CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-001

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA:	21-001
Name of Drug:	Almotriptan malate tablet
Indication:	Acute Migraine
Sponsor:	Pharmacia & Upjohn
Documents Reviewed:	Vols 1-3 & 96-204
Study Reviewed:	M/31416/12R, M/31416/13, M/31416/14
Related IND:	[redacted]

AUG 3 1 2000

1. BACKGROUND

Three phase III multi-center, double-blind, randomized, placebo- and/or active-control, parallel-group, efficacy and safety clinical trials have been conducted using almotriptan (LAS) in the treatment of acute migraine. Study M/3275/0008 was a active-control trial which included only almotriptan 12.5 mg and sumartriptan 50 mg groups in the trial for comparisons. The other two controlled phase III studies were M/31416/13 and M/31416/14 of which were designed to compare treatment effect between almotriptan and placebo. This report is to focus on the results from the latter two studies for drug efficacy.

In addition, a phase II study, M/31416/12, had a large number of treated subjects (N=742) and had a double-blind, placebo-controlled, parallel-group design. The Medical Division decided to include this phase II trial for efficacy review as well.

The three studies reported in this review were quite different in study design. Thus, this review is to discuss each study individually in later sections.

2. Study M/31416/12

The objective of the study was to assess the efficacy and safety of LAS 31416 (Almotriptan) by the oral route at does of 2, 6.25, 12.5 and 25 mg in migraine patients, to compare them with placebo, and to determine the minimum effective dose as a dose-finding study.

2.1.1 Primary efficacy measure: The primary efficacy variable was defined as being the number of migraine attacks resolved at 2 hours after intake of the test medication without the use of escape medication. An attack was considered resolved in case the pain severity had decreased from moderate/severe to mild/none. The primary efficacy variable was to be analyzed using the Cochran-Mentel-Haenszel (CMH) test.

2.1.2 Secondary efficacy measures: The secondary efficacy variables included reduction of migraine pain at 1 hour, pain free at 1 and 2 hours, pain intensity difference at 2 hours, duration of first migraine attack, presence of the associated symptoms (nausea, vomiting, photophobia, phonophobia) at 2 hours, and occurrence of relapses.

2.2 Disposition of patients

A total of 948 patients were screened from 103 centers by 105 investigators for this study, and 903 of them were randomized into either placebo or one of four treatment groups. Table 2.1 shows the distribution of patients among those five test medication groups. The number of patients recruited was similar to the planned in the protocol. Consequently, 742 patients were treated. Among those, 725 patients completed the study. The number of patients that withdrawn did not differ between treatment groups.

Table 2.1. Distribution of Patients, by Treatment Groups

	Placebo	LAS 2 mg	LAS 6.25 mg	LAS 12.5 mg	LAS 25 mg	Total
Randomized	99	209	201	194	200	903
Treated	80	170	167	164	161	742
Completed	79	165	162	162	157	725

The assessment of efficacy was based on the intent-to-treat (ITT) population. The majority of ITT population were female (85.2%) and Caucasian (99.5%).

Demographics and baseline characteristics, such as gender, age, baseline severity, presence of aura, for the ITT population is presented in Table 2.2. All the variables did not significantly differ among the treatment groups.

Table 2.2. Demographic and Baseline Characteristics, by Treatment Group

	Placebo (N=80)	LAS 2 mg (N=170)	LAS 6.25 mg (N=167)	LAS 12.5 mg (N=164)	LAS 25 mg (N=161)
Gender					
Female	69 (86.3%)	144 (84.7%)	144 (86.2%)	137 (83.5%)	138 (85.7%)
Male	11 (13.8%)	26 (15.3%)	23 (13.8%)	27 (16.5%)	23 (14.3%)
Mean age (yrs)	39.4 ± 12.2	41.0 ± 9.7	40.9 ± 9.4	41.2 ± 10.9	41.5 ± 11.6
Baseline severity (%)					
Severe	38.8%	42.9%	40.7%	39.6%	46.0%
Moderate	61.3%	57.1%	58.7%	60.4%	54.3%
% patients with the associated symptoms					
Nausea	65.0%	70.0%	63.5%	72.0%	69.6%
Photophobia	75.0%	75.9%	71.3%	75308	68.3%
Phonophobia	53.8%	61.2%	55.1%	53.7%	61.5%
% with aura presence	26.3%	17.1%	20.4%	20.7%	23.0%

Note: One patient of LAS 25 mg group had mild baseline severity.

2.3 Primary Efficacy Results:

The percentage of patients with reduction of migraine pain at 2 hour after intake of medication for placebo group was 32.5%. Pairwise comparisons results between placebo and each dose of LAS showed that the four higher dose groups were significantly different from placebo (all $p<0.001$), except the 2 mg dose group ($p=0.7692$).

