CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-012/S-016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL CONSULTATIVE REVIEW OF NDA SUPPLEMENT

Brand Name:	**Motrin Migraine**
Generic Name:	**ibuprofen**
Sponsor:	**McNeil**
Indication:	**migraine**
NDA Number:	**19-012**
Original Receipt Date:	**2/26/99**
Clinical Reviewers:	**Armando Oliva, MD**
Review Author:	**Armando Oliva, MD**
Review Completed:	**8/18/99**

Table of Contents

1. Review Sources

I used the following sources for my review:

Volumes 1-3:	NDA summary, Integrated Summaries of Efficacy and Safety, Draft Labeling
Volumes 3-15:	Study Report for study 97-022
Volumes 16-29:	Study Report for study 97-030
Volumes 30-116:	Case Report Tabulations
Volume 117:	Case Report Forms

The sponsor subsequently provided the ISE/ISS, and study reports as PDF files, and the case report tabulations in electronic format as SAS transport files. I also used these for my review.

2. Background

This NDA supplement requests approval of over-the-counter ibuprofen 200mg, to be marketed under the name "Motrin Migraine," for the temporary relief of mild-moderate pain associated with migraine headaches for adults and children over the age of 12. It includes additional labeling intended for the migraine headache population. The sponsor incorporates labeling found in the Excedrin Migraine labeling.

Currently, Motrin IB is indicated "for the reduction of fever and the temporary relief of headache, muscular aches, minor pain or arthritis, toothache, backache, minor aches and pains associated with the common cold, and the pain of menstrual cramps in adults and children 12 years of age and older."

Approved adult dosing of OTC ibuprofen is 1 tablet every six hours while symptoms persist. If pain or fever doesn't respond to one tablet, two tablets (400mg) may be used, but the total dose should not exceed 6 tablets in 24 hours, unless directed by a doctor.

Over the counter ibuprofen enjoys widespread use. The sponsor estimates that approximately 19.6 billion dosage unit equivalents (200mg) of McNeil OTC ibuprofen products (*i.e.*, Motrin, Medipren, Arthritis Foundation, and Nuprin) have been sold through 9/98. Additionally, the product is marketed in 49 countries worldwide in strengths ranging from 200mg to 800mg. Currently, non-prescription Motrin ibuprofen 200mg is available in approximately 27 countries. The sponsor is not aware of any country that has withdrawn any adult OTC ibuprofen product because of safety concerns.

This application contains the results of two randomized controlled clinical studies of ibuprofen in the treatment of migraine pain. In addition, they provide data from

published randomized controlled trials of migraine as supportive evidence for the efficacy and safety of ibuprofen in the treatment of migraine headache pain.

Study 97-022 was a single dose, randomized, double-blind, placebo-controlled study which evaluated 200mg and 400mg for the treatment of migraine headache pain in 660 patients, ages 18-84. It was conducted between February and July, 1998.

Study 97-030 was identical in design to study 22. It studied 649 patients, ages 18-70.[1] It was conducted between March and July 1998.

3. Proposed Labeling

The sponsor plans to market 3 formulations: tablet, caplet, and gelcap. The gelcap labeling differs from the other two in these three areas:

1. For 100 gelcap carton size, the statement "This package for households without young children," has been added to the carton and bottle since this package will not have child-resistant packaging.
2. The inactive ingredient listing is representative of the gelcap product.
3. The phrase "distributed by" is not included with the McNeil Consumer Healthcare name since Motrin IB Gelcaps are manufactured by McNeil.

Below is a copy of the proposed draft labeling for the leaflet. The draft labeling for the carton and bottle are analogous.

Motrin® Migraine Tablets
Ibuprofen Tablets USP
Pain Reliever

Active Ingredient **(In Each Tablet):**	**Purpose:**
Ibuprofen 200 mg	Pain Reliever

Use:
for the temporary relief of mild to moderate pain associated with migraine headache

Warnings
Allergy Alert: ibuprofen may cause a severe allergic reaction which may include:

- hives
- facial swelling asthma (wheezing)
- shock

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do Not Use:

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- with any other pain reliever/fever reducer
- with any other product containing ibuprofen

[1] Neither study enrolled adolescent patients.

- for more than 48 hours for the pain of migraine

Ask a Doctor Before Use If You Have:
- the worst headache of your life
- fever and stiff neck
- daily headaches
- headaches beginning after or are caused by head injury, exertion, coughing or bending
- experienced your first headache after the age of 50
- migraine headaches so severe as to require bed rest
- vomiting with your migraine headache

Ask a Doctor Before Use If:
- you take prescription drugs
- you are under a doctor's care for any serious medical condition
- you have had problems or side effects with any pain reliever/fever reducer

Stop Using This Product and Ask a Doctor If:
- an allergic reaction occurs. Seek medical help right away
- migraine headache pain worsens or continues for more than 48 hours
- stomach pain occurs with use of this product
- stomach upset gets worse or lasts
- any new or unexpected symptoms occur

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

IT IS ESPECIALLY IMPORTANT NOT TO USE IBUPROFEN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.

Keep out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center right away.

Directions:
Adults:
1. **DO not take more than directed.**
2. Take 1 tablet every 4 to 6 hours while symptoms persist.
3. If pain does not respond to 1 tablet, 2 tablets may be used, but do not exceed 6 tablets in 24 hours, unless directed by a doctor.
4. The smallest effective dose should be used.
5. If stomach upset occurs while taking this product, take with food or milk.

Children: Do not give this product to children Under 12 unless directed by a doctor.

4. Efficacy – Studies 22 and 30

4.1 Background and Methodology

The application contains the results of studies 22 and 30. Both studies were adequate and well-controlled trials that by design were capable of demonstrating efficacy. They were single migraine attack studies with identical design. Both studies were randomized, double blind, placebo controlled, multicenter studies.

Both used three treatment arms: placebo, ibuprofen 200mg, and ibuprofen 400mg. Both were single dose studies and both used the tablet formulation.

For entry, subjects were required to have a current frequency of at least one migraine headache every two months to six migraine headaches per month. The protocols excluded patients with severe migraine: those migraineurs experiencing vomiting in > 20% of attacks were excluded, as well as those with incapacitating migraines necessitating bed rest or prohibiting normal daily activities in more than 50% of episodes. These exclusions eliminated the most severe migraineurs, allowing study results to be generalized to a large population likely to use OTC medications. Those taking prophylactic migraine medications could enroll in these studies.

Eligible subjects were given a single dose of blinded medication at randomization. Patients treated a single moderate or severe migraine in an outpatient setting. Efficacy and safety were assessed during the six hours post-dosing at ½, 1, 1 ½, 2, 3, 4, 5, 6 hours. Rescue was permitted after 2 hours. Subjects returned for a follow-up visit within 72 hours after use of study medication for a follow-up interview.

Ibuprofen 200mg and 400mg were chosen for study since they are approved OTC doses for pain relief.

4.2 Disposition of Subjects

Table 1 (ISE table 8.6-2, page 7) summarizes the disposition of the patients enrolled in the two studies. Those who did not take study medication and/or did not return their headache diary were not included in the efficacy analyses. This included 24 patients randomized to ibuprofen 200mg in each of studies 22 and 30; 18 and 20 patients randomized to ibuprofen 400mg in 22 and 30, respectively, and 19 and 20 subjects randomized to placebo in 22 and 30, respectively. The intent to treat population consisted of 660 patients in study 22 and 649 patients in study 30.

Table 1: Disposition of Subjects

	Study 22				Study 30			
	200mg	400mg	PBO	Total	200mg	400mg	PBO	Total
Enrolled/ Randomized	240	241	240	721	240	239	234	713
Took Study Medication	216	223	221	660	216	219	214	649
Withdrew	80	92	108	280	94	91	112	297
Completed Study	136	131	113	380	122	128	102	352

A patient who took rescue medication was counted as a treatment failure were withdrawn, although they were kept in the ITT analysis. In study 22, all but three

of the withdrawals were due to rescue. In study 30, all but one of the withdrawals were due to rescue.

4.3 Demographics and Baseline Characteristics

Overall, 84.6% of the study subjects were women. This is consistent with other migraine studies. The vast majority (82.7%) of patients was Caucasian. The mean age of the patients was 38.6 years and 99.0% were in the 18-64 age group. The distributions of the demographics were similar for both clinical studies (Table 2, ISE Table 8.6-3, page 9).

Within each study, treatment groups had comparable demographic characteristics, with one exception. There was a significant difference among treatment groups in the distribution of subjects by gender in study 22 (p=0.0239); there was a lower percentage of women in the ibuprofen 200mg group (78.7%) than in the other two treatment groups. There were no other statistically significant differences among treatment groups in demographic characteristics at baseline.

Table 2: Demographic Characteristics

	Study 22				Study 30			
	200mg (n=216)	400mg (n=223)	PBO (n=221)	p	200mg (n=216)	400mg (n=219)	PBO (n=214)	p
Age								
Mean	38.9	38.0	39.1	0.5206	38.8	38.5	38.5	0.9407
Range	18-69	18-71	18-64		19-70	18-66	18-65	
Age Group								
18-64	213 (98.6%)	220 (98.7)	218 (98.6)	0.6905	214 (99.1)	218 (99.5)	213 (99.5)	0.7762
65-74	3 (1.4)	3 (1.3)	2 (0.9)		2 (0.9)	1 (0.5)	1 (0.5)	
≥75	0	0	1 (0.5)		0	0	0	
Sex								
Male	46 (21.3)	30 (13.5)	28 (12.7)	0.0239	36 (16.7)	33 (15.1)	29 (13.6)	0.6656
Female	170 (78.7)	193 (86.5)	193 (87.3)		180 (83.3)	186 (84.9)	185 (86.4)	
Race								
White	168 (77.8)	173 (77.6)	174 (78.7)	0.9917	191 (88.4)	185 (84.5)	191 (89.3)	0.4907
Black	17 (7.9)	19 (8.5)	16 (7.2)		14 (6.5)	15 (6.8)	11 (5.1)	
Other	31 (14.3)	31 (13.9)	31 (14.0)		11 (5.1)	19 (8.7)	12 (5.6)	

Across all treatment groups in both studies, approximately two-thirds (66.5% - 72.2%) of the migraines treated were recorded as moderate in intensity at baseline, and these were evenly distributed among all treatment groups in both studies. Other baseline characteristics (nausea, vomiting, photophobia,

phonophobia, functional disability, menstrual migraine) were fairly evenly distributed across groups (Table 3, ISE Table 8.6-4, page 11).

Table 3: Baseline Migraine Characteristics, by Treatment Group

Symptom	Study 22				Study 30			
	200 mg (N=216)	400 mg (N=223)	PBO (N=221)	p	200 mg (N=216)	400 mg (N=219)	PBO (N=214)	p
Pain Intensity, n (%)				0.5835				0.4213
Moderate	151 (69.9)	158 (70.9)	147 (66.5)		144 (66.7)	158 (72.1)	152 (71.0)	
Severe	65 (30.1)	65 (29.1)	74 (33.5)		72 (33.3)	61 (27.9)	62 (29.0)	
Aura, n (%)		(N=222)		0.8988				0.7110
No	158 (73.1)	165 (74.3)	160 (72.4)		164 (75.9)	173 (79.0)	168 (78.5)	
Yes	58 (26.9)	57 (25.7)	61 (27.6)		52 (24.1)	46 (21.0)	46 (21.5)	
Nausea, n (%)	(N=215)		(N=220)	0.1921				0.0756
None	87 (40.5)	101 (45.3)	98 (44.5)		88 (40.7)	95 (43.4)	103 (48.1)	
Mild	82 (38.1)	73 (32.7)	64 (29.1)		75 (34.7)	83 (37.9)	60 (28.0)	
Moderate	41 (19.1)	37 (16.6)	43 (19.5)		46 (21.3)	32 (14.6)	48 (22.4)	
Severe	5 (2.3)	12 (5.4)	15 (6.8)		7 (3.2)	9 (4.1)	3 (1.4)	
Phonophobia, n (%)				0.9994				0.8352
None	18 (8.3)	17 (7.6)	17 (7.7)		18 (8.3)	21 (9.6)	25 (11.7)	
Mild	65 (30.1)	70 (31.4)	67 (30.3)		76 (35.2)	72 (32.9)	64 (29.9)	
Moderate	95 (44.0)	96 (43.0)	95 (43.0)		92 (42.6)	91 (41.6)	95 (44.4)	
Severe	38 (17.6)	40 (17.9)	42 (19.0)		30 (13.9)	35 (16.0)	30 (14.0)	
Photophobia, n (%)				0.7868				0.9497
None	6 (2.8)	13 (5.8)	9 (4.1)		10 (4.6)	9 (4.1)	12 (5.6)	
Mild	52 (24.1)	50 (22.4)	55 (24.9)		59 (27.3)	56 (25.6)	54 (25.2)	
Moderate	109 (50.5)	108 (48.4)	111 (50.2)		100 (46.3)	112 (51.1)	103 (48.1)	
Severe	49 (22.7)	52 (23.3)	46 (20.8)		47 (21.8)	42 (19.2)	45 (21.0)	
Vomiting, n (%)				0.3815				0.1711
Yes	212 (98.1)	215 (96.4)	217 (98.2)		208 (96.3)	213 (97.3)	212 (99.1)	
No	4 (1.9)	8 (3.6)	4 (1.8)		8 (3.7)	6 (2.7)	2 (0.9)	
Function, n (%)		(N=222)		0.0928				0.8688
Normal	7 (3.2)	4 (1.8)	11 (5.0)		4 (1.9)	7 (3.2)	4 (1.9)	
Mildly Impaired	56 (25.9)	73 (32.9)	54 (24.4)		69 (31.9)	77 (35.2)	69 (32.2)	
Moderately Impaired	123 (56.9)	108 (48.6)	130 (58.8)		114 (52.8)	109 (49.8)	117 (54.7)	
Severely Impaired	30 (13.9)	37 (16.7)	26 (11.8)		29 (13.4)	26 (11.9)	24 (11.2)	
Menstruating, n (%)				0.1024				0.4080
No	144 (66.7)	161 (72.2)	168 (76.0)		140 (64.8)	153 (69.9)	157 (73.4)	
Yes	26 (12.0)	31 (13.9)	24 (10.9)		38 (17.6)	32 (14.6)	26 (12.1)	
N/A	46 (21.3)	31 (13.9)	29 (13.1)		38 (17.6)	34 (15.5)	31 (14.5)	

4.4 Endpoints and Analysis Methods

Pairwise comparisons were made between 200mg vs. placebo and 400mg vs. placebo, and 400mg vs. 200mg. The protocols specified primary endpoint was the percentage of subjects who experienced moderate or severe pain at baseline

and mild or no pain at the 2 hour time point (2-hr headache response rate). This was analyzed using Cochran-Mantel-Haenszel test stratified by baseline headache intensity. The pain intensity difference (PID) at 2 hours was also an additional primary endpoint. This was analyzed using ANOVA. Subgroup analyses by age (<65, ≥65), gender, and race were planned for both primary endpoints. All tests of significance were two-sided.

