CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-317

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	21-317
APPLICANT:	Bayer Corporation
NAME OF DRUG:	Aspirin
INDICATION:	Migraine
DOCUMENT REVIEWED:	December 15, 2000
MEDICAL OFFICER:	Kevin Prohaska, D.O. (HFD-120)
STATISTICAL REVIEWER:	Yeh-Fong Chen Ph.D. (HFD-710)

CONTENTS:

I. Introduction and Summary of the Sponsor's Results

The sponsor submitted three well controlled pivotal studies: Study S98-072, Study S98-073 and Study S98-074 in this NDA submission. The objective of these studies was to evaluate the effectiveness of Extra Strength Bayer ® Aspirin Caplets (abbreviated as ESBA) for treating an acute migraine attack of moderate to severe pain intensity, with or without aura (IHS 1.1, IHS 1.2). Studies S98-072 and S98-074 were multi-center, prospective, randomized, double-blind, parallel group, single dose, placebo controlled studies. Study S98-073 was a single center study employing the same study design as the multi-center studies. Except one center for Study S98-074 was located in Canada, other centers were all located in the United States.

Table 1. Summary of the Sponsor's Results (p-values)

Variable	S98-072	S98-073	S98-074
Percent Responders •	<0.001	0.189	0.013
Nausea-Overall Treatment Effect	0.090	0.264	0.166
Photophobia-Overall Treatment Effect	<0.001	0.164	0.017
Phonophobia-Overall Treatment Effect	<0.001	0.174	0.103
Vomiting-Overall Treatment Effect	0.777	0.290	0.725
Functional Ability-Overall Treatment Effect	<0.001	0.236	0.155
Summed Pain Intensity Difference (SPID)	<0.001	0.055	<0.001
Percent Subjects with Headache Recurrence	0.455	0.755	0.606

- The primary endpoint is the percent responders which are those subjects who experience a change in pain intensity from a baseline evaluation of moderate (2) or severe (3), to mild (1) or none (0), at 2 hours post-dose.

Table 1 shows the sponsor's statistical results for each study. The sponsor concluded that the strength of evidence presented by the individual clinical trials (S98-072, S98-073 and S98-074) and the pooled analysis, support the efficacy of Extra Strength Bayer® Aspirin in treating migraine headache pain, and in reducing the symptoms of phonophobia and photophobia. Studies S98-072, S98-074 and the pooled analysis support a reduction for the symptom of nausea. Additionally, the 6-hour summed pain intensity difference (defined on 2. of page 6) significantly favored the Extra Strength Bayer ® Aspirin treatment group.

II. Summary of the Sponsor's Studies

1. Study Objective

To demonstrate the efficacy of Extra Strength Bayer® Aspirin Caplets when used to treat an acute migraine attack of moderate to severe headache pain intensity, with or without aura.

2. Investigational Plan

Overall Study Design

These studies were prospective, randomized, double blind, parallel group comparisons of a single dose of aspirin 1000 mg (2 Extra Strength Bayer® Aspirin Caplets) to placebo over a period of 6 hours.

Selection Phase (Visit 1)

Those subjects who met the screening criteria attended Visit 1. At this visit, subjects who had signed and dated an informed consent had a medical history, a diagnostic interview, a brief neurological and physical examination and a urine pregnancy test (all females) performed.

Those individuals who satisfied the inclusion/exclusion criteria underwent a training session at the site. The subjects were thoroughly trained to identify an eligible migraine attack and how to complete the self-reporting diary. Eligible subjects were enrolled into the treatment phase and assigned a subject number and provided with a timer, a self-reporting diary, and a bottle of study medication.

Treatment Phase

Prior to taking the study medication, subjects were asked to complete a migraine qualifying form which included questions regarding drug use within the previous 72 hours, biofeedback mechanism use, and migraine diagnostic criteria and symptoms (based on IHS Criteria) to determine if the headache was a migraine and eligible for treatment. If the review of the information in the checklist did not identify the headache as migraine, the subject was instructed by the diary to wait for an eligible attack. The initial attack may have become eligible later.

If the migraine qualifying form verified a migraine attack (with or without aura), and the headache pain was of at least moderate intensity, the subject took the assigned study medication. Subjects were to complete all study evaluations in a subject diary at the following intervals: baseline (just prior to taking study medication), 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours and 6 hours post-dose.

The subjects were given 8 weeks from Visit 1 to treat and evaluate a migraine attack. If the subject had not contacted the study site within 2 weeks of Visit 1, the site contacted the subject to determine whether the subject had treated an eligible migraine attack with the study medication. The site continued to contact the subject approximately every 2 weeks until the subject treated and evaluated a migraine attack, or 8 weeks had elapsed from the date of Visit 1. A record of telephone contacts was kept for each subject.

Final Visit (Visit 2)

The subject was to return to the site as soon as possible after treating a migraine attack, preferably the next business day or not later than approximately 1 week. At that time, the

subject diary was reviewed for completeness and to verify whether the treated headache pain was the result of a migraine attack. In addition, the study medication bottle was collected and any adverse experiences were documented.

3. Titles of Each Study

S98-072:
A Multi-center, Prospective, Randomized, Double-Blind, Parallel Group, Single Dose, Placebo Controlled Study of the Efficacy of Extra Strength Bayer Aspirin (1000 mg) in Subjects with Acute Migraine Attacks

S98-073:
A Single Center, Prospective, Randomized, Double-Blind, Parallel Group, Single Dose, Placebo Controlled Study of the Efficacy of Extra Strength Bayer Aspirin (1000 mg) in Subjects with Acute Migraine Attacks

S98-074:
A Multi-center, Prospective, Randomized, Double-Blind, Parallel Group, Single Dose, Placebo Controlled Study of the Efficacy of Extra Strength Bayer Aspirin (1000 mg) in Subjects with Acute Migraine Attacks

4. Number of Subjects (Planned)

Four hundred (400) evaluable subjects (two hundred subjects per group) were planned for each study. Additional subjects were enrolled to ensure 400 completed evaluable subjects.

5. Statistical and Analytical Plans

Two efficacy analyses were planned - a **confirmed migraine ITT analysis** and **an intent-to-treat analysis**. All subjects who took study medication were included in the intent-to-treat analysis. Only those subjects who dosed with the study medication for a confirmed migraine attack were included in the confirmed migraine ITT analysis. Subjects who used the rescue medication prior to the 2 hour evaluation were considered non-responders. Their remaining efficacy data was extrapolated as described in Section 11.4.2.2 of the protocol (see **Note:** below). These subjects were retained in the intent-to-treat efficacy analyses. All validity judgments regarding the status of subjects for the confirmed migraine ITT analysis were made prior to breaking the treatment code.

Statistical significance was based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less. Baseline values of demographic and clinical parameters were analyzed to assess the degree to which randomization achieved comparability between the treatment groups.

Note:
Section 11.4.2.2: Handling of Dropouts or Missing Data

1. If a subject re-medicated with rescue medication before the end of the 6-hour study, the subsequent efficacy variable scores (pain intensity scores, nausea, photophobia, phonophobia, and ability to function) were set equal to either the baseline score or the score recorded immediately prior to re-medication, whichever score was more severe.

2. Efficacy variable scores for the 6-hour study period, excluding baseline, which remained missing after the application of (1) above were replaced by carrying forward the preceding non-missing score.

3. Any missing efficacy variable score for a subject who medicated to treat a recurrence was set equal to either the baseline score or the most recent non-missing score recorded prior to medication, whichever score was more severe.

4. The 2-hour reading was interpolated in the event that the 2-hour evaluation was off-schedule by more than 15 minutes. Linear interpolation was used if there was observed data that preceded and followed the 2-hour clock time. The last observation was carried forward if the data subsequent to the 2-hour value was missing.

Analyses of Efficacy Variables – Confirmed Migraine ITT

The primary efficacy endpoint of percent responders was based on the pain intensity scores. Percent responders was defined as the percent of subjects who experienced a change in pain intensity from a baseline evaluation of moderate (2) or severe (3), to mild (1) or none (0), at 2 hours post-dosing.

The secondary efficacy endpoints were the reduction of the symptoms of nausea, photophobia, and phonophobia throughout the 6-hour study period for the subset of subjects whose migraine attack included the symptom prior to dosing. Additionally, the proportion of subjects who experienced a reduction in nausea, photophobia, and phonophobia were compared.

