CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212157Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	212157
Link to EDR	\\cdsesub1\evsprod\nda212157\0000
Submission Date	07/05/2019
Submission Type	505 (b)(2)
Brand Name	ELYXYB™
Generic Name	celecoxib oral solution
Dosage Form and Strengths	Oral Solution (25 mg/mL) 120 mg in 4.8 mL supplied in (b) (4) disposable glass bottle
Route of Administration	Oral
Proposed Indication	For the acute treatment of migraine with or without aura in adults
Proposed Dose/Regimen	120 mg
Applicant	Dr. Reddy's Laboratories, Inc.
Associated IND	125585
OCP Review Team	Mariam Ahmed, PhD., and Sreedharan Sabarinath, PhD.

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1. EXECUTIVE SUMMARY

The Applicant, Dr. Reddy's Laboratories Limited (Dr. Reddy's), submitted a New Drug Application (NDA) for DFN-15 (ELYXYB™; Celecoxib Oral Solution, 25 mg/mL) through the 505(b)(2) regulatory pathway. The proposed indication is acute treatment of migraine with or without aura in adults. The applicant is relying on FDA's findings on safety of the approved prescription product Celebrex® capsules (NDA # 020998) as the listed drug (LD).

The applicant conducted 8 clinical studies with DFN-15 to support this application. These included four pilot clinical pharmacology (comparative bioavailability) studies in healthy adult subjects with prototype formulations of DFN-15, one Proof of Concept Phase 2 dose ranging study using a prototype formulation of DFN-15 (50 mg/mL), one pivotal comparative bioavailability study (DFN-15-CD-008) with the final to-be marketed formulation of DFN-15 (25 mg/mL) and the listed drug Celebrex® capsule 400 mg, and two Phase 3 studies (DFN-15-CD-006 and DFN-15-CD-007). Both Phase 3 studies used the final, to-be-marketed formulation of DFN-15.

The primary objectives of this review are:

- to evaluate the PK bridging of the proposed product to the LD (Celebrex ® capsules) and,
- to assess the adequacy of the proposed dosing recommendations for general and special populations.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this NDA and the application is acceptable from an OCP perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness:	Two identical, randomized, double blind (DB), placebo-controlled Phase 3 studies were conducted with DFN-15 in subjects with migraine (DFN-15-CD-006 and DFN-15-CD-007). The subjects were randomized in a 1:1 ratio in two separate double-blind (DB) periods to receive either the to-be-marketed formulation of DFN-15 120 mg or a matching

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	placebo. Subjects treated one moderate to severe migraine attack in the first DB treatment period (DB1) and, if eligible, were re-randomized into the second DB treatment period (DB2) to treat another migraine attack at any pain level. The co-primary endpoints in DB1 were headache pain freedom and absence of most bothersome symptom (MBS) at 2 hours postdose, compared between the DFN-15 group and placebo group. Pain freedom and MBS freedom at 2 h post dose was also assessed in DB2. For Study DFN-15-CD-007, DFN-15 was superior to placebo in achieving freedom from headache pain and MBS at 2 hours postdose. In Study DFN-15-CD-006 only the MBS co-primary endpoint was statistically significant, and the co-primary endpoint of headache pain freedom showed a positive trend favoring DFN-15. Please refer to the clinical and biometrics reviews for details.
General dosing instructions:	The recommended dose of ELYXYB is 120 mg given as an oral solution. ELYXYB may be administered with or without food. The maximum dosage in a 24-hour period is 120 mg.
Dosing in patient subgroups (intrinsic and extrinsic factors):	ELYXYB™ can be administered without regard to food as studied in Phase 3. The applicant is relying on the USPI of Celebrex® for information on the impact of intrinsic and extrinsic factors of celecoxib exposure. Dose adjustment is required for the following intrinsic factors: • 60 mg dose is recommended in patients with moderate hepatic impairment (Child-Pugh B) • Avoid use in severe hepatic impairment (Child-Pugh C) • Avoid use in severe renal impairment and ESRD (CLcr<30 mL/min) • Use 60 mg dose in patients who are known CYP2C9 poor metabolizers
Labeling:	The proposed labeling in general is acceptable.

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Bridge between the to-be-marketed and clinical trial formulations:	No bridging is necessary. The to-be-marketed formulation is the same as the formulations used in the Phase 3 studies and in the pivotal PK bridging study.
Bridge between the to-be-marketed formulation and the RLD:	To establish the PK bridge between ELYXYB™ and the LD, Celebrex® capsules, the applicant conducted a relative bioavailability study, DFN-15-CD-008. The peak concentration (C_{max}) and the extent of absorption (AUC_{inf}) of ELYXYB™ under fasting conditions was 42% and 72% lower, respectively, compared to 400 mg Celebrex under fed conditions. With high fat food, the C_{max} of celecoxib from ELYXYB™ decreased by about 50% compared to fasting conditions. There were no changes in AUCs observed between fasting and fed administration. The Office of Clinical Pharmacology consulted the Office of Study Integrity and Surveillance (OSIS) to inspect the analytical and the clinical sites for Study DFN-15-CD-008. The clinical site was inspected, and the final inspection classification is No Action Indicated (NAI). OSIS concluded that no inspection is warranted for the analytical site as the same site was inspected recently with an inspection classification of No Action Indicated (NAI). Therefore, based on the study DFN-15-CD-008, the applicant can rely on the agency's findings of safety for Celebrex® capsules. The applicant has provided their own studies to support the efficacy of their proposed product.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The exact mechanism of action of celecoxib in acute migraine is not known. It is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase2 (COX2).

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2.2 Dosing and Therapeutic Individualization

The recommended dose of ELYXYB is 120 mg given as an oral solution. ELYXYB may be administered with or without food. The maximum dosage in a 24-hour period is 120 mg.

2.2.2 Therapeutic individualization

Dose adjustment is required for patients with moderate hepatic impairment (Child-Pugh B) and in patients who are known CYP2C9 poor metabolizers (*3/*3). Use 60 mg dose in these patients. Avoid use in patients with severe hepatic impairment (Child-Pugh C) and severe renal impairment and in ESRD (CLcr <30 mL/min).

These recommendations are based on the information provided in the USPI of the listed drug Celebrex® capsules.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed package insert for ELYXYB™ and finds it generally acceptable.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

ELYXYB™ (DFN-15; Celecoxib Oral Solution, 25 mg/mL) is an oral solution formulation of celecoxib. The drug product is filled in a 10 mL amber color glass bottle fitted with a child resistant cap. Each DFN-15 product contains a deliverable dose of 120 mg celecoxib in 4.8 mL. The applicant is pursuing a 505(b)(2) pathway, using Celebrex® capsules (NDA# 020998) as the listed drug.

At the End-of-Phase 2 (EoP2) meeting (August 30th, 2016), the Agency concurred with the applicant that the comparative bioavailability study (Study DFN-15-CD-008) can provide the necessary clinical bridge for the to-be-marketed formulation of DFN-15 to Celebrex®. At the pre-NDA meeting (August 23rd, 2018), the Agency noted that a high fat meal resulted in reduction of DFN-15's C_{max} and AUC_{2h} by ~ 50%, as compared to the fasting state and

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recommended conducting a subgroup analysis for subjects who received DFN-15 in the pivotal studies under fed condition.

The listed drug, Celebrex®, is available as 50, 100, 200, and 400 mg capsules and is approved for several indications: osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients 2 years and older, ankylosing spondylitis, acute pain, and primary dysmenorrhea. In adults, the approved dosage for these indications ranges from 200 mg daily to 400 mg daily. The recommended dose for acute pain is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed. As per Celebrex's prescribing information, Celebrex at doses up to 200 mg twice daily, can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Following 120 mg of ELYXYB administration under fasting condition in 24 healthy subjects, the median plasma T_{max} 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 fed condition. The mean (CV%) peak concentration (C_{max}) and the extent of absorption (AUC) of celecoxib from 120 mg of ELYXYB under fasting conditions was 993 ng/mL (21.9%) and 3568 ng.hr/mL (38.5%), respectively. With high fat food, T_{max} of celecoxib from ELYXYB was 3 hours (range 0.55 to 4) with about 50% decrease in C_{max} and no change in AUC_{inf} compared to fasting condition.

Dose proportionality was demonstrated for DFN-15 over a dose range of 120 mg to 240 mg. While the applicant did not study the dose proportionality for this solution for doses below 120 mg, Celebrex® has linear PK over the dose range 50 mg to 200 mg. Given the relative bioavailability of ELYXYB relative to Celebrex®, a dose of 120 mg ELYXB is similar to ~ 100 mg of Celebrex® in terms of total exposure (AUC_{inf}) and to ~200 mg of Celebrex® in terms of C_{max}. Please refer to the USPI of Celebrex® for detailed information on the clinical pharmacology of celecoxib[1].