Secondary endpoints included:
1. Complete relief at 2 hours (no pain)
2. Time to rescue
3. Recurrence rates at 6 hours
4. PID and complete relief at other time points
5. SPID and TOTPAR: sum of the time-interval weighted pain intensity differences, and the time-interval weighted sum of pain relief scores
6. Severity of migraine associated symptoms: nausea, vomiting, photophobia, phonophobia (none, mild, moderate, severe)
7. Overall impression of study medication
8. Time to recurrence
9. Severity of recurrence

The sponsor conducted additional subgroup analyses: baseline pain intensity, and menstrual status. They were analyzed using the same Cochran-Mantel-Haenszel test used for the other planned subgroup analyses.

4.5 Efficacy Results

All results are based on the intent-to-treat analysis. Patients were excluded from the analysis if they did not take study medication or if they took study medication but provided no study diary data. Per protocol analyses were also performed for the primary endpoints and the results were consistent with the intent to treat analysis.

4.5.1 Two-Hour Headache Response Rate

The two hour headache response rates for studies 22 and 30 are shown in Table 4 (ISE Table 8.6-6, page 19). In both studies, ibuprofen 200mg and 400mg were significantly better than placebo, but the 400mg was not superior to the 200mg dose.

Table 4: Studies 22 and 30 – 2-Hour Headache Response Rates

Study	200mg	400mg	PBO	p-value 200mg vs. PBO	p-value 400mg vs. PBO	p-value 200mg vs. 400mg
22	90/216 (41.67)	91/223 (40.81)	62/221 (28.05)	0.004	0.006	0.832
30	86/216 (39.81)	90/219 (41.10)	57/214 (26.64)	0.002	0.002	0.992

Statistical significance assessed using Cochran-Mantel-Haenszel stratified by baseline intensity

Figure 1 and Figure 2 show the cumulative headache response rates between 0-6 hours for each individual study. Both curves are remarkably similar in that both ibuprofen doses are better than placebo, but neither dose appears better than the other. The p values at 6 hours are highly nominally significant for both doses in both studies (0.003 for 200mg vs. placebo and <0.001 for 400mg vs. placebo in study 22, and 0.001 for both ibuprofen doses vs. placebo in study 30).

Figure 1: Study 22 – Cumulative Headache Response Rates 0-6 Hours

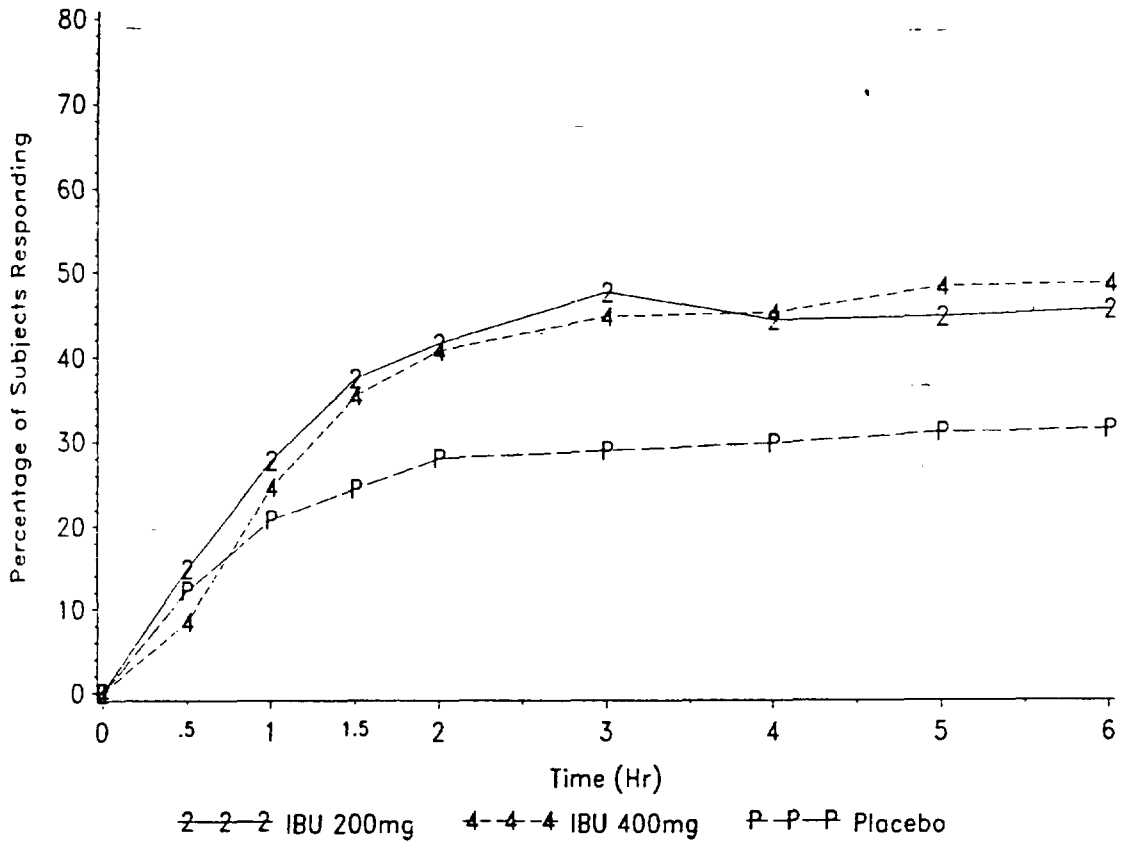

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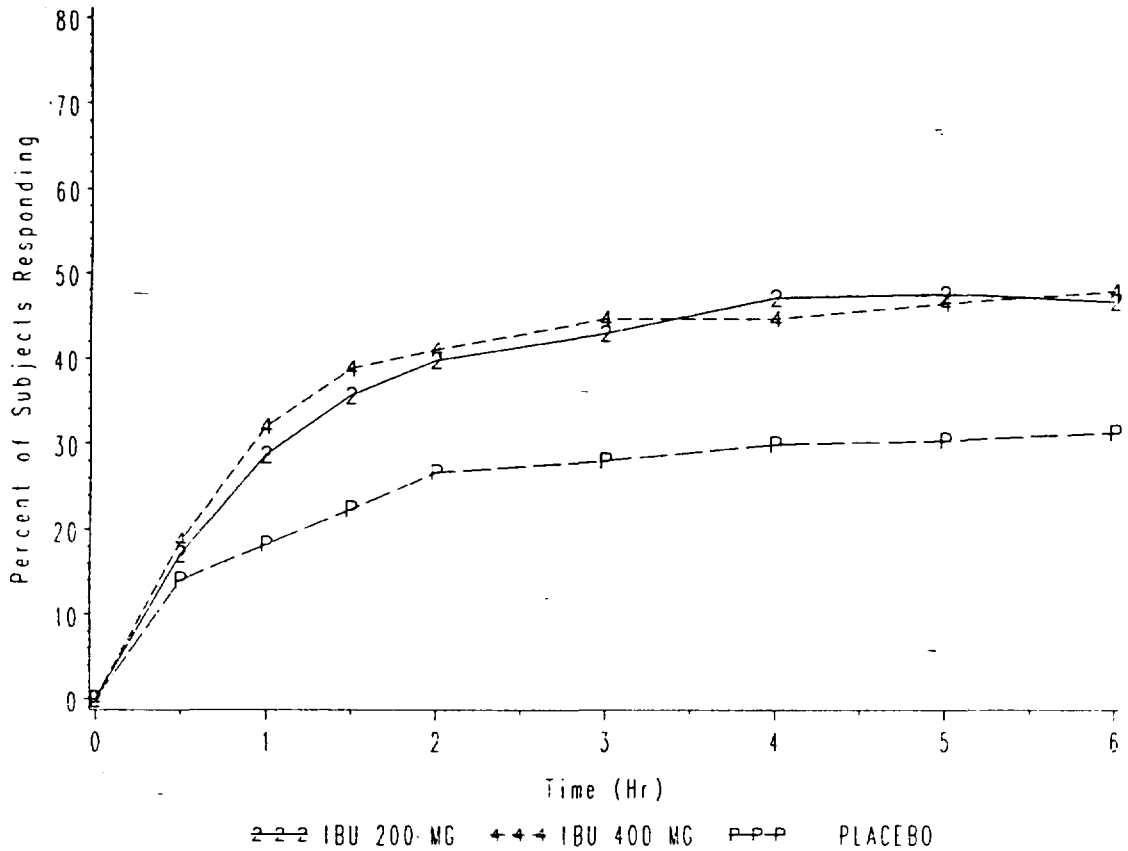
Figure 2: Study 30 – Cumulative Headache Response Rates 0-6 Hours



4.5.2 Two-Hour Pain Intensity Difference (PID)

The PID at 2 hours was the other primary efficacy endpoint. This is shown in Table 5 (ISE table 8.6-9). The mean PID was significantly lower for each dose of ibuprofen (200mg or 400mg) compared to placebo. There was again no difference seen between the two doses of ibuprofen. These results are consistent with those seen with the 2-hr headache response rate.

Table 5: Study 22 and 30 – Mean 2-Hr Pain Intensity Difference

Study	200mg (n)	400mg (n)	PBO (n)	p-value* 200mg vs. PBO	p-value* 400mg vs. PBO	p-value* 200mg vs. 400mg
22	0.68 ±0.94 (216)	0.65±1.01 (223)	0.39±0.92 (221)	<0.001	0.001	0.673
30	0.67±0.92 (216)	0.65±0.99 (219)	0.35±0.91 (214)	0.001	<0.001	0.839

*3-way ANOVA (treatment, investigator, and baseline pain intensity)

4.5.3 Subgroup Analysis: Baseline Pain Intensity

The sponsor analyzed the primary efficacy endpoints according to baseline pain intensity. The majority of patients (69.5%) had moderate pain at baseline. Both

doses were effective in this subgroup (42.4%-49.3% vs. 29.0%-31.3% for placebo, ISE table 8.6-10 not shown here). However, in the subgroup of patients with severe headaches at baseline, the 200mg dose was not effective (study 22: 26% vs. 22%; study 30: 21% vs. 21%) and the 400mg dose was nominally significant for study 22 only (study 22: 37% vs. 22%, p=0.048; study 30: 30% vs. 21%, p=0.277), although it was in the right direction in study 30. Results were similar for the 2 hour PID.

4.5.4 Complete Relief

A patient experienced complete relief if they had a moderate or severe pain at baseline and no pain at a given time point. The sponsor analyzed the percentage of patients experiencing complete relief at 2 and 6 hours post dose. These results are shown in Table 6 (ISE table 8.6-15). Both 200mg and 400mg were associated with a nominally significant increase in complete relief at both 2 and 6 hours compared with placebo. There was no difference between the 200mg and 400mg doses. These results are consistent with those seen with the primary endpoints.

Table 6: Studies 22 and 30 – Complete Relief at 2 and 6 Hours

Study	200mg (n)	400mg (n)	PBO (n)	p-value* 200mg vs. PBO	p-value* 400mg vs. PBO	p-value* 200mg vs. 400mg
2 hours						
22	34/216 (15.7%)	31/223 (13.9%)	17/221 (7.7%)	0.010	0.031	0.583
30	29/216 (13.4%)	35/219 (16%)	14/214 (6.5%)	0.015	0.002	0.533
6 hours						
22	66/216 (30.6%)	68/223 (30.5%)	43/221 (19.5%)	0.008	0.007	0.987
30	61/216 (28.2%)	62/219 (28.3%)	33/214 (15.4%)	0.001	0.001	0.929

*Cochran-Mantel-Haenszel test stratified by baseline pain intensity

4.5.5 Time to Rescue and Rescue Rates at Six Hours

The sponsor calculated the Kaplan-Meier probabilities of using rescue medication, by time and treatment group. These are shown for each study in Figure 3 and Figure 4. Both curves showed that patients treated with either 200mg or 400mg had lower probabilities of requiring rescue compared with placebo; however, there was very little separation of the curves before 4-5 hours in either study. There was no difference between 200mg and 400mg.

