CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-012/S-016

STATISTICAL REVIEW(S)

Comments on Medical Officer's Review

NDA # : 19-012
Sponsor: McNeil
Drug: Motrin Migraine
Medical officer: Armando Oliva, MD
Reviewer: Kallappa M. Koti

1. INTRODUCTION

This refers to Dr. Armando Oliva's review dated December 16, 1999. The NDA 19-012 consists of two studies: 22 and 30. From each study, he has thrown away a part of data. He has defined two sets of populations MIG1 and MIG2. Dr. Oliva has taken the liberty to assume that each of these subsets MIG1 and MIG2 is from a randomized clinical trial so that he could use the CMH test and chi-squared test for proving or disproving the efficacy claim made by the sponsor. This reviewer was asked to verify his results. This review does not make any inference.

2. STUDY 22

Baseline Comparison:

Population MIG1

The chi-square test for independence between DRUG and NAU_BAS is not significant (p-value = 0.512). The chi-square test for independence between DRUG and PN_BAS is not significant (p-value = 0.186). The chi-square test for independence between DRUG and PT_BAS is not significant (p-value = 0.512).

Population MIG2

The chi-square test for independence between DRUG and NAU_BAS is not significant (p-value = 0.293). The chi-square test for independence between DRUG and PN_BAS is not significant (p-value = 0.381). The chi-square test for independence between DRUG and PT_BAS is not significant (p-value = 0.989).

Primary efficacy: Proportion of Responders at 2 hours- CMH test

The MIG1 data give a p-value of 0.051 for the CMH test.
Estimates of proportions of responders under IBU 200 mg, IBU 400 mg and Placebo are

0.406, 0.407 and 0.3, respectively. Other details are shown in Table 2.1.

Table 2.1: **Percentage of Responders (at 2 hours) for MIG1**

Treatment	Baseline Pain Intensity = 2		Baseline Pain Intensity = 3	
	Response = NO	Response = YES	Response = NO	Response = YES
IBU 200 mg	50.49	49.51	76.92	23.08
IBU 400 mg	56.73	43.27	63.79	36.21
PLACEBO	65.74	34.26	77.59	22.41
p-value	0.078		0.176	

The MIG2 data give a p-value of 0.001 for the CMH test.
Estimates of proportions of responders under IBU 200 mg, IBU 400 mg and Placebo are 0.42, 0.44 and 0.286, respectively. Other details are shown in Table 2.2.

Table 2.2: **Percentage of Responders (at 2 hours) for MIG2**

Treatment	Baseline Pain Intensity = 2		Baseline Pain Intensity = 3	
	Response = NO	Response = YES	Response = NO	Response = YES
IBU 200 mg	49.57	50.43	75.0	25.0
IBU 400 mg	52.59	47.41	62.30	37.7
PLACEBO	67.80	32.20	78.57	21.88
p-value	0.011		0.117	

Secondary efficacy endpoints:
Population MIG1

Table 2.3: **Percentages of "Nausea" for MIG1**
Chi-squared test for independence

Treatment	N_P = 0	N_P=1	# of subjects
IBU 200 mg	56.77	43.23	155
IBU 400 mg	61.11	38.89	162
PLACEBO	54.22	45.78	166
# of subjects	277	206	483

p-value = 0.444

Table 2.4: **Percentages of "Phonophobia" for MIG1**
Chi-squared test for independence

Treatment	PN_P = 0	PN_P=1	# of subjects
IBU 200 mg	21.29	78.71	155
IBU 400 mg	21.60	78.40	162
PLACEBO	16.27	83.73	166
# of subjects	95	388	483

p-value = 0.395

Table 2.5: **Percentages of "Photophobia" for MIG1**
Chi-squared test for independence

Treatment	PT_P = 0	PT_P=1	# of subjects
IBU 200 mg	28.39	71.61	155
IBU 400 mg	27.16	72.84	162
PLACEBO	20.48	79.52	166
# of subjects	122	361	483

p-value = 0.21

Secondary efficacy endpoints:
Population MIG2

Table 2.6: **Percentages of "Nausea" for MIG2**
Chi-squared test for independence

Treatment	N_P = 0	N_P=1	# of subjects
IBU 200 mg	56.57	43.43	175
IBU 400 mg	62.71	37.29	177
PLACEBO	54.40	45.60	182
# of subjects	309	225	534

p-value = 0.256

Table 2.7: **Percentages of "Phonophobia" for MIG2**
Chi-squared test for independence

Treatment	PN_P = 0	PN_P=1	# of subjects
IBU 200 mg	21.71	78.29	175
IBU 400 mg	20.90	79.10	177
PLACEBO	17.58	82.42	182
# of subjects	107	427	534

p-value = 0.584

Table 2.8: **Percentages of "Photophobia" for MIG2**
Chi-squared test for independence

Treatment	PT_P = 0	PT_P=1	# of subjects
IBU 200 mg	28.00	72.00	175
IBU 400 mg	27.12	72.88	177
PLACEBO	20.88	79.12	182
# of subjects	135	399	534

p-value = 0.238

3. STUDY 30

Baseline Comparison:

Population MIG1

The chi-square test for independence between DRUG and NAU_BAS is not significant (p-value = 0.135). The chi-square test for independence between DRUG and PN_BAS is not significant (p-value = 0.976). The chi-square test for independence between DRUG and PT_BAS is not significant (p-value = 0.725).

Population MIG2

The chi-square test for independence between DRUG and NAU_BAS is not significant (p-value = 0.117). The chi-square test for independence between DRUG and PN_BAS is not significant (p-value = 0.939). The chi-square test for independence between DRUG and PT_BAS is not significant (p-value = 0.593).

Primary efficacy: Proportion of Responders at 2 hours- CMH test

The MIG1 data give a p-value of 0.001 for the CMH test.
Estimates of proportions of responders under IBU 200 mg, IBU 400 mg and Placebo are 0.39, 0.395 and 0.247, respectively. Other details are shown in Table 3.1.

Table 3.1: **Percentage of Responders (at 2 hours) for MIG1**

Treatment	Baseline Pain Intensity = 2		Baseline Pain Intensity = 3	
	Response = NO	Response = YES	Response = NO	Response = YES
IBU 200 mg	51.72	48.28	77.27	22.73
IBU 400 mg	57.14	42.86	69.23	30.77
PLACEBO	70.77	29.23	86.54	13.46
p-value	0.007		0.106	

The MIG2 data give a p-value of 0.002 for the CMH test.
Estimates of proportions of responders under IBU 200 mg, IBU 400 mg and Placebo are 0.396, 0.393 and 0.261, respectively. Other details are shown in Table 3.2.

