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RESEARCH**

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
 Viveca Livezey, MD
 NDA 212157
 DFN-15 (Celecoxib) - ELYXYB

CLINICAL REVIEW

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Established/Proper Name	Celecoxib Oral Solution 25 mg/mL
(Proposed) Trade Name	ELYXYB
Applicant	Dr. Reddy's
Dosage Form(s)	Oral Solution 25 mg/mL
Applicant Proposed Dosing Regimen(s)	120 mg to take at onset of migraine
Applicant Proposed Indication(s)/Population(s)	Treatment of acute migraine (b) (4) in patients with and without aura
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the acute treatment of migraine with and without aura in adults

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
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
ECG	electrocardiogram
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
IND	Investigational New Drug Application
IR	Informational Request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NOCB	next observation carried backward
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics

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PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard Deviation
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

DFN-15 is an oral liquid formulation of the drug, celecoxib. Celecoxib is a cyclooxygenase-2-selective nonsteroidal anti-inflammatory drug (NSAID) that is currently approved for the treatment of acute pain, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, and primary dysmenorrhea. The DFN-15 formulation of celecoxib is a new oral liquid formulation that has not been previously marketed.

The applicant has submitted this new drug application (NDA) to propose that DFN-15 will be administered as a single dose for the treatment of acute migraine in patients with migraine with and without aura. The maximum dose proposed by the applicant is 120 mg in a 24-hour period.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant provided data from two adequate and well-controlled studies (Study 006 and 007) that both demonstrated a clinically meaningful effect of DFN-15 on the co-primary efficacy endpoints of pain freedom and MBS freedom at 2 hours post-dose for the acute treatment of migraine compared to placebo. Study 007 demonstrated statistically significant superiority compared to placebo on both pre-specified co-primary endpoints. Study 006 failed to demonstrate a statistically significant effect of treatment on the co-primary endpoint of pain freedom at 2 hours post-dose; however, this result was only narrowly non-statistically significant, with a treatment effect size comparable to other FDA approved drugs for this indication. Study 006 did show a highly statistically significant and clinically meaningful benefit on the second co-primary endpoint of MBS freedom at 2 hours post-dose.

This application provides substantial evidence of effectiveness of DFN-15 for the acute treatment of migraine, despite the lack of statistical significance on the co-primary endpoint of pain freedom at 2-hours post-dose in Study 006. The basis for this conclusion includes the following: support from one study with highly statistically significant effects on both prespecified co-primary endpoints, one study with significant effects on one important prespecified co-primary endpoint of migraine-associated symptoms, both studies suggested less rescue medication use within the first 24 hours in the DFN-15 treated arm and higher rates of 24-hour sustained pain freedom in the DFN-15 treated arm, the fact that celecoxib is approved for the treatment of acute pain (a finding that helps to provide some reassurance regarding the lack of statistical significance, albeit narrowly, in analysis of the co-primary endpoint of pain freedom in Study 006), and the arguably elevated prior expectation of efficacy based on the fact that there are currently two NSAIDs that are FDA approved for acute treatment of migraine.

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1.3. **Benefit-Risk Assessment**

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Integrated Assessment

The applicant has developed DFN-15, an oral solution of celecoxib, for the acute treatment of migraine. Celecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID), approved for pain indications, with a safety profile that has been well-characterized over many years. The applicant is seeking an indication for DFN-15 for the acute treatment of migraine in adults with and without aura.

Migraine is a common, debilitating disease characterized by recurrent headaches of moderate to severe intensity with associated symptoms, such as nausea, photophobia, and phonophobia. Migraines can limit physical activity, decrease productivity and significantly impact patients' lives. There are several drugs that are FDA-approved for the acute treatment of migraine and the preventive treatment of migraine. Drug classes that are approved by FDA for the acute treatment of migraine include: triptans, ergotamines, NSAIDs, serotonin (5HT_{1F}) receptor agonists, and calcitonin gene-related peptide (CGRP) receptor antagonists. The applicant has submitted data to support the approval of DFN-15, an NSAID, for the acute treatment of migraine.

The applicant submitted results of two adequate and well-controlled studies (Study 006 and Study 007) both in patients with migraine with and without aura, to evaluate the effect of DFN-15 in treating an acute migraine (b) (4). The two studies, identical in design, randomized patients to either DFN-15 120 mg or placebo. Both studies prespecified the co-primary endpoints of pain freedom at 2 hours post-dose and most bothersome symptom (MBS) freedom at 2 hours post-dose, for the treatment of a single, moderate to severe migraine attack in the first double-blind period.

DFN-15 treatment resulted in pain freedom 2 hours after dosing in approximately 32.4-35.1% of patients, compared to 21.0-25.3% of patients in the placebo arm in the applicant's primary analysis. The effect on pain freedom at 2 hours was statistically significant in Study 007 (p=.003) and did not reach significance in Study 006 (p=.075). Both studies met the co-primary endpoint of MBS freedom at 2 hours. DFN-15 treatment resulted in MBS freedom in 56.8-58.0% of patients, compared to 43.9-44.4% of patients who received placebo – an effect that was both clinically meaningful and statistically significant (p values of .003 (Study 006) and .007 (Study 007)). Subgroup analyses (e.g. race, gender, age) did not reveal clinically significant differences in response to treatment for either study.

Though Study 006 did not statistically meet its prespecified endpoint of pain freedom at 2 hours, the study did demonstrate a strong trend towards pain freedom and a 7% higher rate of responders to DFN-15 than placebo, which is clinically meaningful. Additionally, there was a statistically and clinically significant effect on the endpoint of MBS freedom (an endpoint specific to patients with migraine). Study 007 did meet

both its prespecified co-primary endpoints, and both studies demonstrated that patients in the DFN-15 treated group had less rescue medication use at 24 hours compared to placebo and higher rates of sustained pain freedom at 24 hours compared to placebo (though these latter endpoints were exploratory, and not controlled for Type 1 error).

Celecoxib was first approved in 1998, and since its approval, multiple safety issues have emerged over 20 years of clinical use, including the risk of serious cardiovascular thrombotic events, an increased risk of serious gastrointestinal adverse events, hepatotoxicity and numerous other warnings and precautions that are well described in the prescribing information (PI). The safety analysis of DFN-15 in the two trials indicated dysgeusia as the only new adverse event that occurred at higher rates in the DFN-15 treated group than the placebo treated group. The pharmacokinetic profile of DFN-15 120 mg demonstrates exposures that are less than the approved doses of celecoxib tablets. Therefore, the safety profile of DFN-15 at the dose to be prescribed has already been well-characterized.

Based on the review of the efficacy and safety data from the two studies provided in this application, prior evidence of the effects of celecoxib (including its indication for acute pain), prior approvals of other NSAIDs for the acute treatment of migraine, and the well-characterized safety profile of celecoxib, the data available supports approval of DFN-15 120 mg for the acute treatment of migraine in adults.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Migraine is a very common, chronic neurological disease. • Migraine is characterized by recurrent attacks of headache that are typically moderate to severe in intensity. Attacks tend to be unilateral headaches associated with other symptoms, such as nausea, vomiting, phonophobia, or photophobia. • Typical migraines 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 	<p>The burden of migraine is large. Migraine significantly impacts patients and their lives, the ability to carry out daily activities, and contributes to a significant amount of pain and morbidity.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>general prodrome a day or two prior to the onset of the headache.</p> <ul style="list-style-type: none"> • Migraine can be very disabling and contribute to loss of productivity and diminished quality of life. • Migraine can occur on an episodic or chronic basis. • Migraine is more frequent in females than in males. In one United States population-based study, the one-year prevalence of migraine was 18% in females and 7% in males, and 12% overall (Lipton, Stewart, et al. 2001). • Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton, Bigal, et al. 2007). 	
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • There are many Food and Drug Administration (FDA)-approved treatments for acute migraine, as well as other products, that are used off-label. • Non-specific therapies (not FDA approved but used off-label), include non-specific NSAIDs and acetaminophen. • Currently used acute migraine treatments include: <ul style="list-style-type: none"> ○ Triptans, including oral, oral disintegrating, nasal spray, subcutaneous formulations – however, these treatments are contraindicated in patients with cardiovascular or cerebrovascular disease. ○ The non-steroidal anti-inflammatory (NSAID) diclofenac (Cambia) and the NSAID with a triptan - naproxen/sumatriptan (Treximet) - are two FDA approved acute migraine treatments. Specifically, diclofenac, naproxen and ibuprofen have randomized controlled trial evidence suggesting that they are effective for the acute treatment of 	<p>There are numerous treatment options for the acute treatment of migraine. Drugs that may act more rapidly, have less side effects or are provided in novel formulations, may be advantageous for some patients.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>migraine.</p> <ul style="list-style-type: none"> ○ Dihydroergotamine (nasal spray, subcutaneous or intramuscular) – however, this is contraindicated in patients with cardiovascular disease. ○ Calcitonin gene-related peptide (CGRP) antagonists – recently approved; long-term effects not completely known. ○ The therapeutic gain (active drug minus placebo drug effect) for the endpoint of pain freedom at 2 hours, for drugs recently approved for the acute treatments of migraine, ranges from 7%-17% in clinical trials. 	
<p>Benefit</p>	<ul style="list-style-type: none"> ● The applicant conducted two adequate and well-controlled Phase 3 trials to evaluate the effect of DFN-15 120 mg compared to placebo for the treatment of an acute migraine attack. While both studies contained two double-blind (DB) treatment periods, the first DB period of each study was used as the primary efficacy analysis population. ● Both studies used the co-primary endpoints of pain freedom at 2 hours and MBS freedom at 2 hours. ● In Study 006, for pain freedom at 2 hours, the therapeutic gain (proportion of responders to active drug compared to placebo) was ~7%, with a p value of 0.075; for MBS freedom, the therapeutic gain was ~14% with a p value of <.001. ● Study 006 had a high placebo response rate and a high degree of missing data (at time points 2 hours and earlier). Patients who took rescue medications were excluded from the primary analysis by the applicant. The missing data mostly occurred in the placebo arm, and 	<p>The applicant demonstrated efficacy of DFN-15 120 mg for the acute treatment of migraine in two well-controlled studies. Though, the effect on pain freedom was not statistically significant in one study, the results are clinically meaningful, based on multiple factors. This includes: there was a higher percentage of responders in the DFN-15 treated group compared to placebo (that is in line with other approved drugs for the acute treatment of migraine) in both studies, both studies had significant effects on one important prespecified co-primary endpoint of migraine-associated symptoms, and both studies suggested less rescue medication use within the first 24 hours in the DFN-15 treated</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>in a sensitivity analysis, these patients were analyzed as nonresponders (because future time points did demonstrate they were mostly nonresponders), and the p value moved closer to 0.05 for pain freedom at 2 hours.</p> <ul style="list-style-type: none"> • In Study 007, for pain freedom at 2 hours, the therapeutic gain was ~14% with a p value of <.001; for MBS freedom at 2 hours, the therapeutic gain was ~14% with a p value of .007. • One approved NSAID for the acute treatment of migraine, Cambia (diclofenac), demonstrated therapeutic gains of 11-15% for pain freedom at 2 hours (Cambia compared to placebo). • The NSAID and triptan combination (naproxen and sumatriptan/Treximet) is approved for the acute treatment of migraine. • Rofecoxib (Vioxx) is a COX-2 selective NSAID (with a similar mechanism of action as celecoxib) that was previously approved for the acute treatment of migraine. This was taken off the market in 2004 due to an increased risk of cardiovascular events. • There is one nonprescription NSAID approved for the acute treatment of migraine. • Celecoxib is an NSAID with an acute pain treatment indication. 	<p>arm and higher rates of 24-hour sustained pain freedom in the DFN-15 treated arm.</p> <p>Celecoxib is already approved for the treatment of acute pain.</p> <p>There is a prior expectation of efficacy, based on the fact that there are currently two NSAIDs that are FDA approved for acute treatment of migraine, with each approval based on at least two-well controlled studies.</p>
Risk and Risk Management	<ul style="list-style-type: none"> • The safety profile of celecoxib has been well characterized during approvals of celecoxib for other indications, post-market monitoring and post-market studies. The dosage of DFN-15 displays a pharmacokinetic profile that is well-capped below the maximum dose of celecoxib that has been previously approved. 	<p>All of the warnings, precautions, contraindications and boxed warnings for celecoxib should be included in the label for this new formulation.</p>

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	<ul style="list-style-type: none">Treatment-emergent adverse events (TEAEs) in the two phase 3 studies indicate that dysgeusia occur at a higher rate with DFN-15 (with its oral solution formulation) than placebo.	Given the findings from the clinical trials for DFN-15, the label should be updated to include dysgeusia as a treatment emergent adverse events that occurs with DFN-15 use at an increased frequency compared to placebo. No other new safety signals were detected.

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 checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
<input checked="" 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 type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The proposed indication for DFN-15 is for the acute treatment of migraine with and without aura in adults. Migraine is a common, chronic, neurological disorder that is most prevalent in women and between the ages of 25 and 55 years (Dodick 2018). Patients with migraine experience recurrent attacks of moderate to severe head pain that can cause significant disability and cause an impact on social and functional abilities.

Diagnostic criteria for migraine with and without aura have been established by the International Headache Society (IHS) and are termed the International Classification for Headache Disorders (ICHD-3). Per the ICHD-3 definition, a migraine is a recurrent headache disorder manifesting in recurrent attacks of head pain that must fulfill the following criteria: last 4-72 hours, have two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, and must have associated symptoms of either nausea and/or vomiting, or photophobia and/or phonophobia.

2.2. Analysis of Current Treatment Options

Current treatment options for the acute treatment of migraine include FDA-approved drugs (e.g., triptans, ergotamines, NSAIDs, serotonin (5HT1F) agonists, and CGRP antagonists). There are two FDA-approved NSAIDs for the acute treatment of migraine, diclofenac and the NSAID/triptan combination of naproxen and frovatriptan. Many drugs are used off-label, including opiates, over the counter drugs, including NSAIDs (such as ibuprofen), acetaminophen, and drug combinations such as caffeine/acetaminophen/ aspirin preparations. Patients may also use behavioral techniques or approved devices, for the treatment of acute migraine (Dodick 2018).

In addition to these acute therapies, patients with episodic and chronic migraine are often also prescribed medications for the preventive treatment of migraine that are given on a daily, monthly, or quarterly basis.

Table 1 - Summary of Acute Treatment Options for Migraine

Product (s) Name	Year of Approval	Route	Important Safety and Tolerability Issues	Other Comments (for example, subgroups addressed)
FDA Approved Treatments				
ERGOTS				
Dihydroergotamine (DHE) Nasal Spray 2 mg	1997	Nasal spray	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	

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DHE 1 mg injection	1946	Sub-cutaneous	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
TRIPTANS				
Almotriptan 12.5 mg	2001	Tablet	Contraindicated in patients with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic or basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings/precautions in patients with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage or stroke	Indicated for patients age 12 to 17 years old
Eletriptan 20, 40 mg	2002	Tablet		Interacts with CYP3A4 inhibitors
Frovatriptan 2.5 mg	2001	Tablet		
Naratriptan 1, 2.5 mg	1998	Tablet		
Rizatriptan 5, 10 mg	1998	Tablet		Indicated for patients age 6 to 17 years old
Sumatriptan Oral 25, 50, 100mg	1992	Tablet		
Sumatriptan Nasal Spray 10, 20 mg		Nasal Spray		
Sumatriptan Nasal Powder 22 mg	2016	Nasal Powder		
Sumatriptan SC 4, 6 mg	2009	Sub-cutaneous		
Zolmitriptan NS 2.5, 5 mg	2015	Nasal Spray		Indicated for patients 12 years of age or older
Zolmitriptan Oral 2.5, 5 mg	1997	Tablet		
Sumatriptan/naproxen 85/500 mg	2008	Tablet		NSAID included; Indicated for patients 12 years and older; Cardiovascular risk, increased risk of bleeding due to naproxen component
NSAIDS				
Diclofenac (Cambia) 50 mg	2009	Oral (Packet)	Cardiovascular risk for thrombotic events, myocardial infarction and stroke; gastrointestinal adverse events, especially in elderly	
5-HT1F receptor agonists				
Lasmiditan	2019	Oral	Driving impairment for up to 8 hours; May lower heart rate; Adverse events include dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness;	

CGRP antagonist				
Ubrogepant 50 mg, 100 mg	2019	Oral	Nausea, somnolence, dry mouth	Interacts with CYP3A4 Inhibitors/inducers; substrate of BCRP and P-gp efflux transporters
Rimegepant 75 mg	2020	Oral	Nausea	Interacts with CYP3A4 Inhibitors/inducers; inhibitors of BCRP and P-gp efflux transporters
Devices				
GammaCore device	2017	Device		
Cerena device	2013	Device	Contraindicated in patients with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices	
Cefaly ACUTE device	2017	Device	Contraindicated with recent trauma to skull/face or with skin conditions/rashes	
Nonprescription, FDA approved				
NSAIDs (ibuprofen,)	2000 (Advil Migraine)	Tablet, capsule	Gastrointestinal toxicity, bleeding complications	Advil Migraine is a nonprescription drug indicated for the treatment of migraine.
Acetaminophen/aspirin /caffeine	1998 (Excedrin Migraine)	Tablet	Overuse, see effects for individual categories	Excedrin Migraine is a nonprescription drug indicated for the temporary relief of mild to moderate pain associated with migraine headache.

*I created this table using the Drugs@FDA website, and reviewing the approvals, labels, and dates for drugs and devices indicated for the acute treatment of migraine.

The current treatment options span a wide range of therapeutic targets. While NSAIDs are often used by providers for the acute treatment of migraine, as noted previously and in the table, only two NSAIDs (diclofenac and naproxen (the latter given as a sumatriptan/naproxen combination product)) are FDA approved as prescription drugs for this indication. Advil migraine is a nonprescription NSAID indicated for the treatment of migraine. Rofecoxib (Vioxx) is a COX-2 selective NSAID (similar to celecoxib) that was previously approved for the acute treatment of migraine, prior to being withdrawn from the US market in 2004 due to safety concerns (specifically, increasing the risk for cardiovascular events).

