STATISTICAL REVIEW AND EVALUATION

NDA: 20-626/S-004

Name of Drug : IMITREX (sumatriptan) Nasal Spray

Indication : Addition of adolescent (age 12-17 years) Migraine Patients

Sponsor : Glaxo Wellcome, Inc.

Medical Reviewer : Oliva Armando, M.D. (HFD-120)

I. BACKGROUND

This NDA supplemental application is for revising prescription information to include acute treatment of migraine in adolescent patients (ages 12-17). It is also used to fulfill the requirements in the June 7, 1999 written request.

The original Nasal Spray formulation of sumatriptan was approved for use in adults on August 26, 1997. In general, the sponsor's rationale to select sumatriptan nasal for full treatment development was based on the safety, tolerability, bioavailability, potency, patient acceptance and general ease of use. In addition, they indicated that the shorter time between dosing and headache relief with Sumatriptan nasal spray as compared with tablet made sumatriptan nasal spray a good candidate to treat the adolescent migraineurs since adolescent tends to have shorter duration of migraine attack.

II. PROTOCOL SUMA3005

II.1 Design

This is a double-blind, placebo-controlled, parallel group, single attack, multicenter outpatient study to evaluate three dose levels (5, 10, 20 mg) of sumatriptan nasal spray in the acute treatment of a single migraine attack in adolescent. (12-17 years old). The duration of participation for each patient depended on the migraine frequency and was about 2 weeks to 6 months which include screening visit, treatment phase and exit visit. The treatment phase for each individual patient lasted for approximately 24 hours.

A total of 46 centers in the United States participated in the study. Patients self-administered study medication at home under adult supervision to treat a moderate to severe migraine pain, with other symptoms (nausea, vomiting, photo- or phonophobia) as necessary to meet IHS (International Headache Society) criteria for migraine. Patients were required to enter a diary about the severity and symptoms of the migraine attack

immediately before first dose and 15, 30, 60 and 120 minutes after dose. A second dose/rescue dose can be administered after 2 hours if patients still have moderate or severe pain.

II.2 Efficacy Endpoint

Two efficacy measures were used in the study : a 4-point scale of headache severity (0:no pain; 1: mild pain; 2: moderate pain; 3: severe pain) and the present/absent of migraine-associated symptoms (include nausea, vomiting, photo- or phonophobia).

The primary endpoint is a reduction in headache severity from a baseline severe score of 3 or 2 (severe or moderate pain) to a score of 1 or 0 (mild or no pain) following the first dose of study medication. The primary comparison was made between sumatriptan nasal spray 20 mg versus placebo at 120 minutes after the first dose.

Secondary efficacy endpoint includes:

- The comparison of headache relief /headache-free between all doses at 15, 30,60 and 120 minutes following the first dose of study medication;
- The presence/absence of nausea, vomiting, photophobia, and phonophobia at 15, 30, 60 and 120 minutes;
- Incidence of recurrence of migraine pain (an increase of headache severity score to grade 3 or 2 within 24 hours in those subjects who had headache relief at 120 minutes after first dose) 2-24 hours post dose;
- Use of a rescue medication (a second dose of study medication or other acute migraine medication taken within 24 hours after the initial dose); and
- Headache relief at 120 minutes by subgroup (demographics, migraine history,, and baseline characteristics).

II.3 Analysis Plan

A total of 510 patients were enrolled using a 1:1:1:1 (20 mg: 10mg: 5 mg: placebo) randomization scheme and were treated for a single migraine attack. The sample size calculation was based on assumption that the proportion of subjects with pain relief was 40% for placebo and 60% for 20mg group. Approximately 110 patients per treatment group would provide 80% power to detect a statistically difference between two groups at a significance level of 0.05.

The primary efficacy analysis was based on intent-to-treat (ITT) population. All subjects who used study medication to treat a single migraine attack and returned a diary with evaluable data were included in the intent-to-treat population. In the study report, the sponsor also used the per-protocol population (PP, defined as all ITT subjects who adhered to protocol-specified criteria) for the second efficacy population. A list of

protocol violation criteria which included patients who took rescue medication <2 hours post dose, who did not take study medication within 6 hours of taking analgesics and/or antiemetics, etc., was included in the study report (page 46 of volume 14.6). The safety analysis was based on the safety population that included all patients who received at least one dose of study medication.