By the end of the 6-hour observation period, 48% and 51% of placebo patients in studies 22 and 30, respectively, had used rescue. This compared with 37% and 43% of patients treated with 200mg and 41% for of patients treated with 400mg in both studies. The difference in rescue rates were nominally significant for 200mg in study 22 (p=0.02) and 400mg in study 30 (p=0.03) and were numerically in the right direction for the other two studies.

Figure 3: Study 22 – Probability of Requiring Rescue (Kaplan-Meier Estimate)

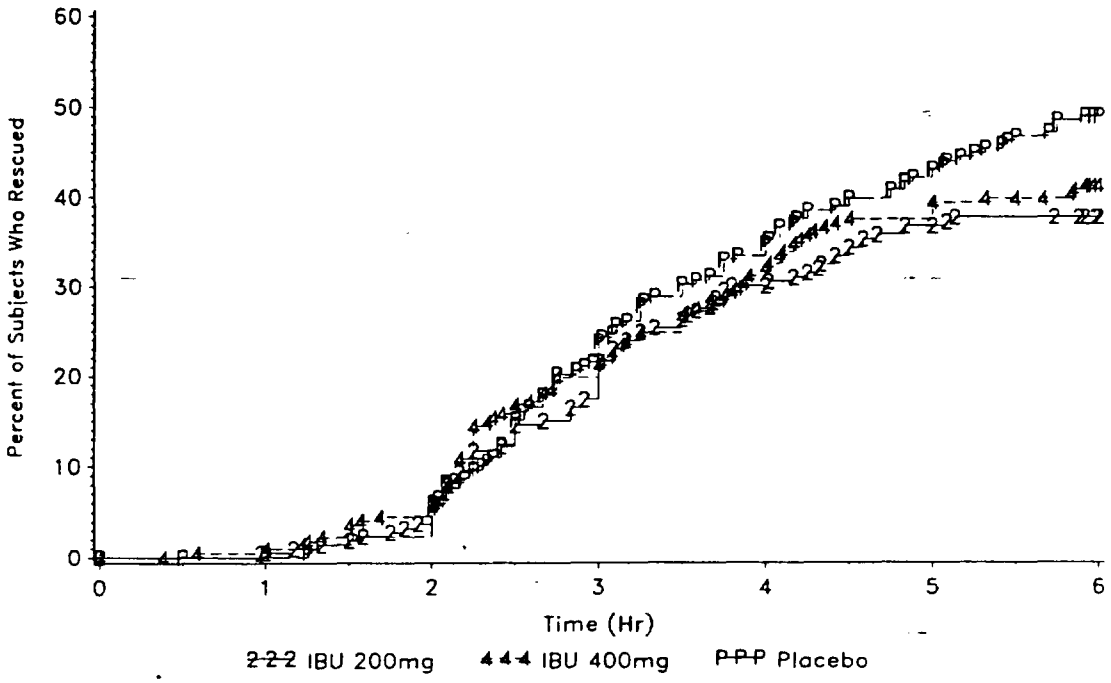
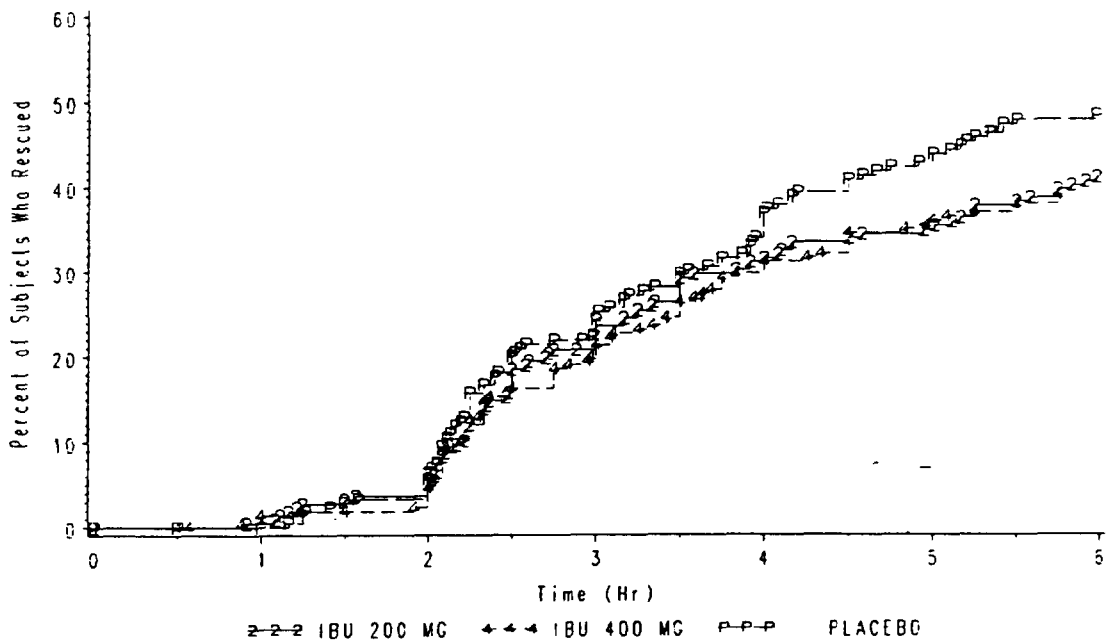


Figure 4: Study 30 - Probability of Requiring Rescue (Kaplan-Meier Estimate)



4.5.6 Migraine Associated Symptoms

4.5.6.1 Methods

The sponsor analyzed nausea, photophobia, phonophobia, and functional disability using two approaches. Both analyses included only those patients who had the symptoms at baseline.

Since each symptom was recorded using a 4 point ordinal scale throughout the six hour observation period (0=none, 1=mild, 2=moderate, 3=severe), the first set of analyses compared the mean difference from baseline in the severity of these symptoms at various time points.

The second set of analyses compared the proportion of patients who were completely relieved of their migraine associated symptom at various time points (*i.e.*, achieved a score of "0" or "none"). I review both sets of analyses below.

4.5.6.2 Changes From Baseline Severity

In general, subjects treated with either dose of ibuprofen had significantly larger mean reductions from baseline in the severity of migraine associated symptoms during the time points two through six hours post dosing, when compared with placebo treated patients. In particular, mean reductions from baseline in the severity of photophobia and functional disability were nominally significantly larger in both the 200mg and 400mg treated groups compared with placebo at the 2 through 6 hour time points.

For the remaining two other migraine associated symptoms, nausea and photophobia, patients almost always had directionally higher, and often significantly larger, mean reductions from baseline in the severity of these symptoms at the 2 through 6 hour time points in both studies. With one exception (nausea at 2 hours in study 30), there were no significant differences between the two doses of ibuprofen in the mean difference from baseline in the severity of migraine associated symptoms.

The sponsor summarized the analyses in Figure 5 and Figure 6 (ISE Figure 8.6-13 and 8.6-14). It shows the p-values for each analysis at each time point. Many had p values <0.10 and often the p value was <0.05. In only one instance (nausea at 6 hours for study 30, 400mg) the results went in the opposite direction, with nausea numerically more severe in the 400mg group compared with placebo.

Figure 5: Studies 22 and 30 – Migraine Associated Symptoms for Ibuprofen 200mg (Mean Differences in Severity of Migraine Associated Symptoms)

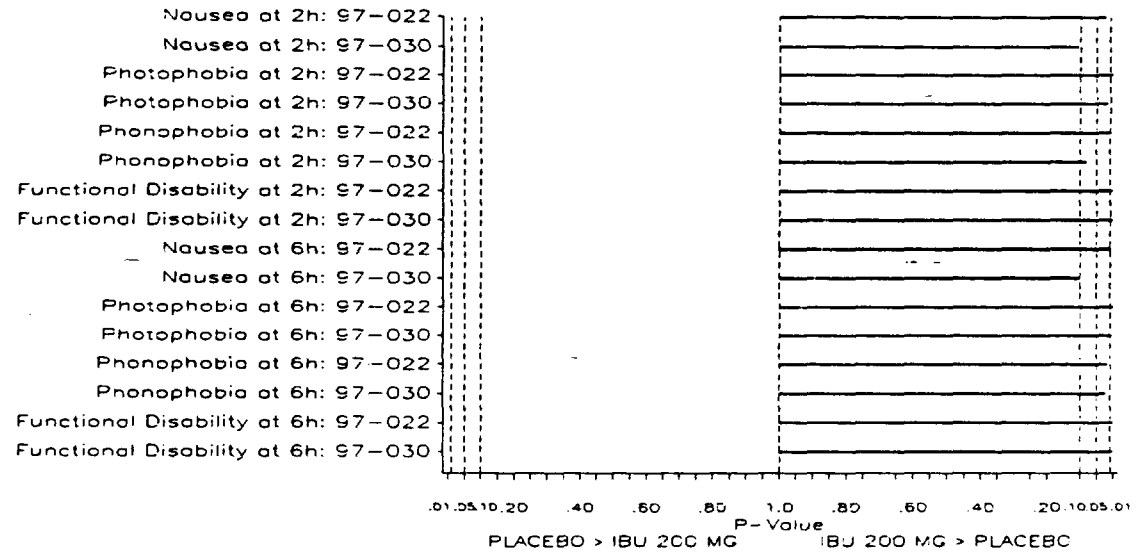
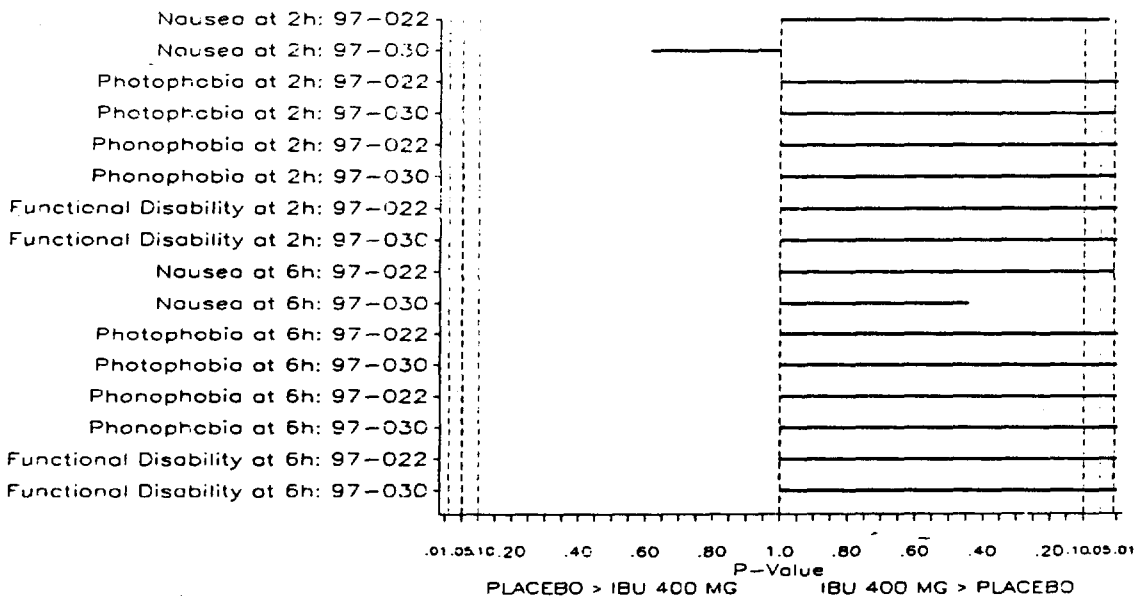


Figure 6: Studies 22 and 30 – Migraine Associated Symptoms for Ibuprofen 400mg (Mean Differences in Severity of Migraine Associated Symptoms)



4.5.6.3 Severity Reduced to "None"

The sponsor also compared the percentage of patients in each treatment group who had a symptom reduced to none at each time point. Pairwise comparisons are provided for the 2 and 6 hour time point. Only patients with these symptoms at baseline were included in the analyses. Results were very similar when compared to the difference in mean severity analyses in the previous section.

A higher percentage of patients treated with either dose of ibuprofen reported a reduction to none in the migraine associated symptoms when compared with placebo patients during the 2-6 hours post-treatment in both studies. The differences between either dose and placebo were statistically significant over 50% of the time at 2 and 6 hours. In particular, the percentage reporting relief of photophobia and functional disability was nominally significantly larger for both ibuprofen groups compared with placebo at the 6 hour time point in both studies, and at the 2 hour time point for study 30. For nausea and phonophobia at two and six hours in both studies, and for photophobia and functional disability at two hours study 22, the percentage of subjects reporting a reduction to none was always directionally larger and sometimes significantly larger for those treated with either dose of ibuprofen compared with those treated with placebo. There were no significant differences at two or six hours between the two doses of ibuprofen in the percentage of subjects with a reduction to none in migraine-associated symptoms.

