CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-802/S002

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA: 20-802

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Name of Drug: Excedrin Migraine

Indication: Migraine

Sponsor: Bristol-Myers

Documents reviewed: Vol. 1 - 3 of 3 and Clinical Trial Report: GHBA-840, -841, -842

Studies Reviewed: GHBA-840, GHBA-841, GHBA-842

1. BACKGROUND

On January 14, 1998, the Food and Drug Administration (FDA) had approved Excedrin Migraine (NDA 20-802), which contains the same formulation as Excedrin ES, for pain associated with migraine headache. Under NDA 20-802 Excedrin Migraine is currently marketed for over-the-counter use by consumers "for the temporary relief of mild to moderate pain associated with migraine headache."

On December 18, 1998, Bristol-Myers submitted an efficacy supplement to the approved NDA 20-802 for Excedrin Migraine to modify the "Use" section of the labeling to read as:

- For the relief of migraine, and
- Excedrin Migraine relieves the symptoms of migraine including headache pain, nausea, sensitivity to light and sound, and difficulty in carrying out normal activities.

The submission of this sNDA contained clinical data from 3 double-blind, randomized, placebo-controlled studies. Data of this sNDA for the purpose of modifying labeling was identical with the data for original NDA 20-802 submission. In this situation many issues need to be addressed before further analyses and conclusions.

The indication of the approved NDA 20-802 was migraine headache pain, one of the associated migraine symptoms. The other symptoms, nausea, sensitivity to light and sound, and difficulty in carrying out normal activities, were secondary efficacy in the original NDA. The FDA medical division of neuropharmacology decided not to review the data of functional disability symptom due to the lack of validity of instrument in measuring functional disability. The data submitted by sponsor may mislead conclusion of drug effect of Excedrin Migraine.

Subjects recruited under the original inclusion and the exclusion criteria targeted the population of patients with moderate to severe migraine headache. Since the three endpoints were secondary efficacy variables, a minority of migraineurs without headache pain but have other symptom at baseline were excluded from the original NDA recruiting. With the sponsor's data, the reviewer focused on the subjects for those who had particular symptom at baseline and examine the proportions of subjects without symptoms after treatment.

The basic issue is that having demonstrated the efficacy of the treatment based on the primary endpoint, how should one determine which clinical effects as measured by the secondary endpoints may be used in the USE section of the drug label. Multiplicity is the primary statistical issue of concern here. To include any secondary endpoint in the labeling, multiplicity adjustment is necessary for protecting the Type I error. In reviewing this sNDA, 3 secondary efficacy variables, nausea, photophobia, and phonophobia, were considered by the Agency for label modification purpose. Without adjusting for the multiple post-dose time points, an adjusted α level of **0.0167** is used as the level of significance based on the Bonferroni method. A more liberal method based on the Hochberg procedure would result in the same conclusion.

Even though the p-values which associated with those secondary endpoints have no inferential values, they still need to be adjusted for multiplicity in order to determine whether they can be included in the labeling.

2. STUDY SPECIFICATIONS

2.1. Objective

The objective of NDA 20-802 was to assess the effectiveness of Excedrin Extra-Strength (ES) in alleviating acute migraine headache pain. The purpose of this sNDA is to extend the "Use" section of the labeling.

2.2. Study population for NDA 20-802

The subjects evaluated in the three studies of NDA 20-802 were migraineurs whose headache pain was of moderate to severe intensity. The subjects, stated in the submission, were a representative sample of migraine sufferers in the community who could self-recognize, self-treat and self rate the headache pain and associated symptoms of a migraine.

A total of 1,220 efficacy-evaluable patients were identified from 20 sites of three protocols. Detailed plan of recruitment can be seen in the original NDA submission. The overall efficacy-evaluable patients had a mean age of 36.7±10.8 years; 79.3% of patients were females; and 86.1%of patients were Caucasians. Table 1 shows the demographic characteristics, overall and by protocol. Excedrin group and placebo were homogeneous in age, gender, and ethnicity, overall and for protocol. Also, according to the sponsor's report in the sNDA, there were no significant differences in the baseline characteristics of migraine, such as age of onset, patient's migraine history, with/without aura, symptoms with migraine attacks, severity of migraine, and so on, between excedrin group and placebo. All the data presented in this review are referred to efficacy-evaluable patients.

2.3 Results and conclusions for headache pain

Based on the Agency's review, the three studies of NDA 20-802 and resulting data provided adequate statistical evidence that excedrin is effective in relieving the headache pain of migraine. The sponsor summarized efficacy results at 2 and 6 hours postdose in the submission of NDA 20-802. For all three studies, the sponsors concluded that for Pain Intensity Difference (PID) and Patient Response Status (PRS), Excedrin was statistically more effective in the relief of migraine pain than placebo, which had been confirmed by the FDA reviewer.