This overview suggests there is already a clear role for the NSAIDs in the treatment of acute migraine attacks. Celecoxib is not specifically approved for the acute treatment of migraine at this time, and this applicant is seeking an indication for this new liquid formulation of celecoxib for this new indication.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Celecoxib first received marketing authorization December 29, 1998, as a capsule, for oral use, for the signs and symptoms of osteoarthritis and rheumatoid arthritis, through a review of NDA 020998. The drug was marketed as Celebrex 100 mg and 200 mg. On October 18, 2001, celecoxib received approval for the additional indications of the management of acute pain in adults and the treatment of primary dysmenorrhea. In June 2002, the label for celecoxib was updated with changes to the Warnings, Precautions, Adverse Events, and Clinical Studies sections, based on a large gastrointestinal outcome study for Celebrex (Supplement 009). In July 2005, the applicant received an approval (Supplement 018) for the additional indication for the use of celecoxib for the relief of signs and symptoms of ankylosing spondylitis. There was an additional supplement (Supplement 019) for a revised package insert to include a boxed warning, with additional information about cardiovascular risk, and the addition of a MedGuide, as requested by FDA in a June 14, 2005, letter. Supplement 027 provided for changes to the package insert to include dosage and administration in special populations, warnings and precautions to include cardiovascular effects, and modifications to the uses in specific populations, clinical pharmacology, and clinical studies sections.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant opened IND 125585 on March 30, 2015, with Study 002, the first dose-finding study to evaluate two doses of DFN-15 compared to placebo.

An End of Phase 2 (EOP2) meeting was held on August 30, 2016, to discuss the applicant's plans to submit an NDA for DFN-15 using the 505(b)(2) pathway to use the findings of Celebrex 400 mg to establish the safety of DFN-15 and to submit its own clinical trial data to support efficacy for the acute treatment of migraine indication.

A Type B Pre-NDA meeting was held in August 2018. The applicant reported the results of their two pivotal studies (Study 006 and Study 007). Study 006 did not achieve statistical significance on both co-primary endpoints of pain freedom and MBS freedom at 2 hours post-dose (the study only met for MBS freedom). The key conclusions regarding these data and recommendations from the Division included:

- 1) The DB2 period from both trials was unlikely to be interpretable because treatment effects were not independent and this was a post-hoc analysis; however, the applicant could attempt to provide an argument that the data from DB2 were independent from DB1.
- 2) 15-20% of patients had missing data for the endpoint of MBS freedom and the applicant was advised to perform sensitivity analyses to address this issue.

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3) The applicant was also advised to conduct sensitivity analyses that treated patients who took rescue medications as non-responders. This was not done during the trials, but is the typical approach for trials in the acute treatment of migraine.

A Type C Written Response Only (WRO) with comments were provided to the applicant in January 2019, which addressed the pooling of safety data sets, the importance of not pooling efficacy data, and focusing on DB1 of each study for the efficacy analyses. The Division also requested that the applicant provide a flag for patients who did not have MBS recorded at migraine onset, since this may have led to a significant amount of missing data.

3.3. Foreign Regulatory Actions and Marketing History

The product has not been marketed outside the US.

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

4.1. Office of Scientific Investigations (OSI)

OSI conducted inspections on 4 sites – 2 from Study 006 (Sites 603 and 609) and 2 from Study 007 (Site 727 and 740). Site 609 was chosen from Study 006 because it was determined by the applicant, in a post hoc analysis, that removing this site led to a change in the results of the efficacy analysis of Study 006 for the primary endpoint because the placebo response rate for one endpoint was 75% at this site. The other three sites were chosen because they were high enrolling sites in the study. Per the Clinical Inspection Summary by Dr. Cara Alfaro, the inspection at site 609 revealed no unusual findings. Site 750 was noted to have several instances of under-reporting of adverse events and concomitant medication use. However, the report concluded that it was unlikely that under-reporting of these events would greatly impact the overall safety analyses for this application, because the greatest impact for the underreporting of concomitant medication occurred in the second double-blind period. The second double-blind period is not the focus of the primary efficacy or safety analysis. Therefore, it is unlikely that findings from the clinical site inspections significantly affect study results.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Controls review by the Office of Product Quality (OPQ) for further details.

4.3. Clinical Microbiology

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Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Celecoxib is a COX-2 inhibitor that blocks prostaglandin synthesis, which per the applicant, decreases the release of neuroactive peptides that lead to migraine pain. For further details, please refer to the review by Dr. Edmund Nesti, nonclinical reviewer.

4.5. Clinical Pharmacology

Celecoxib is an NSAID that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models. The exact mechanism of action is unknown, but it is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2).

Per the clinical pharmacology review, written by Dr. Mariam Ahmed, following 120 mg of DFN-15 administration under the fasting condition in 24 healthy subjects, the median plasma time to reach maximum drug concentration of celecoxib was 1 hour (range 0.67 to 3.00) compared to 3.5 hours (range 1.65 to 6.00) following 400 mg of celecoxib oral capsule administered under the fed condition. Dose proportionality was observed over a dose range of 120 mg to 240 mg of DFN-15. Food may not have a significant effect on the efficacy of DFN-15, based on the review. Please see the review by Dr. Ahmed for additional details.

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 2 – Clinical Studies to Support Safety and Efficacy of DFN-15

Trial/ National Clinical Trial (NCT) No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized and treated	Study Population	No. of Centers and Countries
Study 002	Randomized, placebo-controlled, double-blind, 3-treatment, 6-sequence, 3-period, crossover study.		Primary endpoint of pain relief (from moderate to severe to mild or none) at 2 hours after study drug infusion	Treat first migraine attack in each of 3 treatment periods, crossover to all groups in randomized sequence		Adults with migraine with or without aura, baseline 2-6 migraines per month, 48 hours of headache freedom between migraines.	United States (U.S.)
Study 006 NCT03009019	Randomized, placebo-controlled, double-blind.	DFN-15 120 mg or placebo in each of two double-blind periods, re-randomized between periods to DFN-15 120 mg or placebo.	Co-primary endpoint of pain relief (from moderate to severe to mild or none) and MBS freedom at 2 hours after study drug infusion	Double-blind period 1 (DB1) – treat first migraine attack of moderate-severe intensity; 7 days between attacks; Double-blind period 2 (DB-2) – treat first migraine attack of at least mild severity	631 randomized into DB1; 545 re-randomized into DB2; 544 completed DB1; 504 completed DB2; 578 in safety set	Adults with migraine with or without aura, baseline 2-6 migraines per month, 48 hours of headache freedom between migraines.	43 sites – all U.S.
Study 007 NCT03006276	Randomized, placebo-controlled, double-blind. (This study was identical to Study 006)	DFN-15 120 mg or placebo in each of two double-blind periods, re-randomized between periods to DFN-15 120 mg or placebo.	Co-primary endpoint of pain relief (from moderate to severe to mild or none) and MBS freedom at 2 hours after study drug infusion	Double-blind period 1 (DB1) – treat first migraine attack of moderate-severe intensity; 7 days between attacks; Double-blind period 2 (DB-2) – treat first migraine attack of at least mild severity	622 randomized, into DB1; 535 re-randomized into DB2; 531 completed DB1; 491 completed DB2; 571 for safety set	Adults with migraine with or without aura, baseline 2-6 migraines per month, 48 hours of headache freedom between migraines.	45 sites – all U.S.

5.2. Review Strategy

This review focuses on the efficacy and safety of DFN-15 for the acute treatment of migraine. For the efficacy review (Section 6), I will review the data from Study 006 and Study 007, the two pivotal studies conducted by the applicant. The integrated review of effectiveness will be in Section 7.

For the safety review (Section 8), the applicant is primarily relying on the already approved label for celecoxib. However, given that this is a new formulation, albeit a lower dosage and exposures than the approved indications, I will also review the safety data from Study 002, Study 006, and Study 007, to determine if updates to the label are required based on the clinical trial safety data provided by the applicant.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 006: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura

6.1.1. Study Design

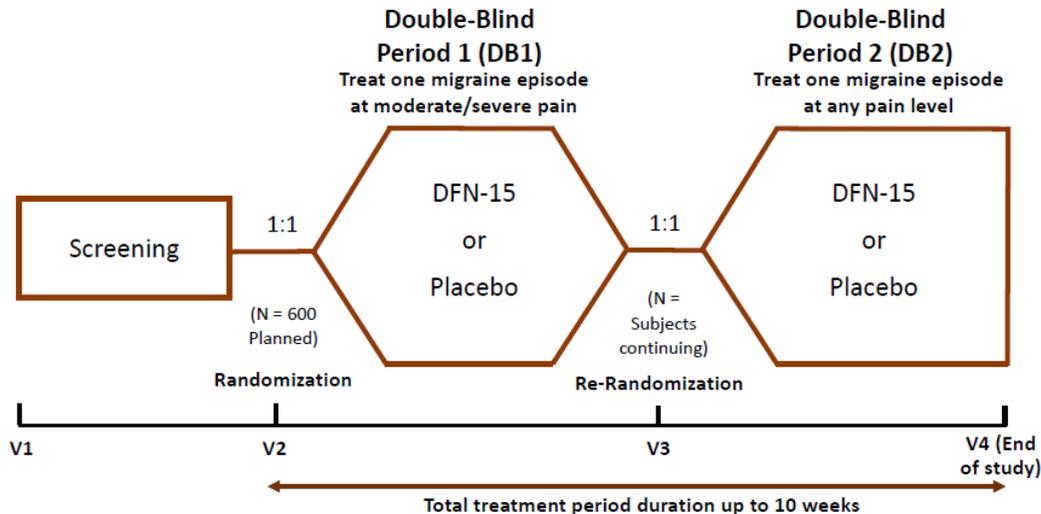
Overview and Objective

Study 006 was prospectively designed to assess the proportion of subjects who were pain-free and MBS free at 2 hours after treating a migraine attack in the first treated double-blind period.

Trial Design

This study was a randomized, 2 double-blind (DB) treatment period study, that enrolled adults (ages 18 to 75, inclusive) with episodic migraine per the International Classification of Headache Disorders [ICHD-3] criteria, with 2 to 8 migraine attacks per month, and 48 hours of headache-freedom between attacks. Patients were randomized in a 1:1 ratio in double-blind period 1 (DB1) to receive either DFN-15 or matching placebo to treat one migraine attack of at least moderate severity. After DB1, patients were asked to return to clinic within 1 week and then, if still eligible, to be re-randomized (in a 1:1 ratio again of DFN-15 or placebo) into double-blind period 2 (DB2) to treat another migraine attack (of any pain level).

Figure 1 – Study Design



V1=Visit 1; V2=Visit 2; V3=Visit 3; V4=Visit 4; DB1=Double blind period 1; DB2=Double blind period 2

Source: NDA 212157 Clinical Study Report (CSR) for Study 006 Figure 1 <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-006\dfn-15-cd-006-report-body.pdf>

Key Inclusion Criteria

1. Able to provide written informed consent
2. Male or female, ages 18 to 75 years of age, inclusive
 - a. Females must have a negative pregnancy test and use contraception or be postmenopausal or sterile
 - b. Males must use contraception or be abstinent during the study
3. History of episodic migraine (per ICHD-3), with 2 to 8 migraine attacks per month for at least 12 months, with no more than 14 headache days per month and 48 hours of headache-free time between migraine attacks
4. Migraine with or without aura with onset prior to 50 years of age
5. Migraines typically of moderate or severe pain severity

Key Exclusion Criteria

1. Medication overuse headache ≥ 10 days of certain medications (opioids, triptans, ergots, combination medications which include opioid or barbiturate) during 90 days prior to screening;
> 14 days of NSAIDs in 90 days prior to screening
2. Treated with botulinum toxin for migraine within 4 months prior to screening
3. Unstable doses of preventive treatments for migraine for prior 30 days

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4. Taking mini-prophylaxis for migraine
5. On chronic warfarin or equivalent
6. History of stroke or transient ischemic attack or other cerebrovascular events
7. History of seizure following a migraine or history of seizure disorder
8. Patients in whom NSAIDs are contraindicated
9. History of uncontrolled hypertension or baseline blood pressure >140/90 mm Hg
10. Any medical condition that would be contraindicated; or abnormal clinical or electrocardiogram abnormality that the investigator thinks may interfere with the study
11. QTcF interval > 450 msec
12. Creatinine > 1.5 x upper limit of normal (ULN), total bilirubin >1.5 x ULN, liver function tests > 2.5 x ULN
13. Uncontrolled diabetes
14. History of alcohol or substance use disorder
15. Treatment with antipsychotics within 30 days
16. Positive toxicology screen
17. Patients who receive cytochrome P450 (CYP) 2C9 inducers or CYP2D6 substrates with a narrow therapeutic range within 7 days prior to randomization
18. History of positive human immunodeficiency virus (HIV), Hepatitis B or C test
19. Cancer (within 5 years) except adequately treated basal cell, squamous cell skin carcinoma or in situ cervical cancer

Rationale for Dose Selection

The applicant conducted Study 003 to test multiple doses of DFN-15 and determined that doses of 120 mg to 240 mg exhibited dose proportional bioavailability. Please refer to Dr. Ahmed's review for details of Study 003. The applicant also conducted Study 002, in which patients with a history of migraine were randomized (in a crossover design) to DFN-15 120 mg, DFN-15 240 mg, or placebo. The greatest improvement in pain freedom (the prespecified primary efficacy endpoint) was observed in the DFN-15 120 mg treatment group, with a response rate of 31.0%, compared to a response rate of 25.6% in the 240 mg group and 18.6% in the placebo group. None of the p values (comparing study treatment to placebo or varying doses of DFN-15 to each other) demonstrated statistical significance; however, these were not adequately powered comparisons.

Overall, 16 patients in Study 002 experienced a treatment-emergent adverse event (TEAE) while in the study, none of which were severe. There was an increase in gastrointestinal side effects (nausea, abdominal pain, diarrhea, vomiting) at the 240 mg dose (compared to the 120 mg dose and placebo). The applicant thus chose the 120 mg dose for the pivotal studies, citing that this is the dose in which the greatest response was seen, and that both doses seemed to be tolerated well. See Safety Review (Section 8) for additional details.

Reviewer comments: The lack of a dose response between the 120 mg and 240 mg arms does

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raise concern about the dose-finding trial, specifically about the adequacy of the doses selected by the applicant; however, this was a small study that was underpowered to show any difference before groups. Although the Division typically prefers pivotal studies to include a range of doses, the applicant's analysis informed the selection of the dose of 120 mg for the pivotal studies. It may have been beneficial for the applicant to pursue two doses in the pivotal studies, in case the dose chosen was too low to demonstrate an effect compared to placebo.

Study Treatments

DFN-15 administered as an oral solution (25mg/mL) was administered as 120 mg dose (4.8 mL) or placebo (also an oral solution of 4.8 mL). Both study treatments were administered in identical amber-colored glass bottles to maintain the blind.

Assignment to treatment

Patients were randomized to the first DB1 in a 1:1 ratio to receive either DFN-15 or matching placebo. Patients who were still eligible after the first DB period were re-randomized to DFN-15 or placebo in a 1:1 ratio for DB2.

Blinding

The study was a double-blind study, in which patients and providers were blinded to treatment assignment. Study kits had an identical appearance and were assigned using an interactive web response system (IWRS).

Dose modification/discontinuation

The dose could not be modified during the study, as this was single dose study. A second dose for any reason was not allowed in a given DB period. Patients could discontinue from the study at any time.

Procedures/Schedule

Table 3 – Study Assessments

	Visit 1 (V1)	Visit 2 (V2)	Visit 3 (V3)	Visit 4 (V4)
	Screening	Randomization	End of DB1	End of DB2
Assessment		Baseline	Re-randomization	End of Study
Informed consent	X			
Inclusion/Exclusion criteria	X	X	X	
Subject eDiary instructions and dispensation	X	X	X	

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Adverse events review	X	X	X	X
Demographics	X			
Medical history and prior medications	X	X		
Migraine history (including MBS for the co-primary analysis) and current treatment status	X			
Physical examination and suicidality check ⁹	X	X	X	X
Height and weight	X			X
Vital signs (sitting SBP/DBP, pulse rate, body temperature)	X	X	X	X
Serum pregnancy test (hCG)	X			
Urine pregnancy test		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis); TSH at Screening	X	X	X	X
Glycosylated hemoglobin (HbA1c)	X			X
Serology (HIV, hepatitis B surface antigen, and hepatitis C virus antibody)	X			
Urine drug test and ethanol screen	X	X	X	X
12-lead ECG	X	X	X	X
Concomitant medication review			X	X
Randomization (V2)/ Re-randomization (V3)		X	X	
Dispense DB study drug		X	X	
Subject study drug compliance and accountability			X	X
Review, confirm, and ensure proper recording of the subject eDiary entries		X	X	X
Collect eDiary				X

Source: NDA 212157 CSR for Study 006 Table 9.1 (modified). <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-006\dfn-15-cd-006-report-body.pdf>

Concomitant medications

Patients could not change medications for the preventive treatment of migraine during the study, and prescribed medications had to be stable for at least 30 days before screening. Prohibited medications included antipsychotics, opioids (if ≥ 4 days per month), CYP2C inducers, CYP2D6 substrates, and marijuana.

Rescue medications, including NSAIDs, migraine medications, and prescription/nonprescription drugs could be taken 2 hours after taking study medication, if a migraine did not resolve.

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Treatment compliance

Patients were instructed on proper administration of study drug and were to use an electronic diary (eDiary) to record timing of dosing of study drug and use of rescue medication. All used and unused study medication from DB1 had to be returned before DB2 period study medication was dispensed.

Patient completion, discontinuation or withdrawal

Patients could discontinue the study at any time.

