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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
 Laura Jawidzik, MD
 NDA 210884
 Tosymra/DFN-02/sumatriptan nasal spray

CLINICAL REVIEW

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Reviewer Name(s)	Laura Jawidzik, MD
Review Completion Date	January 25, 2019
Established/Proper Name	Sumatriptan
(Proposed) Trade Name	Tosymra
Applicant	Dr. Reddy's Lab
Dosage Form(s)	Nasal spray
Applicant Proposed Dosing Regimen(s)	Single dose of 10mg of nasal spray; Maximum dose in a 24-hour period: 30mg, separate doses by at least one hour
Applicant Proposed Indication(s)/Population(s)	Treatment of acute migraine
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of acute migraine

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Glossary

AC	advisory committee
AE	adverse event
AHS	American Headache Society
AR	adverse reaction
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DBP	diastolic blood pressure
DB1	double-blind treatment period 1
DB2	double-blind treatment period 2
DDM	dodecyl maltoside
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
eDiary	electronic diary
EOP2	end-of-phase 2
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
ICH	International Council for Harmonization
ICHD-3	International Classification of Headache Disorders, 3 rd edition
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

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ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

DFN-02, also known as sumatriptan nasal spray, is a serotonin receptor agonist belonging to the class of drugs known as triptans. DFN-02 is intended to be used for the acute treatment of migraine with or without aura in adults. The proposed proprietary name is Tosymra. The applicant's proposed dosing regimen is a single dose of 10mg of nasal spray with a maximum dose of 30mg in 24 hours. The applicant proposes that the doses be separated by at least one hour. The drug product, DFN-02 contains 10mg of sumatriptan and (b) (4) of an excipient known as DDM (1-O-n dodecyl-β-D-maltopyranoside). DDM is (b) (4) intended to act as a (b) (4)

Sumatriptan is an approved product that comes in many formulations including an oral form, nasal spray, nasal powder, and subcutaneous injection. The applicant has submitted a 505(b)(2) application for a new formulation of sumatriptan. The applicant's reference listed drug (RLD) is Imitrex injection (NDA 020080) by subcutaneous administration. Imitrex injection is approved for the treatment of acute migraine and the treatment of acute cluster headache. The approved doses for treatment of acute migraine are single doses of 1mg up to 6 mg and the dose for acute treatment of cluster headache is 6mg. The maximum dose in a 24-hour period is 12mg, and doses should be separated by at least one hour. Sumatriptan is also approved as oral tablets in 25mg, 50mg, and 100mg strengths. There is also an approved nasal spray with sumatriptan in strengths of 5mg, 10mg, and 20mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505(b)(2) application which utilized a bioequivalence study to bridge efficacy of DFN-02 (Tosymra) nasal spray to Imitrex injection. The Office of Clinical Pharmacology has reviewed the results of this pivotal bioequivalence study and concluded that DFN-02 (Tosymra) is bioequivalent to Imitrex 4mg SC. The product is not bioequivalent to the 6mg dose of Imitrex so the sponsor will not receive the indication for acute treatment of cluster headache.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

DFN-02, also known as sumatriptan nasal spray, is a serotonin receptor agonist belonging to the class of drugs known as triptans. DFN-02 is indicated for the acute treatment of migraine with or without aura in adults. It is administered as a single 10mg dose of a nasal spray with a maximum dose of 30mg in 24 hours. DFN-02 contains 10mg of sumatriptan and an additional excipient known as DDM, (b) (4) which acts as a (b) (4)

Migraine is a very common, chronic neurological condition with a broad spectrum of frequency and severity. It is characterized by recurrent attacks of headache with accompanying symptoms of nausea, vomiting, photophobia, and phonophobia. These attacks are generally of moderate to severe intensity and can at times be disabling and impact the quality of patients' lives. There are many FDA approved drugs for the acute treatment of migraine. A nasal formulation of sumatriptan may be beneficial to those patients who are needle phobic and cannot use Imitrex injection.

This 505(b)(2) application utilized a bioequivalence study to bridge the efficacy of DFN-02 to Imitrex injection. The Office of Clinical Pharmacology has reviewed the results of the pivotal bioequivalence study and concluded that DFN-02 is bioequivalent to Imitrex 4mg SC. (b) (4)
Given that the product is bioequivalent to Imitrex 4mg SC, I expect the efficacy of Tosymra to be the same as that product

The safety profile of DFN-02 in the postmarketing setting is expected to be the same as other approved sumatriptan products except for local adverse reactions. Sumatriptan has been marketed in the United States since 1992 and has a well-established safety profile.

Product labeling and routine postmarketing surveillance will address any safety issues associated with the product. The product label will reflect the known safety profile of Imitrex injection with the addition of local toxicity safety data associated with the use of a nasal spray. Use of DFN-02 is associated with nasal discomfort, throat discomfort, and dysgeusia.

The overall benefit-risk assessment of DFN-02 is unchanged from the previously approved sumatriptan products.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Migraine is a very common, chronic neurological disease with a broad spectrum of frequency, and severity. It is characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with other symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last anywhere from 4 hours to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.	Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives.
<u>Current Treatment Options</u>	There are many FDA-approved treatments for acute migraine as well as other products that are used off-label.	A nasal formulation of sumatriptan may be beneficial to those patients who are needle phobic and cannot use Imitrex injection.
<u>Benefit</u>	DFN-02 10mg nasal spray should provide benefit to adult patients treating acute migraine given that the product is bioequivalent to a 4mg dose of Imitrex injection.	
<u>Risk and Risk Management</u>	Product labeling and routine postmarketing surveillance will address any safety issues associated with the product. The product label will reflect the known safety profile of Imitrex injection with the addition of local toxicity safety data associated with the use of a nasal spray.	The safety profile of sumatriptan is well-established.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	<input type="checkbox"/> Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	<input type="checkbox"/> Patient reported outcome (PRO)	
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify)	
<input checked="" type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a very common, chronic neurological disease with a broad spectrum of frequency and severity. Migraine can be a serious and, at times, disabling condition that can impact the quality of patients' lives.

Migraine is a disease characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last from 4 to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.

2.2. Analysis of Current Treatment Options

There are many FDA-approved therapies for the treatment of acute migraine, and many others that are used off-label. In 2015, the American Headache Society (AHS) published a guideline on the treatment of acute migraine therapies (Marmura et al. 2015).

The guideline lists the following drugs as having Level A evidence (established as effective): acetaminophen, acetylsalicylic acid, diclofenac, ibuprofen, naproxen, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, dihydroergotamine (intranasal and pulmonary inhaler), and butorphanol. The following combination products are considered to have Level A evidence as well: sumatriptan/naproxen, and acetaminophen/acetylsalicylic acid/caffeine.

The following drugs and combination products are considered by this guideline to have Level B evidence (probably effective): chlorpromazine, droperidol, metoclopramide, prochlorperazine, flurbiprofen, keoprofen, ketorolac, IV magnesium, isometheptene, dihydroergotamine (SC, IV, IM); ergotamine/caffeine; tramadol/acetaminophen; and codeine/acetaminophen.

The following drugs and combination products are considered by this guideline to have Level C evidence (possibly effective): valproate (IV), phenazone, codeine, ergotamine, butorphanol (IM), meperidine, methadone, tramadol, dexamethasone, lidocaine (intranasal); butalbital/acetaminophen/caffeine, and butalbital/acetaminophen/caffeine/codeine.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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Sumatriptan was initially approved in 1992 under the trade name Imitrex (NDA 020080). It is available for use by SC injection, orally, and nasally as a spray and powder. It is also available in a combination product with naproxen sodium.