Table 1. Demographic Characteristics for Efficacy Evaluable Subjects, Overall and by Protocol

	Protocol			
	GHBA-840 (N=378)	**GHBA-841 (N=427)**	**GHBA-842 (N=415)**	**Pooled (N=1,220)**
Mean Age±SD (yrs)				
Placebo	35.8±10.2	36.1±12.1	37.6±10.8	36.4±11.0
Excedrin	35.3± 9.7	38.0±11.3	37.9±10.7	37.0±10.6
Female				
Placebo	155 (78.3%)	180 (80.7%)	174 (82.5%)	479 (80.4%)
Excedrin	142 (74.0%)	162 (75.7%)	176 (83.0%)	470 (78.1%)
White				
Placebo	166 (83.8%)	197 (88.3%)	188 (89.1%)	542 (87.7%)
Excedrin	151 (78.6%)	180 (84.1%)	191 (90.1%)	508 (84.4%)
Black				
Placebo	32 (16.2%)	12 (5.4%)	15 (7.1%)	54 (8.7%)
Excedrin	39 (20.3%)	23 (10.7%)	8 (3.8%)	69 (11.5%)
Hispanic				
Placebo	0 (0.0%)	9 (4.0%)	4 (1.9%)	13 (2.1%)
Excedrin	0 (0.0%)	6 (2.8%)	9 (4.2%)	14 (2.3%)

2.4. Study populations for the sNDA

In reviewing the sNDA, we focused on those who had migraine symptoms of nausea, photophobia, or phonophobia at baseline, instead of the overall population of the original NDA.

Specifically, the study populations in reviewing the sNDA were defined as the subjects with those migraine symptoms at baseline, which were the subsets of the overall 1,220 efficacy-evaluable patients. For example, in reviewing excedrin effect on nausea symptoms, a total of 729 patients who had mild, moderate, or severe nausea symptom at baseline were identified for data analysis. The patients without any nausea symptom at baseline (N=250 for excedrin group and N=241 for placebo) were excluded from review. Similarly, in reviewing drug effect on photophobia and phonophobia symptoms, 1,158 patients who had photophobia at baseline and 1,116 subjects who had phonophobia at baseline were used for data analyses, respectively.

Among the 1,220 efficacy-evaluable patients of the NDA, 729 patients (59.8%) had nausea symptom at baseline; 1,158 patients (94.4%) had photophobia at baseline; and 1,116 patients (91.5%) had phonophobia at baseline. In addition, 1,080 patients (88.5%) had both photophobia and phonophobia symptoms at baseline (excedrin: 86.7% vs placebo: 90.3%). In contrast, only 28 patients (2.3%) had neither of the two symptoms (excedrin: 2.2% vs placebo: 2.4%).

The distributions of intensity of migraine symptoms at baseline with respect to nausea, photophobia, and phonophobia are shown in Table 2. Excedrin group and placebo had similar distributions of intensity of symptoms. However, we didn't compare more detailed characteristics at baseline between excedrin and placebo groups for those who had particular symptom at baseline. It is another evidence for the inappropriateness of using the original NDA data for the sNDA submission and the difficulties in statistical analysis.

Table 2 Distributions of intensity of Nausea, Photophobia, and Phonophobia at baseline

Symptom	Protocol			
	GHBA-840 (N=378)	GHBA-841 (N=427)	GHBA-842 (N=415)	Pooled (N=1,220)
Nausea				
None				
Placebo	91 (48%)	93 (42%)	66 (32%)	250 (40.5%)
Excedrin	86 (46%)	78 (38%)	77 (37%)	241 (40.0%)
Mild				
Placebo	73 (38%)	96 (43%)	90 (44%)	259 (41.9%)
Excedrin	73 (39%)	92 (45%)	88 (42%)	253 (42.0%)
Moderate				
Placebo	26 (14%)	29 (13%)	48 (23%)	103 (16.7%)
Excedrin	25 (13%)	30 (15%)	40 (19%)	95 (15.8%)
Severe				
Placebo	1 (1%)	3 (1%)	2 (1%)	6 (1.0%)
Excedrin	3 (2%)	6 (3%)	4 (2%)	13 (2.2%)
Photophobia				
None				
Placebo	6 (3%)	12 (5%)	16 (8%)	34 (5.6%)
Excedrin	3 (2%)	16 (8%)	9 (4%)	28 (4.7%)
Mild				
Placebo	44 (23%)	62 (28%)	67 (32%)	173 (28.0%)
Excedrin	56 (30%)	68 (33%)	73 (35%)	197 (32.7%)
Moderate				
Placebo	109 (57%)	116 (53%)	97 (47%)	322 (52.1%)
Excedrin	104 (56%)	98 (48%)	99 (47%)	301 (50.0%)
Severe				
Placebo	32 (17%)	31 (14%)	26 (13%)	89 (14.4%)
Excedrin	24 (13%)	24 (12%)	28 (13%)	76 (12.6%)
Phonophobia				
None				
Placebo	6 (3%)	14 (6%)	20 (10%)	40 (6.5%)
Excedrin	14 (7%)	28 (14%)	22 (10%)	64 (10.6%)
Mild				
Placebo	56 (29%)	84 (38%)	76 (37%)	216 (35.0%)
Excedrin	42 (22%)	58 (28%)	74 (35%)	174 (28.9%)
Moderate				
Placebo	109 (57%)	102 (46%)	89 (43%)	300 (48.5%)
Excedrin	97 (52%)	96 (47%)	88 (42%)	281 (46.7%)
Severe				
Placebo	20 (10%)	20 (9%)	21 (10%)	61 (9.9%)
Excedrin e	34 (18%)	24 (12%)	24 (12%)	82 (13.6%)

2.5. Study Design

The sNDA contained three studies that had identical design of study, similar sample sizes, and homogeneous study populations, except Study GHBA-840 of being single-center. The three studies were double-blind, randomized, parallel-group, single-dose, placebo-controlled. All involved a screening phase, a selection phase, and a double-blind phase. Qualified subjects were randomized to one of excedrin and placebo group as acute treatment for one migraine. The details of study design and disposition of patients have been well-described in the medical review.