The following is a listing of the efficacy measures analyzed:

A. Percent Responders

B. Pain Intensity Indices

1. Pain Intensity Difference (PID) - calculated by subtracting each post-dose pain score from the baseline score: $PID_i = X_b - X_i$, where X_b is the baseline score and X_i is the post-dose score at the ith evaluation time point for i = 1, 2, 3, ..., 7. The 30-minute evaluation was the time point i=1; the 1-hour evaluation was the time point i=2; the 2-hour evaluation was the time point i=3; and so on until the 6-hour evaluation which was the time point i=7.

2. 6-Hour Sum of Pain Intensity Differences (SPID) - computed as a weighted sum of PID scores at the 6-hour evaluation. The algorithm for calculating SPID scores was as follows: 6-HOUR SPID = 0.5 (PID1 + PID2) + PID3 + PID4 + PID5 + PID6 + PID7, where the multiplier assigned to each PID score was equal to the scheduled elapsed time since the previous pain intensity evaluation (i.e., 30 minutes between time point i=1 and baseline, 30 minutes between time point i=2 and time point i=1, etc.).

3. Other Efficacy Measurements

a. Nausea: 4-point categorical scale:
0 = None; 1= Mild; 2 = Moderate; 3 = Severe

b. Photophobia: 4-point categorical scale:
0 = No; 1 = Mild; 2 = Moderate; 3 = Severe

c. Phonophobia: 4-point categorical scale:
0 = No; 1 = Mild; 2 = Moderate; 3 = Severe

d. Vomiting: 2-point categorical scale:
0 = No; 1 = Yes

e. Functional ability: 5-point categorical scale
0 = Able to perform all activities as usual
1 = Daily activities require a little additional effort
2 = Daily activities require some additional effort
3 = Daily activities require a great deal of additional effort
4 = Unable to perform daily activities

f. Percent of subjects who experienced headache recurrence - subject whose pain was reduced to none or mild pain at 2 hours after taking study medication and was followed by an increase to moderate or severe pain within 24 hours after taking the study medication and/or taking back-up medication within 24-hours

g. Time to Recurrence

The percent responders were analyzed using the Cochran-Mantel-Haenszel test stratified by investigator. The symptoms of nausea, photophobia, and phonophobia were analyzed in the following ways. Statistical analysis for the subset of subjects whose migraine attack included the symptom prior to dosing was conducted using a repeated measures analysis of variance with factors of treatment, investigator, time, and treatment by time interaction. A significant treatment by time interaction or between subject effects provided evidence of a treatment effect that was subsequently analyzed by an analysis of covariance at each post-dosing time point during the 6-hour study period. The factors of treatment and investigator were included in the model with baseline symptom severity as a covariant.

The consistency of the treatment effect on the primary variable (percent responders) was investigated for the different races, genders, and ages of the subjects who were enrolled in the study. A SAS PROC CATMOD analysis was conducted with factors of treatment, gender, and treatment by gender interaction. Likewise, an analysis with race in place of

gender and an analysis with baseline severity in place of gender were conducted. A combination of race categories (all races that were not Caucasian were combined) was necessary to group subsets that did not have a sufficient sample size for analysis. The interaction term was used to test for consistency of treatment effect. The subgroup analysis of baseline severity included within severity comparisons that were conducted using contrasts within the PROC CATMOD analysis. Additionally, a logistic regression of the primary variable with factors of age, age squared, treatment, and treatment by age interaction was also conducted. Once again, the interaction term was used to test for consistency.

While each subject was encouraged to complete the full course of the study, the participant could have withdrawn from the study at any time and for any reason. The reason for withdrawal was documented in the End of Study Information section of the Case Report Form.

Each subject who medicated with the study drug was included in the safety and in the intent-to-treat efficacy analysis. Only those subjects who dosed with the study medication for a confirmed migraine attack were included in the confirmed migraine ITT analysis.

Analyses of Demographic and Baseline Characteristics

Variables such as age, weight, and height were considered to be continuous and were analyzed with a two-way analysis of variance (ANOVA) model with factors of treatment and site. For categorical variables such as gender and race, the Cochran-Mantel-Haenszel (CMH) test was used to determine if differences existed between the treatment groups. For the categorical baseline pain intensity score, the Cochran-Mantel-Haenszel test stratified by investigator was also used.

III. The Sponsor's Efficacy Evaluation and Conclusions

Recall that the sponsor analyzed two study populations (i.e., confirmed migraine ITT population and intent to treat population) for their efficacy and safety evaluations. Since the sponsor made the efficacy conclusions based on their confirmed migraine ITT analysis, this section of reviewing the sponsor's efficacy evaluation should be mostly based on their confirmed migraine ITT analysis. However, efficacy evaluation for the primary endpoint and some of the secondary endpoints will be shown for the FDA defined intent to treat (ITT) population. That is due to the fact that the sponsor's defined ITT population was different from the way that FDA generally defined.

The sponsor's defined ITT population includes patients without any post medication measurement but FDA would exclude those patients from the ITT population. The sponsor then re-analyzed data for FDA defined ITT population upon requested after the filing meeting. But, notice that instead of using the method of last observation carried forward (LOCF) that FDA generally considered they used their extrapolated rules (defined on 2. of page 6) for dealing with missing data.

Since the sponsor did not re-write their study reports and the re-analyzed statistical results were very close to what was shown on their study reports. This reviewer will summarize the sponsor's conclusions in this section based on their original study reports but replace the numbers or p-values by their re-analyzed results.

1. Demographic and Other Baseline Characteristics

Table 2 shows the number of subjects analyzed for each study. There are total 1191 patients and 1170 patients for the sponsor's ITT analysis and confirmed migraine analysis, respectively. But, for the FDA defined ITT population, there are total 1180 patients.

According to the tables in Appendix I for the demographic and subject characteristics, it was noticed that for Study S98-073, the average age of subjects in the Extra Strength Bayer® Aspirin group was significantly greater than the mean age of the placebo group (p=0.030). There were no other significant differences among treatment groups in the remaining demographic characteristic or any of the baseline pain, nausea, photophobia, and phonophobia characteristics.

Table 2. Number of Subjects (analyzed) for Each Study

Study	Enrolled	The Spnosr's All ITT Pupulation	The Confirmed Migraine ITT Population	FDA defined ITT Population
S98-072	485 Total Placebo:242 ESBA:243	409 Total Placebo:204 ESBA:205	401 Total Placebo:200 ESBA:201	406 Total Placebo:202 ESBA:204
S98-073	446 Total Placebo:222 ESBA: 224	382 Total Placebo:183 ESBA:199	377 Total Placebo:180 ESBA:197	378 Total Placebo:181 ESBA:197
S98-074	482 Total Placebo:242 ESBA:240	400 Total Placebo:208 ESBA: 192	392 Total Placebo:204 ESBA:188	396 Total Placebo:205 ESBA:191

2. Analysis of Efficacy

2.1 Percent Responders by FDA Defined ITT Population

Table 3 shows the test results for the primary endpoint of percent responders for each study. For **Study S98-072**, there was a significant difference (p<0.001) favoring Extra Strength Bayer® Aspirin (53% responders) over placebo (34% responders). For **Study S98-073**, there was not a significant difference (p=0.189) between the Extra Strength Bayer® Aspirin (49% responders) and placebo (42% responders) groups. For **Study S98-074**, there was a significant difference (p=0.013) favoring Extra Strength Bayer® Aspirin (39% responders) over placebo (27% responders).

Table 3. Numbers of Percent Responders for FDA Defined ITT Population

Study	Placebo	ESBA	p-values
S98-072	69 (34%)	108 (53%)	<0.001
S98-073	76 (42%)	96 (49%)	0.189
S98-074	55 (27%)	74 (39%)	0.013

2.2 Results of Symptom (Nausea, Photophobia, Phonophobia) Analyses by FDA Defined ITT Population

Tables 4 to 6 summarize the mean changes in the symptoms of nausea, photophobia, and phonophobia for the FDA defined ITT subjects for each study.

For **Study S98-072**, in assessing nausea, although there was not a significant overall treatment effect, there was an indication of clinical significance ($p=0.090$) and the treatment×time interaction was significant. The hourly evaluations for nausea did show significance for the 4-hour ($p=0.031$), 5-hour ($p=0.006$) and 6-hour ($p=0.013$) evaluations and an indication of significance at the 3-hour ($p=0.066$). Photophobia and phonophobia both had overall treatment effects that were significant ($p<0.001$) and treatment×time interactions that were also significant ($p=0.002$ and $p<0.001$, respectively). The reduction of photophobia was significant at the 1-hour ($p=0.009$) and 2-hour through 6-hour ($p<0.001$) evaluations. The symptoms of phonophobia was significantly reduced at the 1-hour ($p=0.016$) and 2-hour through 6-hour ($p<0.001$) evaluations.

