CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	212157
Drug Name:	Celecoxib (DFN-15)
Indication(s):	Acute treatment of migraine with or without aura in adults
Applicant:	Dr. Reddy's Laboratories Limited
Date(s):	Submission date: 07/05/2019
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Review Priority:	Standard
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1 EXECUTIVE SUMMARY

The data overall provided evidence to support the efficacy of DFN-15 as acute treatment of migraine with or without aura in adults. The evidence is not strong as one of the two pivotal studies had borderline result for one co-primary endpoint and the data quality was not good (see section 3.1).

For Study 007, DFN-15 was significantly superior to placebo in achieving freedom from headache pain (Odds Ratio [OR] =2.0, p<0.001) and Screening MBS (OR=1.7, p=0.007) at 2 hours postdose. Study 006 met the MBS co-primary endpoint (OR=1.7, p=0.003). However, it failed on the co-primary endpoint of headache pain freedom although a positive trend was observed (OR=1.4, p=0.075). The effect of DFN-15 was generally consistent across demographic subgroups.

In the primary analyses of the co-primary endpoints, subjects who took rescue medication prior to the data collection at the 2-hour postdose time point were not properly handled. Additionally, a substantial number of subjects in the Full Analysis Set (FAS) were excluded from the primary analysis of MBS freedom. However, sensitivity analyses seemed to suggest that the results were not sensitive to the handling of intercurrent events and missing data.

2 INTRODUCTION

2.1 Overview

Two identical trials, DFN-15-CD-006 and DFN-15-CD-007 (referred to as Study 006 and Study 007 respectively thereafter), were conducted under IND 125585 to investigate the efficacy and safety of DFN-15, a new oral liquid formulation of celecoxib for the acute treatment of migraine in adults. Both trials were randomized, placebo-controlled studies, with two independently randomized double-blind (DB) periods. In the first double-blind (DB1) period, DFN-15 was used to treat a moderate to severe migraine attack. After another determination of eligibility, subjects were re-randomized into the second double-blind (DB2) period to treat another migraine attack at any pain level.

Two co-primary endpoints were evaluated on the first treated migraine attack in the DB1 period, including headache pain freedom at 2 hours postdose and absence of Screening most bothersome symptom (MBS) at 2 hours postdose. Study 007 achieved statistical significance on both co-primary endpoints. However, Study 006 failed on the co-primary endpoint of headache pain freedom (p=0.075), although it met the MBS co-primary endpoint.

The applicant proposed to use the two parts (DB1 and DB2) of Study 007 as 2 independent studies to support the efficacy of DFN-15, given the re-randomization and washout period between DB1 and DB2. However, this reviewer does not consider DB2 as an independent 2nd study and does not include it in this review (see details in section 5.1).

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directory: \\CDSESUB1\evsprod\NDA212157\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality was not good and there were discrepancies. For example, the usage of rescue medication recorded in the case report forms and electronic diary was not consistent. Additionally, site #745 was found to have a serious issue of noncompliance.

The Statistical Analysis Plan (SAP) was not submitted to the Agency for review prior to database lock and the SAP has flaws in handling intercurrent events for the primary analysis. The Clinical Study Report (CSR) does not have sufficient description and/or footnote for some of the tables and the reviewer had to check the programming codes to understand the details of the analyses.

3.2 Evaluation of Efficacy

3.2.1 Study 007

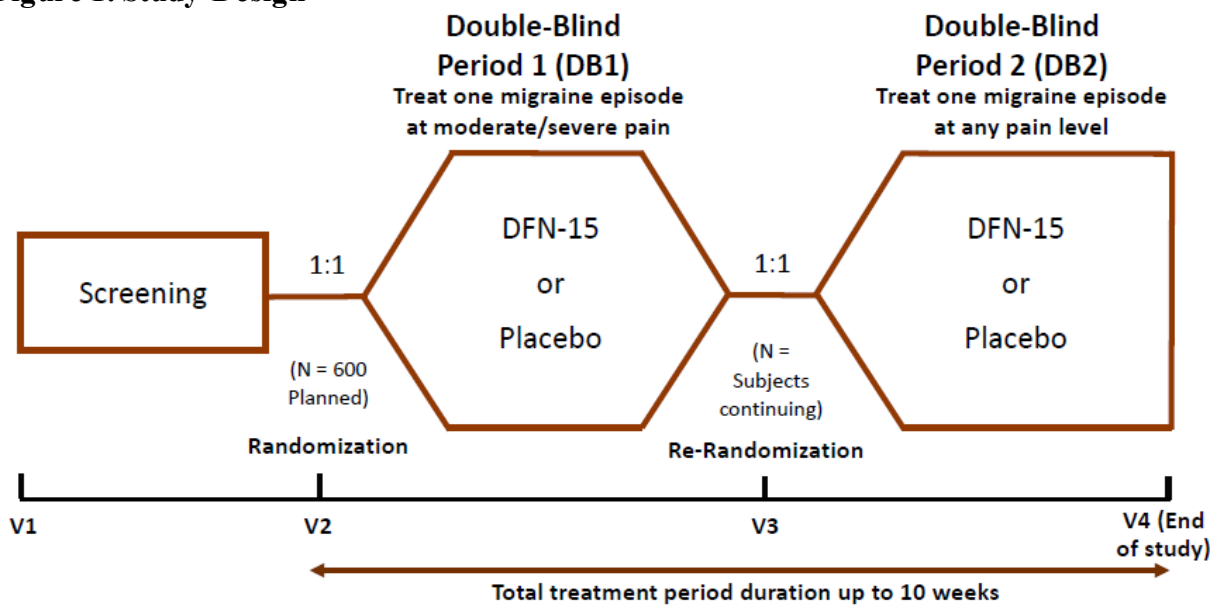
3.2.1.1 Study Design and Endpoints

Study 007 was initiated on December 13, 2016 and completed on October 06, 2017. The final protocol was dated May 9, 2017. The final Statistical Analysis Plan (SAP) was dated November 8, 2017, before the study database was locked and unblinded on November 30, 2017. The SAP was not submitted to the Agency for review prior to database lock.