2.6. Efficacy Measures

To evaluate efficacy on migraine symptoms of nausea, photophobia, and phonophobia, response scale has four categories: 0=None, 1=Mild, 2=Moderate, and 3=Severe. Medication effects on the associated migraine symptoms were assessed by examining the proportions of subjects who had no nausea, no photophobia, and on phonophobia symptom at each postdose time point. These proportions were calculated for all efficacy-evaluable patients who had particular associated migraine symptom at baseline.

2.7. Statistical Analysis

It was described by sponsor in the sNDA that drug effects on the associated migraine symptoms (nausea, photophobia, and phonophobia) were analyzed using the Cochran-Mentel-Haenszel test. The reviewer compared the proportions of patients without associated migraine symptom among those who had that particular symptom at the baseline between treatment and placebo. The responses at all postdose time points were compared between groups. Then, the same analyses were repeated with stratifying the intensity of symptoms and by site.

Missing data were imputed as an average between the adjacent observed values, as stated in the sNDA submission. If the 6-hour observation was missing, it was replaced by the 4-hour observation. If two or more consecutive observations were missing, they remained as missing, and no data were imputed for purpose.

3. NAUSEA

3.1. Subjects

A total of 729 efficacy-evaluable patients (N=361 for excedrin group and N=368 for placebo) who had migraine symptom of nausea at baseline, which included those who had mild, moderate, and severe nausea, were identified. Table 3 illustrates the demographics of the patients overall and for each protocol. There were no significant differences between excedrin group and placebo in those factors, overall and for each protocol. As we mentioned before, no further between group comparisons in baseline characteristics such as severity of illness are conducted for those who had nausea symptoms at baseline.

Table 3. Characteristics of Subjects with Nausea Symptom at Baseline

	GHBA-840	GHBA-840	GHBA-840	Pooled
Mean Age ± SD (yr)				
Excedrin	35.7± 9.6	39.0±11.2	38.6±10.9	37.9±10.7
Placebo	35.7±10.1	36.0±11.2	37.5±11.1	36.5±10.9
Female				
Excedrin	76.7%	79.4%	86.4%	81.2%
Placebo	74.6%	83.6%	85.2%	84.5%
White				
Excedrin	78.6%	87.0%	90.9%	86.1%
Placebo	87.5%	91.4%	90.1%	89.8%

3.2 Treatment effects on nausea

The proportions of patients without nausea among those who had nausea at baseline are illustrated in Table 4. At 2 hour postdose, Studies GHBA-840 and -841 did not exhibit any statistically significant difference between excedrin and placebo groups at the level of 0.0167.

Table 4. Proportion of Subjects without Nausea among Those Who Had Nausea at Baseline

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=101)	8.9%	28.7%	54.5%	64.4%	64.4%	63.4%
Placebo (N=100)	15.0%	32.0%	41.0%	49.0%	49.0%	43.0%
P-value	.183	.612	.056	.019	.028	.004
GHBA-841						
Excedrin (N=128)	8.6%	24.2%	36.7%	51.6%	55.5%	60.9%
Placebo (N=128)	16.4%	27.3%	33.6%	37.5%	33.6%	32.0%
P-value	.059	.568	.601	.024	<.001	<.001
GHBA-842						
Excedrin (N=132)	9.1%	25.0%	44.7%	51.5%	62.9%	63.4%
Placebo (N=140)	7.1%	11.4%	27.9%	32.9%	36.4%	41.4%
P-value	.556	.004	.004	.002	<.001	<.001
Pooled						
Excedrin (N=361)	8.9%	25.8%	44.6%	55.1%	60.4%	62.6%
Placebo (N=368)	12.5%	22.6%	33.4%	38.6%	38.9%	38.6%
P-value	.112	.312	.002	<.001	<.001	<.001

However, the pooled data at both 2 hour and 6 hour and all protocols at 6 hour had significant drug effect on nausea at .0167 level. Over 60% of excedrin patients had no nausea symptom at hour 6, overall and for all individual studies.

In order to investigate the relationship between intensity of nausea at baseline and drug effect on nausea, the reviewer dichotomized the intensity of nausea as 'mild' and 'moderate & severe' and studied the between-group difference of proportion of subjects without nausea after postdose. If the interaction between intensity of baseline symptom and drug effect existed, it implied that excedrin might have effect only for patients within a specific category of baseline severity. Tables 5 and 6 show the proportions for those who had moderate and severe nausea at baseline and for those with only mild nausea at baseline, respectively.

Those two tables demonstrate the drug effect on nausea maintained similar directions for both excedrin group and placebo, with different intensity of nausea symptom at baseline for all postdose time points. Tables 5 and 6 do not show the evidence to the interaction effect of treatment by intensity of nausea at baseline. All the pooled data exhibited the difference of treatment effect both at 2 and 6 hour. All of three studies didn't show significant treatment effect at level of 0.0167 at 2 hour for those who had mild nausea, and only Study GHBA-842 had significant p-value at 0.0167 for those who had moderate and severe nausea.