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Two randomized, Phase 3, double blind (DB), placebo-controlled studies with a similar study design were conducted with DFN-15 in subjects with migraine (DFN-15-CD-006 and DFN-15-CD-

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020998s054lbl.pdf

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007). Male and female subjects 18 to 75 years old, inclusive, previously diagnosed with acute migraine, who had acute migraine that fit the ICHD-3 criteria, did not have medication overuse, and experienced 2 to 8 migraine attacks (with or without aura) per month with 14 or fewer headache days per month and at least 48 hours of headache-free time between migraine attacks were enrolled. The subjects were randomized in a 1:1 ratio in two separate double-blind (DB) periods to receive either the to-be-marketed formulation of DFN-15 120 mg or a matching placebo orally. Subjects treated 1 moderate to severe migraine attack in the first DB treatment period (DB1) and, if eligible, were re-randomized into the second DB treatment period (DB2) to treat another migraine attack at any pain level. In Study DFN-15-CD-007, a total of 531 patients completed the DB1 and a total of 491 re-randomized patients completed the DB2. Similarly, in Study DFN-15-CD-006, a total of 544 patients completed DB1 and a total of 504 re-randomized patients completed the DB2.

The co-primary endpoints in DB1 were headache pain freedom and absence of most bothersome symptom (MBS) at 2 hours postdose, compared between the DFN-15 group and placebo group. Pain freedom and MBS freedom were also assessed in DB2.

In DFN-15-CD-007, DFN-15 was superior to placebo for both co-primary endpoints. Both endpoints were statistically significant in the DB2 as well (Figure 1). In DFN-15-CD-006, only the MBS co-primary endpoint was statistically significant, and the co-primary endpoint of headache pain freedom showed a positive trend favoring DFN-15. Please refer to the clinical and biometrics reviews for details. (Figure 2).

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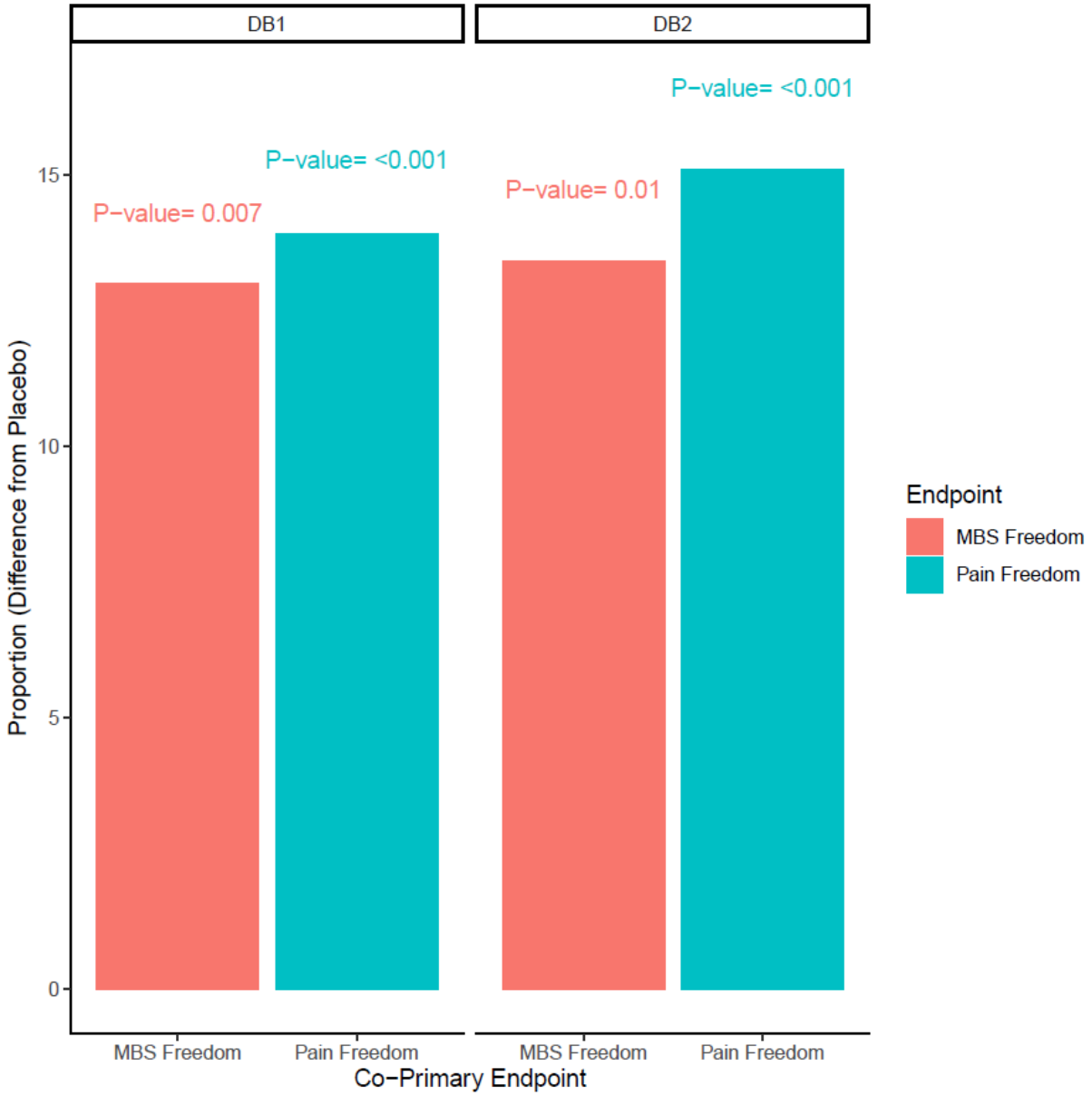
Figure 1: Proportion of Patients Achieving Pain freedom and MBS (Difference from Placebo) in Both Double-Blind Periods: Study DFN-CD-007



Source: Figure Created by The Reviewer Based on DFN-15-CD-007 CSR Table 10 and Table 14.

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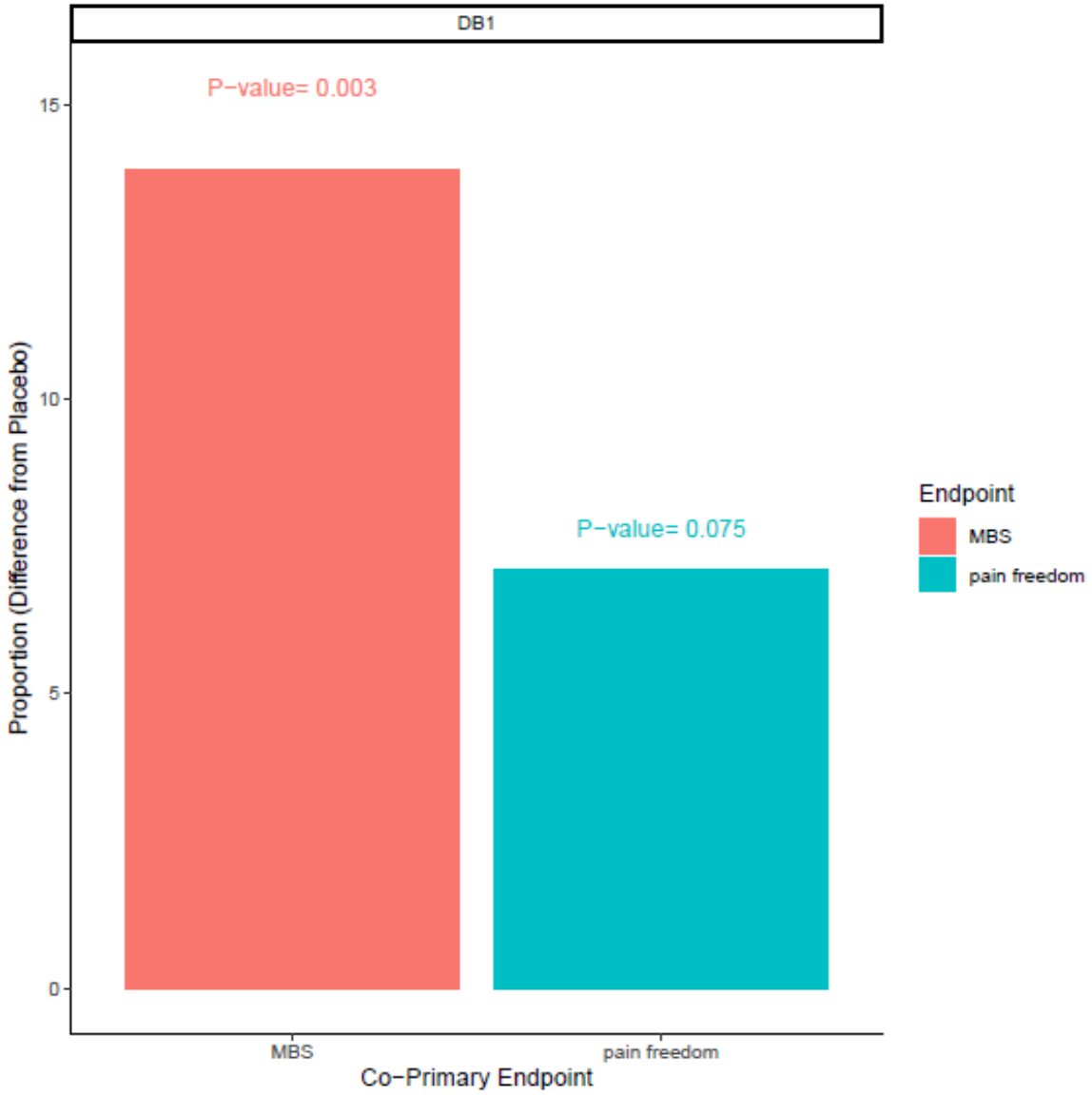
Figure 2: Proportion of Patients Achieving Pain freedom and MBS (Difference from Placebo) in Double-Blind Period 1: Study DFN-CD-006