Figure 7 and Figure 8 (ISE figure 8.6-23 and 8.6-24) graphically depict the p values for the percentage of subjects reporting a reduction to none for migraine associated symptoms at 2 and 6 hours for each treatment group. One can see that nausea had the most consistently highest (*i.e.*, least significant) p values.

Figure 7: Studies 22 and 30 – Migraine Associated Symptoms for Ibuprofen 200mg (Proportion Experiencing a Reduction in Migraine Associated Symptoms to None)

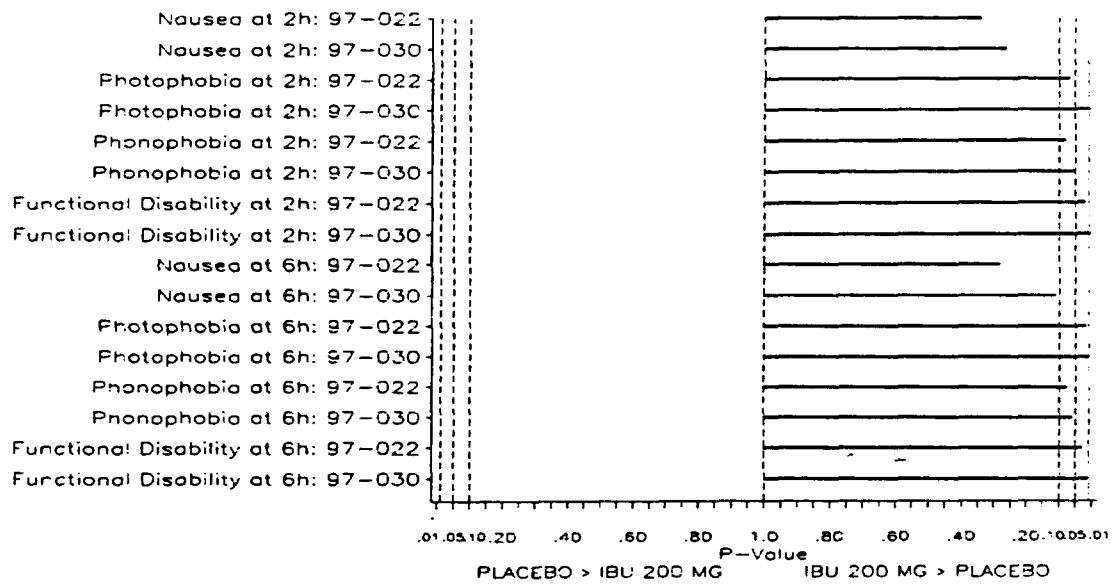
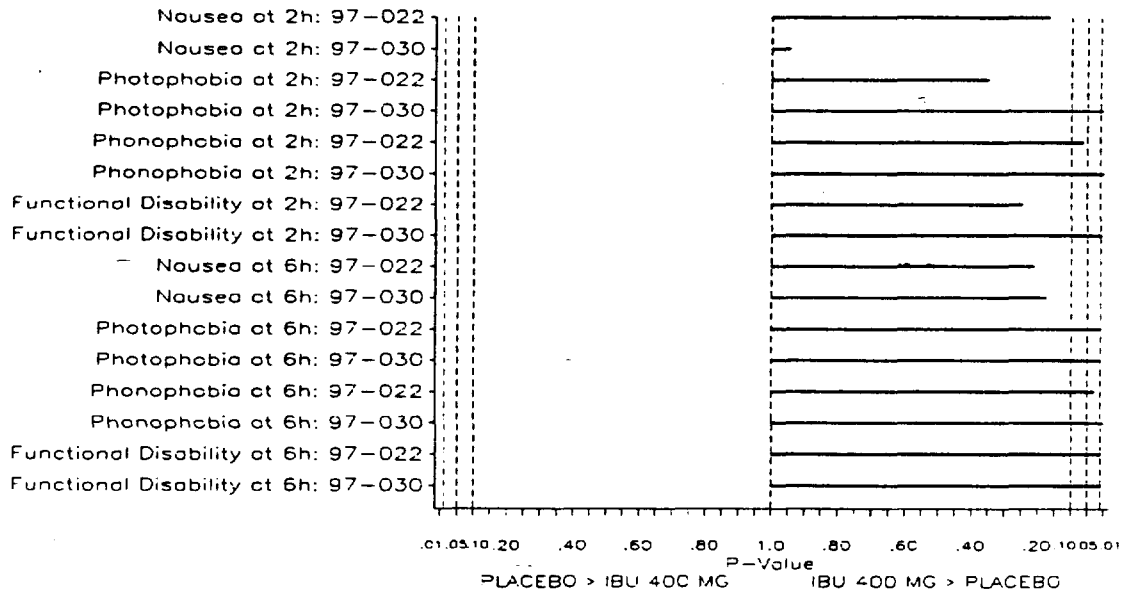


Figure 8: Studies 22 and 30 – Migraine Associated Symptoms for Ibuprofen 400mg (Proportion Experiencing a Reduction in Migraine Associated Symptoms to None)



I review each symptom in more detail below.

4.5.6.4 Nausea

Nausea was reported at baseline by approximately 50-60% of patients across all treatment groups in both studies (Table 3, page 8).

In study 22, patients treated with either dose of ibuprofen consistently had significantly larger mean reduction from baseline in the severity of nausea during the 2-6 hour time points, compared with placebo treated patients (Table 7, from ISE tables 8.6-22/23). There was no difference between each dose of ibuprofen. In addition, the 200mg group also had significantly larger mean reduction in nausea at 1.5 hours (but not the 400mg group). In contrast, the nausea analysis for study 30 was negative. There was no significantly decrease reduction in nausea for either the 200mg or 400mg doses. In fact, patients treated with 400mg in that study had numerically (but not statistically) higher nausea scores at 2 hours compared with placebo patients.

Table 7: Studies 22 and 30 – Mean Nausea Severity Differences from Baseline

Study 22

Treatment	Assessment Time Points (Hours) 5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.16 (0.52)	0.39 (0.74)	0.45 (0.83)	0.48 (0.93)	0.57 (0.97)	0.58 (0.98)	0.58 (0.99)	0.62 (0.97)
	128[a] A[d]	127 A	126 A	121 A	96 A	87 A	79 A	77 A
Ibu 400 mg	0.10 (0.64)	0.27 (0.87)	0.41 (0.93)	0.52 (1.00)	0.55 (1.03)	0.61 (1.04)	0.67 (1.09)	0.67 (1.12)
	122 A	121 A B	118 A B	116 A	101 A	89 A	76 A	75 A
Placebo	0.09 (0.55)	0.24 (0.74)	0.25 (0.98)	0.33 (0.97)	0.32 (1.08)	0.34 (1.13)	0.41 (1.16)	0.45 (1.19)
	122 A	122 B	121 B	116 B	95 B	83 B	74 B	64 B
Treatment p-Values[b]	0.2105	0.0596	0.0428	0.0370	0.0029	0.0021	0.0062	0.0105
Trt*Inv p-Value[c]	0.3204	0.4601	0.2267	0.2796	0.6480	0.4383	0.7161	0.5841
Trt*BLNausea p-Value[c]	0.0444	0.0459	0.5101	0.3371	0.5972	0.7327	0.6191	0.6922
RMS Error[c]	0.54	0.76	0.88	0.91	0.95	0.95	0.97	0.97

a: Number of subjects not rescuing
b: Model: $NAUSEASD=\mu + T_i + I_j + B_k + error$
c: Model: $NAUSEASD=\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik} + error$
d: Based On Model B LSMEANS

Study 30

Treatment	Assessment Time Points (Hours) 5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.16 (0.61)	0.36 (0.77)	0.46 (0.83)	0.52 (0.87)	0.54 (1.00)	0.60 (0.99)	0.61 (1.04)	0.59 (1.03)
	128[a] A[d]	127 A	123 A	122 A	101 A	90 A	82 A	76 A
Ibu 400 mg	0.09 (0.53)	0.21 (0.84)	0.27 (0.87)	0.28 (0.97)	0.39 (1.04)	0.44 (1.06)	0.46 (1.07)	0.46 (1.09)
	122 A	120 AB	119 A	113 B	95 A	86 A	76 A	71 A
Placebo	0.09 (0.58)	0.15 (0.74)	0.32 (0.85)	0.34 (0.81)	0.37 (0.97)	0.39 (1.00)	0.37 (0.98)	0.37 (0.98)
	111 A	111 B	106 A	102 AB	84 A	68 A	58 A	51 A
Treatment p-Values[b]	0.5314	0.1404	0.2080	0.0764	0.4489	0.2786	0.2011	0.2575
Trt*Inv p-Value[c]	0.6538	0.1647	0.3699	0.5828	0.6519	0.6784	0.7431	0.8357
Trt*BLNausea p-Value[c]	0.3821	0.8644	0.7337	0.4542	0.0802	0.2476	0.2265	0.2501
RMS Error[c]	0.57	0.76	0.82	0.85	0.97	0.97	0.99	0.99

a: Number of subjects not rescuing
b: Model: $NAUSEASD=\mu + T_i + I_j + B_k + error$
c: Model: $NAUSEASD=\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik} + error$
d: Based On Model B LSMEANS

Nausea reduced to none was reported in a numerically higher percentage of subjects treated with either dose of ibuprofen 2-6 hours post dose in both studies, when compared to placebo. However, these differences were not statistically significant at either 2 or 6 hours, the two time points tested (Table 8, ISE Table 8.6-30/31).

Table 8: Studies 22 and 30 – Reduction in Nausea to None

Study 22

Drug	Assessment Time Points (Hours) 0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=128)	8.59 (11)	30.47 (39)	35.94 (46)	**39.84 (51)**	47.66 (61)	48.44 (62)	50.00 (64)	**51.56 (66)**
Ibu 400 mg (N=122)	6.56 (8)	23.77 (29)	34.43 (42)	**40.98 (50)**	40.98 (50)	43.44 (53)	50.00 (61)	**50.82 (62)**
Placebo (N=122)	9.02 (11)	20.49 (25)	28.69 (35)	**31.15 (38)**	31.15 (38)	34.43 (42)	40.16 (49)	**42.62 (52)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.3404	0.2818
Ibu 400 mg vs placebo	0.1665	0.2106
Ibu 200 mg vs Ibu 400 mg	0.7585	0.9409

a: Cochran-Mantel-Haenszel test, stratified by baseline nausea severity.

Study 30

	Assessment Time Points (Hours)							
Drug	0.5	1	1.5	2	3	4	5	6
Ibu 200 mg	13.28	28.91	32.81	**36.72**	40.63	44.53	47.66	**46.88**
(N=128)	(17)	(37)	(42)	**(47)**	(52)	(57)	(61)	**(60)**
Ibu 400 mg	8.94	24.39	27.64	**32.52**	40.65	44.72	46.34	**47.15**
(N=123)	(11)	(30)	(34)	**(40)**	(50)	(55)	(57)	**(58)**
Placebo	8.11	18.92	27.93	**28.83**	35.14	37.84	36.04	**35.14**
(N=123)	(9)	(21)	(31)	**(32)**	(39)	(42)	(40)	**(39)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.262	0.110
Ibu 400 mg vs placebo	0.946	0.175
Ibu 200 mg vs Ibu 400 mg	0.256	0.718

a: Cochran-Mantel-Haenszel test, stratified by baseline nausea severity.

4.5.6.5 Photophobia

Photophobia was reported at baseline by approximately 95% of patients across all treatment groups in both studies (Table 3, page 8).

Patients treated with either dose of ibuprofen had significantly larger mean reductions from baseline in the severity of photophobia, when compared to placebo patients (Table 9, from ISE tables 8.6-24/25). This was true in both studies 22 and 30. In study 22, the effect was seen at 1-6 hours, and in study 30, it was seen at 2-6 hours post-treatment. There were no significant differences seen between the two doses of ibuprofen.