Table 5. Proportion of Subjects without Nausea among Those Who Had Moderate and Severe Nausea at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N= 28)	3.6%	25.0%	32.1%	42.9%	53.6%	53.6%
Placebo (N=27)	3.7%	11.1%	18.5%	29.6%	33.3%	29.6%
P-value	.979	.182	.246	.308	.130	.072
GHBA-841						
Excedrin (N=36)	5.6%	16.7%	27.8%	38.9%	52.8%	52.8%
Placebo (N=32)	9.4%	15.6%	15.6%	15.6%	9.4%	3.1%
P-value	.547	.907	.228	.033	<.001	<.001
GHBA-842						
Excedrin (N=44)	2.3%	13.6%	36.4%	38.6%	52.3%	56.8%
Placebo (N=50)	4.0%	0.0%	14.0%	18.0%	24.0%	36.0%
P-value	.635	.007	.012	.026	.005	.043
Pooled						
Excedrin (N=108)	3.7%	17.6%	32.4%	39.8%	52.8%	54.6%
Placebo (N=109)	5.5%	7.3%	15.6%	20.2%	22.0%	24.8%
P-value	.527	.022	.004	.002	<.001	<.001

Table 6. Proportion of Subjects without Nausea among Those Who Had Mild Nausea at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N= 73)	11.0%	30.1%	63.0%	72.6%	68.5%	67.1%
Placebo (N=73)	19.2%	39.7%	49.3%	54.8%	54.8%	48.0%
P-value	.165	.224	.095	.025	.089	.019
GHBA-841						
Excedrin (N=92)	9.8%	27.2%	40.2%	56.5%	56.5%	64.1%
Placebo (N=96)	18.8%	31.3%	39.6%	44.8%	41.7%	41.7%
P-value	.080	.539	.929	.108	.042	.002
GHBA-842						
Excedrin (N=88)	12.5%	30.7%	48.9%	58.0%	67.1%	67.1%
Placebo (N=90)	8.9%	17.8%	35.6%	41.1%	43.3%	44.4%
P-value	.435	.044	.072	.025	.001	.002
Pooled						
Excedrin (N=253)	11.1%	29.3%	49.8%	61.7%	63.6%	66.0%
Placebo (N=259)	15.4%	29.0%	40.9%	46.3%	46.0%	44.4%
P-value	.145	.942	.044	<.001	<.001	<.001

3.3. Treatment effect on nausea by site

Twenty sites involved one of the three protocols in collecting efficacy data. The proportions of patients without nausea symptom (all levels of nausea intensity at baseline) at 2 and 6 hour postdose among those who had nausea at baseline for each site are presented in Table 7.

Table 7. Proportion of Subjects without Nausea among Those Who Had Nausea at Baseline

Site	Group (N)	2 Hr (%)	6 Hr (%)	Site	Group (N)	2 Hr (%)	6 Hr (%)
#1	Excedrin (14) Placebo (15) P-value	28.6% 13.3% (.311)	57.1% 13.3% (.013)	#11	Excedrin (18) Placebo (12) P-value	22.2% 41.7% (.255)	61.1% 58.3% (.879)
#2	Excedrin (2) Placebo (3) P-value	100% 66.7% (.361)	100% 66.7% (.361)	#12	Excedrin (15) Placebo (14) P-value	26.7% 21.4% (.742)	53.3% 35.7% (.340)
#3	Excedrin (15) Placebo (20) P-value	46.7% 40.0% (.693)	73.3% 20.0% (.002)	#14	Excedrin (35) Placebo (37) P-value	31.4% 18.9% (.220)	60.0% 35.1% (.035)
#4	Excedrin (16) Placebo (13) P-value	43.8% 38.5% (.774)	56.3% 7.7% (.006)	#15	Excedrin (18) Placebo (19) P-value	55.6% 26.3% (.070)	66.7% 42.1% (.134)
#5	Excedrin (2) Placebo (0) P-value	50.0% - -	50.0% - -	#16	Excedrin (23) Placebo (26) P-value	39.1% 23.1% (.224)	65.2% 53.9% (.419)
#6	Excedrin (101) Placebo (100) P-value	54.5% 41.0% (.056)	63.4% 43.0% (.004)	#17	Excedrin (21) Placebo (18) P-value	52.4% 22.2% (.054)	76.2% 50.0% (.089)
#7	Excedrin (3) Placebo (6) P-value	100% 33.3% (.058)	66.7% 16.7% (.134)	#18	Excedrin (7) Placebo (10) P-value	57.1% 50.0% (.772)	85.7% 50.0% (.129)
#8	Excedrin (8) Placebo (8) P-value	50.0% 37.5% (.614)	50.0% 50.0% (1.00)	#19	Excedrin (14) Placebo (11) P-value	14.3% 45.5% (.085)	57.1% 27.3% (.135)
#9	Excedrin (16) Placebo (23) P-value	56.3% 43.5% (.433)	81.3% 52.2% (.063)	#20	Excedrin (13) Placebo (13) P-value	53.9% 23.1% (.107)	38.5% 23.1% (.395)
#10	Excedrin (4) Placebo (5) P-value	25.0% 40.0% (.635)	75.0% 40.0% (.294)	#21	Excedrin (16) Placebo (15) P-value	37.5% 33.3% (.809)	43.8% 26.7% (.320)

Comparing excedrin group with placebo in the proportions of patients without nausea at postdose 2 and 6 hour, Sites #2 and #5 were excluded because of the small sample sizes. For sites #10, #11, and #19, placebo had **numerically** higher proportions of subjects ended without nausea symptom at postdose 2 hour. No sites reached a significantly higher percentage of excedrin group than that of placebo at hour 2 time point at the level of 0.05. The site #6 which was the only site of study GHBA-840 with a sample size of N=201 had a p-value of 0.056 at postdose 2 hour. However, all sites at 6 hour time point obtained a numerically higher proportion of subjects without nausea in excedrin group than that of placebo; 3 sites had significant treatment effects at the level of 0.0167.

