a clear dose-related increase in heart rate, which was nominally significant at 2 and 4 hours.

Table 53 (RA): Study CL02 – Mean Heart Rates, by Treatment Group and Time Point

Time Point (hr)	PBO (n=6)	5mg (n=6)	10mg (n=6)	25mg (n=6)	50mg (n=6)	100mg (n=6)	150mg (n=12)	200mg (n=6)	p-value*
0	54.6	57.2	58.8	53.3	52.3	54.5	56.9	55.7	0.825
0.25	53.0	51.8	53.7	52.7	51.8	52.7	57.1	51.2	0.541
1	53.3	53.5	53.3	51.7	54.2	54.7	61.3	59.5	0.064
2	53.7	51.2	54.7	53.7	56.3	58.3	64.5	64.0	0.002
4	58.1	58.0	59.3	61.0	64.7	66.8	76.8	73.8	<0.0001
24	62.4	57.0	68.0	61.7	62.5	60.8	61.6	64.2	0.589

*ANOVA

This confirms the sponsor's report of an almotriptan-associated increase in heart rate in this study, and previously described in this review in section 8.7, on page 44. Therefore, I conclude that the Bazett's correction for QT in this study may not be appropriate, and I employ Dr. Burkhart's recommended correction, as previously described.

As in study CL28, I used all placebo/baseline ECG's to analyze the relationship between QT and heart rate in this study population. There were 132 such tracings available for analysis. Eighty-four of these occurred at various time points during placebo treatment. The remaining 48 tracings occurred at baseline during active treatment (6 each for baseline at all active doses, with the exception of 150mg, for which there were 12 baseline tracings). The relationship between QT and heart rate (using the RR interval) is shown graphically in Figure 9.

Figure 9 demonstrates the familiar relationship between QT and heart rate. As heart rate increases (*i.e.*, smaller RR interval), the QT decreases.

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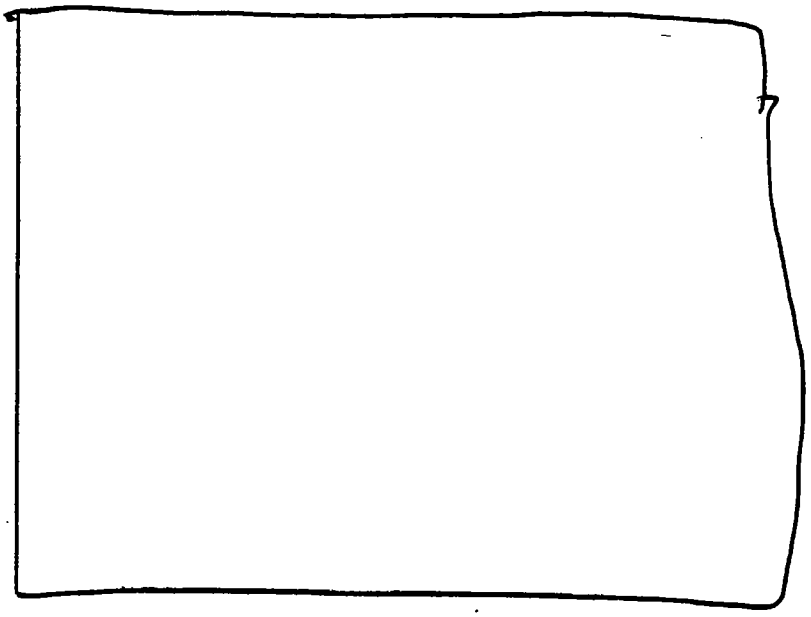
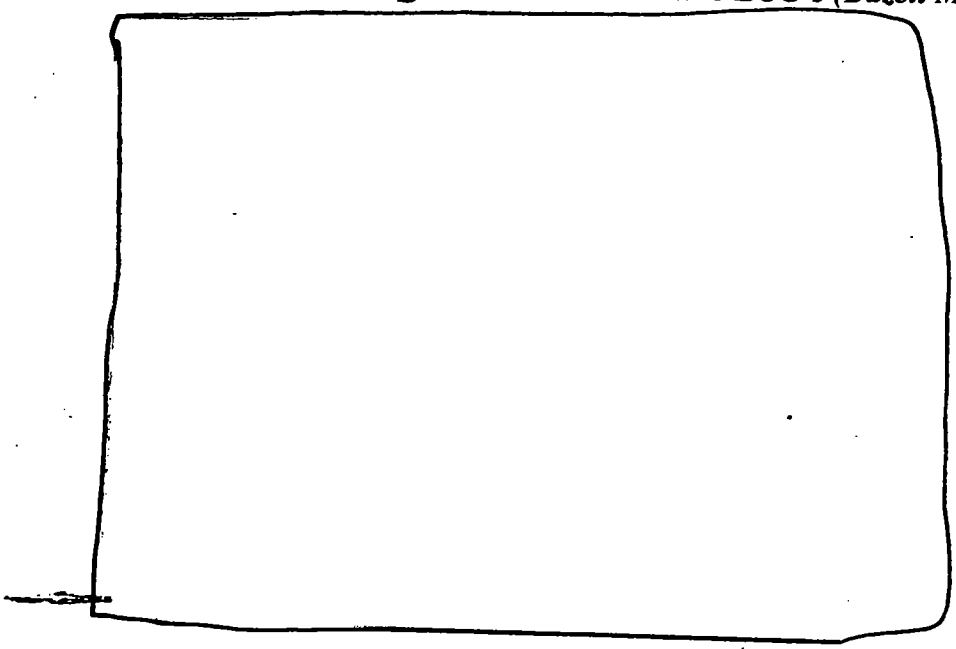
Figure 9 (RA): Study CL02 –RR and QT Relationship in Placebo/Baseline ECG's



I then calculated the QTc using Bazett's formula for this population, and again plotted RR vs. QTc. This is shown in Figure 10. The formula I used is

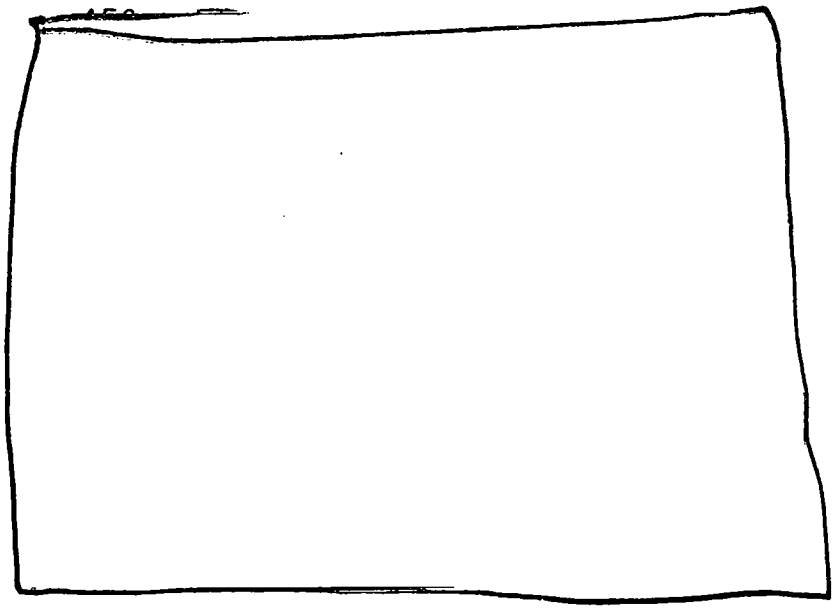
Figure 10 (RA): Study CL02 – RR vs. QTc in Placebo/Baseline ECG's (Bazett Method)



This graph shows that there is still a substantial effect of RR (and therefore, heart rate) on the QTc. It is interesting to note that the slope of the fitted line is positive, whereas in the previous study, it was negative. I discussed this with Dr. Racoosin (safety team leader). Generally, a negative slope is expected using the Bazett correction. The only explanation we could imagine is that this is an unusual population, based, at least in part, on the small sample size of the study.

The ideal correction to the QT for this population should, nonetheless, produce a fitted line with a slope of zero (*i.e.*, a horizontal line). I again explored several values for the fractional exponent in the formula in order to find a fitted line with a slope close to zero. I found that the formula [redacted] produced a fitted line with a slope of almost zero in this population (Figure 11).

Figure 11 (RA): Study CL02 – RR vs. QTc in Placebo/Baseline ECG's (using the correction [redacted]



Using this population-specific correction, the relationship between QTc' and treatment group in this study is shown in Table 54. At four hours post-treatment, there was a nominally significant difference in QTc' intervals, and this appeared to be due to a prolonged mean QTc' in the 150mg group compared to placebo. It is difficult to interpret this finding, given the fact that there is no clear dose-response effect, and the mean QTc' for the 200mg dose was not nominally significantly different from placebo (407 vs. 400). However, if one excludes the data from the 100mg group (which had an unusually high baseline mean QTc'), then there is a suggestion of a numeric trend at 4 hours suggesting increased QTc' with increasing dose.

Table 54 (RA): Study CL02 – Mean QTc' by Treatment Group and Time Point

Time Point (hr)	PBO (n=6)	5mg (n=6)	10mg (n=6)	25mg (n=6)	50mg (n=6)	100mg (n=6)	150mg (n=12)	200mg (n=6)	p-value*
0	404	403	403	403	394	415	405	398	0.378
0.25	399	395	398	402	402	402	409	404	0.397
1	398	400	402	404	399	399	409	401	0.621
2	396	395	396	406	398	406	410	402	0.178
4	400	399	391	405	402	403	420**	407	0.001
24	400	404	404	406	405	402	424**	406	0.132

*ANOVA; QTc' values in msec; ** nominally significantly different from placebo, using pair-wise comparison

The mean changes in QTc' from baseline are shown in Table 55. Once again, the comparison at 4 hours showed nominally significant difference in mean QTc' among the treatment groups. Pairwise comparisons at 4 hours showed that the change from baseline in QTc' for the 150mg group was nominally significantly greater than the placebo group (which itself showed a mild drop in mean QTc'). Although the comparison between 200mg vs. placebo was not nominally significantly different, there was a numerical trend in support of the finding at 150mg. The effect was not seen at 100mg but this group had an unusually high mean QTc' at baseline (415 msec), which makes all changes from baseline negative. Excluding the 100mg group, a small numeric trend at 4 hours suggesting increasing changes in QTc' from baseline with dose is seen

There was also a nominally significant difference between 150mg vs. placebo at 24 hours. Because this occurred at a time well beyond T_{max}, and it was not seen at other dose groups, this finding is of questionable clinical meaning.

Table 55 (RA): Study CL02 – Mean QTc' Changes from Baseline

Time Point (hr)	PBO (n=6)	5mg (n=6)	10mg (n=6)	25mg (n=6)	50mg (n=6)	100mg (n=6)	150mg (n=12)	200mg (n=6)	p-value*
0	0	0	0	0	0	0	0	0	-
0.25	-5	-8	-5	-1	8	-12	5	6	0.231
1	-6	-3	-2	1	5	-16	5	4	0.324
2	-8	-8	-8	3	5	-9	5	4	0.428
4	-4	-4	-12	2	8	-11	16**	10	0.002
24	-4	1	1	3	11	-13	19**	8	0.060

*ANOVA; changes in QTc' values in msec
** nominally significantly different from placebo, using pair-wise comparison

There was one subject, a 24 year old male (ALM416.02.914:21), who had a QTc' greater than 500msec. He had a baseline QTc' of 418 msec and he received almotriptan 150mg. Subsequent post-treatment QTc' intervals were 416, 403, 392, and 444 msec at 0.25, 1, 2, and 4 hours respectively. At the 24 hour measurement, he had a QTc' of 529 msec. Because it occurred so long after the expected T_{max} of the drug, it appears doubtful that this isolated finding is drug related.

There was only one subject who had a change from baseline QTc' of greater than 60 msec. It was the same subject described above, occurring at the same 24 hour time point.

There were 16 ECG's in 8 subjects that had a change from baseline QTc' of greater than 30 msec. One subject received 10mg, 2 subjects received 50mg, 4 subjects received 150mg, and 1 subject received 200mg.

In summary, there is no clear evidence of a dose-dependent effect on the QTc' interval. If one excludes the data from the 100mg group (which had an unusually high baseline mean QTc'), there is a suggestion of mild QTc' prolongation with increasing dose at 4 hours (which is just past T_{max}) and the comparison between 150mg and placebo at this time point reached nominal significance. The study is limited by the small numbers of patients exposed at each dose level.