For **Study S98-073**, in assessing nausea, there was not a significant overall treatment effect ($p=0.264$) or treatment×time interaction ($p=0.725$). The analysis of photophobia showed no overall significant difference between treatment groups ($p=0.164$) and no significant treatment×time interaction ($p=0.109$). There was not a significant difference between treatment groups for the overall evaluation of phonophobia ($p=0.174$) or treatment×time interaction ($p=0.485$).

For **Study S98-074**, in assessing nausea, there was not a significant overall treatment effect ($p=0.166$) or treatment×time interaction ($p=0.283$). Photophobia had a significant overall treatment effect ($p=0.017$) and treatment×time interaction ($p=0.009$). The reduction of photophobia was significant at the 2-hour evaluation through the 6-hour evaluation ($p\leq0.013$) favoring Extra Strength Bayer® Aspirin. The symptom of phonophobia had a significant treatment×time interaction ($p=0.012$) and an indication of an overall treatment effect ($p=0.103$). Phonophobia was significantly reduced at the 2-hour evaluation through the 5-hour evaluation ($p\leq0.030$), with an indication of a significant reduction at the 6-hour evaluation ($p=0.093$) favoring Extra Strength Bayer® Aspirin compared to placebo.

Note that the sponsor also analyzed the proportion of subjects who experienced a reduction in nausea, photophobia, and phonophobia at each evaluation for confirmed

migraine ITT population. According to the results (not shown in this review), they concluded that for **Study S98-072**, there was not a significant difference between groups for the analysis of nausea at any evaluation. But, there was a significant difference in the proportion of subjects experiencing a reduction in photophobia and phonophobia favoring Extra Strength Bayer® Aspirin at 1-hour through the 6-hour evaluation ($p \leq 0.036$). For **Study S98-073**, there was no significant difference between treatments at any evaluation ($p \geq 0.126$) for the analysis comparing the proportion of subjects who experienced a reduction in nausea. For the analysis comparing the proportion of subjects who experienced a reduction in photophobia at each evaluation, there was a significant difference between treatments favoring Extra Strength Bayer ® Aspirin at 1-hour post-dose ($p=0.028$) and an indication of significance at 30-minutes ($p=0.098$) and 2-hours ($p=0.083$). For the analysis comparing the proportion of subjects who experienced a reduction in phonophobia at each evaluation, there was an indication of significance between treatments favoring Extra Strength Bayer ® Aspirin at 1-hour ($p=0.070$) and 3-hours ($p=0.058$) post-dose. For **Study S98-074**, there was a significant difference between treatments favoring the Extra Strength Bayer® Aspirin treatment for the analysis of nausea beginning at the 3-hour evaluation and continued through 6-hour evaluation ($p \leq 0.044$). There was a significant difference in the proportion of subjects experiencing a reduction in photophobia and phonophobia again favoring Extra Strength Bayer® Aspirin beginning at 2-hour through the 5-hour evaluation ($p \leq 0.013$). Photophobia was also significant at the 6-hour evaluation ($p=0.002$) and phonophobia showed an indication of significance ($p=0.084$).

Table 4. Analysis of Symptoms and Pain Scores for Study S98-072 for FDA Defined ITT Population

VARIABLE	PLACEBO		ESBA		
	LSMEAN	LSSD	LSMEAN	LSSD	P-VALUE ++
Nausea	(N=110)		(N=115)		
Baseline	1.45	0.56	1.42	0.56	0.712
Hour .5	1.37	0.65	1.36	0.66	0.894
Hour 1	1.18	0.76	1.14	0.76	0.689
Hour 2	0.83	0.81	0.86	0.81	0.753
Hour 3	0.89	0.88	0.67	0.88	0.066 (*)
Hour 4	0.89	0.88	0.63	0.88	0.031 *
Hour 5	0.93	0.88	0.60	0.88	0.006 **
Hour 6	0.94	0.91	0.63	0.91	0.013 *
Trt x Time Interaction					0.018 *
Overall Trt Effect					0.090 (*)
Photophobia	(N=194)		(N=195)		
Baseline	1.99	0.58	2.01	0.58	0.799
Hour .5	1.89	0.66	1.79	0.65	0.105
Hour 1	1.68	0.79	1.47	0.78	0.009 **
Hour 2	1.45	0.89	1.10	0.88	<0.001***
Hour 3	1.32	0.95	0.90	0.94	<0.001***
Hour 4	1.23	1.02	0.84	1.01	<0.001***
Hour 5	1.16	1.03	0.74	1.03	<0.001***
Hour 6	1.16	1.05	0.75	1.05	<0.001***
Trt x Time Interaction					0.002 **
Overall Trt Effect					<0.001***

Phonophobia	(N=194)		(N=197)		
Baseline	2.00	0.61	2.01	0.61	0.913
Hour .5	1.88	0.70	1.84	0.69	0.510
Hour 1	1.69	0.82	1.49	0.81	0.016 *
Hour 2	1.45	0.92	1.06	0.92	<0.001***
Hour 3	1.30	1.00	0.87	0.99	<0.001***
Hour 4	1.25	1.05	0.81	1.04	<0.001***
Hour 5	1.22	1.06	0.73	1.05	<0.001***
Hour 6	1.19	1.08	0.75	1.07	<0.001***
Trt x Time Interaction					<0.001***
Overall Trt Effect					<0.001***
Vomiting					
Baseline	0.00	.	0.00	.	NA
Hour .5	0.00	.	0.00	.	NA
Hour 1	0.01	0.10	0.01	0.10	0.348
Hour 2	0.01	0.10	0.01	0.10	0.949
Hour 3	0.01	0.09	-0.00	0.09	0.077 (*)
Hour 4	0.01	0.09	0.01	0.09	0.545
Hour 5	0.01	0.11	0.02	0.11	0.680
Hour 6	0.01	0.09	0.01	0.09	0.545
Trt x Time Interaction					0.238
Overall Trt Effect					0.777
Functional Ability					
Baseline	2.30	0.75	2.26	0.74	0.636
Hour .5	2.29	0.81	2.12	0.81	0.031 *
Hour 1	2.12	0.91	1.78	0.91	<0.001***
Hour 2	1.86	1.07	1.37	1.07	<0.001***
Hour 3	1.71	1.20	1.11	1.20	<0.001***
Hour 4	1.61	1.27	1.02	1.26	<0.001***
Hour 5	1.57	1.29	0.90	1.29	<0.001***
Hour 6	1.53	1.32	0.91	1.32	<0.001***
Trt x Time Interaction					<0.001***
Overall Trt Effect					<0.001***
Pain Intensity Difference (PID)++					
Hour .5	0.19	0.50	0.23	0.50	0.347
Hour 1	0.38	0.71	0.62	0.71	0.001 **
Hour 2	0.61	0.92	1.04	0.92	<0.001***
Hour 3	0.73	1.03	1.24	1.03	<0.001***
Hour 4	0.84	1.14	1.36	1.13	<0.001***
Hour 5	0.88	1.17	1.46	1.17	<0.001***
Hour 6	0.90	1.20	1.49	1.19	<0.001***
Summed Pain Intensity Difference (SPID)++	4.24	5.45	7.01	5.43	<0.001***

Note: ESBA = Two, 500 mg unbranded aspirin caplets (Extra Strength Bayer® Aspirin); PLACEBO = Two matching placebo caplets. ITT = Intent to Treat. Trt = Treatment.

+ Subjects included are only those subjects with the particular symptom present at pre-dose. Two subjects were eliminated from the analyses. The diary evaluations for subjects 393 and 507 were recorded inappropriately, rendering them unfit to use in the analysis.

++ P-values for treatment x time interaction and overall treatment effect are from a repeated measures ANOVA with factors of treatment, investigator, time, and treatment x time.