Table 9: Studies 22 and 30 – Mean Photophobia Severity Difference from Baseline

Study 22

	Assessment Time Points (Hours)							
Treatment	5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.08 (0.54)	0.31 (0.75)	0.47 (0.87)	0.57 (0.96)	0.64 (1.02)	0.64 (1.10)	0.68 (1.12)	0.72 (1.13)
	210[a] A[d]	209 A	206 A	197 A	166 A	148 A	134 A	132 A
Ibu 400 mg	0.09 (0.50)	0.36 (0.78)	0.48 (0.89)	0.59 (0.99)	0.69 (1.06)	0.73 (1.08)	0.79 (1.13)	0.83 (1.16)
	210 A	208 A	202 A	198 A	166 A	142 A	126 A	122 A
Placebo	0.06 (0.46)	0.15 (0.69)	0.25 (0.82)	0.30 (0.95)	0.32 (1.03)	0.35 (1.10)	0.40 (1.15)	0.42 (1.15)
	212 A	212 B	219 B	211 B	171 B	149 B	131 B	118 B
Treatment p-Values[b]	0.8229	0.0102	0.0064	0.0009	0.0001	0.0003	0.0006	0.0002
Trt*Inv p-Value[c]	0.5118	0.4131	0.2155	0.3525	0.2341	0.4463	0.3957	0.7361
Trt*BLPhoto p-Value[c]	0.2825	0.1164	0.5212	0.3743	0.2674	0.5351	0.3154	0.3549
RMS Error[c]	0.49	0.70	0.80	0.88	0.94	0.99	1.02	1.04

a: Number of subjects not rescuing
b: Model: $PHOTOSD=\mu + T_i + I_j + B_k + error$
c: Model: $PHOTOSD=\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik} + error$
d: Based On Model B LSMEANS

Study 30

	Assessment Time Points (Hours)							
Treatment	5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.12 (0.58)	0.29 (0.74)	0.41 (0.88)	0.47 (0.93)	0.60 (0.99)	0.67 (1.06)	0.70 (1.11)	0.75 (1.15)
	205[a] A[d]	203 A	196 AB	191 A	158 A	139 A	129 A	119 A
Ibu 400 mg	0.10 (0.55)	0.30 (0.76)	0.42 (0.88)	0.49 (0.97)	0.58 (1.00)	0.66 (1.07)	0.70 (1.10)	0.78 (1.12)
	208 A	205 A	204 A	195 A	164 A	143 A	131 A	123 A
Placebo	0.07 (0.46)	0.17 (0.64)	0.24 (0.78)	0.24 (0.88)	0.36 (1.01)	0.41 (1.10)	0.40 (1.15)	0.40 (1.18)
	202 A	201 A	193 B	186 B	153 B	124 B	109 B	98 B
Treatment p-Values[b]	0.5328	0.1126	0.0669	0.0111	0.0253	0.0217	0.0073	0.0011
Trt*Inv p-Value[c]	0.1611	0.3711	0.8393	0.8601	0.9734	0.9125	0.8316	0.7598
Trt*BLPhoto p-Value[c]	0.7088	0.8241	0.6994	0.4657	0.7014	0.8910	0.8672	0.8726
RMS Error[c]	0.51	0.69	0.81	0.88	0.94	1.00	1.03	1.06

a: Number of subjects not rescuing
b: Model: $PHOTOSD=\mu + T_i + I_j + B_k + error$
c: Model: $PHOTOSD=\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik} + error$
d: Based On Model B LSMEANS

During hours 2-6 in both studies, there was a higher percentage of ibuprofen treated patients reporting reduction of photophobia to none, compared to placebo patients. This was true for both ibuprofen doses. The differences from placebo ranged from 3-12%. Both doses were significantly superior to placebo but not to each other at 2 and 6 hours in study 30 and at six hours in study 22 (Table 10, ISE Table 8.6-32/33).

Table 10: Studies 22 and 30 – Reduction in Photophobia to None

Study 22

	Assessment Time Points (Hours)							
Drug	0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=210)	2.86 (6)	9.05 (19)	14.76 (31)	**21.43 (45)**	27.62 (58)	30.48 (64)	32.86 (69)	**35.71 (75)**
Ibu 400 mg (N=210)	2.38 (5)	10.95 (23)	15.71 (33)	**18.10 (38)**	25.24 (53)	28.57 (60)	31.90 (67)	**36.19 (76)**
Placebo (N=212)	3.30 (7)	7.08 (5)	12.26 (26)	**15.09 (32)**	17.45 (37)	21.23 (45)	24.53 (52)	**25.47 (54)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.0687	0.0185
Ibu 400 mg vs placebo	0.3491	0.0139
Ibu 200 mg vs Ibu 400 mg	0.4222	0.8829

a: Cochran-Mantel-Haenszel test, stratified by baseline photophobia severity.

Study 30

	Assessment Time Points (Hours)							
Drug	0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=206)	5.34 (11)	11.17 (3)	16.99 (35)	**21.84 (45)**	26.70 (55)	30.10 (62)	32.04 (66)	**36.41 (75)**
Ibu 400 mg (N=209)	3.35 (7)	10.05 (21)	17.70 (37)	**22.49 (47)**	25.36 (53)	29.67 (62)	32.54 (68)	**36.36 (76)**
Placebo (N=209)	1.49 (3)	4.95 (10)	8.42 (7)	**11.39 (23)**	15.35 (31)	21.78 (44)	23.27 (47)	**24.75 (50)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.004	0.012
Ibu 400 mg vs placebo	0.003	0.011
Ibu 200 mg vs Ibu 400 mg	0.865	0.983

a: Cochran-Mantel-Haenszel test, stratified by baseline photophobia severity.

4.5.6.6 Phonophobia

Phonophobia was reported at baseline by approximately 90% of patients across all treatment groups in both studies (Table 3, page 8).

In study 22, patients treated with either dose of ibuprofen had significantly larger mean reduction from baseline in the severity of phonophobia, when compared to placebo patients (Table 11, from ISE tables 8.6-26/27). This was true at all time points 1-6 hours post dose. In study 30, only the 400mg treated patients showed significantly larger mean reduction scores (2-6 hours post dose). There were no significant differences between the two doses of ibuprofen.

Table 11: Studies 22 and 30 – Mean Phonophobia Severity Difference from Baseline

Study 22

Treatment	Assessment Time Points (Hours)							
	.5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.08 (0.48)	0.29 (0.75)	0.42 (0.85)	0.51 (0.91)	0.60 (1.02)	0.60 (1.06)	0.62 (1.09)	0.66 (1.10)
	198[a] A[d]	191 A	188 A	180 A	149 A	133 A	120 A	119 A
Ibu 400 mg	0.06 (0.52)	0.28 (0.80)	0.42 (0.96)	0.54 (1.01)	0.63 (1.09)	0.65 (1.12)	0.72 (1.15)	0.74 (1.17)
	206 A	204 A	199 A	195 A	164 A	142 A	126 A	122 A
Placebo	0.02 (0.47)	0.13 (0.65)	0.22 (0.83)	0.29 (0.94)	0.31 (1.02)	0.38 (1.07)	0.42 (1.12)	0.45 (1.14)
	204 A	204 B	201 B	192 B	153 B	132 B	116 B	105 B
Treatment p-Values[b]	0.3623	0.0273	0.0142	0.0046	0.0003	0.0067	0.0045	0.0051
Trt*Inv p-Value[c]	0.5704	0.4282	0.1648	0.1500	0.0970	0.0779	0.1743	0.6149
Trt*BLPhono p-Value[c]	0.2348	0.2497	0.5495	0.5209	0.5275	0.1799	0.2096	0.1207
RMS Error[c]	0.47	0.69	0.80	0.86	0.93	0.95	0.98	1.00

a: Number of subjects not rescuing
b: Model: PHONOSD=$\mu + T_i + I_j + B_k$ + error
c: Model: PHONOSD=$\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik}$ + error
d: Based On Model B LSMEANS

Study 30

Treatment	Assessment Time Points (Hours)							
	.5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.06 (0.47)	0.24 (0.69)	0.33 (0.79)	0.39 (0.83)	0.53 (0.90)	0.59 (0.99)	0.62 (1.03)	0.64 (1.06)
	197[a] A[d]	195 AB	188 AB	184 AB	148 AB	129 AB	118 AB	108 AB
Ibu 400 mg	0.10 (0.56)	0.30 (0.78)	0.42 (0.89)	0.47 (0.98)	0.57 (1.03)	0.67 (1.08)	0.73 (1.11)	0.79 (1.13)
	197 A	195 A	194 A	185 A	154 A	135 A	124 A	116 A
Placebo	0.04 (0.48)	0.15 (0.67)	0.23 (0.85)	0.22 (0.94)	0.34 (1.03)	0.38 (1.12)	0.40 (1.17)	0.36 (1.20)
	189 A	189 B	181 B	175 B	147 B	118 B	103 B	94 B
Treatment p-Values[b]	0.4831	0.1360	0.0614	0.0179	0.0417	0.0168	0.0078	0.0004
Trt*Inv p-Value[c]	0.5500	0.7173	0.8816	0.95618	0.9618	0.7734	0.6018	0.5776
Trt*BLPhono p-Value[c]	0.1274	0.3160	0.1631	0.0727	0.0958	0.1367	0.1914	0.3342
RMS Error[c]	0.49	0.69	0.79	0.87	0.92	0.97	1.01	1.02

a: Number of subjects not rescuing
b: Model: PHONOSD=$\mu + T_i + I_j + B_k$ + error
c: Model: PHONOSD=$\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik}$ + error
d: Based On Model B LSMEANS

In both studies, a numerically higher proportion of patients treated with either dose of ibuprofen experienced reduction of phonophobia to none during 2-6 hours post dose. This was nominally significantly positive for the 400mg at 6 hours in study 22, for both doses at 2 hours in study 30, and for the 400mg dose at 6 hours in study 30. There was no difference between the two ibuprofen doses (Table 12, ISE Tables 8.6-34/35).

Table 12: Studies 22 and 30 – Reduction in Phonophobia to None

Study 22

Drug	Assessment Time Points (Hours)							
	0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=198)	3.03 (6)	10.61 (21)	17.68 (35)	**23.74 (47)**	32.32 (64)	33.84 (67)	35.35 (70)	**37.37 (74)**
Ibu 400 mg (N=206)	1.94 (4)	9.22 (19)	19.90 (41)	**24.27 (50)**	30.58 (63)	32.52 (67)	36.41 (75)	**39.32 (81)**
Placebo (N=204)	3.43 (7)	7.35 (15)	12.75 (26)	**16.67 (34)**	18.14 (37)	23.04 (47)	26.47 (54)	**28.92 (59)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.0797	0.0784
Ibu 400 mg vs placebo	0.0609	0.0279
Ibu 200 mg vs Ibu 400 mg	0.9126	0.6899

a: Cochran-Mantel-Haenszel test, stratified by baseline phonophobia severity.

Study 30

	Assessment Time Points (Hours)							
Drug	0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=198)	4.04 (8)	12.12 (24)	16.67 (33)	**21.21 (42)**	27.78 (55)	31.82 (63)	34.34 (68)	**35.86 (71)**
Ibu 400 mg (N=198)	4.55 (9)	12.12 (24)	20.20 (40)	**26.26 (52)**	30.81 (61)	35.86 (75)	38.89 (77)	**41.92 (83)**
Placebo (N=198)	0.53 (1)	4.76 (9)	9.52 (18)	**13.23 (25)**	18.52 (35)	24.34 (46)	26.98 (51)	**26.46 (50)**
Comparison at two and six hours				p-Value[a]				p-Value[a]
Ibu 200 mg vs placebo				0.051				0.060
Ibu 400 mg vs placebo				0.001				0.001
Ibu 200 mg vs Ibu 400 mg				0.167				0.180

a: Cochran-Mantel-Haenszel test, stratified by baseline phonophobia severity.

4.5.6.7 Functional Disability

At least some functional disability was reported at baseline by approximately 95-98% of patients across all treatment groups in both studies (Table 3, page 8).

Patients treated with either dose of ibuprofen had significantly larger mean reduction from baseline in the severity of functional disability at all time points (1-6 hours) in both studies 22 and 30 (Table 13, from ISE tables 8.6-21/22). There were no significant differences between the two doses of ibuprofen at any time point in either study.

Table 13: Studies 22 and 30 – Mean Functional Disability Difference from Baseline

Study 22

	Assessment Time Points (Hours)							
Treatment	5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.06 (0.47) 209[a] A[d]	0.20 (0.68) 208 A	0.34 (0.83) 205 A	0.45 (0.95) 196 A	0.51 (1.01) 163 A	0.56 (1.07) 145 A	0.56 (1.08) 132 A	0.60 (1.12) 130 A
Ibu 400 mg	0.04 (0.42) 218 A	0.19 (0.74) 216 A	0.36 (0.93) 210 A	0.41 (0.98) 206 A	0.49 (1.07) 172 A	0.54 (1.10) 147 A	0.58 (1.13) 131 A	0.63 (1.19) 127 A
Placebo	0.01 (0.43) 210 A	0.08 (0.67) 210 B	0.12 (0.74) 208 B	0.19 (0.85) 199 B	0.21 (0.97) 162 B	0.22 (1.01) 138 B	0.27 (1.05) 121 B	0.29 (1.06) 108 B
Treatment p-Values[b]	0.4051	0.0548	0.0007	0.0014	0.0002	0.0001	0.0002	0.0001
Trt*Inv p-Value[c]	0.8000	0.6268	0.2041	0.2074	0.0288	0.1291	0.2050	0.3777
Trt*BLFunc p-Value[c]	0.2240	0.0632	0.2626	0.0863	0.2210	0.2824	0.3134	0.2461
RMS Error[d]	0.42	0.65	0.78	0.85	0.93	0.95	0.98	1.00

a: Number of subjects not rescuing
b: Model: $FUNCSD=\mu + T_i + I_j + B_k$ + error
c: Model: $FUNCSD=\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik}$ + error
d: Based On Model B LSMEANS

Study 30

Treatment	Assessment Time Points (Hours) 5	1	1.5	2	3	4	5	6
Ibu 200 mg	0.08 (0.56)	0.23 (0.67)	0.31 (0.78)	0.41 (0.85)	0.48 (0.96)	0.58 (1.04)	0.60 (1.10)	0.59 (1.13)
	211[a] A[d]	209 A	202 A	197 A	160 A	140 A	129 A	119 A
Ibu 400 mg	0.07 (0.47)	0.18 (0.71)	0.28 (0.85)	0.32 (0.92)	0.43 (0.98)	0.49 (1.00)	0.56 (1.06)	0.59 (1.08)
	210 A	206 A	205 A	196 A	164 A	143 A	131 A	124 A
Placebo	0.00 (0.42)	0.06 (0.62)	0.08 (0.75)	0.07 (0.90)	0.21 (0.97)	0.25 (1.04)	0.25 (1.11)	0.24 (1.14)
	210 A	209 B	201 B	194 B	158 B	129 B	114 B	103 B
Treatment p-Values[b]	0.2008	0.0241	0.0038	0.0002	0.0103	0.0032	0.0017	0.0008
Trt*Inv p-Value[c]	0.6136	0.3323	0.6422	0.3402	0.3330	0.2980	0.4323	0.2047
Trt*BLFunc p-Value[c]	0.3314	0.6430	0.7475	0.4698	0.9395	0.7220	0.5610	0.5313
RMS Error[c]	0.47	0.63	0.75	0.83	0.91	0.94	1.00	1.02

a: Number of subjects not rescuing
b: Model: $FUNCSD=\mu + T_i + I_j + B_k + error$
c: Model: $FUNCSD=\mu + T_i + I_j + B_k + TI_{ij} + TB_{ik} + error$
d: Based On Model B LSMEANS

A numerically higher percentage of patients treated with either dose of ibuprofen reported functional disability reduced to none in both studies 2-6 hours post treatment, compared with placebo patients. Both doses were nominally significantly superior to placebo at 6 hours in study 22, and at 2 and 6 hours in study 30. In addition, 200mg was significantly superior to placebo at 2 hours in study 22. Neither dose was superior to the other one (Table 14, ISE Tables 8.6-36/37).