Study Design

The study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in the US. Subjects who experienced 2 to 8 migraine attacks per month, with 14 or fewer headache days per month, were randomized in a 1:1 ratio to receive orally either DFN-15 or matching placebo to treat one migraine attack. The study consisted of 2 double-blind (DB) treatment periods. During DB1 period, 1 migraine attack was treated with study drug as soon as (and no more than 1 hour after) the subject experienced a moderate to severe headache pain. Subjects then returned to the study site within 2 to 7 days of the first treatment and, if continuing to be eligible, were re-randomized, independent of their previous treatment assignment, into DB2 period to treat another migraine of any pain level. Study drug was only to be used to treat a new migraine attack, not a recurrence. Subjects had the option to take rescue medication 2 hours after the medication was administered and after efficacy data was reported via electronic diary (eDiary).

Figure 1. Study Design



Efficacy Endpoints

The co-primary endpoints were

- The proportion of subjects who were pain-free 2 hours postdose in the DB1 period;
- The proportion of subjects who were free from their Screening most bothersome symptom (MBS) among nausea, photophobia, and phonophobia at 2 hours postdose in the DB1 period. A subject's Screening MBS was obtained via Migraine History assessment.

3.2.1.2 Statistical Methodologies

Analysis Populations for DB1

The Full Analysis Set (FAS) included all randomized subjects who took at least 1 dose of study drug during the DB1 period and had at least 1 post-baseline efficacy assessment for either pain or symptom (among nausea, photophobia, phonophobia).

Subjects who took rescue medication prior to the data collection at the 2-hour postdose time point and subjects who had mild or none pain level at predose were not included in the primary analyses. For each of the co-primary endpoints, subjects without respective post-baseline assessment were excluded. The MBS analysis additionally excluded subjects who did not report MBS at Screening or subjects who did not have their Screening MBS symptom present at predose (not necessarily designated as MBS at predose).

The Safety Set (SS) included all subjects who received at least 1 dose of DB study drug and recorded it in their eDiary.

Analysis of the Co-Primary Endpoints
Both co-primary efficacy endpoints were analyzed using Fisher's exact test. Missing primary efficacy endpoint data were imputed using the Last Observation Carried Forward (LOCF) in the primary analysis.

Sensitivity analysis using the observed data were conducted for the co-primary efficacy endpoints. Two additional analyses were planned, in which all subjects with missing assessments at 2 hours postdose were assigned as responders or non-responders respectively.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 622 subjects were randomized at 44 sites in the US. Of these subjects, 563 (90.5%) received at least 1 dose of DFN-15 or placebo and had at least 1 post baseline efficacy assessment and were included in the FAS. About 85% subjects completed the DB1 period. The most common reason for premature discontinuation was that subjects did not experience a migraine attack (18 [3%]; Table 1).

Table 1. Study 007: Subject Disposition in DB1 (Randomized Population)

	Placebo n (%) n=311	DFN-15 n (%) n=311	Total n (%) N=622
Safety Set	282 (90.7)	285 (91.6)	567 (91.2)
Full Analysis Set	280 (90.0)	283 (91.0)	563 (90.5)
Completed DB1 treatment period	266 (85.5)	265 (85.2)	531 (85.4)
Discontinued DB1 treatment period	43 (13.8)	42 (13.5)	85 (13.7)
Primary reason for discontinuation in DB1:			
Subject did not experience a migraine attack	11 (3.5)	7 (2.3)	18 (2.9)
Withdrawal by subject	7 (2.3)	9 (2.9)	16 (2.6)
Lost to follow-up	5 (1.6)	8 (2.6)	13 (2.1)
Other	4 (1.3)	6 (1.9)	10 (1.6)
Protocol deviation	4 (1.3)	4 (1.3)	8 (1.3)
Use of non-permitted medication during the study	1 (0.3)	4 (1.3)	5 (0.8)
Non-compliance with study drug	2 (0.6)	2 (0.6)	4 (0.6)
Adverse event	3 (1.0)	0	3 (0.5)
Study terminated by Sponsor	3 (1.0)	0	3 (0.5)
Physician decision	0	2 (0.6)	2 (0.3)
Pregnancy	2 (0.6)	0	2 (0.3)
Investigator request	1 (0.3)	0	1 (0.2)

There were 6 randomized subjects who were neither considered as having completed nor as having discontinued the DB1 treatment period as they didn't take DB1 dose (in eDiary record) even though they were marked as "completers" in the dataset.
Source: Table 4 of the CSR.

Overall, the demographic and baseline characteristics were balanced (Table 2). The mean age was 40 years and majority of the subjects were female (87%) and white (74%).

