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CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Applicant: ProEthic

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on Study PRO-513301, there is evidence that PRO-513 is effective for the treatment of migraine with and without aura in adults, compared to placebo.

For Study CAT458C2301 ((b) (4) is a PRO-513 equivalent), even though there are issues with sponsor's primary efficacy analysis, it appears that this study shows benefits of 50 mg diclofenac-K sachets in the treatment of migraine, compared to placebo. Please refer to Section 3.1.3 Reviewer's Analysis for details.

1.2 Brief Overview of Clinical Studies

This NDA submission includes two pivotal efficacy studies, Study PRO-513301 and CAT458C2301.

Study PRO-513301 was a Phase III, randomized, double-blind, parallel group, single-dose, placebo-controlled, multi-center study to compare the efficacy and safety of PRO-513 to placebo as a treatment for migraine attacks in adult subjects. This study was conducted in 23 US sites. The ITT population included 690 subjects. During the course of the study, enrolled subjects treated one eligible migraine attack (with or without aura) that presented with at least moderate headache pain intensity. Using a provided diary, subjects assessed their headache pain and other associated symptoms (nausea, photophobia, phonophobia, presence or absence of vomiting, and functional ability with regard to daily activities) just prior to dosing, and then at 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 8, 16, and 24 hours after dosing.

Study CAT458C2301 ((b) (4) is a PRO-513 equivalent) was a double-blind, double-dummy, randomized, international, multi-center, cross-over trial to assess the efficacy and tolerability of single doses of 50 mg diclofenac-K sachets as an acute treatment for migraine attacks in comparison with placebo and 50 mg diclofenac-K tablets in adult migraine patients. This study was conducted in Germany, Hungary, Italy, The Netherlands and Poland. Out of the 328 patients randomized, 317 received at least one treatment and 274 treated all three migraine attacks with study drug (completed the study). In this study, subjects were to treat three migraine attacks over a two-month period. The three treatment sequences were diclofenac-K sachets/diclofenac-K tablet/placebo, diclofenac-K tablets/placebo/diclofenac-K sachets, placebo/diclofenac-K sachets/diclofenac-K tablets.

1.3 Statistical Issues and Findings

1.3.1 STUDY PRO-513301

For Study PRO-513301, the four co-primary efficacy endpoints were headache pain, nausea, photophobia and phonophobia at 2 hours post-dosing, which were analyzed using CMH test

stratified by analysis center for ITT population. Last observation carried forward (LOCF) was used to impute missing data. The percent of subjects in the PRO-513 treatment group for the ITT population who had no headache pain at 2-hours post-dose was 25%, who had no nausea was 65%, who had no photophobia was 41%, and who had no phonophobia was 44%, comparing to 10%, 53%, 27%, and 27% of subjects in the placebo treatment group, respectively. The treatment comparisons between PRO-513 and placebo group for all 4 co-primary endpoints were statistically significant ($p \leq 0.002$).

1.3.2 STUDY CAT458C2301

Study CAT458C2301 was a three-way cross-over study with Latin square design, i.e., every treatment being represented once and only once in each treatment sequence and in each period.

According to the sponsor, the primary objective of this study was to determine whether a single dose of 50 mg diclofenac-K sachets is superior to placebo and non-inferior to 50 mg diclofenac-K tablets in treating the pain and associated symptoms of migraine headache. However, based on this reviewer's discussion with the medical team, the non-inferiority claim of 50 mg diclofenac-K sachets over 50 mg diclofenac-K tablets will not be considered. Therefore, the review for this study focuses on the treatment comparison between 50 mg diclofenac-K sachets and placebo.

The primary efficacy variable was freedom from pain assessed on the verbal scale for headache intensity at 2 hours post dose. The sponsor analyzed this primary efficacy variable using a logistic regression model with treatment, period and patient as fixed effects, and baseline VAS headache intensity as a covariate for ITT population. Based on this analysis, the treatment comparison between 50 mg diclofenac-K sachets and placebo group were statistically significant ($p < 0.0001$).

There are three issues with sponsor's primary efficacy analysis. First, for migraine study, pain, nausea, photophobia and phonophobia are the commonly used four co-primary efficacy endpoints, instead of freedom from pain as a single primary endpoint. Second, this reviewer thinks since the data from each patient were correlated and the model should include a random effect, and sequence should be included in the model as a fixed effect. Third, the overall dropout rate for this study was approximately 14%, which might affect the interpretation of the results from sponsor's primary efficacy analysis.

However, even though there are issues with sponsor's primary efficacy analysis, it appears that diclofenac-K sachet displays better treatment effect than placebo. To further evaluate the efficacy of diclofenac-K sachet compared to placebo, this reviewer conducted three additional analyses.

First, this reviewer summarized the percentages of symptom free by sequence and period for all four symptoms, i.e., pain, nausea, photophobia and phonophobia. This analysis shows that the percentages of symptom free were numerically higher for patients in diclofenac sachet-K group than in placebo group, for each sequence and for each period.

Second, for each symptom, this reviewer conducted a McNemar's test for each of the three sequences to compare diclofenac-K sachet and placebo. In addition, for each symptom, since the McNemar's test statistic for each sequence has a χ_1^2 distribution and the three test statistics are independent, the sum of the three test statistics has a χ_3^2 distribution, which could be considered as an overall test. The results indicate that, for each symptom and for each sequence, the number of patients being symptom free on diclofenac-K sachet but not on placebo was larger than the number of patients being symptom free on placebo but not on diclofenac-K sachet. Even though some of the individual McNemar's tests were not statistically significant, the overall tests were statistically significant (for pain, photophobia and phonophobia) or marginally significant (for nausea), at 0.05 level (two-sided).

Third, for each symptom, this reviewer conducted Cochran-Mantel-Haenszel (CMH) test stratified by analysis center, for the first period. This analysis shows that, for first period, the percentages of symptom free were numerically higher for patients in diclofenac-K sachet group than in placebo group, for all four symptoms. The nominal p-values for pain, photophobia and phonophobia were significant or marginally significant at 0.05 level (two-sided) while the p-value for nausea was 0.14. However, this reviewer would like to point out that the study was designed as a three-way cross-over study so it was not powered for first period analysis.

In summary, this reviewer thinks Study CAT458C2301 shows benefits of 50 mg diclofenac-K sachets in the treatment of migraine, compared to placebo.

2 INTRODUCTION

2.1 Overview

Migraine is a common condition that is reported by nearly 28 million people in the US; overall, migraine affects 18.2% of women and 6.5% of men aged 12 years and older. In general, migraine episodes last up to 72 hours and occur with intermittent frequency (two to six times per month). Migraine usually results in temporary disability and often occurs in otherwise healthy individuals.

Treatment of migraine traditionally has included simple analgesics, certain nonsteroidal anti-inflammatory drugs (NSAIDs), barbiturates, caffeine, and Midrin®-type products, as well as other migraine-specific agents such as ergot preparations and triptans.

Three oral formulations of diclofenac currently are approved in the US. These products are indicated for the treatment of osteoarthritis and rheumatoid arthritis, and include Voltaren® (25, 50, and 75 mg diclofenac sodium, Novartis), Voltaren®-XR (100 mg diclofenac sodium, Novartis), and Cataflam® (50 mg diclofenac potassium, Novartis). (VOLTAREN also is indicated for the treatment of ankylosing spondylitis, and CATAFLAM also is indicated for primary dysmenorrhea or for mild to moderate pain.)

This NDA submission includes two pivotal efficacy studies, Study PRO-513301 and CAT458C2301.