According to the protocol, Mantel-Hanszel analysis (MH) was used as the primary analysis to compare the sumatriptan nasal spray 20mg group versus placebo. . No specific stratification factor was mentioned for the MH test in the protocol. The MH method was also used to assess the other secondary efficacy variables including headache relief/ headache free, presence/absence of symptoms, use of rescue medication. Survival analysis was used to compare the time to recurrence of migraine pain 2-24 hours post dose.

In the report, the sponsor used the Cochran-Mantel-Haenszel (CMH) test, adjusted for center effects as the primary analysis. The CMH test was also used for the other secondary efficacy variables as indicated above.

A set of rules with regard to missing data was applied to the efficacy endpoints in the report :

- If missing data occurred in headache severity or associated symptoms, a last observation carried forward strategy was used;
- Post-dose headache pain relief was defined as a headache pain score of 0 or 1 even if baseline severity grade was missing or scored 0 or 1;
- If rescue medication/a second dose was taken after the first dose or if the patient withdrew due to lack of efficacy, then the headache severity grade 3 was assigned immediately following the time of rescue/withdrawal, and the grade was carried over to all subsequent assessment. However, the present/absent of associated symptoms at the time of rescue/withdrawal was carried forward.

The homogeneity of the association of treatment and headache relief among investigators was evaluated using Breslow-Day statistic.

II.4 Sponsor's Results

A total of 653 patients were randomized into this study and 506 of them completed the study (Table I.1). Majority of patients who were prematurely discontinued from the study were attributed to that they did not take the study medication (44%) (Table I.1). 510 of these randomized patients were treated with study medication (131 patients received placebo, 128, 133, 118 received sumatriptan 5mg, 10mg and 20mg respectively) (Table I.2). Among these treated patients, 3 of them did not have efficacy data (Table I.2). In table I.2, number and percentage of patients who were protocol violators, but in ITT population were tabulated (i.e. PP population, n=463).

The distribution of the demographic and migraine history appears to be comparable between treatment groups (Tables I.3). Most patients had a history of migraine without aura (72%) and greater than one year of migraine history at the time of the screening visit (93%). 55% of the patients reported that their average migraine lasted more than 8 hours. There was an unbalanced age group distribution in males. In female, about half of the patients were in 12-14 year-old age group. But in male, the majority of the patients were in younger age group (i.e. 12-14 year-old)

Baseline characteristics of the treated migraine pain also seem to be comparable between treatment groups (Tables I.4). A few minor imbalance was noticed : 12% higher nausea occurrence in 20 mg group than in placebo group, 6% higher occurrence rate of photophobia and phonophobia in placebo than in 20mg group; 5% more patients in 20mg group had moderate pain than did the placebo patients.

The primary efficacy analysis was performed on 507 patients who were in the ITT population. The secondary efficacy analysis on the primary endpoint was also performed on 463 patients who were in PP population. Table I.5 shows that the percentage of patients who achieved pain relief at 120 minutes was 63% which is higher than 53% of placebo patients and the result was marginally significant based on CMH statistic adjusting for centers (p=0.059). The primary comparison was also significant (p=0.047) based on the PP population.

In the evaluation of the percentage of pain relief at the other time points, 10mg and 20mg sumatriptan had significantly higher percentage of pain relief than that of placebo at 60 minutes (p=0.024 and 0.014, respectively) (Table I.5). 5mg sumatriptan was also significantly superior to placebo at 120 minutes (p=0.045).

In the subgroup analysis of the comparison of pain relief rate between groups, the sponsor concluded that no substantial inconsistent results were found in various subgroups (i.e. gender, age, race, weight and menstrual status, Table I.6). The sponsor noted that due to the small number of patients in some categories (e.g. non-white group or pre-menstrual group), no conclusion was made on those results.

The 20 mg group had a significantly higher headache free rate at 120 minutes than did the placebo (p=0.037), but the significant result was not found at the other time points. There were no other significant findings in the comparison of the headache free rate for any of the other dose groups versus placebo.