Table 2. Study 007: Demographics and Baseline Characteristics

	Placebo	DFN-15
Safety Set	**N=282**	**N=285**
Age (Years)		
n	282	285
Mean (SD)	40.1 (12.59)	40.5 (11.68)
Median	39.0	40.0
Min, Max	18, 74	19, 72
Sex, n (%)		
Male	40 (14.2)	33 (11.6)
Female	242 (85.8)	252 (88.4)
Race, n (%)		
American Indian or Alaska Native	0	1 (0.4)
Asian	6 (2.1)	5 (1.8)
Black or African American	50 (17.7)	75 (26.3)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
White	219 (77.7)	198 (69.5)
Other	7 (2.5)	4 (1.4)
Full Analysis Set	**280**	**283**
Subjects with MBS at Screening, n	279	282
Subjects with Screening MBS of nausea, n (%)	69 (24.6)	82 (29.0)
Subjects with Screening MBS of photophobia, n (%)	166 (59.3)	139 (49.1)
Subjects with Screening MBS of phonophobia, n (%)	44 (15.7)	61 (21.6)

Source: Table 9 and Table 14.2.5.1.5.a h of the CSR.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Analyses of the Primary Endpoints

Co-primary endpoint of headache pain freedom

The primary efficacy analysis on headache pain freedom demonstrated a statistically significant difference between the treatment groups ($p<0.001$), with higher percentage of patients achieving headache pain freedom at 2 hours postdose in the DFN-15 group (36%) compared with placebo group (22%). The odds ratio for headache pain freedom at 2 hours postdose was 2.00 (95% CI: 1.36, 2.94; Table 3).

Table 3. Study 007: Primary Analysis of Headache Pain Freedom

	Placebo	DFN-15
Number of assessments	263	275
Number of responses	57	98
Proportion (%) (95% CI)	21.7 (16.8, 27.1)	35.6 (30.0, 41.6)
P-value		< 0.001
Odds ratio (95% CI)		2.00 (1.36, 2.94)

This table excluded subjects who took rescue medications prior to the 2-hour time point, and subjects with predose pain level = mild or none.
The p-value was obtained from Fisher's exact test and the Confident Interval was obtained from logistic regression.
Source: Table 10 of the CSR, confirmed by the reviewer.

A total of 25 subjects in the FAS set were excluded from the primary analysis of headache pain freedom for the following reasons: (1) took rescue medication prior to the data collection at the 2-hour postdose time point, (2) had predose pain level = mild or none or missing, and (3) had no headache pain assessment by 2 hours postdose (Table 4).

Table 4. Study 007: Analysis Set for the Primary Analysis of Headache Pain Freedom

	Placebo (n)	DFN-15 (n)
Randomized into DB1	311	311
Full Analysis Set	280	283
Analyzed for DB1 2h postdose LOCF headache pain freedom	263	275
Excluded from DB1 2h postdose headache pain freedom analysis*	17	8
Took rescue medication prior to recording the 2h time point	8	4
No 2h postdose headache pain assessment	6	3
DB1 predose pain level = mild or none or missing	4	1

*Subjects may be excluded for multiple reasons.
Source: FDA reviewer.

Usually in migraine studies, subjects who took rescue medication prior to the 2-hour time point were considered treatment failures. Per the Agency's request in pre-NDA meeting, an analysis was conducted in which subjects who took rescue medications prior to the 2-hour time point were considered as treatment failures/non responders. The result was consistent with the primary analysis (Table 5).

Table 5. Study 007: Analysis of Headache Pain Freedom Including Subjects Who Took Rescue Medication as Non-responders

	Placebo	DFN-15
Number of assessments	271	279
Number of responses	57	98
Proportion (%) (95% CI)	21.0 (16.3, 26.4)	35.1 (29.5, 41.0)
P-value		<0.001
Odds ratio (95% CI)		2.03 (1.39, 2.98)

Source: Table 14.2.1.3.1.ah of the CSR, confirmed by the reviewer.

Additionally, subjects in the FAS set who did not have headache pain data by 2 hours postdose but had data from 2 to 24 hours postdose should also be included in the analysis with missing 2-hour data imputed. The reviewer used 2 methods to impute the missing data. One method is using the Next Observations Carried Backward (NOCB) for subjects who did not have data by 2 hours postdose but had data from 2 to 24 hours postdose. There were 3 additional responders (1 in DGN-15 and 2 in placebo group) using NOCB. The other method is a worst-case type of imputation in which only the additional NOCB responder in the placebo group were counted, while all subject in the DFN-15 group with missing 2-hour data were considered as non-responders. The results were consistent with the primary analysis (Table 6).

Table 6. Study 007: Analyses of Headache Pain Freedom with Missing Data Imputation

	Placebo	DFN-15
NOCB		
Number of assessments	276	282
Number of responses	59	99
Proportion (%) (95% CI)	21.4 (16.7, 26.7)	35.1 (29.5, 41.0)
P-value		<0.001
Odds ratio (95% CI)		1.99 (1.36, 2.90)
Worst-Case Imputation		
Number of assessments	276	282
Number of responses	59	98
Proportion (%) (95% CI)	21.4 (16.7, 26.7)	34.8 (29.2, 40.6)
P-value		<0.001
Odds ratio (95% CI)		1.96 (1.34, 2.86)

Subjects who took rescue medication prior to the 2-hour time point were assigned as non-responders.
Missing 2-hour data were imputed using LOCF if data prior to 2 hours postdose is available, otherwise NOCB or a worst-case type of imputation was used.
Source: FDA reviewer.