Study PRO-513301 was a Phase III, randomized, double-blind, parallel group, single-dose, placebo-controlled, multi-center study to compare the efficacy and safety of PRO-513 to placebo as a treatment for migraine attacks in adult subjects. This study was conducted in 23 US sites. The ITT population included 690 subjects. During the course of the study, enrolled subjects treated one eligible migraine attack (with or without aura) that presented with at least moderate headache pain intensity. Using a provided diary, subjects assessed their headache pain and other associated symptoms (nausea, photophobia, phonophobia, presence or absence of vomiting, and functional ability with regard to daily activities) just prior to dosing, and then at 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 8, 16, and 24 hours after dosing.

Study CAT458C2301 was a double-blind, double-dummy, randomized, international, multi-center, cross-over trial to assess the efficacy and tolerability of single doses of 50 mg diclofenac-K sachets as an acute treatment for migraine attacks in comparison with placebo and 50 mg diclofenac-K tablets in adult migraine patients. This study was conducted in Germany, Hungary, Italy, The Netherlands and Poland. Out of the 328 patients randomized, 317 received at least one treatment and 274 treated all three migraine attacks with study drug (completed the study). In this study, subjects were to treat three migraine attacks over a two-month period. The three treatment sequences were diclofenac-K sachets/diclofenac-K tablet/placebo, diclofenac-K tablets/placebo/diclofenac-K sachets, placebo/diclofenac-K sachets/diclofenac-K tablets.

2.2 Data Sources

The sponsor's electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA022165\0003 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The efficacy of PRO-513 for the treatment of migraine was evaluated in two pivotal efficacy studies, Study PRO-513301 and Study CAT458C2301.

3.1.1 PROTOCOL PRO-513301

3.1.1.1 Study Objectives of PRO-513301

The objective of the study was to demonstrate the efficacy and safety of PRO-513 (50 mg diclofenac potassium powder for oral solution) as compared to placebo when used to treat a migraine attack of moderate to severe headache pain intensity with or without aura.

3.1.1.2 Study Design

This prospective, randomized, double-blind, parallel group, single-dose, placebo-controlled, multi-center study compared the efficacy and safety of PRO-513 to placebo as a treatment for migraine attacks in 650 (planned) adult subjects who had histories of migraine. This study was conducted in 23 US sites.

During the course of the study, enrolled subjects treated one eligible migraine attack (with or without aura) that presented with at least moderate headache pain intensity. Using a provided diary, subjects assessed their headache pain and other associated symptoms (nausea, photophobia, phonophobia, presence or absence of vomiting, and functional ability with regard to daily activities) just prior to dosing, and then at 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 8, 16, and 24 hours after dosing.

3.1.1.3 Efficacy Measures

Primary Efficacy Endpoints

The four, co-primary efficacy endpoints were:

- Percent of subjects who had no headache pain at 2 hours post-dosing
- Percent of subjects who had no nausea at 2 hours post-dosing
- Percent of subjects who had no photophobia at 2 hours post-dosing
- Percent of subjects who had no phonophobia at 2 hours post-dosing

Secondary Efficacy Endpoints

The secondary efficacy endpoints were:

- Sustained pain-free rate
- Headache recurrence rate and time to headache recurrence
- Pain intensity difference at each evaluation
- Headache pain intensity at each evaluation time
- Associated symptoms of nausea, photophobia and phonophobia, presence or absence of vomiting, functional ability with regard to daily activities at each evaluation time.

3.1.1.4 Statistical Analysis Plan

The intent-to-treat (ITT) population was the primary efficacy population and included all randomized subjects who took their dose of study medication and had at least one baseline and post-baseline assessment of an efficacy measurement.

Investigational sites with less than eight subjects in each treatment arm were combined with other investigational sites with less than eight subjects in each treatment arm for the purposes of statistical analysis.

For the four co-primary efficacy endpoints, the treatment groups were compared for the ITT and PP populations using a CMH test stratified by analysis center. While each endpoint was tested at a significance level of 0.05, all four tests were required to reach statistical significance in order for the study to demonstrate efficacy.

The secondary efficacy variables were used to characterize the treatment effects. For sustained pain-free and headache recurrence rate, the treatment groups were compared for the ITT and PP populations using a CMH test stratified by analysis center. Additionally, Kaplan-Meier plots of the time to recurrence and the 95% confidence interval for the median time to recurrence were presented for each treatment group. Pain intensity differences (PIDs) were summarized by treatment group for the ITT and PP populations and analyzed using an analysis of variance with treatment and analysis center as factors in the model. The other secondary efficacy variables were summarized by treatment group using descriptive statistics for the ITT and PP populations. No p-values were calculated.

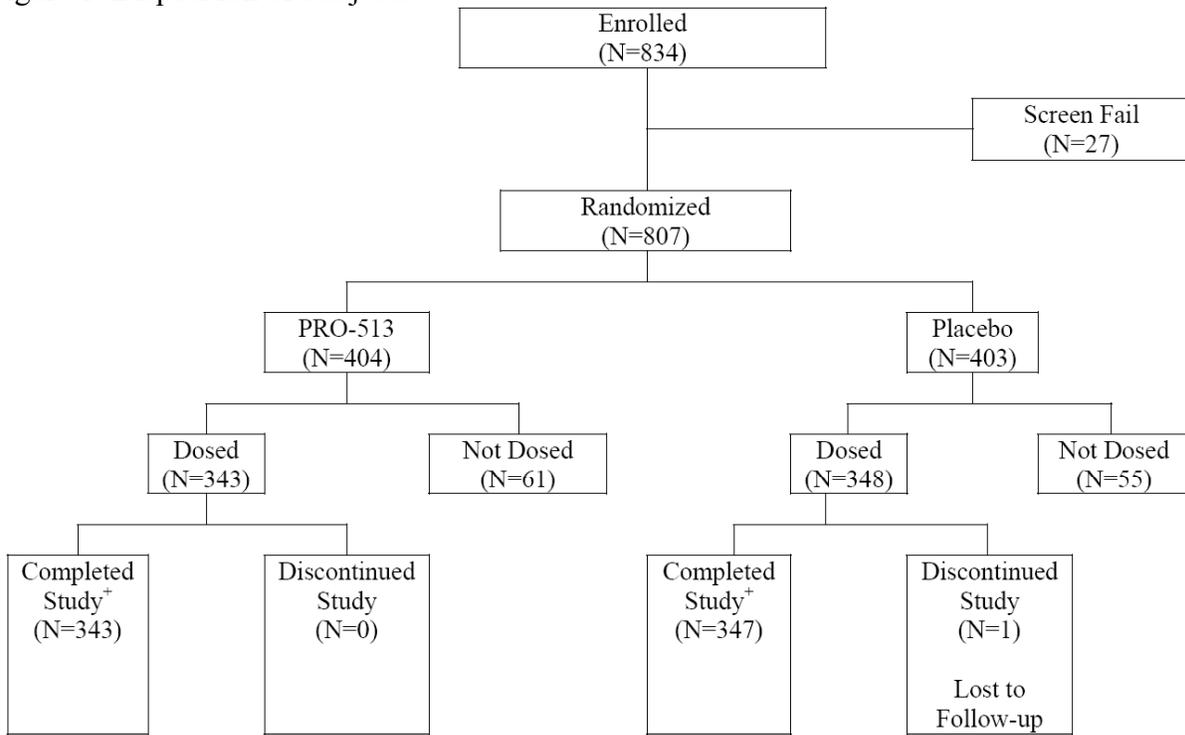
There were no changes in the planned analyses.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Eight hundred thirty-four (834) subjects were enrolled in this study and 807 subjects were randomized. Of the 807 subjects randomized, 116 subjects did not dose. One subject in placebo treatment group, who was randomized and dosed, was lost to follow-up and did not have any post-baseline assessments collected. This subject was not included in the ITT, PP and safety populations. The ITT and safety populations included the same 690 subjects who were randomized, dosed, and had at least one baseline and post-baseline assessment. The overall disposition is presented in Figure 1 and subject completion/discontinuation is summarized in Figure 1.