Assessments

The assessment of pain intensity prior to the time of dosing was made using a 4-point scale (levels included: 0=none, 1=mild, 2=moderate, 3=severe) and patients were asked to only treat a migraine attack of moderate or severe intensity. MBS (among nausea, photophobia and phonophobia) was made at screening during the migraine history evaluation and this screening MBS was used for the co-primary endpoint. The same MBS had to be present pre-dose but did not have to be designated again as the MBS pre-dose prior to dosing. In addition to the use of an e-diary to record the co-primary endpoints, the applicant included several assessments, including additional eDiary assessments (which included information on the treated migraine attack, measures such as time to pain relief, time to pain freedom, pain level, functional disability, presence of associated migraine symptoms (the MBS), and treatment satisfaction (on a 7-point scale)). The applicant also calculated a functional disability score (a 4-point scale with 0 indicating no disability and 3 indicating performance of daily activities severely impaired, bed rest may be necessary) and these scales/questions were administered at various time points. The applicant also used the Patient Perception of Migraine Questionnaire-Revised (PPMQ-R) to assess treatment satisfaction at 24 hours post-dose.

Reviewer comments: The MBS should have ideally been identified at the time of the treated attack, and not necessarily at screening, as the MBS may change within a patient. If the MBS was not listed again as a symptom during the treated attack, it would not be included as part of the endpoint and this could have contributed to missing data. The functional disability score, treatment satisfaction scale and the PPMQ-R have not been previously reviewed by the Division's Clinical Outcomes Assessment staff. Results of these assessments were also not included in the hierarchy to be controlled for multiplicity; therefore, any analyses of these endpoints would be solely exploratory in nature. An eDiary was used for the assessment of the co-primary efficacy endpoints, which should help mitigate the risk of retrospective diary entry and recall bias.

Study Endpoints

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The co-primary endpoint was the following:

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

The secondary endpoints, listed below, were not included in the testing hierarchy and were not controlled for Type 1 error. These endpoints included the following comparisons between DFN-15 and placebo:

- The proportion of patients with treatment-emergent adverse events (TEAEs)
- The proportion of patients who were free from nausea, photophobia, and phonophobia at 15, 30, 45 minutes and 1, 1.5, 2, 4 and 24 hours post-dose
- Time to meaningful pain relief (defined as based on patient's perception) within 2 hours post-dose
- Time to pain freedom within 2 hours post-dose
- The proportion of patients who have pain relief at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours post-dose compared between DFN-15 and placebo. Headache pain relief is defined for DB1 as a reduction from moderate or severe pain prior to dosing to mild or none post-dose, and for DB2 as moderate or severe pain pre-dose reduced to mild or none post-dose, or mild pain pre-dose reduced to none post-dose
- The proportion of patients who are pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours post-dose
- The proportion of patients with their Screening MBS (and have this symptom pre-dose) absent at 15, 30, and 45 minutes, and 1, 1.5, 2 (DB2 period), 4, and 24 hours post-dose
- Change in functional disability score at 2, 4, and 24 hours post-dose
- Among those reporting cutaneous allodynia pre-dose, the proportion of patients who are pain-free at 2 and 4 hours post-dose
- The proportion of patients who are pain-free at 2 and 4 hours post-dose comparing BMI < 30 and ≥ 30, and BMI is < 25 and ≥ 25
- The proportion of patients who have pain recurrence between 2 to 24 hours (i.e., pain-free at 2 hours post-dose, with pain [mild, moderate, or severe] reported at 24 hours post-dose)
- The proportion of patients who have sustained pain relief at 2 to 24 hours post-dose (i.e., pain relief at 2 hours post-dose, with no use of rescue medication and no worsening of headache pain within 2 to 24 hours post-dose)
- The proportion of patients who have sustained pain freedom at 2 to 24 hours post-dose (i.e., pain-free at 2 hours post-dose, with no use of rescue medication, and no

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recurrence of headache pain within 2 to 24 hours post-dose)

- The proportion of patients who use rescue medication after 2 hours (2 to 24 hours) post-dose
- Treatment satisfaction at 2 hours and 4 hours post-dose as determined on a 7-point scale compared between DFN-15 and placebo. DFN-15 compared to same question in the Baseline PPMQ-R.
- Treatment satisfaction as measured by PPMQ-R at 24 hours post-dose

Reviewer comments: It is important to note that only the analyses of the co-primary endpoints in the DB1 portion of the trial were controlled for Type 1 error. Therefore, the secondary endpoints can only be considered to be exploratory in nature, including any analyses on DB2. I will discuss these to help support the primary endpoint, though statistical significance cannot be assessed. Therefore, I will refer to p-values less than 0.05 in these exploratory analyses as nominal.

Statistical Analysis Plan (SAP)

The following definitions were used to define the analysis populations:

- The randomized set is all patients who gave informed consent and were eligible for and randomized into DB1.
- The full analysis set (FAS) is all randomized patients who took at least one dose of study drug during DB1 and have at least one post-baseline efficacy assessment for either co-primary endpoint. These patients also:
 - Should have treated a moderate/severe (qualifying) migraine.
 - Could not have taken a rescue medication (the applicant added this to their amended SAP). The applicant also stated these patients would be excluded from the primary efficacy analysis.
- The safety set (SS) is all patients who took at least one dose of DB study drug during any treatment period and recorded it in their eDiary. There was a safety set 1 (SS1) for DB1 and a safety set 2 (SS2) for DB2.
- The per protocol set included all FAS patients who had at least 1 post baseline primary endpoint assessment for both co-primary endpoints and had no significant protocol deviations.

Hypothesis Testing/Alternate Hypothesis

Sample Size Estimations

The applicant approximated that 600 patients would be needed to provide 88% power at a 5% (2-sided) level of significance to detect an assumed difference between placebo and DFN-15 of 11.6% on the endpoint of pain freedom at 2 hours. This was based on Study 002 results with placebo having a 17.6% response rate and DFN-15 having a 29.2% response rate. The applicant

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also assumed a 15% dropout rate.

Analyses of Primary Endpoint

The first co-primary efficacy endpoint was the proportion of patients who were pain-free 2 hours post-dose comparing DFN-15 to placebo in the DB1 treatment period. The second co-primary efficacy endpoint was the proportion of patients who were free from the screening MBS at 2 hours post-dose comparing DFN-15 to placebo. To test for statistical significance of the co-primary efficacy endpoints, the closed sequential testing procedure was utilized. That is, if the first co-primary endpoint was statistically significant at a two-sided 0.05 level of significance, the second co-primary endpoint could also be tested a two-sided 0.05 level of significance. It was stated in the SAP that the study “must show a significant statistical beneficial experimental treatment effect for both co-primary endpoints to be considered statistically successful.” Fisher’s exact test was used for both co-primary endpoints.

The applicant prespecified in the SAP that missing primary efficacy endpoint data would be imputed using the last observation carried forward (LOCF) and that results would be displayed as both LOCF data and observed data (observed cases (OC)) separately.

The analysis would exclude patients who took rescue medication prior to the data collection of the 2 hours post-dose, as well as patients who had pre-dose pain of 1 or none.

Reviewer comments: The applicant used LOCF, which is not typically recommended for trials in the acute treatment of migraine, since the last observation may not reflect the true value that existed at the last time point. This might over or underestimate the treatment effect in either group, but this would depend on how much missing data exists in either group at 2 hours. Additionally, the applicant prespecified that patients who took rescue medications would be excluded, as well as those who took study medication for a baseline mild or none pain severity level. Patients who took rescue medication should have been treated as non-responders, since they presumably took rescue medication because the migraine did not resolve. The Division will focus the analysis on the LOCF population, since this was prespecified, however we are aware of inherent problems with this type of analysis. We will not review the analysis on OC, because this has the tendency to overestimate within-group changes. LOCF does have the tendency to underestimate within-group mean changes in efficacy (Prakash, Risser, et. al, 2008).

Missing Data

Missing data were handled using LOCF, as this was the prespecified primary analysis. In general, the applicant excluded missing data. However, they were asked by the Division to conduct several sensitivity analyses to handle the missing data in this submission.

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Sensitivity analyses of the co-primary endpoints

The applicant prespecified several scenarios to handle missing data. In one scenario, patients with missing headache pain assessments at 2 hours post-dose would be assigned as having a pain level of 3 at 2 hours (all missing data analyzed as non-responders) and in the second scenario, the patients with missing data would be assigned a 0 for pain level (headache pain freedom). The same two scenarios applied for the second co-primary endpoint of MBS freedom at 2 hours.

Subgroup Analyses

The following subgroup analyses were prespecified to be conducted on the co-primary efficacy endpoints as exploratory analyses:

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

Reviewer comments: It would have been optimal to assess the use of concomitant medications (e.g. preventive treatment of migraine or other NSAID use) as a covariate; however, this was not possible because the applicant stated that a history of concomitant medication for migraine prevention and/or specifically for NSAID use was not specifically obtained.

Protocol Amendments

The original protocol was approved on September 12, 2016. There was one protocol amendment on May 9, 2017, in which the definition of the secondary endpoint of headache pain relief for DB1 and DB2 was re-defined such that DB2 could include a reduction from mild to none. Furthermore, the MBS was clarified as having to be the MBS identified at screening and be present pre-dose. There were other minor changes, as well, and these are included in the summary of changes in the Appendix to the CSR for Study 006.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that the studies were conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

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The applicant provided certification that there were no financial agreements with the clinical investigators, defined in 21 CFR part 54.2, for Study 006, whereby the value of compensation to the investigator could be affected by the outcome of the study, and that no investigators were the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f). The applicant included a supplemental site personnel listing for Form 3454 with all the Primary Investigators and there were no investigators with disclosable information for the study. Please see the financial disclosures section at the end of this document.

Data Quality and Integrity

There were concerns with data quality as the applicant had missing data as noted above. Site inspections and data review did not reveal any findings that would suggest this was intentional. Sensitivity analyses were conducted to investigate the effect of missing data.

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Patient Disposition

Table 4 – Study 006: Patient Disposition

Entire Study	Overall n (%)
Screened	926
Failed screening	295 (31.9)
Randomized into DB1 treatment period	631 (68.1)
Re-randomized into DB2 treatment period	545 (86.4) ^[a]
All patients	
Full Analysis Set 1	567 (89.9)
Full Analysis Set 2	503 (79.7)
Safety Set	578 (91.6)
Per Protocol Set	558 (88.4)
Completed first double-blind treatment period	544 (86.2) ^[a]
Completed second double-blind treatment period	504 (79.9) ^[b]
Completed study	508 (80.5)
Discontinued study	123 (19.5)
Primary reason for discontinuation:	
Patient did not experience a migraine attack	44 (7.0)
Other	22 (3.5)
Protocol deviation	16 (2.5)
Withdrawal by patient	11 (1.7)
Lost to follow-up	8 (1.3)
Non-compliance with study drug	8 (1.3)
Adverse event	7 (1.1)
Investigator request	4 (0.6)
Pregnancy	2 (0.3)
Use of non-permitted medication during the study	1 (0.2)

Double-blind Period 1

	Placebo n=315	DFN-15 n=316	Total n=631
Full Analysis Set 1	280 (44.4)	287 (45.5)	567 (89.9)
Safety Set 1	283 (44.8)	289 (45.8)	572 (90.6)
Per Protocol Set	273 (43.3)	285 (45.2)	558 (88.4)
Completed DB1 treatment period	264 (41.8)	280 (44.4)	544 (86.2)
Discontinued DB1 treatment period	47 (7.4)	34 (5.4)	81 (12.8)
Primary reason for discontinuation in DB1:			
Patient did not experience a migraine attack	15 (2.4)	10 (1.6)	25 (4.0)
Other	8 (1.3)	9 (1.4)	17 (2.7)
Protocol deviation	9 (1.4)	4 (0.6)	13 (2.1)
Non-compliance with study drug	3 (0.5)	4 (0.6)	7 (1.1)
Withdrawal by patient	3 (0.5)	4 (0.6)	7 (1.1)
Adverse event	4 (0.6)	0	4 (0.6)
Lost to follow-up	3 (0.5)	1 (0.2)	4 (0.6)
Investigator request	1 (0.2)	1 (0.2)	2 (0.3)
Pregnancy	0	1 (0.2)	1 (0.2)
Use of non-permitted medication during the study	1 (0.2)	0	1 (0.2)

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Abbreviations: 2h=2-hour; DB1=first double-blind treatment period; DB2=second double-blind treatment;
MBS=Most Bothersome Symptom

[a] 6 patients did not take DB1 dose (per their eDiary record) but were marked “completed study” in the database. These 6 patients were excluded from efficacy and safety analyses for DB1; however, they were re-randomized into DB2.

[b] 4 patients did not take a DB2 dose, but were marked as “completed study.” These patients were excluded from efficacy and safety analyses for DB2.

Source: NDA 212157 CSR for Study 006 Table 4 (modified) <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-006\dfn-15-cd-006-report-body.pdf>

A total of 631 patients were randomized into DB1 and 567 patients received a dose of study drug in DB1 (excludes 5 patients who erroneously were marked as having completed study, but who did not take study drug). Of the 567 patients who were dosed in DB1, 81 patients were discontinued from DB1 (with rates similar between arms). Reasons for discontinuation included: patient did not experience a migraine attack, protocol deviations, withdrawal by patient, adverse event (4 in placebo group, none in DFN-15 group), investigator requests, pregnancy, and use of non-permitted medication during study. The reasons for discontinuation were fairly balanced across arms.

Of the randomized patients in DB1, 545 were re-randomized into DB2, but only 503 were included in the full analysis set for DB2.

Reviewer comments: Sixty-four patients who were randomized were not analyzed in the full analysis set for various reasons. Reasons for discontinuation varied and appeared to be even between groups; however, this is almost 10% of the randomized population that was not analyzed. More than 10% of patients analyzed in DB1 were not analyzed in DB2. This would make results from DB2 difficult to interpret in terms of both efficacy and safety, due to bias from this selected population.

Protocol Violations/Deviations

In DB1, there were 13 (2.1%) protocol deviations in the randomized set, with 9 in the placebo group and 4 in the DFN-15 treated group.

Reviewer comments: There were slightly more protocol deviations in the placebo group than the DFN-15 treated group. However, many of these patients who had protocol deviations did not receive study drug, so they were not analyzed as part of the FAS population.

Demographic Characteristics

Table 5 - Study 006: Demographic Characteristics by Disposition and Study Arm (Full Analysis Set 1 (DB1))

Subgroup	DFN-15 120 mg (N = 287) n (%)	PLACEBO (N = 280) n (%)	Total (N = 567) n (%)
Sex			
Female	236 (82.2)	242 (86.4)	478 (84.3)
Male	51 (17.8)	38 (13.6)	89 (15.7)
Age			
Mean	41.44	40.38	40.92
Standard Deviation	13.92	12.88	13.42
Minimum	18	18	18
Median	41	40	40
Maximum	75	73	75
Age Group			
< 65	269 (93.7)	267 (95.4)	536 (94.5)
≥ 65	18 (6.3)	13 (4.6)	31 (5.5)
Race			
Asian	1 (0.3)	3 (1.1)	4 (0.7)
Black or African American	64 (22.3)	63 (22.5)	127 (22.4)
Other	10 (3.5)	8 (2.9)	18 (3.2)
White	212 (73.9)	206 (73.6)	418 (73.7)
Ethnicity			
Hispanic or Latino	40 (13.9)	39 (13.9)	79 (13.9)
Missing	1 (0.3)	1 (0.4)	2 (0.4)
Not Hispanic or Latino	246 (85.7)	240 (85.7)	486 (85.7)
Region			
United States	287 (100.0)	280 (100.0)	567 (100.0)

Source: Table made by reviewer using ADSL and only including patients in the full analysis set 1 (FAS1FL).

Reviewer comments: The sex distribution was ~86% female in the DFN-15 group compared to 82% in the placebo group. This is about a ~4% difference between groups and unlikely to affect results. While the average age was about 1 year older in the DFN-15 arm, this is not likely to be clinically meaningful. The predominantly White population is common in trials for acute migraine in the US. A recent literature review noted of 36 recent (since 2011) clinical trials studying migraine, 84.2% of participants were women and 82.9% were white (Robbins and Bernat 2017). Overall, the distribution of demographic information, including race and ethnicity,

were balanced across treatment arms.

Other Baseline Characteristics

The number of current smokers or nicotine product users was 9.3-11.3% and similar across all treatment groups. The average age of onset of migraines was 21.8 years (with a standard deviation (SD) of 10.9), 56.2% of patients had migraine associated with aura, 87.5% of patients had nausea as a migraine associated symptoms, 96.2% had photophobia and 87.9% had phonophobia. These characteristics were balanced across groups. At baseline, most patients reported photophobia as the MBS and this was balanced across groups. About 14.4% of patients had a history of hypertension, and 14.2% had gastroesophageal reflux disease.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A second dose of study medication was not administered to treat either a headache that had not resolved (rescue) or a headache that had resolved and then recurred (recurrence). The applicant did not perform a formal treatment compliance analysis. Intake accountability of study drug was documented by patients in the electronic diary (eDiary).

Preventive treatments for migraine were not specifically identified as part of the applicant's data collection. Based on my own review of the concomitant medications and the commonly used medications for the preventive treatment of migraine, 77 patients (13.6%) were on concomitant medications for the prevention of migraine, with 44 in the DFN-15 treated arm and 33 in the placebo arm. Per my review, a total of 295 patients were taking NSAIDs as a concomitant medication (including for acute treatment of migraine) - 139 in the DFN-15 treated group and 156 in the placebo group. Per the applicant, 79% of patients in the DFN-15 arm and 77% in the placebo arm, had taken at least one NSAID for the treatment of migraine.

Efficacy Results – Primary Endpoint

The applicant prespecified the co-primary efficacy endpoints as the proportion of patients who were pain free 2 hours post-dose and MBS free at 2 hours post-dose in DB1.