The ITT analysis of the number and percentage of migraine attacks resolved at 2 hours adjusted for baseline pain severity presented the same pattern for pairwise comparisons. Table 2.3 presents the response rate for each group and by the baseline severity subgroup.

Table 2.3. Response Rates at 2 Hours after Intake of Medication, Overall and by Baseline Severity

	Placebo (N=80)	LAS 2 mg (N=170)	LAS 6.25 mg (N=167)	LAS 12.5 mg (N=164)	LAS 25 mg (N=161)
Overall	26 (32.5%)	51 (30.0%)	94 (56.3%)	96 (58.5%)	107 (66.5%)
Baseline severity (%)					
Severe	21 (42.9%)	32 (33.0%)	62 (63.3%)	66 (66.7%)	65 (75.6%)
Moderate	5 (16.3%)	19 (26.0%)	32 (47.1%)	30 (46.2%)	42 (56.8%)

2.4 Secondary Efficacy Results:

2.4.1. Migraine pain severity score: The migraine pain severity scores at baseline, 0.5, 1, 1.5, 2 and 24 hours were collected. Groups did not differ at baseline, nor at 0.5 hours after treatment. All other differences between treatment groups were statistically different with $p<0.001$.

2.4.2. Migraine attacks resolved: The number and percentage of migraine attacks resolved increased over time. The CMH statistics was significant at 1, 1.5, and 2 hours after treatment (all $p < 0.001$), but not at 0.5 hours.

2.4.3. Migraine attacks ended: The number and percentage of migraine attacks that had ended increased over time. The increase was dose-dependent with significant difference at 1, 1.5 and 2 hours after treatment (all $p < 0.001$), but not at 0.5 hours.

2.4.4. Relapses: The percentages of relapses for patients whose first attack had resolved 2 hours after intake of the test medication ranged between 25.2% and 28.7%. Those were not significant different between treatment groups (all $p >0.1$).

2.4.5. Migraine related symptoms: Nausea, photophobia and phonophobia are most occurred migraine associated symptoms. Table 2.4 presents the relief of the three symptoms 2 hours after intake of medication. The ranges of occurrence at baseline for those symptoms were 63.5%-72.0%, 68.3%-75.9% and 53.7%-61.5%, respectively. There were no statistical differences at baseline between treatment groups. However, the relief of migraine associated symptoms increased dose-dependently for all three symptoms, as indicated by CMH tests (all $p < 0.001$).

Table 2.4. Relief of Migraine Related Symptoms after 2 Hours
(Reproduced from sponsor's submission)

Symptom Change from Baseline	Placebo (N=80)	LAS 2 mg (N=170)	LAS 6.25 mg (N=167)	LAS 12.5 mg (N=164)	LAS 25 mg (N=161)
Nausea					
Better	23.8%	24.1%	39.5%	42.1%	42.2%
Equal	67.5%	68.2%	54.5%	48.8%	47.8%
Worse	6.3%	4.7%	4.2%	6.1%	5.6%
Missing	2.5%	2.9%	1.8%	3.0%	4.3%
Photophobia					
Better	26.3%	24.1%	44.3%	45.7%	44.1%
Equal	70.0%	72.9%	53.9%	50.6%	49.7%
Worse	1.3%	0.0%	0.0%	0.6%	1.9%
Missing	2.5%	2.9%	1.8%	3.0%	4.3%
Phonophobia					
Better	16.3%	20.0%	34.7%	31.1%	39.8%
Equal	77.5%	75.3%	62.9%	64.0%	54.0%
Worse	3.8%	1.8%	0.6%	1.8%	1.9%
Missing	2.5%	2.9%	1.8%	3.0%	4.3%

2.4.6. Pain intensity difference (PID): The difference between the pain intensity at the different assessment times and the pain intensity at baseline was decrease dose-dependently at all assessment times ($p = 0.0081$ at 0.5 hours, $p < 0.001$ at other assessment times).

2.5 Reviewer's Comments

1. This reviewer reanalyzed the data submitted along with the NDA 21-001 and agreed with the sponsor's reported results. It was true for both primary and secondary efficacy outcomes.

2. **Multiplicity:** This is a phase II study. There were 4 almotriptan treatment groups and placebo to assess the efficacy of almotriptan with different level of dose in the treatment of acute migraine. With consideration of multiplicity, the treatment groups with dose of almotriptan 6.25, 12.5 and 25 mg had statistically significant higher relief rates than placebo after a conservative adjustment using Bonferroni method.

3. **Percentage of migraine attacks resolved at 2 hours by country:** Table 2.5 shows the response rate of treatment at 2 hours after intake of test medication. The sponsor suggested the deviating results obtained in Portugal, Estonia and Denmark (the last 3 countries in the table) are most probably due to the insufficient sample sizes in those countries.