Table 3.2: **Percentage of Responders (at 2 hours) for MIG2**

Treatment	Baseline Pain Intensity = 2		Baseline Pain Intensity = 3	
	Response = NO	Response = YES	Response = NO	Response = YES
IBU 200 mg	50.00	50.00	78.87	21.13
IBU 400 mg	57.04	42.96	69.49	30.51
PLACEBO	69.34	30.66	84.48	15.52
p-value	0.005		0.143	

Secondary efficacy endpoints:
Population MIG1

Table 3.3: **Percentages of "Nausea" for MIG1**
Chi-squared test for independence

Treatment	N_P = 0	N_P=1	# of subjects
IBU 200 mg	52.75	47.25	182
IBU 400 mg	52.97	47.03	185
PLACEBO	52.75	47.25	182
# of subjects	290	259	549

p-value = 0.999

Table 3.4: **Percentages of "Phonophobia" for MIG1**
Chi-squared test for independence

Treatment	PN_P = 0	PN_P=1	# of subjects
IBU 200 mg	23.63	76.37	182
IBU 400 mg	28.11	71.89	185
PLACEBO	18.68	81.32	182
# of subjects	129	420	549

p-value = 0.103

Table 3.5: **Percentages of "Photophobia" for MIG1**
Chi-squared test for independence

Treatment	PT_P = 0	PT_P=1	# of subjects
IBU 200 mg	20.88	79.12	182
IBU 400 mg	21.62	78.38	185
PLACEBO	12.64	87.36	182
# of subjects	101	448	549

p-value = 0.049

Secondary efficacy endpoints:
Population MIG2

Table 3.6: **Percentages of "Nausea" for MIG2**
Chi-squared test for independence

Treatment	N_P = 0	N_P=1	# of subjects
IBU 200 mg	22.34	77.66	197
IBU 400 mg	20.40	79.60	201
PLACEBO	12.82	87.18	195
# of subjects	110	483	593

p-value = 0.038

Table 3.7: **Percentages of "Phonophobia" for MIG2**
Chi-squared test for independence

Treatment	PN_P = 0	PN_P=1	# of subjects
IBU 200 mg	24.37	75.63	197
IBU 400 mg	27.86	72.14	201
PLACEBO	18.97	81.03	195
# of subjects	141	452	593

p-value = 0.113

Table 3.8: **Percentages of "Photophobia" for MIG2**
Chi-squared test for independence

Treatment	PT_P = 0	PT_P=1	# of subjects
IBU 200 mg	22.34	77.66	197
IBU 400 mg	20.40	79.60	201
PLACEBO	12.82	87.18	195
# of subjects	110	483	593

p-value = 0.038

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MEMORANDUM SEP 14 1999

Statistical Review and Evaluation

SEP 14 1999

NDA :	19-012
Sponsor:	McNeil Consumer Healthcare
Drug Name:	Motrin IB Migraine (ibuprofen, 200 mg). Tablets, Caplets, and Gelcaps
Indication:	Migraine Headache pain
Studies for Review:	Protocol 97-022 and Protocol 97-030
Medical officer:	Dr. Armando Oliva
Reviewer :	Kallappa M. Koti

Contents

1. Introduction

This SNDA demonstrates the effectiveness of OTC doses of ibuprofen in the treatment of migraine headache pain. This SNDA requests the approval of Motrin® Migraine 200 mg with a sole indication for the relief of mild-to-moderate migraine headache pain for adults and children over 12 years of age. In May 1984, FDA approved NDA 19-012 for OTC Motrin® IB 200 mg tablet. Currently, Motrin® IB is indicated for the reduction of fever and the temporary relief of headache, muscular aches, minor pain of arthritis, toothache, backache, minor aches and pains associated with the common cold, and pain of menstrual cramps in adults and children 12 years of age and older. Approved adult dosing of OTC ibuprofen is to take one tablet (200 mg) every four to six hours, while symptoms persist. If pain or fever does not respond to one tablet (200 mg), two tablets (400 mg) may be used, but consumers should not exceed six tablets (1200 mg) in 24 hours, unless directed by a doctor.

Migraine headache is a very common disorder in the United States with an estimated 23 million sufferers 12 years of age and older. Approximately 18% of women and 6% of men report having one or more migraine headaches per year. It is estimated that 50% to 59% of migraineurs experience one or more attacks per month. Disability from migraine headache occurs in over 80% of migraineurs and ranges from impaired ability to work or perform activities to required bed rest. Studies indicate that as many as 67% to 90% of migraineurs self-treat with OTC analgesic products for migraine pain relief, and the majority use OTC analgesic products exclusively. At the July 15, 1997 meeting, the Nonprescription Drugs, Arthritis, and Peripheral and Central Nervous Systems Drugs Committees agreed that migraine sufferers with mild-to-moderate headache pain can recognize a migraine headache attack and that it is appropriate to self-treat with an OTC analgesic product.

Efficacy data presented in this SNDA include results from the two pivotal McNeil randomized controlled clinical studies of ibuprofen in the treatment of migraine headache pain. In addition, data from published randomized controlled trials of migraine provide further support for the efficacy and safety of ibuprofen in the treatment of migraine headache pain.
Collectively, these data support the efficacy of OTC doses of ibuprofen in the treatment of migraine headache pain and are consistent with the current labeling which directs consumers to take an initial dose of 200 mg and, if pain does not respond, a dose of 400 mg. These data, combined with almost 15 years of OTC use, establish ibuprofen as an effective, well-tolerated, single-ingredient OTC treatment for migraine headache pain.

2. Excerpts from sponsor's application

2.1 Protocol 97-022

Title: A single-Dose, Randomized, Double-Blind, Placebo-Controlled Study evaluating the safety and efficacy of Ibuprofen 200 mg and Ibuprofen 400 mg for the treatment of migraine headache pain.
It is a Phase III study.

Objective: The purpose of this study is to evaluate the safety and efficacy of Ibuprofen 200 mg and Ibuprofen 400 mg for the treatment of pain assocaited with migraine headache.

Methodology:

This is a multicenter, single-dose, randomized, double-blind, parallel, placebo-controlled study of approximately 600 subjects, 18 years of age and older, experiencing at least moderate pain associated with migraine headache. Following a screening visit, eligible subjects will be randomly assigned to either ibuprofen 200 mg, ibuprofen 400 mg or placebo. Subjects will leave the investigative center with one dose of blinded study drug, a timing device and a subject diary. After the occurrence of a migraine headache of at least moderate intensity, subjects will dose with study medication and record in the diary the data and time of study medication administration. Efficacy and safety will be assessed at specified intervals for six hours following the use of study medication. Subjects will return to the site for a follow-up visit within 72 hours after dosing with study medication.
Study was conducted in 15 centers. It was planned to have at least 600 subjects in the study. The data were available for 660 subjects. The demographic characteristics are shown in Table 1 below.