Table 14: Studies 22 and 30 – Reduction in Functional Disability to None

Study 22

Drug	Assessment Time Points (Hours) 0.5	1	1.5	2	3	4	5	6
Ibu 200 mg	1.44	5.74	13.40	**21.05**	24.40	28.71	28.71	**32.54**
(N=209)	(3)	(12)	(28)	**(44)**	(51)	(60)	(60)	**(68)**
Ibu 400 mg	0.46	6.88	16.06	**17.89**	25.23	26.61	30.28	**35.32**
(N=218)	(1)	(15)	(35)	**(39)**	(55)	(58)	(66)	**(77)**
Placebo	1.43	7.14	9.52	**12.86**	17.62	18.57	22.38	**23.33**
(N=210)	(3)	(15)	(20)	**(27)**	(37)	(39)	(47)	**(49)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.0213	0.0294
Ibu 400 mg vs placebo	0.2462	0.0066
Ibu 200 mg vs Ibu 400 mg	0.3091	0.5256

a: Cochran-Mantel-Haenszel test, stratified by baseline severity of functional disability.

Study 30

Drug	Assessment Time Points (Hours) 0.5	1	1.5	2	3	4	5	6
Ibu 200 mg	4.72	8.96	16.51	**20.28**	25.00	30.19	33.49	**34.43**
(N=212)	(10)	(19)	(35)	**(43)**	(53)	(64)	(71)	**(73)**
Ibu 400 mg	3.32	8.06	15.64	**21.33**	25.12	28.44	34.60	**36.97**
(N=211)	(7)	(17)	(33)	**(45)**	(53)	(60)	(73)	**(78)**
Placebo	1.90	6.67	8.57	**10.95**	17.14	19.05	22.86	**23.81**
(N=211)	(4)	(14)	(8)	**(23)**	(36)	(40)	(48)	**(50)**

Comparison at two and six hours	p-Value[a]	p-Value[a]
Ibu 200 mg vs placebo	0.006	0.014
Ibu 400 mg vs placebo	0.005	0.005
Ibu 200 mg vs Ibu 400 mg	0.986	0.701

a: Cochran-Mantel-Haenszel test, stratified by baseline severity of functional disability.

4.5.7 Emergence of Migraine Symptoms During Treatment

Since the analyses just presented excluded patients who lacked migraine associated at baseline, the sponsor analyzed the percentage of patients who developed migraine associated symptoms during treatment. This analysis only included those who lacked such symptoms at baseline. The analysis demonstrated that there was no difference in the emergence of any migraine associated symptom during treatment among the various treatment groups in either study. In general, while not statistically significant, the rates of emergence of migraine associated symptoms were highest in the placebo group when compared with ibuprofen treated groups, with only one exception (Table 15, ISE table 8.6-38).

Table 15: Studies 22 and 30 – Emergence of Migraine Associated Symptoms

Endpoint	200mg n/N (%)	400mg n/N (%)	PBO n/N (%)	p-value 200 mg vs. PBO	p-value 400 mg vs. PBO	p-value 200mg vs. 400mg
Study 22						
Nausea	26/88 (29.6)	23/101 (22.8)	32/99 (32.3)	0.752	0.155	0.321
Photophobia	3/6 (50.0)	3/13 (23.1)	5/9 (55.6)	1.000	0.187	0.320
Phonophobia	5/18 (27.8)	6/17 (35.3)	8/17 (47.1)	0.305	0.728	0.725
Functional Disability	2/7 (28.6)	2/5 (40.0)	7/11 (63.6)	0.335	0.596	1.000
Study 30						
Nausea	24/88 (27.3)	23/96 (24.0)	31/103 (30.1)	0.749	0.344	0.616
Photophobia	3/10 (30.0)	3/10 (30.0)	6/12 (50.0)	0.415	0.415	1.000
Phonophobia	6/18 (33.3)	3/21 (14.3)	9/25 (36.0)	1.000	0.176	0.255
Functional Disability	0/4 (0.0)	6/8 (75.0)	3/4 (75.0)	0.143	1.000	0.061

4.5.8 Vomiting

The sponsor analyzed vomiting separately, since it was a relatively infrequent symptom. The incidence of vomiting at baseline and at 6 hours is shown in Table 16 (ISE table 8.6-39). At six hours, vomiting was nominally significantly less with 200mg in study 22, compared to placebo; however, the numbers were too small to draw any meaningful conclusions.

Table 16: Studies 22 and 30 – Incidence of Vomiting

Study No. Incidence of Vomiting, n (%)	Ibu 200 mg	Ibu 400 mg	Placebo	p-values[a] Ibu 200 vs Placebo	Ibu 400 vs Placebo	Ibu 200 vs Ibu 400
Study 97-022	(N=216)	(N=223)	(N=221)			
Baseline	4 (1.85)	8 (3.59)	4 (1.81)			
Within 6 hours post medication	10 (4.63)	12 (5.38)	22 (9.96)	0.042	0.076	0.828
Study 97-030	(N=216)	(N=219)	(N=214)			
Baseline	8 (3.70)	5 (2.23)	2 (0.93)			
Within 6 hours post medication	10 (4.63)	17 (7.76)	16 (7.48)	0.231	1.000	0.233

a: Fisher's Exact test.

4.5.9 Patient's Overall Impression

The investigators asked patients to describe their overall impression of the study medication (poor, fair, good, very good, excellent). This was assessed at the end of the study (6 hours) or at the time the patient used rescue. These results showed that the mean overall impression of study medication was significantly higher for those treated with either dose of ibuprofen compared with placebo (Table 17, ISE table 8.6-40). The sponsor does not explain how the "ridit score" was determined.

Table 17: Studies 22 and 30 – Mean Overall Impression of Study Medication

Study	200mg (n)	400mg (n)	PBO (n)	p-value 200mg vs. PBO	p-value 400mg vs. PBO	p-value 200mg vs. 400mg
22	1.17 (216)	1.21 (223)	0.81 (221)	0.003	<0.001	0.700
30	1.14 (216)	1.14 (219)	0.66 (214)	0.001	0.001	0.884

Mean modified ridit scores; Cochran-Mantel-Haenszel test, stratified by baseline pain intensity

4.5.10 Recurrence

The sponsor analyzed the incidence of recurrence at 24 hours in the two studies. Recurrence rates were similar for all three treatment groups and there was no statistically significant differences in either study. Twenty-four hour recurrence rates in study 22 were 32%, 30% and 35% for 200mg, 400mg, and placebo, respectively. For study 30, the numbers were 31%, 31%, and 33% for the same groups.

Eight-two percent (82%) of the recurrent migraine pain were moderate in intensity and there were no statistically significant differences between treatment groups in the intensity of the recurrent migraine pain in both studies.

4.5.11 Subgroup Analyses

Results of the primary efficacy endpoints for gender and racial subgroups were generally consistent with the overall study results with variations in achieving statistical significance for treatment comparisons likely due to the small size of some of the subgroups. Table 18 (ISE Table 8.6-49) shows the 2-hr headache response rates for various subgroups.

Table 18: Studies 22 and 30 – Response Rates in Subgroups

Subgroup Study No. Subjects With a Reduction, n/N (%)	Ibu 200 mg	Ibu 400 mg	Placebo	p-Values[a] Ibu 200 vs Placebo	 Ibu 400 vs Placebo	 Ibu 200 vs Ibu 400
Sex: Male						
Study 97-022	24/46 (52.17)	11/30 (36.67)	13/28 (46.43)	0.612	0.465	0.159
Study 97-030	15/36 (41.67)	17/33 (51.51)	10/29 (34.48)	0.884	0.543	0.673
Sex: Female						
Study 97-022	66/170 (38.82)	80/193 (41.45)	49/193 (25.39)	0.008	0.001	0.627
Study 97-030	71/180 (39.44)	73/186 (39.25)	47/185 (25.41)	0.002	0.004	0.841
Race: Caucasian						
Study 97-022	64/168 (38.10)	62/173 (35.84)	46/174 (26.44)	0.031	0.080	0.610
Study 97-030	78/191 (40.84)	71/185 (38.38)	50/191 (26.18)	0.001	0.013	0.408
Race: African-American						
Study 97-022	10/17 (58.82)	13/19 (68.42)	6/16 (37.50)	0.363	0.061	0.387
Study 97-030	3/14 (21.43)	8/15 (53.33)	3/11 (27.27)	0.801	0.171	0.042
Race: Other						
Study 97-022	16/31 (51.61)	16/31 (51.61)	10/31 (32.26)	0.110	0.119	0.841
Study 97-030	5/11 (45.45)	11/19 (57.89)	4/12 (33.33)	0.608	0.330	0.630
Menstrual Status: Yes						
Study 97-022	11/26 (42.31)	15/31 (48.39)	6/24 (25.00)	0.290	0.107	0.510
Study 97-030	13/38 (34.21)	12/32 (37.50)	5/26 (19.23)	0.117	0.099	0.711
Menstrual Status: No						
Study 97-022	55/144 (38.19)	64/161 (39.75)	43/168 (25.60)	0.014	0.008	0.869
Study 97-030	58/142 (40.85)	61/154 (39.61)	42/159 (26.42)	0.006	0.013	0.655

a Cochran-Mantel-Haenszel test

Overall, 85% of the patients were women, which is typical of migraine studies of this type. Two-hour headache response rates in women were significantly higher with ibuprofen treatment (either dose) compared with placebo treatment. There were no significant differences in 2-hr response rates in men in either study, although numerically rates were higher for ibuprofen-treated men in 3 of the 4 comparisons (all except 400mg in study 22).

The largest racial group was Caucasians (82.7%). Not surprisingly, the response rates for Caucasians generally reflected the results seen in the overall population. The number of non-Caucasians enrolled were rather small and it is difficult to draw any meaningful conclusions from such small numbers.

Approximately 16% of the women were menstruating at the time of treatment. Response rates for menstruating women were numerically higher for ibuprofen compared to placebo but none reached nominal significance, likely due to subgroup size. There was a slight directional trend favoring 400mg in this subgroup.

4.5.12 Modified Analysis of Study 22

[redacted]

In this modified analysis, a total of 637 patients remained in the study.

Exclusion of these patients from analysis had little effect on the overall results (Table 19, from Clinical Supplement Report, Study 22, table 9-3). Two hour response rates were still significantly higher with either dose of ibuprofen (p=0.0045 for 200mg vs. placebo, and p=0.0022 for 400mg vs. placebo). There was still no difference between 200mg and 400mg.

Table 19: Study 22 – Modified Analysis of Response Rates

	Assessment Time Points (Hours)							
Drug	0.5	1	1.5	2	3	4	5	6
IBU200mg (N=188)	13.30 (25)	27.66 (52)	38.83 (73)	**43.09 (81)**	51.06 (96)	47.87 (90)	48.94 (92)	**50.00 (94)**
IBU400mg (N=195)	7.69 (15)	26.67 (52)	37.95 (74)	**44.10 (86)**	48.21 (94)	49.23 (96)	51.79 (101)	**52.31 (102)**
Placebo (N=194)	11.86 (23)	22.16 (430	24.74 (48)	**28.87 (56)**	30.41 (59)	31.96 (62)	32.99 (64)	**34.54 (67)**

4.6 Sponsor's Efficacy Conclusions

The sponsor concludes that the results of these studies support the efficacy of OTC doses of ibuprofen in the treatment of moderate-to-severe migraine headache pain.

- Ibuprofen at OTC doses of 200 mg and 400 mg is an effective treatment for the temporary relief of migraine headache pain and evidence supports its efficacy for the relief of associated symptoms of migraine including nausea, photophobia, phonophobia, and functional disability.