Table 6 - Study 006: Co-Primary Efficacy Endpoints

Endpoint	Double-Blind Period 1/Study Arm	
		Placebo N=280

Headache Pain Freedom at 2 H Proportion (95% CI) p value Odds Ratio for Pain Freedom at 2 H (95% CI) Difference from placebo	69/267 25.8% (20.7, 31.5)	92/280 32.9% (27.4, 38.7) 0.075 1.40 (0.97, 2.03) 7.1% NNT¹=14
Most Bothersome Symptom Freedom at 2 H Proportion (95% CI) p value Odds Ratio for MBS Freedom at 2 H (95% CI) Difference from placebo	104/231 45.0% (38.5, 51.7)	142/241 58.9% (52.4, 65.2) 0.003 1.75 (1.22, 2.55) 13.9% NNT=7

¹ NNT=Number needed to treat

Source: NDA 212157 CSR for Study 006 Table 11 <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-006\dfn-15-cd-006-report-body.pdf>

Reviewer comments:

This analysis demonstrates that the therapeutic gain or difference from placebo in the DFN-15 arm is 7.1% for the endpoint of pain freedom at 2 hours post-dose, and the Number Needed to Treat (NNT) for pain freedom at 2 hours is 14 – which means that 14 patients need to be treated for one patient to have pain freedom at 2 hours with DFN-15. Though study designs of other recently approved drugs may vary slightly, the therapeutic gains of this study appear to be in line with recent approvals of drugs by FDA for acute migraine treatment. The results for both endpoints are clinically meaningful, though, for the co-primary endpoint of pain freedom at 2 hours, the p value did not reach the applicant’s prespecified p value of <0.05 to be considered statistically significant. For this endpoint, the study had an unusually high placebo response rate (25.8%) compared to what is typically seen in acute migraine trials (ranges from 10.9% to 21.3%), and this may have contributed to the inability of Study 006 to demonstrate statistical significance on the pain freedom at 2 hours post-dose endpoint.

This analysis excludes those subjects who took rescue medication and there were 13 patients in the placebo arm and 7 patients in the DFN-15 arm who were missing post-dose assessments at 2 hours for the pain freedom endpoint. The applicant prespecified they would exclude patients who took rescue medications (the Division typically evaluates these patients as non-responders), and those with missing data were also excluded from the analysis if time points at < 2 hours were not present (due to the applicant’s use of the LOCF for the primary analysis). This issue was

analyzed by our statistician in two ways and addressed in the sensitivity analyses (see below).

The applicant demonstrated a therapeutic gain with DFN-15 of almost 14% for MBS freedom at 2 hours compared to placebo. This difference is both clinically meaningful and statistically significant. However, there was also a high degree of patients missing pre-dose MBS and these patients were excluded from the endpoint of MBS freedom at 2 hours. This was also evaluated as part of the sensitivity analyses requested by the Division.

Sensitivity Analyses of the Co-Primary Endpoints

Headache Pain Freedom at 2 hours - Sensitivity Analysis

Table 7 - Study 006: Sensitivity Analysis 1 of Headache Pain Freedom at 2 Hours¹

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=273	DFN-15 120 mg N=284
Headache Pain Freedom at 2 H Proportion (95% CI) p value Odds Ratio for Pain Freedom at 2 H (95% CI) Difference from placebo	69/273 25.3% (20.2, 30.9)	98/284 32.4% (27.0, 38.2) 0.076 1.42 (0.98, 2.05) 7.1%

¹This analysis analyzed patients who took rescue medications as nonresponders, instead of simply excluding them as in Table 6. This is the Division’s preferred analysis of the primary endpoint.
Source: Table 14.2.1.3.1.ah of CSR of Study 006.

Table 8 – Study 006: Sensitivity Analysis 2 of Headache Pain Freedom at 2 Hours¹

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=286
Headache Pain Freedom at 2 H Proportion (95% CI) p value Odds Ratio for Pain Freedom at 2 H (95% CI) Difference from placebo	71/280 25.4% (20.4, 30.9)	94/286 32.8% (27.5, 38.6) 0.052 1.44 (1.00, 2.08) 7.4%

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¹Source: FDA reviewer, Dr. Xiang Ling's, analysis. Of note, patients who took rescue medication prior to the 2-hour post-dose were assigned as non-responders and patients missing 2-hour data were imputed using LOCF if data prior to 2 hours post-dose was available, otherwise using the next available observations carried backward (NOCB).

Reviewer comments: The first sensitivity analysis above sets patients who took rescue medications to being non-responders. This is the Division's preferred analysis for the primary endpoint and what should be conveyed in any future labeling. This analysis does not change the difference from placebo or the p value of the analysis from the initial analysis, because very few patients in both groups took rescue medication prior to 2 hours.

The second sensitivity analysis above was undertaken by Dr. Ling to investigate missing data. Patients who took rescue medications were still analyzed as non-responders and patients with missing data at 2 hours were imputed from future time points (if data prior to 2 hours was not available). There were very few patients who used rescue medications within the first 2 hours in this study. Notably, there were also more patients with missing data at 2 hours in the placebo arm of the study (compared to the DFN-15 treated arm). When analyzed in this manner, the difference from placebo was still 7%, but the p value moved closer to 0.05 because the placebo responder rate went down. A worse case imputation was also performed and did not change the results significantly.

An analysis for MBS freedom at 2 hours (not shown, but in Dr. Ling's review) when rescue medication users were analyzed as non-responders did not change the results in a clinically or statistically relevant way.

The applicant also conducted two additional prespecified sensitivity analyses for the co-primary endpoint of pain freedom at 2 hours, at the request of the Division, to help investigate the missing data.

First, patients with a missing 2-hour assessment were assigned as NOT having pain freedom at 2 hours post-dose. With this analysis, the placebo group had a 23.0% responder rate for pain freedom and the DFN-15 treated group had a 31.6% response rate, demonstrating a therapeutic gain of 8.6% (nominal $p=0.03$). Second, patients with a missing 2-hour assessment were assigned as having pain freedom at 2 hours post-dose. With this analysis, the placebo group had a 29.6% responder rate for pain freedom and the DFN-15 treated group had a 34.0% response rate, demonstrating a therapeutic gain of 4.4% (nominal $p=0.28$).

Reviewer comments: These sensitivity analyses demonstrate that the p value was very sensitive to changes in how patients were imputed or analyzed for the primary endpoint of pain freedom at 2 hours. The first few analyses help strengthen the association and the latter analysis weakens it (because more patients were missing from the placebo arm of the study, so the placebo response rate goes up and the difference from placebo goes down). I believe the first sensitivity analysis helps handle missing data in the most relevant way, and the clinical

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significance of a 7% difference from placebo in the DFN-15 treated group remains clinically significant, though it still did not reach statistical significance.

MBS freedom at 2 hours - Sensitivity Analysis

There were also many patients with missing data for the MBS freedom at 2 hours endpoint. This is because if patients did not record an MBS pre-dose when they treated their moderate to severe migraine attack or if they had missing data, they were excluded from the analysis. The analysis thus excluded 49 patients in the placebo arm and 46 patients in the DFN-15 arm, which is an exclusion of ~17% of patients for the second co-primary endpoint. Excluding a high number of patients would be concerning for the integrity of the data, and sensitivity analyses were done to handle this high degree of missing data.

The sensitivity analyses analyzed all patients who did not meet original MBS analysis criteria or if they took rescue medication were analyzed as non-responders. Results of this analysis did not change from the primary endpoint analysis in a meaningful way (please see Dr. Ling's review for results of these analyses).

Reviewer comment: There was still a robust statistical difference between groups for MBS freedom at 2 hours, after the sensitivity analyses for this endpoint were conducted on DB1.

Secondary and other relevant endpoints

The applicant the following secondary endpoints as exploratory for each DB period in the SAP:

- The proportion of patients with treatment-emergent adverse events (TEAEs) after study drug compared between DFN-15 and placebo.
- The proportion of patients who were free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours post-dose compared between DFN-15 and placebo.
- Time to meaningful pain relief (defined as based on patient's perception) within 2 hours post-dose between DFN-15 and placebo in each treated attack.
- Time to pain freedom within 2 hours post-dose between DFN-15 and placebo.
- The proportion of patients with pain relief at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours post-dose between DFN-15 and placebo. Headache pain relief was defined for DB1 as a reduction from moderate or severe pain prior to dosing to mild or none post-dose, and for DB2 as moderate or severe pain pre-dose reduced to mild or none post-dose, or mild pain pre-dose reduced to none post-dose.
- The proportion of patients pain-free at 15, 30, and 45 minutes and 1, 1.5, 2 (DB2 period), 4, and 24 hours post-dose compared between DFN-15 and placebo.
- The proportion of patients with their Screening MBS (and have this symptom pre-dose) absent at 15, 30, and 45 minutes, and 1, 1.5, 2 (DB2 period), 4, and 24 hours

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

Reviewer comments: While there were numerous secondary endpoints, I will focus on the endpoints with the most clinical relevance and that might provide supportive information regarding efficacy of DFN-15 for the acute treatment of migraine. Importantly, none of these secondary endpoints were controlled for Type 1 error or included in the applicant's testing hierarchy. Therefore, they are all exploratory in nature.

Freedom from specific associated symptoms of migraine

The applicant studied the proportion of patients free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours post-dose compared between DFN-15 and placebo.

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The results of the analysis of freedom from these associated symptoms at 2 hours and 24 hours are presented below.

Table 9 - Study 006: Freedom from Nausea, Photophobia and Phonophobia at 2 and 24 Hours Post-dose

Endpoint	Double-Blind Period 1/Study Arm – using LOCF	
	Placebo N=280	DFN-15 120 mg N=287
Freedom from Nausea		
2 hours post-dose	76/142	102/153
Proportion	53.5%	66.7%
p value ¹		0.279
24 hours post-dose	131/147	138/154
Proportion	89.1%	89.6%
P value ¹		1.000
Freedom from Photophobia		
2 hours post-dose	102/238	141/243
Proportion	42.9%	58.0%
p value ¹		0.001
24 hours post-dose	203/242	212/245
Proportion	83.9%	86.5%
P value ¹		0.445
Freedom from Phonophobia		
2 hours post-dose	95/202	116/196
Proportion	47%	59.2%
p value ¹		0.016
24 hours post-dose	170/206	176/198
Proportion	82.5%	88.9%
P value ¹		0.088

Source: NDA 212157 CSR for Study 006 Table xx <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-006\dfn-15-cd-006-report-body.pdf>

¹None of the p values were controlled for Type 1 error, as these were all exploratory analyses.

Reviewer comments: Importantly, these endpoints were exploratory; however, we can examine effect of study drug on individual migraine associated symptoms. While numerically, nausea had similar rates of improvement with DFN-15 compared to placebo, the nominal p value was not different between groups. Photophobia and phonophobia improved at 2 hours in the DFN-15 treated group (with nominal significance) compared to placebo, but the identified symptom had resolved in > 80% of both groups at 24 hours.

Pain Relief

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Headache pain relief was defined for DB1 as a reduction from moderate or severe pain prior to dosing to mild or none post-dose.

This exploratory endpoint demonstrated an increased proportion of responders with time (see table below).

Table 10 - Study 006: Headache Pain Relief at 2 Hours

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=287
Headache Pain Relief at 2 H % Responders (95% CI) p value Difference from placebo	152/267 56.9% (50.8, 62.9)	192/280 68.6% (62.8, 74.0) .006 ¹ 11.7% NNT=9

¹=nominal p value, not controlled for Type 1 error

Reviewer comments: The study demonstrated a strong numerical effect on pain relief and while this is a lower bar to reach than pain freedom, it was the primary endpoint for pain assessment used in many older clinical trials for acute treatment of migraine. The p value, while not controlled for Type 1 error, does suggest there was a descriptive difference between groups, with the treated group demonstrating a higher percent of responders than the placebo group. Less patients need to be treated for pain relief (9 patients) compared to pain freedom (14 patients) at 2 hours. This is a lower bar to reach than pain freedom and was not prespecified in the testing hierarchy, and thus should not be conveyed in the label.

Headache Pain Freedom at Various Time Points

The applicant examined pain freedom at various time points (Table 17 of CSR of Study 006).

Table 11 - Study 006: Headache Pain Freedom at Various Time Points

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=287
Headache Pain Freedom at Various Time Points		

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Predose Migraine Pain Level		
None	0	0
Mild	0	1 (0.3%)
Moderate	193 (68.9%)	193 (67.2%)
Severe	81 (28.9%)	89 (31.0%)
15 minutes post-dose		
Responders/assessments	7/239	3/247
Proportion	2.9%	1.2%
P value		0.22
30 minutes post-dose		
Responders/assessments	14/254	10/269
Proportion	5.5%	3.7%
P value		0.41
45 minutes post-dose		
Responders/assessments	25/257	26/275
Proportion	9.7%	9.5%
P value		1.0
1 hour post-dose		
Responders/assessments	33/261	50/278
Proportion	12.6%	18.0%
P value		0.095
1.5 hour post-dose		
Responders/assessments	52/262	69/279
Proportion	19.8%	24.7%
P value		0.181
2 hours post-dose	69/267	92/280
Proportion	25.8%	32.9%
p value		0.075
4 hours post-dose		
Responders/assessments	109/271	138/281
Proportion	40.2%	49.1%
P value		0.040
24 hours post-dose		
Responders/assessments	197/274	224/282
Proportion	71.9%	79.4%
P value		0.05

Source: NDA 212157 Table 17 of CSR (modified by reviewer).

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Reviewer comments: The numerical proportion of responders was slightly greater in the DFN-15 treated group compared to placebo for all time points after 1 hour. Though this endpoint was not controlled for Type 1 error, nominal significance only occurred at 4 hours post-dose and remained at 24 hours. The clinical significance of an improvement as these time points (at 4 hours and beyond) is unclear, since rescue medication could be used.

Sustained headache pain freedom

Sustained headache pain freedom would indicate the length of time of a drug’s effect and lack of recurrence of a migraine. The applicant examined the effect of the treatments over various time points up to 24 hours in patients who had a non-missing pain assessment at 2 hours, 4 hours and 24 hours, and did not use rescue medication.

Table 12 - Study 006: Sustained Pain Freedom

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo	DFN-15
Freedom from headache pain at 2 hours post-dose	24.6%	32.1%
Sustained pain freedom at 24 hours post-dose Responses/Assessments (%) ¹	38/201 (18.9%)	62/225 (27.6%)
P value compared to placebo ²		0.039

Source: NDA 212157 – Table 14.2.6.1.1.ah of CSR.

¹Headache pain freedom at 2 hours post-dose and no headache pain recurrence at 4 hours and 24 hours post-dose and no use of rescue medications.

²Nominal p value, not controlled for Type 1 error

Reviewer comments: These results indicate that sustained pain freedom at 24 hours was achieved by more patients in the DFN-15 treated group compared to placebo, with nominal significance achieved. This could provide further evidence of a benefit of DFN-15, though this endpoint was not controlled for Type 1 error.

Functional disability score

The applicant used a functional disability scale in which 0=no disability, able to function normally, 1=performance of daily activities mildly impaired, can still do everything but with

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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.

Thus, for this score, a greater decrease in scale score reflects a greater reduction in disability.

Table 13 - Study 006: Functional Disability Score

Functional Disability Score	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=287
Baseline score (n)	274	282
0	20 (7.3%)	12 (4.3%)
1	70 (25.5%)	71 (25.2%)
2	130 (47.4%)	153 (54.3%)
3	54 (19.7%)	46 (16.3%)
Score at 2 hours post-dose	256	275
0	78 (30.5%)	104 (37.8%)
1	92 (35.9%)	96 (34.9%)
2	71 (27.7%)	59 (21.5%)
3	15 (5.9%)	16 (5.8%)

Source: NDA 212157 Table 14.2.2.7.1 of CSR.

In the DB1 treatment period, the mean change in score from baseline for DFN-15 and placebo, respectively, was -0.9 and -0.7 at 2 hours, -1.2 and -1.0 at 4 hours, and -1.7 and -1.7 at 24 hours post-dose. P-values were obtained from the Wilcoxon rank-sum test for the comparison between treatment groups. The comparison between treatment groups in change from baseline showed nominal statistical significance for DFN-15 at 2 hours (p=0.049) and 4 hours (p=0.010) post-dose.

Reviewer comments: Of note, this score was not reviewed by the clinical outcomes assessment staff or the Division prior to its use. The nominal p value suggests a numerical treatment benefit at 2 hours post-dose, although both groups did quite well on this exploratory endpoint.

Rescue Medication Use

The applicant examined rescue medication use. There were 67 patients in the placebo group and 32 in the DFN-15 treated group that used a rescue medication at some point during the treated migraine attack in DB1. Three patients in the placebo group and 2 in the DFN-15 group used a rescue medication prior to recording at 2 hours. The mean time until use of rescue medication was 4.5 hours for the placebo group compared to 6.2 hours for the DFN-15 treated

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group.

Reviewer comments: These results suggest that less patients in the DFN-15 treated group required use of a rescue medication compared to those in the placebo group. This does provide support of benefit of taking DFN-15 compared to placebo in that less patients needed a second treatment, though again, this endpoint was not controlled for Type 1 error.

Other exploratory endpoints – Including Subgroup Analyses

Age, Gender, Ethnicity

Efficacy findings by age, gender, and ethnicity were all similar for both co-primary efficacy endpoints at 2 hours post-dose.

Dose/Dose Response

The applicant only studied one dose of DFN-15 in the pivotal trial, thus a dose-response was not assessed.

Additional Analyses Conducted on the Individual Trial

Double Blind Period 2

In Study 006, the applicant examined the effect of a second dose of study drug. If still eligible, patients entered a second double-blind period (DB2) in which they received either DFN-15 or placebo during a re-randomization that occurred after their follow up for DB1.

Of the 315 patients randomized to placebo in DB1, 253 were analyzed for DB2. Of the 316 patients randomized to DFN-15 in DB1, 250 were analyzed in DB2. At 2 hours post-dose, 24.3% (58/239) of patients were pain free at 2 hours in the placebo arm compared to 36.7% (88/240) in the DFN-15 treated arm (p nominally significant at <.01).

Reviewer comments: The analyses of the second DB period were not controlled for Type 1 error, so a table is not included above. This analysis was also not prespecified as the primary analysis population for this study. There are many issues with using the DB2 period to evaluate efficacy that are discussed in further detail below as it pertains to Study 007. The information from DB2 may be more helpful for evaluating safety of DFN-15, since some patients received more than one dose of DFN-15, however it is still a biased sample because of self-selection and other factors.