4. PHOTOPHOBIA

4.1. Subjects

A total of 1,158 efficacy-evaluable patients (excedrin: N=574 vs Placebo: N=584) who had photophobia at baseline were identified for determining drug effect on photophobia. Table 8 shows the demographic characteristics of the patients for data analysis, overall and for each protocol. There were no significant differences between excedrin group and placebo regarding those factors, overall and within protocol.

Table 8. Characteristics of Subjects with Photophobia at Baseline, Overall and by Protocol

	GHBA-840	GHBA-840	GHBA-840	Pooled
Mean Age ± SD (yr)				
Excedrin	35.2± 9.7	37.3±10.8	37.6±10.7	37.6±10.7
Placebo	35.9±10.1	36.0±12.1	37.1±10.5	37.1±10.5
Female				
Excedrin	73.5%	75.6%	83.5%	83.5%
Placebo	78.1%	81.4%	82.8%	82.8%
White				
Excedrin	78.8%	83.8%	90.0%	90.0%
Placebo	84.5%	88.1%	89.1%	89.1%

4.2. Treatment effects on photophobia

The proportions of patients without photophobia among those who had nausea at baseline are shown in Table 9. At postdose 2 hour and all time points after 2 hour, most studies had statistically significant difference between excedrin and placebo groups in the proportion of subjects without photophobia, except Study GHBA-841 at 2 hour (p=0.028).

Table 9. Proportion of Subjects without Photophobia among Those Who Had Photophobia at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=184)	3.8%	17.4%	38.4%	54.4%	59.8%	65.8%
Placebo (N=185)	1.6%	4.9%	10.8%	20.5%	29.2%	33.0%
P-value	.197	<.001	<.001	<.001	<.001	<.001
GHBA-841						
Excedrin (N=190)	2.1%	9.5%	23.2%	38.4%	47.4%	54.2%
Placebo (N=209)	3.8%	9.1%	15.3%	18.7%	20.6%	23.0%
P-value	.314	.895	.028	<.001	<.001	<.001
GHBA-842						
Excedrin (N=200)	2.0%	13.0%	33.0%	41.5%	47.5%	50.5%
Placebo (N=190)	1.6%	4.2%	13.2%	19.0%	23.7%	27.8%
P-value	.756	.002	<.001	<.001	<.001	<.001
Pooled						
Excedrin (N=574)	2.6%	13.2%	31.5%	44.6%	51.4%	56.6%
Placebo (N=584)	2.4%	6.2%	13.2%	19.4%	24.3%	27.7%
P-value	.814	<.001	<.001	<.001	<.001	<.001

The magnitude of proportions of subjects without photophobia of treatment group was around two-fold as those of placebo group. Two studies (GHBA-840 and -842) demonstrated treatment effect on photophobia even starting at 1 hour. Obviously, the pooled data had a stronger evidence of treatment effect in probability because of the consistency among three studies and the larger N of the pooled data.

The reviewer also dichotomized the intensity of photophobia at baseline as 'mild' and 'moderate & severe' and studied the between-group difference of proportion of subjects without photophobia after postdose. Table 10 shows the proportions of subjects without photophobia postdose for those who had moderate and severe nausea at baseline and Table 11 for those with only mild nausea at baseline.

Table 10. Proportion of Subjects without Photophobia among Those Who Had Moderate and Severe Photophobia at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=128)	1.6%	8.6%	28.9%	46.1%	50.8%	59.4%
Placebo (N=141)	0.7%	3.6%	9.2%	17.7%	27.7%	32.6%
P-value	.506	.080	<.001	<.001	<.001	<.001
GHBA-841						
Excedrin (N=122)	0.8%	3.3%	13.1%	28.7%	38.5%	48.4%
Placebo (N=147)	1.4%	5.4%	10.9%	11.6%	14.9%	19.1%
P-value	.196	.392	.574	<.001	<.001	<.001
GHBA-842						
Excedrin (N=127)	0.8%	9.5%	26.0%	30.7%	38.6%	42.5%
Placebo (N=123)	0.0%	1.6%	7.3%	12.2%	17.1%	22.0%
P-value	.324	.007	<.001	<.001	<.001	<.001
Pooled						
Excedrin (N=377)	0.8%	7.2%	22.8%	35.3%	42.7%	50.1%
Placebo (N=4116)	0.7%	3.7%	9.3%	13.9%	20.0%	24.6%
P-value	.915	.028	<.001	<.001	<.001	<.001

Table 11. Proportion of Subjects without Photophobia among Those Who Had Mild Photophobia at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=56)	8.9%	37.5%	60.7%	73.2%	80.4%	80.4%
Placebo (N=44)	4.6%	9.1%	15.9%	29.6%	34.1%	34.1%
P-value	.394	<.001	<.001	<.001	<.001	<.001
GHBA-841						
Excedrin (N=68)	5.9%	20.6%	41.2%	55.9%	63.2%	64.7%
Placebo (N=62)	9.7%	17.7%	25.8%	35.5%	33.9%	32.3%
P-value	.417	.681	.064	.020	<.001	<.001
GHBA-842						
Excedrin (N=73)	4.1%	19.2%	45.2%	60.3%	63.0%	64.4%
Placebo (N=67)	4.5%	9.0%	23.9%	31.3%	35.8%	38.8%
P-value	.914	.084	.008	<.001	<.001	<.001
Pooled						
Excedrin (N=197)	6.1%	24.9%	48.2%	62.4%	68.0%	69.0%
Placebo (N=173)	6.4%	12.1%	22.5%	32.4%	34.7%	35.3%
P-value	.915	.002	<.001	<.001	<.001	<.001

Studies GHBA-840 and -842 had treatment effect on photophobia at and after 2 hour, no matter of the level of intensity of photophobia at baseline. In contrast, Study GHBA-841 did not demonstrate treatment effect for those with moderate and severe symptom at baseline at 2 hour and had borderline effect for those with mild baseline photophobia symptom. The pooled data demonstrated treatment effect starting at 1 hour postdose.