Least Squares Means and Standard Deviations and p-values for comparison of treatments at individual evaluation times are from an analysis of covariance with factors of treatment and investigator with baseline symptom severity as a covariate.
(*) .05<=p<.10, * .01<=p<.05, ** .001<=p<.01, *** p<.001

Table 5. Analysis of Symptoms and Pain Scores for Study S98-073 for FDA defined ITT Population

VARIABLE	PLACEBO LSMEAN	LSSD	ESBA LSMEAN	LSSD	P-VALUE ++
Nausea	(N=108)		(N=124)		
Baseline	1.45	0.57	1.42	0.57	0.715
Hour .5	1.38	0.69	1.33	0.69	0.593
Hour 1	1.16	0.78	1.09	0.78	0.487
Hour 2	0.94	0.77	0.79	0.77	0.144
Hour 3	0.89	0.85	0.74	0.85	0.181
Hour 4	0.80	0.89	0.68	0.89	0.297
Hour 5	0.66	0.86	0.56	0.86	0.350
Hour 6	0.72	0.85	0.55	0.85	0.131
Trt x Time Interaction					0.725
Overall Trt Effect					0.264
Photophobia	(N=176)		(N=193)		
Baseline	1.91	0.59	1.95	0.59	0.521
Hour .5	1.88	0.62	1.81	0.62	0.270
Hour 1	1.67	0.73	1.59	0.73	0.287
Hour 2	1.45	0.87	1.27	0.87	0.042 *
Hour 3	1.30	0.94	1.11	0.94	0.052 (*)
Hour 4	1.14	1.00	0.99	1.00	0.151
Hour 5	1.03	1.02	0.93	1.02	0.357
Hour 6	1.01	1.05	0.87	1.05	0.224
Trt x Time Interaction					0.109
Overall Trt Effect					0.164
Phonophobia	(N=172)		(N=187)		
Baseline	1.90	0.62	1.85	0.62	0.476
Hour .5	1.85	0.67	1.79	0.67	0.376
Hour 1	1.61	0.75	1.51	0.75	0.236
Hour 2	1.33	0.88	1.14	0.88	0.049 *
Hour 3	1.19	0.94	1.03	0.94	0.112
Hour 4	1.03	0.96	0.91	0.96	0.232
Hour 5	0.95	1.00	0.87	1.00	0.442
Hour 6	0.93	1.03	0.81	1.03	0.242
Trt x Time Interaction					0.485
Overall Trt Effect					0.174
Vomiting					
Baseline	0.01	0.09	0.01	0.09	0.510
Hour .5	0.00	0.05	0.01	0.05	0.342
Hour 1	0.00	.	0.00	.	NA
Hour 2	0.00	.	0.00	.	NA
Hour 3	0.01	0.09	0.01	0.09	0.502
Hour 4	0.03	0.13	0.01	0.13	0.042 *
Hour 5	0.02	0.11	0.01	0.11	0.575
Hour 6	0.02	0.11	0.01	0.11	0.575
Trt x Time Interaction					0.334

Overall Trt Effect					0.290
Functional Ability					
Baseline	2.46	0.67	2.41	0.67	0.449
Hour .5	2.40	0.75	2.43	0.75	0.763
Hour 1	2.18	0.89	2.11	0.89	0.442
Hour 2	1.90	1.05	1.68	1.05	0.048 *
Hour 3	1.69	1.18	1.51	1.18	0.119
Hour 4	1.53	1.27	1.31	1.27	0.088 (*)
Hour 5	1.34	1.32	1.23	1.32	0.409
Hour 6	1.28	1.36	1.16	1.36	0.361
Trt x Time Interaction					0.077 (*)
Overall Trt Effect					0.236
Pain Intensity Difference (PID)++	0.10	0.40	0.15	0.40	0.239
Hour .5	0.35	0.69	0.45	0.69	0.122
Hour 1	0.65	0.84	0.84	0.84	0.030 *
Hour 2	0.78	0.98	0.99	0.98	0.033 *
Hour 3	0.93	1.08	1.13	1.08	0.066 (*)
Hour 4	1.08	1.13	1.24	1.13	0.175
Hour 5	1.13	1.18	1.29	1.18	0.169
Hour 6					
Summed Pain Intensity Difference (SPID)++	4.79	5.11	5.80	5.11	0.055 (*)

Note: ESBA = Two, 500 mg unbranded aspirin caplets (Extra Strength Bayer® Aspirin); PLACEBO = Two matching placebo caplets. ITT = Intent to Treat. Trt = Treatment.

\+ P-values for treatment x time interaction and overall treatment effect are from a repeated measures ANOVA with factors of treatment, time, and treatment x time. Least Squares Means and Standard Deviations and p-values for comparison of treatments at individual evaluation times are from an analysis of covariance with factor of treatment and with baseline symptom severity as a covariate.

(*) .05<=p<.10, * .01<=p<.05, ** .001<=p<.01, *** p<.001

Table 6. Analysis of Symptoms and Pain Scores for Study S98-074 for FDA defined ITT Population

VARIABLE	PLACEBO LSMEAN (N=137)	LSSD	ESBA LSMEAN (N=122)	LSSD	P-VALUE ++
Nausea					
Baseline	1.38	0.59	1.39	0.58	0.937
Hour .5	1.33	0.71	1.39	0.70	0.524
Hour 1	1.25	0.88	1.26	0.86	0.904
Hour 2	1.19	0.96	1.02	0.94	0.151
Hour 3	1.27	0.97	1.03	0.95	0.038 *
Hour 4	1.29	0.97	1.04	0.96	0.032 *
Hour 5	1.35	0.97	1.10	0.96	0.039 *
Hour 6	1.34	0.97	1.11	0.95	0.050 (*)
Trt x Time Interaction					0.283
Overall Trt Effect					0.166
Photophobia	(N=198)		(N=185)		
Baseline	1.82	0.64	1.81	0.64	0.884
Hour .5	1.72	0.70	1.79	0.69	0.365
Hour 1	1.64	0.82	1.54	0.81	0.253
Hour 2	1.56	0.95	1.32	0.94	0.013 *
Hour 3	1.58	0.98	1.30	0.97	0.004 **

Hour 4	1.59	1.01	1.27	1.00	0.002 **
Hour 5	1.58	1.03	1.26	1.02	0.002 **
Hour 6	1.58	1.04	1.27	1.03	0.003 **
Trt x Time Interaction					0.009 **
Overall Trt Effect					0.017 *
Phonophobia	(N=189)		(N=176)		
Baseline	1.76	0.65	1.79	0.64	0.728
Hour .5	1.67	0.74	1.73	0.73	0.431
Hour 1	1.57	0.82	1.52	0.81	0.560
Hour 2	1.48	0.94	1.25	0.93	0.019 *
Hour 3	1.51	0.98	1.26	0.97	0.016 *
Hour 4	1.51	1.03	1.25	1.02	0.015 *
Hour 5	1.49	1.02	1.26	1.01	0.030 *
Hour 6	1.45	1.04	1.27	1.03	0.093 (*)
Trt x Time Interaction					0.012 *
Overall Trt Effect					0.103
Vomiting					
Baseline	0.01	0.11	0.01	0.11	0.711
Hour .5	0.01	0.12	0.01	0.12	0.912
Hour 1	0.01	0.10	0.01	0.10	0.936
Hour 2	0.03	0.17	0.02	0.17	0.416
Hour 3	0.03	0.17	0.02	0.17	0.417
Hour 4	0.03	0.18	0.03	0.17	0.946
Hour 5	0.03	0.17	0.03	0.17	0.820
Hour 6	0.03	0.17	0.03	0.17	0.820
Trt x Time Interaction					0.802
Overall Trt Effect					0.725
Functional Ability					
Baseline	2.14	0.83	2.31	0.82	0.041 *
Hour .5	2.15	0.88	2.30	0.88	0.085 (*)
Hour 1	2.05	0.99	2.07	0.98	0.843
Hour 2	2.06	1.18	1.84	1.17	0.060 (*)
Hour 3	2.04	1.26	1.79	1.25	0.041 *
Hour 4	2.06	1.33	1.70	1.31	0.006 **
Hour 5	2.08	1.31	1.69	1.30	0.003 **
Hour 6	2.07	1.35	1.69	1.34	0.005 **
Trt x Time Interaction					0.002 **
Overall Trt Effect					0.155
Pain Intensity Difference (PID)++					
Hour .5	0.11	0.48	0.13	0.48	0.677
Hour 1	0.24	0.68	0.38	0.68	0.043 *
Hour 2	0.28	0.85	0.54	0.84	0.002 **
Hour 3	0.26	0.97	0.61	0.96	<0.001***
Hour 4	0.26	1.03	0.66	1.02	<0.001***
Hour 5	0.30	1.06	0.66	1.05	<0.001***
Hour 6	0.31	1.09	0.68	1.08	0.001 **
Summed Pain Intensity Difference (SPID)++	1.58	4.98	3.40	4.92	<0.001***

Note: ESBA = Two, 500 mg unbranded aspirin caplets (Extra Strength Bayer® Aspirin); PLACEBO = Two matching placebo caplets. ITT = Intent to Treat. Trt = Treatment.