Outlier Analysis

In Study 006, the applicant performed an outlier detection analysis and found that one site (Site

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609) had a responder rate of 75% in the placebo arm. The applicant removed this site from the analysis and determined that the p value for Study 006 was significant when this one site, which included 27 patients total (23 in the placebo arm and 15 in the DFN-15 arm), was removed.

The results of the applicant's analysis are presented below.

Table 14 - Study 006: Outlier Detection at Site 609

	DB1		P value
	Placebo N=273	DFN-15 N=285	
Prespecified Results			
Headache Pain Freedom at 2 hrs postdose			
Number of assessments at 2 hrs	267	280	
Proportion of responders (%) (95% CI)	25.8 (20.7, 31.5)	32.9 (27.4, 38.7)	0.075
Absence of Screening MBS at 2hrs postdose			
Number of assessments at 2 hrs	231	241	
Proportion of responders (%) (95% CI)	45.0 (38.5, 51.7)	58.9 (52.4, 65.2)	0.003
<hr/>			
Without Site 609^[a]	Placebo N=268	DFN-15 N=272	
Headache Pain Freedom at 2hrs postdose			
Number of assessments at 2 hrs	255	265	
Proportion of responders (%) (95% CI)	23.5 (18.5, 29.2)	32.8 (30.0, 41.6)	0.020
Absence of Screening MBS at 2hrs postdose			
Number of assessments at 2 hrs	221	229	
Proportion of responders (%) (95% CI)	43.9 (37.2, 50.7)	58.1 (51.4, 64.5)	0.003

Abbreviations: CI=confidence interval; DB1=first double-blind treatment period; DB2=second double-blind treatment period; hrs=hours; LOCF=last observation carried forward; MBS=most bothersome symptom.

Note: This table excludes Site 609 subjects (N=12, Placebo; N=15, DFN-15).

Source: This table was copied from Table 17.2.1.1.1.ah and Table 14.2.1.1.1. from the applicant's CSR for Study 006.

Reviewer comments: The applicant's outlier detection analysis determined that one site had an unusually high rate of placebo responders. The reasons for this are unclear, but could include selection bias, the Hawthorne effect, patient-investigator relationship, etc. Removing this one site, which included 27 patients or about 5% of the total analyzed population, alters the results of the study, such that results of the primary endpoint of pain freedom at 2 hours becomes statistically significant (p <.05). However, the therapeutic gain compared to placebo is still only 9.3% (compared to 7.1% with all the sites analyzed as prespecified) and the NNT goes down from 14 to 11.

We did investigate this site through the Office of Compliance to determine if there were any

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causes for this at the site level itself, and this report did not reveal any findings of concern. Please refer to Dr. Alfaro's OSI review for further details.

FDA statistician, Dr. Ling, performed an analysis removing each site individually, and found that there were two other sites (Site 606 and Site 615), that when removed, also changed the p value of the primary endpoint of pain freedom at 2 hours. Thus site 609 is not a true outlier, although the placebo responder rate may have been high at this site. Site 606 had a placebo responder rate of 100% (2/2 patients in placebo had pain freedom at 2 hours, compared to 20% (1/5) in DFN-15 treated group) and Site 615 had a 67% responder rate (2/3 patients) in placebo, compared to 0% responders (0/4) in the DFN-15 treated group had pain freedom at 2 hours.

When removing individual sites can sway the statistical significance of the results, it does call into question the robustness of a clinical study. Removing sites post hoc is not a valid method of analyzing data, and this analysis provided by the applicant was not taken into consideration when evaluating the efficacy of DFN-15 for the acute treatment of migraine.

6.2. Study 007 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy, Tolerability, and Safety Study of DFN-15 in Episodic Migraine With or Without Aura

6.2.1. Study Design

Overview of Trial Design

Study 007 was identical in design to Study 006. For that reason, I will not repeat the objectives, trial design, endpoints or statistical analysis plan here. The reader is referred to these sections in Section 6.2.1, as all this information is identical in both studies.

Protocol Amendments

There was one protocol amendment, dated May 9, 2017, which included the following changes to the protocol: specified that screening MBS had to be present pre-dose, added secondary endpoints for proportion of patients free from nausea, photophobia and phonophobia at various time points, the definition of headache pain was defined as moderate or severe pain reduction in DB1 to any pain reduction (moderate or severe to mild or none, or mild to none) in DB2. The statistical methods were changed to include endpoint assessments of observed cases and LOCF for DB1 and to analyze the screened and randomized set. There were several other changes to improve clarity, that would not affect the primary analysis.

6.2.2. Study Results

Compliance with Good Clinical Practices

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The applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human patients (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

There was one site with a serious issue of noncompliance. Site 745 was not responsive to questions from the [REDACTED] (b) (4) during attempts at communication. The investigator reported he had no knowledge of the study. It was later learned that the study coordinator had been fraudulently conducting the study under the investigator's name, including forging his signature on documents. The investigator stated that the study coordinator had died [REDACTED] (b) (6), and that 17 patients were screened, 5 were screen failed, 6 withdrawn and 6 completed the study this one site, and most completed their termination visit prior to the death of the study coordinator. He did follow up with patients to ensure safety. FDA was notified of this serious noncompliance at the time of the discovery.

Reviewer comments: The primary efficacy analysis was conducted by Dr. Ling, with and without Site 745 included, and the results did not change.

Financial Disclosure

The applicant included a supplemental site personnel listing for Form 3454 with all the Primary Investigators and there were no investigators with disclosable information for the study. Please see the financial disclosures section at the end of this document.

Data Quality and Integrity

The applicant attested to the quality and the integrity of the submitted data.

Patient Disposition

In Study 007, 926 patients with episodic migraine were screened, 622 were randomized into DB1 and 535 were randomized into DB2. Of the 535 who were re-randomized into DB2, 267 (42.9%) were randomized to DFN-15 in DB2 and 268 were randomized to placebo (43.1%). The full analysis set for DB1 included 563 patients and 491 patients for DB2. The safety set included 571 patients and the per protocol set included 554 patients.

Reasons for discontinuation included the following (number of patients in parentheses): patient did not experience a migraine (29), withdrawal by patient (22), lost to follow up (17), other (15), adverse event (6), use of non-permitted medication during the study (6), physician decision (3), pregnancy (2) and a few patients in other categories.

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Table 15 - Study 007 - Patient Disposition

Entire Study **Overall n (%)**

	Overall N=926 n (%)		
Screened	926		
Failed screening	304 (32.8)		
Randomized into DB1 treatment period	622 (67.2)		
Re-randomized into DB2 treatment period	535 (86.0) ^[a]		
All Subjects			
Full Analysis Set 1	563 (90.5)		
Full Analysis Set 2	491 (78.9)		
Safety Set	571 (91.8)		
Per Protocol Set	554 (89.1)		
Completed first double-blind treatment period (DB1)	531 (85.4) ^[a]		
Completed second double-blind treatment period (DB2)	491 (78.9) ^[b]		
Completed study	498 (80.1)		
Discontinued study			
Primary reason for discontinuation:			
Subject did not experience a migraine attack	29 (4.7)		
Withdrawal by subject	22 (3.5)		
Lost to follow-up	17 (2.7)		
Other	15 (2.4)		
Protocol deviation	13 (2.1)		
Non-compliance with study drug	7 (1.1)		
Adverse event	6 (1.0)		
Use of non-permitted medication during the study	6 (1.0)		
Physician decision	3 (0.5)		
Study terminated by Sponsor	3 (0.5)		
Pregnancy	2 (0.3)		
Investigator request	1 (0.2)		
	Randomized		
DB1 Treatment Period	Placebo n (%)^[c] N=311	DFN-15 n (%)^[c] N=311	into DB1 n (%) N=622
Full Analysis Set 1	280 (45.0)	283 (45.5)	563 (90.5) ^[d]
Safety Set 1	282 (45.3)	285 (45.8)	567 (91.2)
Per Protocol Set	274 (44.1)	280 (45.0)	554 (89.1)
Completed DB1 treatment period	266 (42.8)	265 (42.6)	531 (85.4)
Discontinued DB1 treatment period	43 (6.9)	42 (6.8)	85 (13.7)
Primary reason for discontinuation in DB1:			
Subject did not experience a migraine attack	11 (1.8)	7 (1.1)	18 (2.9)
Withdrawal by subject	7 (1.1)	9 (1.4)	16 (2.6)
Lost to follow-up	5 (0.8)	8 (1.3)	13 (2.1)
Other	4 (0.6)	6 (1.0)	10 (1.6)
Protocol deviation	4 (0.6)	4 (0.6)	8 (1.3)
Use of non-permitted medication during the study	1 (0.2)	4 (0.6)	5 (0.8)
Non-compliance with study drug	2 (0.3)	2 (0.3)	4 (0.6)
Adverse event	3 (0.5)	0	3 (0.5)
Study terminated by Sponsor	3 (0.5)	0	3 (0.5)
Physician decision	0	2 (0.3)	2 (0.3)
Pregnancy	2 (0.3)	0	2 (0.3)
Investigator request	1 (0.2)	0	1 (0.2)

Source: NDA 212157 Table 4 of CSR for Study 007 (<\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>)

Protocol Violations/Deviations

In DB1, there were 8 patients (1.3%) in the randomized set who had at least one major protocol deviation during the study.

Reviewer comments: The reasons for protocol deviations were reviewed in detail. The deviations were balanced across groups and do not raise any particular concerns about trial conduct.

Demographic Characteristics

Table 16 - Study 007: Demographic Characteristics (Full Analysis Set (DB1))

Subgroup	DFN-15 120 mg (N = 283) n (%)	PLACEBO (N = 280) n (%)	Total (N = 563) n (%)
Sex			
Female	250 (88.3)	240 (85.7)	490 (87.0)
Male	33 (11.7)	40 (14.3)	73 (13.0)
Age			
Mean	40.52	39.98	40.25
Standard Deviation	11.69	12.59	12.13
Minimum	19	18	18
Median	40	39	39
Maximum	72	74	74
Age Group			
< 65	279 (98.6)	272 (97.1)	551 (97.9)
≥ 65	4 (1.4)	8 (2.9)	12 (2.1)
Race			
American Indian or Alaska Native	1 (0.4)	0 (0.0)	1 (0.2)
Asian	5 (1.8)	6 (2.1)	11 (2.0)
Black or African American	75 (26.5)	50 (17.9)	125 (22.2)
Native Hawaiian or Other Pacific Islander	2 (0.7)	0 (0.0)	2 (0.4)
Other	4 (1.4)	7 (2.5)	11 (2.0)
White	196 (69.3)	217 (77.5)	413 (73.4)
Ethnicity			

Hispanic or Latino	38 (13.4)	37 (13.2)	75 (13.3)
Missing	3 (1.1)	1 (0.4)	4 (0.7)
Not Hispanic or Latino	242 (85.5)	242 (86.4)	484 (86.0)
Region			
United States	283 (100.0)	280 (100.0)	563 (100.0)

Source: This analysis was conducted by the reviewer on the ADSL dataset provided by the applicant on the full analysis set (FAS1FL) for DB1.

Reviewer comments: The percentage of females in this study is higher than for most acute migraine treatment trials (in which the average is ~80%). The ages and ethnicity were balanced across arms. There were more Blacks/African Americans than Whites in the DFN-15 arm compared to placebo. It is unclear whether these areas of imbalance would affect study results, but during subgroup analysis (section 7 of this review), the presence of interaction terms was examined.

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

The average BMI in the study was a mean of 30.3 kg/m² (SD of 7.8), and 10.7% of patients were current smokers or nicotine product users. Regarding migraine specific history, the average age of onset of migraines was 22.4 years, 54.6% of patients has migraine associated with aura and patients reported the following associated symptoms: 88.8% with nausea, 96.3% with photophobia and 88.6% with phonophobia, with most reporting photophobia as the MBS at screening. These characteristics were all balanced across groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In DB1, there were 4 patients who were discontinued due to non-compliance with study drug (2 in each arm). Concomitant medication and rescue medication were recorded by the applicant. In Study 007, but medication specifically used for prevention of migraine was not. Based on my review of the medications commonly used as preventive treatments for migraine (and with migraine indications in the concomitant medications data set), 61 (10.8%) patients were on concomitant medications for the prevention of migraine, with 27 in the DFN-15 arm and 34 in the placebo arm. However, the applicant confirmed that the use of preventive treatments for migraine was not specifically identified as part of their data collection. Per my review of concomitant medications, 290 total patients in Study 007 were taking an NSAID for various indications, including for the acute treatment of migraine, with 148 patients in the DFN-15 treated group and 142 in the placebo group. Patients who took any rescue medication for migraine within 2 hours after dosing with study drug were excluded from the primary analysis.

Per the applicant, 76% of patients in the DFN-15 arm and 75% in the placebo arm, had taken at least one NSAID for the treatment of migraine at some point during the study.

Efficacy Results – Primary Endpoint

The applicant prespecified the co-primary endpoints as the following:

- The proportion of patients pain-free 2 hours post-dose compared between DFN-15 and placebo in the DB1 treatment period (defined as a reduction from pre-dose moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0]).
- The proportion of patients free from their Screening MBS among nausea, photophobia, and phonophobia (and have this symptom pre-dose) at 2 hours post-dose compared between DFN-15 and placebo in DB1.

Table 17 - Study 007: Co-Primary Efficacy Endpoint Analysis

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=283
Headache Pain Freedom at 2 H Proportion (95% CI) p value Difference from placebo	57/263 21.7% (16.8, 27.1)	98/275 35.6% (30.0, 41.6) <.001 13.9% (CI) NNT=7
Most Bothersome Symptom Freedom at 2 H Proportion (95% CI) p value Difference from placebo	104/232 44.8% (38.3, 51.5)	134/232 57.8% (51.1, 64.2) 0.007 13% NNT=8

Source: CSR of Study 007: <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>

Reviewer comments: This analysis demonstrates that the therapeutic gain for the primary endpoint of pain freedom at 2 hours is 13.9%, with an NNT of 7. The p value is statistically significant, and the therapeutic gain is consistent with that seen in other trials of recent FDA approvals for drugs for the acute treatment of migraine. This analysis excludes those who took rescue medication (however, there were very few patients who did this) and those with missing pre-dose MBS. Patients who took rescue medications should have been treated as non-responders. A sensitivity analysis was conducted to analyze patients who took rescue

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medications as non-responders and the results did not change (see below, confirmed by statistician, Dr. Ling).

If patients did not record an MBS when they treated their moderate to severe migraine attack, they were excluded from the analysis for the co-primary endpoint of MBS freedom. Thus, this analysis excluded 48 patients in the placebo arm and 51 patients in the DFN-15 arm or 99/563 patients, which is an exclusion of 17.6% of patients for the second co-primary endpoint of MBS freedom at 2 hours. Sensitivity analyses were conducted to account for missing data (see below).

The analysis above provides evidence that one dose of DFN-15 120 mg has a statistically significant and clinically meaningful effect on the acute treatment of migraine on both co-primary endpoints of pain freedom and MBS freedom at 2 hours.

Sensitivity Analyses of the Co-Primary Endpoints

Headache Pain Freedom at 2 hours - Sensitivity Analysis

To analyze the missing data for the primary endpoint, Dr. Ling performed an analysis analyzing patients who took rescue medications as nonresponders and then also imputing missing data at the 2-hour time point using the next available time point of information (Next Observation Carried Backward (NOCB)) or a worst-case type of imputation (latter not shown in table).

Table 18 - Study 007: Sensitivity Analysis 1 and 2 of Headache Pain Freedom at 2 Hours with Missing Data Imputation¹

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo	DFN-15 120 mg
Sensitivity Analysis 1		
Headache Pain Freedom at 2 H Proportion (95% CI)	57/271 21.0 (16.3, 26.4)	98/279 35.1 (29.5, 41.0)
p value		<.001
Odds Ratio for Pain Freedom at 2 H (95% CI)		2.03 (1.39, 2.98))
Difference from placebo		14.1%
Sensitivity Analysis 2 - NOCB		

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Headache Pain Freedom at 2 H Proportion (95% CI) p value Odds Ratio for Pain Freedom at 2 H (95% CI) Difference from placebo	59/276 21.4 (16.7, 26.7)	99/282 35.1 (29.5, 41.0) <.001 1.99 (1.36, 2.90) 13.7%
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¹This first analysis analyzed patients who took rescue medications as nonresponders. The second analysis also analyzed patients who took rescue medication as nonresponders, and missing 2-hour data was imputed using LOCF if data prior to 2 hours post-dose was available, otherwise NOCB or a worst-case type of imputation was used.

Source: FDA statistician, Dr. Ling.

Reviewer comments: The sensitivity analyses on the primary endpoint did not change the results (in terms of statistical or clinical significance) for either pain freedom or MBS freedom (latter not shown here, please see Dr. Ling’s review). The first sensitivity analysis should be the information conveyed in any future labeling as it analyzes patients most appropriately.

Secondary Exploratory Endpoints

The applicant examined numerous secondary endpoints that were not prespecified in the hierarchy of endpoints or controlled for Type 1 error. These endpoints could provide further insight into the efficacy of the drug from the clinical perspective, but should be viewed as exploratory only.

Freedom from nausea, photophobia and phonophobia post-dose

In patients who specified nausea as their pre-dose MBS, the proportions with freedom from nausea at various time points was higher than placebo, however, none of the values had nominal p values <.05 when compared to placebo.

In patients who specified photophobia as their pre-dose MBS, there were more improvements in the treatment groups at all time points from 30 minutes including up to 2 hours post-dose, but not at other time points after.

In patients who specified phonophobia as their pre-dose MBS, the proportion of responders was numerically greater at all time points.

Time to headache pain freedom and pain relief post-dose

Time to headache pain freedom was defined as time in minutes from when a patient took study drug until the time pain freedom or pain relief occurred. Not enough patients completed this assessment (only 27 in the DFN-15 arm and 17 in the placebo arm for pain freedom) in DB1, to

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draw conclusions.

Headache pain relief

Pain relief was defined as a reduction from moderate or severe pain pre-dose to mild or none post-dose for DB1.