8.14.3.3 Study CL11

Study CL11 was a randomized, double blind, parallel group, dose-finding clinical trial that studied the efficacy and safety of almotriptan administered orally as a single dose in migraine patients during a migraine attack. The trial was performed in 14 centers in Hungary and Poland. Males and females 18-65 years old with migraine (according to IHS criteria) were randomized to receive either placebo, 5mg, 25mg, 50mg, 100mg, or 150 mg. ECG's were done at screening, and then again at 2 hours post-treatment. The study was limited because it did not record a baseline ECG and only recorded an ECG at 2 hours. However, with an expected T_{max} of 1-3 hours, the 2-hour time point seems a reasonable choice for the single post-treatment tracing, although additional time points would have been ideal. I used the interval data from the screening EEG as the "baseline" for purposes of analysis.

The study treated 168 patients. The distribution of among the treatment groups were 31, 35, 34, 33, and 35 for placebo, 5mg, 25mg, 100mg, and 150mg, respectively. Each patient had two ECG's (screening and 2 hours); therefore there were 336 ECG's available for analysis.

As in the previous two studies, I first analyzed the relationship between dose and heart rate in this study. The mean heart rate, for each treatment group, grouped by time point, is shown in Table 56. Unlike the previous two studies, there appeared to be no nominally significant effect on heart rate, although numerically there here higher mean heart rate seen in 3 of the 4 almotriptan doses compared with placebo.

Table 56 (RA): Study CL11 – Mean Heart Rates, by Treatment Group and Time Point

Time Point (hr)	PBO (n=31)	5mg (n=35)	25mg (n=34)	100mg (n=33)	150mg (n=35)	p-value*
Screening	72.0	71.8	70.9	71.5	71.1	0.993
2	69.3	74.1	68.0	73.5	70.5	0.158

*ANOVA

The mean changes from baseline (screening) heart rates are shown in Table 57. Again, there were no nominally significant changes from baseline heart rates seen.

Table 57 (RA): Study CL11 – Mean Change from Baseline Heart Rates

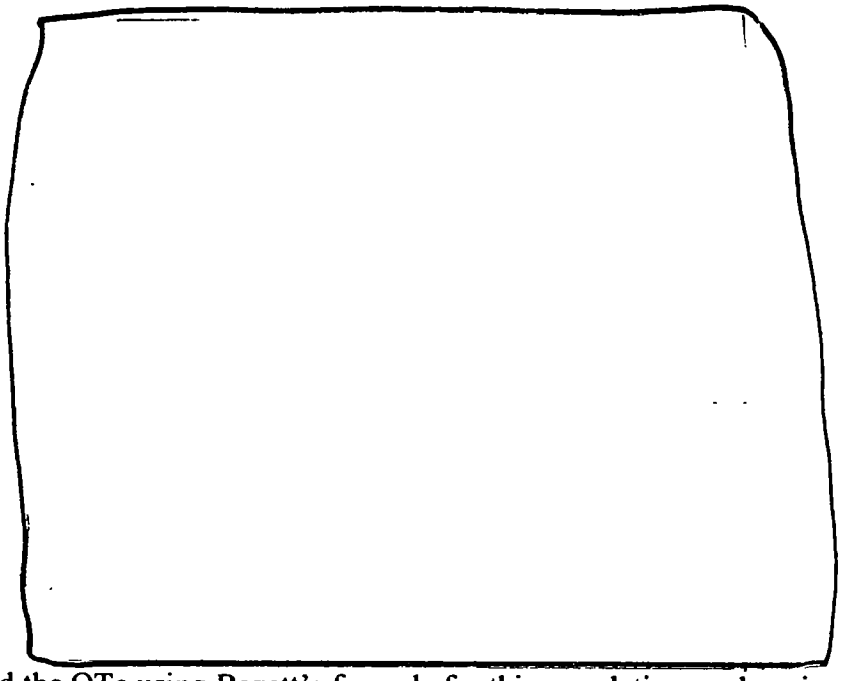
Time Point (hr)	PBO (n=31)	5mg (n=35)	25mg (n=34)	100mg (n=33)	150mg (n=35)	p-value*
Screening	0	0	0	0	0	-
2	-2.7	2.3	-2.9	2.0	-0.5	0.164

*ANOVA

Without a clear drug effect on heart rate in this study, the Bazett correction of the QT should be adequate. Nonetheless, because of the effect on heart rate seen in the previous two studies, and because of the possibility of individual variability, I decided to correct the QTc' using both the Bazett formula, and Dr. Burkhart's technique.

As in the previous two studies, I used all placebo/baseline ECG's to analyze the relationship between QT and heart rate in this study population. There were 199 placebo/baseline tracings (168 from screening ECG's and the remaining 31 from placebo patients at 2 hours). The relationship between QT and heart rate (using the RR interval) is shown graphically in Figure 12, which once again confirms the shortening of the QT as heart rates increase.

Figure 12 (RA): Study CL11 –RR and QT Relationship in Placebo/Baseline ECG's



I then calculated the QTc using Bazett's formula for this population, and again plotted RR vs. QTc. This is shown in Figure 13. The formula I used is [redacted]

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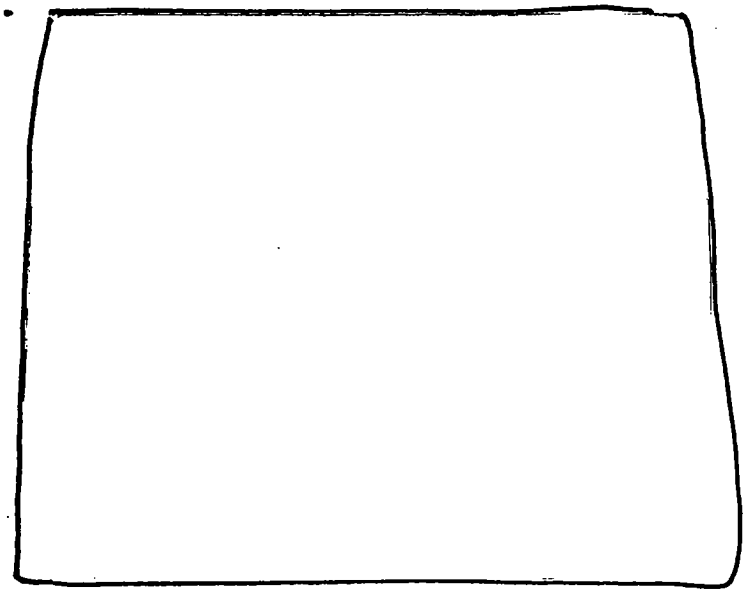
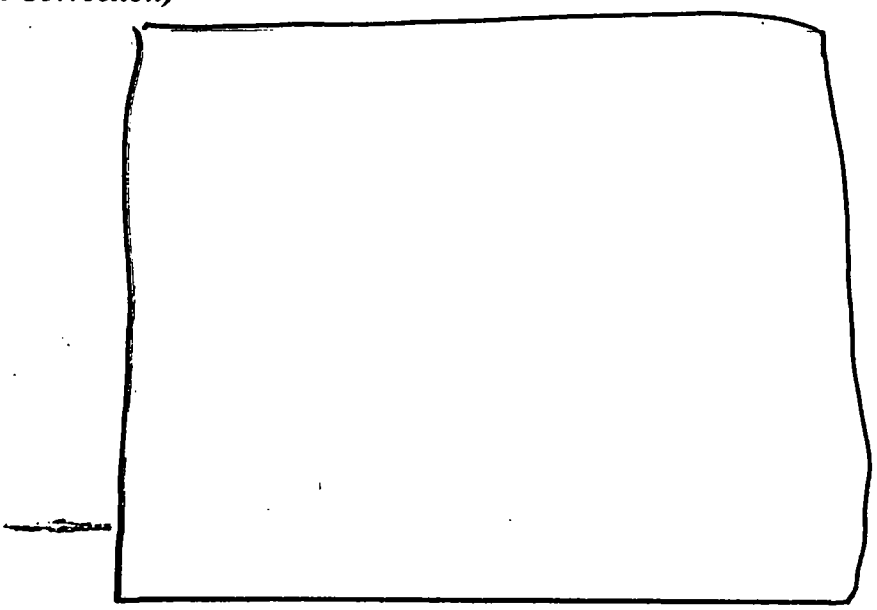
Figure 13 (RA): Study CL11 – RR vs. QTc in Placebo/Baseline ECG's (Bazett Method)



I again explored several values for the fractional exponent in the formula in order to find a fitted line with a slope close to zero. I found that the formula [redacted] (Fridericia's correction) produced a fitted line with a slope of almost zero in this population (Figure 11).

Figure 14 (RA): Study CL11 – RR vs. QTc in Placebo/Baseline ECG's (using the Fridericia Correction)



Using both the Bazett and Fridericia corection of the QT in this population, the relationship between QTc and treatment group in this study is shown in Table 58. There were no nominally significant differences in mean QTc intervals (with either correction method) in any treatment group.

Table 58 (RA): Study CL11 – Mean QTc' by Treatment Group and Time Point

Time Point (hr)	PBO (n=31)	5mg (n=35)	25mg (n=34)	100mg (n=33)	150mg (n=35)	p-value*
Bazett Correction						
Screening	399	393	395	393	399	0.697
2	402	400	400	403	401	0.985
Fridericia Correction						
Screening	387	381	384	382	389	0.567
2	393	387	392	391	390	0.836

*ANOVA; QTc' values in msec;
** nominally significantly different from placebo, using pair-wise comparison

The mean changes in QTc' from baseline are shown in Table 55. There was no nominally significant differences between treatment groups and placebo in mean changes from baseline in QTc intervals, using either correction method. There was no numeric trend for a dose-response effect. This study has distinct advantages and disadvantages when compared with the previous study, CL28. The advantages are that it is a larger study (approximately 30 per treatment group, as opposed to only 6-12 in CL28), and that it treated migraine patients during an attack, as opposed to normal, healthy, asymptomatic subjects; however, the disadvantages are that there was no baseline ECG and the screening ECG was used instead as the baseline, and only the 2 hour time point was sampled (although this should be near T_{max}).

The mean changes in QTc' from baseline are shown in Table 59. There was no nominally significant differences between treatment groups and placebo in mean changes from baseline in QTc intervals, using either correction method. There was no numeric trend for a dose-response effect. This study has distinct advantages and disadvantages when compared with the previous study, CL28. The advantages are that it is a larger study (approximately 30 per treatment group, as opposed to only 6-12 in CL28), and that it treated migraine patients during an attack, as opposed to normal, healthy, asymptomatic subjects; however, the disadvantages are that there was no baseline ECG and the screening ECG was used instead as the baseline, and only the 2 hour time point was sampled (although this should be near T_{max}). It should be noted that the slight numeric trend seen towards increasing QTc' in study CL28 was seen at 4 hours post-dosing, a time point which this study did not evaluate.

Table 59 (RA): Study CL11 – Mean QTc' Changes from Baseline

Time Point (hr)	PBO (n=31)	5mg (n=35)	25mg (n=34)	100mg (n=33)	150mg (n=35)	p-value*
Bazett Correction						
Screening	0	0	0	0	0	-
2	10	1	13	4	2	0.500
Fridericia Correction						
Screening	0	0	0	0	0	-
2	6	5	8	8	2	0.750

*ANOVA; QTc' values in msec;
** nominally significantly different from placebo, using pair-wise comparison

Since the Bazett correction resulted in higher numeric QTc intervals, I used this correction to look for outliers. There were no patients with QTc intervals greater than 500 msec in this study. There were 6 patients who had changes from screening QTC of at least 60 msec. Two received placebo, one received 25mg, one received 10mg, and two received 150mg. There were 34 patients who had changes from screening QTc of at least 30msec: 6 received placebo, 5 received 5mg, 9 received 25mg, 8 received 100mg, and 6 received 150mg.

8.14.3.4 Pooled Dataset

The next analysis focused on the pooled dataset consisting of the 18 phase 1/2 studies that had immediate post-treatment ECG intervals recorded, as described earlier in this section (see Table 48, page 56). Thirteen of these 18 studies involved oral administration of either placebo or almotriptan at doses ranging from 5mg to 200mg, involving 4446 ECG's in 391 subjects. The dataset consisted of ECG data from 567 subjects and patients, and contained data from 6,807 ECG's. Of these subjects, 340 (60%) were female and 227 (40%) were male. The mean age was 36.4 years, and the vast majority (94.5%) were white. 14 subjects (3.5%) were black.