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug application 108088 was opened for DFN-02 on December 27, 2012, for the treatment of acute migraine. A “May Proceed Letter” was issued January 24, 2013, via email communication.

At the pre-IND meeting in 2010, the Division agreed that establishing the bioequivalence of DFN-02 to Imitrex 6mg SC could form the basis of a 505(b)2 application. At end-of-phase 2 (EOP2) in 2013, the sponsor proposed to conduct a three-way cross-over bioavailability study using DFN-02, Imitrex 4mg SC, and Imitrex 6mg SC. The Division found this approach acceptable.

At the EOP2 meeting, the Division informed the applicant that “At a minimum, we require that you provide safety data on 100 patients who treated an average of at least 2 migraines per month, for a minimum of 6 months.”

At EOP2, the Division also informed the applicant that the Division will not allow language into labeling that suggests a second dose of medication at 1 hour is safe and effective unless there is data to support it. The applicant was told that they would need to evaluate the safety and efficacy of a second dose in patients with an inadequate response to the first dose by re-randomizing those who had an inadequate response to the first dose. The applicant responded stating that information for their product will be consistent with language used in Imitrex labels.

At EOP2, the applicant was also told that their development program did not appear to trigger PREA. At the pre-NDA meeting, the applicant was informed that the PK profile of their product appears to support the acute migraine indication, but not the acute cluster indication because the PK profile is closer to the 4mg SC dose of Imitrex, but not close enough to the PK profile of the 6mg SC dose of Imitrex.

Summary of dates for regulatory interactions:

Pre-IND meeting: April 28, 2010

Initial IND: December 27, 2012

End of phase 2 meeting: November 5, 2013

Pre-NDA meeting: December 13, 2017

NDA filing: March 27, 2018

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No inspections by OSI are required. The study forming the basis of approach is a pharmacokinetics study which will be inspected by the Office of Study Integrity and Surveillance (OSIS).

Reviewer Comment: OSIS recommended accepting the sponsor's data without an on-site inspection. Please see the memo from Shila Nkah for further details.

4.2. Product Quality

DFN-02 is composed of sumatriptan and a (b) (4) called DDM.

4.3. Clinical Microbiology

Please see the review by microbiologist, Laura Wasil.

4.4. Nonclinical Pharmacology/Toxicology

The applicant is relying on the FDA's findings of safety for Imitrex injection. Please see the review by Edmund Nesti, nonclinical reviewer.

4.5. Clinical Pharmacology

Please see the review by clinical pharmacologist, Priya Brunsdon.

4.6. Devices and Companion Diagnostic Issues

Please see the review from CDRH by device specialist, Marc Neubauer.

4.7. Consumer Study Reviews

N/A

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 1 Listing of Clinical Trials Relevant to NDA 210884

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
DFN-02- CD-012	Randomized, double-blind, placebo-controlled	Single 10mg nasal dose with option for a second dose	2-hour pain freedom	Single attack/ Within 2 to 7 days post dose	107 randomized; 93 treated; 74 completed	Migraine patients	9/1
<i>Studies to Support Safety</i>							
DFN-02- CD-010	Open-label safety study	Single 10mg nasal dose with option for a second dose	Safety/tolerability	6 months/ Every 30 days for 6 months	173 enrolled; 167 treated; 134 completed	Migraine patients	25/1
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							
DFN-02- CD-009	Open-label, single dose, 3-way crossover study	Single 10mg nasal, 4mg SC, or 6mg SC	PK parameters	Total study duration: 6 weeks	78 enrolled; 77 completed	Healthy volunteers	1/1

Note: Throughout this review, I will use the following short-hand for the study titles: 009, 010, and 012.

5.2. Review Strategy

The applicant has submitted a 505(b)(2) application using a scientific bridging strategy to the subcutaneous form of Imitrex. This strategy employs a pharmacokinetic method to establish bioequivalence to NDA 020080. The efficacy study (DFN-02-CD-012) that is described in Table 1 above, and throughout the review is not required for approval of this product. (b) (4)

or safety, I will review studies 009, 010, and 012.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. DFN-02-CD-012: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of DFN-02 (Sumatriptan Nasal Spray 10mg) in Episodic Migraine with or without Aura

6.1.1. Study Design

Overview and Objective

The primary objective of the study was to assess the proportion of patients who were pain-free at 2 hours post-dose during the first double-blind treatment period. The secondary objective of the study was to assess the proportion of patients who were pain-free at 2 hours post-dose in the second double-blind treatment period.

Trial Design

Study 012 was conducted in the United States. Study 012 was a randomized, double-blind, placebo-controlled, parallel group study of patients with migraine. Patients were randomized in a 1:1 ratio to either DFN-02 or placebo.

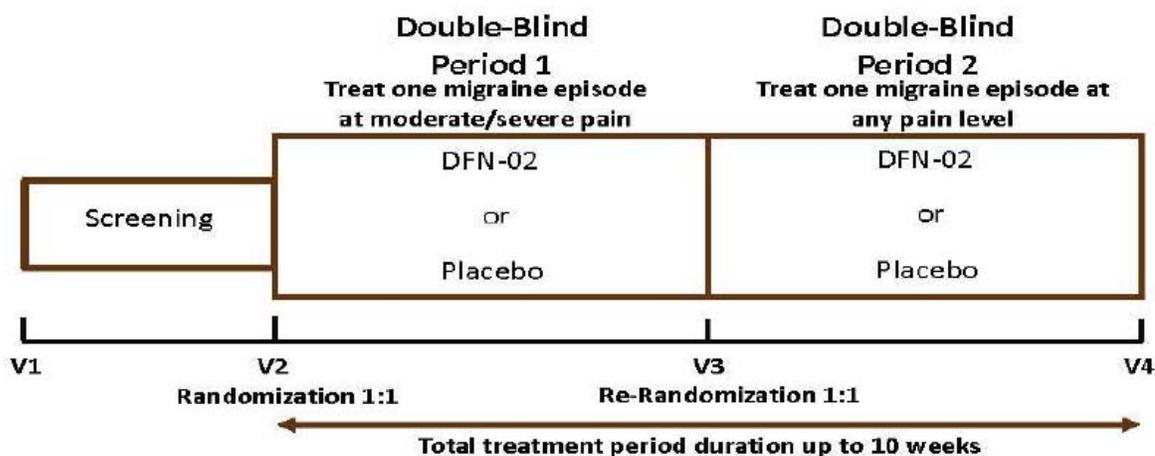
Basic Study Design

There was a screening phase of up to 21 days during which patients were evaluated for eligibility to enroll in the study. During the screening period, patients were given an electronic diary (eDiary) to record at least one migraine attack, and to record rescue medication. Eligible patients were then randomized in to double-blind treatment period 1 (DB1). In DB1, patients were instructed to treat a single migraine attack of moderate to severe pain within one hour of onset. After treating a single migraine attack, patients were asked to return to the study site within 2 to 7 days. Those patients who treated a single migraine attack in DB1 were then

eligible to be re-randomized into double-blind treatment period 2 (DB2). In DB2, patients were instructed to treat one migraine attack of **any** pain level. After treating a single attack, patients again returned to the study site within 2 to 7 days of the second treatment. Once a patient was randomized, the total duration of participation was up to 10 weeks.