Inspection conducted by the Agency suggested that the site #745 had a serious issue of noncompliance. Analysis excluding this site resulted an odds ratio of 1.94 for the co-primary endpoint of headache pain freedom (95% CI: 1.32, 2.85; nominal p<0.001; results not shown in table).

Co-primary endpoint of MBS freedom

The primary efficacy analysis demonstrated a statistically significant difference in the proportion of subjects who were free from Screening MBS between the treatment groups (p=0.007). There were a higher proportion of responders for MBS freedom at 2 hours postdose in the DFN-15 group (58%) compared with placebo group (45%). The odds ratio for MBS freedom at 2 hours postdose was 1.68 (95% CI: 1.17, 2.43; Table 7).

Table 7. Study 007: Primary Analysis of Screening MBS Freedom

	Placebo	DFN-15
Number of assessments	232	232
Number of responses	104	134
Proportion (%) (95% CI)	44.8 (38.3, 51.5)	57.8 (51.1, 64.2)
P-value		0.007
Odds ratio (95% CI)		1.68 (1.17, 2.43)

This table excluded subjects who took rescue medications prior to the 2-hour time point, and subjects with predose pain level = mild or none.
The p-value was obtained from Fisher's exact test and the Confident Interval was obtained from logistic regression.
Source: Table 10 of the CSR, confirmed by the reviewer.

To be included in the primary analysis of Screening MBS freedom, subjects needed to have their Screening MBS symptom present at predose (but it did not have to be designated as MBS at predose), as was specified in the SAP. A substantial number of subjects in the FAS set were

excluded from the primary analysis on MBS freedom (48 in placebo group and 51 in NFN-15 group), mostly due to Screening MBS not presented at predose (Table 8).

Table 8. Study 007: Analysis Set for the Primary Analysis of MBS Freedom

	Placebo (n)	DFN-15 (n)
Randomized into DB1	311	311
FAS	280	283
Analyzed for DB1 2h postdose LOCF MBS freedom	232	232
Excluded from DB1 2h postdose LOCF MBS freedom analysis*	48	51
Screening MBS was not presented at predose	37	43
No Screening MBS	1	1
Took rescue medication prior to recording the 2h time point	8	4
No 2h postdose symptom assessment	5	2
DB1 predose pain level = mild or none or missing	4	1

*Subjects may be excluded for multiple reasons.
Source: FDA reviewer.

Subjects who took rescue medication prior to the 2-hour postdose time point should be considered as non-responders. The analysis including subjects who took rescue medication resulted an odds ratio of 1.68 (Table 9), same as the primary analysis. Additionally, in migraine studies, MBS is usually associated with the migraine episode being treated so that a treatment response of MBS freedom can be defined for all patients who took the study drug. For example, MBS of the treated migraine episode can be identified prior to taking the study drug. The analysis on predose MBS included additional 57 subjects who were excluded from the analysis on Screening MBS and showed similar result (OR=1.65; Table 9).

Table 9. Study 007: Analysis of MBS Freedom Including Subjects Who Took Rescue Medication

	Placebo	DFN-15
Absence of Screening MBS		
Number of assessments	237	236
Number of responses	104	134
Proportion (%) (95% CI)	43.9 (37.5, 50.5)	56.8 (50.2, 63.2)
P-value		0.006
Odds ratio (95% CI)		1.68 (1.17, 2.42)
Absence of predose MBS		
Number of assessments	267	263
Number of responses	120	151
Proportion (%) (95% CI)	44.9 (38.9, 51.1)	57.4 (51.2, 63.5)
P-value		0.004
Odds ratio (95% CI)		1.65 (1.17, 2.33)

Subjects who took rescue medication prior to the 2-hour time point were assigned as non-responders.
Source: FDA reviewer.

Inspection conducted by the Agency suggested Site 745 had a serious issue of noncompliance. Analysis excluding this site resulted an odds ratio of 1.70 for the co-primary endpoint of MBS freedom (95% CI: 1.17, 2.46; nominal p=0.007; results not shown in table).

3.2.2 Study 006

3.2.2.1 Study Design, Endpoints, and Statistical Methodologies

The study 006 was initiated on December 5, 2016 and completed on October 12, 2017. The final protocol was dated May 9, 2017. The original SAP was dated May 4, 2017 and the final SAP (Amendment 3.0) was dated 08 Nov 2017. The SAP was not submitted to the Agency for review prior to database lock.

The study design, endpoints, and statistical methodologies were the same as study 007.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 631 subjects were randomized at 41 sites in the US. Of these subjects, 567 (90%) received at least 1 dose of DFN-15 or placebo and had at least 1 post baseline efficacy assessment. About 86% patients completed the DB1 period. The most common reason for premature discontinuation was that subjects did not experience a migraine attack (25 [4%]; Table 10).