Figure 1: Disposition of Subjects



+Completed the 2-hour evaluations: 339 subjects in PRO-513 treatment group, 345 subjects in placebo treatment group.

Completed the 24-hour evaluations: 339 subjects in the PRO-513 treatment group, 344 subjects in placebo treatment group.

Source: [Listing 16.2.1.1.1](#), [Listing 16.2.1.1.2](#), [Listing 16.2.1.2](#), [Listing 16.2.1.3](#), [Table 10.1-2](#)

Source: Figure 10.1-1 of sponsor’s Clinical Study Report

Table 1: Summary of Subjects Completion/Discontinuation

	<u>PRO-513</u>	<u>Placebo</u>	<u>Total</u>
Number of Subjects Randomized	404	403	807
Number of Subjects Who Did Not Take Study Medication	61	55	116
Reasons for Not Taking Study Medication			
Did not medicate within acceptable enrollment period	22	21	43
He/She voluntarily withdrew	4	3	7
Lost to follow-up	15	13	28
Adverse event or intercurrent illness	2	0	2
Other ^a	18	18	36
Number of Subjects Who Took Study Medication	343	348 ^b	691 ^b
Subject completed the 2-hour evaluations	339	345	684
Subject took rescue medication prior to 2 hours	0	3	3
Adverse event or intercurrent illness	1	0	1
Inappropriate enrollment	1	0	1
Headache treated was not an eligible migraine attack	2	6	8

^a See the End of Study listing for complete specifications.

^b One subject in the placebo treatment group was lost to follow-up, had no post-screening efficacy or safety data, and was excluded from the ITT, PP and safety populations.

SOURCE: [Table 14.0.3](#)

Source: 10.1-2 in sponsor's clinical study report.

Demographic Characteristics

The demographic characteristics are presented in Table 2. The treatment groups appeared generally similar with respect to demographic characteristics.

Table 2: Summary of Demographic Characteristics (ITT)

	PRO-513 (N=343)	Placebo (N=347)
Age (years)		
Mean	40.5	39.9
Median	41.0	41.0
STD	11.4	11.2
Range	18.0-65.0	19.0-65.0
Gender		
Male	50 (14.6%)	55 (15.9%)
Female	293 (85.4%)	292 (84.1%)
Ethnicity		
Hispanic/Latino	33 (9.6%)	33 (9.5%)
Not Hispanic/Latino	310 (90.4%)	314 (90.5%)
Race		
American Indian/Alaska Native	0 (0.0%)	1 (0.3%)
Asian	3 (0.9%)	3 (0.9%)
Black/African American	52 (15.2%)	59 (17.0%)
Native Hawaiian/Other Pacific Islander	0 (0.0%)	0 (0.0%)
White	276 (80.5%)	276 (79.5%)
Other	12 (3.5%)	8 (2.3%)

^a P-value from a two-way analysis of variance with factors of treatment group and analysis center.

^b P-value from a Cochran-Mantel-Haenszel test, stratified by analysis center.

SOURCE: KGLYNN\PROETHIC\PRO513301\ANALYSIS\I_DEMO (Apr 16, 2007 09:25)

Source: Excerpt from Table 14.1.2.1 of sponsor's Clinical Study Report

Baseline Characteristics

The baseline characteristics are summarized in Table 3. It appears that the baseline characteristics were similar for PRO-513 group and placebo group.

Table 3: Baseline Characteristics (ITT)

	PRO-513 (N=343)	Placebo (N=347)
Primary Migraine Diagnosis		
Migraine without aura	303 (88.3%)	297 (85.6%)
Migraine with aura	40 (11.7%)	50 (14.4%)
Headache Pain		
Moderate	250 (72.9%)	242 (69.7%)
Severe	93 (27.1%)	105 (30.3%)
Nausea		
None	119 (34.7%)	123 (35.4%)
Mild	146 (42.6%)	138 (39.8%)
Moderate	66 (19.2%)	78 (22.5%)
Severe	12 (3.5%)	8 (2.3%)
Photophobia		
None	10 (2.9%)	17 (4.9%)
Mild	105 (30.6%)	105 (30.3%)
Moderate	178 (51.9%)	162 (46.7%)
Severe	50 (14.6%)	63 (18.2%)
Phonophobia		
None	31 (9.0%)	17 (4.9%)
Mild	109 (31.8%)	106 (30.5%)
Moderate	156 (45.5%)	166 (47.8%)
Severe	47 (13.7%)	58 (16.7%)

SOURCE: KGLYNN\PROETHIC\PRO513301\ANALYSIS\I_BASE (Jan 15, 2007 11:09)

Source: Excerpt from Table 14.1.5.1 of sponsor's Clinical Study Report

3.1.1.6 Sponsor's Primary Efficacy Results

Analysis results for the four co-primary endpoints of headache pain, nausea, photophobia and phonophobia at 2 hours post-dosing are presented in Table 4 for ITT population. These four co-primary endpoints were analyzed using CMH test stratified by analysis center. Last observation carried forward (LOCF) was used to impute missing data.

Table 4: Analysis of the Co-Primary Endpoints (ITT)

	PRO-513	Placebo
<u>Headache Pain^a</u>		
Number of Subjects	343	347
No Pain	86 (25%)	35 (10%)
Mild, Moderate, or Severe Pain	257 (75%)	312 (90%)
P-Value ^b	<0.001	
<u>Nausea^a</u>		
Number of Subjects	343	347
No Nausea	222 (65%)	183 (53%)
Mild, Moderate, or Severe Nausea	121 (35%)	164 (47%)
P-Value ^b	0.002	
<u>Photophobia^a</u>		
Number of Subjects	343	347
No Photophobia	139 (41%)	95 (27%)
Mild, Mod., or Severe Photophobia	204 (59%)	252 (73%)
P-Value ^b	<0.001	
<u>Phonophobia^a</u>		
Number of Subjects	343	347
No Phonophobia	152 (44%)	95 (27%)
Mild, Mod., or Severe Phonophobia	191 (56%)	252 (73%)
P-Value ^b	<0.001	

^a Based on Assessments at 2 Hours Post-Dose

^b P-Value from a Cochran-Mantel-Haenszel test, stratified by analysis center.

Source: Table 11.4.1-1 of sponsor's Clinical Study Report

The percent of subjects in the PRO-513 treatment group for the ITT population who had no headache pain at 2-hours post-dose was 25%, who had no nausea was 65%, who had no photophobia was 41%, and who had no phonophobia was 44%, comparing to 10%, 53%, 27%, and 27% of subjects in the placebo treatment group, respectively. The treatment comparisons between PRO-513 and placebo group for all 4 co-primary endpoints were statistically significant ($p \leq 0.002$).

3.1.1.7 Selected Sponsor's Secondary Efficacy Results

Analysis results for sustained pain free and headache recurrence rate are presented in Table 5.