A patient was permitted to take a second dose of medication for the same attack if the relief was insufficient but provided at least some relief. The second dose of medication was permitted only after completing the 2-hour post-dose assessment in the eDiary. After 2 hours, if the patient did not experience any relief from the first dose of study medication, then the patient was permitted to use rescue medication, but not study medication.

Figure 1 Basic Study Design for Study 012



This figure was taken from the applicant's materials from study protocol 012

Screening (Visit 1): Written informed consent was obtained, and the patients were given their unique patient identification number at this visit. Screening lasted three weeks.

Randomization (Visit 2): Patients who met the eligibility criteria were randomized at this visit into DB1. The patient then had 4 weeks in which to treat a migraine. The patient then returned to the site within 2 to 7 days after treating a migraine with study drug.

Re-randomization (Visit 3): Patients who treated a migraine in DB1 were eligible for re-randomization into DB2 at visit 3. Again, patients had 4 weeks in which to treat a migraine. In DB2, patients could treat a migraine of any severity.

End-of-study visit (Visit 4): This visit occurred within 2 to 7 days of the migraine attack treated in DB2 or was the end-of-treatment/early termination visit.

Diagnostic Criteria

The applicant utilized the ICHD-3 for the diagnosis of migraine with or without aura. For this study, patients had to experience on average 2 to 8 migraines per month for at least one year prior to enrollment.

ICHD-3 Diagnostic Criteria for Migraine without Aura

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours
- C. Headache has at least two of the following four characteristics:
 1. Unilateral location
 2. Pulsating quality
 3. Moderate or severe pain intensity
 4. Aggravation by or causing avoidance of routine physical activity
- D. During the headache, at least one of the following:
 1. Nausea and/or vomiting
 2. Photophobia and phonophobia

ICHD-3 Diagnostic Criteria for Migraine with Aura

- A. At least two attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
 1. Visual
 2. Sensory
 3. Speech and/or language
 4. Motor
 5. Brainstem
 6. Retinal
- C. At least two of the following four characteristics:
 1. At least one aura symptom spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession
 2. Each individual aura symptom lasts 5 to 60 minutes
 3. At least one aura symptom is unilateral
 4. The aura is accompanied, or followed within 60 minutes by headache

Key Inclusion Criteria

- Male or female, age 18 to 75
- History of episodic migraine with or without aura, with no more than 14 headaches per

month, and with 48 hours of headache-free time between migraine headaches

Key Exclusion Criteria

- Medication overuse headache:
 - Opioid use ≥ 10 days during the 90 days prior to screening
 - Combination products containing opioids or butalbital ≥ 10 days during the 90 days prior to screening
 - Triptans or ergots ≥ 10 days a month during the 90 days prior to screening
- Treated with Botox or other botulinum toxin within 4 months prior to screening
- Unstable dosage of migraine prophylactic medications within 30 days prior to screening
- Mini-prophylaxis for menstrual migraine
- Hemiplegic migraine
- History of stroke or transient ischemic attack
- History of 'migralepsy' defined as seizure following a migraine, or other seizure disorder
- History of cluster headache or history of frequent tension headache
- Non-responsiveness to SC sumatriptan ≤ 6 mg
- Prior ischemic coronary artery disease, angina pectoris, history of myocardial infarction, documented 'silent' ischemia, or coronary artery vasospasm including Prinzmetal's angina
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders
- Uncontrolled hypertension or SBP > 140 mmHg or DBP > 90 mmHg; uncontrolled diabetes
- Peripheral vascular disease or ischemic bowel disease
- Use of MAO-A inhibitors
- SSRIs, SNRIs, TCAs, and steroids unless the dose has been stable for at least 3 months prior to randomization
- Patients with any conditions that are likely to affect the physiology of the nasal mucosa (colds, influenza, nasal septum surgery, chronic nasal rhinitis)
- Any abnormal nasal physiology or pathology
- Acute or chronic sinusitis
- Severe renal impairment
- History of alcohol or substance abuse
- Positive HIV, Hep B surface antigen, or Hep C antibody serology testing

Rationale for Dose Selection

The applicant selected the sumatriptan dose in combination with DDM that produced exposures similar to Imitrex injection.

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Study Treatments

DFN-02 and placebo were provided in a single-use nasal spray device calibrated to deliver 100uL per spray. One spray contains 10mg of DFN-02 or matching placebo.

Assignment to Treatment

All patients who entered screening were assigned a unique patient identification number. The patient ID number was assigned by an interactive web response system (IWRS).

For DB1, patients were randomized in a ratio of 1:1 to either DFN-02 or placebo if the patient met all the eligibility requirements during screening. For DB2, eligible patients were re-randomized to either DFN-02 or placebo.

Blinding

This was a double-blind placebo-controlled trial. Study medication kits had identical labeling and were assigned a unique kit number. Patients and site personnel were blinded to the treatment group assignment.

Procedures and Schedule

The schedule of trial procedures and assessments is summarized in Table 2. I have modified this table from the sponsor's materials to include only key assessments.

Table 2 Schedule of Procedures and Assessments for Study 012

Period (duration)	V1 Screening (21 days)	V2	V3	V4
Dispense study medication		X	X	
Vitals signs	X	X	X	X
ECGs	X	X	X	X
Pregnancy testing	X	X	X	X
Chemistry, hematology	X	X	X	X
Adverse Event Recording	X	X	X	X

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Concurrent Medications

Patients could be taking concurrent migraine prophylaxis; however, changes in the dose were not permitted during the study.

The following medications were not permitted during the study:

- MAO inhibitors
- Triptans (except study medication)
- 5-HT₁ receptor agonists
- Ergotamine
- Antipsychotics
- Opioids if used for ≥ 4 days per month
- Tramadol was not permitted within 24 hours of use of study medication

Treatment Compliance

Patients were instructed to return all used and unused study medication from DB1 before entering DB2. At the end of study visit, patients were required to return all used and unused study medication, medication containers, and the completed eDiary.

Rescue Medication

Patients could take a second dose of study medication or take rescue medication two hours after taking the first dose of study medication and after completing the eDiary 2-hour post-dose assessment. If no relief at all was experienced with the first dose, then the patient was instructed not to take study medication but was to use rescue medication instead.

Rescue medication could not include other triptans or ergotamines.

Patient Completion, Discontinuation, or Withdrawal

Patients could withdraw from the study at any time. Patients who withdrew from the study have all data listed and are included in patient summaries.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the proportion of patients who were free from moderate to severe headache pain at 2 hours after the first dose study medication during the DB1 treatment period. Headache pain of moderate (grade 2) or severe (grade 3) reduced to none (grade 0).

Secondary Endpoints

The secondary efficacy endpoint was the proportion of patients who were free from headache pain at 2 hours after the first dose of study medication taken for a migraine of any pain level during DB2.

Statistical Analysis Plan

Please note that the SAP was not submitted to the IND for review. The SAP was submitted with the clinical study report in 2017.