Table 2.5. Percentage of migraine attacks resolved at 2 hours by country

Country (N)	Placebo (N=80)	LAS 2 mg (N=170)	LAS 6.25 mg (N=167)	LAS 12.5 mg (N=164)	LAS 25 mg (N=161)
Germany (198)	47.8%	36.0%	68.3%	66.7%	74.4%
Poland (114)	40.0%	44.0%	57.1%	66.7%	75.0%
Hungary (109)	16.7%	29.2%	58.3%	56.5%	65.4%
Sweden (82)	28.6%	11.1%	61.9%	55.0%	81.3%
UK (80)	16.7%	30.8%	50.0%	58.8%	70.0%
Netherlands (63)	25.0%	14.3%	30.8%	52.9%	26.7%
France (36)	25.0%	27.3%	25.0%	50.0%	85.7%
Portugal (29)	66.7%	25.0%	66.7%	20.0%	42.9%
Estonia (24)	0.0%	40.0%	57.1%	25.0%	60.0%
Denmark (7)	50.0%	0.0%	0.0%	--	0.0%

2.6. Summary of Study M/31416/12

This study demonstrated the superiority of almotriptan effect to placebo in the treatment of acute migraine for the 6.25, 12.5, 25 mg groups.

3. Study M/31416/13

The objectives of this study were to assess the efficacy and safety of LAS 12.5 and 25 mg in acute migraine patients, and to compare it with the treatment of sumatriptan and placebo.

Primary efficacy was assessed by measuring migraine pain relief from severe/moderate to mild/pain free at 2 hours after initial dosing. **Secondary efficacy variables** included pain free within 2 hours after initial dosing, use of escape medication, relief of nausea, vomiting, photophobia and phonophobia, time between test drug intake and end of the attack, time between test drug intake and amelioration of pain, duration of the attack, relapse of the attack within 24 hours after the initial dose, relief of pain after treating the relapse.

The analyses were performed on an intention-to-treat (ITT) basis. Every patient who had been randomized, had received the study medication, and had recorded at least one measurement of efficacy after this point, was included in the ITT analysis. The primary efficacy analysis, which was addressed in the protocol, was to compare placebo with active drugs (best dose of LAS and sumatriptan) by using a Fisher's Exact Test.

3.1 Patients disposition:

A total of 794 patients were screen for this study, and 668 treated patients were evaluated. Those patients were in placebo, 12.5 mg LAS, 25 mg LAS and 100 mg sumatriptan in a ratio of 1:2:2:2. Specifically, after excluding 2 patients who did not have baseline headache pain measure, 99 patients were in placebo group, 183 patients in 12.5 mg LAS group, 191 patients in 25 mg LAS group, and 193 patients in 100 mg sumatriptan group.

Female patients consisted of the majority of the ITT population (84.9%). The mean ages for the four treatment groups were 40 to 43 years. The distributions of gender, baseline severity and aura presence were similar among those four groups. Those demographic data for each group are shown in Table 3.1.

Table 3.1. Demographic data for the Four Treatment Groups

	Placebo	LAS 12.5 mg	LAS 25 mg	Sumatriptan
Gender				
Male	11 (11.1%)	26 (14.1%)	32 (16.6%)	32 (16.5%)
Female	88 (88.9%)	158 (85.9%)	159 (83.2%)	162 (83.5%)
Mean Age (years)	40.16 ± 10.10	42.78 ± 10.70	41.45 ± 10.99	42.05 ± 10.47
Baseline Severity				
Moderate	67 (67.7%)	93 (50.5%)	105 (55.0%)	111 (57.2%)
Severe	32 (32.3%)	90 (48.9%)	86 (45.0%)	82 (42.3%)
Aura Present				
No	78 (78.8%)	142 (77.2%)	146 (76.4%)	155 (79.9%)
Yes	21 (21.2%)	41 (22.3%)	45 (23.6%)	38 (19.6%)

3.2.1 Primary efficacy results: The response rate at 2 hour after initial intake of drug and the 95% confidence interval are shown in Table 3.2 for each treatment group. Both 12.5 mg and 25 mg LAS groups had 56.5% patients response to drug effect. The 95% confidence intervals for those two groups did not show a significant difference from placebo group at 0.05 level.

Table 3.2. Response rate and 95% Confidence Interval at 2 Hour after the Initial Treatment

	Placebo	LAS 12.5 mg	LAS 25 mg	Sumatriptan
Response at 2 Hour No Yes	 57 (57.6%) 42 (42.4%)	 79 (42.9%) 104 (56.5%)	 83 (43.5%) 108 (56.5%)	 70 (36.1%) 123 (63.4%)
Lower 95% Limit	34.01%	50.19%	50.34%	57.33%
Upper 95% Limit	51.19%	62.69%	62.60%	69.16%

Table 3.3 shows the reduction of migraine headache pain at 2 hours after intake of test medication for moderate and severe baseline severity separately. As could be expected, the response rate was higher if the baseline headache was moderate.