Source: Figure Created by The Reviewer Based on DFN-15-CD-007 CSR Table 10

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dose of 120 mg, as tested in Phase 3 studies, is acceptable.

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The applicant indicted that the choice of the 120 mg dose for the pivotal Phase 3 clinical studies was based on a phase 2 study (DFN-15-CD-002) which evaluated 2 dose levels: 120 mg and 240 mg. Study DFN-15-CD-002 was a proof of concept (POC), randomized, placebo-controlled, DB, 3-treatment, 6-sequence, 3-period crossover study to assess the proportion of patients who achieved pain freedom at 2 hours postdose in a moderate to severe migraine attack. Freedom of the MBS at 2 hours was assessed as a secondary endpoint. Subjects were randomized to receive 3 treatments [DFN-15 120 mg (N=51), DFN-15 240 mg (N=51), and placebo (N=53)] in a crossover design with randomized treatment sequencing. Primary efficacy results showed only numerical difference in pain freedom response rate between DFN-15 treatment group and placebo with no statistically significant difference between treatment groups at 2 hours postdose (29.2% for DFN-15 120 mg, 26.1% for DFN-15 240 mg, and 17.6% for the placebo group[2]). Likewise, only numerical differences were observed between DFN-15 treatment group and placebo in MBS freedom response rate (50% for DFN-15 120 mg, 39.5% for DFN-15 240 mg, and 28.2% for the placebo group[3]). Overall, the numerical differences in response rates supported further evaluation of DFN-15 in a fully powered study.

Since no clear dose-response relationship was observed between 120 and 240 mg dose in the Phase 2 study (DFN-15-CD-002), a dose of 120 mg of DFN-15 which elicited maximal clinical response (headache pain freedom at 2 hours) was selected for the two Phase 3 studies.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic/extrinsic factors?

Hepatic/Renal Impairments and CYP2C9 Metabolizing Phenotypes

As per Celebrex® prescribing information, the daily recommended dose of Celebrex® capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of Celebrex® in patients with severe hepatic impairment is not recommended. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. The prescribing information recommends lowering the starting treatment at half the lowest recommended dose in poor metabolizers. Celebrex® is not recommended in patients with severe renal insufficiency.

ELYXB is intended to be a single use per migraine attack per day and has a deliverable dose of 120 mg celecoxib in 4.8 mL solution (See section 3.1). Patients with moderate hepatic impairment or those who are poor CYP2C9 metabolizers are instructed to receive 2.4 mL of the

[2] Using LOCF for missing data

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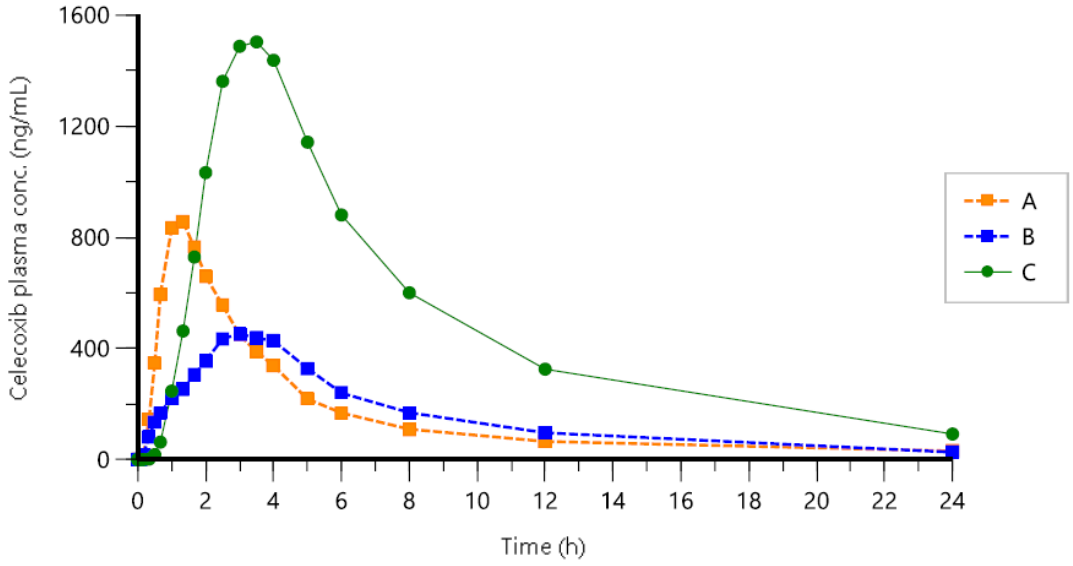
drug product (equal to 60 mg). An oral dosing syringe is recommended to measure and deliver the recommended dose accurately.

Food Effect

Following high-fat and high-calorie meal, no effect of food on celecoxib total AUC was observed. However, a 50% decrease in celecoxib peak concentrations with an associated T_{max} delay of 2 hours was found. The Celecoxib early exposure up to 2 hours post-dose were ~66% lower under fed conditions compared to fasting conditions. The PK profiles of celecoxib following administration of DFN-15 120 mg under both fasting and fed states are presented in Figure 3. The effect of different meal content or timing of food administration on PK was not studied.

Figure 3: Arithmetic Mean Plasma Celecoxib Concentration-Time Profiles Following Administration of: DFN-15 120 mg under Fasting State (Treatment A), DFN-15 120 mg under Fed State (Treatment B), and Celebrex® 400 mg Capsules under Fed State (Treatments C)



A: DFN-15 (Celecoxib Oral Solution, 25mg/mL), 120 mg under fasting state
B: DFN-15 (Celecoxib Oral Solution, 25 mg/mL), 120 mg under fed state
C: Celebrex capsules 400 mg under fed state

Notably, the phase 3 efficacy studies were conducted without regard to food. However, there was a concern that lower exposure in the first 2 hours and delayed T_{max} as a result of food effect may affect the efficacy. In the absence of dose-response information for doses lower than 120 mg, the agency recommended the sponsor to collect information on the timing,

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composition, and type of meal during the phase 3 studies and recommended the applicant to conduct a subgroup analyses by fast/fed status of the study subjects for the co-primary endpoints.

The applicant reported the impact of subject-reported predose timing of food intake (≤4 hours prior to dosing (non-fasting) and >4 hours prior to dosing (fasting)), and for non-fasting subjects, by food amount (meal vs snack) and food fat content (high vs low fat) and food type (meal vs. snack) on the efficacy. The number of subjects included in these analyses for Study DFN-15-CD-007 is presented at Table 1. Results of food effect on the proportion of patients who achieved pain freedom or MBS freedom over the first 2 hours for Study DFN-15-CD-007 is presented in Figure 4. These analyses revealed that the impact of fed condition on efficacy endpoints is not consistent across endpoints or across double blind periods, suggesting that food has no significant impact on efficacy. Additional analyses conducted by the reviewer also confirmed these findings. Moreover, Study DFN-15-CD-006 also showed similar proportion of patients administered DFN-15 120 mg with food and results of food effect evaluations were consistent with that from Study DFN-15-CD-007. This suggests that the differences in the primary outcome between Study DFN-15-CD-007 and Study DFN-15-CD-006 is unlikely to be related to food effect. Please refer to Section 4.3 for more details.