Table 5: Analysis of Sustained Pain Free and Headache Recurrence (ITT)

	Sustained Pain Free Response Rates	
	PRO-513 (N=343)	Placebo (N=347)
Sustained PF		
Yes	65 (19%)	25 (7%)
No	278 (81%)	322 (93%)

	Recurrence Rates	
	PRO-513 (N=86)	Placebo (N=35)
Recurrence		
Yes	21 (24%)	10 (29%)
No	65 (76%)	25 (71%)

SOURCE: [Table 14.2.10.1.1](#)

Source: Excerpt from Table 11.4.1-3 of sponsor's Clinical Study Report

For sustained pain free rate, 19% of the subjects had a sustained pain free response through 24 hours for the PRO-513 treatment group compared with 7% for the placebo treatment group.

For the subjects who were pain free at 2 hours post-dose, 24% (21/86) in the PRO-513 treatment group had a recurrence, defined as mild, moderate or severe pain and/or taking rescue medication within 24 hours, compared with 29% (10/35) in the placebo treatment group.

3.1.2 PROTOCOL CAT458C2301

3.1.2.1 Study Objectives of CAT458C2301

Primary: To determine whether a single dose of 50 mg diclofenac-K sachets is superior to placebo and non-inferior to 50 mg diclofenac-K tablets in treating the pain and associated symptoms of migraine headache. The primary efficacy parameter was the percentage of patients pain free at 2 hours after intake of study medication, as assessed using a verbal scale.

Secondary: To further evaluate the safety and efficacy of a single dose of 50 mg diclofenac-K sachets in treating the pain and associated symptoms of migraine headache in comparison to 50 mg diclofenac-K tablets and placebo. The main secondary interest was the time to onset of analgesic effect, as assessed by a visual analog scale (VAS).

3.1.2.2 Study Design

This was a double-blind, double-dummy, randomized, international, multi-center, cross-over trial to assess the efficacy and tolerability of single doses of 50 mg diclofenac-K sachets as an acute treatment for migraine attacks in comparison with placebo and 50 mg diclofenac-K tablets in

adult migraine patients. This study was conducted in Germany, Hungary, Italy, The Netherlands and Poland. In this study, subjects were to treat three migraine attacks over a two-month period. It was planned to randomize 300 patients, 100 to each treatment sequence, i.e., diclofenac-K sachets/diclofenac-K tablet/placebo, diclofenac-K tablets/placebo/diclofenac-K sachets, placebo/diclofenac-K sachets/diclofenac-K tablets.

3.1.2.3 Efficacy Measures

Primary efficacy parameter:

- Percentage of patients pain free at 2 hours post-dose (assessed using a verbal scale)

Secondary efficacy parameters:

- Time to onset of analgesic effect assessed using a VAS of headache intensity
- Headache response at 2 hours post-dose (pain free or reduction from moderate or severe to mild)
- Sustained headache response (no recurrence/worsening or rescue medication within 24 hours)
- Sustained pain free (no recurrence or rescue medication within 24 hours)
- Reduction of VAS headache intensity from baseline at single time points to 8 hours post-dose
- Average reduction of VAS headache intensity during the first 2, 4, and 8 hours post-dose
- Change of headache intensity from baseline on a verbal scale at 1, 2, and 8 hours post-dose
- Presence of nausea, vomiting, photophobia, and phonophobia at 1, 2, 4, 6, and 8 hours post-dose
- Working / functional ability evaluated on a verbal scale at 2 and 8 hours post-dose
- Use of rescue medication within 8 hours post-dose and time to use of rescue medication
- Time to attack completely resolved
- Recurrence of attack within 24 and 48 hours
- Patient's global evaluation of medication.

3.1.2.4 Statistical Analysis Plan

The primary efficacy variable was the binary variable freedom from pain (yes or no) assessed on the verbal scale for headache intensity at 2 hours after intake of study medication. If the 2 hour assessment of headache intensity was missing according to the verbal scale, the last post-dose headache intensity data obtained before 2 hours and the first data obtained after 2 hours, irrespective whether the data were from the VAS scale or from the verbal scale, were used to impute the 2 hour value for freedom from pain according to the pre-defined rules. If no post-dose data at all were available from the entire 2 hour period, the patient was considered as not pain free. The details of the imputation rule were specified in Appendix 5.

The objective of the study was formulated in two parts: first, to show superiority of diclofenac-K sachets over placebo and second, to show non-inferiority of diclofenac-K sachets to diclofenac-K

tablets. Superiority was considered when the proportion of pain free patients on diclofenac-K sachets was statistically significantly higher than the proportion on placebo at the one-sided 2.5% level. Non-inferiority was considered when the proportion of pain free patients on diclofenac-K sachets was at worst 10% lower than the proportion of pain free patients on diclofenac-K tablets at the one-sided 2.5% level.

A logistic regression analysis was performed for freedom from pain with the explanatory variables of treatment, period, patient, and baseline VAS headache intensity. The primary efficacy analysis was analyzed for ITT population, defined as all randomized patients who took at least one dose of double-blind study treatment and had at least one efficacy measurement available.

Reviewer's Note:

According to the sponsor, no protocol amendments were made.

3.1.2.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

The patient disposition is described in Table 6. In this study, 328 subjects were randomized to treatment, and 317 subjects received at least one dose of study medication (i.e., completed at least one period). Of these, 274 subjects (86.4%) completed all three periods, 23 subjects (7.3%) completed only two periods, and 20 subjects (6.3%) completed only one period. According to the sponsor, Novartis terminated the trial after the number of completed subjects was considered sufficient to allow for conduct of the planned statistical analyses. Therefore, subjects who failed to complete one or two periods for this reason were discontinued because of “administrative problems.” Of the 43 subjects who failed to complete all three periods, the majority (28, 65.1%) discontinued because they had treated less than three migraine attacks when the study was terminated. In addition, 6 patients withdrew their consent, 6 discontinued for AEs, and 3 were lost to follow-up after use of at least one study treatment.

Table 6: Patient Disposition

	Dic-K Sachet	Dic-K Tablet	Placebo	Total
Total no. of patients – n (%)				
Screened	-	-	-	337
Randomized	-	-	-	328
Randomized but received no treatment	-	-	-	11
Received at least one treatment	291 (100.0)	298 (100.0)	299 (100.0)	317 (100.0) ^a
Received only one treatment	5 (1.7)	6 (2.0)	9 (3.0)	20 (6.3)
Received only two treatments	12 (4.1)	18 (6.0)	16 (5.4)	23 (7.3) ^a
Received all three treatments	274 (94.2)	274 (91.9)	274 (91.6)	274 (86.4) ^a
Discontinuations^b – n (%)				
Total	10 (3.4)	13 (4.4)	20 (6.7)	43 (13.6)
Administrative problems ^c	5 (1.7)	9 (3.0)	14 (4.7)	28 (8.8)
Subject withdrew consent	3 (1.0)	1 (0.3)	2 (0.7)	6 (1.9)
Adverse events	2 (0.7)	3 (1.0)	1 (0.3)	6 (1.9)
Lost to follow-up	0 (0.0)	0 (0.0)	3 (1.0)	3 (0.9)

^a Since this is a cross-over study, the number of patients receiving each treatment do not add up to the total number of patients.

^b Discontinuations were attributed to the last treatment used.

^c Patients who did not experience 3 migraine attacks were considered as discontinuations due to administrative problems.

Dic-K = Diclofenac-K (diclofenac potassium)

Source: PT tables 7.1-1, 7.1-2, PT listing 7.1-1

Source: Table 7-1 of sponsor's Clinical Study Report

Baseline Demographic and Background Characteristics

Demographic data and background characteristics are summarized in Table 7 and Table 8, respectively, for safety population (identical to ITT population). It appears that the demographic and predose migraine attack characteristics were similar for Dic-K Sachet group, Dic-K Tablet group and Placebo group.

