in DB1
- Number (%) of subjects who took at least one dose of study medication
- Number (%) of subjects who treated their migraine attack with 1 dose of study medication
- Number (%) of subjects who treated their migraine attack with 2 doses of study medication
- Number (%) of subjects who took a second dose of study medication prior to recording the 2 hours time point (LOCF)
- Duration between the first and second dose of study medication administered for one migraine attack (for subjects with 2 doses administered)

The following will be presented for the SS and FAS2:

- Number (%) of subjects who treated a second migraine attack with study medication
- The number of days between the first dosing dates of DB1 and DB2

All study medication 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 medication) within 24 hours after the first dose of study medication. 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 dose level 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 medication-related AEs
- Serious adverse events (SAEs)
- AEs leading to death
- Adverse events leading to study medication 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 medication-related TEAEs
- Serious TEAEs
- TEAEs leading to study medication 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-medication 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, 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, 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 sitting blood pressure, 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 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.

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 1.0, 01JUN2016).

- Section 4.3: The removal of these exploratory endpoints:
  - [redacted]
  - [redacted]
- Section 5.3: The modification of the SS definitions:
  - The Safety Set (SS) will include all subjects who receive at least one dose of DB study medication during one or both treatment periods. Subjects will be analyzed according to the treatment they receive. The Safety Set 1 (SS1) will include randomized subjects who receive at least one dose of DB study medication during the DB1 treatment period. The Safety Set 2 (SS2) will include subjects who were re-randomized and received at least one dose of DB study medication during the DB2 treatment period.The SS, SS1, and SS2 will be used for all analyses of safety endpoints including summaries of treatment emergent adverse events (TEAEs), ECGs, and clinical laboratory results.
- Section 5.4: The modification of the FAS definitions:
  - The FAS1 will include all randomized subjects who took at least one dose of study medication during the DB1 treatment period and have at least one post-baseline efficacy time point assessment in DB1. The FAS2 will include all re-randomized subjects who took at least one dose of study medication during the DB2 treatment period and have at least one post-baseline efficacy time point assessment in DB2. The FASs will be used for all analyses of efficacy endpoints.
- Section 7.1: The modification of the subject disposition and withdrawals summary:

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 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

- Section 7.2: The modification of the demographics and other baseline characteristics summary:
  - 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.
- Section 8.1.1: The modification of the primary efficacy endpoint analysis:
  - The number of subjects with response, the number of subjects with non-missing assessment, proportions for the DFN-02 10 mg 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 a second dose of study medication or rescue medication prior to the data collection of the 2 hours postdose time point (inclusive).
- Section 8.2: The modification of the secondary efficacy endpoint analysis:
  - The secondary efficacy 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 efficacy endpoint analyses will be conducted as indicated for the FAS1 and FAS2 and will exclude subjects who took a second dose of study medication or rescue medication prior to the data collection of the 2 hours postdose time point (inclusive).

- Section 8.2.1: The modification of the secondary endpoint analysis for headache pain freedom at 2 hours postdose during DB2:
  - The 95% exact CIs for those proportions, the odds ratio for response, and corresponding p-value from Fisher's exact test will be computed for the comparison between treatment groups.
- Section 8.2.9: The addition of this analysis for change in functional disability score postdose:
  - The following levels of change from baseline will be compared between DFN-02 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.
- Section 8.2.11: The addition of these analyses for subject-rated treatment satisfaction at 2 hours postdose:
  - The subject-rated treatment satisfaction score at 2 hours postdose and the baseline PPMQ-R response for the same question will be compared for the DFN-02 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 hours post-dose and the baseline PPMQ-R response for the same question will be summarized between treatment group for the FAS1 and FAS2. The corresponding p-values from the Wilcoxon signed-rank test will be computed for the comparison between treatment groups.
  - Additionally, the subject-rated treatment satisfaction scores will be categorized to report "satisfied" versus "neither/dissatisfied" as well as "satisfied/neither" versus "dissatisfied". The "satisfied" group will consist of the scores 1-3, and the "neither/dissatisfied" group will consist of the scores 4-7. The "satisfied/neither" group will consist of the scores 1-4, and the "dissatisfied" group will consist of the scores 5-7. Proportions of subjects in the "satisfied" versus "neither/dissatisfied", and the "satisfied/neither" versus "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.

- Section 8.2.12: The addition of these analyses for the PPMQ-R subject-rated treatment satisfaction at 24 hours postdose:

  - Each subscale score and the total score will be transformed to range from 0 to 100 with higher scores indicating better satisfaction or tolerability. Scale scores 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. The total score consists of the average of the efficacy, function, and ease of use subscale scores. 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.

  - The scores at 24 hours postdose for each subscale, each global item, 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, 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. The total score at 24 hours postdose and the total score at baseline will be compared for the DFN-02 group only. A similar comparison for the total raw scores for the DFN-02 group will be performed. The corresponding p-value from the Wilcoxon rank-sum test will be computed for those two comparisons.

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-02-CD-012 (1007752)
- 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. INC Research Standard Operation Procedure (SOP) 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research 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, INC 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.

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Note to File

Document Type:	Template	Document ID:	11.002A.00
Issue Date:	01 OCT 2013	Effective Date:	29 OCT 2013

PROJECT/PROTOCOL NO. 1007752 / DFN-02-CD-012

FROM: [redacted]

RE: Removal of Analyses Associated with the Optimal Migraine Freedom [redacted]

DATE: 06JAN2017

CC: [redacted]

This Note to File documents the removal of two tables associated with the optimal migraine freedom [redacted]

[redacted] will be removed in all TLF deliverables. Additionally, the [redacted]

AUTHOR SIGNATURE: [redacted] **DATE:** 06JAN2017

[redacted] *Senior Biostatistician*

APPROVAL SIGNATURE: _____ [redacted] _____ Date: 2017.01.06 13:21:21 -05'00' DATE: _____

[redacted] *Associate Director Clinical Development, Proprietary Products*

Note to File

Document Type:	Template	Document ID:	11.002A.00
Issue Date:	01 OCT 2013	Effective Date:	29 OCT 2013

PROJECT/PROTOCOL NO. 1007752 / DFN-02-CD-012

FROM: [redacted]

RE: Listing Renumbering and Clarification of Footnote in Table, Listing and Figure Shells

DATE: 23MAR2017

CC: [redacted]

This Note to File documents the following two items:

1) The renumbering of listings 16.2.2 and 16.2.3

In order to be compatible with FDA guidance with respect to Appendices, these two listings will be renumbered in the actual listing outputs compared to the listing shells (version Final V1.0, 16SEP2016). Listing 16.2.2 titled "Subject Enrollment and Screen Failures" will be renumbered to listing 16.2.3 ; listing 16.2.3 titled "Protocol Deviations" will be renumbered to listing 16.2.2.

2) Clarification of footnote "03.007A.01" in Table, Listing, and Figure (TLF) shells

In the TLF shells, a footnote of "03.007A.01" is presented as a template control ID. This footnote should have been removed as no template was used during the TLF shells development. Since this footnote will not be displayed in the actual TLFs or the CSR, a clarification is documented in this Note to File. No further action will be taken to update the TLF shells.

AUTHOR SIGNATURE: [redacted] **DATE:** 23MAR2017
Senior Biostatistician

APPROVAL SIGNATURE: [redacted] **DATE:** 3/23/17
Associate Director Clinical Development, Proprietary Products