With respect to the analysis of time to the first pain relief within 120 minutes, the sponsor showed that 20mg, 10mg and 5mg were statistically superior to placebo (p=0.006, 0.007 and 0.049, respectively) (Table I.7).

With regard to associated symptoms, there was no significant treatment difference in the incidence of vomiting or nausea at any time point. The sponsor found a significant lower photophobia in 20mg group than that in placebo at 120 minutes (p=0.025) based on CMH

statistic adjusting for centers. The sponsor also found 20mg group had significantly lower phonophobia incidence than did the placebo at 30, 60, and 120 minutes (p=0.032, 0.023, 0.001, respectively) post dosing.

The sponsor did not have any significant finding based on CMH test, adjusting for centers, in comparing the percentage of patients taking either second dose or rescue medication between each treatment dose level and placebo.

Table I.1
Summary of Subjects Withdrawn Post Randomization
SUMATRIPTAN (mg/ dose)

	Placebo (N= 166)	5 (N = 163)	10 (N=164)	20 (N = 160)	Total (N = 487)	Total (N = 653)
Completed[1]	131 (79%)	126 (77%)	132 (80%)	117 (73%)	375(77%)	506 (77%)
Prematurely Discontinued	35 (21%)	37 (23%)	32 (20%)	43 (27%)	112 (23%)	147 (23%)
Reason for Premature Discontinuation:						
Adverse event	0	0	0	0	0	0
Consent withdrawn	5 (14%)	5 (14%)	4 (13%)	6 (14%)	15 (13%)	20 (14%)
Lost to follow up	2 (6%)	6 (16%)	2 (6%)	3 (7%)	11 (10%)	13 (9%)
Protocol violation	0	0	0	1 (2%)	1 (< 1%)	1 (< 1%)
Sponsor ended study	11 (31%)	9 (24%)	5 (16%)	17 (40%)	31 (28%)	42 (29%)
Subject did not take trial medication	16 (46%)	16 (43%)	20 (63%)	13 (30%)	49 (44%)	65 (44%)
Other	1 (3%)	1 (3%)	1 (3%)	3 (7%)	5 (4%)	6 (4%)

[1] One subject (3215, Placebo) was recorded as completing the study although he never treated with study medication, and is not in the Safety Population. Five subjects treated with study medication before prematurely discontinuing from the study. They are therefore in the Safety Population but are not included in the number of completed subjects. The subject number, treatment, and reason for discontinuation are: 3848, Placebo, consent withdrawn; 3547, 5mg, consent withdrawn; 3839, 5mg, lost to follow up; 4075, 10mg, consent withdrawn; 3361, 20mg, lost to follow up.

Table I.2
Summary of Subject Accountability
SUMATRIPTAN (mg/ dose)

	Placebo (N = 166)	5 (N = 163)	10 (N = 164)	20 (N = 160)	Total (N = 653)
Randomized Subjects	166	163	164	160	653 (100%)
Never treated an attack	35 (21%)	35 (21%)	31 (19%)	42 (26%)	143 (22%)
Subjects in Safety Population	131 (79%)	128 (79%)	133 (81%)	118 (74%)	510 (78%)
No Efficacy Data[1]	1 (< 1%)	1 (< 1%)	0	1 (< 1%)	3 (< 1%)
Subjects in Intent- to- Treat Population[2]	130 (> 99%)	127 (> 99%)	133 (100%)	117 (> 99%)	507 (> 99%)
Grade 0/ 1 baseline headache severity	0	0	0	0	0
Took migraine drugs[3] <= 24 hrs prior	0	0	0	0	0
Took analgesics/ antiemetics <= 6 hrs prior	1 (< 1%)	3 (2%)	1 (< 1%)	1 (< 1%)	6 (1%)
Took rescue meds < 2 hrs after dose	3 (2%)	1 (< 1%)	1 (< 1%)	2 (2%)	7 (1%)
Took second dose < 2 hrs after dose	1 (< 1%)	0	0	0	1 (< 1%)
No efficacy data 1.5- 2.5 hrs postdose	3 (2%)	2 (2%)	9 (7%)	0	14 (3%)
More than 6 hrs from headache to treatment	1 (< 1%)	6 (5%)	2 (2%)	4 (3%)	13 (3%)
No associated symptoms	2 (2%)	1 (< 1%)	1 (< 1%)	1 (< 1%)	5 (< 1%)
Total Excluded Due to Protocol Variations[4]	10 (8%)	12 (9%)	14 (11%)	8 (7%)	44 (9%)
Subjects in Per- Protocol Population[2]	120 (92%)	115 (90%)	119 (89%)	109 (92%)	463 (91%)