Table 10. Study 006: Subject Disposition in DB1 (Randomized Population)

	Placebo n (%) n=315	DFN-15 n (%) n=316	Total n (%) N=631
Safety Set	283 (89.8)	289 (91.5)	572 (90.6)
Full Analysis Set	280 (88.9)	287 (90.8)	567 (89.9)
Completed DB1 treatment period	264 (83.8)	280 (88.6)	544 (86.2)
Discontinued DB1 treatment period	47 (14.9)	34 (10.8)	81 (12.8)
Primary reason for discontinuation in DB1:			
Subject did not experience a migraine attack	15 (4.8)	10 (3.2)	25 (4.0)
Other	8 (2.5)	9 (2.8)	17 (2.7)
Protocol deviation	9 (2.9)	4 (1.3)	13 (2.1)
Non-compliance with study drug	3 (1.0)	4 (1.3)	7 (1.1)
Withdrawal by subject	3 (1.0)	4 (1.3)	7 (1.1)
Adverse event	4 (1.3)	0	4 (0.6)
Lost to follow-up	3 (1.0)	1 (0.3)	4 (0.6)
Investigator request	1 (0.3)	1 (0.3)	2 (0.3)
Pregnancy	0	1 (0.3)	1 (0.2)
Use of non-permitted medication during the study	1 (0.3)	0	1 (0.2)

There were 6 randomized subjects who were neither considered as having completed nor as having discontinued the DB1 treatment period as they didn't take DB1 dose (in eDiary record) even though they were marked as "completers" in the dataset.
Source: Table 4 of the CSR.

Overall, the demographic and baseline characteristics were balanced (Table 11). The mean age was 41 years and majority of the subjects were female (84%) and white (74%).

Table 11. Study 006: Demographics and Baseline Characteristics

	Placebo	DFN-15
Safety Set	**N=283**	**N=289**
Age (Years)		
n	283	289
Mean (SD)	40.4 (12.99)	41.4 (13.94)
Median	40.0	41.0
Min, Max	18, 73	18, 75
Sex, n (%)		
Male	38 (13.4)	52 (18.0)
Female	245 (86.6)	237 (82.0)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	3 (1.1)	1 (0.3)
Black or African American	63 (22.3)	64 (22.1)
Native Hawaiian or Other Pacific Islander	0	0
White	209 (73.9)	214 (74.0)
Other	8 (2.8)	10 (3.5)
Full Analysis Set	**280**	**287**
Subjects with MBS at Screening, n	278	283
Subjects with Screening MBS of nausea, n (%)	60 (21.4)	72 (25.1)
Subjects with Screening MBS of photophobia, n (%)	169 (60.4)	158 (55.1)
Subjects with Screening MBS of phonophobia, n (%)	49 (17.5)	53 (18.5)

Source: Table 9 and Table 14.2.5.1.5.a h of the CSR.

3.2.2.3 Results and Conclusions

3.2.2.3.1 Analyses of the Primary Endpoints

Co-primary endpoint of headache pain freedom

The primary efficacy analysis on headache pain freedom failed to show a statistical difference between the treatment groups (p=0.075), although there was a higher proportion of responders for headache pain freedom at 2 hours postdose in the DFN-15 group (33%) compared with placebo group (26%). The odds ratio for headache pain freedom at 2 hours postdose was 1.40 (95% CI: 0.97, 2.03; Table 12).

Table 12. Study 006: Primary Analysis of Headache Pain Freedom

	Placebo	DFN-15
Number of assessments	267	280
Number of responses	69	92
Proportion (%) (95% CI)	25.8 (20.7, 31.5)	32.9 (27.4, 38.7)
P-value		0.075
Odds ratio (95% CI)		1.40 (0.97, 2.03)

This table excluded subjects who took rescue medications prior to the 2-hour time point, and subjects with predose pain level = mild or none.
The p-value was obtained from Fisher's exact test and the Confident Interval was obtained from logistic regression.
Source: Table 10 of the CSR, confirmed by the reviewer.

A total of 20 subjects in the FAS set were excluded from the primary analysis of headache pain freedom for the following reasons: (1) took rescue medication prior to the data collection at the 2-hour postdose time point, (2) had predose pain level = mild or none, and (3) had no headache pain assessment by 2 hours postdose (Table 13).

Table 13. Study 006: Analysis Set for the Primary Analysis of Headache Pain Freedom

	Placebo (n)	DFN-15 (n)
Randomized into DB1	315	316
Full Analysis Set	280	287
Analyzed for DB1 2h postdose LOCF headache pain freedom	267	280
Excluded from DB1 2h postdose pain freedom analysis*	13	7
Took rescue medication prior to recording the 2h time point	6	5
No 2h postdose headache pain assessment	7	2
DB1 predose pain level = mild or none	0	1

*Subjects may be excluded for multiple reasons.
Source: FDA reviewer.

An analysis was conducted in which subjects who took rescue medications prior to the 2-hour time point were considered as treatment failures/non responders. The result was similar to the primary analysis (OR=1.42; nominal p=0.076; Table 14).

Table 14. Study 006: Analysis of Headache Pain Freedom Including Subjects Who Took Rescue Medication as Non-responders

	Placebo	DFN-15
Number of assessments	273	284
Number of responses	69	92
Proportion (%) (95% CI)	25.3 (20.2, 30.9)	32.4 (27.0, 38.2)
P-value		0.076
Odds ratio (95% CI)		1.42 (0.98, 2.05)

Source: Table 14.2.1.3.1.ah of the CSR, confirmed by the reviewer.