+ P-values for treatment x time interaction and overall treatment effect are from a repeated measures ANOVA with factors of treatment, investigator, time, and treatment x time. Least Squares Means and Standard Deviations and p-values for comparison of treatments at individual evaluation times are from an analysis of covariance with factors of treatment and investigator with baseline symptom severity as a covariate.

(*) .05<=p<.10, * .01<=p<.05, ** .001<=p<.01, *** p<.001

2.3 Results of Vomiting and Functional Ability Analyses by FDA Defined ITT Population

Tables 4 to 6 also demonstrate the analysis of the mean change in the supplementary symptoms of vomiting and functional ability. For **Study S98-072**, there was no difference in the supplementary symptom of vomiting between placebo subjects and those who took Extra Strength Bayer® Aspirin (p-value for treatment×time interaction = 0.238, for overall treatment effect = 0.777). There were too few subjects who vomited to form a statistical basis for comparison. The mean changes in functional ability (improvement) significantly favored the Extra Strength Bayer Aspirin® group compared to placebo for Hour .5 through 6 ($p<0.031$).

For **Study S98-073**, there was no difference in the supplementary symptom of vomiting between placebo subjects and subjects who dosed with Extra Strength Bayer® Aspirin (p-value for treatment×time interaction = 0.334, overall treatment effect = 0.290). There were too few subjects who committed to form a statistical basis for comparison. The overall treatment effect for the analysis of mean functional ability was not significant ($p=0.236$), however, the treatment×time interaction effect showed an indication of significance favoring the Extra Strength Bayer® Aspirin group ($p=0.077$).

For **Study S98-074**, there was no difference in the supplementary symptom of vomiting between placebo subjects and subjects who dosed with Extra Strength Bayer® Aspirin (p-value for treatment×time interaction = 0.802, overall treatment effect = 0.725). There were too few subjects who vomited to form a statistical basis for comparison. The treatment×time interaction for the analysis of mean functional ability was significant ($p=0.002$), however, the overall treatment effect was not significant ($p=0.155$). The placebo subjects functioned significantly better than the Extra Strength Bayer® Aspirin subjects at baseline ($p=0.041$) although mean change in functional ability showed an indication of significance favoring placebo at the 30-minute evaluation ($p=0.085$). There was a minimal increase at this evaluation for the placebo and a minimal decrease for the Extra Strength Bayer® Aspirin group. Despite the impairment due to the imbalance of the randomization at baseline, the Extra Strength Bayer®Aspirin group showed an indication of significance in its favor at 2-hours ($p=0.060$). At the 3 through 6-hour evaluations, mean change in functional ability (improvement) significantly favored the Extra Strength Bayer® Aspirin group compared to placebo ($p\leq 0.041$).

2.4 Results of Pain Scores Analyses by FDA Defined ITT Population

Tables 4 to 6 also demonstrate the results of pain score analyses for each study. For **Study S98-072,** it shows that Extra Strength Bayer® Aspirin was significantly more effective than placebo for pain intensity differences beginning at 1-Hour and continuing throughout the remainder of the 6-hour evaluation period ($p<0.001$) and for the 6-hour SPID as well ($p<0.001$). For **Study S98-073**, it shows that Extra Strength Bayer® Aspirin was significantly more effective than placebo for pain intensity differences at the 1-hour and 2-hour evaluations ($p\leq0.033$) with an indication of significance at the 3-hour evaluation ($p=0.066$). The 6-hour SPID also showed an indication of a significant effect favoring the Extra Strength Bayer® Aspirin group compared to placebo ($p=0.055$). For **Study S98-074**, it shows that Extra Strength Bayer® Aspirin was significantly more effective than placebo for pain intensity differences beginning at 1-Hour and continuing throughout the remainder of the 6-hour evaluation period ($p\leq0.043$). The 6-hour SPID also demonstrated a significant effect for the Extra Strength Bayer® Aspirin group compared to placebo ($p<0.001$).

2.5 Results of Headache Recurrence Analyses by FDA Defined ITT Population

Tables 7 to 9 show the analysis of percent subjects with headache recurrence for each study. For **Study S98-072**, there was no significant difference between treatment groups ($p=0.455$). A maximum of 13 (6%) subjects in the Extra Strength Bayer® Aspirin group and 15 (7%) subjects in the placebo group experienced headache recurrence at the 3 through 6- hour evaluations. At 24 hours post-dosing, 24 (12%) subjects in the Extra Strength Bayer® Aspirin group and 19 (9%) subjects in the placebo group experienced headache recurrence.

For **Study S98-073**, there was no significant difference between treatment groups ($p=0.755$). A maximum of 13 (7%) subjects in the Extra Strength Bayer® Aspirin group and 14 (8%) subjects in the placebo group experienced headache recurrence at the 3 through 6-hour evaluations. At 24 hours post-dosing, 23(12%) subjects in the Extra Strength Bayer® Aspirin group and 19 (10%) subjects in the placebo group experienced headache recurrence.

For **Study S98-074,** there was also no significant difference between treatment groups ($p=0.606$). A maximum of 17 (9%) subjects in the Extra Strength Bayer® Aspirin group and 28 (14%) subjects in the placebo group experienced headache recurrence at the 3 through 6-hour evaluations. At 24 hours post-dosing, 28 (15%) subjects in the Extra Strength Bayer® Aspirin group and 34 (17%) subjects in the placebo group experienced headache recurrence.

Table 7. Analysis of Percent Subjects with Headache Recurrence for Study S98-072

VARIABLE	PLACEBO (N=202)	ESBA (N=204)	P-VALUE +
Percent Subjects With Headache Recurrence			
Hour 3	6 (3%)	2 (1%)	
Hour 4	8 (4%)	7 (3%)	
Hour 5	12 (6%)	10 (5%)	
Hour 6	15 (7%)	13 (6%)	
Hour 24	19 (9%)	24 (12%)	
95% Confidence Interval For Percent Of Subjects With Headache Recurrence Over 24 Hours	0.06 - 0.14	0.08 – 0.17	0.455

Note: ESBA = Two, 500 mg unbranded aspirin caplets (Extra Strength Bayer® Aspirin); PLACEBO = Two matching placebo caplets. ITT = Intent to Treat.
Recurrence for a subject is defined as a subject having had pain reduced to none or mild pain at 2 hours after taking study medication followed by an increase to moderate or severe pain within 24 hours after taking study medication. Recurrence at a given time point indicates a return to moderate or severe pain at or before that evaluation.
+ P-Value is based on an investigator adjusted Log-Rank test.
(*) .05<=p<.10, * .01<=p<.05, ** .001<=p<.01, *** p<.001

Table 8. Analysis of Percent Subjects with Headache Recurrence for Study S98-073

VARIABLE	PLACEBO (N=181)	ESBA (N=197)	P-VALUE +
Percent Subjects With Headache Recurrence			
Hour 3	9 (5%)	6 (3%)	
Hour 4	13 (7%)	10 (5%)	
Hour 5	14 (8%)	12 (6%)	
Hour 6	14 (8%)	13 (7%)	
Hour 24	19 (10%)	23 (12%)	
95% Confidence Interval For Percent Of Subjects With Headache Recurrence Over 24 Hours	0.06 - 0.16	0.08 – 0.17	0.755

Note: ESBA = Two, 500 mg unbranded aspirin caplets (Extra Strength Bayer® Aspirin); PLACEBO = Two matching placebo caplets. ITT = Intent to Treat.
Recurrence for a subject is defined as a subject having had pain reduced to none or mild pain at 2 hours after taking study medication followed by an increase to moderate or severe pain within 24 hours after taking study medication. Recurrence at a given time point indicates a return to moderate or severe pain at or before that evaluation.
+ P-Value is based on a Log-Rank test.
(*) .05<=p<.10, * .01<=p<.05, ** .001<=p<.01, *** p<.001

Table 9. Analysis of Percent Subjects with Headache Recurrence for Study S98-074

VARIABLE	PLACEBO (N=205)	ESBA (N=191)	P-VALUE +
Percent Subjects With Headache Recurrence			
Hour 3	8 (4%)	6 (3%)	
Hour 4	20 (10%)	10 (5%)	
Hour 5	27 (13%)	15 (8%)	
Hour 6	28 (14%)	17 (9%)	
Hour 24	34 (17%)	28 (15%)	
95% Confidence Interval For Percent Of Subjects With Headache Recurrence Over 24 Hours	0.12 - 0.22	0.10 - 0.20	0.606

Note: ESBA = Two, 500 mg unbranded aspirin caplets (Extra Strength Bayer® Aspirin); PLACEBO = Two matching placebo caplets. ITT = Intent to Treat. Recurrence for a subject is defined as a subject having had pain reduced to none or mild pain at 2 hours after taking study medication followed by an increase to moderate or severe pain within 24 hours after taking study medication. Recurrence at a given time point indicates a return to moderate or severe pain at or before that evaluation.