Table 1: Number of subjects per each treatment group in each dosing period (DB1 and DB2): Study DFN-15-CD-007

Information on food intake	**DB1**		**DB2**	
	Placebo	**DFN-15**	**Placebo**	**DFN-15**
Food intake > 4 h*	71	62	62	67
Food intake <=4 h	208	219	184	176
High Fat	76	85	67	69
Low Fat	132	134	117	107
Meal	126	139	119	101
Snack	82	80	65	75

*considered as fasting state for analysis

Source: Tables created by the reviewer based on Study DFN-15-CD-007: Tables 14.2.4.8.1-4.ah, Tables 14.2.4.9.1-4.ah, Tables 14.2.4.9.2.ah, and Tables 14.2.4.10.1-4.ah.

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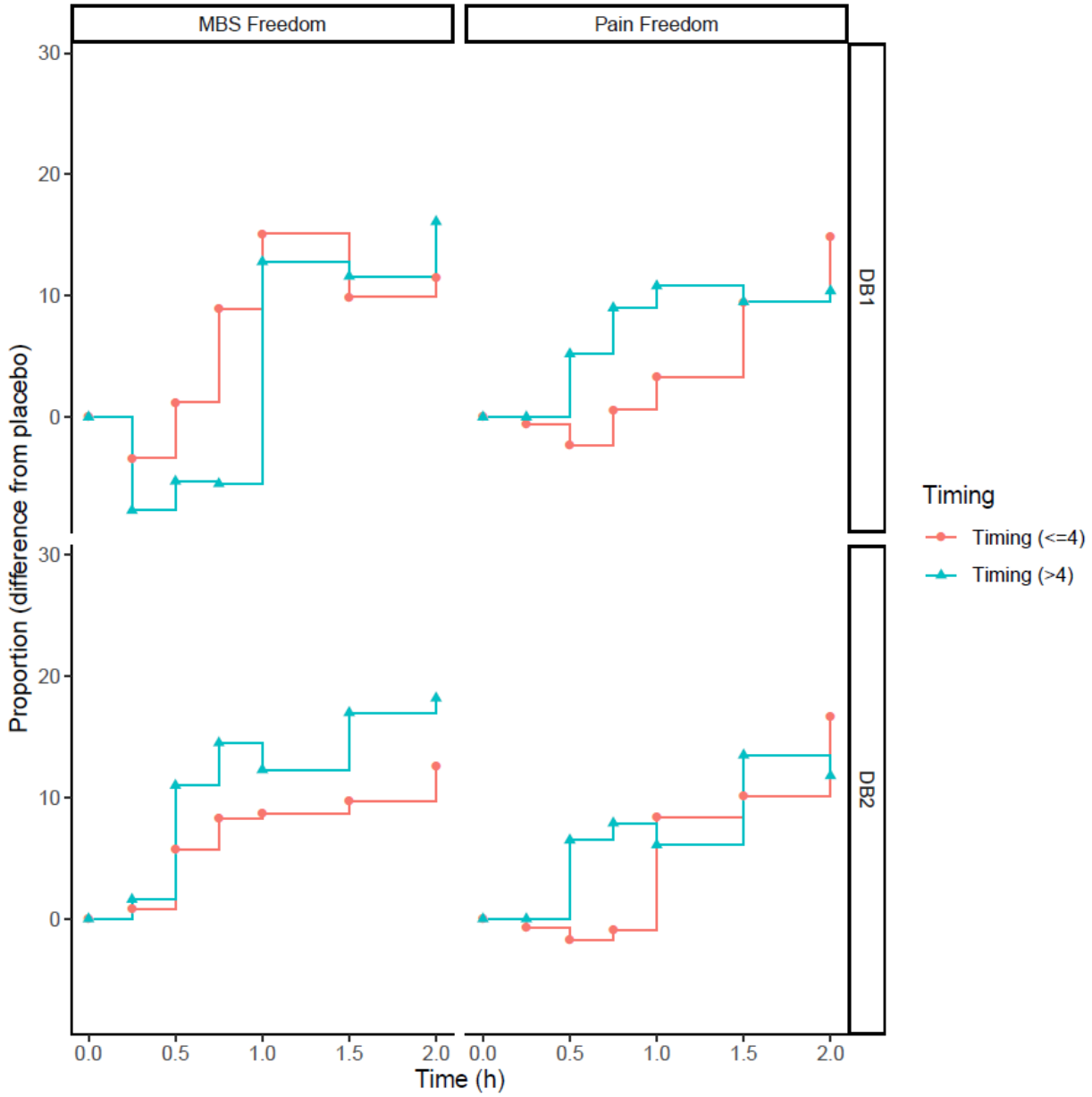
Figure 4: Proportions of Patients Achieving Pain freedom and MBS freedom (Difference from Placebo) in Both Double-Blind Periods Stratified by Fed Conditions Over the First 2 Hours based on A) Timing of Food (i.e. ≤4 hours vs >4 hours; B) Food Content in the Subset Who Administered Food in ≤4 hours Prior to Dosing; C) Food Type in the Subset Who Administered Food in ≤4 hours Prior to Dosing: Study DFN-CD-007

A) Timing of Food (i.e. <=4 hours vs >4 hours)



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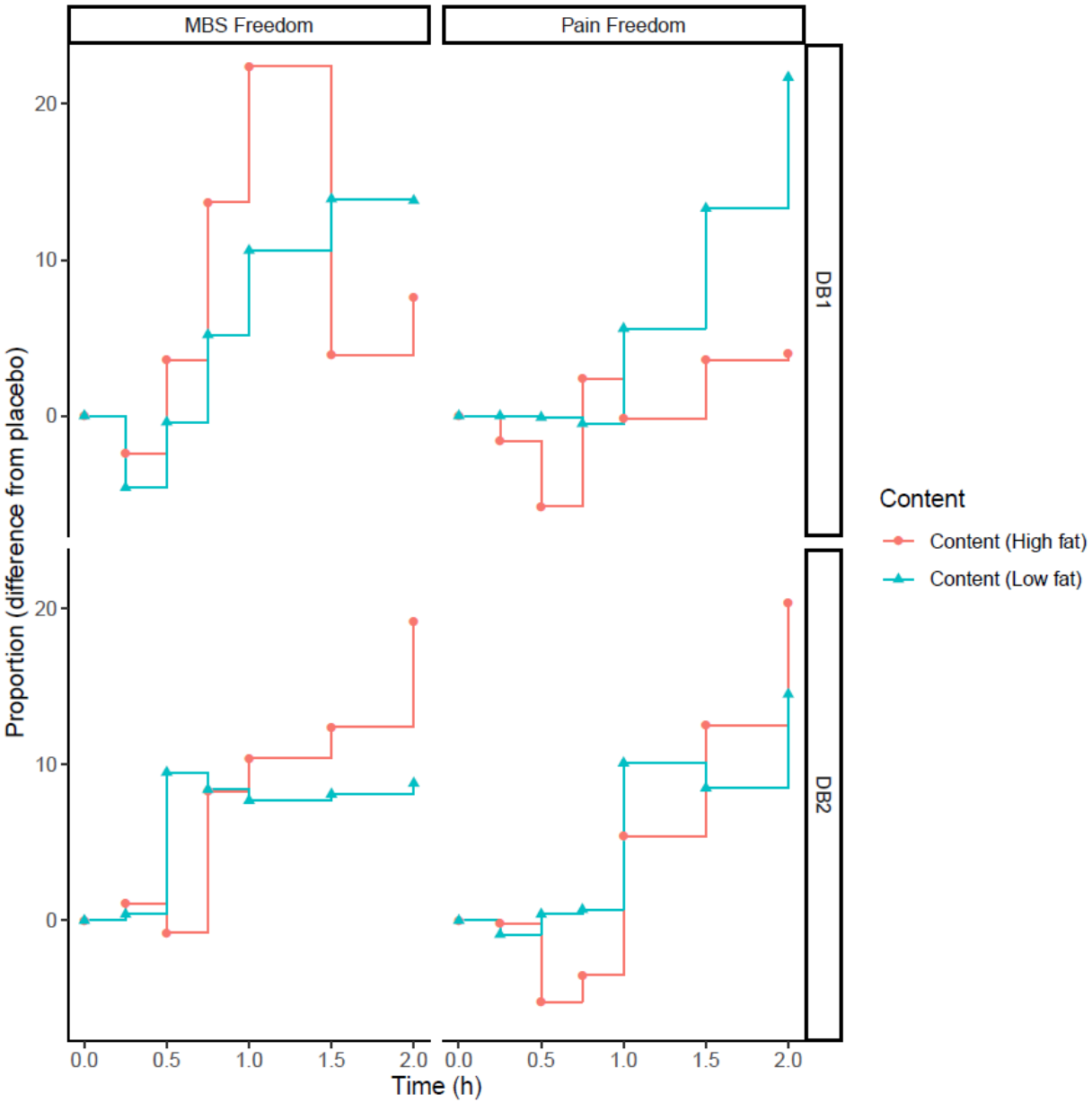
B) Food Content in the Subset Who Administered Food in ≤4 hours Prior to Dosing