4.3. Treatment effects on photophobia by site

As discussed in the section on nausea, there were 20 sites that involved 3 three studies. The proportions of patients without photophobia symptom at postdose 2 hour and 6 hour among those who had nausea at baseline for each site are presented in Table 12. Sites #2 and #5 had only 5 patients with photophobia at baseline for each. It is not meaningful in discussing treatment effect of the two sites individually.

Table 12. Proportion of Subjects without Photophobia among Those Who Had Photophobia at Baseline, By Site

Site	Group (N)	2 Hr (%)	6 Hr (%)	Site	Group (N)	2 Hr (%)	6 Hr (%)
#1	Excedrin (17) Placebo (18) P-value	23.5% 0.0% (.029)	52.9% 0.0% (.001)	#11	Excedrin (22) Placebo (28) P-value	40.9% 21.4% (.136)	63.6% 28.6% (.013)
#2	Excedrin (2) Placebo (3) P-value	50.0% 66.7% (.709)	100% 66.7% (.361)	#12	Excedrin (21) Placebo (23) P-value	28.6% 13.0% (.202)	42.9% 21.7% (.133)
#3	Excedrin (30) Placebo (34) P-value	16.7% 17.7% (.917)	70.0% 35.3% (.006)	#14	Excedrin (50) Placebo (45) P-value	24.0% 13.3% (.185)	46.0% 26.7% (.051)
#4	Excedrin (22) Placebo (22) P-value	27.3% 13.6% (.262)	63.6% 13.6% (.001)	#15	Excedrin (31) Placebo (28) P-value	32.3% 10.7% (.046)	51.6% 28.7% (.072)
#5	Excedrin (2) Placebo (3) P-value	0.0% 33.3% (.361)	50.0% 33.3% (.709)	#16	Excedrin (43) Placebo (47) P-value	16.3% 8.5% (.261)	46.5% 27.7% (.064)
#6	Excedrin (184) Placebo (185) P-value	38.6% 10.8% (.001)	66.8% 33.3% (.001)	#17	Excedrin (22) Placebo (20) P-value	18.2% 20.0% (.881)	40.9% 30.0% (.461)
#7	Excedrin (5) Placebo (6) P-value	60.0% 16.7% (.137)	60.0% 16.7% (.137)	#18	Excedrin (10) Placebo (12) P-value	30.0% 41.7% (.571)	50.0% 41.7% (.696)
#8	Excedrin (12) Placebo (12) P-value	41.7% 8.3% (.059)	41.7% 33.3% (.673)	#19	Excedrin (18) Placebo (19) P-value	33.3% 10.5% (.092)	50.0% 15.8% (.026)
#9	Excedrin (37) Placebo (36) P-value	54.1% 11.1% (.001)	75.7% 33.3% (.001)	#20	Excedrin (19) Placebo (18) P-value	36.8% 5.6% (.021)	21.1% 5.6% (.168)
#10	Excedrin (6) Placebo (5) P-value	16.7% 20.0% (.887)	83.3% 60.0% (.387)	#21	Excedrin (21) Placebo (20) P-value	4.8% 20.0% (.136)	33.3% 10.0% (.071)

For those sites of #10, #17, and #18, placebo had numerically slightly higher proportions of subjects without photophobia at postdose 2 hour than that of excedrin group. Meanwhile, 2 sites had shown significant treatment effect on photophobia at 2 hour at the level of 0.0167 and other 3 sites presented borderline treatment effect at 2 hour. Regarding treatment effect at 6 hour, all sites had numerically higher proportions of subjects with photophobia in excedrin group than those of placebo. Five sites had significant treatment effect and other two sites had borderline treatment effect.

5. PHONOPHOBIA

5.1. Subjects

A total of 1,114 efficacy-evaluable patients (N=537 for excedrin group and N=577 for placebo) who had migraine symptom of phonophobia at baseline were identified for determining drug effect on phonophobia. Table 13 presents the demographic characteristics of the patients for data analysis, overall and by protocol. There were no significant differences between excedrin group and placebo with respect to those factors.

Table 13. Characteristics of Subjects with Phonophobia at Baseline, Overall and by Protocol

	GHBA-840	GHBA-840	GHBA-840	Pooled
Mean Age ± SD (yr)				
Excedrin	35.1±9.5	37.0±10.2	37.5±10.6	36.5±10.2
Placebo	35.6±10.2	36.0±12.3	37.4±10.7	36.3±11.1
Female				
Excedrin	73.9%	77.2%	83.6%	78.3%
Placebo	78.4%	81.2%	82.5%	80.7%
White				
Excedrin	79.6%	83.2%	91.0%	84.7%
Placebo	83.7%	87.9%	88.9%	86.9%

5.2. Treatment effects on phonophobia

The proportions of patients without phonophobia among those who had at least mild phonophobia symptom at baseline, at postdose 0.5, 1, 2, 3, 4, and 6 hour, are shown in Table 14. The results of phonophobia were very similar to those of photophobia in Table 9 regarding the magnitudes of proportions of patients without symptom, proportion difference between excedrin and placebo, and statistical significance.