Table 3.3. Reduction of Migraine Headache Pain at 2 Hour, by Baseline Severity

Moderate Baseline Headache	Placebo	LAS 12.5 mg	LAS 25 mg	Sumatriptan
Response at 2 Hour No Yes	 36 (53.7%) 31 (46.3%)	 26 (28.0%) 67 (72.0%)	 35 (33.3%) 70 (66.7%)	 29 (26.1%) 82 (73.9%)
Lower 95% Limit	35.79%	63.39%	58.33%	66.13%
Upper 95% Limit	57.00%	79.61%	74.28%	80.63%

Severe Baseline Headache	Placebo	LAS 12.5 mg	LAS 25 mg	Sumatriptan
Response at 2 Hour No Yes	 21 (65.6%) 11 (34.4%)	 53 (58.9%) 37 (41.1%)	 48 (55.8%) 38 (44.2%)	 41 (50.0%) 41 (50.0%)
Lower 95% Limit	20.62%	32.35%	35.06%	40.43%
Upper 95% Limit	50.42%	50.32%	53.62%	59.57%

3.3. Secondary efficacy Results

3.3.1. Reduction of migraine pain after 1 hour: The response rates of reduction of migraine pain after 1 hour were 29.3%, 35.3%, 30.9%, and 37.6% for placebo, 12.5 mg LAS, 25 mg LAS, and sumatriptan groups, respectively. The sponsor concluded that there was no considerable difference between the four groups after 1 hour.

3.3.2. Pain-free after 1 and 2 hours: After 1 hour, all treatments failed to show any relevant efficacy, and no difference between the treatment group. After 2 hours, the number of patients of the placebo without migraine pain was distinctly lower. The percentage of pain free at 2 hours were 15.2%, 27.7%, 34.6% and 33.5% for placebo, 12.5 mg LAS, 25 mg LAS, and sumatriptan groups, respectively.

3.3.3. Duration of the first migraine attack: The mean duration of the migraine attack were 17.33, 13.26, 12.48, and 12.88 hours for placebo, 12.5 mg LAS, 25 mg LAS, and sumatriptan groups, respectively. The placebo group shows considerably longer duration of first migraine attacks.

3.3.4. Use of escape medication: The patients of the placebo took the escape medication most frequently. The percentage of patients taking escape medication were 55.5%, 38.6%, 38.2% and 32.4% for placebo, 12.5 mg LAS, 25 mg LAS, and sumatriptan groups, respectively.

3.3.5. Relief of nausea, photophobia and phonophobia: Table 3.4 shows the occurrence of migraine-associated symptoms, nausea, photophobia and phonophobia, at the baseline and after 2 hour. At the baseline, 436 patients (65.3%) suffered from nausea, 388 patients (58.1%) from photophobia, and 323 patients (484.4%) from phonophobia. There were no significant differences between the four groups at the baseline for all three symptoms.

After intake, the symptoms usually decreased in all groups, but for the placebo group, the decrease in frequency is **not marked** as for the treatment groups, where no relevant differences were found.

Table 3.4. Percentage of Patients with Nausea, Photophobia and Phonophobia at the Baseline And 2 Hours after Intake

Time Point	Placebo	LAS 12.5 mg	LAS 25 mg	Sumatriptan
Baseline				
Nausea	67 (67.7%)	125 (67.9%)	118 (61.8%)	126 (64.9%)
Photophobia	58 (58.6%)	110 (59.8%)	113 (59.2%)	107 (55.2%)
Phonophobia	52 (52.5%)	84 (45.7%)	95 (49.7%)	92 (47.4%)
2 Hr after Intake				
Nausea	43 (43.4%)	59 (32.1%)	57 (29.8%)	60 (30.9%)
Photophobia	37 (37.4%)	49 (26.6%)	53 (27.7%)	48 (24.7%)
Phonophobia	33 (33.3%)	37 (20.1%)	44 (23.0%)	34 (17.5%)

3.3.6. Occurrence of relapses: The relapse is defined as "another migraine attack within 24 hours only in responders who had taken escape medication." The percentages of relapse for placebo, 12.5 mg LAS, 25 mg LAS, and sumatriptan groups were 19.5%, 18.0%, 15.4% and 24.5%, respectively. Sumartriptan group had the highest rate of relapse.

3.4. Reviewer's Comments:

1. With the entire data set of which submitted by the sponsor, this reviewer compared the relief rates between two almotriptan treatment groups with placebo using the Cochran-Mentel-Haenszel test. The overall p-value was 0.044. Both 12.5 and 25 mg LAS groups had significantly higher relief rate after 2 hours of the intake (p=0.021 and p=0.023, respectively). With the consideration of multiplicity, the two LAS treatment groups were still significant.