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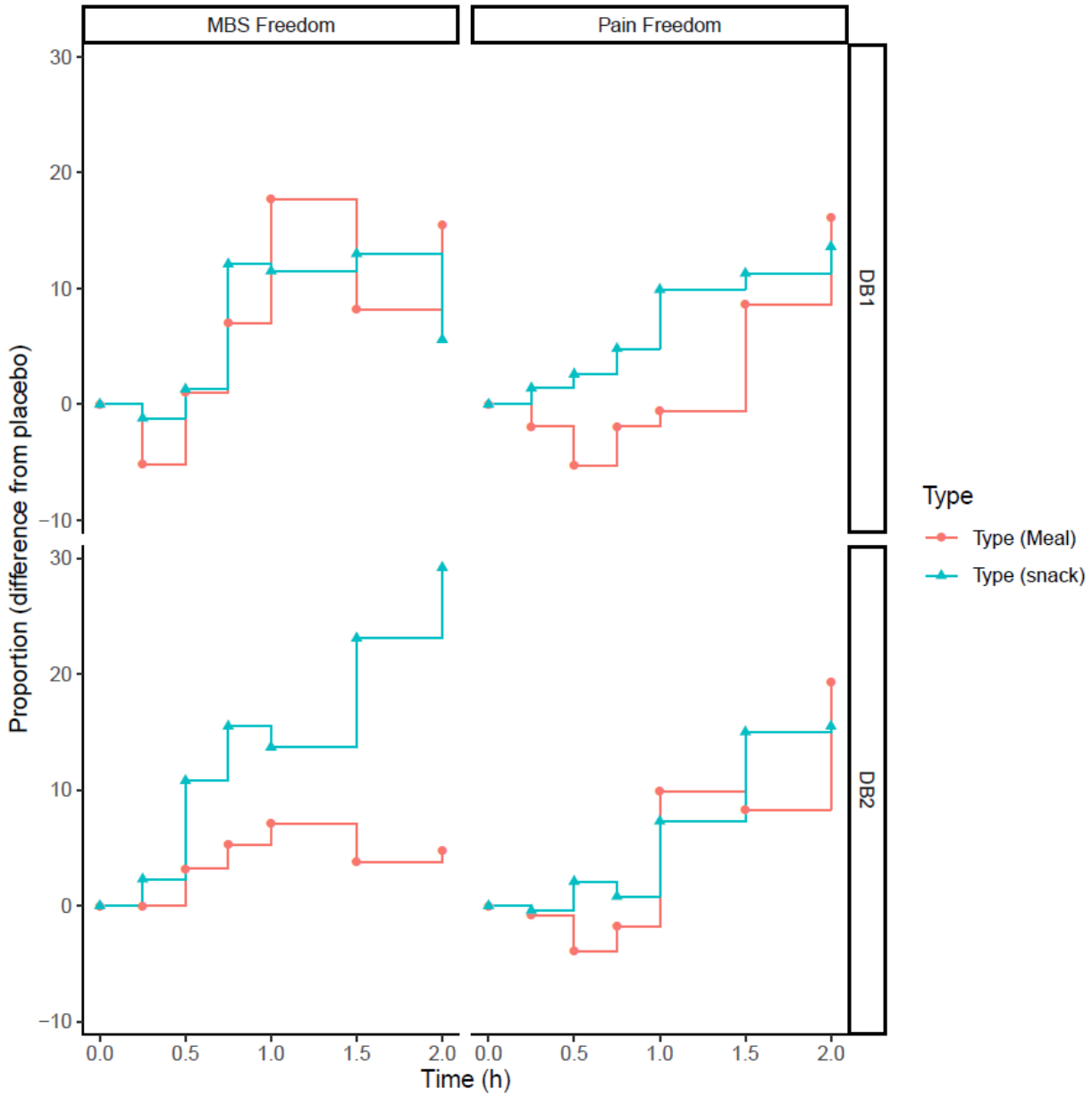
C) Food Type in the Subset Who Administered Food in ≤4 hours Prior to Dosing



Source: Figure Created by the Reviewer Based on Post-hoc Food Effect Analyses in Study DFN-15-CD-007.

The analyses conducted by the applicant indicates no significant impact of food intake on efficacy. However, it should be noted that these analyses have several limitations. Notably, the dedicated food effect study tested the worst-case scenario with high fat, high calorie meal and

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the proportion of participants in the Phase 3 studies who reported administering such meals with ELYXYB were low. Similarly, the subjects who reported taking a meal >4 hours before administering ELYXYB were considered as in "fasted state" for the purpose of this analysis. Unadjusted analyses with low sample size can affect our ability to derive firm conclusions. Since the two Phase 3 studies that demonstrated efficacy of ELYXYB were carried out without any dietary restrictions, and there may be practical limitations to have dietary restrictions with a drug intended to treat acute migraine, we recommend administration of ELYXYB without regard to food.

3.3.4 Is the PK bridging information provided in the application adequate?

Bridging between the clinical trial formulations and the to-be-marketed formulation:

The pivotal PK study and the Phase 3 studies were conducted using to be marketed formulation. Therefore, no PK bridging study is necessary.

Bridging between the to-be-marketed formulation and the LD Celebrex®:

The applicant conducted Study DFN-15-CD-008 to establish the PK bridge between the to-be-marketed formulation and Celebrex®. This was a single-dose, single-center, randomized, three-period crossover study in healthy subjects (N=24) designed to assess the comparative bioavailability of single dose of 120 mg DFN-15 oral solution under fasting condition relative to 400 mg Celebrex® capsule under fed condition and the food effect on the rate and extend of absorption of 120 mg DFN-15.

The plasma celecoxib AUC_{last} and AUC_{inf} following administration of DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg under fasting conditions were approximately 73% and 72% lower compared to the 400 mg Celebrex® capsule administered under fed conditions. The peak levels were also lower by approximately 43% for the DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg compared to the Celebrex® capsule.

The plasma celecoxib AUC_{last} and AUC_{inf} following administration of DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg under fed and fasting conditions were similar. However, C_{max} decreased to approximately half that observed under fasting conditions and was delayed by 2 hours after a high-fat meal.

The PK profiles of celecoxib following administration of Celebrex® 400 mg capsules under fed state and DFN-15 120 mg under both fasting and fed states are presented in Figure 3.

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4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Celecoxib is quantified in plasma samples from different clinical studies using validated liquid chromatography tandem mass spectrometry (LC/MS/MS) methods. The bioanalytical validation method for the pivotal PK bridging study was reported in ZZ41514-01 study report. Briefly, celecoxib and its internal standard Celecoxib-d7 were extracted from Human plasma using Liquid extraction technique. The extracted samples were analyzed using reverse phase chromatography and detected in positive MRM mode using APCI technique in Mass spectrometer. Quantitation was determined using a weighted linear regression analysis (1/concentration2) of peak area ratios of the analyte and internal standard. Summary of the performance characteristics and validation attributes for plasma apomorphine are provided in Table 2. To demonstrate that the analysis of incurred sample concentrations was reproducible for the bioanalytical method, 132 study samples were re-assayed. The results from this evaluation demonstrate that 96.2% of the pairs matched and hence the method is considered reproducible.

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Table 2: Validation Study Summary for Study DFN-15-CD-008.