Table 1: **Demographic Characteristics**

Characteristic	Ibu 200 mg	Ibu 400 mg	Placebo	Total
Sex (n, %)				
Male	46 (21.3)	30 (13.5)	28 (12.7)	104 (15.8)
Female	170 (78.7)	193 (86.5)	193 (87.3)	556 (84.2)
Mean age (yrs)	38.9	38.0	39.1	38.6
Race (n, %)				
Caucasian	168 (77.8)	173 (77.6)	174 (78.7)	515 (78.0)
African-American	17 (7.9)	19 (8.5)	16 (7.2)	52 (7.9)
Other	31 (14.3)	31 (8.8)	31 (14.0)	93 (14.1)

Inclusion criteria: Subjects required to have history of one migraine headache every two (2) months to six (6) migraine headaches per month that are not debilitating or incapacitating.

Dose: MotrinIB, 200 mg and 400 mg, oral tablets, C-779-1.

Duration of treatment: Six hour evaluation after a single-dose.

Efficacy: **The primary efficacy endpoint is the percentage of subjects who respond at the two hour postmedication assessment where response is defined as a change in baseline pain intensity from severe (3) or moderate (2) to mild (1) or none (0). An additional primary efficacy endpoint will be the pain intensity difference at two hours.**

Statistical Methods: The Cochran-Mantel-Haenszel (CMH) test of general association stratified by baseline level of pain intensity was used to make pair-wise treatment comparisons of response rates.

A summary of sponsor's results is presented in Table 2 below.

Table 2: **Percentage (Number) of Subjects Responding by Time- McNeil Study 97-022**

Drug	Assessment Time Points (Hours) 0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=216)	14.81 (32)	27.78 (60)	37.50 (81)	41.67 (90)	47.69 (103)	44.44 (96)	44.91 (97)	45.83 (97)
Ibu 400 mg (N=223)	8.52 (19)	24.66 (55)	35.43 (79)	40.81 (91)	44.84 (100)	45.29 (101)	48.43 (108)	48.88 (109)
Placebo (N=221)	12.22 (27)	20.81 (46)	24.43 (54)	28.05 (62)	28.96 (64)	29.86 (66)	31.22 (69)	31.67 (70)
Comparison at two and six hours				**p-value**				**p-value**
Ibu 200 mg vs. placebo				0.004				0.003
Ibu 400 mg vs. placebo				0.006				<0.001
Ibu 200 mg vs. Ibu 400 mg				0.832				0.530

p-value: Cochran-Mantel-Haenszel test, stratified by baseline pain intensity level

A three-way ANOVA (Treatment, Baseline Pain, Investigator) was used in the analysis of pain intensity difference from baseline at two hours (PID2); pairwise treatment comparisons were made using Fisher's protected LSD technique. The sponsor's results are shown in Tables 3 and 4 below.

Table 3: **Mean Pain Intensity Differences from Baseline at Two Hours Postdose- ITT Study 97-022**

Treatment	PID2 (Std)	ANOVA Summary Model Term	p-values
Ibu 200 mg (N = 216)	0.68 (0.94)	Treatment [a]	0.0001
Ibu 400 mg (N = 223)	0.65 (1.01)	Treatment*Investigator [b]	0.4883
Placebo (N = 221)	0.39 (0.92)	Treatment*BLPain [b]	0.2022

a: Model PID2 = $\mu + T_i + B_k$ + error

b: Model PID2 = $\mu + T_i + B_k + Tl_{ij} + Tb_{ik}$ + error

Table 4: **Mean Pain Intensity Differences from Baseline at Two Hours Postdose: Pairwise Comparison- ITT Study 97-022**

Comparison	p-value
Ibu 200 mg vs. Placebo	0.0001
Ibu 400 mg vs. Placebo	0.0006
Ibu 200 mg vs. Ibu 400 mg	0.6726

Subgroup analysis: The two primary measures were analyzed by baseline pain, gender and race. In addition, the percentage of responders at two hours was analyzed by menstrual status (yes/no). The sponsor's results are reproduced in Section 3 below.

Conclusion:
Ibuprofen at OTC doses of 200 mg and 400 mg is an effective treatment for the temporary relief of migraine headache pain and the associated symptoms of migraine headache 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 versus the 200 mg dose.

2.2 Protocol 97-030

Title: A Single-Dose, Randomized, Double-Blind, Placebo-Controlled Study evaluating the Safety and Efficacy of Ibuprofen 200 mg and 400 mg for the Treatment of Migraine Headache Pain.
It is a Phase III study.

Objectives: The purpose of this study was to evaluate the efficacy and safety of Ibuprofen 200 mg and ibuprofen 400 mg for the treatment of pain associated with migraine headache.
Methodology:
This was a multicenter, single-dose, randomized, double-blind, parallel, placebo-controlled study of approximately 600 subjects, 18 years of age and older, experiencing at least moderate pain associated with migraine headache. Following a screening visit, eligible subjects were randomly assigned to either ibuprofen 200 mg, ibuprofen 400 mg or placebo. Subjects left the investigative center with one dose of blinded study drug, a timing device, and a subject diary. After the occurrence of a migraine headache of at least moderate intensity, subjects dosed with study medication and recorded in the diary the date and time of study medication administration. Efficacy and safety were assessed at specified intervals for six hours following the use of study medication. Subjects returned to the site for a follow-up visit within 72 hours after dosing with study medication.
Study included 18 centers. The study was designed for the completion of at least 600 subjects. Data were available for 649 subjects all of whom were included in an intent-to-treat efficacy analysis. Data were available for 641 subjects in the per-protocol analysis. The demographic characteristics are shown in Table 5 below.

Table 5: **Demographic Characteristics**

Characteristic	Ibu 200 mg	Ibu 400 mg	Placebo	Total
Sex (n, %)				
Male	42 (17.5)	35 (14.6)	34 (14.5)	111 (15.6)
Female	198 (82.5)	204 (85.4)	200 (85.5)	602 (84.4)
Mean age (yrs)	38.9	38.5	38.2	38.6
Race (n, %)				
Caucasian	214 (89.2)	200 (83.7)	206 (88.0)	620 (87.0)
African-American	15 (6.2)	18 (7.5)	12 (5.2)	45 (6.3)
Other	11 (4.6)	21 (8.8)	16 (6.8)	48 (6.7)

Inclusion: Subjects were required to have history of one migraine headache every two months to six migraine headaches per month that were not debilitating or incapacitating.
Dose: Study drug treatment was Motrin IB, 200 mg and 400 mg, oral tablet, control number C-779-1B.
Duration of treatment: Subjects were treated with a single dose of study drug when they experienced a migraine. Subjects were evaluated for six hours after starting treatment. After dosing with study medication, subjects returned to the investigative site for a follow-up visit.
Efficacy: **The primary efficacy endpoint was the percentage of subjects who experienced a reduction in baseline pain intensity from severe (3) or moderate (2) to mild (1) or none (0) at the two hour postmedication assessment time (defined as responders). An additional primary efficacy endpoint was the pain intensity difference from baseline at two hours.**
Statistical Methods:
There were three pairwise comparisons of interest for analysis: ibuprofen 200 mg vs. placebo, ibuprofen 400 mg vs. placebo, and ibuprofen 200 mg vs. ibuprofen 400 mg.
The intent-to-treat analysis was the primary analysis. The sponsor's results are shown in Table 6 below. The Cochran-Mantel-Haenszel test of general association stratified by baseline level of pain intensity was used to make pairwise treatment comparisons of response rates.