Additionally, the 9 subjects in the FAS set (7 in placebo group and 2 in DFN-15 group) who did not have data by 2 hours postdose but had data from 2 to 24 hours postdose should also be included in the analysis with missing 2-hour data imputed. Using the Next Observations Carried

Backward (NOCB) assigned 4 more responders (2 in each group) among these subjects, with an estimated odds ratio (OR) of 1.44 (nominal p=0.052; Table 15). For the worst-case type of imputation in which only the additional NOCB responder in the placebo group were counted while all subject in the DFN-15 group with missing 2-hour data were considered as non-responders, the results were consistent with the primary analysis (OR=1.40; nominal p=0.078; Table 15).

Table 15. Study 006: Analysis of Headache Pain Freedom with Missing Data Imputation

	Placebo	DFN-15
NOCB		
Number of assessments	280	286
Number of responses	71	94
Proportion (%) (95% CI)	25.4 (20.4, 30.9)	32.8 (27.5, 38.6)
P-value		0.052
Odds ratio (95% CI)		1.44 (1.00, 2.08)
Worst-Case Imputation		
Number of assessments	280	286
Number of responses	71	92
Proportion (%) (95% CI)	25.4 (20.4, 30.9)	32.2 (26.8, 37.9)
P-value		0.078
Odds ratio (95% CI)		1.40 (0.97, 2.01)

Subjects who took rescue medication prior to the 2-hour time point were assigned as non-responders.
Missing 2-hour data were imputed using LOCF if data prior to 2 hours postdose is available, otherwise NOCB or a worst-case type of imputation was used.
Source: FDA reviewer.

The applicant indicated that site #609 was an outlier because of its high placebo responder rate (75%) and reported a nominal statistical significance (p=0.02) for the analysis of 2-hour headache pain freedom after removing this site (n=27). However, there was no evidence of misconduct in this site and the removal of the site was not justified in the reviewer's opinion.

Co-primary endpoint of MBS freedom

The primary efficacy analysis on MBS freedom showed a statistically significant difference between the treatment groups (p=0.003). There were a higher proportion of responders for MBS freedom at 2 hours postdose in the DFN-15 group (59%) compared with placebo group (45%). The odds ratio for MBS freedom at 2 hours postdose was 1.75 (95% CI: 1.22, 2.52; Table 16).

Table 16. Study 006: Primary Analysis of Screening MBS Freedom

	Placebo	DFN-15
Number of assessments	231	241
Number of responses	104	142
Proportion (%) (95% CI)	45.0 (38.5, 51.7)	58.9 (52.4, 65.2)
P-value		0.003
Odds ratio (95% CI)		1.75 (1.22, 2.52)

This table excluded subjects who took rescue medications prior to recording the 2-hour time point, and subjects with predose pain level = mild or none.
The p-value was obtained from Fisher's exact test and the Confident Interval was obtained from logistic regression.
Source: Table 10 of the CSR, confirmed by the reviewer.

A substantial number of subjects in the FAS set were excluded from the primary analysis on MBS freedom (49 in placebo group and 46 in NFN-15 group; Table 17). The most common reasons for exclusion were that the Screening MBS was not presented at predose and subjects took medication prior to 2 hours postdose.

Table 17. Study 006: Analysis Set for the Primary Analysis of MBS Freedom

	Placebo (n)	DFN-15 (n)
Randomized into DB1	315	316
FAS	280	287
Analyzed for DB1 2h postdose LOCF MBS freedom	231	241
Excluded from DB1 2h postdose LOCF MBS freedom analysis*	49	46
Screening MBS was not presented at predose	41	37
No Screening MBS	2	4
Took rescue medication prior to recording the 2h time point	6	5
No 2h postdose symptom assessment	3	1
DB1 predose pain level = mild or none	0	1

*Subjects may be excluded for multiple reasons.
Source: FDA reviewer.

Subjects who took rescue medication prior to the 2-hour postdose time point should be considered as non-responders. The analysis including subjects who took rescue medication showed similar results (OR=1.72; Table 18) as the primary analysis. The analysis on predose MBS included additional 51 subjects who were excluded from the analysis on Screening MBS and showed consistent results (OR=1.75; Table 18).

Table 18. Study 006: Analysis of MBS Freedom Including Subjects Who Took Rescue Medication

	Placebo	DFN-15
Absence of Screening MBS		
Number of assessments	234	245
Number of responses	104	142
Proportion (%) (95% CI)	44.4 (38.0, 51.1)	58.0 (51.5, 64.2)
P-value		0.003
Odds ratio (95% CI)		1.72 (1.20, 2.47)
Absence of predose MBS		
Number of assessments	257	273
Number of responses	109	154
Proportion (%) (95% CI)	42.4 (36.3, 48.7)	56.4 (50.3, 62.4)
P-value		0.001
Odds ratio (95% CI)		1.75 (1.25, 2.48)

Subjects who took rescue medication prior to the 2-hour time point were assigned as non-responders.
Source: FDA reviewer.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Race

Table 19 to Table 22 are the results of the analyses by demographic subgroups. Overall, the DFN-15 group had a higher proportion of responders compared with placebo, except for some subgroups with small sample size.