Method	ZZ41514-01
Celecoxib	
Methodology	LC-MS/MS
Biological Matrix	Human plasma
Internal Standard (IS)	d7-Celecoxib
Calibration Curve	10 - 2500 ng/mL
QC concentrations	10,30,150, and 1900 ng/mL
Accuracy, and Precision	
QC Inter-run accuracy, range (%Bias)	-2.1 to 4.7%
QC Inter-run precision, range	3.0 to 6.6%
QC Intra-run accuracy, range (%Bias)	1.2 to 8.2%
QC Intra-run precision, range	1.2 to 8.2%
Selectivity and Specificity	No significant interference at the retention time and mass transition of celecoxib was observed from endogenous components or of d7-celecoxib (IS) in any of the 10-human plasma (EDTA) lots screened
Stability	
Short term stability	24 hours in polypropylene tubes at ambient temperature under white light
Long term stability	Long-Term Stability: 768 days in polypropylene tubes at -20°C Long-Term Stability for Stock Solutions (Stock): 517 days at approximately 400 µg/mL in methanol in a polypropylene container at -20°C Post-Preparative Stability: 200 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 145 hours in a polypropylene 96
Freeze and thaw stability	6 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light

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Reviewer's Comments:

The methods satisfied the criteria for method validation and application to routine analysis as per the FDA Guidance for Industry: Bioanalytical Method Validation[3], and hence are acceptable.

4.2 Bridging to the RLD and Dose Proportionality of the To-be-marketed Product

Bridging Studies

Study DFN-15-CD-008

Title of Study:

An Open-Label, Three-Way, Randomized, Single Dose Crossover Study Comparing Bioavailability of DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg of Dr. Reddy's Laboratories Limited, India Under Fasting Conditions Versus Celebrex® (Celecoxib) 400 mg Capsules of G.D. SEARLE LLC Under Fed Conditions and to Determine Food-Effect of DFN-15 in Healthy Adult Subjects

Objectives:

The primary objectives are to evaluate the single-dose comparative bioavailability (BA) of the test formulation, DFN-15 (Celecoxib) Oral Solution (25 mg/mL), 120 mg under fasting conditions relative to Celebrex® (celecoxib) capsules 400 mg under fed conditions in healthy adult subjects and To determine effect of food on the single-dose BA of the test formulation, DFN-15 (Celecoxib) Oral Solution (25 mg/mL), 120 mg in healthy adult subjects.

Methodology:

This was an open-label, randomized, 3-treatment, 3-period, 6-sequence, crossover study. Subjects received a single oral 120 mg dose of DFN-15 (celecoxib oral solution 25 mg/mL) under fasting conditions (Treatment A) in one treatment period, a single oral 120 mg dose of DFN-15 under fed conditions (Treatment B) in another treatment period, and a single oral 400 mg dose of celecoxib capsules under fed conditions (Treatment C) in the third treatment period according to their assigned randomization sequences. Each treatment was followed by blood sampling (including pre-dose samples) up to 72 hours post-dose for the determination of

[3] Available from: [https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf].

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celecoxib pharmacokinetics (PK). There was a washout period of at least 7 days between treatment administrations.

Study Population:

A total of 24 healthy, adult, non-tobacco using subjects were enrolled in the study and 23 subjects completed the study. Subject (b) (6) (Treatment Sequence BAC) was withdrawn on Day 1 of Period 3 (Treatment C) as the subject tested positive for a restricted substance (cocaine) upon urine screen. The data from 24 subjects were included in the PK and safety analyses.

Pharmacokinetics:

Blood samples for PK assessments of celecoxib were collected from all subjects at the following time points: sampling before dosing (pre-dose or 0 hour), followed by sampling at 0.08, 0.17, 0.33, 0.5, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0, and 72.0 hours after dosing.

Statistical Methods:

The ratio of geometric least-square means (Geo LSM) (Treatment A/Treatment C and Treatment B/Treatment A) and their 90% confidence interval (CI) based on the ANOVA of the ln-transformed primary PK data, were calculated for C_{max}, AUC_{last}, AUC_{inf} (primary) and, $AUC0_{0.25h}$, $AUC0_{0.5h}$, AUC_{1h}, and AUC_{2h} (secondary) and reported for comparability between the treatments.

Results:

Mean plasma celecoxib concentration-time profiles following DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg (4.8 mL Dr. Reddy's Laboratories Limited, India) (1 x 120 mg unit dose bottle) administered under fasting (Treatment A) and fed (Treatment B) conditions and a single oral dose of Celebrex® (celecoxib) capsules 400 mg (G.D. SEARLE LLC) (1 x 400 mg capsule) administered under fed condition (Treatment C) on linear scale are presented in Figure 5.

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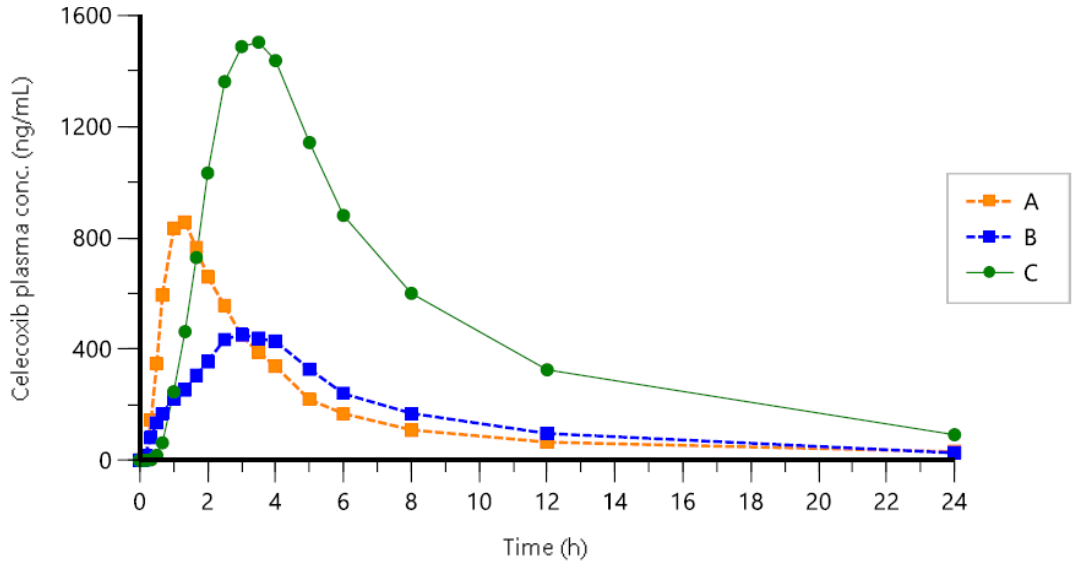
Figure 5: Mean (± SD) Celecoxib Plasma Concentration vs Time Plot with Treatments Overlaid (Linear Scale)



A: DFN-15 (Celecoxib Oral Solution, 25mg/mL), 120 mg under fasting state
B: DFN-15 (Celecoxib Oral Solution, 25 mg/mL), 120 mg under fed state
C: Celebrex capsules 400 mg under fed state

Source: Study DFN-15-CD-008; Figure 14.2.21

Plasma celecoxib AUC_{last} and AUC_{inf} following administration of DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg under fasting conditions were approximately 73% and 72% lower compared to the 400 mg Celebrex® capsule administered under fed conditions. The peak levels were also lower by approximately 43% for the DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg compared to the Celebrex® capsule. The DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg under fasting conditions showed much higher early exposure to celecoxib than that of the reference capsule under fed conditions (Table 3).

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Table 3: Results from Statistical Assessment of Celecoxib Comparative Bioavailability Following 120 mg DFN-15 Oral Solution Under Fasting Condition (Treatment A) and 400 mg Celebrex® Capsule under Fed Condition (Treatment C)

	Treatment A Geometric LSMs	Treatment C Geometric LSMs	GMR (%)	90% CI
C_{max} (ng/mL)	970.3	1707	56.84	51.68 - 62.51
$AUC_{0.5h}$ (ng*hr/mL)	40.53	0.5897	6872.79	395.74 - 119359.2
AUC_{1h} (ng*hr/mL)	304.6	13.73	2218.26	793.14 - 6204.05
AUC_{2h} (ng*hr/mL)	1143	407.1	280.81	187.02 - 421.63
AUC_{last} (ng*hr/mL)	3122	11600	26.92	25.68 - 28.21
AUC_{inf} (ng*hr/mL)	3343	12070	27.70	26.44 - 29.01

Treatment A: Dr. Reddy's DFN-15, 120 mg Celecoxib Oral Solution (Fasting); Treatment C: G.D. SEARLE LLC Celebrex® 400 mg Celecoxib Capsule (Fed). Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference). Intra-subject CV (CV%) = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA. $AUC0\text{-}_{0.25h}$ could not be calculated for all subjects for Treatment C hence the ANOVA for this parameter could not be performed. Subject (b) (6) was withdrawn from the study on Day 1 of Period 3 (Treatment C) as she tested positive for the contraband substance cocaine upon urine screen. Subject (b) (6) was not included in the comparison for any parameter as the subject did not have data for Treatment C. All ANOVAs were based on a sample size of 23 with the exception of the ANOVAs for $AUC0_{0.5h}$ (n = 9), AUC_{1h}

Source: Study DFN-15-CD-008; Table 11-3; page 41

The plasma celecoxib AUC_{last} and AUC_{inf} following administration of 120 mg celecoxib oral solution under fed and fasting conditions were similar. However, celecoxib C_{max} decreased to approximately half that observed under fasting conditions and was delayed by 2 hours after a high-fat meal. The celecoxib early exposure AUCs up to 2 hours post-dose were all lower under fed conditions compared to fasting conditions, with decreases ranging between 46% and 76% (Table 4).