2. The DSI of the FDA found a problematic site of this study. The investigator of this site was Dr. Ingo Zintzsch (center code #205). Two recommendations were provided by the DSI: (1) To reject the data from the diaries for 11 subjects and to reject the screening chloride laboratory results for nine subjects since entries in these diaries and these particular lab results could not be validated; and (2) Alternatively, to reject all of the data from this site.

A total of 44 subjects among ITT population were recruited from that center. This reviewer removed the site that identified by the DSI and reanalyzed the data. Using the Chi-square test, both 12.5 and 25 mg LAS groups became more significant than before removing the center #205, i.e. LAS treatment groups had significantly higher relief rate after 2 hours of the intake (p=0.007 and p=0.013, respectively).

Instead of removing the entire center #205 from data set, data analysis was conducted with excluding those 12 subjects identified by the DSI. The results were similar to those without excluding those problematic data. Both 12.5 and 25 mg LAS groups had significantly higher relief rate after 2 hours of the intake (p=0.018 and p=0.022, respectively).

3. The sponsor acknowledged that the analysis of response rates of the five countries revealed rather inconsistent results and hardly showed any clinically relevant results.

3.5. Summary of Study M/31416/13

Based on the information presented in Table 3.2, primary efficacy results from sponsor's analyses did not show the significance between almotriptan groups and placebo in the treatment of acute migraine. It did not demonstrate the significant effects on the migraine associated symptoms, nausea, photophobia and phonophobia.

The Cochran-Mentel-Haenszel test provided a test statistic for 2 almotriptan groups and placebo in response rate at 2 hours with a p-value of 0.044.

4. Study M/31416/14

This is a randomized, double-blind, parallel-group, placebo-controlled, phase-III clinical trial for the study of the efficacy and safety of using single dose of almotriptan at doses of 6.25 and 12.5 mg in the treatment of patients with acute migraine during three migraine attacks.

The primary efficacy variable was defined as being the number of migraine attacks (out of three) resolved at 2 hours after intake of the test drug without the use of escape medication. For the three migraine attacks, the reduction of migraine pain from moderate or severe to mild or pain-free was used to count the number of resolved migraine attacks.

The study was conducted in 133 centers of nine European countries (Spain, Czech Republic, Estonia, Hungary, Poland, Germany, Belgium, The Netherlands and United Kingdom).

4.1. Efficacy Measures

4.1.1. Primary efficacy: The primary efficacy measure was relief of migraine of the migraine attack at 2 hours after intake of test drug, i.e. pain intensity decrease from moderate/severe to mild/pain-free without use of escape medication. The primary efficacy variable was the number of positive responses in the three treated attacks (0, 1, 2 or 3 attacks with mild or pain-free at 2 hours after the initial dosing of test drug) in the ITT population.

Results of an overall treatment efficacy and differences in the response rates between the treatment groups were examined by the Cochran-Mentel-Haenszel test.

4.1.2. Secondary efficacy: The analysis of secondary efficacy variables was restricted to the ITT population. Those secondary efficacy parameters included 1) pain reduction after 1 hour; 2) pain free 1 and 2 hours after test drug intake; 3) pain intensity difference at 2 hours; 4) duration of migraine attack; 5) relief of migraine related symptoms at 2 hours; and 6) occurrence of relapses.

4.2 Disposition of patients

The ITT patient population consisted 909 patients who were randomized, took the correct study medication, and recorded at least one measurement of efficacy: 170 for placebo, 360 for 6.25 mg LAS group, and 373 for 12.5 mg LAS group. The females and Caucasian were the majority of the ITT population. There were 81.8%, 89.4% and 86.3% females for placebo, 6.25 mg and 12.5 mg LAS groups, respectively. Only 0.3% of the whole ITT population were not Caucasian. The mean ages are 40.3, 40.5 and 40.9 years for the three groups, respectively. There was no difference between treatment groups for each of these variables.

Table 4.1 presents an overview of the number patients randomized treated and that completed the study. The sponsor reported that the percentage of patients withdrawn was higher in the placebo than the other two treatment groups.

Table 4.1. Distribution of Patients, by Treatment Group

	Placebo	LAS 6.25 mg	LAS 12.5 mg	Total
Randomized	201	404	408	1013
Treated	176	360	374	910
1st attack	176	360	374	910
2nd attack	147	314	324	785
3rd attack	131	290	303	724
Completed	131	287	304	722

4.3. Primary efficacy

4.3.1. Primary efficacy results: Table 4.2 shows the number and percentages of migraine attack out of 3 resolved at 2 hours. The overall percentages of migraine attacks resolved were 33.9%, 57.3% and 64.6% for the placebo, 6.25 mg and 12.5 mg LAS groups, respectively. The sponsor claimed that the dose-dependent increase was highly significant ($p < 0.001$). Pairwise comparisons showed that the percentage of attacks resolved was higher after treatment with both 6.25 mg and 12.5 mg LAS as compared to placebo (both $p < 0.001$).