Table 7: Demographic Data (Safety Population)

	Dic-K Sachet (N = 291)	Dic-K Tablet (N = 298)	Placebo (N = 299)	Total ^a (N = 317)
Sex - n (%)				
Male	41 (14.1)	43 (14.4)	42 (14.0)	46 (14.5)
Female	250 (85.9)	255 (85.6)	257 (86.0)	271 (85.5)
Race - n (%)				
Caucasian	290 (99.7)	297 (99.7)	298 (99.7)	316 (99.7)
Black	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Age (yr)				
Mean (SD)	39.1 (11.6)	39.3 (11.5)	39.4 (11.5)	39.2 (11.5)
Range	18 – 63	18 – 64	18 – 64	18 – 64
Weight (kg)				
Mean (SD)	66.2 (12.6)	66.2 (12.4)	66.3 (12.5)	66.2 (12.5)
Range	39.0 – 118.0	39.0 – 118.0	39.0 – 118.0	39.0 – 118.0
Height (cm) ^b				
Mean (SD)	167 (8)	167 (8)	167 (8)	167 (8)
Range	145 – 192	150 – 192	150 – 192	145 – 192

^a The total group represents the randomized patients who received at least one study treatment.

^b Height was missing for 1 patient receiving Dic-K tablet and placebo.

Source: PT tables 7.4-1, 7.4-3

Source: Table 7-3 of sponsor's clinical Study Report

Table 8: Predose Migraine Attack Data (Safety Population)

	Dic-K Sachet (N = 291)	Dic-K Tablet (N = 298)	Placebo (N = 299)
Early migraine symptoms			
Yes – n (%)	205 (70.4)	208 (69.8)	201 (67.2)
Time prior to drug intake (min) – mean (SD) ^a	210 (339)	222 (353)	238 (452)
median (Q25 –Q75) ^a	90 (30 – 240)	90 (30 – 245)	90 (30 – 247)
Migraine aura symptoms			
Yes – n (%)	54 (18.6)	52 (17.4)	57 (19.1)
Time prior to drug intake (min) – mean (SD) ^a	315 (782)	271 (528)	277 (531)
median (Q25 –Q75) ^a	90 (30 – 330)	80 (40 – 235)	90 (20 – 240)
Accompanying symptoms - n (%)			
Nausea	167 (57.4)	166 (55.7)	168 (56.2)
Vomiting	23 (7.9)	24 (8.1)	26 (8.7)
Photophobia	184 (63.2)	188 (63.1)	183 (61.2)
Phonophobia	160 (55.0)	167 (56.0)	158 (52.8)
None	38 (13.1)	48 (16.1)	39 (13.0)
Missing data	6 (2.1)	5 (1.7)	2 (0.7)
Headache intensity			
VAS (mm) - mean (SD)	67.2 (22.9)	67.3 (23.2)	67.7 (24.0)
VAS (mm) - range	0 – 100	8 – 100	8 – 100
Verbal scale: None - n (%)	1 (0.3)	0 (0.0)	0 (0.0)
Verbal scale: Mild - n (%)	23 (7.9)	30 (10.1)	40 (13.4)
Verbal scale: Moderate - n (%)	153 (52.6)	146 (49.0)	133 (44.5)
Verbal scale: Severe - n (%)	112 (38.5)	119 (39.9)	124 (41.5)
Verbal scale: Missing - n (%)	2 (0.7)	3 (1.0)	2 (0.7)
Working ability - n (%)			
Normal	14 (4.8)	15 (5.0)	25 (8.4)
Mild impairment	117 (40.2)	116 (38.9)	100 (33.4)
Severe impairment	115 (39.5)	108 (36.2)	113 (37.8)
Bed rest required	34 (11.7)	54 (18.1)	55 (18.4)
Missing assessment	11 (3.8)	5 (1.7)	6 (2.0)

Q25 / Q75 = 25% / 75% quantile, respectively

^a Considering patients with symptoms only.

Source: PT table 7.4-5

Source: Table 7-4 of sponsor's Clinical Study Report

3.1.2.6 Sponsor's Primary Efficacy Results

The primary efficacy variables was percentage of patients pain free at 2 hours post-dose, which was analyzed by a logistic regression model with the explanatory variables of treatment, period, patient, and baseline VAS headache intensity for ITT population.

Comparing diclofenac-K sachets and placebo, there were 279 patients who took the two medications, 19 of these were pain free on both and 196 were not pain free on both. Thus,

64 discordant pairs remained; of these 50 were pain free on diclofenac-K sachets and not on placebo while 14 were pain free on placebo and not on diclofenac-K sachets. This resulted in a difference of 36 more patients being pain free at 2 hours post-dose on diclofenac-K sachets than on placebo.

Sponsor's primary efficacy analysis results are presented in Table 9.

Table 9: Number (%) of patients pain free at 2 hours post-dose (ITT and PP population)

Population	Treatment ^a / Treatment contrast ^b	N	Number (%) of patients pain free		
			n (%)	95% CI (%)	p-value ^c
ITT population	Dic-K Sachet	291	72 (24.7)	19.9 – 30.1	-
	Dic-K Tablet	298	55 (18.5)	14.2 – 23.3	-
	Placebo	299	35 (11.7)	8.3 – 15.9	-
	Dic-K Sachet – Placebo	279	36 (12.9)	7.5 – 18.3	<0.0001
	Dic-K Sachet – Dic-K Tablet	281	19 (6.8)	0.7 – 12.8	0.0035
	Dic-K Tablet – Placebo	285	18 (6.3)	1.0 – 11.6	0.0040
PP population	Dic-K Sachet	225	53 (23.6)	18.2 – 29.7	-
	Dic-K Tablet	225	40 (17.8)	13.0 – 23.4	-
	Placebo	225	29 (12.9)	8.8 – 18.0	-
	Dic-K Sachet – Placebo	225	24 (10.7)	4.8 – 16.5	<0.0001
	Dic-K Sachet – Dic-K Tablet	225	13 (5.8)	-0.9 – 12.4	0.0089
	Dic-K Tablet – Placebo	225	11 (4.9)	-0.8 – 10.6	0.0712
Subgroup of patients with moderate or severe starting pain (ITT population)	Dic-K Sachet	265	64 (24.2)	19.1 – 29.8	-
	Dic-K Tablet	265	45 (17.0)	12.7 – 22.1	-
	Placebo	257	32 (12.5)	8.7 – 17.1	-
	Dic-K Sachet – Placebo	223	26 (11.7)	5.5 – 17.8	<0.0001
	Dic-K Sachet – Dic-K Tablet	234	11 (4.7)	-1.8 – 11.2	0.0214
	Dic-K Tablet – Placebo	230	12 (5.2)	-0.4 – 10.8	0.0087

CI = confidence interval

^a considering all patients on the respective treatment

^b considering only those patients who received both of the compared treatments, n is the difference of the number of pain free patients

^c two-sided for pairwise treatment comparison, derived from a logistic regression analysis with explanatory variables treatment, period, patient, and baseline VAS headache intensity

Source: PT tables 9.1-1, 9.1-2, 9.1-3, 9.1-4, 9.1-5, 9.1-6

Source: Table 9-1 of sponsor's Clinical Study Report

It appears that 50 mg diclofenac-K sachets displays better treatment effect than placebo.