Table 19 - Study 007: Headache Pain Relief at 2 Hours

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=283
Headache Pain Relief at 2 H	159/263	205/275
Proportion	60.5%	74.5%
(95% CI)	(54.3, 66.4)	(69.0, 79.6)
p value		<.001
Difference from placebo		14%

Source: CSR for Study 007 (confirmed by reviewer) ([\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf](#))

Reviewer comments: Pain relief is a lower bar to reach than pain freedom, and the applicant was already able to demonstrate a difference between DFN-15 and placebo for the pain freedom endpoint. A similar difference from placebo (~14%) was found for the endpoint of pain relief. Notably, the difference between groups was only apparent at about 1-hour post-dose, but after 4 hours, there was no difference between treatment groups (not shown).

Headache Pain Freedom

Headache pain freedom at various time points was assessed for DB1.

Table 20 - Study 007: Headache Pain Freedom at Various Time Points

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=283
Headache Pain Freedom at Various Time Points		
Pre-dose Migraine Pain Level		
None	0	0
Mild	3 (1.1%)	1 (0.4%)
Moderate	198 (70.7%)	190 (67.1%)
Severe	70 (25%)	88 (31.1%)

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15 minutes post-dose Responders/assessments Proportion P value	3/235 1.3%	1/246 0.4% 0.36
30 minutes post-dose Responders/assessments Proportion P value	9/253 3.6%	8/267 3.0% 0.81
45 minutes post-dose Responders/assessments Proportion P value	22/256 8.6%	30/271 11.1% 0.38
1 hour post-dose Responders/assessments Proportion P value	33/257 12.8%	49/273 17.9% 0.12
1.5 hour post-dose Responders/assessments Proportion P value	45/259 17.4%	74/273 27.1% 0.01
2 hours post-dose Proportion (95% CI) p value	57/263 21.7% (16.8, 27.1)	98/275 35.6% (30.0, 41.6) <.001
4 hours post-dose Responders/assessments Proportion P value	118/266 44.4%	155/276 56.4% 0.006
24 hours post-dose Responders/assessments Proportion P value	207/268 77.2%	215/278 77.3% 1.0

Source: CSR of Study 007: <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>

Reviewer comments: Pain freedom was achieved in a higher proportion of patients in the DFN-15 treated group by 1.5 hours and the statistically significant difference persisted to 4 hours post-dose. However, by 24 hours there was no difference between groups. From the prior table,

it appears that pain relief (but not freedom) was achieved by more patients in the DFN-15 group at 1 hour, but pain freedom took longer to achieve. Patients after 2 hours may have used rescue medications, so it is difficult to draw conclusions from the time points after 2 hours in this analysis.

Sustained Pain Freedom at 24 hours

Table 21 - Study 007: Sustained Pain Freedom at 24 hours post-dose

Endpoint	Double-Blind Period 1/Study Arm	
	Placebo	DFN-15
Sustained headache pain freedom at 24 hours post-dose Responses/Assessments (%) ¹	17.0%	26.8%
	36/212	55/205
P value compared to placebo ²		.018

Source: NDA 212157 – Table 14.26.1.1.ah of CSR. <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>

¹Headache pain freedom at 2 hours post-dose and no headache pain recurrence at 4 hours and 24 hours post-dose and no use of rescue medications.

²Nominal p value, not controlled for Type 1 error

Reviewer comments: More patients in the DFN-15 treated group had 24 hours of sustained headache pain freedom (without use of rescue medications) compared to those in the placebo treated group. The results were also nominally significant and could support evidence of efficacy of DFN-15, though this endpoint was not controlled for Type 1 error.

Absence of MBS at Various Time Points

While the applicant did meet the endpoint of MBS freedom at 2 hours (which was prespecified as the clinically meaningful time point for this trial), they also examined other time points before and after 2 hours.

Table 22 - Study 007: Absence of MBS at Various Time Points

Endpoint	Double-Blind Period 1/Study Arm	
MBS Freedom	Placebo N=280	DFN-15 120 mg N=283

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15 minutes post-dose Responders/assessments Proportion P value	22/207 10.6%	13/207 6.3% 0.16
30 minutes post-dose Responders/assessments Proportion P value	39/224 17.4%	39/225 17.3% 1.00
45 minutes post-dose Responders/assessments Proportion P value	51/227 22.5%	65/228 28.5% 0.16
1 hour post-dose Responders/assessments Proportion P value	57/228 25.0%	91/230 39.6% <.001
1.5 hour post-dose Responders/assessments Proportion P value	89/230 38.7%	113/230 49.1% 0.03
2 hours post-dose Proportion (95% CI) p value	104/232 44.8%	134/232 57.8% 0.007
4 hours post-dose Responders/assessments Proportion P value	144/235 61.3%	157/233 67.4% 0.18
24 hours post-dose Responders/assessments Proportion P value	203/236 86.0%	193/234 82.5% 0.32

Source: NDA 212157 – CSR of Study 007. <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>

Reviewer comments: Notably, there was only a statistically significant difference between groups on the endpoint of MBS freedom at 1 hour, 1.5 hours and 2 hours. By 4 hours and until 24 hours, there was no difference between groups. The 2-hour time point is the most clinically

meaningful and is the only time point that should be conveyed in labeling. Earlier and later time point analyses were not controlled for multiple comparisons and patients could have used rescue medications after 2 hours.

Functional Disability Score

The applicant also examined changes in their functional disability score at various time points post-dose. A greater decrease in scale score reflects a greater reduction in disability.

Table 23 - Study 007: Functional Disability Score

Functional Disability Score	Double-Blind Period 1/Study Arm	
	Placebo N=280	DFN-15 120 mg N=283
Baseline score (n)		
0	5	10
1	65	74
2	150	153
3	49	41
Score at 2 hours post-dose		
0	65 (25.1%)	112 (41.3%)
1	100 (38.6%)	95 (35.1%)
2	69 (26.6%)	52 (19.2%)
3	25 (9.7%)	12 (4.4%)

Source: NDA 212157 – CSR of Study 007. <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>

Note, a higher score means higher disability. This table excludes patients who took rescue medications prior to recording the 2-hour time point.

Reviewer comments: This functional disability score was not reviewed prior to its use in this clinical trial. Additionally, the analysis of this endpoint was not controlled for Type I error. Therefore, the results should be reviewed as exploratory.

Rescue Medication Use

The applicant examined rescue medication use. There were 4 patients in the placebo group and 0 in the DFN-15 treated group that used a rescue medication in the first 2 hours after taking study medication and there were 54 patients in the placebo arm and 34 in the DFN-15 arm that took rescue medication at an average of 5.2 hours (in both groups) after taking study medication for a migraine attack in DB1.

Reviewer comments: The use of rescue medication appears to be much less in the DFN-15

treated group compared to placebo. A sensitivity analysis analyzing the patients who took rescue medication as non-responders did not change the primary efficacy analysis for either headache pain freedom at 2 hours, or MBS freedom at 2 hours. Using less rescue medication is clinically meaningful to patients; however, this endpoint was exploratory.

Subgroup Analyses

Age, gender, ethnicity

In Study 007, none of the p values for interaction terms by any subgroup (age, gender, or ethnicity) were statistically significant.

Additional Analyses Conducted on the Individual Trial

Due to concerns about Study 006, the applicant did propose using DB2 of Study 007 as a separate, independent study to support the effect of DFN-15 in the treatment of acute migraine (with DB1 as the first study). Per our discussion (see Regulatory History), the Division did state we would consider this approach if the applicant could supply an adequate rationale. The applicant stated that the rationale to use DB2 included the following aspects:

- Study prospectively designed to have DB1 and DB2
- Independent re-randomization between DB1 and DB2
- Analysis plan was designed “a priori” to evaluate treatment periods separately (but did not allocate alpha)
- Sufficient washout period between dosing (average of 14-15 days)
- Though there was a patient response tendency effect detectable across DB periods, no interaction terms were significant (not related to DB1/DB2 treatment arm assignment)

The applicant provided the following analyses to support their proposal.

Table 24 – Study 007: Analyses of DB1 and DB2 as Applicant’s Proposed Two Independent Studies

Endpoint	Study 007 (DB1)/arm		Study 007 (DB2)/arm	
	Placebo N=280	DFN-15 120 mg N=283	Placebo N=248	DFN-15 120 mg N=243
Headache Pain Freedom at 2 H Proportion responders (95% CI)	LOCF			
	57/263 21.7% (16.8, 27.1)	98/275 35.6% (30.0, 41.6)	76/244 31.1% (25.4, 37.4)	110/238 46.2% (39.8, 52.8)

p value (vs placebo)		<.001		<.001
MBS Freedom at 2 H Proportion responders (95% CI)	104/232 44.8% (38.3, 51.5)	134/232 57.8% (51.1, 64.2)	98/196 50.0% (42.8, 57.2)	121/191 63.4% (56.1, 70.2)
p value (vs placebo)		0.007		0.010

Source: Applicant provided tables. <\\cdsesub1\evsprod\nda212157\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\migraine\5351-stud-rep-contr\dfn-15-cd-007\dfn-15-cd-007-report-body.pdf>

Reviewer comments: The Division considered the request to analyze DB1 and DB2 of Study 007 as two independent studies during the pre-NDA meeting. However, I have the following concerns with this analysis:

- *DB2 was not pre-specified in SAP as an independent study, so allocation of alpha for the endpoints in DB2 did not occur.*
- *DB2 was not an independent population of patients, as the results are highly correlated to DB1.*
- *There was selection bias in DB2 with a 14% drop-out rate from DB1 to DB2.*
- *There was the strong potential for unblinding in DB2, as there was knowledge of study drug effect (or not) from DB1.*
- *Notably, the response rate for both placebo and DFN-15 treated arms increased ~10% from the DB1 period to the DB2 period - likely from a combination of the factors listed above.*

For these reasons, I would not consider DB2 of Study 007 as an independent study. While DB2 might lend some insight into the efficacy of a second dose (in those patients who received two doses of DFN-15), it is a biased sample. Only the results from the DB1 period of Study 007 should serve as the primary efficacy analysis to assess the efficacy of this product for the acute treatment of migraine. DB2 information should be primarily reserved to evaluate the effects of a second dose in terms of safety, for the few patients who did receive DFN-15 in both DB periods. However, there may be bias in reporting of adverse events in DB2 and there was at least a 7-day washout between dosing, so this may not be very informative.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The applicant conducted two identical studies to examine the effects of DFN-15 compared to

placebo for the acute treatment of migraine. Both studies had identical inclusion and exclusion criteria, co-primary endpoints, and study designs. I will now provide a side-by-side comparison of the trials with an overall assessment of efficacy. Of note, the average age across both trials was a mean 40.6 (18-75), 85.7% of patients were female, and 74% of patients were White and the demographics were similar across trials.

7.1.1. Primary Endpoints

The co-primary endpoints for the pivotal clinical trials were headache pain freedom at 2 hours and MBS freedom at 2 hours.

Table 25 – Studies 006 and 007: Co-Primary Efficacy Endpoints Results

Endpoint	Study 006 DB1/Study Arm		Study 007 DB1/Study Arm	
	Placebo	DFN-15 120 mg	Placebo	DFN-15 120 mg
Headache Pain Freedom at 2 H (N)	273	284	271	279
% Responders	25.3%	32.4%	21.0%	35.1%
Difference from placebo		7%		14%
P value		0.076		<0.001
MBS Freedom at 2 H (N)	234	245	237	236
Proportion	44.4%	58.0%	43.9%	56.8%
Difference from placebo		14%		13%
p value		0.003		0.006

Note: This analysis analyzes patients who took rescue medications as nonresponders.

Source: NDA 212157: FDA statistician, Dr. Ling.

Reviewer comments: Both Study 006 and 007 were identical in design, and both were well-controlled investigations. While Study 007 met both co-primary endpoints (with clinically and statistically meaningful results), Study 006 only met one co-primary endpoint (MBS freedom) both statistically and clinically. The results of Study 006 for the primary endpoint of pain freedom demonstrated a lower difference from placebo (or therapeutic gain) that was not statistically significant, though there was a strong trend (p=0.075).

There are many points to note about the analyses of the co-primary endpoints of these two studies:

- 1) *The DFN-15 treated group had a similar proportion of responders in both studies.*
 - a. *However, the placebo response rate for pain freedom at 2 hours in Study 006 was higher than for Study 007, and this may have led to an overall lower difference between treatment groups and loss of statistical significance for the analysis of this endpoint.*
 - b. *The applicant excluded patients with missing data at ≤ 2 hours and excluded patients who had taken a rescue medication in their primary analysis. The applicant should have analyzed those who took rescue medication as nonresponders (shown above), Missing data should not have been handled by exclusion or use of LOCF as it may have led to underestimating within-group mean changes in efficacy.*
- 2) *Both trials met the endpoint of MBS freedom at 2 hours, such that this was both statistically and clinically meaningful for both clinical trials. Given that resolution of pain alone is not the cornerstone of migraine treatment, and that resolution of associated symptoms is important, this effect signifies that the benefit of celecoxib goes beyond pain treatment.*
- 3) *The therapeutic gains on the endpoint of pain freedom for both studies are in line with other recently approved drugs for the acute treatment of migraine.*

The 25.3% placebo-response rate for the pain-freedom endpoint in Study 006 is higher than is typically observed in acute migraine trials (i.e., 10.9-21.3%). This finding was influenced by notably higher placebo response rates in some individual study sites (e.g., 3 study sites had placebo response rates greater than the overall observed response in the active treatment arm, including Site 609 which had a 75% placebo response); however, any post hoc analyses of the impact of these sites on the prespecified efficacy analyses are only exploratory.

7.1.2. Secondary and Other Endpoints

The applicant examined numerous secondary endpoints in an exploratory manner.

The endpoints the Division considers important in acute migraine trials include: headache pain freedom at various time points, sustained pain freedom, use of rescue medications within 24 hours, and incidence of pain relapse. The latter was not studied.

As stated previously, Sections 6.1.2 and 6.2.2., both studies examined numerous secondary endpoints in an exploratory manner without controlling for Type 1 error. Therefore, I will present these results again, and will only include the p values to interpret if it is nominally significant.

Headache pain freedom at various time points was achieved in Study 006 only at 4 hours and the 24-hour time points with nominal significance, though responder rates were numerically higher in the DFN-15 treated group than placebo 1-hour post-dose. In Study 007, nominal

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significance was achieved at 1.5 hours and persisted at 4 hours, but both groups had similar results at 24 hours post-dose. Responder rates were numerically higher in the DFN-15 treated group than placebo after 45 minutes post-dose.

The endpoint of sustained pain freedom in Study 006, sustained pain freedom (defined as headache pain freedom at 2 hours post-dose with no recurrence at 4 or 24 hours without the use of rescue medications) occurred in 27.6% of the DFN-15 arm and 18.9% of the placebo arm with a nominal p value of 0.039. In Study 007, 28.7% of the DFN-15 arm and 18.1% of the placebo arm had sustained pain freedom at 24 hours with a nominal p value of 0.009 (defined the same as for Study 006).

In Study 006, within 2 hours of treating the first migraine attack in DB1, 2 patients in the DFN-15 group and 3 in the placebo group used a rescue medication. On the day of treating the migraine attack, rescue medication use within 24 hours was significantly less in the DFN-15 treated arm (32 patients) compared to the placebo arm (67 patients) with a mean time until use of rescue medication of 4.5 hours for the placebo group compared to 6.2 hours for the DFN-15 treated group.

The same trend was observed in Study 007, with 0 patients in the DFN-15 treated arm and 4 patients in the placebo arm taking a rescue medication within 2 hours of the first migraine attack treated in DB1. In the DFN-15 treated arm, 54 patients took a rescue medication within 24 hours at an average of 5.2 hours after taking study medication for a migraine attack in DB1, compared to 34 in the placebo group.

Reviewer comments: The consistency of the results of the analyses of the described secondary endpoints, although exploratory due to the lack of Type I error control, provide further support of the treatment benefit of DFN-15 on important considerations for patients when treating an acute migraine.

7.1.3. Subpopulations

The applicant examined subgroup analyses based on age (18-34 years, 35-49 years, 50-64 years and ≥ 65 years), gender (male, female) and ethnicity (Hispanic and non-Hispanic).

Differences in headache pain freedom or MBS freedom at 2 hours were not observed based on age, gender or ethnicity. All age groups had higher DFN-15 responder rates compared to placebo except for ≥ 65 (likely due to the low number in that age group).

7.1.4. Dose and Dose-Response

The applicant only studied one dose and thus a dose response could not be assessed in these

pivotal studies. The applicant did study the effect of a second dose of DFN-15 or placebo (after patients were re-randomized after DB1 > 7 days after the first dose) and in Study 007, DB2 provided evidence that a second dose of DFN-15 can be as effective as the first dose in treating an acute migraine. The results of the DB2 of Study 006 did not provide evidence of the benefit of a second dose of DFN-15 compared to placebo, because, though headache pain freedom showed a 12% difference from placebo with a nominal p value of 0.003, MBS freedom showed only a 6% difference from placebo, with a p value of 0.25. It is important to note that none of these endpoints on DB2 in either study was controlled for Type 1 error. No information should be provided in labeling regarding efficacy of a second dose.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The applicant examined onset of effect as a post-hoc analysis (reported above individually for each study) and this varied from 1 hour in Study 007 to 4 hours in Study 006. The duration of the effect demonstrated that more patients in the DFN-15 treated arm had sustained pain freedom at 24 hours (without use of rescue medications) compared to the placebo treated arm (as stated above).

7.2. Integrated Assessment of Effectiveness

The applicant conducted two identical studies (Study 006 and Study 007). These studies had the same inclusion/exclusion criteria, study design, doses, and co-primary endpoints. The applicant only met one of its two co-primary endpoints (in terms of statistical significance) for Study 006 and met both co-primary endpoints for Study 007, for both clinical meaningfulness and statistical significance.