Table 4.2. Number and Percentages of Patients Migraine Attacks Resolved at 2 Hours

	Placebo	LAS 6.25 mg	LAS 12.5 mg
0 attack resolved out of 3	83 47.2%	82 22.8%	73 19.6%
1 attack resolved out of 3	37 21.0%	60 16.7%	49 13.1%
2 attack resolved out of 3	26 14.8%	95 26.4%	79 21.2%
3 attack resolved out of 3	30 17.0%	60 16.7%	172 46.7%

4.3.2. Response rate of migraine attacks resolved at 2 hours by baseline severity for each attack: Table 4.3 shows the percentages of migraine attacks resolved at 2 hour by baseline pain severity.

Table 4.3. Response Rates Per Separate Attack and by Pain Severity

Moderate Attack at Baseline	Placebo	LAS 6.25 mg	LAS 12.5 mg
1st attack	39.3%	61.2%	73.5%
2nd attack	40.0%	65.5%	69.7%
3rd attack	43.7%	63.7%	77.3%

Severe Attack at Baseline	Placebo	LAS 6.25 mg	LAS 12.5 mg
1st attack	18.8%	44.4%	51.0%
2nd attack	31.9%	49.1%	61.2%
3rd attack	22.7%	54.6%	57.9%

4.4. Secondary efficacy

4.4.1. Migraine attack resolved at 1 hour and pain-free at 1 and 2 hours: The rates of migraine attacks resolved and pain-free at 1 and 2 hours after intake of medication without use of escape medication are presented in Table 4.4.

The number of percentage of attacks that resulted in a pain-free at 2 hour increased dose-dependently with an overall $p < 0.001$. All pairwise comparisons between treatment groups for the three attacks combined were statistically significant (all $p < 0.001$). Comparisons between 12.5 mg LAS and placebo for all three attacks separately were significant at $p < 0.05$.

Pairwise comparisons for the number of attacks that was resolved at 1 hour after treatment for all three attacks combined were significant between two almotriptan groups and placebo (both $p < 0.01$). When all three attacks were considered separately, the comparisons between 12.5 mg LAS and placebo were statistically significant for all three attacks (all $p < 0.01$).

Pairwise comparison for the pain-free at 1 hour after treatment for all three attacks combined were significant between 12.5 mg LAS and placebo ($p < 0.01$). When all three attacks were considered separately, the p-values for the comparisons between 12.5 mg LAS and placebo were 0.059, 0.063 and 0.016 for the first, second and third attack respectively.

Table 4.4. Percentages of Patients with 0, 1, 2 or 3 Migraine Attacks Resolved And Ended at 1 and 2 hours
(Reproduced from sponsor's submission)

	Placebo	LAS 6.25 mg	LAS 12.5 mg
Percentage of patients who had:			
- 0 attack resolved out of 3 at 1 hour	61.9%	48.6%	45.8%
- 1 attack resolved out of 3 at 1 hour	19.3%	24.2%	19.3%
- 2 attack resolved out of 3 at 1 hour	10.8%	15.6%	20.4%
- 3 attack resolved out of 3 at 1 hour	8.0%	11.7%	14.5%
Percentage of patients who had:			
- 0 attack resolved out of 3 at 2 hours	47.2%	22.8%	19.6%
- 1 attack resolved out of 3 at 2 hours	21.0%	16.7%	13.1%
- 2 attack resolved out of 3 at 2 hours	14.8%	26.4%	21.2%
- 3 attack resolved out of 3 at 2 hours	17.0%	34.2%	46.1%
Percentage of patients who had:			
- 0 attack ended out of 3 at 1 hour	89.2%	85.3%	76.7%
- 1 attack ended out of 3 at 1 hour	6.3%	9.4%	13.4%
- 2 attack ended out of 3 at 1 hour	2.8%	3.3%	5.6%
- 3 attack ended out of 3 at 1 hour	1.7%	1.9%	4.3%
Percentage of patients who had:			
- 0 attack ended out of 3 at 2 hours	71.6%	51.1%	40.8%
- 1 attack ended out of 3 at 2 hours	15.3%	21.9%	20.4%
- 2 attack ended out of 3 at 2 hours	8.0%	13.1%	20.6%
- 3 attack ended out of 3 at 2 hours	5.1%	13.9%	18.2%

4.4.2. Pain intensity difference: The distribution of pain intensity difference scores indicated

4.4.2. Pain intensity difference: The distribution of pain intensity difference scores indicated higher efficacy of 6.25 and 12.5 mg LAS as compared to placebo. The overall CMH statistic was significant for all three attacks with $p < 0.001$. All pairwise comparisons between groups for all three attacks were statistically significant with $p < 0.05$.