Table 19. Study 007: Subgroup Analysis of Pain Freedom

	Placebo	DFN-15
Age: 18-34 years		
Number of assessments	101	96
Number of responses (Proportion %)	22 (21.8%)	36 (37.5%)
Odds ratio (95% CI)		2.15 (1.15, 4.04)
Age: 35-49 years		
Number of assessments	101	111
Number of responses (Proportion %)	23 (22.8%)	42 (37.8%)
Odds ratio (95% CI)		2.06 (1.13, 3.77)
Age: 50-64 years		
Number of assessments	55	64
Number of responses (Proportion %)	9 (16.4%)	19 (29.7%)
Odds ratio (95% CI)		2.16 (0.88, 5.27)
Age: ≥65 years		
Number of assessments	6	4
Number of responses (Proportion %)	3 (50.0%)	1 (25.0%)
Odds ratio (95% CI)		0.33 (0.02, 5.33)
Race: White		
Number of assessments	205	191
Number of responses (Proportion %)	40 (19.5%)	56 (29.3%)
Odds ratio (95% CI)		1.71 (1.07, 2.72)
Race: Black or African American		
Number of assessments	47	72
Number of responses (Proportion %)	15 (31.9%)	36 (50.0%)
Odds ratio (95% CI)		2.13 (0.99, 4.60)
Race: Asian		
Number of assessments	6	5
Number of responses (Proportion %)	0 (0.0%)	2 (40.0%)
Odds ratio (95% CI)		--
Race: Other		
Number of assessments	5	4
Number of responses (Proportion %)	2 (40.0%)	3 (75.0%)
Odds ratio (95% CI)		4.50 (0.25, 80.57)
Gender: Female		
Number of assessments	230	243
Number of responses (Proportion %)	51 (22.2%)	84 (34.6%)
Odds ratio (95% CI)		1.85 (1.23, 2.79)
Gender: Male		
Number of assessments	33	32
Number of responses (Proportion %)	6 (18.2%)	14 (43.8%)
Odds ratio (95% CI)		3.50 (1.13, 10.80)

Source: FDA reviewer.

Table 20. Study 007: Subgroup Analysis of MBS Freedom

	Placebo	DFN-15
Age: 18-34 years		
Number of assessments	92	89
Number of responses (Proportion %)	40 (43.5%)	53 (59.6%)
Odds ratio (95% CI)		1.91 (1.06, 3.46)
Age: 35-49 years		
Number of assessments	88	89
Number of responses (Proportion %)	40 (45.5%)	48 (53.9%)
Odds ratio (95% CI)		1.40 (0.78, 2.54)
Age: 50-64 years		
Number of assessments	48	52
Number of responses (Proportion %)	21 (43.8%)	33 (63.5%)
Odds ratio (95% CI)		2.23 (1.00, 4.98)
Age: ≥65 years		
Number of assessments	4	2
Number of responses (Proportion %)	3 (75.0%)	0 (0.0%)
Odds ratio (95% CI)		--
Race: White		
Number of assessments	179	157
Number of responses (Proportion %)	72 (40.2%)	87 (55.4%)
Odds ratio (95% CI)		1.85 (1.20, 2.85)
Race: Black or African American		
Number of assessments	43	65
Number of responses (Proportion %)	26 (60.5%)	41 (63.1%)
Odds ratio (95% CI)		1.12 (0.51, 2.47)
Race: Asian		
Number of assessments	6	4
Number of responses (Proportion %)	3 (50.0%)	1 (25.0%)
Odds ratio (95% CI)		0.33 (0.02, 5.33)
Race: Other		
Number of assessments	4	4
Number of responses (Proportion %)	3 (75.0%)	4 (100.0%)
Odds ratio (95% CI)		--
Gender: Female		
Number of assessments	207	207
Number of responses (Proportion %)	95 (45.9%)	122 (58.9%)
Odds ratio (95% CI)		1.69 (1.15, 2.50)
Gender: Male		
Number of assessments	25	25
Number of responses (Proportion %)	9 (36.0%)	12 (48.0%)
Odds ratio (95% CI)		1.64 (0.53, 5.09)

Source: FDA reviewer.

Table 21. Study 006: Subgroup Analysis of Pain Freedom

	Placebo	DFN-15
Age: 18-34 years		
Number of assessments	96	105
Number of responses (Proportion %)	23 (24.0%)	39 (37.1%)
Odds ratio (95% CI)		1.88 (1.02, 3.46)
Age: 35-49 years		
Number of assessments	108	95
Number of responses (Proportion %)	31 (28.7%)	33 (34.7%)
Odds ratio (95% CI)		1.32 (0.73, 2.39)
Age: 50-64 years		
Number of assessments	52	62
Number of responses (Proportion %)	13 (25.0%)	16 (25.8%)
Odds ratio (95% CI)		1.04 (0.45, 2.43)
Age: ≥65 years		
Number of assessments	11	18
Number of responses (Proportion %)	2 (18.2%)	4 (22.2%)
Odds ratio (95% CI)		1.29 (0.19, 8.53)
Race: White		
Number of assessments	195	208
Number of responses (Proportion %)	44 (22.6%)	64 (30.8%)
Odds ratio (95% CI)		1.53 (0.98, 2.38)
Race: Black or African American		
Number of assessments	61	61
Number of responses (Proportion %)	23 (37.7%)	23 (37.7%)
Odds ratio (95% CI)		1.00 (0.48, 2.08)
Race: Asian		
Number of assessments	3	1
Number of responses (Proportion %)	0 (0.0%)	1 (100.0)
Odds ratio (95% CI)		--
Race: Other		
Number of assessments	8	10
Number of responses (Proportion %)	2 (25.0%)	4 (40.0%)
Odds ratio (95% CI)		2.00 (0.26, 15.38)
Gender: Female		
Number of assessments	234	230
Number of responses (Proportion %)	61 (26.1%)	77 (33.5%)
Odds ratio (95% CI)		1.43 (0.96, 2.13)
Gender: Male		
Number of assessments	33	50
Number of responses (Proportion %)	8 (24.2%)	15 (30.0%)
Odds ratio (95% CI)		1.34 (0.49, 3.64)

Source: FDA reviewer.