+ P-Value is based on an investigator adjusted Log-Rank test.
(*) .05<=p<.10, * .01<=p<.05, ** .001<=p<.01, *** p<.001

2.6 Examination of Subgroups

(Note: the sponsor's tables were not shown in this review)

For **Study S98-072**, the treatment by gender interaction term was not significant, the treatment by race interaction was not significant, nor was the treatment by baseline severity significant. Comparison of responders within baseline severity showed a significant difference between treatments for the subjects with baseline pain of moderate (p=0.008) as well as severe (p=0.005) favoring the Extra Strength Bayer® Aspirin treatment.

For **Study S98-073**, the treatment by gender interaction term was not significant, the treatment by race interaction showed an indication of significance. The treatment by baseline severity showed a significant difference between treatments for the subjects with baseline pain of moderate (p = 0.026) favoring the Extra Strength Bayer® Aspirin treatment and no significant difference between subjects with severe pain at baseline.

For **Study S98-074**, the treatment by gender interaction term was not significant, the treatment by race interaction was not significant, nor was the treatment by baseline severity significant though it showed an indication of significance. Comparison of responders within baseline severity showed a significant difference between treatments for the subjects with baseline pain of moderate (p=0.004) favoring the Extra Strength Bayer® Aspirin treatment and no significant difference for severe.

3. Efficacy Conclusions

Study S98-072:

Treatment of an acute migraine attack with Extra Strength Bayer® Aspirin resulted in a significantly greater number of responders (53%), the primary efficacy variable, at the 2-hour post-dose evaluation compared to placebo (34%)($p<0.001$). The Extra Strength Bayer® Aspirin treated group also experienced a significant reduction in pain intensity ($p<0.001$) and the symptoms of photophobia ($p<0.001$) and phonophobia ($p<0.001$), and an improvement in the ability to function at 1, 2, 3, 4, 5, and 6 hours post-dosing, $p<0.001$). In addition, the 6-hour SPID for this group was significant compared to the placebo group ($p<0.001$). Extra Strength Bayer® Aspirin also significantly reduced the symptom of nausea at 4, 5 and 6 hours post-dosing ($p\leq0.031$). There were no significant treatment differences for the symptom of vomiting.

Study S98-073:

Treatment of an acute migraine attack with Extra Strength Bayer® Aspirin resulted in a lack of significant treatment differences for percent of responders, nausea, photophobia, phonophobia, vomiting, ability to function, and headache recurrence. The Extra Strength Bayer® Aspirin treated group did experience a significant reduction in pain intensity at the 1-hour ($p=0.030$) and 2-hour ($p=0.033$) evaluations and showed an indication of significance at 3-hours ($p=0.066$). Likewise, there was also an indication of a significant difference favoring the Extra Strength Bayer® Aspirin group for the 6-hour SPID ($p=0.055$). Also, there was an indication of significance of the treatment by time interaction for improvement in functional ability ($p=0.077$) with an indeed significant difference at the 2-hour ($p=0.048$) evaluation and an indicated difference at the 4-hour ($p=0.088$) evaluations.

Study S98-074:

Treatment of an acute migraine attack with Extra Strength Bayer® Aspirin resulted in a significantly greater number of responders (39%), the primary efficacy variable, at the 2-hour post-dose evaluation ($p=0.013$) compared to placebo (27%). The Extra Strength Bayer® Aspirin treated group also experienced a significant reduction in pain intensity at the 1-hour evaluation and continuing through the 6-hour evaluation ($p\leq0.043$). Additionally, the 6-hour SPID for the Extra Strength Bayer® Aspirin group was significant compared to the placebo group ($p<0.001$). A reduction in the symptoms of photophobia ($p<0.013$) and phonophobia ($p<0.030$) significantly favored Extra Strength Bayer® Aspirin at the 2-hour through 5-hour evaluations. In addition, photophobia was significant at the 6-hour evaluation ($p=0.003$), while there was an indication of significance at the 6-hour evaluation for phonophobia ($p=0.093$).

The analysis of the proportion of confirmed migraine ITT subjects who experienced a reduction in nausea, photophobia, and phonophobia at each evaluation showed a significant difference between groups for the reduction in nausea at the 3-hour through 6-

hour evaluations ($p \leq 0.044$) favoring the Extra Strength Bayer® Aspirin treatment. A significant difference between groups again favoring Extra Strength Bayer® aspirin for the reduction in photophobia and phonophobia was noted beginning at 2-hours continuing through the 5-hour evaluation ($p \leq 0.013$). Photophobia was also significant at the 6-hour evaluation ($p=0.002$) and phonophobia showed an indication of significance at 6-hours ($p=0.084$).

An improvement in functional ability was indicated at the 30-minute evaluation favoring Placebo compared to Extra Strength Bayer® Aspirin ($p=0.085$). Extra Strength Bayer® Aspirin was significantly favored for mean change in improvement in the ability to function at the 3-, 4-, 5-, and 6-hour evaluations ($p<0.041$), and approached significance at the 2-hour evaluation ($p \leq 0.060$) compared to placebo. At baseline, the placebo group was less impaired in functional ability compared to the Extra Strength Bayer® Aspirin group ($p=0.041$). There were no significant treatment differences for nausea, vomiting, or headache recurrence.

IV. The Reviewer's Findings and Comments

1. The sponsor performed efficacy analyses based on their confirmed migraine ITT population. Since their confirmed migraine ITT population was different from what the FDA generally defined ITT population, they were asked to re-analyze the data for their primary and some important secondary endpoints for the FDA defined ITT population after the filing meeting.

   Since the sponsor analyzed the symptoms of nausea, photophobia, and phonophobia for the subset of subjects whose migraine attack included the symptoms prior to dosing only, it was considered that the randomization of patients was not reserved. It was also noticed that the sponsor dealt with missing values by their pre-specified extrapolated rules (see **Note:** on page 5), rather than used the LOCF that FDA generally considered. So, in addition to evaluate the sponsor's analyses according to their protocols and amendments, this reviewer also re-analyzed the data by LOCF and by comparing the percentages of patients whose symptoms of nausea, photophobia and phonophobia were resolved at two hours between treatment groups for FDA defined ITT population. Using this method of comparison was after this reviewer's personal discussion with the medical officer. It was notice that this method can capture those subjects that develop those symptoms after baseline.

   Tables 10 to 12 show the detailed results for comparing 2-hour responders and percentages of patients whose symptoms of nausea, photophobia and phonophobia were resolved at 2 hours between treatment groups. Noticed that there were only two p-values that did not convey same conclusions as the sponsor's p-values on Tables 4 to 6. Those p-values are for Study S98-073, symptoms of photophobia and phonophobia at 2 hours. According to Table 11, p-values for symptoms of photophobia and phonophobia at 2 hours are 0.127 and 0.117, respectively. But, they are 0.042 and 0.049, respectively on Table 5 for the corresponding symptom at 2 hours.

Table 10. The Efficacy Analyses for the 2 hour Responders and Symptoms of Nausea, Photophobia and Phonophobia Relieved at 2 hours based on the FDA defined ITT Population for Study S98-072

Study S98-072	Number of Responders, Without Symptom at Baseline, Or Symptom Relieved at 2 Hours	P-value by CMH Stratified by Center
Headache Response	Placebo: 72 (35.64%) ESBA: 112 (54.9%)	0.001
Nausea – baseline	Placebo: 92 (45.54%) ESBA: 88 (43.14%)	0.654
– two hours	Placebo: 132 (65.35%) ESBA: 123 (60.29%)	0.299
Photophobia – baseline	Placebo: 8 (3.96%) ESBA: 8 (3.92%)	0.959
– two hours	Placebo: 38 (18.81%) ESBA: 69 (33.82%)	0.001
Phonophobia – baseline	Placebo: 7 (3.47%) ESBA: 6 (2.94%)	0.734
– two hours	Placebo: 43 (21.29%) ESBA: 75 (36.76%)	0.001

Note: There are 202 patients in Placebo group and 204 patients in ESBA group.