The mean heart rate at each time point, for each oral treatment group is shown in Table 60. There is evidence for a dose dependent increase in heart rate, which is most evident at 2-4 hours, particularly at the high doses. Therefore it seems again appropriate not to use Bazett's formula to correct the QT interval.

Table 60 (RA): Pooled ECG Dataset – Mean Heart Rates, by Oral Treatment Group

Time (hr)	N*	PBO (n=101)	5mg (n=41)	10mg (n=6)	12.5mg (n=200)	25mg (n=100)	50mg (n=30)	100mg (n=39)	150mg (n=47)	200mg (n=6)	p-value
0	450	58.9	57.2	58.8	60.4	58.4	55.5	54.5	56.9	55.7	0.166
0.25	62	53.0	51.8	53.7	.	52.7	51.8	52.7	57.1	51.2	0.541
0.5	152	56.8	.	.	57.5	55.0	54.9	.	.	.	0.337
0.75	65	.	.	.	54.2	53.9	.	.	.	.	0.856
1	381	55.6	53.5	53.3	58.5	55.8	56.6	54.7	61.3	59.5	0.094
1.5	193	58.0	.	.	56.9	55.7	56.2	.	.	.	0.590
2	492	61.7	70.7	54.7	57.9	62.7	57.2	71.1	69.0	64.0	<0.0001
2.5	95	65.2	.	.	65.6	64.9	64.7	.	.	.	0.985
3	390	58.8	.	.	59.8	62.3	67.0	.	.	.	0.0003
3.5	96	66.0	.	.	64.1	63.2	66.0	.	.	.	0.501
4	295	63.4	58.0	59.3	59.7	63.1	64.4	66.8	76.8	73.8	<0.0001
5	96	69.3	.	.	67.6	67.7	66.9	.	.	.	0.716
6	381	65.1	.	.	65.6	65.8	66.7	.	.	.	0.908
7	96	65.9	.	.	63.5	65.4	66.4	.	.	.	0.589
8	184	63.9	.	.	63.6	64.5	64.9	.	.	.	0.917
10	24	.	.	.	61.5	.	.	.	.	.	-
12	249	60.3	.	.	61.0	60.1	59.6	.	.	.	0.807
16	120	57.3	.	.	58.1	58.3	56.6	.	.	.	0.866
24	339	62.7	57.0	68.0	60.1	59.5	59.8	60.8	61.6	64.2	0.218

* number of ECG's; p-value is ANOVA

As in the previous analyses of studies CL28 and CL02, I used ECG's done at baseline or during placebo treatment to analyze the relationship between the RR interval and the QT

interval in order to derive a correction that closely eliminated the effect of heart rate. There were 2503 ECG tracings that fit that category (1251 done during pre-treatment or baseline, and the remaining done during placebo treatment). There were an additional 156 tracings that were done at the end of study completion. I did not use any of these tracings because of the remote possibility of a persistent drug effect at study exit. The relationship between heart rate (RR interval) and QT for the entire placebo/baseline group is shown in Figure 15. As expected, it shows a decrease in the QT interval as the heart rate increases (*i.e.*, as RR decreases).

Figure 15: Pooled ECG Dataset – RR and QT Relationship in Placebo/Baseline ECG's

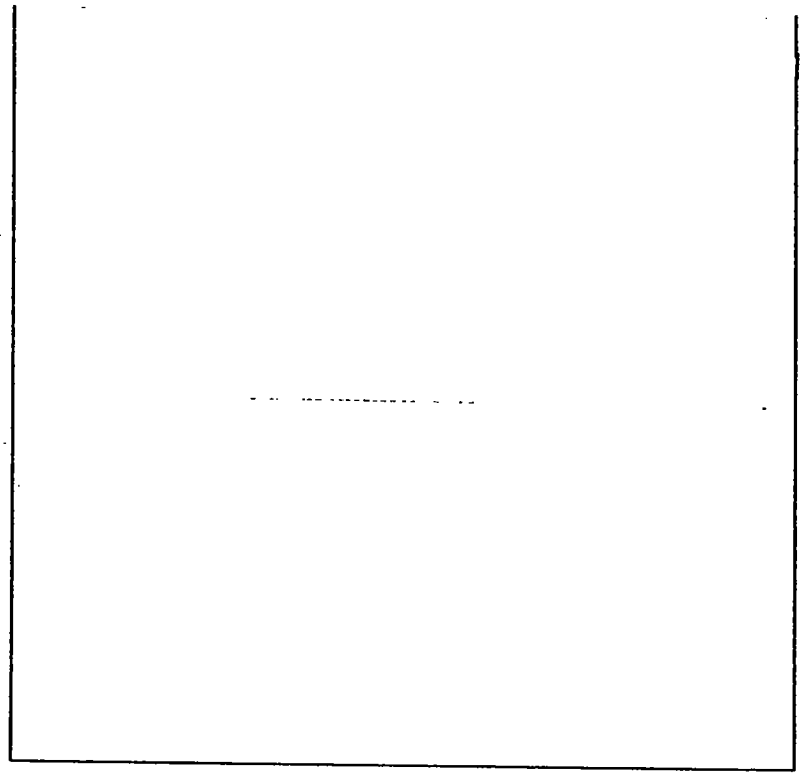


Figure 16 shows that the Bazett's correction of the QT results in a negative slope to a fitted line, whereas a slope of zero is ideal.

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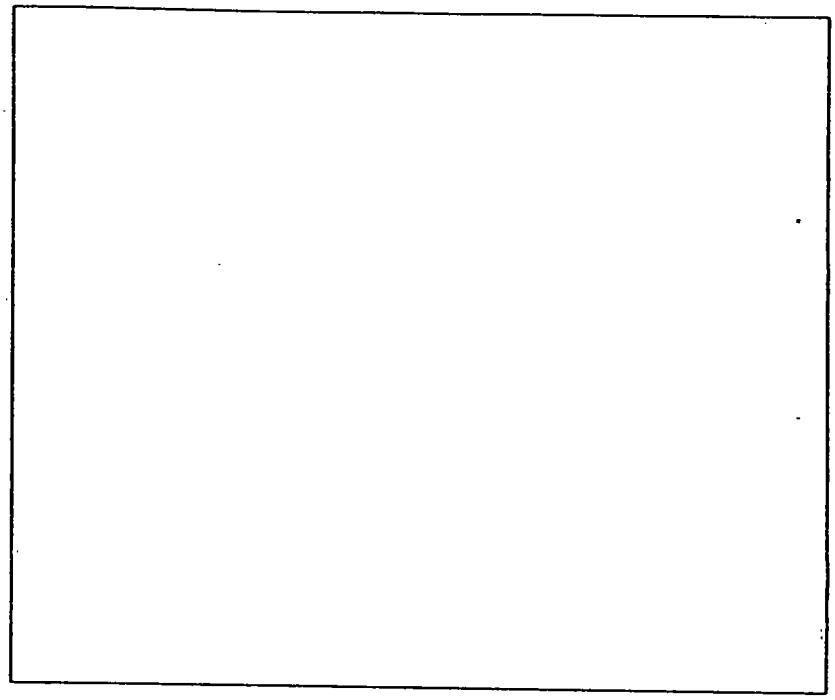
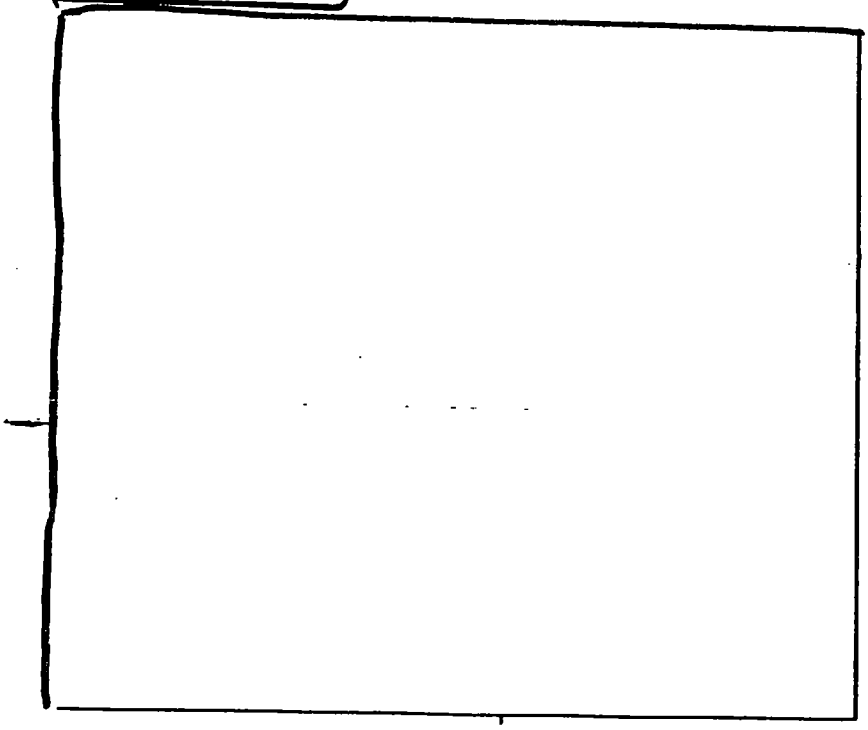
Figure 16 (RA): Pooled ECG Dataset – RR vs. QTc in Placebo/Baseline ECG (Bazett Method)



For this larger dataset, the formula [redacted] produces a slope of nearly zero and is suitable for correcting the QTc in this pooled population (Figure 17).

Figure 17 (RA): Pooled ECG Dataset – RR vs. QTc in Placebo/Baseline ECG's (using the formula [redacted]



I then applied the formula to correct the QT in subjects who received oral doses of almotriptan (or placebo). There were 391 such subjects. The range of oral almotriptan doses were 5mg to 200mg. The number of subjects who received a particular treatment is shown in Table 61. The total adds up to considerably more than the 391 unique subjects receiving oral medication because many studies used a crossover design and a subject may have received several different treatments.

Table 61: Pooled ECG Dataset – Distribution of Oral Treatments in Phase 1 Studies

Treatment	N
PBO	101
5 mg	41
10 mg	6
12.5 mg	200
25 mg	100
50 mg	30
100 mg	39
150 mg	47
200 mg	6

For the oral treatment groups, the mean QTc' intervals at each time point are shown in Table 62.

Table 62 (RA): Pooled ECG Dataset – Mean QTc' Intervals in Oral Treatment Groups

Time (hr)	N*	PBO (n=101)	5mg (n=41)	10mg (n=6)	12.5mg (n=200)	25mg (n=100)	50mg (n=30)	100mg (n=39)	150mg (n=47)	200mg (n=6)	p-value
0	450	411	408	406	408	417	400	425	410	404	0.007
0.25	62	410	408	408	.	414	415	414	415	417	0.941
0.5	152	396	.	.	401	393	392	.	.	.	0.053
0.75	65	.	.	.	416	417	.	.	.	.	0.834
1	381	407	410	413	405	403	399	407	409	402	0.713
1.5	193	398	.	.	405	406	392	.	.	.	0.006
2	492	401	393	404	401	401	398	396	396	397	0.478
2.5	95	404	.	.	405	400	401	.	.	.	0.643
3	390	410	.	.	404	409	394**	.	.	.	0.007
3.5	96	400	.	.	395	394	394	.	.	.	0.374
4	295	399	402	393	399	395	392	395	400	390	0.723
5	96	397	.	.	397	399	393	.	.	.	0.589
6	381	407	.	.	403	404	394**	.	.	.	0.045
7	96	396	.	.	400	393	395	.	.	.	0.278
8	184	394	.	.	399	393	391	.	.	.	0.141
10	24	.	.	.	394	.	.	.	.	.	-
12	249	391	.	.	402**	400	390	.	.	.	0.003
16	120	404	.	.	401	405	404	.	.	.	0.656
24	339	403	409	394	404	407	392	401	423	401	0.020

* N = number of ECG's; p-value is ANOVA
** nominally significantly different from placebo, using pair-wise comparison

The overall comparison of QTc' intervals reached nominal significance at several time points (0.5, 1.5, 3, 6, 12, and 24 hours); however, pairwise comparisons vs. placebo were

nominally positive in only 3 settings: 50mg at 3 and 6 hours (QTc' was lower than placebo) and 12.5mg at 12 hours. This last comparison showed a nominally significant increase in QTc' compared to placebo. However, since there was no evidence of a dose-response at that time point, and since 12 hours is well beyond the expected T_{max} of the drug, this result is probably spurious.