Table 22. Study 006: Subgroup Analysis of MBS Freedom

	Placebo	DFN-15
Age: 18-34 years		
Number of assessments	82	97
Number of responses (Proportion %)	33 (40.2%)	59 (60.8%)
Odds ratio (95% CI)		2.31 (1.26, 4.20)
Age: 35-49 years		
Number of assessments	95	82
Number of responses (Proportion %)	42 (44.2%)	55 (67.1%)
Odds ratio (95% CI)		2.57 (1.39, 4.75)
Age: 50-64 years		
Number of assessments	44	46
Number of responses (Proportion %)	24 (54.5%)	25 (54.3%)
Odds ratio (95% CI)		0.99 (0.43, 2.27)
Age: ≥65 years		
Number of assessments	10	16
Number of responses (Proportion %)	5 (50.0%)	3 (18.8%)
Odds ratio (95% CI)		0.23 (0.04, 1.35)
Race: White		
Number of assessments	169	176
Number of responses (Proportion %)	72 (42.6%)	96 (54.5%)
Odds ratio (95% CI)		1.62 (1.06, 2.47)
Race: Black or African American		
Number of assessments	52	55
Number of responses (Proportion %)	30 (57.7%)	38 (69.1%)
Odds ratio (95% CI)		1.64 (0.74, 3.62)
Race: Asian		
Number of assessments	2	1
Number of responses (Proportion %)	0 (0.0%)	1 (100.0)
Odds ratio (95% CI)		--
Race: Other		
Number of assessments	8	9
Number of responses (Proportion %)	2 (25.0%)	7 (77.8%)
Odds ratio (95% CI)		10.50 (1.11, 98.91)
Gender: Female		
Number of assessments	208	200
Number of responses (Proportion %)	96 (46.2%)	122 (61.0%)
Odds ratio (95% CI)		1.82 (1.23, 2.71)
Gender: Male		
Number of assessments	23	41
Number of responses (Proportion %)	8 (34.8%)	20 (48.8%)
Odds ratio (95% CI)		1.79 (0.62, 5.12)

Source: FDA reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The applicant proposed to use the two parts (DB1 and DB2) of Study 007 as 2 independent studies to support the efficacy of DFN-15, given the re-randomization and washout period between DB1 and DB2. However, DB2 was designed to be an exploratory part of the study instead of formally answering a study question. The observations or measurements from the same subject were not independent, and consequently the outcome in DB1 would provide information on the outcome in DB2. For example, the probability of DB2 headache pain response was much greater (571%) for DB1 responders compared to DB1 non-responders. Therefore, the statistical tests and inferences for DB1 and DB2 were based on highly correlated data and were not independent. The sponsor claimed that conditional independence of DB1 and DB2 was achieved through a modeling strategy. However, that was just one analysis conducted on data from both DB1 and DB2, which was not equivalent to 2 analyses conducted on 2 independent datasets separately. Furthermore, if a proper 2nd trial was to be conducted, one of the common exclusion criteria in clinical trials would be "prior exposure to the study drug" (which was the exclusion criterion #2 in both studies 006 and 007). Thus, patients in DB1 of Study 007 would not be eligible to enroll into the 2nd trial. Consequently, DB2 can only be considered exploratory instead of an independent 2nd study.

The Statistical Analysis Plans (SAP) was not submitted to the Agency for review prior to database lock and the SAPs had flaws in handling intercurrent events for the primary analyses. Subjects who took rescue medication prior to the data collection at the 2-hour postdose time point were usually considered treatment failures in migraine studies. However, these subjects were excluded from the primary analyses in both studies. Additionally, a substantial number of subjects in the FAS were excluded from the primary analysis on MBS freedom, mostly due to the Screening MBS not presented at predose. Sensitivity analyses assessing the impact of intercurrent events and missing data yielded consistent results. Therefore, the handling of intercurrent events and missing data was not a major concern.

5.2 Collective Evidence

For Study 007, DFN-15 was significantly superior to placebo in achieving freedom from headache pain (OR=2.0, $p<0.001$) and Screening MBS (OR=1.7, $p=0.007$) at 2 hours postdose. Study 006 met the MBS co-primary endpoint (OR=1.7, $p=0.003$). However, it failed on the co-primary endpoint of headache pain freedom although a positive trend was observed (OR=1.4, $p=0.075$). The effect of DFN-15 was generally consistent across demographic subgroups.

5.3 Conclusions and Recommendations

The data overall provided evidence to support the efficacy of DFN-15 as acute treatment of migraine with or without aura in adults. The evidence is not strong as one of the two pivotal studies had borderline result for one co-primary endpoint and the data quality was not good (see section 3.1).

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/s/

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03/31/2020 08:42:46 AM

KUN JIN
03/31/2020 10:21:11 AM
I concur with the review.

HSIEN MING J HUNG
03/31/2020 10:32:50 AM