4.4.3. Migraine related symptoms: The changes of migraine-related symptoms for nausea, photophobia and phonophobia are shown in Table 4.5, a reproduction from sponsor's submission. Nausea decrease dose-dependently, the overall CMH statistic was significant for all three attacks separately with all $p \leq 0.001$. The overall CMH test results indicated the rates of photophobia were significantly lower for 6.25 mg and 12.5 mg LAS groups compared to placebo with all $p < 0.01$. It was also similar for the symptom of phonophobia that overall CMH test results had $p < 0.001$.

Table 4.5. Changes in Migraine-related Symptoms Nausea, Photophobia and Phonophobia at 2 Hours after Intake for Those Who Had Symptoms at Baseline
(Reproduced from sponsor's submission)

		First attack			*Second attack*			*Third attack*		
		placebo	*LAS 6.25mg*	*LAS 12.5mg*	*placebo*	*LAS 6.25mg*	*LAS 12.5mg*	*placebo*	*LAS 6.25mg*	*LAS 12.5mg*
Number of patients		117	246	250	95	216	216	88	196	206
Nausea	better	42.7	52.8	62.0	36.8	58.3	63.9	37.5	58.2	65.5
	equal	55.6	44.3	37.2	62.1	40.7	36.1	61.4	40.8	33.0
	missing	1.7	2.8	0.8	1.1	0.9	0.0	1.1	1.0	1.5
Number of patients		25	41	50	9	33	40	11	33	35
Vomiting	better	60.0	70.7	80.0	55.6	78.8	80.0	63.6	66.7	82.9
	equal	40.0	24.4	18.0	44.4	21.2	20.0	36.4	33.3	11.4
	missing	0.0	4.9	2.0	0.0	0.0	0.0	0.0	0.0	5.7
Number of patients		132	252	258	100	218	227	86	196	213
Photo-phobia	better	38.6	52.0	62.0	34.0	55.0	60.4	24.4	52.0	57.3
	equal	60.6	44.8	36.8	64.0	44.0	39.2	75.6	45.9	40.8
	missing	0.8	3.2	1.2	2.0	0.9	0.4	0.0	2.0	1.9
Number of patients		96	206	207	77	175	175	72	160	163
Phono-phobia	better	29.2	51.9	65.7	23.4	53.1	57.7	22.2	51.3	57.7
	equal	69.8	44.2	33.8	74.0	45.7	41.7	77.8	46.9	39.9
	missing	1.0	3.9	0.5	2.6	1.1	0.6	0.0	1.9	2.5

4.4.4. Relapses: The percentage of patients who had a relapse for all three attacks combined ranged from 23.3% in the placebo group to 30.1% in the 12.5 mg LAS group. None of the comparisons between treatment groups reached statistical significance.

4.5. Reviewer's comments

Firstly, Study M/31416/14 combined results from 3 migraine attacks. This reviwer reanalyzed the rates of patients with migraine attack resolved at 2 hour for each attack separately. The analysis results show that both 6.25 mg and 12.5 mg treatment groups had significant higher rates of migraine attack relief after 2 hours of intake for each individual attack (all $p < 0.001$). This finding indicate that the treatment effect of almotriptan is superior to placebo.

Secondly, this reviewer also examined the presence of migraine-related symptoms after 2 hour of intake for each attack separately. The p-values of comparisons between 6.25 mg LAS group and placebo on **nausea** for the first, second and third attacks were 0.007, 0.020 and <0.001, respectively. For the symptom of **photophobia**, the p-values were 0.003, 0.003 and <0.001, respectively, for the three attacks. For the symptom of **phonophobia**, the p-values were 0.003, 0.002 and <0.001, respectively, for the three attacks. In comparing 12.5 mg group and placebo, for all the symptoms of **nausea**, **photophobia** and **phonophobia**, the p-values were all less than 0.001 for all three attacks individually.

4.6. Summary of Study M/31416/14

The results demonstrate the superiority of almotriptan to placebo from analyzing the primary efficacy and the treatment effects on the migraine-associated symptoms for each attack separately.

5. Conclusion

At lease two of the three studies presented positive results in primary efficacy. Although Study M/31416/13 did not show treatment effect on the migraine-related symptoms of nausea, photophobia and phonophobia, the other two studies provides evidence in support of treatment effect on those.

/S/

Y. Richard Chen, Ph.D.
Statistical Reviewer

This review consists of 15 pages and 12 tables.