Although the difference at baseline in QTc' intervals was nominally significant in the overall analysis (p=0.007), there was no significant differences compared to placebo using pairwise comparisons. Nonetheless, a change from baseline analysis is also important in order to account for this baseline imbalance. This is shown in Table 63.

Table 63 (RA): Pooled ECG Dataset – Changes from Baseline QTc' Intervals

Time (hr)	N*	PBO (n=101)	5mg (n=41)	10mg (n=6)	12.5mg (n=200)	25mg (n=100)	50mg (n=30)	100mg (n=39)	150mg (n=47)	200mg (n=6)	p-value
0	450	0	0	0	0	0	0	0	0	0	-
0.25	62	-3	0	2	.	0	9	-11	5	13	0.328
0.5	152	-6	.	.	-3	-6	-6	.	.	.	0.395
0.75	65	.	.	.	1	1	.	.	.	.	0.926
1	381	-1	2	7	-1	-8	-1	-18	-1	-2	0.034
1.5	193	-4	.	.	-3	-3	-6	.	.	.	0.707
2	492	-2	5	-2	-5	0	-2	5	-0	-7	0.060
2.5	95	3	.	.	2	1	2	.	.	.	0.982
3	390	-1	.	.	-4	-9**	-5	.	.	.	0.025
3.5	96	-1	.	.	-9	-5	-4	.	.	.	0.300
4	295	-7	-6	-13	-5	-7	-8	-30**	-10	-14	0.041
5	96	-5	.	.	-7	0	-5	.	.	.	0.455
6	381	-3	.	.	-5	-14**	-5	.	.	.	0.001
7	96	-6	.	.	-3	-6	-4	.	.	.	0.833
8	184	-7	.	.	-6	-6	-7	.	.	.	0.934
10	24	.	.	.	-10	.	.	.	.	.	-
12	249	-11	.	.	-5	-9	-8	.	.	.	0.123
16	120	3	.	.	-2	6	5	.	.	.	0.049
24	339	-11	1	-12	-6	-11	-8	-24	13**	-3	0.002

* N = number of ECG's; p-value is ANOVA
** nominally significantly different from placebo, using pair-wise comparison

The overall comparison of changes in QTc' intervals from baseline reached nominal significance at several time points (2, 3, 4, 6, and 24 hours); however, pairwise comparisons vs. placebo were nominally positive in only 4 settings: 25mg at 3 and 6 hours (QTc' was lower than placebo), 100mg at 4 hours (also lower mean changes in the 100mg group), and 150mg at 24 hours. This latter finding showed an increased QTc' interval from baseline in the 150mg group of 13 msec, but the finding is difficult to interpret in isolation given the fact that it occurred so late after drug administration, and was not seen earlier (near T_{max}), and that no dose-response effect is seen at that time point.

There were 4 subjects who had 6 ECG's that demonstrated QTc' intervals above 500msec.

One subject (ALM416-.06.296.07) was a healthy 70 year old female in study CL06 (PK in young vs. elderly study). She had a baseline QTc' of 427. After administration of 12.5mg, her QTc' at 2 hours was 516 and at 8 hours was 515. Her QTc' intervals are shown in Table 64. The QTc' at other times were below 500 msec.

Table 64: Study CL06 – QTc' Intervals for Subject ALM416.06.296.07

Time (hr)	QTc' (msec)
0	429
0.5	426
1	413
1.5	415
2	516
3	435
4	493
6	432
8	515
12	433
24	417

A second subject (study CL02 – ALM416.02.914.21) received 150mg and had a QTc of 550 msec at 24 hours. QTc' intervals at earlier time points were below 500 msec

A third subject (study 007 – 0007.20846.1016) had a QTc' of 502 msec at baseline, prior to receiving 25mg. All subsequent QTc' intervals were normal.

The fourth subject (also study 007 – 0007.20846.1021), had received placebo and had a QTc' at 3 hours of 502 and at 24 hours of 500 msec.

There were 11 ECG's (in 9 subjects) who had changes from baseline QTc' of ≥ 60 msec. One subject received placebo (1%, 1/101), 6 subjects received 12.5mg (3%, 6/200) and one subject each received 100mg (2.5%, 1/39) or 150mg (2.1%, 1/47).

There were 74 ECG's in 50 patients that had changes from baseline of ≥30 msec. The treatments that resulted in these abnormalities are shown in Table 65. Again, the total does not add up to 50 because 5 patients received more than one treatment.

Table 65 (RA): Pooled ECG Dataset – Oral Treatments Resulting in QTc' ≥ 30 msec

Treatment	ECG's with QTc' ≥30 msec	%
PBO (n=101)	14	14
5 mg (n=41)	4	10
10 mg (n=6)	1	17
12.5 mg (n=200)	17	8
25 mg (n=100)	7	7
50 mg (n=30)	1	3
100 mg (n=39)	5	13
150 mg (n=47)	5	11
200 mg (n=6)	1	17

8.14.3.5 Reviewer's Conclusion Regarding ECG Analysis

There were 18 phase 1/2 studies that measured QT intervals in the immediate post-dosing period (within 24 hours). Thirteen of these 18 studies involved oral administration of either placebo or almotriptan at doses ranging from 5mg to 200mg, involving 4446 ECG's in 391 subjects. The results of my ECG analyses described above do not support a drug-induced prolongation of the QTc interval at the recommended maximum dose of 12.5mg. There is a suggestion of a numeric trend seen in study CL02 suggesting a possible dose-dependent effect on QTc' at very high oral doses at 4 hours post-dose (150mg, or >10x the highest recommended marketing dose). This trend was not seen at 2 hours, nor in study CL11, which also examined 2-hour post-dose ECG's after high oral doses.

8.15 Four-Month Safety Update

At the time of the NDA filing, all studies were complete and submitted. However, during the early review process, we noted that almotriptan is at least partially metabolized by CYP3A4. Given the experience with a recent triptan and CYP3A4 inhibitors, we asked the sponsor to conduct an *in vivo* drug-drug interaction study using the potent CYP3A4 inhibitor, ketoconazole. The four month safety update contains this study report (study 012).

The safety update also includes two follow-up reports on two pregnancies described in section 8.10, Human Reproduction Data, page 48. These reports refer to the two patients in study 0011 (2300 and 2905). Patient 2300 delivered a normal female baby on 10/3/99. Patient 2905 delivered a normal male baby on 10/21/99.

The ketoconazole interaction study was a randomized, open-label, two-way crossover study. Treatment A consisted of daily doses of ketoconazole 400mg orally for 3 days (*i.e.*, days 1-3) along with a single dose of almotriptan 12.5mg on day 2. Treatment B consisted of 12.5mg of almotriptan on day 2 only. There was a 7-day washout period between treatments.

Sixteen (16) healthy male and non-pregnant females (18-55 years) were treated and analyzed. Plasma and urine levels of almotriptan were determined for all subjects in both treatments. AUC, C_{max}, T_{max}, oral clearance, volume of distribution, terminal rate constant, terminal half-life, amount excreted in urine, and renal clearance were determined by non-compartmental techniques.

Vital signs, clinical laboratory tests, and adverse events were recorded. Vital signs were measured each day, on days 1-4 of each treatment sequence. In addition, blood pressure and pulse were measured on day 2 (day of almotriptan administration) at baseline, 1, 2, 4, 8, and 12 hours. Blood and urine samples were collected at screening and end of study. An ECG was done at screening only.

The PK results indicated that ketoconazole use was associated with a 57% increase in almotriptan AUC and 61% increase in C_{max}. Oral clearance and volume of distribution

were decreased. Renal clearance was decreased by 16%. Ketoconazole had no effect on T_{max} and $T_{1/2}$.

Ten of the 16 subjects reported at least one adverse event. All were mild except two. These were a rash (described below) and a headache (rated as moderate). The most commonly reported AE was headache (six subjects, all in the ketoconazole + almotriptan group). Three mild AE's reported in the almotriptan only group included abdominal pain, nausea, and sore throat. The other AE's (all mild) reported in the ketoconazole + almotriptan group were nausea, sore throat, unintended pregnancy (see below), epistaxis, pruritus, and rash (see below).

No clinically significant laboratory abnormalities were seen. There was a statistically significant increase in mean systolic blood pressure at 3 hours post-dose associated with ketoconazole use. The mean change in systolic BP at this time point was less than 7 mm Hg. No clinically significant change in diastolic blood pressure, heart rate, temperature, or respirations.

There was one notable adverse event in the study. Subject 15 had a positive pregnancy test 37 days following her last dose of ketoconazole. The estimated date of conception was within 30 days following this dose. Therefore, the event was recorded as a serious adverse event report – exposure in utero. The pregnancy ended in an elective abortion based on personal circumstances.

One subject experienced a moderate macular rash 37 hours after the day 2 dose of almotriptan + ketoconazole. The rash lasted for 6 days. The subject's last dose of ketoconazole was withheld because of the rash. The AE was considered related to the investigational medications. The subjected was treated with calamine lotion and recovered.

8.16 Reviewer's Safety Conclusions

- Almotriptan 6.25mg and 12.5mg are generally safe for the acute treatment of migraine.
- Almotriptan is generally well tolerated. The most common AE's were nausea, headache, paresthesia, somnolence, and dry mouth
- Almotriptan does not exhibit systematic ECG or laboratory abnormalities. Although there was a trend toward QTc prolongation at very high doses (150mg) in one study, this was not confirmed in a second, larger study in migraine patients that used similar doses.
- There ~~are no~~ clinically meaningful differences in the safety profile with regard to age, race or gender.
- There was one case of myocardial ischemia associated with almotriptan. No definite conclusions regarding causality can be drawn from this case, but it illustrates, at the very least, the need to apply triptan class labeling with regard to cardiovascular events.
- The database does not support the use of more than 2 doses within 24 hours because such a regimen was not studied (either short-term or long-term)

- The long-term safety database meets ICH and Division guidelines for long-term exposure in the at least 300 patients were treated for six months, and at least 100 patients were treated for one year, each treating at least 2 headaches per month. The database is, however, insufficient to support the treatment of ≥3 migraines/month since those numbers do not meet ICH and Division guidelines.

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

10. Conclusions

- Almotriptan 6.25mg and 12.5mg are both effective in relieving migraine headache pain as measured by the 2-hour headache response rates. Both the 6.25mg and 12.5mg doses are also effective in relieving the migraine-associated symptoms of nausea, photophobia, and phonophobia; therefore, almotriptan is effective for the acute treatment of migraine.
- The 2mg dose is a no-effective dose. The 5mg dose is numerically superior to placebo but this comparison was not nominally significant, possibly due to small sample size.
- Efficacy was generally unaffected by baseline pain, age, sex, weight, or other baseline characteristics.
- Although numerically the 12.5mg dose appears better than the 6.25mg dose on many measures, there is no conclusive evidence that the 12.5mg dose is superior to the 6.25mg dose.
- Escape medication use was lower in patients treated with almotriptan compared with placebo. It is not clear whether a dose-response relationship exists between the two doses (it appears to exist in study CL14, but not in study CL12).
- Almotriptan had higher sustained response and sustained pain-free rates compared to placebo. Numerically, the 12.5mg dose was better than the 6.25mg dose.
- Response rates are consistently in favor of almotriptan across three attacks in the study CL14; however, the data were not analyzed by patient (*e.g.*, number of patients who responded to 3/3 attacks, 2/3 attacks, 1/3 attacks, etc.). Therefore, consistency of response for an individual patient is not established by the analysis presented.
- There is no evidence that almotriptan 12.5mg is superior to sumatriptan. In many comparisons, sumatriptan 100mg was numerically superior to almotriptan.
- Almotriptan 6.25mg and 12.5mg are generally safe for the acute treatment of migraine.
- Almotriptan is generally well tolerated. The most common AE's were nausea, headache, paresthesia, somnolence, and dry mouth
- Almotriptan does not exhibit systematic ECG or laboratory abnormalities. Although there was a trend toward QTc prolongation at very high doses (150mg) in one study, this was not confirmed in a second, larger study in migraine patients that used similar doses.
- There are no clinically meaningful differences in the safety profile with regard to age, race or gender.
- There was one case of myocardial ischemia associated with almotriptan. No definite conclusions regarding causality can be drawn from this case, but it illustrates, at the very least, the need to apply triptan class labeling with regard to cardiovascular events.
- The database does not support the use of more than 2 doses within 24 hours because such a regimen was not studied (either short-term or long-term)
- The long-term safety database meets ICH and Division guidelines for long-term exposure in the at least 300 patients were treated for six months, and at least 100 patients were treated for one year, each treating at least 2 headaches per month. The database is, however, insufficient to support the treatment of ≥3 migraines/month since those numbers do not meet ICH and Division guidelines.