[1] Completed diary cards were not available for these subjects.
[2] The denominator for percentages is the number of subjects in the Safety population.
[3] Sumatriptan, ergotamine, or dihydroergotamine
[4] Subjects may have more than one protocol variation.

Table I.3
Summary of Screening Demographics and Migraine History
SUMATRIPTAN (mg/ dose)

	Placebo (N = 131)	(N = 128)	(N = 133)	(N = 118)	Total (N = 510)
		5	10	20	
Age (Years)					
n	131	128	133	118	510
Mean	14.153	14.063	14.038	13.992	14.063
SD	1.619	1.720	1.644	1.577	1.638
Median	14.000	14.000	14.000	14.000	14.000
Min.	12.00	12.00	12.00	12.00	12.00
Max.	17.00	17.00	17.00	17.00	17.00
Sex					
n	131	128	133	118	510
Female	65 (50%)	63 (49%)	73 (55%)	61 (52%)	262 (51%)
Male	66 (50%)	65 (51%)	60 (45%)	57 (48%)	248 (49%)
Females					
n	65	63	73	61	262
< 12 yrs	0	0	0	0	0
12- 14 yrs	28 (43%)	30 (48%)	39 (53%)	28 (46%)	125 (48%)
15- 17 yrs	37 (57%)	33 (52%)	34 (47%)	33 (54%)	137 (52%)
≥ 17 yrs	0	0	0	0	0
Males					
n	66	65	60	57	248
< 12 yrs	0	0	0	0	0
12- 14 yrs	47 (71%)	49 (75%)	46 (77%)	42 (74%)	184 (74%)
15- 17 yrs	19 (29%)	16 (25%)	14 (23%)	15 (26%)	64 (26%)
17 yrs	0	0	0	0	0
Race					
n	131	128	133	118	510
White	119 (91%)	117 (91%)	119 (89%)	107 (91%)	462 (91%)
Black	5 (4%)	4 (3%)	9 (7%)	4 (3%)	22 (4%)
Asian	1 (< 1%)	1 (< 1%)	1 (< 1%)	0	3 (< 1%)
American Hispanic	6 (5%)	5 (4%)	4 (3%)	5 (4%)	20 (4%)
Other	0	1 (< 1%)	0	2 (2%)	3 (< 1%)

Table I.3
Summary of Screening Demographics and Migraine History
SUMATRIPTAN (mg/ dose)
(Continued)

	Placebo (N= 131)	(N= 128)	(N= 133)	(N= 118)	Total (N= 510)
		5	10	20	
Migraine history					
n	131	128	133	118	510
with aura	17 (13%)	14 (11%)	12 (9%)	17 (14%)	60 (12%)
without aura	94 (72%)	89 (70%)	97 (73%)	88 (75%)	368 (72%)
both with and without aura	20 (15%)	25 (20%)	24 (18%)	13 (11%)	82 (16%)
Duration of migraine					