Concur:

/S/

Dr. Kun Jin
Team Leader

/S/

Dr. George Chi
Director, Division of Biometrics I

Statistical Review and Evaluation

Review for Stability Data

OCT 5 2000

NDA#: 21-001

APPLICANT: Pharmacia and Upjohn

NAME OF DRUG: Axert (almotriptan) Tablets

DOCUMENT REVIEWED: Amendments Dated 10-MAY-2000, 30-JUN-2000

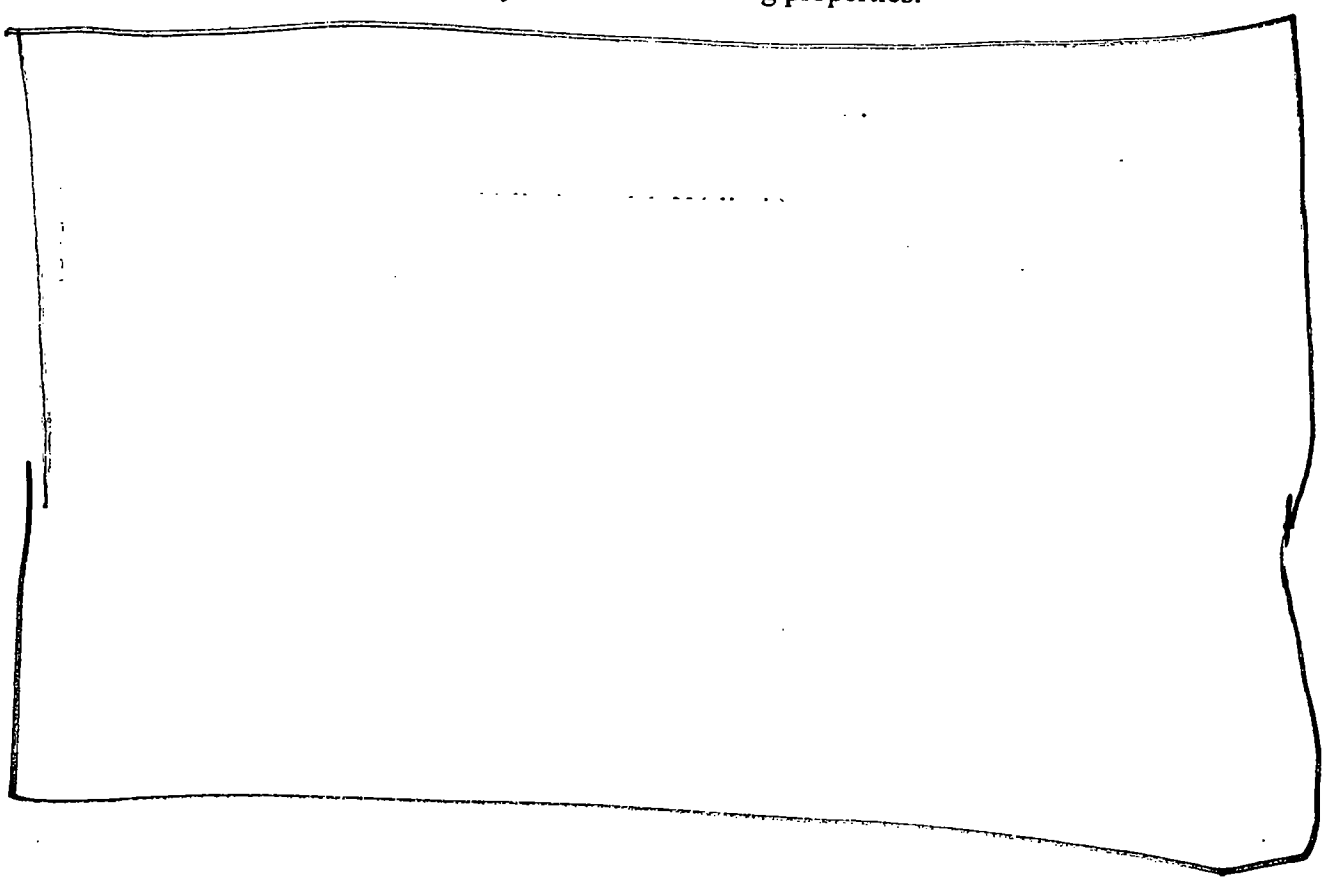
CHEMISTRY REVIEWER: Martha Heimann, Ph.D. (HFD-120)

STATISTICAL REVIEWER: Yeh-Fong Chen, Ph.D. (HFD-710)

Background

The sponsor's statistical methods are described in the 10-MAY-00 Stability Update. The sponsor was asked to reanalyze stability data using data from primary batches only. This review is for checking the requested analyses and answering specific questions raised by the chemistry reviewer. They are:

1. Please perform regression analysis for the following properties.



3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[redacted]

Additional Comments

[redacted]

Summary

The sponsor should use two-sided 95% confidence limits around the mean regression line to determine the estimated shelf life based on potency assay or any assay with two-sided registration limits. It is not appropriate to draw conclusions only from the analyses for the pooled data. One should find the best fitting model and test the goodness of fit first and then calculate the estimated shelf life. Since the estimated shelf life for potency of the 12.5mg tablets in blister packages is [redacted] as calculated by the sponsor, the requested [redacted] shelf life is not supported.

/S/ 10/04/00

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

/S/ 10/4/00

Roswitha Kelly, M.S.
Preclinical Coordinator

/S/ 10/5/2000

George Chi, Ph.D.
Director, Dvision of Biometrics I

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.