Table 6: **Percentage (Number) of Subjects Responding by Time- McNeil Study 97-030**

	Assessment Time Points (Hours)							
Drug	0.5	1	1.5	2	3	4	5	6
Ibu 200 mg (N=216)	17.13 (327)	28.70 (62)	35.65 (77)	39.81 (86)	43.06 (93)	47.22 (102)	47.69 (103)	46.76 (101)
Ibu 400 mg (N=219)	18.72 (41)	31.96 (70)	38.81 (85)	41.10 (90)	44.75 (98)	44.75 (98)	46.58 (102)	47.95 (105)
Placebo (N=214)	14.02 (30)	18.22 (39)	22.43 (48)	26.64 (57)	28.04 (60)	29.91 (64)	30.37 (65)	31.31 (67)
Comparison at two and six hours				**p-value**				**p-value**
Ibu 200 mg vs. placebo				0.002				0.001
Ibu 400 mg vs. placebo				0.002				0.001
Ibu 200 mg vs. Ibu 400 mg				0.992				0.862

p-value: Cochran-Mantel-Haenszel test, stratified by baseline pain intensity level

A three-way ANOVA (Treatment, Baseline Pain, Investigator) was used in the analysis of pain intensity difference from baseline at two hours (PID2); pairwise treatment comparisons were made using Fisher's protected LSD technique. The sponsor's results are shown in Tables 7 and 8 below.
Subgroup analysis: The two primary measures were analyzed by baseline pain, gender, and race. In addition, the percentage of responders at two hours was analyzed by menstrual status (yes/no). The sponsor's results are reproduced in Section 3 below.

Table 7: **Mean Pain Intensity Differences from Baseline at Two Hours Postdose- ITT**
Study 97-030

		ANOVA Summary	
Treatment	PID2 (Std)	Model Term	p-values
Ibu 200 mg (N = 216)	0.67 (0.92)	Treatment [a]	0.0002
Ibu 400 mg (N = 219)	0.65 (0.99)	Treatment*Investigator [b]	0.4378
Placebo (N = 214)	0.35 (0.91)	Treatment*BLPain [b]	0.1448

a: Model PID2 = $\mu + T_i + B_k$ + error

b: Model PID2 = $\mu + T_i + B_k + Tl_{ij} + Tb_{ik}$ + error

Table 8: **Mean Pain Intensity Differences from Baseline at Two Hours Postdose: Pairwise Comparison- ITT**
Study 97-030

Comparison	p-value
Ibu 200 mg vs. Placebo	0.0005
Ibu 400 mg vs. Placebo	0.0002
Ibu 200 mg vs. Ibu 400 mg	0.8386

Analysis results of the primary endpoints for both studies as reported by the sponsor are presented in Table 9 below.

Table 9: **Number and Percentage of Subjects With a Reduction in Baseline Pain Intensity From Severe/Moderate to Mild/None at Two Hours Post-Medication Treatment Group- McNeil Studies 97-022 and 97-030**

				p-value [a]		
	Ibu 200 mg	Ibu 400 mg	Placebo	Ibu 200 vs. Placebo	Ibu 400 vs. Placebo	Ibu 200 vs. Ibu 400
Study 97-022	90/216 (41.67)	91/223 (40.81)	62/221 (28.05)	0.004	0.006	0.832
Study 97-030	86/216 (39.81)	90/219 (41.10)	57/214 (26.64)	0.002	0.002	0.992

a: CMH test stratified by initial level of pain intensity

3. Sponsor's Overall Conclusions

The primary efficacy measures of percent responders and pain intensity difference at two hours were significantly superior to placebo for both ibuprofen 200 mg and 400 mg but there was no significant difference between the two doses of ibuprofen at two hours. Time profiles for both pain intensity difference and pain relief were consistent with those results. Significant separation of both ibuprofen doses in pain intensity difference from placebo occurred as early as one hour after dosing. In addition, for the outcome of pain relief, both doses of ibuprofen separated from placebo as early as 30 minutes after dosing. Response rate at two hours for the 200 mg ibuprofen dose was approximately 40% compared to 41% for the 400 mg dose and 27% for placebo. The magnitude of the difference from placebo of two hour response rate for the ibuprofen doses (13% to 14%) is comparable to that seen with recently introduced migraine therapies [11].

Assessment of the primary endpoint of response rate stratified by baseline pain intensity demonstrated evidence of dose response for the more severe migraine sufferers. In subjects with moderate baseline headache pain both ibuprofen doses were significantly superior to placebo but not different from one another. In the subset of subjects with severe baseline headache pain the response rate with the 400 mg dose of ibuprofen was numerically superior to that of with the 200 mg dose at most time points in the interval from one to six hours, although the differences between doses were not statistically significant. Results for pain intensity difference from baseline were consistent with the results for response rate.

For females, the doses of ibuprofen were not significantly different from one another and both doses were significantly superior to placebo. For female subjects menstruating at baseline, there were no significant differences between treatments. For female subjects not menstruating at baseline, the two doses of ibuprofen were not significantly different from one another and both doses were superior to placebo.

There were no significant differences between treatments for males.

The results for Caucasians are generally consistent with the overall findings, i.e., the two doses of ibuprofen were not significantly different from one another and both doses were significantly superior to placebo. And, according to Study 97-022, ibuprofen 400 mg was significantly superior to ibuprofen 200 mg for African-Americans.

4. Reviewer's Data Analyses and Comments

In both studies the protocol defined primary efficacy endpoint is the **percentage of subjects who respond** at the 2 hour post-medication assessment where response is defined as a change in baseline pain intensity from severe/moderate to mild/none. In both studies, the **Cochran-Mantel-Haenszel** test of general association stratified by baseline level of pain intensity was the protocol defined primary method of analysis. An additional primary efficacy endpoint is the pain intensity difference from baseline at two hours (PID2) and is analyzed using analysis of variance (ANOVA).

Demographic characteristics of subjects in Study 97-022 and 97-030 are shown earlier in Table 1 and Table 5, respectively.

4.1 PROTOCOL 97-022

A total of 84 study subjects were enrolled at this site. In the following, the data from this site are excluded from statistical analysis.

4.1.1 Baseline comparison:

Table 10 below contains treatment-wise percentage (and number) of subjects in each category of baseline pain intensity.