Reviewer comments: The applicant proposed many methods to analyze their dataset, including removing an outlier site (with a high placebo response rate which may have driven the results of the first study) and suggested using the two double-blind periods of Study 007 as independent studies. The Division does not believe that either of these two methods is statistically or scientifically sound. The applicant also proposed pooled results of their pivotal studies (Table 8 of the applicant's Integrated Summary of Efficacy), which demonstrated that both co-primary endpoints of pain freedom and MBS freedom were met when the data was pooled. The Division does not typically accept pooling studies, even if identical, due to the need for two independent studies to demonstrate efficacy and to ensure that results are not due to chance alone.

Ideally, both studies would have independently demonstrated evidence of effectiveness (with both statistically significant and clinically meaningful results) of DFN-15 compared to placebo to support approval.

Efficacy conclusions from Study 006:

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- *The applicant pre-specified the primary endpoint analysis to use LOCF. This method (LOCF) is not recommended by the Division or the National Research Council's Panel on Handling Missing Data in Clinical Trials (2012) as it has multiple flaws, including a positive or negative bias that can inflate or deflate the probability of a statistically significant result under either the null or alternative hypothesis. In the case of this submission, due to a higher degree of missing data at points 2 hours and earlier in the placebo group, it is likely that the placebo response was overestimated.*
- *The applicant inappropriately excluded rescue medication users within 2 hours of dosing from the primary analysis, when these patients should have been analyzed as nonresponders.*
 - *FDA sensitivity analyses, in which patients with missing data for the endpoint of pain freedom were analyzed using NOCB and rescue medication users were analyzed as nonresponders, demonstrated that the p value for pain freedom at 2 hours approached <0.05.*
- *The study did not reach one of the pre-specified co-primary endpoints of pain freedom at 2 hours, in terms of statistical significance. However, there was a 7% difference from placebo for this endpoint and this is clinically relevant. Notably, there have been several other recently approved drugs in the U.S. with similar therapeutic gains for pain freedom at 2 hours, when compared to placebo, in clinical trials.*
- *The study met the other co-primary endpoint of MBS freedom at 2 hours, and the results demonstrated a strong clinical benefit (with a therapeutic gain of ~15%) and strong statistical significance. MBS freedom at 2 hours is a migraine-specific symptom that further illustrates the specificity of this drug in treating migraine.*
- *Although the secondary endpoints were not controlled for Type 1 error, the endpoint of rescue medication use within 24 hours was less in the DFN-15 treated arm and the endpoint of sustained 24-hour pain freedom was higher in the DFN-15 treated arm. Both of these exploratory endpoints were nominally significant.*

Based on these prespecified results of the analyses of the co-primary endpoints alone, this study would appear to have limitations with respect to its ability to serve as an independent study that could provide evidence of the efficacy of DFN-15 for the acute treatment of migraine. It is important to note, though, that though the study did not reach a p value of <.05 for one of the co-primary endpoints, this study did show a positive trend.

Efficacy conclusions from Study 007:

- *Study 007 met both its pre-specified co-primary endpoints in a statistically significant and clinically meaningful way.*
- *Sensitivity analyses to handle missing data did not change the results.*
- *The secondary endpoints (though not controlled for Type 1 error), demonstrated that, compared to placebo, rescue medication use within 24 hours was less in the DFN-15 treated arm, and sustained 24-hour pain freedom was higher in the DFN-15 treated arm.*

Both exploratory endpoints were nominally significant.

Based on my review of the data provided by the applicant, I believe Study 006 can be used as the second study to support evidence of the efficacy of DFN-15 for the acute treatment of migraine for the following reasons:

- 1) The endpoint of pain freedom demonstrated a p value suggestive of a positive trend ($p=0.075$), with a clinically meaningful effect size of 7% (and in line with clinical trial results on this endpoint for other recently approved drugs for acute migraine treatment).*
- 2) While migraine pain is different from other types of pain, it is typically differentiated by its location and nature in the head, and the associated symptoms of nausea, photophobia and phonophobia. Both studies demonstrated a benefit on the clinically important associated symptoms of migraine (MBS freedom) that was statistically significant and clinically meaningful.*
- 3) There are two NSAIDs that were approved for the acute treatment of migraine (diclofenac (Cambia) and rofecoxib (Vioxx – which has since been taken off the market for reasons of safety) with both drugs demonstrating evidence of a beneficial effect on acute migraine treatment in at least two clinical trials.*
- 4) Celecoxib has clinical trial evidence of a known beneficial effect on the symptom of pain and already has an indication for pain in its label.*
- 5) Though the analyses of the secondary endpoints in the studies were exploratory and not controlled for Type 1 error, both studies suggested consistent numerical results favoring active treatment in the following generally accepted endpoints in trials for the acute treatment of migraine: less rescue medication use at 24 hours, and higher proportions of patients with 24-hour pain freedom (without use of rescue medication).*

I believe that the evidence in this application, including the factors above, and specifically the data from the two pivotal studies in this application, support the efficacy of DFN-15 120 mg for the acute treatment of migraine. The DB1 period of Study 007 demonstrates the strongest evidence for efficacy of DFN-15 for the acute treatment of migraine, and the DB1 period of Study 006 provides further evidence of the efficacy, given that the therapeutic gain is comparable to other products FDA has approved for this indication. There is additional supportive evidence of efficacy demonstrated from the nominal significance achieved for the exploratory endpoints of less rescue medication use at 24 hours and greater rates of 24-hour pain freedom in the DFN-15 treated arms in both studies.

8. Review of Safety

8.1. Safety Review Approach

Celecoxib is approved for multiple indications and the PI for celecoxib includes multiple warnings and precautions. This safety information should also be included in the label for DFN-15 since the drug product is the same, though the formulation is different. Specifically, boxed warnings for risk of serious cardiovascular and gastrointestinal warnings should be included. The existing warnings and precautions for celecoxib pertaining to hepatotoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, premature closure of fetal ductus arteriosus, and hematologic toxicity should be included in the label.

In order to evaluate the adverse event profile of this new formulation with a new dose, this safety review will specifically focus on local toxicity (from the oral liquid formulation) and any new treatment emergent adverse events (TEAEs) from the trials submitted with this application. This involved reviewing the Phase 2 and 3 studies in which the to-be-marketed formulation of DFN-15 or placebo was given to patients, and included the review of data from Study 002, Study 006 and Study 007.

The safety populations were defined as all patients who were randomized and received at least 1 dose of study drug. The applicant was asked to provide 3 safety pools to analyze safety outcomes.

Pool A: Phase 2 and 3 studies, DFN-15 treated only

Pool B: Phase 3 studies, DB1 only, DFN-15 and placebo

Pool C: All controlled trials (Phase 2 and 3), DB1 and DB2 (DFN-15 and placebo)

Reviewer comments: Pool A allows the analysis of all-treated patients and would most resemble the type of data from an open-label study of how a drug would be used (with the potential for multiple exposures in a single patient). Since DFN-15 is only proposed to be administered once in a 24-hour period, this would most resemble real-world use of this drug. Pool B will be the most unbiased analysis, because this is the sample of patients that were used for the primary efficacy analysis. Since both Study 006 and Study 007 had identical designs, pooling the results from DB1 will allow a comparison of the 120 mg dose of DFN-15 versus placebo. Finally, Pool C will allow a comparison of the DFN-15 240 mg and 120 mg dose, although numbers in this higher dose group are small and we will likely not be able to draw conclusions about the 240 mg dose. This pool will help understand if there are dose-related effects, though. One thing to note, though, is that this pool will also examine multiple doses and this is a biased sample, since not all patients took a second dose of study drug (so those who experienced an adverse event may not have gone on to DB2 by choice), and the second dose had a minimum of 1 week washout period, so cumulative effects cannot be examined.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The two pivotal studies included 2 treatment periods, DB1 and DB2, in which patients treated 1 migraine attack in each period and received either DFN-15 or placebo. There was a subgroup of patients who received two doses of DFN-15, but with a minimum 7-day washout period between doses.

In the Phase 2 and 3 studies, a total of 875 patients received at least 1 dose of DFN-15. 60 patients were exposed to a dose of 240 mg. The Phase 1 studies are not included because many involved different formulations of DFN-15 at various doses.

In the Phase 3 studies, a total of 815 patients received at least one dose of DFN-15 and 254 patients received two doses of DFN-15.

Table 26 - Safety Set by Study Arm and Double-Blind Period: Phase 2 and 3 Studies

Study Arm and Double-blind Period	DB1			DB2			DB3		
	DFN-15 120 mg	DFN-15 240 mg	Placebo	DFN-15 120 mg	DFN-15 240 mg	Placebo	DFN-15 120 mg	DFN-15 240 mg	Placebo
Study 002	21	18	21	18	20	20	20	19	16
Study 006	289	-	283	251	-	254	-	-	-
Study 007	285		282	244	-	249	-	--	
Totals	595	18	586	513	20	523	20	19	16

Table 27 - Safety Set by Number of Doses and Study Arm: Phase 3 Studies

Study Arm and Number of Doses	DFN-15			Placebo		Total
	First Dose DFN-15	One Dose DFN-15	Two Doses DFN-15	First Dose Placebo	Only Placebo	Overall
Phase 3 Safety Population	574	561	254	565	334	1149

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Completed Study	508	493	254	484	257	1004
Discontinued Study	66	68	0	79	77	145

Reviewer comments: There was no open-label or long-term extension study of DFN-15 conducted by the applicant. The highest number of exposures from Phase 3 data is from patients who received two doses of DFN-15 (254 patients total). Importantly, these patients did have at least a 7-day washout period between doses of DFN-15 due to protocol requirements for both Phase 3 studies. Therefore, there are no data on cumulative exposure (over any time period) or multiple doses in a one-day period. Any cumulative exposure information would be derived from data on celecoxib at other doses and in the oral tablet form - which is already in the PI. In total, 815 patients in the Phase 3 studies received at least one dose of DFN-15. Of these, 254 received two doses of DFN-15.

8.2.2. Relevant characteristics of the safety population:

The safety pool has similar demographic characteristics as what was described above for the FAS for each individual study.

8.2.3. Adequacy of the safety database:

The safety database within this application contains a moderate pool of patients in which to glean data on the safety profile of DFN-15. However, it is important to note that the information is mostly from a single use of DFN-15 for treating one acute migraine attack. There is a wealth of data on celecoxib, based on controlled trials, post-market information and post-market studies on this drug, though. The applicant is relying on FDA's findings on safety data of the approved prescription product (Celebrex capsules (NDA 020998) as the listed drug for this application.

The data in this submission is sufficient to evaluate the safety of one dose of DFN-15 120 mg, but is inadequate to evaluate multiple doses, higher doses, or long-term use of this drug.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the integrity of the safety database.

8.3.2. Categorization of Adverse Events

Adverse events were categorized as treatment-emergent.

8.3.3. Routine Clinical Tests

Routine clinical tests were done at screening and at follow up visits, which occurred on average 7 days after treatment.

8.4. Safety Results

8.4.1. Deaths

In the Phase 1 studies, there were no deaths reported.

In the Phase 2 study, Study 002, there were no deaths reported.

In the Phase 3 studies, Study 006 and Study 007, there were no deaths reported.

8.4.2. Serious Adverse Events (SAEs)

In the Phase 1 studies, there were no SAEs.

In the Phase 2 study, there were no SAEs.

In the Phase 3 studies, there were a total of 6 SAEs.

In Study 006, there were 4 patients with SAEs, all considered nontreatment emergent by the applicant. Three patients were in the DFN-15 treated arm and had the following SAEs: pulmonary embolism, acute cystitis requiring hospitalization and noncardiac chest pain. There was 1 patient in the placebo arm of this study who had an SAE of a miscarriage. Of note, one patient ((b) (6)) had an SAE of asthma exacerbation while in the screening period and had not yet received study drug.

The following are the narratives for the three SAEs in DFN-15 treated patients:

- Patient (b) (6) had an SAE of pulmonary embolism. The patient was a 36-year-old woman who had a history of obesity and anemia, she received study drug on March 15, 2017 and then again on April 3, 2017 and then went on a road triptan from Detroit to Dallas on (b) (6), she was hospitalized with “multiple pulmonary emboli,” as reported by her spouse. The event was reported as not related by the investigator.
- Patient (b) (6) had an SAE of acute cystitis requiring hospitalization. The patient was a 43-year-old female with a history of recurrent urinary tract infections and history of pyelonephritis who presented to the hospital with

moderately severe suprapubic and right lower quadrant pain, fever, burning urination and CT scan suggestive of cystitis on [REDACTED] (b) (6). She was discharged home 3 days later with oral antibiotics. She had received her first dose of study drug (placebo) on August 7, 2017 and her second dose of study drug (DFN-15) on August 27, 2017. The event was report as not related by the investigator.

- Patient [REDACTED] (b) (6) was a female with a history of hypercholesterolemia, hypothyroidism, hot flashes, migraine who had an SAE on [REDACTED] (b) (6) of chest pain that ended [REDACTED] (b) (6) (she required a one-day hospitalization for evaluation). Cardiac enzymes were normal and electrocardiogram not suggestive of ischemia. This patient received her first dose of study medication (placebo) on March 26, 2017 and then still went to take the second dose (this time she was randomized to DFN-15) on April 9, 2017.

Reviewer comments. The first SAE of pulmonary embolism that occurred 25 days after taking DFN-15 and in the context of a car ride of ~1200 miles (which would take roughly 19 hours by car) is unlikely related to DFN-15. The second event of acute cystitis occurring one week after treatment with DFN-15 is unlikely related in this patient with a history of recurrent urinary tract infections and pyelonephritis. This third SAE is not related to DFN-15 as it occurred before taking DFN-15, and after taking placebo.

In Study 007, there were 2 SAEs, also considered nontreatment emergent by the applicant, and both occurred in patients in the placebo arms, one patient who was in a motor vehicle accident on [REDACTED] (b) (6) and had received placebo study drug on March 18, 2017. and one with a hospitalization for noncardiac chest pain (Patient [REDACTED] (b) (6)) on [REDACTED] (b) (6), who had received study drug (placebo) on March 12, 2017.

I will not summarize the narratives of the SAEs in Study 007, because they occurred in patients in the placebo arm, and after my detailed review, were unlikely related to the study.

Reviewer comments: Given the low number of SAEs in the studies the applicant conducted, I have only provided an overview of the events in patients who did receive DFN-15. Given that patients only received one dose of DFN-15 at a time in the study and only 125 patients in Study 006 and 128 patients in Study 007 received two doses of DFN-15 (and a minimum of seven days apart), it is hard to draw any conclusions on the long-term safety or repeated use of DFN-15 from this study population.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study 002, there were no patients who discontinued due to TEAEs.

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In Study 006, six patients had 7 AEs leading to study drug discontinuation, and selected narratives follow.

Patients who received DFN-15 in Study 006:

- Patient (b) (6) a 31-year-old woman, received DFN-15 on March 31, 2017. Her concomitant medications included tizanidine, naratriptan, eletriptan, Astelin and Lyrica. On (b) (6), she experienced a mild adverse event of urticaria and study drug was withdrawn. This was considered possibly related to study drug. The event resolved on April 17, 2017.

Patients who received placebo in Study 006:

- Patient (b) (6) 1, a 43-year-old woman, on Fioricet and promethazine, received placebo on January 2, 2017 and on January 4, had a drug screen positive for barbiturates (it was noted she was on Fioricet which contains a barbiturate). She was withdrawn from the study.
- Patient (b) (6) received placebo on April 12, 2017 and on (b) (6) had a benign neoplasm of thyroid gland. Study drug was withdrawn, though this was deemed not related to study drug.
- Patient (b) (6) is a 38-year-old woman who received placebo on (b) (6) and had a mild TEAE of nausea and noncardiac chest pain the same day. She was withdrawn from the study.
- Patient (b) (6) received placebo on March 13, 2017 and had a moderate event of vomiting that day.
- Patient (b) (6) received placebo on January 16, 2017 and experienced urticaria on (b) (6). The patient was withdrawn from the study.

Per my review of the safety set for Study 007, there were 6 patients that discontinued the study due to adverse events:

The following are brief narratives for the patients who received DFN-15 in Study 007:

- Patient (b) (6) 0 randomized to DFN-15 and received DFN-15 on July 20, 2017, had elevated blood pressure on July 27, 2017, and drug was withdrawn. This 40-year-old woman had a baseline blood pressure of 121/74 mm Hg and this ranged from 143-

154/99-108 mm Hg seven days after receiving DFN-15. She was withdrawn from the study.

- Patient (b) (6), who was a 34-year-old man, was noted to have an increased ALT level of 110 U/L and 115 U/L (normal 0-44 U/L) at baseline not considered clinically significant by the investigator. He received DFN-15 on February 18, 2017 in DB1. On February 24, 2017, his ALT was increased to 126 U/L, also considered not clinically significant, but study drug was withdrawn. On March 6, his ALT was 111 U/L. This was considered not related to study drug.

Patients who received placebo:

- Patient (b) (6) received placebo in DB1 on February 23, 2017 and had increased Creatine phosphokinase and lowered calcium (two adverse events) on March 2, 2017 (ongoing) and March 23, 2017 (ending April 12, 2017), respectively.
- Patient (b) (6) randomized to placebo in DB1, received study drug on March 3, 2017, and abnormal electrocardiogram reading on March 8, 2017.
- Patient (b) (6) 7, randomized to placebo in DB1 received study drug on May 10, 2017 and had an adverse event of vomiting on May 11, 2017.
- Patient (b) (6) 1 had placebo in DB1, and had an abnormal electrocardiogram reading on June 14, 2017.

All these patients had study drug withdrawn due to the adverse event.

Reviewer comments: I do not think the rate of discontinuations for either study raises any alarm about toxicity of DFN-15 in this patient population. It is difficult to know from the narratives provided if the adverse events were related to study drug in any of the patients who received DFN-15. The discontinuations do not warrant any label recommendations.

8.4.4. Significant Adverse Events

In Study 006, there were no serious TEAEs and there were 4 patients with serious non-treatment emergent AEs.

Narratives of SAEs, followed by reviewer comments in italics:

Patient (b) (6) was a 36-year-old white female, who was randomized and received placebo on January 7, 2017. During the post treatment follow up on January 12, 2017, her pregnancy test came back positive. On February 14, 41 days post study drug, she had a spontaneous abortion. She was terminated from the study that day. In July 2017, she reported another miscarriage.