Reviewer's Note:

First of all, based on this reviewer's discussion with the medical team, the non-inferiority claim of 50 mg diclofenac-K sachets over 50 mg diclofenac-K tablets will not be considered. Therefore, this reviewer will not discuss sponsor's non-inferiority results in this review.

Even though this reviewer does not agree with the model the sponsor used to analyze the primary endpoint, this reviewer's additional analyses (presented in Section 3.1.3 Reviewer's Analysis) also indicates that 50 mg diclofenac-K sachets seemingly performs better than placebo.

3.1.2.7 Sponsor's Secondary Efficacy Results

Associated Migraine Symptoms

Presence of nausea, vomiting, photophobia and phonophobia is summarized in Table 10.

Table 10: Presence of nausea, vomiting, photophobia and phonophobia at predose, 1, 2 and 8 hours post-dose and after drug intake (ITT population)

Treatment	Time point	N	Number (%) of patients				
			Nausea	Vomiting	Photophobia	Phonophobia	None
Dic-K Sachets	Predose	285	167 (58.6)	23 (8.1)	184 (64.6)	160 (56.1)	38 (13.3)
	1 hour	253	104 (41.1)	20 (7.9)	125 (49.4)	104 (41.1)	72 (28.5)
	2 hour	253	87 (34.4)	16 (6.3)	104 (41.1)	89 (35.2)	106 (41.9)
	8 hour ^a	147	25 (17.0)	8 (5.4)	27 (18.4)	27 (18.4)	100 (68.0)
	After drug intake ^b	282 ^c	127 (45.0)	33 (11.7)	146 (52.0)	126 (44.8)	82 (29.1)
Dic-K Tablets	Predose	293	166 (56.7)	24 (8.2)	188 (64.2)	167 (57.0)	48 (16.4)
	1 hour	255	118 (46.3)	21 (8.2)	134 (52.5)	107 (42.0)	70 (27.5)
	2 hour	259	101 (39.0)	20 (7.7)	112 (43.2)	90 (34.7)	105 (40.5)
	8 hour ^a	162	20 (12.3)	7 (4.3)	37 (22.8)	31 (19.1)	115 (71.0)
	After drug intake ^b	291	144 (49.5)	32 (11.0)	156 (53.6)	130 (44.7)	76 (26.1)
Placebo	Predose	297	168 (56.6)	26 (8.8)	183 (61.6)	158 (53.2)	39 (13.1)
	1 hour	257	128 (49.8)	26 (10.1)	137 (53.3)	127 (49.4)	59 (23.0)
	2 hour	270	123 (45.6)	26 (9.6)	137 (50.7)	129 (47.8)	80 (29.6)
	8 hour ^a	135	30 (22.2)	8 (5.9)	41 (30.4)	32 (23.7)	81 (60.0)
	After drug intake ^b	294	159 (54.1)	39 (13.3)	164 (55.8)	158 (53.7)	59 (20.1)

^a 8 hour or early termination

^b presence of a symptom on at least 1 post-dose time point reported in the diary or as AE within 8-72 hours post-dose (or the absence from all symptoms after taking study medication).

^c N = 281 for vomiting, photophobia, and phonophobia

Source: PT tables 9.2-12, 9.2-13, 9.2-14, 9.2-15, 9.2-16

Source: Table 9-6 of sponsor's Clinical Study Report

For nausea the number of patients symptom free at 2 hours post-dose was 166 (65.6%) for diclofenac-K sachets and 147 (54.4%) for placebo.

For presence of vomiting the number of patients symptom free at 2 hours post-dose was 237 (93.7%) for diclofenac-K sachets and 244 (90.4%) for placebo.

For presence of photophobia the number of patients symptom free at 2 hours post-dose was 149 (58.9%) for diclofenac-K sachets and 133 (49.3%) for placebo.

For presence of phonophobia the number of patients symptom free at 2 hours post-dose was 164 (64.8%) for diclofenac-K sachets and 141 (52.2%) for placebo.

The proportion of patients reporting none of the four symptoms at 2 hours post-dose was 106 (41.9%) for diclofenac-K sachets and 80 (29.6%) for placebo.

3.1.3 REVIEWER'S ANALYSIS

This reviewer confirmed sponsor's efficacy analyses results presented in this review for Study PRO-513301 and thinks it is not necessary to conduct additional analysis for this study.

Study CAT458C2301 was a three-way cross-over study with Latin square design, i.e., every treatment being represented once and only once in each treatment sequence and in each period. Based on this reviewer's discussion with the medical team, the non-inferiority claim of 50 mg diclofenac-K sachets over 50 mg diclofenac-K tablets will not be considered. Therefore, this reviewer will only present some descriptive statistics for 50 mg diclofenac-K tablets.

For Study CAT458C2301, the sponsor analyzed the primary efficacy variable, pain free at 2 hour post-dose, using a logistic regression model with treatment, period and patient as fixed effects, and baseline VAS headache intensity as a covariate for ITT population.

There are three issues with sponsor's primary efficacy analysis. First, for migraine study, pain, nausea, photophobia and phonophobia are the commonly used four co-primary efficacy endpoints, instead of freedom from pain as a single primary endpoint. Second, this reviewer thinks since the data from each patient were correlated and the model should include a random effect, and sequence should be included in the model as a fixed effect. Third, the overall dropout rate for this study was approximately 14%, which might affect the interpretation of the results from sponsor's primary efficacy analysis.

However, even though there are issues with sponsor's primary efficacy analysis, it appears that Dic-sachet displays better treatment effect than placebo. To further evaluate the efficacy of Dic-sachet compared to placebo, this reviewer conducted the following additional analyses.

3.1.3.1 Summary of Four Symptoms by Sequence and Period

The percentages of symptom free by sequence and period are summarized in Table 11 and

Table 12.

Table 11: Percentages of Symptom Free by Sequence (ITT)

Symptoms	Sequence	Dic Sachet n (%)	Placebo n (%)	Dic Tablet n (%)
Pain	S/T/P	30 (28.0%)	13 (13.7%)	27 (26.5%)
	T/P/S	22 (24.4%)	15 (14.9%)	14 (13.1%)
	P/S/T	20 (21.3%)	7 (6.8%)	14 (15.7%)
Nausea	S/T/P	58 (64.4%)	52 (59.1%)	59 (64.1%)
	T/P/S	57 (69.5%)	46 (50.6%)	54 (60.0%)
	P/S/T	51 (60.7%)	51 (54.9%)	47 (59.5%)
Photophobia	S/T/P	52 (57.8%)	48 (54.6%)	54 (58.7%)
	T/P/S	46 (56.1%)	39 (42.9%)	47 (52.2%)
	P/S/T	52 (61.9%)	49 (52.7%)	45 (57.0%)
Phonophobia	S/T/P	60 (66.7%)	51 (58.0%)	61 (66.3%)
	T/P/S	53 (64.6%)	43 (47.2%)	59 (65.6%)
	P/S/T	53 (63.1%)	48 (51.6%)	51 (64.6%)

Source: Reviewer's Analysis

Table 12: Percentages of Symptom Free by Period (ITT)

Symptoms	Period	Dic Sachet n (%)	Placebo n (%)	Dic Tablet n (%)
Pain	1	30 (28.0%)	7 (6.8%)	14 (13.1%)
	2	20 (21.3%)	15 (14.9%)	27 (26.5%)
	3	22 (24.2%)	13 (13.7%)	14 (15.7%)
Nausea	1	58 (64.4%)	51 (54.9%)	54 (60.0%)
	2	51 (60.7%)	46 (50.6%)	59 (64.1%)
	3	57 (69.5%)	52 (59.1%)	47 (59.5%)
Photophobia	1	52 (57.8%)	49 (52.7%)	47 (52.2%)
	2	52 (61.9%)	39 (42.9%)	54 (58.7%)
	3	46 (56.1%)	48 (54.6%)	45 (57.0%)
Phonophobia	1	60 (66.7%)	48 (51.6%)	59 (65.6%)
	2	53 (63.1%)	43 (47.3%)	61 (66.3%)
	3	53 (64.6%)	51 (58.0%)	51 (64.6%)

Source: Reviewer's Analysis

From the summary tables, it seems that the percentages of symptom free were numerically higher for patients in diclofenac sachet-K group than in placebo group, for each sequence and for each period.