Analysis Populations

Table 3 Analysis Sets for Study 012

Analysis Set	Definition	Analyses Performed
Screened Set	All screened patients	Patient listings, summary tables of patient disposition
Randomized Set	For DB1, this includes all patients who gave informed consent and meet eligibility. For DB2, this includes all patients who completed DB1 and are eligible for re-randomization.	
Full Analysis Set 1	All randomized patients who took at least one dose of study medication during DB1 AND have at least one post-baseline efficacy time point.	Efficacy endpoints
Full Analysis Set 2	All re-randomized patients who took at least one dose of study medication during DB2 AND have at least one post-baseline efficacy time point.	Efficacy endpoints
Per Protocol Set	All FAS1 patients who have at least one post-baseline endpoint assessment, and who have no significant protocol deviations	
Safety Set	All patients who receive at least one dose of study medication during one or both treatment periods.	Safety Endpoints

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Sample Size Estimation

The applicant planned to randomize 100 patients into DB1. Patients who discontinued participation were not replaced. The applicant assumed that 15% of placebo patients and 42% of DFN-02 treated patients would be pain-free at 2 hours. A sample size of 50 patients in each DB1 treatment arm would provide 86% power to detect this difference between placebo and DFN-02 treated patients with a 5% (2-sided) level of significance.

Analysis of the Primary Endpoint

The primary efficacy endpoint was analyzed using the Fisher's exact test. The proportion of patients who were headache-free at 2 hours post-dose was calculated as the number of patients who are pain-free at 2 hours post-dose divided by the number of patients with non-missing assessment at 2 hours post-dose.

The number of patients with a response, the number of patients with non-missing assessment, 95% confidence intervals, the odds ratio, and corresponding p-values were calculated. This analysis excludes patients who took a second dose of study medication or rescue medication prior to the 2-hour post-dose time point.

Reviewer Comment: I do not agree with the sponsor's plan for the analysis of the primary endpoint. The sponsor has described the full analysis set (FAS) as all randomized patients who took at least one dose of study medication during DB1 and have at least one post-baseline efficacy time point. Patients who take rescue medication prior to the 2-hour time point should not be excluded from the analysis. They should be included in the analysis and treated as a treatment failure. Alternatively, if these patients were excluded from the primary analysis, the sponsor should have proposed a sensitivity analysis where these patients are called treatment failures. I also do not agree with the sponsor's statement that the proportion should be calculated by the number of patients who are pain-free at 2 hours divided by those patients with a non-missing assessment. The sponsor should analyze the FAS population, and then conduct sensitivity analyses on various ways to handle missing data. Overall, I would expect little missing data in an acute migraine trial.

Pre-Specified Methods of Handling Missing Data

Analyses on quantitative and categorical variables will include data from patients with non-missing values. Imputation of missing or incomplete dates will only be performed for summaries of AEs and concomitant medications.

Missing primary efficacy endpoint data will be imputed using the last observation carried

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forward (LOCF).

Reviewer Comment: The LOCF method is not acceptable to handle missing data. Please see the statistical review by Dr. Jinnan Liu. Missing data should be minimal for an acute migraine trial. A sensitivity analysis using 'worst case scenario' for the missing data should be performed and the results should be consistent with the planned primary analysis.

Statistical Methodology for Adjusting for Multiplicity

The sponsor has noted numerous secondary and exploratory endpoints in the SAP. There does not appear to be any plan to control for multiplicity for these endpoints.

Protocol Amendments

There were no amendments made to the original protocol dated June 1, 2016 or to the statistical analysis plan (SAP) dated September 16, 2016. The SAP was not submitted to the IND for review. The SAP was submitted to the IND with the completed clinical study report in 2017.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that this study was conducted in accordance with ICH GCP regulations; the GCPs applicable to the regions where the study was conducted; and in accordance with the ethical principles in the Declaration of Helsinki.

Financial Disclosure

This study would not qualify as a "covered clinical study" under 21 CFR 54 as it is not needed to establish the efficacy of this product.

Patient Disposition

Screened: 141
Randomized into DB1: 107
Received 1 or more doses of IP in DB1 (FAS1): 93
Randomized into DB2: 86
Received 1 or more doses of IP in DB2: 75

In DB1, 8 patients who were randomized into the study, but discontinued early did not experience a migraine attack. Of the other randomized patients who were not included in the FAS, but were randomized: 4 withdrew, 1 was terminated by the sponsor, and 1 was lost to

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follow-up (Table 4). In DB2, 9 patients who were randomized, but discontinued early, did not experience a migraine attack.

Table 4 Randomized Patients Not Included in FAS1

	Placebo (N=10)	DFN-02 (N=4)
No Migraine	6	2
Withdrawal by Patient	3	1
Study Terminated by Sponsor	1	0
Lost to Follow-Up	0	1

*This table was created by the reviewer from dataset ADSL for study 012 where RNDDDB1FL=Y and ACTARM=Not Treated

Reviewer Comment: There is imbalance between placebo and DFN-02 in patients who were randomized but not included in FAS1. Even when removing the patients who did not experience a migraine from the group of randomized patients, an imbalance remains between placebo and DFN-02 treatment arms.

Protocol Violations/Deviations

There were 21 patients of the randomized population of DB1 who had at least one major protocol deviation during the study. The majority of these deviations related to a lack of serum pregnancy testing not being performed at the screening visit

Table of Demographic Characteristics

No baseline imbalances in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 5).

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Table 5 Study 012: Demographic Characteristics of All Randomized Patients

Demographic Parameters	Placebo (N=53) n (%)	DFN-02 10mg (N=54) n (%)	Total (N=107) n (%)
Sex			
Male	8 (15.1)	12 (22.2)	20 (18.7)
Female	45 (85.0)	42 (77.8)	87 (81.3)
Age			
Mean years (SD)	39.3 (11.5)	43.6 (12.0)	41.4
Median (years)	41	45.5	43
Min, max (years)	19, 63	20, 68	19, 68
Race			
White	48 (90.6)	44 (81.5)	92 (86.0)
Black or African American	3 (5.6)	7 (13.0)	10 (9.5)
Asian	1 (1.9)	0	1 (0.9)
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (1.9)	1 (0.9)
Other	1 (1.9)	2 (3.7)	3 (2.8)
Ethnicity			
Hispanic or Latino	8 (15.1)	9 (16.7)	17 (15.9)
Not Hispanic or Latino	45 (84.9)	45 (83.3)	90 (84.1)
Region			
United States	53 (100)	54 (100)	107 (100)

This table was created by the reviewer in JMP using the SDTM dataset DM for study 012. This table was created using the treatment assignment for DB1.

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Patients in this study had a median onset of migraine at age 20 years, with an average of 3 to 4 migraines per month. The average BMI was 28.2 kg/m². Approximately 46% of the patients reported experiencing migraine aura, and 54% reported experiencing migraine without aura.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A formal treatment compliance analysis was not conducted.

The most frequent concomitant medications were Excedrin migraine, ibuprofen, and Excedrin. These medications could also be considered rescue medication and were also cited as the most frequently used rescue medications.

In DB1, 12/43 (27.9%) placebo-treated patients took rescue medication while 6/50 (12%) DFN-02 treated patients took rescue medication.

Reviewer Comment: Although not formally analyzed, DFN-02 appears to reduce the need for rescue medication as compared to placebo.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of patients who were pain-free at 2 hours after the first dose of medication. A responder was defined as a patient who experienced a reduction in pain from moderate (grade 2) to severe (grade 3) to pain-free (grade 0).

According to the sponsor’s analysis, using last observation carried forward (LOCF), there was a statistically significant difference between treatment and placebo using this responder definition (b) (4). For DFN-02, 21 (b) (4) patients were pain-free at 2 hours compared to 9 (b) (4) placebo treated patients. The sponsor-reported odds ratio for headache pain freedom at 2 hours post-dose (b) (4).