Table 10: **Baseline Comparison**

Treatment	Baseline Pain Intensity		Total
	2 (Moderate)	3 (Severe)	
IBU 200 mg	68.09 (128)	31.91 (60)	188
IBU 400 mg	68.72 (134)	31.28 (61)	196
Placebo	65.46 (127)	34.54 (67)	194
Total	389	188	577

The chi-square test indicates that there is no statistically significant association between treatment groups and baseline pain intensity (p-value = 0.77).

4.1.2 Primary efficacy endpoint:

The percentages of response at 2 hours for the 3 treatment groups are presented in Table 11 below. The numbers of subjects in each category are shown in parentheses along with the percentages. There exists a significant association between treatment groups and subject's response at 2 hours (p-value = 0.003).

Table 11: **Summary of Response at 2 Hours**

Treatment	Did Subject Respond at 2 Hours ?		Total
	No	Yes	
IBU 200 mg	56.91 (107)	**43.09** (81)	188
IBU 400 mg	55.90 (109)	**44.10** (86)	196
Placebo	71.13 (138)	**28.87** (56)	194
Total	354	223	577

The CMH, the protocol defined primary analysis of these data stratified by baseline pain intensity indicates a significant association between treatment groups and headache response at 2 hours after medication (p-value = 0.003).

Pair-wise comparison: (i) The CMH test for general association stratified by baseline pain severity for the subset of data consisting IBU 200mg and placebo indicated statistically significant association between treatments and headache response (adjusted p-value = 0.01). (ii) The CMH test for the subset of data consisting of IBU 400mg and placebo indicated statistically significant association between treatments and headache response (adjusted p-value = 0.004). (iii) However, the CMH test for the subset of data consisting of IBU 200mg and IBU 400mg was not statistically significant (p-value = 0.856).

In addition, the following logistic regression model

$$\text{Logit}(p) = \alpha + \beta_1 \text{ BASEPAIN} + \beta_2 \text{ TRTMT},$$

where p is the probability of headache response is used to compare (i) ibuprofen 200mg vs. placebo and (ii) ibuprofen 400mg vs. placebo. The data indicate the following.
The odds of responding to IBU 200mg increased to 1.86-fold that of placebo. The odds of responding to IBU 400mg increased to 1.93-fold that of placebo. However, the odd ratio

comparing IBU 400mg with IBU 200mg is 1.04 (p-value = 0.855). The model based estimates of proportions of patients with mild or no headache pain under placebo and ibuprofen are presented by baseline pain intensity in Table 12 below.

Table 12: **Model based Proportions of Responders**

	IBU 200mg vs. Placebo		IBU 400mg vs. Placebo	
Baseline Pain Intensity	Placebo	IBU 200mg	Placebo	IBU 400mg
2 (Moderate)	0.3405	0.4902	0.3186	0.4742
3 (Severe)	0.1902	0.3042	0.2320	0.3682

4.1.3 Subgroup analysis:

Baseline pain intensity: A total of 389 out of 577 in Study 97-022 reported to have moderate headache pain during the baseline period and the remaining 188 experienced severe headache pain during the baseline period. The data for the subgroup of patients with moderate baseline pain intensity indicated a significant association between treatment groups and headache response at 2 hours (p-value = 0.007). But for the other subgroup, there was no significant association between treatment groups and headache response at hours (p-value = 0.147). That is, for patients with severe headache pain, ibuprofen may not be different from placebo with respect to headache response. In fact, for this subgroup, the chi-squared test for comparing the proportions of headache response under IBU 200mg vs. placebo has a p-value of 0.575. For IBU 400mg vs. placebo it (p-vale) is 0.058. Table 13 contains the percentages of responders for the three treatment groups under the two subgroups. The numbers of subjects in various categories are shown in parentheses.

Table 13: **Percentages of Responders**

	Baseline Pain Intensity = 2		Baseline Pain Intensity = 3	
Treatment	No	Yes	No	Yes
IBU 200mg	49.22 (63)	50.78 (65)	73.33 (44)	26.67 (16)
IBU 400mg	52.99 (71)	47.01 (63)	62.30 (38)	37.70 (23)
Placebo	67.72 (86)	32.28 (41)	77.61 (52)	22.39 (15)

Subgroup analysis by center:
The sponsor does not present center-wise subgroup data analysis. However, this reviewer noted the following. The general association statistic in the CMH procedure stratified by INV (investigator) is highly significant (p-value = 0.001). The Breslow-Day test in the CMH procedure stratified by INV (investigator) does not contradict the assumption of homogeneous odds ratio for the subset of data that includes IBU 200mg and placebo (p-value = 0.511).

Subgroup analysis by Sex: Study 97-022 included 481 females and 96 males. The data analysis for females suggests a significant association between treatment groups and

headache response at 2 hours (p-value = 0.001). For males, with respect to headache response, ibuprofen is not significantly different from placebo (p-value = 0.463). Gender-wise percentages of headache response at 2 hours for the three treatment groups are shown in Table 14 below.

Table 14: **Percentages of Responders**

	FEMALE		MALE	
Treatment	No	Yes	No	Yes
IBU 200mg	59.18 (87)	40.82 (60)	48.78 (20)	51.22 (21)
IBU 400mg	54.55 (90)	45.45 (75)	63.33 (19)	36.67 (11)
Placebo	73.96 (125)	26.04 (44)	52.00 (13)	48.00 (12)

The sponsor reports that approximately 15% females menstruating during the migraine attack and that there were no significant differences between treatment groups.

Subgroup analysis by Race: There were 52 African-Americans, 434 Caucasians and 91 belonged to other ethnic groups. The data for the Caucasians indicate a significant association between the treatment groups and headache response at 2 hours (p-value = 0.036). For the remaining two subgroups, ibuprofen is not significantly different from placebo. Table 15 contains the race-wise percentages of headache response for the 3 treatment groups.

Table 15: **Percentages of Responders**

	African American		Caucasian		Others	
Treatment	No	Yes	No	Yes	No	Yes
IBU 200mg	41.2 (7)	58.8 (10)	60.7 (85)	39.3 (55)	48.4 (15)	51.6 (16)
IBU 400mg	31.6 (6)	68.4 (13)	60.7 (88)	39.3 (57)	48.4 (15)	51.6 (16)
Placebo	62.5 (10)	37.5 (6)	73.2 (109)	26.8 (40)	65.5 (19)	34.5 (10)