3.1.3.2 McNemar's Test

For the primary endpoint, pain free at 2-hour post-dose, a McNemar's test was conducted for each of the three sequences to compare Dic-sachet and Placebo. Since for each of the three McNemar's tests the test statistic has a χ_1^2 distribution and the three test statistics are independent, the sum of the three test statistics has a χ_3^2 distribution, which could be considered as an overall test. The results are presented in Table 13.

Table 13: McNemar's Test for Pain Free at 2-hour post-dose (ITT)

		S/T/P		T/P/S		P/S/T	
		Placebo		Placebo		Placebo	
		Yes	No	Yes	No	Yes	No
Sachet	Yes	6	21	9	13	4	16
	No	7	61	5	63	2	72
Test Statistic 1		7.0		3.56		10.89	
P-value 1		0.0082		0.0593		0.0010	
Test Statistic 2, P-value 2		Test statistic=21.45, p-value<0.0001					

Source: Reviewer's Analysis

*Test statistic 1 and p-value 1 are for the individual McNemar's test for each sequence.

*Test statistic 2 is the sum of the three individual McNemar's test statistic and p-value 2 is its corresponding p-value.

* All p-values are nominal p-values.

Similarly, McNemar's tests were performed for three other associated symptoms, i.e., nausea, photophobia and phonophobia. The results are summarized in Table 14, Table 15, and Table 16.

Table 14: McNemar's Test for Nausea (ITT)

		S/T/P		T/P/S		P/S/T	
		Placebo		Placebo		Placebo	
		Yes	No	Yes	No	Yes	No
Sachet	Yes	33	14	32	20	32	15
	No	11	16	7	18	10	21
Test Statistic 1		0.36		6.26		1.0	
P-value 1		0.5485		0.0124		0.3173	
Test Statistic 2, P-value 2		Test statistic=7.62, p-value=0.0546					

Source: Reviewer's Analysis

*Test statistic 1 and p-value 1 are for the individual McNemar's test for each sequence.

*Test statistic 2 is the sum of the three individual McNemar's test statistic and p-value 2 is its corresponding p-value.

* All p-values are nominal p-values.

Table 15: McNemar's Test for Photophobia (ITT)

		S/T/P		T/P/S		P/S/T	
		Placebo		Placebo		Placebo	
		Yes	No	Yes	No	Yes	No
Sachet	Yes	29	12	28	15	32	16
	No	9	24	4	30	10	20
Test Statistic 1		0.43		6.37		1.38	
P-value 1		0.5127		0.0116		0.2393	
Test Statistic 2, P-value 2		Test statistic=8.18, p-value=0.0424					

Source: Reviewer's Analysis

*Test statistic 1 and p-value 1 are for the individual McNemar's test for each sequence.

*Test statistic 2 is the sum of the three individual McNemar's test statistic and p-value 2 is its corresponding p-value.

* All p-values are nominal p-values.

Table 16: McNemar’s Test for Phonophobia (ITT)

		S/T/P		T/P/S		P/S/T	
		Placebo		Placebo		Placebo	
		Yes	No	Yes	No	Yes	No
Sachet	Yes	31	19	32	19	33	15
	No	12	12	6	20	6	24
Test Statistic 1		1.58		6.76		3.86	
P-value 1		0.2087		0.0093		0.0495	
Test Statistic 2, P-value 2		Test statistic=12.2, p-value=0.0067					

Source: Reviewer’s Analysis

*Test statistic 1 and p-value 1 are for the individual McNemar’s test for each sequence.

*Test statistic 2 is the sum of the three individual McNemar’s test statistic and p-value 2 is its corresponding p-value.

* All p-values are nominal p-values.

For each symptom and for each sequence, the number of patients being symptom free on Dic-sachet but not on Placebo was larger than the number of patients being symptom free on Placebo but not on Dic-sachet. Even though some of the individual McNemar’s tests were not statistically significant, the overall tests were statistically significant (for pain, photophobia and phonophobia) or marginally significant (for nausea), at 0.05 level (two-sided).

3.1.3.3 First Period Analysis

For each of the four symptoms, this reviewer conducted Cochran-Mantel-Haenszel (CMH) test stratified by analysis center, for the first period. The results are displayed in Table 17.

Table 17: Results of CMH for the First Period

Symptom	Dic Sachet n (%*)	Placebo n (%*)	p-value** for Diclofenac Sachet vs Placebo
Pain	30 (28.0%)	7 (6.8%)	<0.0001
Nausea	58 (64.4%)	51 (54.9%)	0.1446
Photophobia	52 (57.8%)	49 (52.7%)	0.0644
Phonophobia	60 (66.7%)	48 (51.6%)	0.0037

*: percentages of symptom free

** : p-values are nominal p-values.

Source: Reviewer’s Analysis

For first period, the percentages of symptom free were numerically higher for patients in Dic-sachet group than in placebo group, for all four symptoms. The nominal p-values for pain, photophobia and phonophobia were significant or marginally significant at 0.05 level (two-sided) while the p-value for nausea was 0.14. However, this reviewer would like to point out that the study was designed as a three-way cross-over study so it was not powered for first period analysis.

3.2 Evaluation of Safety

Please read Dr. Ronald Farkas' review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

4.1.1 STUDY PRO-513301

The percentages of symptom free by age, gender and ethnic group was summarized in Table 18.

Table 18: Percentage of Symptom Free by Age, Gender and Ethnic Group (ITT Population)

Symptom	Subgroup	N	PRO-513 n (%*)	Placebo n (%*)
Pain	<=41 yrs**	356	43 (25.0%)	17 (9.2%)
	>41 yrs	334	43 (25.2%)	18 (11.0%)
	Female	585	75 (25.6%)	26 (8.9%)
	Male	105	11 (22%)	9 (16.4%)
	White	552	62 (22.5%)	24 (8.7%)
	African American	111	19 (36.5%)	11 (18.6%)
	Other	27	5 (33.3%)	0 (0%)
Nausea	<=41 yrs	356	111 (64.9%)	99 (53.8%)
	>41 yrs	334	111 (64.9%)	84 (51.5%)
	Female	585	187 (64.8%)	147 (50.3%)
	Male	105	35 (70.0%)	36 (65.5%)
	White	552	178 (64.5%)	144 (52.2%)
	African American	111	33 (63.5%)	36 (61.0%)
	Other	27	11 (73.3%)	3 (25.0%)
Photophobia	<=41 yrs	356	70 (40.1%)	48 (26.1%)
	>41 yrs	334	69 (40.4%)	47 (28.8%)
	Female	585	120 (41.0%)	78 (26.7%)
	Male	105	19 (38.0%)	17 (30.9%)
	White	552	110 (39.9%)	72 (26.1%)
	African American	111	22 (42.3%)	22 (37.3%)
	Other	27	7 (46.7%)	1 (8.3%)
Phonophobia	<=41 yrs	356	76 (44.2%)	46 (25.0%)
	>41 yrs	334	76 (44.4%)	49 (30.1%)
	Female	585	133 (45.4%)	75 (25.7%)
	Male	105	19 (38.0%)	20 (36.4%)
	White	552	121 (43.8%)	73 (26.5%)
	African American	111	23 (44.2%)	21 (35.6%)
	Other	27	8 (53.3%)	1 (8.3%)

*: Percentages of symptom free

** : Median age is 41 years.

Source: Reviewer’s Analysis

It appears that the point estimates of percentages of symptom free were in the same direction across the patient subgroups investigated.