11. Recommendations

I recommend approval of the NDA, with changes to labeling as described above, and detailed in Appendix A - page 84.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. /S/ 12/14/00

ao 8/18/00
cc:
HFD-120
NDA 21-001

13 page(s) of revised draft labeling has been redacted from this portion of the review.

TABLE OF CONTENTS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

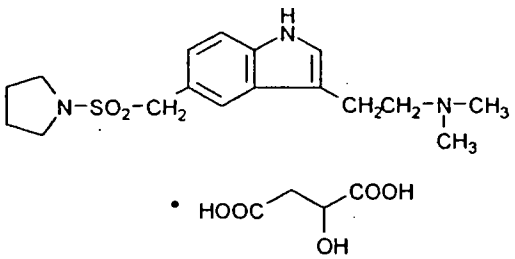
DRUG: Axert (Almotriptan)
FORMULATION: Tablets
STRENGTH: 6.25, 12.5 mg
TYPE: NME
NDA: 21001

PRIMARY REVIEWERS: Jogarao Gobburu, PhD
Vanitha J. Sekar, PhD
APPLICANT: Pharmacia & Upjohn
DATE OF REVIEW: 9/15/00

INTRODUCTION AND BACKGROUND

CHEMISTRY

Axert tablets contain almotriptan malate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist. Almotriptan D,L hydrogen malate is chemically designated as 1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine hydroxybutanedioate, and its structural formula is:



Its empirical formula is $C_{17}H_{25}N_3O_2S$-$C_4H_6O_5$, representing a molecular weight of 469.56. Almotriptan is a white to slightly yellow crystalline powder that is freely soluble in water and methanol but practically insoluble in ethanol and methylene chloride. Axert tablets are available for oral administration in strengths of 6.25 and 12.5 mg (corresponding to 8.75 mg and 17.5 mg of the hydrogen malate salt, respectively). Each compressed tablet contains the following inactive ingredients: mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium oxide, and carnauba wax.

PROPOSED MECHANISM OF ACTION

Almotriptan binds with high affinity to 5-HT$_{1D}$, 5-HT$_{1B}$, and 5-HT$_{1F}$ receptors, with higher affinity for meningeal tissue than for pulmonary or coronary 5-HT tissue. Almotriptan has weak affinity for 5-HT$_{1A}$ and 5-HT$_7$ receptors, but has no significant affinity or pharmacological activity at 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_6$; alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK_1, NK_2, NK_3) binding sites. Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack, and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways.

INDICATION

Axert tablets are indicated for the acute treatment of migraine with or without aura in adults.

PROPOSED DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 6.25 mg and 12.5 mg of AXERT Tablets were effective for the acute treatment of migraines in adults. Since individuals may vary in response to doses of Axert, the sponsor recommends that the choice of dose should be made on an individual basis. The label recommends that doses should be separated by at least 2 hours, not to exceed 50 mg within a 24-hour period.

CLINICAL PHARMACOLOGY

What is the dose response (effectiveness, safety) relationship?

Effectiveness: The primary endpoint in the pivotal clinical trials was a change in the pain intensity score by one unit (severe or moderate to mild or no pain) from the baseline. Figure 1 shows the number of patients having treatment failure or success per each dose group. The number of patients having a successful treatment effect seems to be similar for the highest 3 doses. Data from the CL11 study were used to characterize the dose – effect relationship. Unfortunately, no concentrations were measured in this study. The baseline pain score seems to have an influence on the effect. Logistic regression using SAS and NONMEM indicated an Emax model best describes the all or none end point. Figure 2 shows the observed and predicted probability of success.

Figure 1. Number of patients responding to the treatment for each dose group (Study CL011).

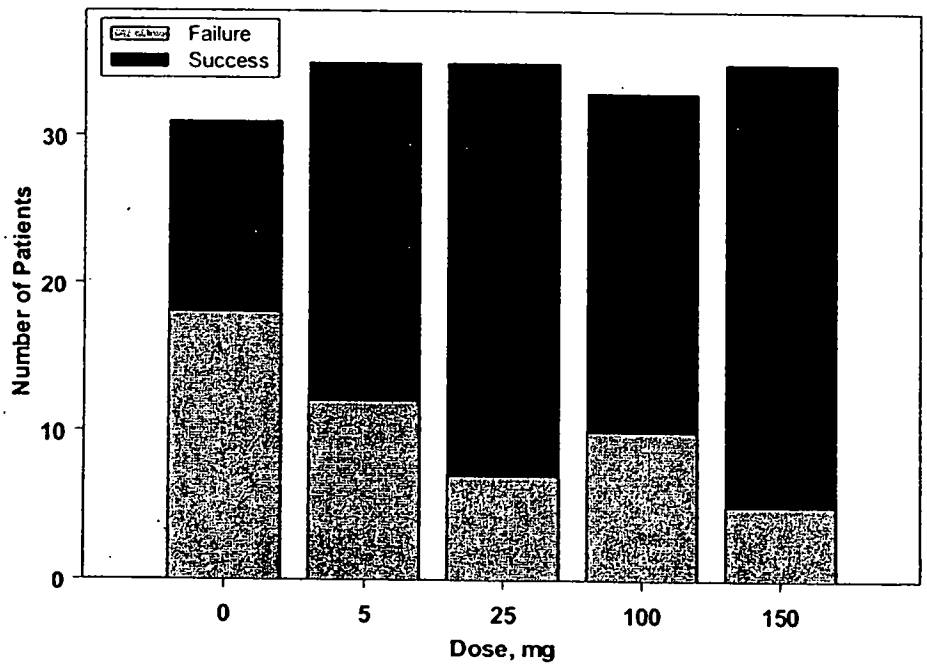
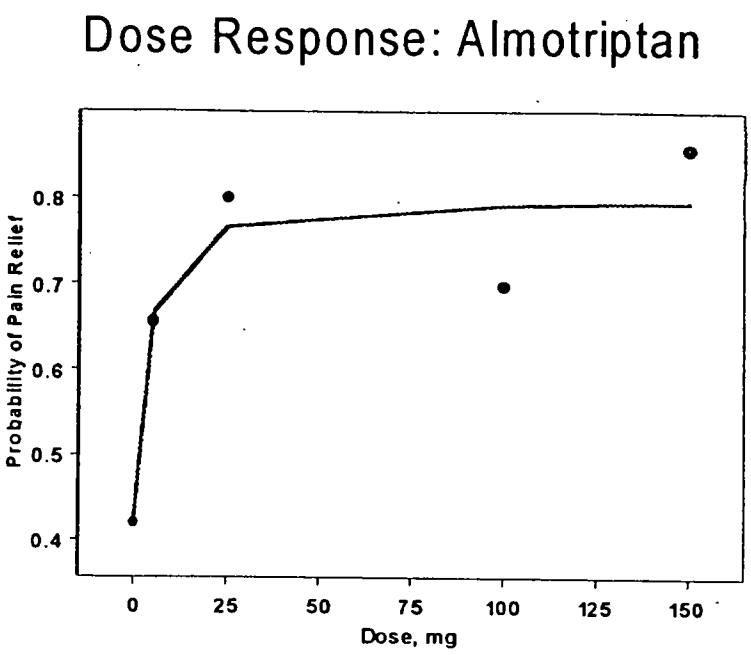


Figure 2. Observed and predicted probability of success for each dose group (Study CL011).



Safety: The most important side-effect of interest was the ability of almotriptan to prolong QT interval. The study with the widest dose/concentration range investigated (Study CL02; 0 – 200 mg) was considered for this analysis. Figure 3 shows the concentration – QTc interval data along with the linear model prediction. No strong concentration – QTc relationship could be found. The worst case scenario is when almotriptan is taken concurrently with ketoconazole. In this case, the maximum concentrations increase by about 60% and are around 150 – 200 ug/L. Figure 4 shows a stronger relationship of almotriptan concentration with heart rate.

Figure 3. Observed and predicted concentration – QTc relationship (Study CL02).

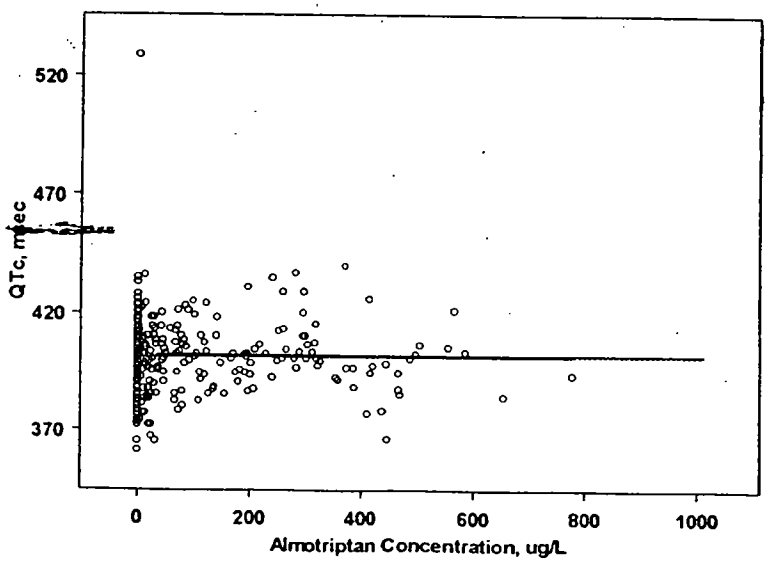
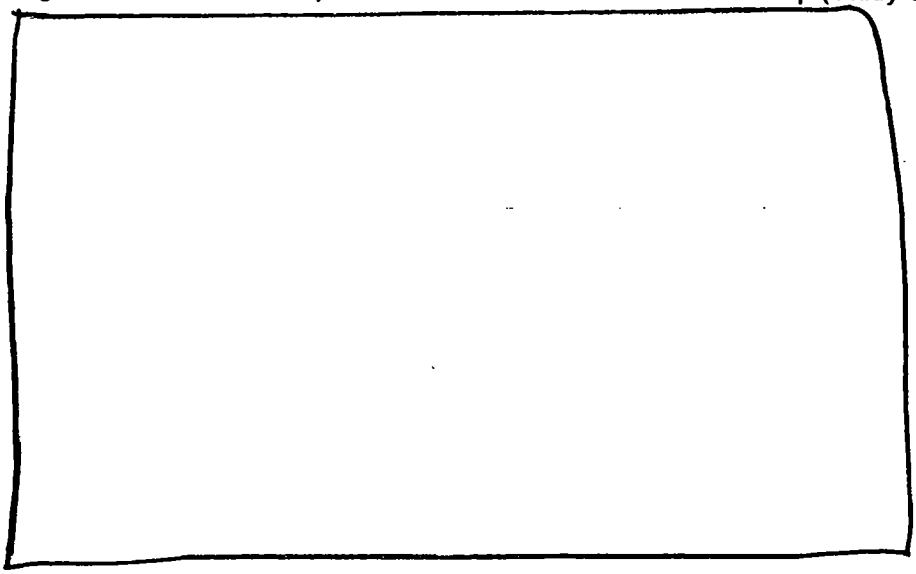


Figure 4. Observed and predicted concentration – HR relationship (Study CL02).



PHARMACOKINETICS (PK)

What is the PK behavior of almotriptan in healthy subjects?