Table 11. The Efficacy Analyses for the 2 hour Responders and Symptoms of Nausea, Photophobia and Phonophobia Relieved at 2 hours based on the FDA defined ITT Population for Study S98-073

Study S98073	Number of Responders, Without Symptom at Baseline, Or Symptom Relieved at 2 Hours	P-value by CMH (Note: single center)
Headache Response	Placebo: 76 (41.99%) ESBA: 97 (49.24%)	0.158
Nausea – baseline	Placebo: 73 (40.33%) ESBA: 73 (37.06%)	0.514
– two hours	Placebo: 96(53.04%) ESBA: 118(59.90%)	0.179
Photophobia – baseline	Placebo: 5 (2.76%) ESBA: 4(2.03%)	0.641
– two hours	Placebo: 30 (16.57%) ESBA: 45(22.84%)	0.127
Phonophobia – baseline	Placebo: 9 (4.97%) ESBA: 10 (5.08%)	0.963
– two hours	Placebo: 43(23.76%) ESBA: 61(30.96%)	0.117

Note: There are 181 patients in Placebo group and 197 patients in ESBA group.

Table 12. The Efficacy Analyses for the 2 hour Responders and Symptoms of Nausea, Photophobia and Phonophobia Relieved at 2 hours based on the FDA defined ITT Population for Study S98-074

Study S98074		Number of Responders, Without Symptom at Baseline, Or Symptom Relieved at 2 Hours	P-value by CMH Stratified by Center
Headache Response		Placebo: 55 (26.83%) ESBA: 76 (39.79%)	0.007
Nausea	– baseline	Placebo: 68(33.17%) ESBA: 68(35.60%)	0.667
	– two hours	Placebo: 98(47.80%) ESBA: 91(47.64%)	0.869
Photophobia	– baseline	Placebo: 7 (3.41%) ESBA: 6 (3.14%)	0.925
	– two hours	Placebo: 30(14.63%) ESBA: 51(26.70%)	0.003
Phonophobia	– baseline	Placebo: 16 (7.80%) ESBA: 15(7.85%)	0.917
	– two hours	Placebo: 37(18.05%) ESBA: 62(32.46%)	0.001

Note: There are 205 patients in Placebo group and 191 patients in ESBA group.

2. When the sponsor's efficacy results were evaluated according to their protocols and amendments, there was no inconsistency found by this reviewer.

3. **(Conclusion)** The sponsor made the efficacy conclusion based on their pooled study analysis, which was not suitable. The p-value from the pooled study analysis is not appropriate for the decision making. So, the final efficacy conclusion should be made according to the analyses for separate studies. Based on this reviewer's analyses, 2 out of 3 studies were concluded positive for the primary endpoints, i.e., percent responders. Regarding the symptoms of nausea, photophobia and phonophobia, there was no positive result shown on any study for nausea, there were, however, 2 studies were concluded positive for both photophobia and for phonophobia.

4. By using LOCF on FDA defined ITT population, this reviewer did subgroup analyses for each study, which were shown in Appendix II. Comparing with the sponsor's examination of subgroups, there were two p-values that resulted different conclusions. For Study S98-072, this reviewer had p-value for baseline severity 0.1857 but the sponsor had 0.04. For Study S98-074, this reviewer had p-value for gender 0.0585 but the sponsor had 0.031. After carefully observing the results for subgroup analyses, this reviewer wishes to point out that for Study S98-074, the group of patients with baseline pain of severe did not show any difference between treatment groups ($p = 0.952$) although its primary endpoint had significant result.

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

Concurrence:

Dr. Jin

Dr. Mahjoob

cc:
HFD-120/Dr. Katz.
HFD-120/Dr. Oliva
HFD-120/Dr. Prohaska
HFD-120/Ms. Chen, L.
HFD-700/Dr. Anello
HFD-120/Dr. Chi
HFD-120/Dr. Mahjoob
HFD-710/Dr. Jin
HFD-710/Dr. Chen, Y.
This review consists of 23 pages and 2 Appendices. MS Word:

V. Appendix I: Demographic and Subject Characteristics (for Confirmed Migraine Population)

Study S98-072:

Variable	Placebo (N=200)	ESBA (N=201)	Total (N=401)	P-value
Age (yrs) Mean & SD	37.86 & 9.39	37.30 & 8.69	37.58 & 9.04	0.556
Race				
Caucasian	154 (77%)	155 (77%)	309 (77%)	0.838
Black	44 (22%)	43 (21%)	87 (22%)	
Hispanic	0 (0%)	1 (0%)	1 (0%)	
Asian	1 (1%)	2 (1%)	3 (1%)	
Other	1 (1%)	0 (0%)	1 (0%)	
Gender				
Male	42 (21%)	43 (21%)	85 (21%)	0.906
Female	158 (79%)	158 (79%)	316(79%)	
Weight Mean & SD	167.30 & 42.18	171.88 & 44.46	169.59 & 43.35	0.311
Height Mean & SD	65.63 & 3.44	65.55 & 3.41	65.59 & 3.42	0.897
Pulse (bpm) Mean & SD	69.88 & 8.84	70.05 & 9.01	69.97 & 8.92	0.931
Systolic BP (mm Hg) Mean & SD	114.17 & 13.97	114.13 & 14.42	114.15 & 14.18	0.885
Diastolic BP (mm Hg) Mean & SD	73.73 & 9.72	74.54 & 9.67	74.13 & 9.69	0.374
Baseline Pain Intensity				
Moderate	127 (64%)	121 (60%)	248 (62%)	0.504
Severe	73 (37%)	80 (40%)	153(38%)	
Baseline Nausea				
None	90 (45%)	85 (42%)	175 (44%)	0.740
Mild	65 (33%)	69 (34%)	134 (33%)	
Moderate	41 (21%)	44 (22%)	85 (21%)	
Severe	4 (2%)	3 (1%)	7 (2%)	
Baseline Photophobia				
None	6 (3%)	6 (3%)	12 (3%)	0.534
Mild	35 (18%)	39 (19%)	74 (18%)	
Moderate	128(64%)	112 (56%)	240 (60%)	
Severe	31(16%)	44 (22%)	75 (19%)	
Baseline Phonophobia				
None	7 (4%)	5 (2%)	12 (3%)	0.348
Mild	49 (25%)	38 (19%)	87 (22%)	
Moderate	101 (51%)	115 (57%)	216 (54%)	
Severe	43 (22%)	43 (21%)	86 (21%)	

Study S98-073:

Variable	Placebo (N=180)	ESBA (N=197)	Total (N=377)	P-value
Age (yrs) Mean & SD	29.52 & 9.51	31.74 & 10.24	30.68 & 9.95	0.030
Race				
Caucasian	124 (69%)	150 (76%)	274 (73%)	0.115
Black	12 (7%)	24 (12%)	36 (10%)	
Hispanic	39 (22%)	21 (11%)	60 (16%)	
Asian	2 (1%)	2 (1%)	4 (1%)	
Other	3 (2%)	0 (0%)	3 (1%)	
Gender				
Male	43 (24%)	40 (20%)	83 (22%)	0.402
Female	137 (76%)	157 (80%)	294(78%)	
Weight Mean & SD	163.97 & 42.77	161.79 & 38.11	162.83 & 40.37	0.601
Height Mean & SD	65.98 & 3.47	65.99 & 3.68	65.99 & 3.58	0.975
Pulse (bpm) Mean & SD	70.72 & 8.53	71.45 & 8.91	71.10 & 8.73	0.418
Systolic BP (mm Hg) Mean & SD	117.30& 12.55	118.28 & 13.13	117.80 & 12.85	0.475
Diastolic BP (mm Hg) Mean & SD	71.53 & 9.23	71.77 & 8.84	71.66 & 9.01	0.794
Baseline Pain Intensity				
Moderate	116 (64%)	125 (63%)	241 (64%)	0.841
Severe	64 (36%)	72 (37%)	136(36%)	
Baseline Nausea				
None	72 (40%)	73 (37%)	145 (38%)	0.664
Mild	66 (37%)	77 (39%)	143 (38%)	
Moderate	37 (21%)	41 (21%)	78 (21%)	
Severe	5 (3%)	6 (3%)	11 (3%)	
Baseline Photophobia				
None	5 (3%)	4 (2%)	9 (2%)	0.415
Mild	43 (24%)	44 (22%)	87 (23%)	
Moderate	105(58%)	114 (58%)	219 (58%)	
Severe	27(15%)	35 (18%)	62 (16%)	
Baseline Phonophobia				
None	8 (4%)	10 (5%)	18 (5%)	0.526
Mild	46 (26%)	58 (29%)	104 (28%)	
Moderate	98 (54%)	98 (50%)	196 (52%)	
Severe	28 (16%)	31 (16%)	59 (16%)	