Table 6 Sponsor’s Analysis of the Primary Endpoint

LOCF	Placebo N=43	DFN-02 N=50
Headache pain freedom at 2 hours postdose	(b) (4)	
Number of assessments		
Number of responses		
Proportion (%) (95% CI)		
P-value		
Odds ratio for headache pain freedom at 2 hours postdose (95% CI)		

Table 7 Treated Patients Excluded from the Sponsor’s Primary Efficacy Analysis

Subject ID	Treatment Arm	Sponsor reason for exclusion	Headache Status per Database	Reviewer Proposed Primary Analysis	Worst Case Scenario Analysis
(b) (6)	PBO	24-hour efficacy data only	No HA at 24 hours	Failure	Success
(b) (6)	DFN-02	24-hour efficacy data only	Mild HA at 24 hours	Failure	Failure
(b) (6)	DFN-02	Took rescue prior to 2 hours	Moderate HA at 2 hours	Failure	N/A
(b) (6)	PBO	Took rescue prior to 2 hours	Severe HA at 2 hours	Failure	N/A
(b) (6)	PBO	Took rescue prior to 2 hours	No HA at 2 hours	Success*	N/A

Reviewer created table from dataset ADEFF where EPOCH=Treatment-1, PARAMCD=pfree2, ANL01FL ≠ Y

*Patients who treat a HA with rescue medication prior to the 2-hour time point ordinarily should be counted as a failure. However, my review of this patient’s data revealed a significant data quality problem. See table 10.

Reviewer’s comment: I do not agree with the sponsor’s calculation of the primary endpoint. The FAS1 includes 93 patients who treated a migraine and had a post-baseline reported efficacy measurement. The analysis presented above by the sponsor (Table 6) includes only 88 of 93 patients who received study medication to treat a migraine. I reviewed CSR listing 16.2.6.2.1 which shows eDiary data for 93 out of 93 patients who took IP to treat a migraine.

There were three patients who the sponsor states took rescue medication prior to the 2-hour time point. From the placebo group, the sponsor excluded two patients (Subject ID (b) (6) and (b) (6)) from the analysis who took rescue medication prior to the two-hour time point and one patient from the DFN-02 treated group. I will discuss these patients further under data quality and integrity below. Additionally, the sponsor excluded one placebo-treated patient and one DFN-02 treated patient (Subject IDs (b) (6) and (b) (6)) because they provided only efficacy data at 24 hours, but not at 2 hours.

I have created two additional analyses: “Reviewer Proposed” and “Worst Case Scenario.” For the “Reviewer Proposed” analysis, I categorized all patients “failures” if it could not be certain of their 2-hour status ((b) (6) and (b) (6)). For subjects (b) (6) and (b) (6), I also categorized as “failures” because they took rescue medication. Patients (b) (6) I called a “success” after a close examination of the eDiary data for this patient. It appears the patient was migraine-free prior to taking rescue medication, which calls into question whether the patient took rescue medication (see Table 10 under Data Quality and Integrity).

For the “Worst Case Scenario” analysis, I categorized the placebo-treated patients as “success” that the sponsor excluded and the DFN-02 patients that the sponsor excluded as “failures.” However, for patients who took rescue prior to 2 hours, I classified them as failures (except subject 30-18).

My suggested primary efficacy analysis is as follows using a Chi-square calculator:

Table 8 Reviewer Proposed Primary Efficacy Analysis

	PBO N=43	DFN-02 N=50
<i>Pain-free at 2 hours</i>	(b) (4)	
<i>Not pain-free at 2 hours</i>		
<i>p-value</i>		
<i>% pain free</i>		

In this analysis, I included the placebo patient that took rescue medication as pain-free at 2 hours. The other two placebo treated patients that were excluded by the sponsor were included in this analysis as failures as were the other two DFN-02 treated patients.

In the worst-case scenario analysis (Table 9), I included the sponsor’s excluded patients in the analysis of the primary endpoint. I considered placebo-treated patients as successes and DFN-02 treated patients as failures. I used a Chi-square analysis to calculate the p-value.

Table 9 Reviewer Proposed ‘Worst Case Scenario’ Analysis

	PBO N=43	DFN-02 N=50
<i>Pain-free at 2 hours</i>	(b) (4)	
<i>Not pain free at 2 hours</i>		
<i>p-value</i>		
<i>% pain free</i>		

Data Quality and Integrity

Table 10 Subject (b) (6) eDiary Data

Times	Headache Severity		Action
14:20	Moderate	Pre-dose	Headache onset

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14:34	Moderate		Study medication taken
14:45	None	10 min	
14:50	None	15 min	
14:54	None	20 min	
15:05	None	30 min	
15:29	Mild	60	
16:05	None	90	
16:27			Rescue medication taken
16:36	None	2 hours	

This information was taken from dataset ADQS2.

Twenty-four hours after dosing, this patient recorded 'very satisfied' as to how well the medication prevented the need for other medication to treat the migraine attack. The patient also recorded 'very satisfied' as to how quickly the medication allowed her to return to daily activities.

Subject (b) (6) eDiary data

There also appears to be a significant data quality problem with subject (b) (6) as well.

Table 11 Subject (b) (6) eDiary Data

Times	Headache Severity		Action
20:27	Severe	Pre-dose	Headache onset
20:49			Study medication taken
20:51			Rescue medication taken
21:03	Severe	10 min	
21:05	Severe	15 min	
21:10	Severe	20 min	
21:20	Severe	30 min	
21:50	Severe	60	
22:20	Severe	90	
22:50	Severe	2 hours	

This information was taken from table listing 16.2.6.2.1 and 16.2.6.6.1 from the CSR and dataset ADQS2.

According to the CSR, the patient took study medication at 20:49 and then took rescue medication at 20:51. In the corresponding dataset (ADQS2), the patient was listed as taking study medication at 20:50. In either case, it does not make sense that the patient took rescue medication within 1 or 2 minutes of taking study medication.

Reviewer Comment: After examining the data from subject (b) (6) carefully, I believe that this placebo-treated patient should be treated as a 'success' in the analysis of the primary endpoint. Either the patient's migraine severity data has been incorrectly captured, or her use of rescue medication has been incorrectly captured. It does not seem logical that a patient who is migraine-free would take rescue medication ten minutes prior to the assessment of the primary endpoint.

In my opinion, the most logical conclusion from the information in Table 10 is that the patient did not take rescue medication 10 minutes prior to 2-hour time point. It is not logical that a patient who was pain free for 2 hours with only a brief notation of mild pain would take rescue medication during a time when she was pain-free.

There also appears to be a data quality problem with subject (b) (6) as described above. This patient likely did not take rescue medication within 1 to 2 minutes of taking study medication. The patient should not be excluded from the analysis of the primary endpoint and should be counted as a failure because the patient had migraine at the 2-hour time point.

Other Data Quality Issues

Another data quality issue of concern is the post-randomization patient counts in each treatment arm that eventually contributes to the analysis of the primary endpoint. Overall, the sponsor randomized 107 patients into the study, but only included 88 patients into the proposed efficacy analysis.