n	131	128	133	118	510
6 months to 1 yr	8 (6%)	5 (4%)	16 (12%)	6 (5%)	35 (7%)
> one year	123 (94%)	123 (96%)	117 (88%)	112 (95%)	475 (93%)
Avg migraine attack duration					
n	131	128	133	118	510
4- 8 hours	61 (47%)	56 (44%)	61 (46%)	49 (42%)	227 (45%)
>8 hours	70 (53%)	72 (56%)	72 (54%)	69 (58%)	283 (55%)
Sumatriptan use					
n	130	125	132	118	505
None	75 (58%)	79 (63%)	80 (61%)	66 (56%)	300 (59%)
Any formulation	54 (42%)	46 (37%)	51 (39%)	52 (44%)	203 (40%)
Oral 100mg	0	1 (< 1%)	0	0	1 (< 1%)
Oral 50mg	10 (8%)	16 (13%)	15 (11%)	14 (12%)	55 (11%)
Oral 25mg	35 (27%)	24 (19%)	36 (27%)	32 (27%)	127 (25%)
Subcutaneous	8 (6%)	6 (5%)	8 (6%)	10 (8%)	32 (6%)
Intranasal	2 (2%)	6 (5%)	4 (3%)	3 (3%)	15 (3%)
Suppository	0	0	0	0	0
Other 5- HT1 agonists	10 (8%)	9 (7%)	5 (4%)	9 (8%)	33 (7%)
Weight (kg)					
n	131	128	133	118	510
< 50	40 (31%)	32 (25%)	39 (29%)	43 (36%)	154 (30%)
>= 50	91 (69%)	96 (75%)	94 (71%)	75 (64%)	356 (70%)

Table I.4
Summary of Baseline Characteristics of the Treated Migraine
SUMATRIPTAN (mg/ dose)

				Total
	(N= 127)	(N= 133)	(N= 117)	(N= 507)
Pain Severity	5	10	20	
n	127	133	117	507
Moderate	79 (62%)	86 (65%)	82 (70%)	332 (65%)
Severe	48 (38%)	47 (35%)	35 (30%)	175 (35%)
Time to Treatment (Hours)	130			
n	85 (65%)	127	133	117	507
Mean	45 (35%)	2.088	1.899	1.959	1.909
SD	130	1.997	1.649	2.269	1.888
Median	1.701	1.567	1.667	1.333	1.367
Min.	1.612	0	0	0	0
Max.	1.100	10.17	7.00	18.30	18.30
Time to Treatment (Hours)	0				
Placebo	6.83	127	133	117	507
0 - <2 (N= 130)		71 (56%)	77 (58%)	77 (66%)	309 (61%)
2 - <4	130	37 (29%)	41 (31%)	26 (22%)	133 (26%)
4+	84 (65%)	19 (15%)	15 (11%)	14 (12%)	65 (13%)
Aura	29 (22%)				
n	17 (13%)	127	133	116	506
	130				

Yes	22 (17%)	17 (13%)	19 (16%)	89 (18%)	
No	105 (83%)	116 (87%)	97 (84%)	417 (82%)	
Nausea					
n	127	132	117	506	
Yes	58 (46%)	65 (49%)	60 (51%)	234 (46%)	
No	69 (54%)	67 (51%)	57 (49%)	272 (54%)	
Vomiting					
n	126	131	116	503	
Yes	4 (3%)	5 (4%)	9 (8%)	24 (5%)	
No	122 (97%)	126 (96%)	107 (92%)	479 (95%)	
Photophobia					
n	127	132	117	506	
Yes	111 (87%)	110 (83%)	98 (84%)	436 (86%)	
No	16 (13%)	22 (17%)	19 (16%)	70 (14%)	
Phonophobia					
n	127	132	117	506	
Yes	104 (82%)	100 (76%)	90 (77%)	402 (79%)	
No	23 (18%)	32 (24%)	27 (23%)	104 (21%)	

Table I.5
Summary of Headache Relief Rates Within 120 Minutes Post First Dose - Intent to Treat Population

				Comparison P- values[1]					
				PBO vs	PBO vs	5 vs	5 vs	10 vs	
SUMATRIPTAN (mg/ dose)	Placebo (N= 130)	5 (N= 127)	10 (N= 133)	20 (N= 117)	5	10	20	10	20	20
No. of Subjects with Headache Relief at Post- Dose Time:					PBO vs					
15 minutes	11 (8%)	14 (11%)	18 (14%)	20 (17%)	NS	NS	0.054	NS	0.136	NS
30 minutes	33 (25%)	32 (25%)	44 (33%)	39 (33%)	NS	0.107	0.089	NS	0.148	NS
60 minutes	53 (41%)	60 (47%)	74 (56%)	66 (56%)	NS	0.024	0.014	NS	NS	NS
120 minutes	69 (53%)	84 (66%)	85 (64%)	74 (63%)	0.045	0.107	0.059	NS	NS	NS
No. of Subjects with Headache Relief within 120 Minutes	74 (57%)	89 (70%)	95 (71%)	84 (72%)						
Median Minutes to First Relief [2]	[3]	60	60	60						

Note: Headache severity is defined on a four- point scale (0= no pain, 1= mild pain, 2= moderate pain, 3= severe pain). Headache relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain).