Absorption

- Almotriptan is well absorbed following oral administration (see Figure 5)
- The mean (n=18 healthy males) oral bioavailability was estimated to be about 70% after oral dosing.
- In healthy volunteers, the pharmacokinetics of almotriptan are dose-proportional in the 5 – 200 mg (oral doses) range (see Table 1)

Figure 5

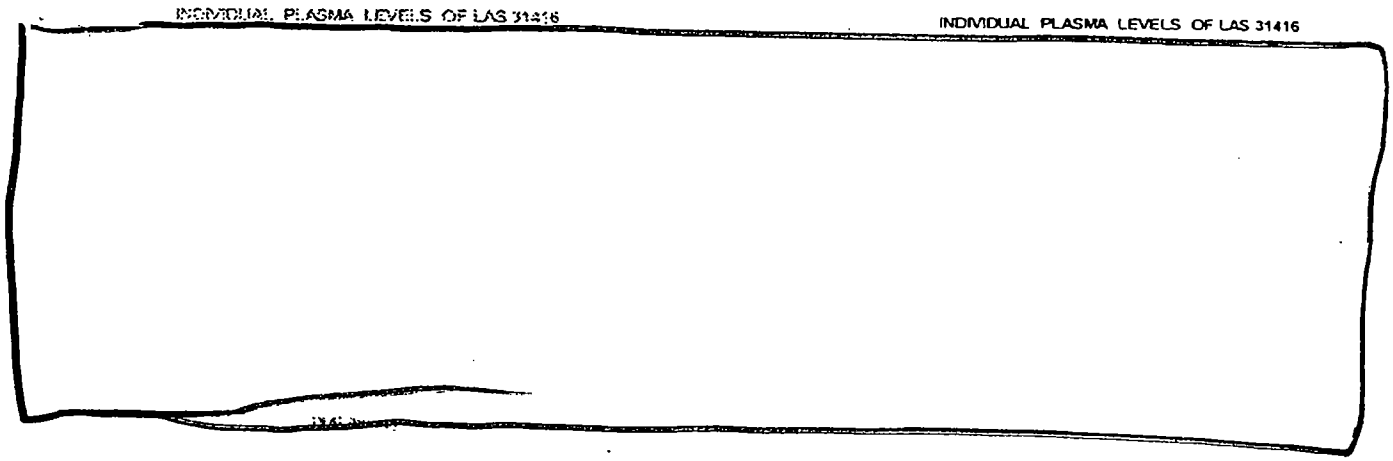


Table 1

Variable	Units	Mean (±SD)						
		5 mg (n=6)	10 mg (n=6)	25 mg (n=6)	50 mg (n=6[a])	100 mg (n=6)	150 mg (n=12[b])	200 mg (n=6[c])
C_{max}	ng/mL	18.0 (±3.8)	33.0 (±9.7)	103.0 (±18.2)	145.3 (±32.8)	299.9 (±70.5)	426.6 (±201.7)	565.5 (±158.4)
t_{max}	h	1.42 (±0.85)	1.88 (±1.24)	1.46 (±0.91)	2.67 (±1.03)	2.79 (±1.08)	2.90 (±0.85)	3.83 (±2.04)
AUC_{0-t}	h.ng/mL	94.0 (±14.4)	187.8 (±30.1)	508.6 (±46.1)	864.1 (±160.4)	1584.9 (±201.1)	2797.9 (±926.0)	3301.2 (±690.2)
$AUC_{0-\infty}$	h.ng/mL	105.1 (±17.7)	208.2 (±29.8)	558.5 (±51.0)	1100.3 (±70.9)	1824.3 (±292.8)	3319.3 (±1129.0)	3833.3 (±693.4)
k_z	/h	0.205 (±0.035)	0.209 (±0.031)	0.217 (±0.025)	0.188 (±0.030)	0.198 (±0.038)	0.217 (±0.038)	0.217 (±0.020)
$t_{1/2}$	h	3.38	3.32	3.19	3.69	3.50	3.19	3.19

Variable	Units	Range

Distribution

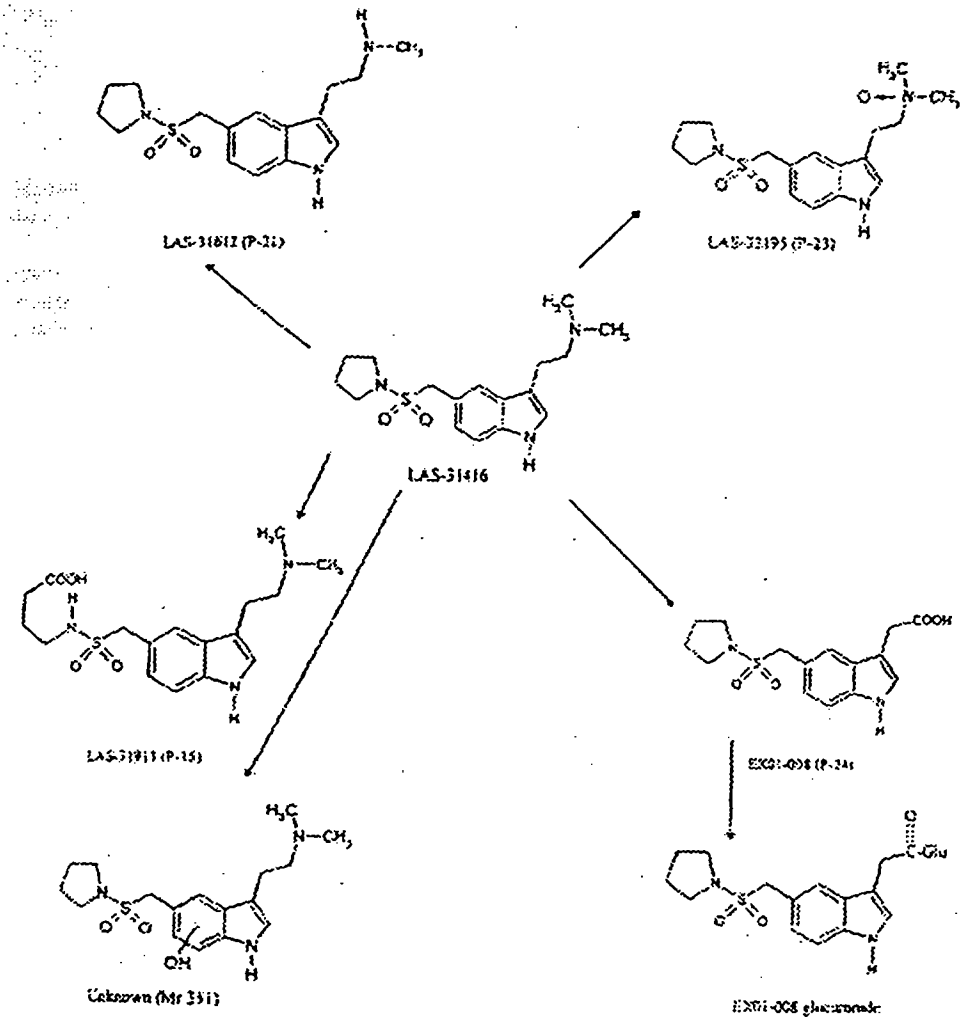
- Almotriptan is extensively distributed
- Mean apparent volume of distribution at steady – state is about 160 L
- The *in vitro* plasma binding ranged from 22.7 to 29.9% as measured by equilibrium dialysis.

Metabolism:

- Almotriptan is metabolized by two major and one minor pathways:
  - Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose). MAO-A is responsible for the formation of the indoleacetic acid metabolite
  - cytochrome P450-mediated oxidation (approximately 12% of the dose). Cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative
  - flavin monooxygenase is the minor route.
- All metabolites are inactive

Figure 6

METABOLIC SCHEME FOR ALMOTRIPTAN (LAS 31416)



Excretion

- The mean half-life of almotriptan is between 3 and 4 hours
- The primary route of elimination is via renal clearance, accounting for 75% of the administered dose
- Approximately 40% of an administered dose is excreted unchanged in urine
- Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism
- Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

SPECIAL POPULATIONS

What is the PK behavior of almotriptan during and outside a migraine attack?

- Since the absorption of almotriptan may be altered during a migraine attack (because of delay in gastric emptying during a migraine), pharmacokinetic parameters were compared during and outside a migraine attack.
- The rate and extent of absorption found during a migraine attack do not show significant differences compared to the administration outside the attack after a single dose of 12.5 mg.

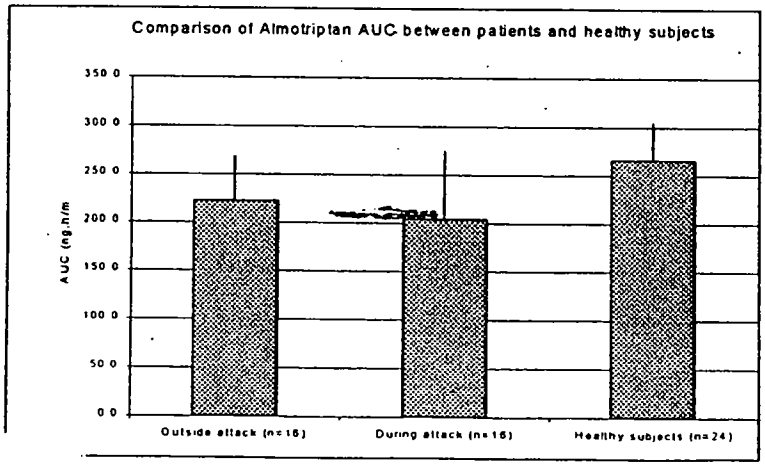
Table 2

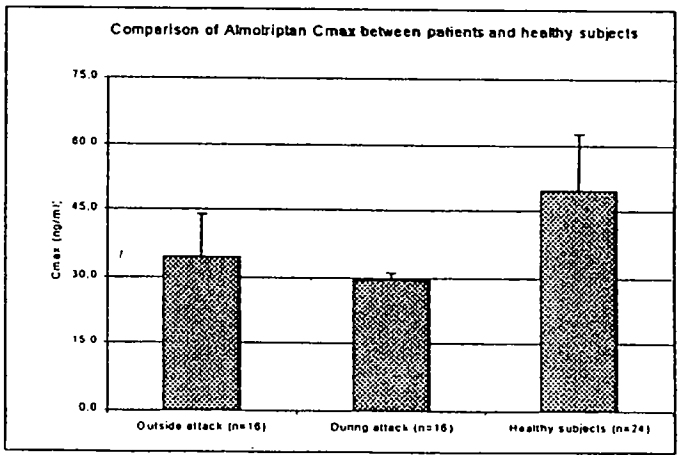
	Pharmacokinetic parameters during a migraine attack					
	Cmax (ng/ml)	Cmax (ng/ml)/kg	tmax(h)	t1/2(h)	AUC(ng.h/ml)	CL/F (ml/min/kg)
Overall Mean (n=15)	31.31	0.46	2.63	3.68	216.53	14.62
SD	9.00	0.18	1.54	0.90	51.81	3.39
%CV	28.74	35.25	58.51	24.37	23.93	23.16
Mean (females, n=10)	31.69	0.49	2.65	3.61	220.65	15.15
SD	10.22	0.18	1.36	1.00	54.21	3.71
%CV	32.23	37.85	51.13	27.59	24.57	24.50
Mean (males, n=5)	30.56	0.40	2.60	3.82	208.30	13.57
SD	6.91	0.09	2.04	0.74	51.53	2.65
%CV	22.60	22.14	78.59	19.36	24.74	19.55
	Pharmacokinetic parameters outside a migraine attack					
	Cmax (ng/ml)	Cmax (ng/ml)/kg	tmax(h)	t1/2(h)	AUC(ng.h/ml)	CL/F (ml/min/kg)
Overall Mean (n=15)	33.53	0.50	2.07	3.80	217.43	14.39
SD	8.90	0.19	0.88	0.54	44.06	3.04
%CV	26.54	37.84	42.76	14.17	20.26	21.12
Mean (females, n=10)	33.77	0.52	2.05	3.65	220.30	15.01
SD	9.32	0.19	0.80	0.53	45.70	3.40
%CV	27.59	36.29	38.91	14.51	20.74	22.67
Mean (males, n=5)	33.06	0.45	2.10	4.10	211.70	13.15
SD	9.02	0.20	1.14	0.46	45.10	1.84
%CV	27.29	43.77	54.29	11.31	21.30	14.01

How does almotriptan pharmacokinetics compare in migraine patients and healthy volunteers?