- Efficacy results for subjects with severe migraine pain intensity support the use of the 400 mg dose of ibuprofen compared with the 200 mg dose and are consistent with the current labeling regarding OTC ibuprofen dosing which directs consumers to take 400 mg if pain does not respond to 200 mg.

- All secondary efficacy measures including pain relief and pain intensity difference showed effects consistent with the primary efficacy outcome measures.

4.7 Reviewer's Analyses

4.7.1 Headache Characteristics

Even though the two studies employed clinic based recruiting technique (*i.e.*, not population based), patients were chosen because they did not have severe migraines. This raised at least the possibility that other, non-migraine headache sufferers, could be recruited. I chose to analyze whether the headaches that were treated were in fact migraine headaches. The sponsor provided case report tabulations in SAS transport format. The dataset base.xpt contained baseline headache information.

The dataset for studies 22 and 30 contained baseline headache records for 721 and 713 patients, respectively, for a total of 1434 records (one per patient). Not all of these patients experienced a headache. There were 125 such patients, leaving 1309 who actually experienced and treated a headache. I used the IHS

criteria for migraine with (1.1) or without aura (1.2) to determine whether the headache treated was a migraine. There was insufficient information provided about the attacks so I could not apply the criteria strictly. I made certain assumptions, which I describe below in detail.

The sponsor failed to provide detailed aura characteristics in patients who had an aura (reversibility, time between aura and headache, etc.); therefore, I could not apply the strict migraine with aura criteria. I assumed that if a patient had an aura with their headache, then the headache was a migraine. There were 320 such patients that reported an aura with their headaches.

For those with migraine without aura, criterion 1.1a requires that patients have at least 5 attacks. This applies to diagnosis of a migraine disorder, but does not apply for an individual migraine, so I did not apply this criterion. I did not have duration of the attack, so I could not apply criterion 1.1b (duration 4-72 hours with or without treatment). Criterion 1.1c requires that the headache have two of the following: unilateral, pulsating, moderate or severe, or aggravated by routine physical activity. The sponsor provided information regarding 3 of the 4 symptoms (all except aggravation by routine activity).. I checked to make sure each headache had at least 2 of the 3 symptoms provided. Criterion 1.1d requires the presence of at least one of the following: nausea and/or vomiting, or photophobia and phonophobia. I checked for the presence of this criterion. Lastly, criterion 1.1e requires that no other explanation be present for the headache. This information was not provided.

Applying these criteria as best I could, I made sure that the patient either had an aura OR meet criterion 1.1c AND 1.1d above. When I applied this modified definition. I discovered that 1048/1309 patients (80%) had headaches which met these modified criteria, and 261 (20%) did not. This is a best guess estimate based on the data provided. I conclude that most headaches treated were migraine.

4.7.2 Migraine Associated Symptoms

The sponsor's analyses show a clear reduction in migraine headache pain with treatment with either 200mg or 400mg when used as a single dose. This is supported by the analyses of the 2-hour headache response rates and PID scores for both studies 22 and 30. I saw very little reason to repeat these analyses of the primary endpoints.

I chose, instead, to focus on the effect of ibuprofen on the migraine associated symptoms of nausea, photophobia, and phonophobia. It is here where one can evaluate the effects of ibuprofen on the entire migraine syndrome, not just the headache. The sponsor chose to analyze mean changes from baseline in symptom severity in the subgroup of patients who had the symptom at baseline, as well as the percentage of patients experiencing a reduction of symptoms to none at various time points. Both analyses included only those patients who experienced those symptoms at baseline.

I chose a slightly different approach that is more in line with reviews of previous migraine applications. I chose to analyze the percentage of subjects who had no associated symptom at a particular time point. I took the 2 hour time point as the primary time point. It has the advantage that it includes the possibility that the treatment may cause some of the symptoms in patients who don't have the symptom at baseline since all treated patients are included in the analyses. It is worth noting that other anti-migraine therapies have positive effects on all three of these symptoms. I wanted to see if ibuprofen had the same effect.

The sponsor provided efficacy data in two files, one for each study. Each was named interp.xpt. I pooled the data for the two studies and worked on one pooled dataset. The datasets included one row for each time point, per patient. Each patient had diary entries at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 hours; therefore, there were 9 rows per patient. I took the data at time point 0 as baseline for each patient.

Although each of the symptoms nausea, photophobia, and phonophobia were rated on a 4 point scale, I collapsed the data to either present or absent. I first checked to see if the symptoms at baseline were evenly distributed among the treatment groups in each study. Table 20 shows the distribution of nausea, photophobia, and phonophobia among the three treatment groups in each study. As one can see, nausea was present in about 55-59% of patients across all treatment groups. Photophobia and phonophobia were present in about 88-97% of all patients. There were no significant differences in the distribution of these symptoms among the various treatment groups, although there were minor numerical imbalances noted.

Table 20: (RA) Studies 22 and 30 –Migraine Associated Symptoms at Baseline

Symptom	200mg	400mg	PBO	p-value*
Study 22				
Nausea	128/216 (59.3%)	122/223 (54.7%)	122/221 (55.2%)	0.57
Photophobia	198/216 (91.7%)	206/223 (92.4%)	204/221 (92.3%)	0.96
Phonophobia	210/216 (97.2%)	210/223 (94.2%)	212/221 (95.9%)	0.28
Study 30				
Nausea	128/216 (59.3%)	123/219 (56.2%)	111/214 (51.9%)	0.30
Photophobia	206/216 (95.4%)	209/219 (95.4%)	202/214 (94.4%)	0.86
Phonophobia	198/216 (91.7%)	198/219 (90.4%)	189/214 (88.3%)	0.50

* chi-square for overall comparison

I then compared the incidences of these same symptoms among the 3 treatment groups at various time points, concentrating on 2 and 4 hours. These are shown in Table 21 and Table 22.

Table 21: (RA) Studies 22 and 30 – Migraine Associated Symptoms at 2 Hours

Symptom	200mg	400mg	PBO	p-value*
Study 22				
Nausea	94/216 (43.5%)	86/223 (38.6%)	103/221 (46.6%)	0.22
Photophobia	154/216 (71.3%)	160/223 (71.8%)	174/221 (78.7%)	0.13
Phonophobia	168/216 (77.8%)	175/223 (78.5%)	182/221 (82.4%)	0.43
Study 30				
Nausea	97/216 (44.9%)	95/219 (43.4%)	99/214 (46.3%)	0.83
Photophobia	162/216 (75%)	164/219 (74.9%)	185/214 (86.4%)	0.002
Phonophobia	158/216 (73.2%)	149/219 (68%)	170/214 (79.4%)	0.03

* chi-square for overall comparison

Table 22: (RA) Studies 22 ad 30 – Migraine Associated Symptoms at 4 Hours

Symptom	200mg	400mg	PBO	p-value*
Study 22				
Nausea	84/216 (38.9%)	82/223 (36.8%)	99/221 (44.8%)	0.20
Photophobia	133/216 (61.6%)	144/223 (64.7%)	163/221 (73.8%)	0.02
Phonophobia	148/216 (68.5%)	153/223 (68.6%)	171/221 (77.4%)	0.057
Study 30				
Nausea	85/216 (39.3%)	81/219 (37%)	84/214 (39.2%)	0.85
Photophobia	146/216 (67.6%)	149/219 (68%)	163/214 (76.2%)	0.08
Phonophobia	137/216 (63.4%)	128/219 (58.4%)	150/214 (70.1%)	0.04

* chi-square for overall comparison

These results show that the incidences of nausea, photophobia, and phonophobia were numerically lower for both 200mg and 400mg at 2 and 4 hours in both studies, when compared to placebo. However, the results reached nominal significance for photophobia and phonophobia in study 30 at 2 hours, and photophobia in study 22 at 4 hours and phonophobia in study 30 at 4 hours.

4.7.3 Subgroup Analysis – Known Migraine Headaches

As shown in section 4.7.1, approximately 80% of patients actually treated a migraine. This number is just an estimate, since the studies did not collect baseline information whether the headache was aggravated by physical activity (one of the IHS criteria for migraine). I do note that the studies did collect functional disability information (*i.e.*, did the headache interfere with physical

activity?), but this was sufficiently different information from that required for the IHS criterion and I chose not to use it as a substitute.

After discussion of the data with Dr. Levin, I chose to analyze the important efficacy variables (response rate, nausea, photophobia, phonophobia) in the subset of patients that actually had a migraine, based on the migraine identification criteria I described previously.

As shown in Table 1, page 6, there were 660 patients in study 22 and 649 patients in study 30 that took study medication and made up the intent to treat population (total = 1,309). I determined that 80% actually treated a migraine, and I wasn't sure, based on the data provided, about the type of headache treated in the remaining 20%. I acknowledge that some, if not most or all, of those headaches could be migraine, but sufficient information was lacking to make that determination.

I created a subgroup of those 80% of patients with "definite migraine" (see section 4.7.1, page27) and identified them as follows:

Table 23: Studies 22 and 30 – Patients that Treated a "Definite Migraine"

Study	Total N	"Definite Migraine"	200mg	400mg	PBO
22	660	525 (80%)	169	177	179
30	649	523 (81%)	176	177	170
Total	**1309**	**1048 (80%)**	**345**	**354**	**349**

The baseline headache characteristics of this subgroup are shown in Table 24. Overall, there were no nominally significant differences in the distribution of the baseline characteristics of pain intensity, nausea, photophobia, or phonophobia among the treatment groups in either study. There were minor numerical imbalances noted.

Table 24: Studies 22 and 30 - Baseline Headache Characteristics of Patients that Treated a Definite Migraine

Symptom	Study 22				Study 30			
	200 mg (n=169)	400 mg (n=177)	PBO (n=179)	p*	200 mg (n=176)	400 mg (n=177)	PBO (n=170)	p*
Pain Intensity, n (%)				0.925				0.164
Moderate	113 (67%)	119 (67%)	117 (65%)		111 (63%)	127 (72%)	120 (71%)	
Severe	56 (33%)	58 (33%)	62 (35%)		65 (37%)	50 (28%)	50 (29%)	
Nausea, n (%)				0.431				0.112
None	65 (39%)	76 (43%)	73 (41%)		65 (37%)	68 (38%)	76 (45%)	
Mild	62 (37%)	56 (31%)	58 (33%)		62 (35%)	73 (41%)	48 (28%)	
Moderate	37 (22%)	34 (19%)	34 (19%)		42 (24%)	30 (17%)	43 (25%)	
Severe	4 (2%)	11 (6%)	13 (7%)		7 (4%)	6 (3%)	3 (2%)	
Photophobia, n (%)				0.911				0.661
None	11 (7%)	6 (3%)	9 (5%)		3 (2%)	1 (1%)	4 (2%)	
Mild	48 (28%)	56 (32%)	54 (30%)		45 (26%)	45 (25%)	41 (24%)	
Moderate	74 (44%)	79 (45%)	80 (45%)		84 (48%)	96 (54%)	83 (49%)	
Severe	36 (21%)	36 (20%)	36 (20%)		44 (25%)	35 (20%)	42 (25%)	
Phonophobia, n (%)				0.158				0.964
None	1 (1%)	6 (3%)	1 (1%)		13 (7%)	10 (6%)	15 (9%)	
Mild	40 (24%)	34 (19%)	43 (24%)		59 (34%)	61 (34%)	54 (32%)	
Moderate	83 (49%)	87 (49%)	96 (54%)		77 (44%)	78 (44%)	74 (44%)	
Severe	45 (27%)	50 (28%)	39 (22%)		27 (15%)	28 (16%)	27 (16%)	

*chi-square

Table 25 shows the key efficacy results at 2 hours for the same subgroup. The 2 hour headache response rates were numerically lower for either ibuprofen dose in both studies, but reach nominal significance in only in study 30. All secondary endpoints tested were numerically in favor of ibuprofen but failed to reach nominal significance in any analyses.

Table 25: Studies 22 and 30 – 2-Hr Efficacy Data in Patients that Treated a Definite Migraine

Symptom	Study 22				Study 30			
	200 mg (n=169)	400 mg (n=177)	PBO (n=179)	p*	200 mg (n=176)	400 mg (n=177)	PBO (n=170)	p*
Response Rate, n (%)	66 (39.5%)	64 (36.2%)	52 (29%)	0.122	68 (38.6%)	68 (38.9%)	41 (24.6%)	0.003
Nausea, present (%)	75 (44.4%)	73 (41.2%)	85 (47.5%)	0.495	84 (47.7%)	84 (47.5%)	82 (48.2%)	0.989
Photophobia, present (%)	121 (71.6%)	134 (75.7%)	144 (80.4%)	0.154	140 (79.6%)	139 (78.5%)	148 (87.1%)	0.083
Phonophobia, present (%)	134 (79.3%)	144 (81.4%)	151 (84.4%)	0.468	135 (76.7%)	126 (71.2%)	138 (81.2%)	0.090

* p value for response rate is Cochran-Mantel-Haenszel stratified by baseline intensity; for other analyses is chi-square

The next table (Table 25) shows the response rates according to baseline headache intensity. Ibuprofen was significantly better than placebo in patients treating moderate pain in study 30 only. There were numerical trends favoring ibuprofen in the other groups, but the analyses failed to reach nominal significance. Ibuprofen 400mg was numerically better than placebo for severe pain in both studies (36% vs. 21% in study 22, and 30% vs. 13% in study 30), but the numbers were relatively small.