Reviewer comments: It is unlikely that the first spontaneous abortion was related to study drug,

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given this was a single dose.

Patient (b) (6) was a 35-year-old woman who received DFN-15 on March 15, 2017 and was re-randomized and received DFN-15 again on April 3, 2017. She did experience severe vomiting with the second dose, this resolved that day. On (b) (6), the patient experienced an SAE of pulmonary embolism. Outcome is unknown. The investigator did not think this was drug-related.

Reviewer comments: It is difficult to assess if this is study drug related, but it is unlikely.

Patient (b) (6) is a 43-year-old white female who received placebo on August 7, 2017 and DFN-15 on August 27, 2017. She then had an SAE of cystitis requiring hospitalization on (b) (6).

Reviewer comments: This is not related since she received placebo.

Patient (b) (6) is a 63-year-old white female received placebo on March 26, 2017 and had an SAE of noncardiac chest pain on (b) (6).

Reviewer comments: This is not related since she received placebo.

In Study 007, there were no TEAEs and there were 2 non-treatment emergent SAEs.

The brief narratives for the nontreatment emergent SAEs follows:

Patient (b) (6) was a 36-year-old white female who received placebo on March 18, 2017, she was re-randomized on (b) (6) and involved in a serious road traffic accident the same day, requiring hospitalization.

Reviewer comments: This is not related as she received placebo and this was (b) (6) days prior.

Patient (b) (6) was a 57-year-old white female who received placebo on March 12, 2017 and placebo on March 29, 2017. On (b) (6) she was hospitalized for a mild event of non-cardiac chest pain with normal investigations.

Reviewer comments: This is not related as the patient received placebo.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The results for the TEAEs are presented in the following manner:

- 1) Office of Drug Evaluation (ODE-1) queries, which will avoid duplications for the same

patient and broadly group similar AE terms into categories that have been developed by ODE.

- a. Phase 2 and 3, DB1, by first dose only
 - b. Phase 3, by Number of Doses
- 2) Will then perform an analysis of the AE terms (AEDECOD) from the following pools:
- a. Study 006 and Study 007, separately, DB1 and DB2
 - b. Phase 3 studies, DB1
 - c. Phase 2 and 3, DB1

Table 28 - ODE1 Query: Treatment Emergent Adverse Events, Phase 2 and 3 Studies, by First Dose

Analysis Columns	First Dose DFN-15 120 mg	First dose DFN-15 240 mg	First Dose Placebo
N	595	18	586
Infection, all	19 (3.2%)	0	15 (2.6%)
Cold, Rhinitis, Upper Respiratory Tract Infection, Flu-like Illness	9 (1.5%)	0	9 (1.5%)
Dyspepsia, Nausea, Vomiting, Indigestion, Epigastric pain, Gastritis	21 (3.5%)	3 (16.7%)	23 (3.9%)
Nausea, Vomiting	19 (3.2%)	3 (16.7%)	21 (3.6%)
Dysgeusia	19 (3.2%)	1 (5.6%)	10 (1.7%)
Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-diff	6 (1.0%)	1 (5.6%)	2 (0.3%)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	6 (1.0%)	0	5 (0.9%)
Fall, Dizziness	6 (1.0%)	0	6 (1.0%)

Source: Used TRTEMFL and SAFFL on ADSL and ADAE, using ODE-1 query (avoid duplications for the same patient and broadly group similar AE terms into categories that have been developed by ODE), and then analyzing by TRT01A for pooled Phase 2 and 3 data.

Table 29 – ODE1 Query: Treatment Emergent Adverse Events ≥ 1%, Phase 3 Studies, by Number of Doses

Analysis Columns	First Dose DFN-15 120 mg	Two Doses DFN-15 120 mg	First Dose Placebo
N	574	254	565
Infection, all	17 (2.9%)	6 (2.3%)	13 (2.3%)
Cold, Rhinitis, Upper Respiratory Tract Infection, Flu-like Illness	9 (1.6%)	3 (1.2%)	9 (1.6%)
Dyspepsia, N, V, Indigestion, Epigastric pain, Gastritis	21 (3.6%)	7 (2.8%)	21 (3.7%)
Nausea, Vomiting	19 (3.3%)	6 (2.4)	19 (3.4%)

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Dysgeusia	17 (2.9%)	9 (3.5)	7 (1.2%)
Infection, Viral	4 (0.7%)	2 (0.8)	0 (0%)
Fall, Dizziness, Balance Disorder	6 (1.0%)	3 (1.2)	2 (0.4%)
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	6 (1.0%)	4 (1.6)	4 (0.7%)

Source: I created this table using the TRTEMFL and SAFFL on ADAE, merging with ADSL and a coding file (avoid duplications for the same patient and broadly group similar AE terms into categories that have been developed by ODE), and then analyzing by TRT01A for pooled Phase 2 and 3 data.

Reviewer comments: The only adverse event that occurs at a higher percentage ($\geq 2\%$) than placebo is dysgeusia in the analyses above. There is a higher rate of nausea and/or vomiting with DFN-15 at the 240 mg dose (first safety table above), but there were very few patients who received this dose, so it is difficult to draw conclusions.

Table 30 - Study 006: Treatment Emergent Adverse Events $\geq 1\%$ AEDECOD by DB Period

	DB1 DFN-15 N=289	DB1 Placebo N=283	DB2 DFN-15 N=251	DB2 placebo N=254
Dysgeusia	5 (1.7%)	3 (1.1%)	4 (1.6%)	3 (1.2%)
Nausea	6 (2.1%)	7 (2.5%)	6 (2.4%)	4 (1.6%)
Vomiting	2 (0.7%)	3 (1.1%)	1 (0.4%)	3 (1.2%)
Nausea, Vomiting	8 (2.8%)	10 (3.5%)	7 (2.8%)	7 (2.8%)
Dizziness	5 (1.7%)	2 (0.7%)	2 (0.8%)	4 (1.6%)

Source: I created this table using the ADAE file removed patients who have the same AE twice and were in the TRTEMFL population only and separated by DB period. This was not separated by EPOCH, so numbers varied slightly from the applicant.

Reviewer comments: In Study 006, the rates of dysgeusia are slightly higher, but do not reach the threshold of $\geq 2\%$ difference from placebo. DB2 is a biased sample, since there was self-selection of patients that would enter this period and possible unblinding from having known effects of study drug (either DFN-15 or placebo) from having possibly taken it in DB1. Therefore, it is hard to draw conclusions from DB2. The analysis will focus on AEs from DB1. Of note, though I did not examine this by EPOCH, similar results were obtained by the applicant and did not change the interpretation of results in this analysis or any analysis below.

Table 31 - Study 007: Treatment Emergent Adverse Events $\geq 1\%$ AEDECOD by DB Period

	DB1 DFN-15 N=285	DB1 placebo N=282	DB2 DFN-15 N=244	DB2 placebo N=249
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Dysgeusia	12 (4.2%)	4 (1.4%)	7 (2.9%)	8 (3.2%)
Nausea	10 (3.5%)	6 (2.1%)	5 (2.1%)	10 (4.0%)
Vomiting	2 (0.7%)	0 (0%)	0 (0%)	1 (0.4%)
Nausea, Vomiting	12 (4.2%)	6 (2.1%)	5 (2.1%)	11 (0.4%)
Dizziness	1 (0.4%)	0 (0%)	4 (1.6%)	1 (0.4%)
Nasopharyngitis	3 (1%)	0 (0%)	5 (2.1%)	2 (0.8%)

Source: I created this table using the ADAE file removed patients who have the same AE twice and were in the TRTEMFL population only and separated by DB period. This was not separated by EPOCH, so numbers varied slightly from the applicant.

Reviewer comments: In DB1 of Study 007, dysgeusia and nausea and vomiting (when the two different AE terms were combined) were the only adverse events that occurred at a rate $\geq 2\%$ than the placebo group. This difference was not seen in the DB2 period for either groups of terms, but again DB2 is a biased sample.

Table 32 - Phase 3 Studies (Study 006 and Study 007 Pooled): Treatment Emergent Adverse Events $\geq 1\%$ by DB Period

	DB1 DFN-15 N=574	DB1 placebo N=565	DB2 DFN-15 N=495	DB2 placebo N=503
Dysgeusia	17 (3.0%)	7 (1.2%)	11 (2.2%)	11 (2.2%)
Nausea	16 (2.8%)	13 (2.3%)	11 (2.2%)	14 (2.8%)
Nausea, Vomiting	20 (3.5%)	16 (2.8%)	12 (2.4%)	19 (3.8%)
Dizziness	6 (1.0%)	2 (0.4%)	11 (2.2%)	8 (1.6%)

Source: I created this table by including only patients with the TRTEMFL and counting each patient once for any specific AE and pooling data from Study 006 and Study 007. This was not separated by EPOCH, so numbers varied slightly from the applicants.

Table 33 - Treatment Emergent Adverse Events, DB1 only AE Terms $\geq 1\%$ - Study 002, Study 006, Study 007

AESOC	AEDECOD	DFN-15 240		
		DFN-15 120 mg N=595	mg N=18	Placebo N=586
Gastrointestinal disorders	Nausea	16 (2.7)	2 (11.1)	15 (2.6)
Nervous system disorders	Dysgeusia	19 (3.2)	1 (5.6)	10 (1.7)

Source: I created this table using the SAFFL and TREMFL of Study 002, Study 006 and Study 007 and then subgrouping, so each patient was only counted once for a given AEDECOD. I then grouped by TRT01A, USUBID and AEDECOD and then summary-> grouping by TRT01A, USUBID and subgroup AEDECOD)) and then created a data

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table of AEDECOD by TRT01A. Of note, the applicant's numbers varied slightly from my analyses (by 1 or 2 patients and did not affect overall interpretation of these results). I did not use EPOCH for these calculations, so numbers varied slightly from the applicant.

Table 34 - Treatment Emergent Adverse Events, DB1 only AE Terms ≥ 1%, Phase 3 Studies, DB1 only

System Organ Class	AE Term	DFN-15 120	
		mg	Placebo
		N=574	N=565
Gastrointestinal	Nausea	13 (2.3%)	10 (1.8%)
Nervous system disorders	Dysgeusia	17 (3.0%)	7 (1.2%)

Source: Informational Request from applicant.

Reviewer comments: I examined all the phase 2 and 3 studies and the first DB period, as this would have the least bias (selection bias, potential unblinding) from not having received a prior dose of study drug in this patient group. Rates of nausea and dysgeusia are highest for the DFN-15 120 mg group. However, the rates for nausea are also similar to that in the placebo group and there is not a greater than 2% difference between placebo and DFN-15. There does appear to be a dose-response with adverse events occurring at higher rates in the 240 mg group. For example, rates for nausea were highest for the DFN-15 240 mg group with higher rates of many other AEs, as well, including dysgeusia, upper respiratory tract infection, diarrhea, vomiting, abdominal pain, insomnia and abdominal tenderness (not included in above table). The numbers in the Phase 2 study were small (N=18), though, so it is hard to make conclusions on such a small data set. Additionally, this is not the to-be-marketed dose and repeat dosing with DFN-15 120 mg is not suggested. Therefore, this data on the DFN-15 240 mg dose may shed light on potential side effects at higher doses of DFN-15, but it should not necessarily be included in the label. Even including data from the phase 2 study and by doses, it is clear dysgeusia is the most relevant AE that occurs at a higher rate in DFN-15 treated patients than placebo, for each study alone, and in combination with and without phase 2 data included.

The analyses with DB1 of both Study 006 and Study 007 only are the least biased and most representative sample of patients. The rate of AEs in DB1 for the pooled Phase 3 studies indicate that AEs were similar between DFN-15 and placebo treated groups and the only AE that stands out is dysgeusia as having an almost 2% increase in the DFN-15 treated group – which is similar to the rates in the individual studies. Dysgeusia is the only new TEAE that I recommend we include in the label.

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8.4.6. Laboratory Data

In Study 002, the applicant asserted that no laboratory data was collected.

In Study 006, there was one patient who had ALT or AST ≥ 2 ULN and TB ≥ 1.5 ULN and normal ALP in the DFN-15 arm and none in the placebo arm.

Patient (b) (6) was a 22 year old white female who had a dose of DFN-15 120 mg on February 25, 2017 and March 14, 2017, and was taking ibuprofen, eletriptan and etonogestrel as concomitant medications. She was noted to have elevated ALT 88, AST 102 and CK on March 3, 2017 until March 9, 2017. Of note, she had a direct bilirubin of 6.8 umol/L on screening (normal 0-5.1) and this peaked to 8.6 umol/L. Total bilirubin peaked at 1.5x the ULN and AST at 2x ULN. This did not meet Hy's Law criteria.

In Study 007, no patients met Hy's law criteria.

Reviewer comments: Per the Prescribing Information (PI) of celecoxib, elevations of Alt or AST (three or more times the upper limit of normal, have been reported in approximately 1% of NSAID-treated patients in clinical trials. Furthermore, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Given this finding of one patient with an elevated ALT and total bilirubin, this is likely consistent with the warnings already present in the celecoxib label. This one patient would not trigger any additional warnings to be added to the label, as this is a known potential effect of NSAIDs.

8.4.7. Vital Signs

The vital signs of patients were examined and no relevant trends were noted. Of note, vital signs that were taken in close proximity to actual dosing only occurred in Study 002.

8.4.8. Electrocardiograms (ECGs)

The applicant did not evaluate electrocardiogram results in these studies and is relying on prior studies of celecoxib to understand these effects.

Reviewer comments: The cardiac effects of celecoxib are well known and should be included in the PI.

8.4.9. Immunogenicity

There are no concerns with immunogenicity with celecoxib, as this is an NSAID.

8.5. Analysis of Submission-Specific Safety Issues

No specific submission-specific safety issues arose during the review of the IND associated with this application or during the NDA review process.

8.6. Safety Analyses by Demographic Subgroups

I examined the trends for the two most common adverse events (and those that the applicant had identified as the most common in the proposed labeling) and conducted the following subgroup analyses on the Phase 2 and 3 dataset, DB1 only, on the AEDECOD data (merging ADSL with ADAE, removing patients with multiple duplicate adverse events) and subgrouping by SEX (M/F), AGE (≥ 40 or < 40), and RACE (focusing on black/white since the n in other groups was ≤ 1).

Table 35 - Subgroup Analysis of Most Common TEAEs ($\geq 2\%$) in Phase 2 and 3 Studies

Preferred Term	Females		Males		Age ≤ 40		Age > 40		White		Black	
	DFN-15	PBO	DFN-15	PBO	DFN-15	PBO	DFN-15	PBO	DFN-15	PBO	DFN-15	PBO
N	572	561	94	89	333	338	333	312	489	493	145	130
Dysgeusia	3.0%	1.8%	2.1%	0%	3.6%	1.5%	2.1%	1.6%	3.1%	2.0%	0.7%	0%
Nausea	2.4%	3.4%	3.2%	2.2%	3.0%	4.1%	2.1%	2.2%	2.7%	2.6%	2.1%	5.4%

Reviewer comments: The rate of adverse events was generally low, such that subgroup analyses are unlikely to lead to clinically interpretable findings. The table above demonstrates that dysgeusia tended to occur more often in males on DFN-15 compared to placebo and more often in those ≤ 40 ($> 2\%$ difference between groups). However, the overall number of males in these studies was small, so it is difficult to draw conclusions from this subgroup analysis. The total number of patients ≤ 40 years old is large, so it is possible that dysgeusia is more common in younger patients who receive DFN-15. However, I do not believe the data is compelling enough to support a statement in the label that a difference in dysgeusia rates exists based on any of these subgroup analyses.

8.7. Specific Safety Studies/Clinical Trials

No special safety studies were conducted as part of this new drug application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

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Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

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

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The data does not suggest that any new safety concerns have emerged from the review of this application.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety profile of celecoxib has been well characterized from years of marketing and use. It has black box warnings, and numerous warnings and precautions that should be included in the label for DFN-15. Given that the exposure of 120 mg DFN-15 is well-capped by the exposures of celecoxib 400 mg orally (with food), I do not think new safety concerns will emerge if patients follow dosing instructions as directed by the PI.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

All of the currently available safety information for celecoxib should be included in the label for DFN-15 since the drug product is the same, though the formulation is different. That is, boxed warnings for risk of serious cardiovascular and gastrointestinal warnings should be included in the label. Warnings and precautions pertaining to hepatotoxicity, hypertension, heart failure and edema, renal toxicity, anaphylactic reactions, exacerbation of asthma related to aspirin sensitivity, serious skin reactions, premature closure of fetal ductus arteriosus and hematologic toxicity should be included in the label. I recommend only adding dysgeusia as a new TEAE based on my safety review of the clinical trials in this application.

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9. Advisory Committee Meeting and Other External Consultations

An advisory committee is not recommended.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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Please see label for recommendations.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS will not be required for this application.

12. Postmarketing Requirements (PMR) and Commitments

Pediatric PMR:

- 1) A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of DFN-15 versus placebo in treating a single migraine attack in patients aged 6 to < 17 years old. No long-term study will be required.

13. Appendices

13.1. References

1. Dodick, D. Migraine. Seminar. Lancet 2018; 391:1315-1330.
2. Lipton R, Bigal M, Diamond M, Freitag F, Reed M, and W Stewart. Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy. Neurology. 2007 Jan 30; 68(5):343-349.
3. Prakash A, Risser RC, Mallinckrodt CH. The impact of analytic method on interpretation of outcomes in longitudinal clinical trials. International Journal of Clinical Practice. 2008 Aug; 62(8): 1147-58.
4. Robbins, NM, Bernat JL. Minority Representation in Migraine Treatment Trials. Headache. 2017 Mar; 57 (3): 525-533.

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 006

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>43</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</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: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Applicant of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study 007

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from
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		Applicant)
Total number of investigators identified: <u>45</u>		
Number of investigators who are Applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</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: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Applicant of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
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/

VIVECA B LIVEZEY
04/29/2020 01:12:25 PM

HEATHER D FITTER
04/29/2020 02:54:27 PM