4.1.2 STUDY CAT458C2301

The percentages of symptom free by age and gender (for all three sequences) was presented in Table 19. Study CAT458C2301 was a European study. Among 317 subjects in ITT population, only one subject was African American. Thus, ethnic subgroup analysis was not conducted.

Table 19: Percentage of Symptom Free by Age and Gender Group (ITT Population)

Symptom	Subgroup	N	Dic Sachet n (%)	Dic Tablet n (%)	Placebo n (%)
Pain	<=38 yrs**	442	42 (28.4%)	32 (21.6%)	18 (12.3%)
	>38 yrs	446	30 (21.0%)	23 (15.3%)	17 (11.1%)
	Female	762	63 (25.2%)	50 (19.6%)	31 (12.1%)
	Male	126	9 (22.0%)	5 (11.6%)	4 (9.5%)
Nausea	<=38 yrs	394	82 (63.6%)	81 (62.3%)	81 (60.0%)
	>38 yrs	395	84 (66.1%)	79 (60.3%)	68 (49.6%)
	Female	672	135 (62.2%)	133 (59.9%)	125 (53.7%)
	Male	117	31 (79.5%)	27 (69.2%)	24 (61.5%)
Photophobia	<=38 yrs	394	80 (62.0%)	78 (60.0%)	66 (48.9%)
	>38 yrs	395	70 (55.1%)	68 (51.9%)	70 (51.1%)
	Female	672	129 (59.5%)	123 (55.4%)	114 (48.9%)
	Male	117	21 (53.9%)	23 (59.0%)	22 (56.4%)
Phonophobia	<=38 yrs	394	88 (68.2%)	89 (68.5%)	74 (54.8%)
	>38 yrs	395	78 (61.4%)	82 (62.6%)	68 (49.6%)
	Female	672	140 (64.5%)	149 (67.1%)	118 (50.6%)
	Male	117	26 (66.7%)	22 (56.4%)	24 (61.5%)

*: Percentages of symptom free

** : Median age is 38 years.

Source: Reviewer's Analysis

Comparing Dic-K Sachet and Placebo, it seems that the point estimates of percentages of symptom free were in the same direction across the patient subgroups investigated, except for male patients for the symptom of photophobia.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 STUDY PRO-513301

For Study PRO-513301, the four co-primary efficacy endpoints were headache pain, nausea, photophobia and phonophobia at 2 hours post-dosing, which were analyzed using CMH test stratified by analysis center for ITT population. Last observation carried forward (LOCF) was used to impute missing data. The percent of subjects in the PRO-513 treatment group for the ITT population who had no headache pain at 2-hours post-dose was 25%, who had no nausea was 65%, who had no photophobia was 41%, and who had no phonophobia was 44%, comparing to 10%, 53%, 27%, and 27% of subjects in the placebo treatment group, respectively. The treatment comparisons between PRO-513 and placebo group for all 4 co-primary endpoints were statistically significant ($p \leq 0.002$).

5.1.2 STUDY CAT458C2301

Study CAT458C2301 was a three-way cross-over study with Latin square design, i.e., every treatment being represented once and only once in each treatment sequence and in each period.

According to the sponsor, the primary objective of this study was to determine whether a single dose of 50 mg diclofenac-K sachets is superior to placebo and non-inferior to 50 mg diclofenac-K tablets in treating the pain and associated symptoms of migraine headache. However, based on this reviewer's discussion with the medical team, the non-inferiority claim of 50 mg diclofenac-K sachets over 50 mg diclofenac-K tablets will not be considered. Therefore, the review for this study focuses on the treatment comparison between 50 mg diclofenac-K sachets and placebo.

The primary efficacy variable was freedom from pain assessed on the verbal scale for headache intensity at 2 hours post dose. The sponsor analyzed this primary efficacy variable using a logistic regression model with treatment, period and patient as fixed effects, and baseline VAS headache intensity as a covariate for ITT population. Based on this analysis, the treatment comparison between 50 mg diclofenac-K sachets and placebo group were statistically significant ($p < 0.0001$).

There are three issues with sponsor's primary efficacy analysis. First, for migraine study, pain, nausea, photophobia and phonophobia are the commonly used four co-primary efficacy endpoints, instead of freedom from pain as a single primary endpoint. Second, this reviewer thinks since the data from each patient were correlated and the model should include a random effect, and sequence should be included in the model as a fixed effect. Third, the overall dropout rate for this study was approximately 14%, which might affect the interpretation of the results from sponsor's primary efficacy analysis.

However, even though there are issues with sponsor's primary efficacy analysis, it appears that diclofenac-K sachet displays better treatment effect than placebo. To further evaluate the

efficacy of diclofenac-K sachet compared to placebo, this reviewer conducted three additional analyses.

First, this reviewer summarized the percentages of symptom free by sequence and period for all four symptoms, i.e., pain, nausea, photophobia and phonophobia. This analysis shows that the percentages of symptom free were numerically higher for patients in diclofenac sachet-K group than in placebo group, for each sequence and for each period.

Second, for each symptom, this reviewer conducted a McNemar's test for each of the three sequences to compare diclofenac-K sachet and placebo. In addition, for each symptom, since the McNemar's test statistic for each sequence has a χ^2_1 distribution and the three test statistics are independent, the sum of the three test statistics has a χ^2_3 distribution, which could be considered as an overall test. The results indicate that, for each symptom and for each sequence, the number of patients being symptom free on diclofenac-K sachet but not on placebo was larger than the number of patients being symptom free on placebo but not on diclofenac-K sachet. Even though some of the individual McNemar's tests were not statistically significant, the overall tests were statistically significant (for pain, photophobia and phonophobia) or marginally significant (for nausea), at 0.05 level (two-sided).

Third, for each symptom, this reviewer conducted Cochran-Mantel-Haenszel (CMH) test stratified by analysis center, for the first period. This analysis shows that, for first period, the percentages of symptom free were numerically higher for patients in diclofenac-K sachet group than in placebo group, for all four symptoms. The nominal p-values for pain, photophobia and phonophobia were significant or marginally significant at 0.05 level (two-sided) while the p-value for nausea was 0.14. However, this reviewer would like to point out that the study was designed as a three-way cross-over study so it was not powered for first period analysis.

In summary, this reviewer thinks Study CAT458C2301 shows benefits of 50 mg diclofenac-K sachets in the treatment of migraine, compared to placebo.

5.2 Conclusions and Recommendations

Based on Study PRO-513301, there is evidence that PRO-513 is effective for the treatment of migraine with and without aura in adults, compared to placebo.

For Study CAT458C2301 (b) (4) is a PRO-513 equivalent), even though there are issues with sponsor's primary efficacy analysis, it appears that this study shows benefits of 50 mg diclofenac-K sachets in the treatment of migraine, compared to placebo. Please refer to Section 3.1.3 Reviewer's Analysis for details.

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/s/

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