Table 12 Post-Randomization Patient Counts

	Placebo	DFN-02	Total
Randomized initially	53	54	107
FAS1	43	50	93
Excluded from Primary Analysis	3	2	5
Included in Sponsor's Proposed Primary Analysis	40	48	88

Reviewer Comment: Approximately 25% of randomized placebo patients, and 12% of randomized DFN-02 patients were not included in the sponsor's final analysis. There is a significant post randomization imbalance between placebo and DFN-02 treated patients who were not included in the sponsor's proposed primary analysis. This imbalance suggests a study conduct problem. Please see Table 4 for details regarding the reasons for exclusion from the FAS1 and Table 7 for reasons for exclusion from the sponsor's proposed analysis of the FAS1.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoint was the proportion of patients who were free from headache pain at 2 hours post-dose in DB2. DB2 differed from DB1 in that patients could treat a migraine of any severity level, and not just those of moderate to severe intensity. This result was not statistically significant (b) (4). For DFN-02, 19 (b) (4) patients were pain-free at 2 hours compared to 17 (b) (4) of placebo patients.

Additional Analyses Conducted on the Individual Trial

The sponsor has conducted numerous secondary analyses on this study. There appeared to be no plan to control for multiplicity for these other secondary analyses.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

N/A. Only one efficacy trial was submitted.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

I expect the benefit of DFN-02 to be similar to other sumatriptan products.

7.2.2. Other Relevant Benefits

DFN-02 has pharmacokinetic properties comparable to that of Imitrex injection. This product may be desirable to those patients who respond to Imitrex injection but are needle-phobic.

7.3. Integrated Assessment of Effectiveness

(b) (4)
The study had a small sample size with significant concerns regarding post-randomization imbalances between treatment arms, accurate data collection, and proper analysis of the primary endpoint. As described in section 6, a single patient's data was called into question and potentially sways the p-value of the primary endpoint. The results of a reliable study should not be swayed by the inclusion/exclusion of a single patient.

The analysis of the primary endpoint was not done properly. The sponsor excluded 3 patients from the analysis who took rescue medication prior to the 2-hour time point. The sponsor also

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excluded two other patients who met the definition for inclusion into the primary analysis but did not have a plan in place for how to handle these patients' missing data.

The SAP was not submitted to the IND for review. The SAP was received with the CSR in 2017. There is no way to verify that the sponsor 'pre-specified' the plan to exclude patients who took rescue from the analysis. Ultimately, the proper way to handle patients who took rescue prior to the measurement of the primary endpoint is to consider them treatment failures.

After closely examining the data on the patients who were excluded from the primary analysis, some significant problems with accuracy in data collection were noted. One (possibly 2) of the patients who was reported as taking rescue medication (and excluded from the primary analysis) likely did not take rescue medication. Inclusion of this patient into the analysis changes the p-value from significant to non-significant.

The sponsor's secondary endpoint did not reach statistical significance by their calculation. The other numerous proposed secondary endpoints did not have a pre-specified plan for multiplicity as the study was designed as a phase 2 study.

The sponsor has shown that DFN-02 is bioequivalent to Imitrex injection 4mg. Given the product's pharmacokinetic properties, I expect the product to be as efficacious as Imitrex 4mg SC.

8. Review of Safety

8.1. Safety Review Approach

The safety review includes studies 009, 010, and 012. Study 010 was a 6-month safety study to assess the long-term safety of repeat use of DFN-02. In this study DFN-02 was administered intranasally at the onset of acute migraine and could be repeated once, at least one hour after the initial dose. No more than 2 doses of DFN-02 were to be taken in a 24-hour period. Study 012 is described in detail in section 6. Study 009 is an open, label PK study used to establish the bridge from Imitrex SC to DFN-02.

In this review, I summarize information from the applicant's materials, and supplement them with analyses that I conducted using the applicant provided datasets. Because this is a 505(b)(2) and sumatriptan is an approved product with a well-established safety profile, this safety review will focus on product specific safety related to the use of sumatriptan as a nasal spray.

Table 13 Clinical Studies Contributing to the Integrated Analysis of Safety

CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

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Study	Dose	Patients in double-blind safety set	Patients in open-label safety set
009	10mg	0	78
010	10mg	0	167*
012 (DB1)	10mg	50	0
012 (DB2)	10mg	37**	0

*Received at least one dose of DFN-02

**Some of these patients received DFN-02 in DB1 as well

Anticipated Areas of Interest for the Safety Review

This product is a different formulation of sumatriptan which is an already approved product. The safety profile of sumatriptan is already well-established. The primary safety review of interest for this formulation relates to local toxicity of the product as this is a nasal spray. The safety review will primarily focus on adverse events related to this issue.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 14 Safety Population, Size, and Denominators for DFN-02 across Studies

Safety Database for DFN-02		
Clinical Trial Groups	DFN-02	Placebo
Study 012 DB1 at least one dose	50	43
Study 012 DB1 second dose	3	7
Study 012 DB2 at least one dose	37	38
Study 012 DB2 second dose	6	6
Uncontrolled trial for migraine (Study 010)	167	0
Healthy volunteers (PK Study 009)	78	0

At EOP2, the applicant was told to provide safety data on 100 patients, who treated an average of at least 2 migraines per month, for a minimum of 6 months. The applicant interpreted this

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statement mathematically to mean an average of 2 migraines per month for 6 months of all the patients in the study, rather than on a per patient basis. The applicant has 134 patients who completed a 6-month study (study 010). These 134 patients treated an average of 2.5 migraines per month. On average, 3.7 doses of medication per patient per month were taken over this 6-month period with an average of 22.6 doses per patient.

From the Division's perspective, as per the migraine guidance, to be counted in the long-term safety database, adult patients should treat, on average, a minimum of two migraine attacks per month. Study 010 provided the long-term safety data for Table 15. To be included in Table 15, a patient had to have treated, on average, ≥ 2 migraines per month. The applicant had 173 enrolled patients, of which 167 received at least one dose of DFN-02 (Safety Set). The applicant considered 134 of the patients to have completed the study.

Table 15 Overall Extent of Relevant Exposure to DFN-02 (Study 010)

	Number of patients exposed to sumatriptan nasal spray: Safety Set			
	≥ 3 months	≥ 6 months	≥ 12 months	≥ 18 months
Dose	N=	N=	N=	N=
10mg	103	97	0	0

*Reviewer created table from dataset ADMG using the safety analysis set for study DFP-02-CD-010 where SAFFL=Y and PARAMC=DFN-02 Treated Migraine Episodes per Month, and AVAL ≥ 2

	Number of patients exposed to sumatriptan nasal spray: Completers Set			
	≥ 3 months	≥ 6 months	≥ 12 months	≥ 18 months
Dose	N=	N=	N=	N=
10mg	94	94	0	0

*Reviewer created table from the dataset ADMG using the completers analysis set for study DFP-02-CD-010 where COMPLFL=Y and PARAM=DFN-02 Treated Migraine Episodes per Month, and AVAL ≥ 2

Note: There were three patients included in the safety set, but who were not included in the completers set. These three patients had ≥ 2 migraine treated per month. The applicant has excluded them from the completers set because of loss to follow up by two patients, and withdrawal by another. I have included these patients in my analyses.

In study 012, there were 19 patients who treated a migraine with DFN-02 in both DB1 and DB2 (Table 16).

Table 16 Overall Extent of Exposure to DFN-02 (Study 012)

DB1/DB2	placebo/placebo	placebo/DFN-02	DFN-02/placebo	DFN-02/DFN-02
	N=18	N=18	N=20	N=19

Reviewer Comment: While the applicant is a few patients short of the 100 patients requested at EOP2, I think their overall exposure (134 patients) is sufficient to make an assessment of the local toxicity of the product which is the primary safety concern in this review.