[1] P- values are based on the Cochran-Mantel-Haenszel test adjusted for investigator.

[2] Subjects who took second medication or had second dose of study medication were considered to have headache severity grade 3 from that point forward.

[3] P- values > 0.15 are denoted as NS.

[2] Among subjects who report headache relief within 120 minutes.

Table I.6
Summary of Headache Relief Rates at 120 Minutes Post First Dose by Subgroup Factors

	Placebo (N=130)	SUMATRIPTAN (mg/ dose) 5 mg (N=127)	10 mg (N=133)	20 mg (N=117)
Sex				
Female	31 (48%)	41 (66%)	44 (60%)	37 (61%)
Male	38 (58%)	43 (66%)	41 (68%)	37 (66%)
Race				
White	63 (53%)	76 (66%)	77 (65%)	66 (62%)
Black	2 (40%)	3 (75%)	5 (56%)	3 (75%)
Asian	0	0		0
American Hispanic	4 (67%)	4 (80%)	2 (50%)	3 (60%)
Other	0	1 (100%)	0	2 (100%)
Age (years)			1 (100%)	
12- 14 yrs	41 (55%)	56 (72%)	59 (69%)	44 (63%)
15- 17 yrs	28 (50%)	28 (57%)	26 (54%)	30 (64%)
Weight (kg)				
< 50	18 (46%)	23 (72%)	27 (69%)	28 (65%)
>= 50	51 (56%)	61 (64%)	58 (62%)	46 (62%)
Menarcheal status				
Potentially able to bear children	29 (51%)	39 (68%)	35 (56%)	29 (57%)
Premenarche	2 (29%)	2 (40%)	9 (82%)	8 (80%)

Note: Headache relief is defined as a reduction of headache severity from grade 2 or 3 (moderate or severe pain) to grade 1 or 0(mild or no pain). Percentages are the percent of subjects in each subgroup who achieved headache relief at 120 minutes post first dose.

Table I.7
Estimated Probability of Achieving Initial Headache Response Within 120 Minutes

Comparison	(mins)	Comparator 1 N	Comparator 1 n	Comparator 1 cum %	Comparator 2 N	Comparator 2 n	Comparator 2 cum %	Hazards Ratio Ratio	Hazards Ratio 95% CI	Log- rank p- value
20mg vs PBO		117	20	17.09	130	11	8.46			
	15	97	20	34.19	119	23	26.15			
		77	31	60.68	96	19	40.77			
		30	13	71.79	49	21	56.92	1.14	1.02 - 1.26	0.006
10mg vs PBO		133	18	13.53	130	11	8.46			
	15	115	28	34.59	119	23	26.15			
		87	33	59.40	96	19	40.77			
		35	16	71.43	49	21	56.92	1.20	1.03 - 1.40	0.007
5mg vs PBO	15	127	14	11.02	130	11	8.46			
		113	20	26.77	119	23	26.15			
		93	31	51.18	96	19	40.77			
		43	24	70.08	49	21	56.92	1.31	0.96 - 1.79	0.049

Time
Comparator 1
30
60
120
30
60
120
30
60
120

Note: Estimates are from survival analysis procedures.
N = Number of subjects who have not obtained relief or been censored.
n = Number of subjects with first report of headache relief within the time interval.
cum % = Cumulative percent of subjects with headache relief.

III. REVIEWER'S EVALUATION AND COMMENTS

This reviewer had confirmed the sponsor's primary efficacy result on the comparison of the proportion of patients with pain relief at 120 minutes between 20mg sumatriptan and placebo. However, this reviewer found that the primary result was not robust based on this reviewer's calculation.