Table 26: Studies 22 and 30 – 2-Hr Response Rates, by Baseline Pain Intensity

Symptom	Study 22				Study 30			
	200 mg (n=169)	400 mg (n=177)	PBO (n=179)	p*	200 mg (n=176)	400 mg (n=177)	PBO (n=170)	p*
Response Rate, n (%)								
Baseline Mod Pain	53/113 (46.9%)	43/119 (36.1%)	39/117 (33.3%)	0.084	53/111 (47.8%)	53/125 (42.4%)	35/120 (29.2%)	0.011
Baseline Severe Pain	13/54 (24.1%)	21/58 (36.2%)	13/62 (21%)	0.144	15/65 (23.1%)	15/50 (30%)	6/47 (12.8%)	0.122

* chi-square

I conclude that, in the subgroup of patients who definitely treated a migraine, the efficacy of ibuprofen for the treatment of acute migraine, the full syndrome, is not established.

4.8 Reviewer's Efficacy Conclusions

- Motrin Migraine is an effective treatment for headache in a population of migraine sufferers
- There is little, if any, evidence that 400mg is any better than 200mg.
- There is little evidence that Motrin is effective against severe headache pain.
- In the subgroup of patients who definitely treated a migraine, the efficacy of ibuprofen for the treatment of acute migraine is not established.
- The efficacy of Motrin Migraine in adolescents is not established because adolescents were not studied
- The efficacy of multiple doses in the treatment of migraine is not established because a multiple dose regimen was not studied.

5. Safety – Studies 22 and 30

5.1 Background and Methodology

In this section, I review the safety data generated from the two controlled clinical trials in this efficacy supplement: studies 22 and 30. I do not review the post-marketing experience of the many other marketed products containing ibuprofen. By mutual agreement, this is being reviewed by the primary review division (OTC drug products).

There were a total 1309 patients in both studies who had exposure and safety data for review. Of these, 432 were exposed to 200mg, 442 were exposed to 400mg, and 435 received placebo. Both trials involved single dose treatments. I

reviewed the demographic and baseline characteristics of these patients in section 4.3, page 7 and I don't repeat that information here.

5.2 Deaths

There were no deaths reported in either study.

5.3 Serious Adverse Events

There were no serious adverse events reported in either study.

5.4 Adverse Dropouts

There were 8 subjects (0.6%) who enrolled and subsequently dropped out due to an adverse event. None were in the 200mg group. There were four in the 400mg group (0.9%) and four in the placebo group (0.9%).

Seven of the eight withdrew due to vomiting, and the eighth withdrew due to nausea. Although reported as a drug related AE in all eight, the relationship to study drug was recorded as unlikely in five of the eight: 2 in the 400mg group and 3 in the placebo group. A list of the adverse dropouts is shown in Table 27 (modified from ISS, Table 8.7-17).

Table 27: Studies 22 and 30 – Adverse Dropouts

Study	ID	Age/Sex	Dose	Event	Intensity	Duration	Relation to Drug
22	214328	29 F	400mg	Vomit	Mod	1 min	Possible
22	214385	68 M	400mg	Vomit	Sev	1 min	Unlikely
30	486520	24 F	400mg	Vomit	Mod	Unk	Unlikely
30	496378	27 M	400mg	Vomit	Mild	10 min	Possible
22	154120	39 F	PBO	Nausea	Mild	1 day	Unlikely
22	154796	46 F	PBO	Vomit	Mod	2 hrs	Unlikely
22	214322	31 F	PBO	Vomit	Sev	1 min	Unlikely
30	306321	38 F	PBO	Nausea Vomit	Mod	12 hrs	Likely

5.5 Adverse Events

Of the 1309 patients in the safety database who received study medication, 456 (34.8%) reported a total of 566 adverse events. Of these, 145 took 20mg (34%), 153 took 400mg (35%), and 158 took placebo (36%). These are summarized in Table 28 (adapted from ISS table 8.7-5).

Table 28: Studies 22 and 30 – Summary of All Adverse Events

	200mg N=432	400mg N=442	PBO N=435	p-value*
Subjects with AE's	145 (33.6%)	153 (34.6%)	156 (36.3%)	0.695
AE's	172	190	204	
Deaths	0	0	0	

Adverse Dropouts	0	4 (0.9%)	4 (0.9%)	0.141
SAE's	0	0	0	

* Fisher's exact test

The most commonly affected body system was the digestive system. There were no statistically significant differences among treatments in the frequency of subjects reporting AE's in any body system (Table 29, from ISS table 8.7-6).

Table 29: Studies 22 and 30 – Summary of Adverse Events, by Body System

Body System	200mg (N=432) n (%)	400mg (N=442) n (%)	PBO (N=435) n (%)	p-value*
Any adverse event	145 (33.6)	153 (34.6)	158 (36.3)	0.695
Body as a whole	9 (2.1)	13 (2.9)	12 (2.8)	0.743
Cardiovascular	6 (1.4)	2 (0.5)	1 (0.2)	0.112
Digestive	126 (29.2)	134 (30.3)	145 (33.3)	0.392
Musculoskeletal	1 (0.2)	1 (0.2)	0 (0.0)	0.775
Nervous	11 (2.5)	10 (2.3)	5 (1.1)	0.285
Respiratory	1 (0.2)	4 (0.9)	1 (0.2)	0.381
Skin and appendages	1 (0.2)	0 (0.0)	2 (0.5)	0.329
Special senses	0 (0.0)	2 (0.5)	2 (0.5)	0.555
Urogenital	0 (0.0)	0 (0.0)	1 (0.2)	0.662

* Fisher's Exact Test

The next table shows a summary of all AE's that were reported at a frequency of ≥1% (adapted from ISS table 8.7-7). Overall, nausea was the most frequently reported AE for all treatment groups, and numerically it was highest in the placebo group. Vomiting was also reported more frequently in the placebo group. These symptoms most likely represent normal sequelae of migraine. None of the incidences of other suggests a drug related phenomenon, either due to comparable incidences with placebo, or the small number of events reported, or both. Seven patients reported migraine, although only one event was felt to be treatment-related by the investigator.

Table 30: Studies 22 and 30: Most Commonly Reported Adverse Events (≥1%)

	200mg (N=432) n (%)	400mg (N=442) n (%)	PBO (N=435) n (%)
Any adverse event	145 (33.6)	153 (34.6)	158 (36.3)
Body as a whole	9 (2.1)	13 (2.9)	12 (2.8)
Asthenia	1 (0.2)	5 (1.1)	3 (0.7)
Digestive	126 (29.2)	134 (30.3)	145 (33.3)
Nausea	119 (27.5)	120 (27.1)	133 (30.6)
Vomiting	17 (3.9)	24 (5.4)	35 (8.0)
Nervous	11 (2.5)	10 (2.3)	5 (1.1)
Migraine	5 (1.2)	2 (0.5)	0 (0.0)
Dizziness	3 (0.7)	5 (1.1)	3 (0.7)
Somnolence	6 (1.4)	3 (0.7)	0 (0.0)

A complete listing of all adverse events reported is located in Appendix 1 - page 38.

5.6 Other Safety Data

There were no additional safety data collected in either study, since the doses used are currently approved OTC doses for ibuprofen. In particular, there were no:

- Laboratory data
- Vital signs data
- ECG data
- Withdrawal phenomenon and abuse potential
- Human reproduction data
- Overdose information

5.7 Sponsor's Safety Conclusions

- Overall, 34% of patients reported adverse events. There was no significant difference among treatment groups. Drug-related events were 26.8% and there was no significant difference among treatment groups.

- The most common AE's were in the digestive system (mainly nausea and vomiting), occurring in 30.9% of study subjects. There was no significant difference among treatment groups. It is more likely these represent normal migraine sequelae.

- No serious adverse events were reported.

5.8 Reviewer's Safety Conclusions

I concur with the sponsor's conclusions. The safety results from studies 22 and 30 do not disclose any significant clinical safety concerns with either the 200mg or 400mg dose.

6. Conclusions

I conclude:

- Motrin Migraine is an effective treatment for headache in a population of migraine sufferers
- There is little, if any, evidence that 400mg is any better than 200mg.
- There is little evidence that Motrin is effective against severe headache pain.
- In the subgroup of patients who definitely treated a migraine, the efficacy of ibuprofen for the treatment of acute migraine is not established.
- The efficacy of Motrin Migraine in adolescents is not established because adolescents were not studied
- The efficacy of multiple doses in the treatment of migraine is not established because a multiple dose regimen was not studied.
- The safety results from studies 22 and 30 do not disclose any significant clinical safety concerns with either the 200mg or 400mg dose.

7. Recommendations

Since OTC ibuprofen is already approved for the treatment of headache, I recommend a non-approval action.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. _____

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cc:
HFD-120
NDA 19-012
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Appendix 1 - All Adverse Events

Table 31: Studies 22 and 30 – All Adverse Events

AE	200mg (n=432)	400mg (n=442)	PBO (n=435
Any adverse event	145 (33.6)	153 (34.6)	158 (36.3)
Body as a whole	9 (2.1)	13 (2.9)	12 (2.8)
Allergic reaction	0 (0.0)	1 (0.2)	1 (0.2)
Asthenia	1 (0.2)	5 (1.1)	3 (0.7)
Chills	0 (0.0)	0 (0.0)	1 (0.2)
Flu syndrome	1 (0.2)	0 (0.0)	0 (0.0)
Headache	1 (0.2)	2 (0.5)	1 (0.2)
Infection	0 (0.0)	1 (0.2)	0 (0.0)
Injury accidental	0 (0.0)	1 (0.2)	0 (0.0)
Malaise	0 (0.0)	1 (0.2)	0 (0.0)
Neck rigidity	0 (0.0)	0 (0.0)	2 (0.5)
Pain	0 (0.0)	0 (0.0)	1 (0.2)
Pain abdominal	3 (0.7)	2 (0.5)	3 (0.7)
Pain back	1 (0.2)	0 (0.0)	1 (0.2)
Pain chest	1 (0.2)	0 (0.0)	0 (0.0)
Pain chest substernal	1 (0.2)	0 (0.0)	0 (0.0)
Pain neck	1 (0.2)	0 (0.0)	0 (0.0)
Cardiovascular	6 (1.4)	2 (0.5)	1 (0.2)
Migraine	5 (1.2)	2 (0.5)	0 (0.0)
Tachycardia	1 (0.2)	0 (0.0)	1 (0.2)
Digestive	126 (29.2)	134 (30.3)	145 (33.3)
Appetite increase	0 (0.0)	1 (0.2)	0 (0.0)
Diarrhea	0 (0.0)	2 (0.5)	2 (0.5)
Dyspepsia	4 (0.9)	4 (0.9)	3 (0.7)
GI disorder	0 (0.0)	1 (0.2)	0 (0.0)
Nausea	119 (27.5)	120 (27.1)	133 (30.6)
Vomiting	17 (3.9)	24 (5.4)	35 (8.0)
Musculoskeletal	1 (0.2)	1 (0.2)	0 (0.0)
Arthritis	0 (0.0)	1 (0.2)	0 (0.0)
Myalgia	1 (0.2)	0 (0.0)	0 (0.0)
Nervous	11 (2.5)	10 (2.3)	5 (1.1)
Anxiety	1 (0.2)	0 (0.0)	0 (0.0)
Depersonalization	1 (0.2)	0 (0.0)	0 (0.0)
Dizziness	3 (0.7)	5 (1.1)	3 (0.7)
Dry mouth	0 (0.0)	0 (0.0)	1 (0.2)
Hypokinesia	0 (0.0)	1 (0.2)	0 (0.0)
Nervousness	0 (0.0)	2 (0.5)	0 (0.0)
Paresthesia	0 (0.0)	0 (0.0)	1 (0.2)
Somnolence	6 (1.4)	3 (0.7)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	1 (0.2)
Vasodilation	1 (0.2)	1 (0.2)	0 (0.0)
Respiratory	1 (0.2)	4 (0.9)	1 (0.2)
Bronchitis	0 (0.0)	1 (0.2)	0 (0.0)
Pharyngitis	1 (0.2)	1 (0.2)	0 (0.0)
Rhinitis	0 (0.0)	1 (0.2)	1 (0.2)
Sinusitis	0 (0.0)	2 (0.5)	0 (0.0)

AE	200mg (n=432)	400mg (n=442)	PBO (n=435
Skin and appendages	1 (0.2)	0 (0.0)	2 (0.5)
Rash	0 (0.0)	0 (0.0)	1 (0.2)
Sweating	1 (0.2)	0 (0.0)	1 (0.2)
Special senses	0 (0.0)	2 (0.5)	2 (0.5)
Amblyopia	0 (0.0)	0 (0.0)	1 (0.2)
Eye disorder	0 (0.0)	1 (0.2)	0 (0.0)
Tinnitus	0 (0.0)	1 (0.2)	1 (0.2)
Urogenital	0 (0.0)	0 (0.0)	1 (0.2)
Dysmenorrhea	0 (0.0)	0 (0.0)	1 (0.2)