8.2.2. Relevant characteristics of the safety population:

Migraine occurs more commonly in women than in men. The demographic characteristics in this development program are not entirely representative of the intended treatment population. Migraine is more prevalent in women than men (3:1), but the ratio in these studies of women to men is on the order of 5:1 or 6:1.

Table 17 Summary of Demographic Characteristics for Study 010 and 012

Demographic Parameters	DFN-02 Study 010 N=167 n (%)	DFN-02 Study 012 N= 93 n (%)
Sex		
Male	31 (18.6)	18 (19.4)
Female	136 (81.4)	75 (80.6)
Age		
Mean years (SD)	43.3 (11.4)	42.3 (11.6)
Median	45.0	43
Min, Max	19, 64	19, 68
Race		
Asian	2 (1.2)	1 (1.1)
Black	25 (15.0)	7 (7.5)
Native Hawaiian or Pacific Islander	1 (0.6)	1 (1.1)
White	136 (81.4)	82 (88.2)
Other	3 (1.8)	2 (2.2)
Weight (kg)		
Mean (SD)	78.6 (18.6)	78.5 (20.0)

This table was adapted from the applicant's materials from the CSR for study 010 and study 012.

8.2.3. Adequacy of the safety database:

As discussed in section 8.2.1 Overall Exposure, the applicant is a few patients short of the requested 100 patients treating an average of two migraines per month for 6 months. The applicant has data on 97 patients who have treated an average of two migraines per month for 6 months. However, I think the 134 patients who treated an average, in aggregate, of 2.5 migraines per month over 6 months provides enough safety data to draw conclusions about the local adverse events of the product.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The product appears to cause significant nasal discomfort, burning, and other local application site reactions in a significant percentage of patients in studies 009, and 010. However, in study 012 (placebo-controlled trial), there are overall very few AEs (20 in total). Given this discrepancy, it calls into question the sponsor's process for collecting AEs for study 012.

8.3.2. Categorization of Adverse Events

Applicant's Definitions of AEs, SAEs, and TEAEs

All AEs that occurred during the study were documented. An AE was defined as any untoward medical occurrence in a clinical study patient who was administered a study medication, and which did not necessarily have a causal relationship to the study medication. Fluctuations of pre-existing conditions, including migraine, were not considered AEs. A TEAE was defined as an AE that had a start date on or after the date of the first dose of study medication, and up to five days after the last dose of study medication.

An SAE was defined as any untoward medical occurrence or effect that caused one of the following:

- Death
- Life-threatening
- Prolonged hospitalization
- Persistent or significant disability
- Congenital anomaly or birth defect
-

Process of Recording, Coding, and Categorizing AEs

Adverse events were reported from the time of informed consent through the end of study visit and documented on the eCRF. AE data that was captured included the following: description of symptom, classification of severity, date of occurrence, date of resolution, action taken, causal

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relationship, and outcome of event. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.0.

Assessment of Applicant's Verbatim Terms and Coding

The applicant provided verbatim terms and coded them to preferred terms. I reviewed all AEs in the ADAE dataset for study 012 to see if recoding or adding terms was needed. Overall the coding appeared acceptable. I did not review the coding for studies 009 and 010.

8.3.3. Routine Clinical Tests

Methodology and Frequency of Routine Clinical Testing

For study 010, safety assessments were performed monthly and included the following: physical examination, urine pregnancy test, labs, urine drug testing, vital signs, ECG, medication review, and adverse event review.

8.4. Safety Results

8.4.1. Deaths

N/A

8.4.2. Serious Adverse Events

Study 010: There were 5 SAEs reported by 4 patients. The SAEs were diverticulitis, cholecystitis, menometorrhagia, pyelonephritis, and myocardial infarction.

Study 009 and 012: There were no SAEs reported in these studies.

Reviewer Comment: No labeling changes will be recommended from this information. The label for sumatriptan already includes a warning and precaution for myocardial infarction and a contraindication for patients with ischemic or vasospastic coronary artery disease.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 010: There were five patients (3%) who experienced 10 AEs that lead to discontinuation from study medication. These AEs included 2 events of dizziness, and one each of the following: dyspepsia, pain, lethargy, diarrhea, nausea, vomiting, dyspnea, and jitteriness.

Study 009 and 012: There were no reported dropouts or discontinuations due to AEs.

Reviewer Comment: No labeling changes will be recommended from this information.

8.4.4. Significant Adverse Events

AEs by Intensity

Each AE was assigned a category by the investigator as follows:

Mild: an AE that was easily tolerated by the patient, caused minimal discomfort, and did not interfere with daily activities

Moderate: an AE that was sufficiently discomforting to interfere with normal everyday activities; intervention may have been needed

Severe: an AE that prevented normal everyday activities; treatment or intervention was needed

Study 010: There were 120 patients (71.9%) who experienced a treatment emergent adverse event (TEAE) during study 010. Nine (5.4%) patients experienced a severe TEAE. For most patients, the TEAEs were mild (36.5%) or moderate (29.9%). Local application site reactions were evaluated for severity, and the majority of those were mild in nature as well (Table 18).

Table 18 Study 010: Product Specific Reactions by Severity

	Total (N=167) AEs by Severity		
	Mild	Moderate	Severe
Application site reactions*	53 (31.7)	14 (8.4)	1 (0.6)
Dysgeusia	30 (18.0)	5 (3.0)	0
Throat irritation	6 (3.6)	2 (1.2)	0

*This table was created by the reviewer using the following PTs: application site irritation, application site pain, application site paresthesia, and application site reaction.

**A patient may be counted in more than once in this table

There was one application site reaction (LLT: application site burning) that was recorded as severe. The patient did not discontinue from the study due to this AE.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study 009:

Overall 27 of 78 patients (35%) reported a total of 56 adverse events during the study. The most common adverse event reported was dysgeusia (17%). Six percent of patients experienced headache (5), nasal discomfort (5), and throat irritation (5).

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There were 18 patients (23%) who experienced a total of 33 TEAEs that could potentially be attributed to local effects of the product. These AE terms include the following: cough (2), dysgeusia (13), gingival pain (1), increased lacrimation (1), nasal congestion (1), nasal discomfort (5), oropharyngeal pain (2), rhinorrhea (2), stomatitis (1), and throat irritation (5).

Study 010:

Overall 120 of 167 patients in the safety set reported a total of 1264 TEAEs during the study. There were 76 patients (45.5%) reporting a TEAE that could be attributed to local effects of the product. These AE terms include the following: application site irritation, application site pain, application site paresthesia, application site reaction, cough, dysgeusia, glossodynia, increased upper airway secretion, increased lacrimation, oropharyngeal pain, sneezing, throat irritation, and throat tightness. Of these AEs, only one (0.5%) was reported to be severe.

The most commonly reported AEs related to local effects were application site reactions (35.9%), dysgeusia (21.0%), throat irritation (4.8%), and increased lacrimation (1.8%). Within application site reactions, application site pain was most common (30.5%).

Sixty out the 167 (35.9%) reported an application site reaction. This analysis includes the following grouped PT terms: application site reaction, application site irritation, application site pain, and application site paresthesia.