- Peak concentrations and AUC are approximately 40% and 25% higher, respectively in healthy subjects compared to migraine patients during an attack (see Figure 7).
- These differences are probably not clinically relevant

Figure 7

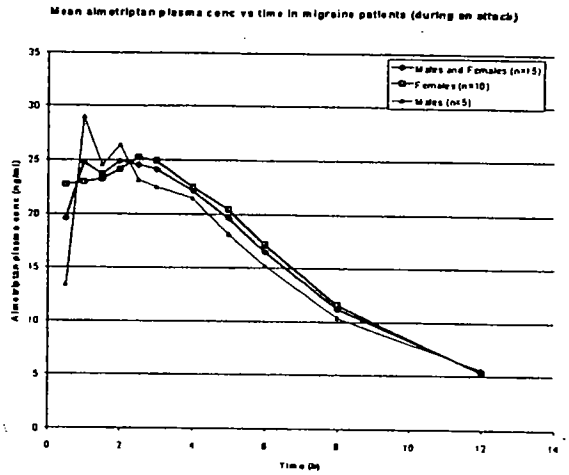




How does almotriptan pharmacokinetics compare between males and females?

- There appears to be no gender-related differences in almotriptan pharmacokinetics in migraine patients following a single dose of 12.5 mg (see Figure 8)

Figure 8



How does almotriptan pharmacokinetics compare between young adults and the elderly?

- The oral and renal clearance of almotriptan are lower in the elderly (33 L/h and 10 L/h, respectively) compared to the young subjects (40 L/h and 16 L/h, respectively) following 12.5 mg single dose
- The AUC in the elderly is about 25% higher compared to that in the younger population
- The label recommends that dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. The recommended dose of Axert for elderly patients with normal renal function for their age is the same as that recommended for younger adults.

Table 3

Parameter	Young	Elderly	p value
C_{max} (ng/mL)	46.22 (12.72)	56.82 (17.96)	ns
T_{max} (h)	1.8 (0.9)	1.8 (0.9)	ns
λ_z (h^{-1})	0.218 (0.026)	0.189 (0.025)	0.003
$t_{½}$ (h)	3.2 (0.4)	3.7 (0.5)	0.005
λ_3 (h^{-1})	0.089 (0.017)	0.082 (0.014)	ns
$t_{½}\lambda_3$ (h)	8.2 (2.1)	8.8 (1.5)	ns
MRT (h)	7.1 (2.1)	8.5 (1.6)	0.049
AUC (ng·h/mL)	324.6 (53.0)	405.4 (98.1)	0.007
CL/f (L/h)	40 (7)	33 (8)	0.012
$Ae_{0-32\,h}$ (mg)	4.97 (0.59)	3.67 (0.81)	0.0001
CL_R (L/h)	16 (3)	10 (3)	0.0001
Vz/f (L)	185 (42)	176 (52)	ns

What is the pharmacokinetic behavior of almotriptan in renally impaired patients?

- Pharmacokinetics of a single dose of 12.5 mg almotriptan in subjects with renal impairment was compared to those in subjects with normal renal function
- The apparent oral clearance of almotriptan is highly dependent on the creatinine clearance (CLCR) as evident from the equation: CL (L/h) = 0.47*(CLCR [ml/min]) + 11.69
- The clearance of almotriptan was approximately 65% lower in patients with severe renal impairment and approximately 40% lower in patients with moderate renal impairment compared to normal volunteers.
- Renal function is an important determinant of almotriptan clearance
- The label recommends that Axert should be administered with caution to patients with impaired renal function. The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be considered

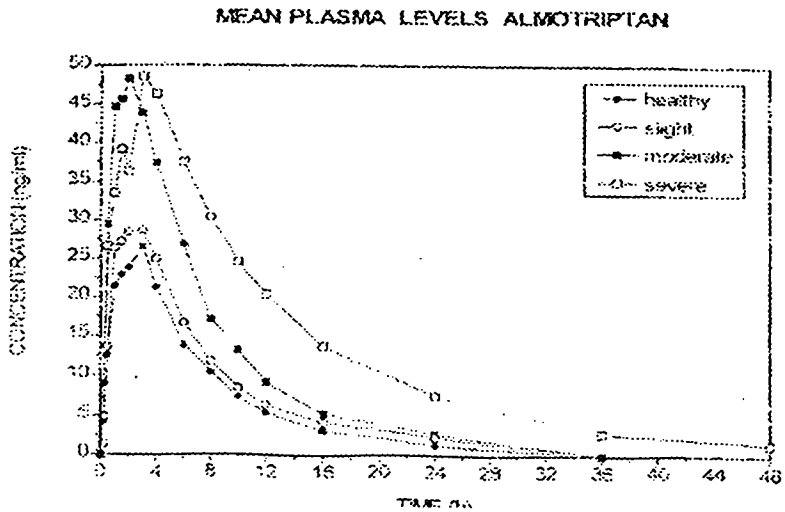
Table 4

The main pharmacokinetic parameters obtained after administration of a single oral dose of 12.5 mg in healthy volunteers and in volunteers with various degrees of renal impairment are summarized in the table below (mean ± SD):

PARAMETER	UNITS	HEALTHY	SLIGHT	MODERATE	SEVERE
C_{max}	ng/ml	29.33 ± 12.27	32.09 ± 9.48	53.99 ± 22.12	60.45 ± 11.07
t_{max}	h	2.2 ± 1.3	2.2 ± 1.0	2.4 ± 0.7	3.1 ± 0.9
λ_z	h^{-1}	0.178 ± 0.020	0.169 ± 0.036	0.176 ± 0.036	0.102 ± 0.021
$t_{1/2}$	h	4.0 ± 0.5	4.3 ± 1.0	4.1 ± 0.8	7.0 ± 1.6
λ_3	h^{-1}	0.079 ± 0.026	0.074 ± 0.020	0.096 ± 0.019	0.072 ± 0.023
$t_{1/2}\lambda_3$	h	9.8 ± 4.0	10.0 ± 2.6	7.5 ± 1.2	10.2 ± 2.5
MRT	h	9.8 ± 3.4	11.0 ± 2.5	8.8 ± 0.8	13.8 ± 2.1
AUC	ng.h/ml	228.5 ± 58.5	261.7 ± 60.7	410.3 ± 139.9	675.2 ± 205.2
CL/f	l/h	57.0 ± 11.1	45.5 ± 7.6	34.2 ± 13.5	19.8 ± 5.3
A_{e8}	mg	4.40 ± 0.56	3.69 ± 0.62	2.54 ± 1.18	0.67 ± 0.62
Cl_R	l/h	19.7 ± 2.1	13.1 ± 2.1	7.6 ± 5.5	1.2 ± 1.2
Vz/f	l	320 ± 61	284 ± 100	209 ± 120	196 ± 40

The elimination half-life value ($t_{1/2}$), calculated as ln2/mean λ_z, was 3.9 h in healthy volunteers and 4.1, 3.9 and 6.8 h in volunteers with slightly, moderately and severely impaired renal function, respectively.

Figure 9



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What is the pharmacokinetic behavior of almotriptan in hepatic impairment?

- The pharmacokinetics of almotriptan have not been assessed in this population.
- Based on the known mechanisms of clearance of almotriptan, approximately 40% of the dose of almotriptan is metabolized (MAO and CYPs).
- The label recommends that Axert should be administered with caution to patients with impaired hepatic function. The maximum daily dose should not exceed 25 mg over a 24-hour period, and a starting dose of 6.25 mg should be considered
- A hepatic impairment study for almotriptan will be requested as a Phase 4 commitment

What is the PK behavior of almotriptan in patients with hypertension?

- The label states that because Axert may increase blood pressure, it should not be given to patients with uncontrolled hypertension. Axert is contraindicated in patients with uncontrolled hypertension
- Almotriptan pharmacokinetics were assessed in patients with controlled hypertension. Plasma almotriptan concentrations in this population were not significantly different from those in healthy volunteers
- The relationship between dose and safety parameters (blood pressure and ECG parameters) and in patients with controlled hypertension was assessed
- As in healthy volunteers, almotriptan increased blood pressure in patients with hypertension controlled by medication. The blood pressure changes were modest and not considered clinically significant.
- Axert is not contraindicated in patients with hypertension that is controlled using antihypertensives.

DRUG-DRUG INTERACTIONS

Does almotriptan coadministration affect the pharmacokinetics of any of the coadministered drug(s) requiring a dosage adjustment for the coadministered drug(s)?

- In-vitro studies suggest that almotriptan does not inhibit or induce any CYP450 enzymes at therapeutic concentrations.
- Therefore, no in-vivo drug interaction studies were conducted to study the effects of almotriptan on coadminsitered drugs.

Do(es) any coadministered drug(s) affect the PK of almotriptan, requiring a dosage adjustment for almotriptan?

See Table 5

Table 5

Effect of Coadministered Drugs on Almotriptan Pharmacokinetics

Coadministered Drug	Coadministered drug Dose	Almotriptan Dose	N	Almotriptan PK parameters as Mean (SD)				Dose adjustment
				Cmax (ng/ml)		AUC (ng.h/ml)		
				Alone	with coadm. drug	Alone	with coadm. drug	
Ergotamine[a] (CYP3A inhibitor)	1 mg ergotamine and 100 mg caffeine (single dose)	12.5 mg (single dose)	12	45 (19)	38 (6)	291 (63)	300 (46)	No
Fluoxetine (CYP2D6 inhibitor)	3 x 20 mg qd for 8 days	12.5 mg (single dose)	15	44 (11)	53 (12)	333 (56)	353 (56)	No
Ketoconazole[b] (CYP3A4 inhibitor)	400 mg qd for 3 days	12.5 mg (single dose)	16	53 (9)	85 (20)	312 (38)	490 (24)	Yes
Propranolol (CYP450 inhibitor)	80 mg bid propranolol for 7 days	12.5 mg (single dose)	12	46 (8)	43 (8)	281 (55)	300 (56)	No
Verapamil (CYP3A4 inhibitor)	120 mg bid for 7 days	12.5 mg (single dose)	12	40 (9)	49 (14)	268 (51)	323 (66)	No

[a] Coadministration of ergotamine and almotriptan is contraindicated within 24 hours of each other

[b] Coadministration of ketoconazole and almotriptan resulted in approximately 60% increase in almotriptan exposure. A lower starting dose of 6.25 mg almotriptan is recommended when these two drugs are given together.

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BIOPHARMACEUTICS

- Almotriptan has a pka of 8.77 and the pH of a 1% solution in water is 4.1
- It is very soluble in water (66 mg/mL) and 0.1 M HCl (117.1 mg/mL)
- Almotriptan has a pH solubility profile ranging from > 1000 mg/mL at pH 2 to 2 mg/mL at pH 12. At pH 6, the solubility is > 20 mg/mL. Given the maximum tablet strength of 12.5 mg, this compound is considered to be highly soluble.
- Almotriptan permeability has been measured in Caco-2 cells and was found to be a low permeability drug
- Almotriptan belongs to Class III of the Biopharmaceutics Classification System
- Tablets available in 2 strengths of 6.25 mg and 12.5 mg

Table 6

Table 8.1. Permeability of almotriptan and other drugs

Drug	Caco-2 Cell Measurements	Permeability Class
Naproxen	50×10^{-6} cm/sec	High
Metoprolol	30×10^{-6} cm/sec	Medium*
Almotriptan	8×10^{-6} cm/sec	Low
Hydrochlorothiazide	1.5×10^{-6} cm/sec	Low

*Defines breakpoint between high and low permeability.

Table 7
Composition of to-be marketed formulation 'E' of almotriptan

Table 8.10. Almotriptan D,L-hydrogen malate tablets - Formulation C

Ingredient	6.25 mg Tablet: Quantity (mg)	12.5 mg Tablet: Quantity (mg)	Function	Reference to standards
Active Substance				
Almotriptan D,L-hydrogen malate	8.75*	17.50*	Active	In-house
Other Ingredients				
Mannitol				
[redacted] cellulose				
Povidone				
Sodium starch glycolate				
Sodium stearyl fumarate				
[redacted]				
Carnauba Wax				
[redacted]				

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

Is the clinical trial formulation the same as the tablet to-be marketed-in-USA?