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Table 4: Results from Statistical Assessment of Celecoxib Comparative Bioavailability Following 120 mg DFN-15 Oral Solution Under Both Fasting Condition (Treatment A) and Fed Condition (Treatment B)

Parameter	Treatment B (Test) LSMs	Treatment A (Reference) LSMs	GMR (%)	90% Confidence Interval
C_{max} (ng/mL)	490.4	970.9	50.51	46.42 - 54.95
$AUC_{0.25h}$ (ng*hr/mL)	1.293	2.383	54.27	28.12 - 104.76
$AUC_{0.5h}$ (ng*hr/mL)	8.903	37.32	23.86	9.01 - 63.20
AUC_{1h} (ng*hr/mL)	81.93	291.2	28.14	18.82 - 42.07
AUC_{2h} (ng*hr/mL)	348.1	1039	33.51	25.51 - 44.02
AUC_{last} (ng*hr/mL)	3290	3134	104.96	100.54 - 109.58
AUC_{inf} (ng*hr/mL)	3489	3359	103.85	100.28 - 107.55

Treatment A: Dr. Reddy's DFN-15, 120 mg Celecoxib Oral Solution (Fasting); Treatment B: Dr. Reddy's DFN-15, 120 mg Celecoxib Oral Solution (Fed). Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA. Geometric Mean Ratio (GMR) = 100*(test/reference). Intra-subject CV (CV%) = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA. All ANOVAs were based on a sample size of 24 with the exception of the ANOVAs for $AUC0_{0.25h}$ (n = 22) and AUC_{inf}

Source: Study DFN-15-CD-008; Table 11-4; page 42

Conclusion and Reviewer Comments:

- *DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg undergoes rapid absorption under fasting conditions with much higher early exposure to celecoxib within 2 hours post-dose and quicker attainment of peak concentrations than those from Celebrex® 400 mg capsules under fed conditions.*
- *Celecoxib total AUC (i.e. AUC_{inf}) from DFN-15 (Celecoxib) Oral Solution (25 mg/mL) 120 mg under fasting conditions is > 70% lower compared to Celebrex® 400 mg capsule under fed conditions while C_{max} is 43% lower.*
- *The relative bioavailability of DFN-15 under fasting condition relative to Celebrex® 400 mg capsules under fed condition is approximately 189% for C_{max} and 92% for AUC_{inf}.*
- *While high-fat and high-calorie meal has no effect on celecoxib total AUCinf following DFN-15 administration, there is a 50% decrease in C_{max} with an associated delay of 2 hours.*

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4.3 Assessment of Food Effect on efficacy (Headache Pain Freedom and Absence of Screening MBS)

The applicant conducted a post-hoc subgroup analyses to understand the effect of food on the co-primary endpoint (i.e. headache pain freedom and absence of screening MBS) for both Studies DFN-15-CD-007 and DFN-15-CD-006.

The sustainability of pain freedom was evacuated as secondary endpoint in Studies DFN-15-CD-007 and DFN-15-CD-006. However, because the concern of food effect is arising from differences in exposures under fed and fasting conditions and given that the differences in exposures is seen in the first 2 hours, we report only the first 2 hours.

We will focus our review on Study DFN-15-CD-007 as this was considered as the pivotal successful trial.

Applicant's Analyses: Study DFN-15-CD-007

The impact of subject-reported pre-dose timing of food intake (i.e., ≤4 hours prior to dosing (i.e., non-fasting) and >4 hours prior to dosing (i.e., fasting)) on the co-primary endpoint was evaluated. Additionally, the sponsor evaluated the effect of food type (i.e., amount; meal vs. snack) and food fat content (high fat vs. low fat) in the subset of individuals who administered the drug within 4 hours of food intake on efficacy in both DFN-15 and placebo group. Additionally, the sponsor reported the odds ratios between fed and fasting group to determine the interaction between the effect of food on pain freedom and absence of MBS in this subgroup analyses across different time points (i.e. at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 24 hours postdose). Summary of the proportion of subject who achieved pain freedom and absence of screening MBS over the first 2 hours (the co-primary endpoint) under different fed conditions is presented in Figure 4. The odds ratio of achieving pain freedom or MBS freedom in different over the first 2 hours for fed versus fasting (i.e. ≤4 hours versus >4 hours) and for meal versus snack and high fat content versus low fat content in fed subjects (i.e. administered food 4 hours prior dosing) is presented in Figure 6. An odds ratio lower than one, represent therapeutic loss (i.e. the odds of achieving the outcome is lower when the drug is administered under fed conditions).

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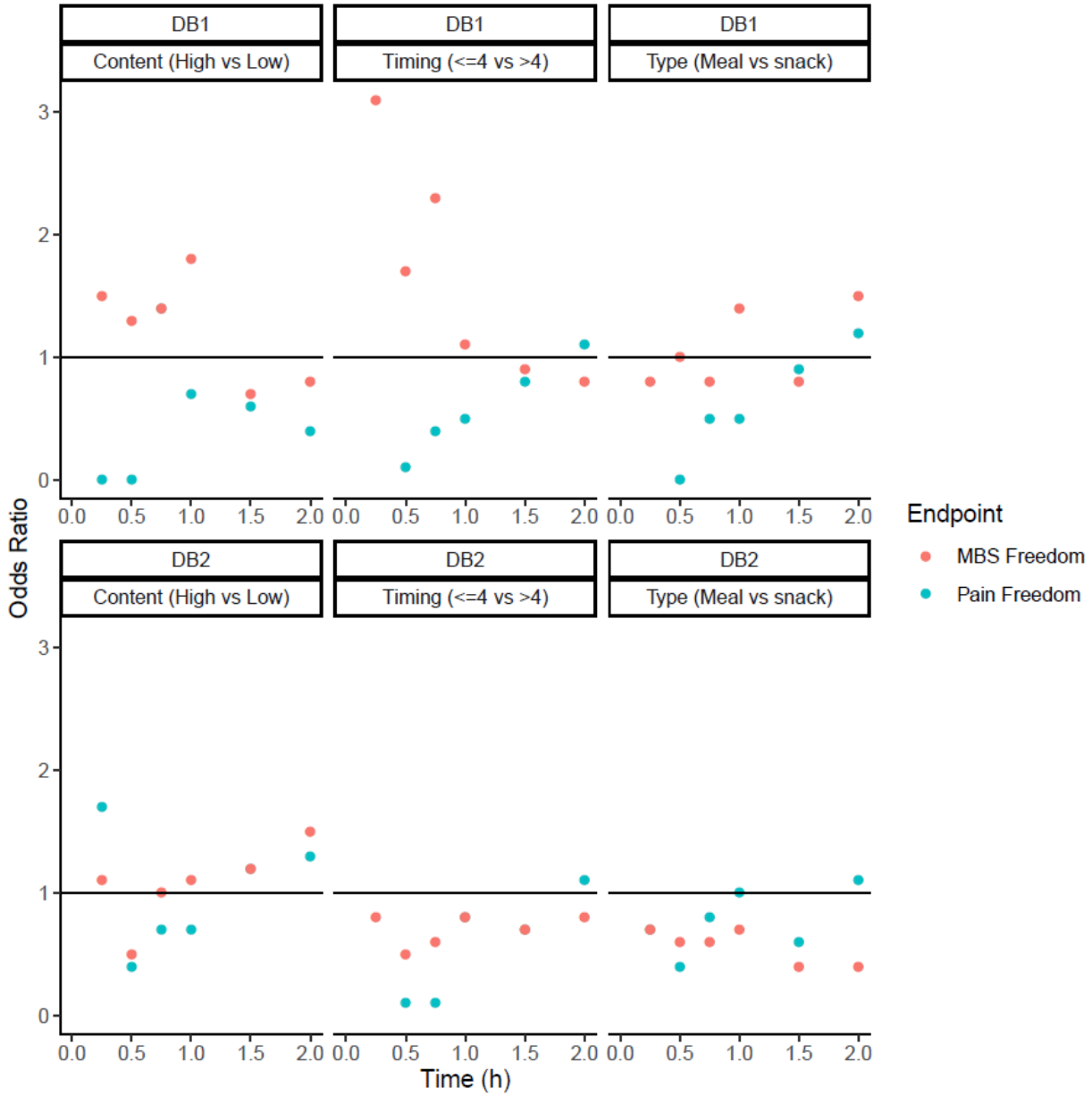
Figure 6: Odds Ratio of Achieving Pain freedom (Green Circles) and MBS (Red Circles) in Both Double-Blind Periods Stratified by Food Conditions Over the First 2 Hours: Study DFN-CD-007