Study GHBA-841 did not have treatment effect on phonophobia at 2 hour (p=.082). The other two studies presented significantly higher percentages of patients without phonophobia at and after 2 hour. The pooled data had shown the same pattern as Study GHBA-840 and -841. At postdose 6 hour, the proportion of subjects without phonophobia of excedrin group was about twice as that of placebo. All studies presents significant drug effect on phonophobia at 6 hour at the level of 0.0167.

Table 14. Proportion of Subjects without Phonophobia among Those Who Had Phonophobia at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=173)	3.0%	16.2%	38.2%	52.6%	59.0%	63.6%
Placebo (N=185)	1.6%	8.1%	14.6%	21.6%	31.4%	33.5%
P-value	.417	.019	<.001	<.001	<.001	<.001
GHBA-841						
Excedrin (N=178)	3.4%	11.2%	22.5%	42.1%	47.2%	50.6%
Placebo (N=206)	4.4%	8.3%	15.5%	21.4%	24.8%	26.7%
P-value	.615	.323	.082	<.001	<.001	<.001
GHBA-842						
Excedrin (N=186)	3.2%	11.8%	29.0%	40.9%	49.5%	50.0%
Placebo (N=186)	3.8%	5.9%	12.9%	16.1%	23.1%	28.0%
P-value	.778	.045	<.001	<.001	<.001	<.001
Pooled						
Excedrin (N=537)	3.2%	13.0%	29.8%	45.7%	51.8%	54.6%
Placebo (N=577)	3.2%	7.5%	14.4%	19.8%	26.3%	29.3%
P-value	.905	.002	<.001	<.001	<.001	<.001

Repeated the same analyses in examining treatment effects on nausea and photophobia, the proportions of subjects without phonophobia at postdose between excedrin and placebo were assessed separately for those with 'mild' baseline phonophobia and for those with 'moderate & severe' baseline photophobia. Table 15 shows the proportions of subjects without phonophobia for those who had moderate and severe phonophobia at baseline and Table 16 for those with mild symptom at baseline.

Table 15. Proportion of Subjects without Phonophobia among Those Who Had Moderate and Severe Phonophobia at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=131)	1.5%	10.7%	32.8%	48.9%	55.0%	58.8%
Placebo (N=129)	0.8%	7.8%	12.4%	21.7%	28.1%	32.6%
P-value	.570	.414	<.001	<.001	<.001	<.001
GHBA-841						
Excedrin (N=120)	0.0%	4.2%	13.3%	34.2%	39.2%	45.8%
Placebo (N=122)	2.5%	4.1%	10.7%	15.6%	20.5%	25.4%
P-value	.084	.979	.521	<.001	<.001	<.001
GHBA-842						
Excedrin (N=112)	1.8%	8.0%	21.4%	33.9%	41.1%	42.9%
Placebo (N=110)	0.9%	0.9%	4.6%	9.1%	18.2%	22.7%
P-value	.572	.010	<.001	<.001	<.001	<.001
Pooled						
Excedrin (N=363)	1.1%	7.7%	22.9%	39.4%	45.5%	49.6%
Placebo (N=361)	1.4%	4.4%	9.4%	15.8%	22.7%	27.2%
P-value	.731	.065	<.001	<.001	<.001	<.001

Except GHBA-841 of not showing a significant treatment effect on phonophobia at 2 hour for those who had **moderate and severe** phonophobia at baseline, the other two studies and the pooled data presented the treatment effect at and after 2 hour. In contrast, only Study GHBA-840 demonstrated treatment effect at and after 2 hour at the level of 0.0167 for those who had **mild** phonophobia at baseline. The other two studies had significant treatment at and after 3 hour. Like the treatment effect on photophobia (see Tables 10 & 11), the proportion of subjects without phonophobia of excedrin group was about twice as that of placebo at 6 hour, both for those who had moderate & severe phonophobia at baseline and for those who only had mild symptom at baseline.

Table 16. Proportion of Subjects without Phonophobia among Those Who Had Mild Phonophobia at Baseline, Overall and by Protocol

	0.5 hour	1 hour	2 hour	3 hour	4 hour	6 hour
GHBA-840						
Excedrin (N=42)	7.1%	33.3%	54.8%	64.3%	71.4%	78.6%
Placebo (N=56)	3.6%	8.9%	19.6%	21.4%	37.5%	35.7%
P-value	.427	.002	<.001	<.001	<.001	<.001
GHBA-841						
Excedrin (N=58)	10.3%	25.9%	41.4%	58.6%	63.8%	60.3%
Placebo (N=84)	7.1%	14.3%	22.6%	29.8%	31.0%	28.6%
P-value	.500	.084	.017	<.001	<.001	<.001
GHBA-842						
Excedrin (N=74)	5.4%	17.6%	40.5%	51.4%	62.2%	60.8%
Placebo (N=76)	7.9%	13.2%	25.0%	26.3%	30.3%	35.5%
P-value	.541	.454	.042	.002	<.001	<.001
Pooled						
Excedrin (N=174)	7.5%	24.1%	44.3%	56.9%	64.9%	64.9%
Placebo (N=216)	6.5%	12.5%	22.7%	26.4%	32.4%	32.9%
P-value	.702	.003	<.001	<.001	<.001	<.001

5.3. Treatment effects on phonophobia by site

A total 20 sites involved in the studies. The proportions of patients without phonophobia symptom at postdose 2 hour and 6 hour among those who had phonophobia at baseline for each site are presented in Table 17. Again, sites #2 and #5 are ignored from the discussion in this section because of their small sample sizes.