This reviewer noticed that two patients from placebo group (patient 3331 from site 4251 and patient 3465 from site 6118) were classified as failures at 120 minutes **in the sponsor's report** since they took rescue medication /second dose before hour two after dose. But they both obtained a mild pain score at 120 minutes from which they were supposed to be counted as success **based on the protocol definition**. This reviewer believes that counting the placebo patients as failure due to taking rescue medication would favor the active treatment. Placebo patients were known to be more likely to take the rescue medication during the treatment phase, so it further biased in favor of the treatment effect. Note that there were four placebo patients who took rescue medication/second dose before hour 2 after dose (patient 3331 took two doses within 2 hours, while patient 3465 used the rescue medication one hour after dosing), while only two patients from 20mg sumatriptan group did that. Those two sumatriptan treated patients who took rescue medication/second dose before hour two were both non-responder at hour two. This reviewer counted these two placebo patients as winners according to the protocol definition, performed the CMH test adjusting for center and obtained p-value=0.088 which was not statistical significant (Table II.1).

The sponsor indicated that the MH test will be used for the primary efficacy analysis in the protocol, but did not specify the stratification factor for the MH test. In the report, the sponsor performed the analysis and stratified by center which, although was consistent with the method used in one of the previous trial (e.g. protocol S2b-340), may result in an ambiguous result. In protocol S2b-340, the patient allocation was stratified by center, while in this study, the treatment assignment was in accordance with the randomization schedule that was allocated centrally (study report, volume 6-24, page 28). There were maximum of 13 patients, minimum of 1 patient, with a median of 5 in a center for 20 mg and placebo subgroup in the ITT population. Most of the treatment allocations within the centers were unbalanced. It is known that the adjustment for center is to provide a more accurate estimate of the treatment effect in the presence of unbalance in the treatment allocation between centers. However, it may introduce a spurious result in the case of many centers with very small sample size in each center unless a pooling scheme was predetermined prior to data unblinding.

Table II.1 shows the p-values using the sponsor's and reviewer's created pain relief endpoint based on stratified or un-stratified analyses. The stratified analysis based on CMH was the sponsor's primary analysis method specified in the protocol. This reviewer's un-stratified analysis using the χ^2 statistic was used to show the inconsistency of the primary result which seems to depend on whether the center was adjusted for or

not. Note that the analyses based on the sponsor's and the reviewer's created variables using the per-protocol population achieved the same results.

Table II.1 P-values of Comparing 20 mg Sumagriptan versus Placebo at Various Time, With or Without Stratification ‡

Stratification Status	Time (Hours post dosing) (In minutes)	Sponsor created pain relief endpoint (ITT)	Sponsor created pain relief endpoint (per-protocol)	Reviewer Created Pain relief Endpoint (ITT)
Stratified	15	0.054	0.102	0.054
	30	0.089	0.115	0.089
	60	0.014	0.020	0.014
	120	0.059	0.047	0.088
Un-stratified	15	0.041	0.065	0.041
	30	0.171	0.232	0.171
	60	0.014	0.030	0.014
	120	0.107	0.096	0.170

Note : ‡ : P-values were based on Cochran-Mantel-Haenszel Chi-square statistic adjusting for center in the stratified analysis
P-values were based on Chi-square statistic for two by two tables in the un-stratified analysis

IV. SUMMARY

The sponsor found a marginal significant result of pain relief for sumatriptan 20 mg group at 120 minutes (p=0.059). The primary results seem consistent across different subgroups, such as age and gender. The lower associated symptoms (photophobia and phonophobia) were also found for the sumatriptan 20 mg group at 120 minutes (p=0.025 and 0.032 for photophobia and phonophobia, respectively).

However, this reviewer showed that the sponsor's primary result was not robust. The result became non-significant when two patients who took rescue medication/second dose were classified according to the protocol specification (p=0.088). In addition, the issue about many centers with very small sample size also posed a dilemma in the analyses which result in an inconsistent conclusion. Therefore, in this reviewer's judgement, the sponsor's primary result was inconclusive.

Yuan-Li Shen, Dr. PH
Mathematical Statistician

Concur :

Dr. Jin Dr. Chi

CC:
NDA: 20-764/S-002; 20-241/S-008
HFD-120/Dr. Katz
HFD-120/Dr. Oliva
HFD-120/Ms. Chen
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Shen

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/s/

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Kun Jin
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George Chi
11/6/00 09:35:44 AM
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