Study 012:

A total of 20 AEs were reported by 16 patients. Per the applicant, only 12 of them reported by 9 patients met the applicant's definition of TEAE. There were 9 AEs reported in DB1, and 11 reported in DB2. In DB1, there were no AEs reported by placebo-treated patients. In DB1, there were four patients who reported AEs that could be attributed to local site reactions or product specific AEs: dysgeusia, application site pain, rhinorrhea, and burning sensation in the sinuses (Table 13). In DB2, only one AE was reported by one placebo treated patient (upper respiratory tract infection). In DB2, there were four patients who reported AEs that could be attributed to local site reactions or product specific AEs: application site pain (1), and dysgeusia (3) (Table 14). In total, three unique DFN-02 treated patients reported dysgeusia compared to no reports in placebo-treated patients. There was a total of 2 patients who reported application site pain compared to none in placebo-treated patients.

In Study 012, there were 18 patients who received placebo/placebo in DB1/DB2, and 19 patients who received DFN-02/DFN-02. None of the placebo/placebo patients reported local AEs attributable to investigational product. Two out of 19 (10.5%) patients receiving DFN-02/DFN-02 reported local site reactions.

Table 19 AEs Reported by Patients at a Greater Frequency than Placebo in Study 012 (DB1)

	DFN-02 N=50 n (%)	Placebo N=43 n (%)
Application site reactions	3 (6.0)	0
Dysgeusia	1 (2.0)	0
Chest discomfort	1 (2.0)	0
Diarrhea	1 (2.0)	0
Hyperkalemia	1 (2.0)	0
Laceration	1 (2.0)	0

Reviewer created table

Table 20 AEs Reported by Patients at a Greater Frequency than Placebo in Study 012 (DB2)

	DFN-02 N=37 n (%)	Placebo N=38 n (%)
Dysgeusia	3 (8.0)	0
Sinusitis	2 (5.0)	0
Application site pain	1 (3.0)	0
Rash (Allergic dermatitis)	1 (3.0)	0
Malaise	1 (3.0)	0
Ear infection	1 (3.0)	0
Laceration	1 (3.0)	0

Reviewer created table

Reviewer Comment: The rates of TEAEs were low in the double-blind treatment period (study 012). However, patients only treated one or two migraines during this time and it was a very small study.

(b) (4)

I think it appropriate to include the local adverse event rate from the open-label long-term safety study as well (study 010). The double-blind period has highlighted that there is an imbalance from placebo in local site reactions. However, the open-label period shows that the rate is higher in patients treating multiple migraines. The open-label study is more in line with how the product will be used (e.g. to treat multiple migraine headaches). In addition, study 009 shows that the local site reactions are much higher than would be suggested by study 012. Again, it is not apparent as to why the number of AEs in study 012 is so low.

8.4.6. Laboratory Findings

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In study 010, patients had monthly labs done including hematology, chemistry, and urinalysis. I reviewed the applicant's analyses of laboratory findings and did not conduct independent analyses of laboratory data.

8.4.7. Vital Signs

In study 010 patients had their vital signs collected at monthly intervals. I reviewed the applicant's analyses of vital signs and did not conduct independent analyses of vital signs.

Reviewer's comment: Section 5 of the label for sumatriptan includes a warning and precaution for significant elevation in blood pressure and recommends monitoring blood pressure in patients. Sumatriptan is contraindicated in patients with uncontrolled hypertension. These warnings, precautions, and contraindications will remain in the label for DFN-02. No new information on vital signs will be included in the label.

8.4.8. Electrocardiograms (ECGs) and QT

In study 010, ECGs were collected at monthly intervals. I reviewed the applicant's analyses of ECGs and did not conduct independent analyses of ECG intervals.

Reviewer Comment: Section 5 of the label for sumatriptan includes a warning and precaution for arrhythmias and is contraindicated in patients with Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders. These warnings, precautions, and contraindications will remain in the label for DFN-02. No new information on ECG intervals will be included in the label.

8.4.9. Immunogenicity

N/A

8.5. Analysis of Submission-Specific Safety Issues

Sumatriptan is already approved in multiple different formulations. The applicant was asked to conduct a long-term safety study to evaluate the local toxicity of the product.

8.5.1. Local Toxicity

Local toxicity is summarized and discussed in sections 8.4.4 and 8.4.5.

8.6. Safety Analyses by Demographic Subgroups

In the placebo-controlled trial (012) there were too few AEs to conduct analyses by demographic subgroups.

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8.7. **Specific Safety Studies/Clinical Trials**

N/A

8.8. **Additional Safety Explorations**

8.8.1. **Human Carcinogenicity or Tumor Development**

No human carcinogenicity studies were conducted for this product.

8.8.2. **Human Reproduction and Pregnancy**

Patients who were pregnant or lactating were excluded from the clinical studies of DFN-02. Information on pregnancy/lactation will come from the FDA-approved label for Imitrex.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

This section is not applicable to this review. Pediatric patients were not exposed to DFN-02. The FDA-approved label for sumatriptan states that safety and effectiveness in pediatric patients has not been established and is not recommended for use in patients younger than 18 years of age. This language will be included in the label for DFN-02.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No studies of abuse potential were conducted. No potential for abuse has been identified with the use of sumatriptan.

8.9. **Safety in the Postmarket Setting**

8.9.1. **Safety Concerns Identified Through Postmarket Experience**

Sumatriptan has been marketed since 1992. Cardiovascular adverse events related to triptans were identified in the postmarket setting and added to the label.

8.9.2. **Expectations on Safety in the Postmarket Setting**

The safety profile of DFN-02 in the postmarket setting is expected to be the same as other sumatriptan products with the exception of local adverse reactions.

8.9.3. **Additional Safety Issues from Other Disciplines**

At the time of this writing, I am not aware of any other safety issues from other disciplines.

8.10. **Integrated Assessment of Safety**

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Sumatriptan was first approved in the U.S in 1992. The safety profile of sumatriptan is well-established with more than 25 years of experience and data collection. This product has established bioequivalence to Imitrex injection; therefore, we can rely on the cumulative safety data and the label for Imitrex injection. However, because DFN-02 is a nasal spray and not a SC injection, we cannot rely on the label for safety related to the local toxicity.

9. Advisory Committee Meeting and Other External Consultations

N/A

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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This is a 505(b)(2) application. The applicant is relying on the findings of safety and efficacy of Imitrex injection (NDA 020080). The label will be consistent with the prescribing information for FDA-approved label for sumatriptan.

 (b) (4)
I
recommend including safety data as discussed in section 8 from study 010 into the final approved labeling.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

N/A

12. Postmarketing Requirements and Commitments

N/A

13. Appendices

13.1. References

Marmura MJ, Silberstein SD, and TJ Schwedt. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. *Headache*. 2015 Jan; 55(1): 3-20.

13.2. Financial Disclosure

The only study conducted by the applicant that would qualify as a “covered clinical study” under 21 CFR 54 would be study 009, which establish the scientific bridge from the applicant’s product to the already approved sumatriptan product

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Covered Clinical Study (Name and/or Number): Study 009

Was a list of clinical investigators provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>2</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>none</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>none</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>none</u></p> <p>Significant payments of other sorts: <u>none</u></p> <p>Proprietary interest in the product tested held by investigator: <u>none</u></p> <p>Significant equity interest held by investigator in Applicant of covered study: <u>none</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>none</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA A JAWIDZIK
01/25/2019 01:57:55 PM

HEATHER D FITTER
01/25/2019 02:00:52 PM