Table 17. Proportion of Subjects without Phonophobia among Those Had Phonophobia at Baseline, by Site

Site	Group (N)	2 Hr (%)	6 Hr (%)	Site	Group (N)	2 Hr (%)	6 Hr (%)
#1	Excedrin (16)	31.3%	56.3%	#11	Excedrin (24)	33.3%	62.5%
	Placebo (18)	5.6%	0.0%		Placebo (27)	25.9%	44.4%
	P-value	(.050)	(.001)		P-value	(.562)	(.197)
#2	Excedrin (2)	50.0%	100%	#12	Excedrin (23)	17.4%	39.1%
	Placebo (3)	67.7%	100%		Placebo (22)	9.1%	18.2%
	P-value	(.709)	--		P-value	(.413)	(.121)
#3	Excedrin (31)	22.6%	67.7%	#14	Excedrin (42)	31.0%	45.2%
	Placebo (36)	19.4%	36.1%		Placebo (45)	13.3%	28.9%
	P-value	(.753)	(.010)		P-value	(.047)	(.114)

#4	Excedrin (18) Placebo (21) P-value	27.8% 19.1% (.519)	55.6% 9.5% (.002)	#15	Excedrin (29) Placebo (29) P-value	34.8% 3.5% (.003)	53.1% 24.1% (.030)
#5	Excedrin (2) Placebo (2) P-value	0.0% 50.0% (.500)	0.0% 100% (.167)	#16	Excedrin (39) Placebo (46) P-value	15.4% 6.5% (.186)	46.2% 28.3% (.088)
#6	Excedrin (173) Placebo (185) P-value	38.2% 14.6% (.001)	64.0% 33.5% (.001)	#17	Excedrin (21) Placebo (19) P-value	14.3% 15.8% (.894)	47.6% 21.1% (.079)
#7	Excedrin (5) Placebo (6) P-value	40.0% 16.7% (.387)	60.0% 16.7% (.137)	#18	Excedrin (8) Placebo (12) P-value	25.0% 33.3% (.690)	25.0% 50.0% (.264)
#8	Excedrin (12) Placebo (12) P-value	25.0% 0.0% (.064)	41.7% 33.3% (.673)	#19	Excedrin (15) Placebo (18) P-value	27.6% 5.6% (.092)	40.0% 22.2% (.269)
#9	Excedrin (33) Placebo (34) P-value	48.5% 23.5% (.033)	69.7% 38.2% (.010)	#20	Excedrin (18) Placebo (17) P-value	11.1% 5.9% (.581)	27.8% 5.9% (.086)
#10	Excedrin (6) Placebo (5) P-value	33.3% 20.0% (.621)	83.3% 60.0% (.387)	#21	Excedrin (20) Placebo (20) P-value	5.0% 15.0% (.292)	30.0% 10.0% (.114)

With 2 sites (#18 and #21), the placebo had numerically higher proportions of subjects without phonophobia at 2 hour than excedrin group. On the other hand, there 2 sites had demonstrated significant treatment effect on phonophobia at 2 hour at the level of 0.0167. In contrast, most sites (except Site #18) had numerically higher proportions of subjects with phonophobia in excedrin group than those of placebo. Like the treatment effect on photophobia, 5 sites had treatment effect with p-values less not great than 0.0167. The results for treatment effect on phonophobia were consistent among the sites.

6. CONCLUSION

To have an overall look at the Excedrin treatment effect on the migraine symptoms of nausea, photophobia, and phonophobia which present with migraine headache, Table 18 lists the p-values adjusted conservatively for multiplicity, by protocol, at 2,4, and 6 hour postdose. The adjusted p-value derived from the p-values in Tables 4, 9, and 14 by multiplying with 3. We don't adjust p-value for multiple observations, but present the p-values for three time points (at 2, 4, and 6 hour) and leave it to the medical division to select the right time point.

Table 18. Adjusted p-values in Testing Between-group Effect on Nausea, Photophobia, and Phonophobia, by Protocol and by Time

Nausea	**2 hour**	**4 hour**	**6 hour**
GHBA-840	.168	.084	.012
GHBA-841	ns	<.003	<.003
GHBA-842	.012	<.003	<.003
Photophobia	2 hour	4 hour	6 hour
GHBA-840	<.003	<.003	<.003
GHBA-841	.084	<.003	<.003
GHBA-842	<.003	<.003	<.003
Phonophobia	2 hour	4 hour	6 hour
GHBA-840	<.003	<.003	<.003
GHBA-841	.246	<.003	<.003
GHBA-842	<.003	<.003	<.003

Note: ns = non-significant

The major purpose of this sNDA submission is to change the "Use" section of the labeling in using secondary endpoints data. Based on the sponsor's resulting data, we suggested the following labeling changes:

USE:

- For the temporary relief of mild to moderate pain associated with migraine headache
- <u>May</u> relieve symptoms of nausea, sensitivity to light, and sensitivity to sound, present with migraine headache pain

/S/

Y. Richard Chen, Ph.D.
Mathmatical Statistician

This review consists of 17 pages

Concur:

/S/

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Team Leader

/S/

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Archival of NDA #20,802/S-~~001~~ 002

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