Source: Tables created by the reviewer based on Study DFN-15-CD-007

<u>Reviewer Comments and Additional Analyses:</u>

- It appears that fasting for more than 4 hours is associated with more proportion of subjects who achieved MBS freedom in the DB1 and DB2. This finding was not

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consistent for the pain freedom endpoint. Additionally, a high fat food appeared to be associated with more proportions of subjects who achieve freedom of MBS in DB2 which counter the observation of the effect of timing of food on the MBS. Further inspection of the components of the MBS (i.e. photophobia, phonophobia, and nausea) showed that freedom from nausea as the MBS seemed to be consistently associated with fasting for more than 4 hours across both periods and both studies (i.e. Study DFN-15-CD-006 and DFN-15-CD-007). This finding doesn't necessarily relate to the exposure of the drug but more to the nature of the MBS, since it was not consistent for the other MBS (i.e. photophobia and phonophobia).

- The review team tried to understand if the proportion of subjects who administered the treatment under fed condition is similar across both Phase 3 studies. The proportion of subjects who administered ELYXYB with food were similar in both studies (Table 1 and Table 5). This finding suggests that the differences in the efficacy outcome between both studies are not really related to differences in fed conditions.

Table 5: Number of subjects per each treatment group in each dosing period (DB1 and DB2): Study DFN-15-CD-006

Information on food intake	DB1		DB2	
	Placebo	DFN-15	Placebo	DFN-15
Food intake > 4 h*	70	75	67	67
Food intake <=4 h	209	210	185	183
High Fat	74	70	71	63
Low Fat	135	140	114	120
Meal	137	135	119	109
Snack	72	75	66	74

*considered as fasting state for analysis

Source: Tables created by the reviewer based on Study DFN-15-CD-006: Tables 14.2.4.8.1-4.ah, Tables 14.2.4.9.1-4.ah, Tables 14.2.4.9.2.ah, and Tables 14.2.4.10.1-4.ah.

- The review team tried to understand if subjects who took the treatment under same fed condition (irrespective if it is fasting (i.e. >4 hours) or fed (i.e. ≤4 hours)) in both DB periods irrespective of their assignment to either DFN-15 or placebo tended to have the same outcome (irrespective if it is positive (yes) or negative (no) outcome) in both periods. The percentage of subjects who achieved same outcome in both periods (i.e. either pain freedom/MBS freedom or no pain freedom/MBS freedom in both periods versus achieving a pain freedom/MBS freedom in one period and no pain freedom/MBS freedom in the other period) stratified by whether they administered the drug under

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same fasting or fed condition as defined by (i.e. >4 h or <=4 hours) in both periods irrespective of the food content or type seemed to be higher is presented in Table 5. These results show that irrespective of food condition (i.e. fasting or fed state), half of the patients achieved same outcome in both periods indicating that the outcome is not correlated with fed conditions. Also, whether subjects administered drug under same fed conditions on both periods or not, the proportion who achieved same outcome was the same as those who did not achieve the same outcome in both periods. Again, this suggests lack of correlation of efficacy with fed conditions.

Table 6: The percentage of patients who achieved same outcome in both periods stratified by whether they administered ELYXYB either on fasting (i.e. >4 hours food prior drug administration) versus fed state (i.e. <=4 hours food prior drug administration) in both periods of Study DFN-15-CD-007

	Achieved Same Pain Freedom Outcome on Both Periods		Achieved Same MBS Freedom Outcome on Both Periods	
	Yes	No	Yes	No
Administer under either fed or fasting condition on both periods	%	%	%	%
Yes	50%	22%	51%	19%
No	20%	7%	18%	11%

- In absence of the effect of the different timing and meal content on the PK of ELYXYB®, it is hard to figure out what is the best way to group the data to avoid dilution of the interaction between food effect and drug efficacy, if any. Given that the fed condition in the PK food effect study (i.e. Study DFN-15-CD-008) was defined as administration of the drug within 30 min of a high-fat meal (as per the current FDA guidance for food effect), the reviewer thought to define the fed condition as the shortest time available where a high fat meal was administered prior to drug administration (i.e. the high fat meal was administered in less than 1 hour prior to drug administration). However this classification resulted in a very limited number of subjects defined as fed status in both placebo and treatment in both periods (for example, there was only 26 subjects who administered the drug under fed condition in the DFN-15 120 mg group in DB1; 23 subjects who administered the drug under fed condition in the placebo group in DB1; 20 subjects who administered the drug under fed condition in the DFN-15 120 mg group in DB2; and 23 subjects who administered the drug under fed condition in the placebo group in DB2.

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- As the choice of a 4 hours cut-off is not clear and also resulted in unbalanced number of subjects in the group of > 4hours versus those in the <=4 hours (see Table 1), the review team aimed at understanding if grouping by different timing of food administration can affect the results. The reviewer classified the subjects who administered DFN-15 120 mg by different timing (i.e.>1hour vs <=1 hour; >2 hours vs <=2 hours; >2-4 hours vs <=2-4 hours. However, this grouping did not appear to change the sponsor findings. Same analyses were repeated but by combining both periods from the treatment groups. however, no difference to the conclusion can be made. Interestingly, when same analysis was conducted for placebo, a significant difference was observed for the pain freedom endpoint for study 007. The analysis indicated that subjects who were fed (as defined by administering food in less than 2 hours prior dosing) and received placebo had more probability to achieve pain freedom at 2 hours. This trend was consistent for the MBS freedom and also in study 006 but with no observed statistical significance. This finding may be explained by the fact that skipping meal or fasting is a trigger for migraine. So, it could be subjects who are fed are more likely to get relief from their migraine.

Conclusion:

Although there is a significant reduction in celecoxib exposure in the first 2 hours, where the end point is measured, post-hoc analyses does not seem to suggest that food may affect effectiveness. There may be several explanations for this finding: 1) the exposure of ELYXYB under fasting condition in the first 1 and 2 hours is approximately 22- and 2.8-fold higher as compared to Celebrex® 400 mg capsules under fed condition. Under fed conditions, the exposure in the first 1 and 2 hours following ELYXYB is approximately 6-fold higher and similar, respectively, to what was observed for Celebrex® 400 mg capsule. Celebrex® approved dose for management of acute pain and treatment of primary dysmenorrhea is 400 mg initially. Given the 11-hour half-life of celecoxib, an additional 200 mg dose on the first day may be administered, if needed. On subsequent days, the recommended dose is 200 mg twice daily as needed. According to Celebrex's label, single doses of Celebrex® provided pain relief within 60 minutes. Based on the exposure in the first 2 hours from Celebrex® 400 mg capsule and ELYXYB 120 mg under fed condition, one may conclude that the effectiveness may be similar in pain management in the first 2 hours following initial dose (although exposure response in migraine may be different than acute pain indications approved for Celebrex®).While ELYXYB doses under 120 mg for migraine was not studied and therefore, the dose/exposure-response relationship is not really known, one may conclude that food may not have significant effect on efficacy based on these post-hoc analyses and comparison with Celebrex® 400 mg capsules exposure in the first 2 hours. Given that in both Studies 007 and 006, ELYXYB was administered

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without regard to food and the unpracticality of recommendations to administer ELYXYB on empty stomach, the review team recommend administering ELYXYB without regard to food. A word of caution for these analyses should be given. The data is collected in the study based on the subject's reported and assessment of meal content, type, and timing. This of course cause noise. Nonetheless, the review team think that all in all, there is no sufficient evidence to suggest that food may impact the efficacy of ELYXYB and as such no adjustment for dosing or timing of dose is necessary.

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/s/

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