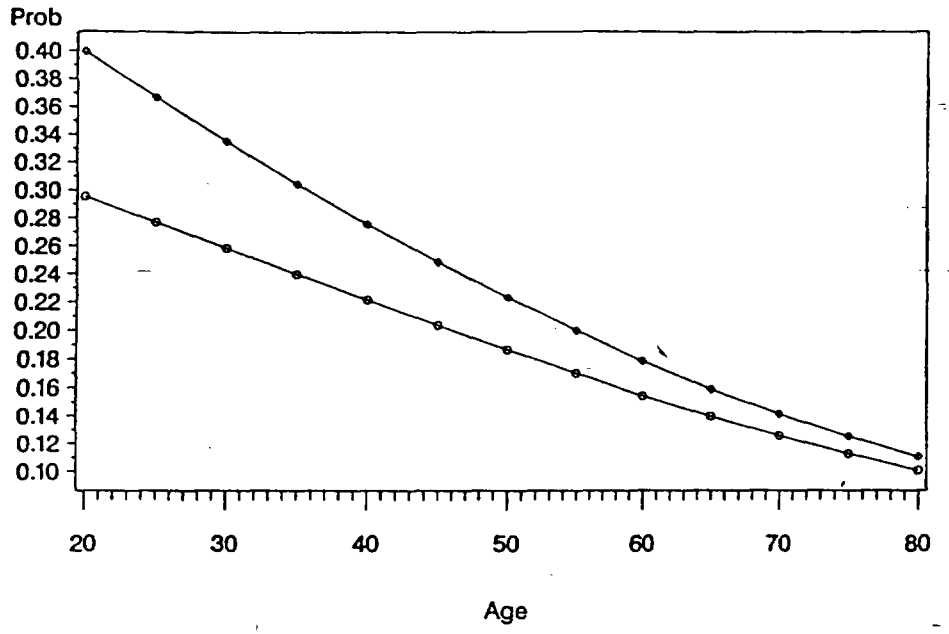
For the Caucasian women with severe (3) baseline headache pain, there is no statistically significant association between the 3 treatment groups and headache response at 2 hours. In addition, it may be pointed out that for this subgroup of subjects, the proportion of desired headache response under IBU 200mg is not higher than that of placebo.

Subgroup analysis by age:
Logistic regression model

$$\text{Logit}(p) = \alpha + \beta_1 \text{ AGE} + \beta_2 \text{ TRTMT},$$

where p is the probability of headache response is used to compare ibuprofen 200mg vs. placebo. The covariate age is significant (p-value = 0.0056). The summary of this model is seen in Figure 1 below. The IBU 200mg treatment group has a higher response rate compared to placebo over the whole range (20, 80) of age. Both treatment groups are less effective for older subjects- close to 80 years of age. For subjects over 45 years of age, the proportions of headache response under IBU 200mg and placebo are not significantly different (p-value = 0.27).

Figure 1: Probability of Response
IBU 200mg vs. Placebo / Study 97-022



4.1.3 Additional Endpoint: Pain Intensity Difference at 2 hours (PID2)

This reviewer considers the ANOVA model

Pain Intensity Difference = TRTMT.

The data provide sufficient evidence to claim that there exist differences among the treatment groups. The results of LSMEANS procedure are as follows.

General Linear Models Procedure
Least Squares Means

TRTMT	PID2 LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
IBU 200mg	0.73402482	1	.	0.9113	0.0027
IBU 400mg	0.72307692	2	0.9113	.	0.0036
Placebo	0.43814433	3	0.0027	0.0036	.

These results indicate: (i) The mean PID2 under IBU 200mg is significantly different from that of placebo (p-value = 0.0027), (ii) The mean PID2 under IBU 400mg is significantly different from that of placebo (0.0036) and (iii) The mean PID2 for IBU 200mg is not significantly different from that of IBU 400mg (p-value = 0.9113).

Subgroup analysis for PID2:
The LSMEANS procedure for subjects with severe baseline pain intensity (3) indicates that IBU 200mg is not significantly different from placebo (p-value = 0.3841), and IBU 400mg is different from placebo (p-value = 0.0098). However, the two IBU treatment groups are not significantly different (p-value = 0.094).

4.2 PROTOCOL 97-030

4.2.1 Baseline comparison: Table 16 below contains treatment-wise percentage (and number) of subjects in each category of baseline pain intensity.

Table 16: **Baseline Comparison**

Treatment	Baseline Pain Intensity		Total
	2 (Moderate)	3 (Severe)	
IBU 200 mg	66.67 (144)	33.33 (72)	216
IBU 400 mg	72.15 (158)	27.15 (61)	219
Placebo	71.03 (152)	28.97 (62)	214
Total	454	195	649

The chi-square test indicates that there is no statistically significant association between treatment groups and baseline pain intensity (p-value = 0.421).

4.2.1 Primary efficacy endpoint:
The percentages of response at 2 hours for the 3 treatment groups are presented in Table 17 below. The numbers of subjects in each category are shown in parentheses along with the percentages. There exists a significant association between treatment groups and subject's response at 2 hours (p-value = 0.001).

Table 17: **Summary of Response at 2 Hours**

Treatment	Did Subject Respond at 2 Hours ?		Total
	No	Yes	
IBU 200 mg	60.19 (130)	**39.81** (86)	216
IBU 400 mg	59.36 (130)	**40.64** (89)	219
Placebo	74.30 (159)	**25.70** (55)	214
Total	419	230	649

The CMH, the protocol defined primary analysis of these data stratified by baseline pain intensity indicates a significant association between treatment groups and headache response at 2 hours after medication (p-value = 0.001).

Pair-wise comparison: (i) The CMH test for general association stratified by baseline pain severity for the subset of data consisting IBU 200mg and placebo indicated statistically significant association between treatments and headache response (adjusted p-value = 0.002). (ii) The CMH test for the subset of data consisting of IBU 400mg and placebo indicated statistically significant association between treatments and headache response

(adjusted p-value = 0.002). (iii) However, the CMH test for the subset of data consisting of IBU 200mg and IBU 400mg was not statistically significant (p-value = 0.932).

In addition, the following logistic regression model

$$\text{Logit}(p) = \alpha + \beta_1 \text{ BASEPAIN} + \beta_2 \text{ TRTMT},$$

where p is the probability of headache response is used to compare (i) ibuprofen 200mg vs. placebo and (ii) ibuprofen 400mg vs. placebo. The data indicate the following. The odds of responding to IBU 200mg increased to 2.05-fold that of placebo. The odds of responding to IBU 400mg increased to 1.99-fold that of placebo. However, the odd ratio comparing IBU 400mg with IBU 200mg is 1.38 (p-value = 0.0647). The model based estimates of proportions of patients with mild or no headache pain under placebo and ibuprofen are presented by baseline pain intensity in Table 18 below.

Table 18: **Model based Proportions of Responders**

	IBU 200mg vs. Placebo		IBU 400mg vs. Placebo	
Baseline Pain Intensity	Placebo	IBU 200mg	Placebo	IBU 400mg
2 (Moderate)	0.3064	0.4752	0.2903	0.4486
3 (Severe)	0.1360	0.2440	0.1754	0.2972

4.2.3 Subgroup analysis:

Baseline pain intensity: A total of 454 out of 649 in Study 97-030 reported to have moderate headache pain during the baseline period and the remaining 195 experienced severe headache pain during the baseline period. The data for the subgroup of patients with moderate baseline pain intensity indicated a significant association between treatment groups and headache response at 2 hours (p-value = 0.001). But for the other subgroup, there was no significant association between treatment groups and headache response at hours (p-value = 0.268). That is, for patients with severe headache pain, ibuprofen may not be different from placebo with respect to headache response. In fact, for this subgroup, the chi-squared test for comparing the proportions of headache response under IBU 200mg vs. placebo has a p-value of 0.652. For IBU 400mg vs. placebo it (p-value) is 0.124. The two ibuprofen groups are not significantly different (p-value = 0.248). Table 19 contains the percentages of responders for the three treatment groups under the two subgroups. The number of subjects in various categories are shown in parentheses.