Study S98-074:

Variable	Placebo (N=204)	ESBA (N=188)	Total (N=392)	P-value
Age (yrs) Mean & SD	40.78 & 11.71	41.75 & 10.27	41.24 & 11.04	0.364
Race				
Caucasian	174 (85%)	163 (87%)	337 (86%)	0.757
Black	18 (9%)	11 (6%)	29 (7%)	
Hispanic	7 (3%)	3 (2%)	10 (3%)	
Asian	3 (1%)	7 (4%)	10 (3%)	
Other	2 (1%)	4 (2%)	6 (2%)	
Gender				
Male	36 (18%)	40 (21%)	76 (19%)	0.347
Female	168 (82%)	148 (79%)	316(81%)	
Weight Mean & SD	156.43 & 36.86	162.43 & 39.29	159.31 & 38.11	0.120
Height Mean & SD	65.55 & 3.64	65.64 & 3.52	65.60 & 3.58	0.750
Pulse (bpm) Mean & SD	73.13 & 9.69	73.14 & 8.96	73.14 & 9.33	0.954
Systolic BP (mm Hg) Mean & SD	116.75 & 13.60	117.04 & 14.88	116.98 & 14.21	0.948
Diastolic BP (mm Hg) Mean & SD	74.65 & 9.74	74.49 & 9.66	75.06 & 9.70	0.470
Baseline Pain Intensity				
Moderate	160 (78%)	143 (76%)	303(77%)	0.642
Severe	44 (22%)	45 (24%)	89(23%)	
Baseline Nausea				
None	67 (33%)	65 (35%)	132 (34%)	0.985
Mild	93 (46%)	80 (43%)	173 (44%)	
Moderate	37 (18%)	35 (19%)	72 (18%)	
Severe	7 (3%)	7 (4%)	14 (4%)	
Not Reported	0	1	1	
Baseline Photophobia				
None	7 (3%)	5 (3%)	12 (3%)	0.854
Mild	61 (30%)	59 (31%)	120 (31%)	
Moderate	110(54%)	97 (52%)	207 (53%)	
Severe	26(13%)	27 (14%)	53 (14%)	
Not Reported	0	0	0	
Baseline Phonophobia				
None	16 (8%)	13 (7%)	29 (7%)	0.658
Mild	69 (34%)	61 (32%)	130 (33%)	
Moderate	95 (47%)	90 (48%)	185 (47%)	
Severe	24 (12%)	24 (13%)	48 (12%)	
Not Reported	0	0	0	

Appendix II. Subgroup Analyses by This Reviewer

Study S98-072:

Analysis of Percent Responders by Gender

Variable	Placebo	ESBA	Total
Male			
Responders	14 (33%)	21 (48%)	35 (41%)
Non-Responders	28 (67%)	23 (52%)	51 (59%)
Female			
Responders	58 (36%)	91 (57%)	149 (47%)
Non-Responders	102 (64%)	69 (43%)	171 (53%)
	Gender	**Treatment**	**Gender×Treatment**
P-value	0.3068	0.003	0.5976

Analysis of Percent Responders by Race

Variable	Placebo	ESBA	Total
White			
Responders	56 (36%)	84 (54%)	140 (45%)
Non-Responders	98 (64%)	73 (47%)	171 (55%)
Non-White			
Responders	16 (33%)	28 (60%)	44 (47%)
Non-Responders	32 (67%)	19 (40%)	51 (53%)
	Race	**Treatment**	**Race×Treatment**
P-value	0.7884	0.0001	0.4219

Analysis of Percent Responders by Age

Variable	Placebo	ESBA	Total
< 65 Years			
Responders	72 (36%)	112 (55%)	184 (45%)
Non-Responders	130 (64%)	92 (45%)	222 (55%)
≥ 65 Years			
Responders	0	0	0
Non-Responders	0	0	0

Analysis of Percent Responders by Severity

Variable	Placebo	ESBA	Total
Moderate			
Responders	50 (39%)	69 (56%)	119 (48%)
Non-Responders	77 (61%)	54 (44%)	131 (52%)
Severe			
Responders	22 (29%)	43 (53%)	65 (42%)
Non-Responders	53 (71%)	38 (47%)	91 (58%)
	Severity	**Treatment**	**Severity×Treatment**
P-value	0.1857	≈ 0	0.4761

Study S98-073:

Analysis of Percent Responders by Gender

Variable	Placebo	ESBA	Total
Male			
Responders	16 (36%)	16 (40%)	32 (38%)
Non-Responders	28 (64%)	24 (60%)	52 (62%)
Female			
Responders	60 (44%)	81 (52%)	141 (48%)
Non-Responders	77 (56%)	76 (48%)	153 (52%)
	Gender	**Treatment**	**Gender×Treatment**
P-value	0.1160	0.3448	0.7310

Analysis of Percent Responders by Race

Variable	Placebo	ESBA	Total
White			
Responders	51 (41%)	79 (53%)	130 (47%)
Non-Responders	74 (59%)	71 (47%)	145 (53%)
Non-White			
Responders	25 (45%)	18 (38%)	43 (42%)
Non-Responders	31 (55%)	29 (62%)	60 (58%)
	Race	**Treatment**	**Race×Treatment**
P-value	0.3566	0.6286	0.1107

Analysis of Percent Responders by Age

Variable	Placebo	ESBA	Total
< 65 Years			
Responders	76 (42%)	97 (49%)	173 (46%)
Non-Responders	105 (58%)	100 (51%)	205 (54%)
≥ 65 Years			
Responders	0	0	0
Non-Responders	0	0	0

Analysis of Percent Responders by Severity

Variable	Placebo	ESBA	Total
Moderate			
Responders	55 (47%)	78 (62%)	133 (55%)
Non-Responders	61 (53%)	47 (38%)	108 (45%)
Severe			
Responders	21 (32%)	19 (26%)	40 (29%)
Non-Responders	44 (68%)	53 (74%)	97 (71%)
	Severity	**Treatment**	**Severity×Treatment**
P-value	≈ 0	0.3667	0.0374

Study S98-074:

Analysis of Percent Responders by Gender

Variable	Placebo	ESBA	Total
Male			
Responders	16 (44%)	17 (41%)	33 (43%)
Non-Responders	20 (56%)	24 (59%)	44 (57%)
Female			
Responders	39 (23%)	59 (39%)	98 (31%)
Non-Responders	130 (77%)	91 (61%)	221 (69%)
	Gender	Treatment	Gender×Treatment
P-value	0.0585	0.2850	0.1213

Analysis of Percent Responders by Race

Variable	Placebo	ESBA	Total
White			
Responders	43 (25%)	65 (39%)	108 (32%)
Non-Responders	132 (75%)	101 (61%)	233 (68%)
Non-White			
Responders	12 (40%)	11 (44%)	23 (42%)
Non-Responders	18 (60%)	14 (56%)	32 (58%)
	Race	Treatment	Race×Treatment
P-value	0.1553	0.1296	0.4581

Analysis of Percent Responders by Age

Variable	Placebo	ESBA	Total
< 65 Years			
Responders	53 (27%)	76 (40%)	129 (33%)
Non-Responders	144 (73%)	114 (60%)	258 (67%)
≥ 65 Years			
Responders	2 (25%)	0 (0%)	2 (22%)
Non-Responders	6 (75%)	1 (100 %)	7 (78%)
	Age	Treatment	
P-value	0.0663	0.0048	

Analysis of Percent Responders by Severity

Variable	Placebo	ESBA	Total
Moderate			
Responders	44 (27%)	65 (45%)	109 (36%)
Non-Responders	117 (73%)	81 (55%)	198 (65%)
Severe			
Responders	11 (25%)	11 (24 %)	22 (25%)
Non-Responders	33 (75%)	34 (76%)	67 (75%)
	Severity	Treatment	Severity×Treatment
P-value	0.035	0.1174	0.0949

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yeh-Fong Chen
7/23/01 12:15:11 PM
BIOMETRICS

Kun Jin
7/23/01 01:28:49 PM
BIOMETRICS

Kooros Mahjoob
7/23/01 02:29:13 PM
BIOMETRICS