Table 19: **Percentages of Responders**

	Baseline Pain Intensity = 2		Baseline Pain Intensity = 3	
Treatment	No	Yes	No	Yes
IBU 200mg	50.69 (73)	49.31 (71)	79.17 (57)	20.83 (15)
IBU 400mg	55.06 (87)	44.94 (71)	70.49 (43)	29.51 (18)
Placebo	71.30 (108)	28.95 (44)	82.26 (51)	17.74 (11)

Subgroup analysis by center:

The sponsor does not present center-wise subgroup data analysis. However, this reviewer noted the following. The general association statistic in the CMH procedure stratified by

INV (investigator) is highly significant (p-value = 0.001). The Breslow-Day test in the CMH procedure stratified by INV (investigator) does not contradict the assumption of homogeneous odds ratio for the subset of data that includes IBU 200mg and placebo (p-value = 0.172).

Subgroup analysis by Sex: Study 97-030 included 551 females and only 98 males. The data analysis for females suggests a significant association between treatment groups and headache response at 2 hours (p-value = 0.003). For males, with respect to headache response, ibuprofen is not significantly different from placebo (p-value = 0.394). Gender-wise percentages of headache response at 2 hours for the three treatment groups are shown in Table 20 below.

Table 20: **Percentages of Responders**

	FEMALE		MALE	
Treatment	No	Yes	No	Yes
IBU 200mg	60.56 (109)	39.44 (71)	58.33 (21)	41.67 (15)
IBU 400mg	61.29 (114)	38.71 (72)	48.48 (16)	51.52 (17)
Placebo	75.68 (140)	24.32 (45)	65.52 (19)	34.48 (10)

The sponsor reports that approximately 18% females menstruating during the migraine attack and that there were no significant differences between treatment groups.

Subgroup analysis by Race: There were 40 African-Americans, 567 Caucasians and 42 belonged to other ethnic groups. The data for the Caucasians indicate a significant association between the treatment groups and headache response at 2 hours (p-value = 0.003). For the remaining two subgroups, ibuprofen is not significantly different from placebo. Table 21 contains the race-wise percentages of headache response for the 3 treatment groups.

Table 21: **Percentages of Responders**

	African American		Caucasian		Others	
Treatment	No	Yes	No	Yes	No	Yes
IBU 200mg	78.6 (11)	21.4 (3)	59.2 (113)	40.8 (78)	54.6 (6)	45.5 (5)
IBU 400mg	46.7 (7)	53.3 (8)	62.2 (115)	37.8 (70)	42.1 (8)	57.9 (11)
Placebo	72.7 (8)	27.3 (3)	74.9 (143)	25.1 (48)	66.4 (8)	33.3 (4)

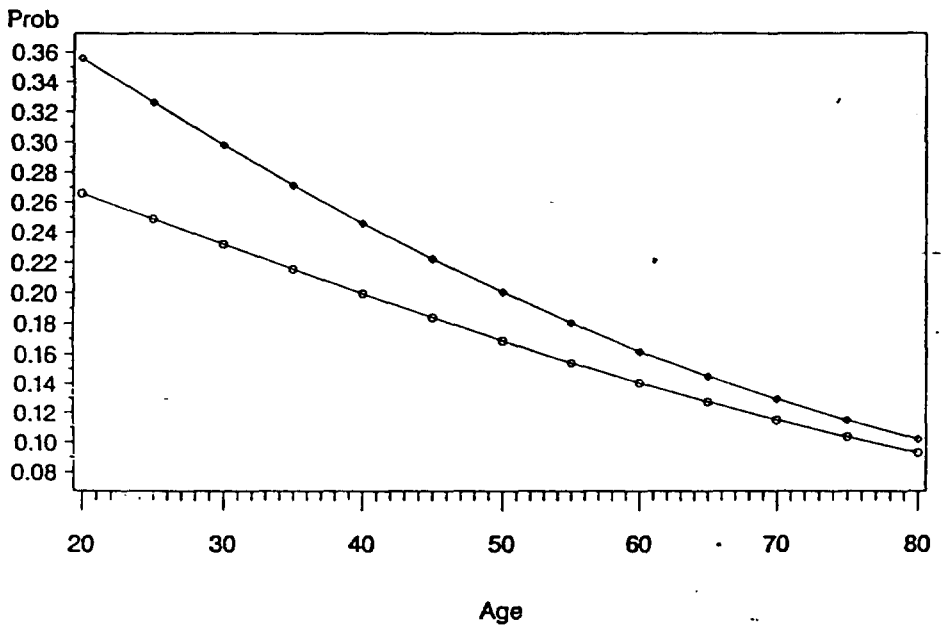
For the Caucasian women with severe (3) baseline headache pain, there is no statistically significant association between the 3 treatment groups and headache response at 2 hours (p-value = 0.728). In addition, it may be pointed out that for this subgroup of subjects, the proportion of desired headache response under IBU 200mg is not higher than that of placebo (p-value = 0.621). Also, IBU 400mg is not better than placebo (p-value = 0.427).

Subgroup analysis by age:
Logistic regression model

$$\text{Logit}(p) = \alpha + \beta_1 \text{ AGE} + \beta_2 \text{ TRTMT},$$

where p is the probability of headache response is used to compare ibuprofen 200mg vs. placebo. The covariate age is significant (p-value = 0.0071). The summary of this model is seen in Figure 2 below. The IBU 200mg treatment group has a higher response rate compared to placebo over the whole range (20, 80) of age. Both treatment groups are less effective for older subjects- close to 80 years of age. For subjects over 50 years of age, the proportions of headache response under IBU 200mg and placebo are not significantly different (p-value = 0.095).

Figure 2: Probability of Response
IBU 200mg vs. Placebo / Study 97-030



4.2.4 Additional Endpoint: Pain Intensity Difference at 2 hours (PID2)
This reviewer considers the ANOVA model: Pain Intensity Difference = TRTMT.
The data provide sufficient evidence to claim that there exist differences among the treatment groups. The results of LSMEANS procedure are as follows.

General Linear Models Procedure
Least Squares Means

TRTMT	PID2 LSMEAN	Pr > |T| HO: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
IBU 200 MG	0.67356902	1	.	0.8306	0.0004
IBU 400 MG	0.65427267	2	0.8306	.	0.0008
PLACEBO	0.34879840	3	0.0004	0.0008	.

These results indicate: (i) The mean PID2 under IBU 200mg is significantly different from that of placebo (p-value = 0.0004), (ii) The mean PID2 under IBU 400mg is significantly different from that of placebo (0.0008) and (iii) The mean PID2 for IBU 200mg is not significantly different from that of IBU 400mg (p-value = 0.8306).

Subgroup analysis for PID2:
The LSMEANS procedure for subjects with severe baseline pain intensity (3) indicates that IBU 200mg is not significantly different from placebo (p-value = 0.7142), and IBU 400mg is not different from placebo (p-value = 0.3312). However, the two IBU treatment groups are also not significantly different (p-value = 0.5201).

4.3 ADDITIONAL ANLYSIS

This additional data analysis was requested by Dr. Armando Oliva on August 24, 1999.
In the following the indicator variable N_P denotes if nausea present or not. N_P = 1 means nausea present and N_P = 0 means otherwise. The variable PN_P indicates whether phonophobia present or not. PN_P = 1 means it is present and PN_P = 0 means it is not present. The variable PT_P denotes whether photophobia present or not. PT_P = 1 means it is present and PT_P = 0 means it is not present The indicator variable MIG denotes whether the patient had a migraine (1=yes, 0=no).

4.3.1 Study 22

The chi-square test for the data for all subjects in Study 22 indicates that there is no significant association between the treatment groups and N_P (p-value = 0.275). The chi-square test for the data for the subgroup of subjects with migraine also indicates that there is no significant association between the treatment groups and N_P (p-value = 0.489).
The chi-square test for the data for all subjects in Study 22 indicates that there is no significant association between the treatment groups and PN_P (p-value = 0.518). The chi-square test for the data for the subgroup of subjects with migraine also indicates that there is no significant association between the treatment groups and PN_P (p-value = 0.635).
The chi-square test for the data for all subjects in Study 22 indicates that there is no significant association between the treatment groups and PT_P (p-value = 0.15). The chi-square test for the data for the subgroup of subjects with migraine also indicates that there is no significant association between the treatment groups and PN_P (p-value = 0.317).

Primary efficacy endpoint for subjects with migraine: A total of 463 subjects (out of 577) were identified to have migraine. The percentages of response at 2 hours for the 3 treatment groups are presented in Table 22 below. The numbers of subjects in each category are shown in parentheses along with the percentages. There does not exists a significant association between treatment groups and subject's response at 2 hours (p-value = 0.164).

Table 22: **Summary of Response at 2 Hours for Subgroup MIG=1**
Study 22

Treatment	Did Subject Respond at 2 Hours ?		Total
	No	Yes	
IBU 200 mg	60.81 (90)	**39.19** (58)	148
IBU 400 mg	60.13 (95)	**39.87** (63)	158
Placebo	69.43 (109)	**30.57** (48)	157
Total	294	169	463

The CMH analysis of these data stratified by baseline pain intensity indicates no significant association between treatment groups and headache response at 2 hours after medication (p-value = 0.159).

4.3.2 Study 30

The chi-square test for the data for all subjects in Study 30 indicates that there is no significant association between the treatment groups and N_P (p-value = 0.833). The chi-square test for the data for the subgroup of subjects with migraine also indicates that there is no significant association between the treatment groups and N_P (p-value = 0.989).
The chi-square test for the data for all subjects in Study 30 indicates that there is significant association between the treatment groups and PN_P (p-value = 0.027). But the chi-square test for the data for the subgroup of subjects with migraine indicates that there is no significant association between the treatment groups and PN_P (p-value = 0.09).
The chi-square test for the data for all subjects in Study 30 indicates that there is significant association between the treatment groups and PT_P (p-value = 0.003). However, the chi-square test for the data for the subgroup of subjects with migraine indicates that there is no significant association between the treatment groups and PN_P (p-value = 0.083).

Primary efficacy endpoint for subjects with migraine: A total of 523 subjects (out of 649) were identified to have migraine. The percentages of response at 2 hours for the 3 treatment groups are presented in Table 23 below. The numbers of subjects in each category are shown in parentheses along with the percentages. There does exists a significant association between treatment groups and subject's response at 2 hours (p-value = 0.006).

Table 23: **Summary of Response at 2 Hours for Subgroup MIG=1**
Study 30

Treatment	Did Subject Respond at 2 Hours ?		Total
	No	Yes	
IBU 200 mg	61.36 (108)	**38.64** (68)	176

IBU 400 mg	61.02 (108)	38.98 (69)	177
Placebo	75.29 (128)	24.71 (42)	170
Total	344	179	523

The CMH analysis of these data stratified by baseline pain intensity indicates significant association between treatment groups and headache response at 2 hours after medication (p-value = 0.004).

Pair-wise comparison for subjects with migraine: (i) The CMH test for general association stratified by baseline pain severity for the subset of data consisting IBU 200mg and placebo indicated statistically significant association between treatments and headache response (adjusted p-value = 0.004). (ii) The CMH test for the subset of data consisting of IBU 400mg and placebo indicated statistically significant association between treatments and headache response (adjusted p-value = 0.01). (iii) However, the CMH test for the subset of data consisting of IBU 200mg and IBU 400mg was not statistically significant (p-value = 0.8).

However, for the subgroup of patients who were identified to have migraine and who had severe baseline pain (PAIN_BAS=3), there does not exist statistically significant association between the treatment groups and headache response at 2 hours (chi-square p-value = 0.157).

5. REVIEWER'S OVERALL CONCLUSIONS

The sponsor concluded that the primary efficacy measures of percent responders at 2 hours were significantly superior to placebo for both ibuprofen 200 mg and 400 mg and that there was no significant difference between the two doses of ibuprofen. These conclusions are in agreement with this reviewer's conclusions:

The primary analysis of the data for Study 97-022 provided sufficient evidence to indicate that Ibuprofen 200 mg and Ibuprofen 400 mg are efficacious compared to placebo for the treatment of pain associated with migraine headache (p-value = 0.003).

The primary analysis of the data for Study 97-030 provided sufficient evidence to conclude that Ibuprofen 200 mg and Ibuprofen 400 mg are efficacious compared to placebo for the treatment of pain associated with migraine headache (p-value = 0.001).

However, Dr. Armando Oliva observed that not all the subjects included in Study 97-022 and Study 97-030 had migraine. He identified the subjects who had migraine and who did not have it. The data for the subgroup of subjects in Study 97-022 having migraine (as identified by Dr. Oliva) did not provide sufficient evidence to support the superiority of ibuprofen 200 mg and ibuprofen 400 mg over placebo (p-value = 0.159). The data for the subgroup of subjects in Study 97-030 having migraine (as identified by Dr. Oliva) provided sufficient evidence to conclude that both doses of ibuprofen are efficacious compared to placebo (p-value = 0.004).

/S/

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Arch. NDA 19-012
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HFD-560 / Kerry Rothschild
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