- The bioequivalence of almotriptan 'B' tablets (used in adequate and well-controlled clinical studies) and 'E' tablets (final, scaled-up, production lot) was assessed in 24 healthy volunteers
- The log-transformed AUC (0 – infinity) and Cmax test – reference ratios were reported to be 0.97 and 0.92, respectively. The 90% confidence intervals are with-in the 85 – 125% equivalence criteria (AUC(0 – infinity): 93.22 – 100.48; Cmax: 83.78 – 101.15)
- The two formulations E and B (12.5 mg) are bioequivalent

Is there adequate justification for a waiver of BE study for the lower 6.25 mg strength of Axert?

- The clinical trial formulation (B) is identical to the to-be-marketed formulation (C/E) for both 6.25 and 12.5 mg strengths, except that "E" is scaled-up. The 6.25 mg formulation "B" has been used in clinical trials.
- The sponsor has performed in-vitro dissolution testing in 3 media (refer to Dissolution section for more details). Both the 12.5 mg and 6.25 mg formulations showed similar dissolution profiles in all the 3 media. The similarity factor, f2, values are between 57 – 86 and thus suggest that the profiles are similar
- Based on this information, the request for a biowaiver is granted.

EFFECT OF FOOD

What is the effect of food on almotriptan PK and how does it influence dosing recommendations?

- Food does not alter almotriptan PK. The label states that the rate and extent of absorption are not affected by food intake or by administration during a migraine attack.

Table 9

The main pharmacokinetic parameters obtained after administration of LAS 31416 under fasting condition and after food intake are summarized in the table below (mean ± SD):

PARAMETER	UNITS	TREATMENT	
		FASTING	FOOD
C_{max}	ng/ml	70.04 ± 20.15	78.12 ± 26.12
t_{max}	h	2.3 ± 1.4	1.7 ± 0.8
λ_z	h^{-1}	0.215 ± 0.028	0.186 ± 0.026
$t_{1/2}$	h	3.3 ± 0.4	3.8 ± 0.6
MRT	h	5.9 ± 0.9	6.1 ± 1.1
AUC	ng.h/ml	440.1 ± 106.2	461.9 ± 104.1
$f_{(max)}$	%	-	113.4 ± 25.6
$f_{(\infty)}$	%	-	108.3 ± 13.6

RECOMMENDATION: The clinical pharmacology and biopharmaceutics information provided in NDA 21-001 is adequate to support the approval of Axert for the treatment of migraine. The following deficiencies in the Clinical Pharmacology/Biopharmaceutics section have been identified:

1. A study in hepatic impairment will be requested as a Phase 4 commitment
2. Since coadministration of ketoconazole and almotriptan results in an increase in almotriptan concentration by approximately 60% (similar to severe renal impairment), a lower starting dose of 6.25 mg almotriptan is recommended when these two drugs are given together. A statement of caution will also be included for other potent CYP3A inhibitors such as ritonavir, erythromycin and itraconazole.

Labeling Comments: Please see Appendix (OCPB Labeling Comments)

/S/

Jogarao Gobburu, Ph.D. 9/19/2000
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

/S/

9/15/00

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9/19/2000

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cc: HFD-120 NDA 21-001
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HFD-340 /Viswanathan
HFD-860 /DPE I
CDR

84 page(s) of revised draft labeling has been redacted from this portion of the review.

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21-001**
Sponsor:	**Pharmacia & Upjohn**
Drug:	**almotriptan**
Proposed Indication:	**migraine**
Material Submitted:	**Response to Approvable Letter**
Correspondence Date:	**1/23/01**
Date Received / Agency:	**1/24/01**
Date Review Completed	**4/5/01**
Reviewer:	**Armando Oliva, MD**

1. Introduction

On 12/20/00, the Agency issued an approvable letter for almotriptan tablets. This submission represents the sponsor's complete response to the issues raised in the letter. The issues can be broadly divided into three major disciplines: clinical, clinical pharmacology, and CMC. I focus primarily on the clinical and clinical pharmacology issues in this review and refer the reader to the separate CMC review that addresses the responses to the CMC issues.[1]

The submission also contains marked-up draft labeling, which differs substantially from the approvable labeling that we sent with the letter. A large portion of the labeling changes involve pharmacology-toxicology sections, and I refer the reader to the pharm-tox review for their comments on the proposed changes.

2. Clinical

The approvable letter raised several clinical questions regarding five specific topics.

1. There was an apparent discrepancy in the reported results of study CL13 (one of the pivotal efficacy studies), as described in the study report and the ISE.
2. A clinical investigator site for study CL13, one of the pivotal trials, failed inspection. We requested a re-analysis of CL13 with data from this center excluded.
3. We requested additional clinical information on subject 756 in study CL25, who developed elevated hepatic transaminases while on chronic-intermittent almotriptan therapy.
4. We requested an explanation of the observed difference in reported adverse event incidences between the U.S and European long-term studies 0011 and CL25.
5. We requested an outlier analysis of blood-pressure data from appropriate phase1/2 studies that measured vital signs immediately post-dosing (*i.e.*, within the first 24 hours).

[1] In a subsequent meeting and teleconference with the sponsor, we determined that the CMC response was insufficient and we did not consider this submission a complete response. The sponsor has since submitted additional CMC information and the response is now complete and we began the two-month review time-clock.

Finally, the approvable letter contains a request for safety update as well as a request for their pediatric development plan, using standard "boiler plate" language. I describe below in detail the response to reach request.

2.1 Results of Study CL13

The report for study CL13 included an analysis of the 2-hour headache response rate between the 12.5mg and placebo groups. It reported a 95% confidence intervals for each group that overlapped with each other, yet the ISE reported a nominally significant p-value for this comparison. We asked that the sponsor explain this apparent discrepancy.

Study CL13 was one of the pivotal efficacy studies. It was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study that compared the 2-hour headache response rates among 25mg, 12.5mg, and placebo groups.

I show the two tables below. Table 1 shows the results, as described in the study report for study CL13 and as referenced in Dr. Chen's biostatistical review (sponsor table 4.2.1.1A, Item 8/10, Volume 15, page 35). The 95% confidence intervals for placebo, 12.5mg, and 25mg overlap.

Table 1: Study CL13 – Response Rates at 2 Hours and 95% Confidence Intervals

	Placebo	12.5 mg	25 mg	Sumatriptan 100mg
Response at 2 Hour				
No	57 (57.6%)	79 (43.2%)	83 (43.5%)	70 (36.3%)
Yes	42 (42.4%)	104 (56.8%)	108 (56.5%)	123 (63.7%)
Lower 95% Limit	34.01%	50.19%	50.34%	57.33%
Upper 95% Limit	51.19%	62.69%	62.60%	69.16%

Table 2 is the table reported in the ISE (sponsor Table 10, Item 8/10, Volume 91/ page 28). It shows a nominal p-value of 0.025 for the comparison between 12.5mg and placebo.

Table 2: Studies CL12, 13, 14 – Two-Hour Headache Response Rates

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	Almotriptan 6.25mg p-value	Almotriptan 12.5mg n/N (%)	Almotriptan 12.5mg p-value	Sumatriptan 100mg n/N (%)	Sumatriptan 100mg p-value
CL12	27/80 (33.8)	92/166 (55.4)	0.002	96/164 (58.5)	<0.001	[redacted]	
CL13	42/99 (42.4)	[redacted]		104/183 (56.8)	0.025	123/193 (63.7)	0.001
CL14	~~58/176~~ (33.0)	200/360 (55.6)	<0.001	240/370 (64.9)	<0.001	[redacted]	

p-values are Fisher's exact test vs. placebo
results for CL14 are for first attack only.

In response to our comment, the sponsor believes there is no discrepancy. They note that although the 95% confidence intervals in Table 1 (as reported in the study report) do indeed overlap, this should not be interpreted as indicating that the difference between the two proportions are not statistically significant. This criterion, they argue, is too stringent

for determining whether the difference between two proportions is statistically significant.

In order to support this argument, they performed a simulation to determine the alpha level of a test comparing two proportions. They used a sample size of 99 and 183 patients per treatment group (the number of placebo and almotriptan 12.5mg patients in study CL13) that was randomly generated from a binomial population with a response rate of .50. So, the assumption was that both treatment are equally effective with a true response rate of .50. The 95% confidence intervals for the response rates in each sample were calculated and compared to see if they overlapped. This was replicated 100,000 times. The number of replications where the confidence intervals did not overlap was 332. This suggests that if this criteria were used, the alpha level would be 332/100,000, or 0.00332, which is well below 0.05.

Table 2 (as reported in the ISE), reports a nominally significant difference between 12.5mg and placebo in study CL13 (p=0.025, Fisher's Exact Test). In this table, the sponsor notes, the proportions are compared appropriately.

Reviewer note: It is my understanding that the 95% confidence interval indicates that there is a 95% probability that the true proportion would lie somewhere within this interval. Conversely, there is a 5% probability that the true proportion lies outside that interval. I admit that this is different than the interpretation of a p-value of 0.05, which indicates that there is a 5% chance the results observed in the experiment could be due to chance, assuming that the null hypothesis were true.

2.2 Effect of the Zintsch Center

The on-site inspection of the one of the clinical sites in study CL13 (investigator – Dr. Zintsch) that was conducted on June 13-15, 2000 revealed significant irregularities that placed the data generated from that center in serious doubt. The Agency conveyed these findings to Dr. Zintsch in a letter dated 8/8/2000. As a result, we asked the sponsor to resubmit the results of study CL13 that both include and exclude the data from this center. The analysis of interest is the comparison of 12.5mg vs. placebo, since this is the analysis that will go in labeling.

The following table (sponsor table 1, Vol. 1, page 6) reports the comparison between 12.5mg and placebo groups from study CL13.

Table 3: Study CL13 – Two Hour Response Rates

	Placebo	Almotriptan 12.5mg	p-value
With Dr. Zintsch site	42.4% (n=99)	56.8% (n=183)	0.025
Without Dr. Zintsch site	40.0% (n=95)	57.1% (n=175)	0.008

The table reports that without the Zintsch site, the response rate for almotriptan was essentially unchanged at approximately 57%. The proportion of placebo-treated patients that responded at 2 hours fell from 42% to 40%, resulting in a lower p-value (0.008).

I performed my own analysis of this study, using the dataset for study CL13 that the sponsor provided in the original NDA. The efficacy dataset contained the investigator number (INV) as well as the country (COUNTRY). Although I did not know Dr. Zintsch's investigator number (this information was not provided in the metadata for the file), it was simple to determine that information. According to the sponsor's analysis, 4 placebo-treated patients and 8 patients treated with almotriptan 12.5mg were dropped from the analysis when the Zintsch data were excluded. I inspected all the German centers and found only once center (INV = 19797) that treated 4 patients with placebo and 8 patients with 12.5mg. No other German center had this distribution. The center treated 28 patients total, and it was the largest German center in the study. When Connie Lewin (of DSI) and I selected a center for inspection, we intentionally chose the largest center in that study, which turned out to be Dr. Zintsch's center. Therefore, I am confident that center 19797 was the Zintsch center.

Table 4 shows my analysis (RA = reviewer's analysis) of study CL13 which includes the data from the Zintsch center. The results for the PBO and 12.5mg group are identical to that reported by the sponsor in Table 3 above. The p-value for the 12.5mg vs. placebo comparison was 0.0247 (using Fisher's exact test), which is again the same as reported by the sponsor.

Table 4 (RA): CL13 – Two-Hour Response Rates (with Zintsch Center)

Treatment	No Response %	Response %	Total
PBO	57 57.58	42 42.42	99
12.5mg*	79 43.17	104 56.83	183
25mg	83 43.46	108 56.54	191
Suma 100mg	70 36.27	123 63.73	193
Total	289	377	666

p=0.0247 compared with placebo (Fisher's exact test)

Table 5 shows my analysis of study CL13 that excludes the data from the Zintsch center. The results for the PBO and 12.5mg groups are again identical to that reported by the sponsor in Table 3 above. The p-value for the 12.5mg vs. placebo comparison was 0.0077 (using Fisher's exact test), which is again the same as reported by the sponsor.

Table 5 (RA): CL13 – Two-Hour Response Rates (without Zintsch Center)

Treatment	No Response %	Response %	Total
PBO	57 60.00	38 40.00	95
12.5mg*	75 42.86	100 57.14	175
25mg	81 44.26	102 55.74	183
Suma 100mg	68 36.76	117 63.24	185
Total	281	357	638

p=0.0077 compared with placebo (Fisher's exact test)

In summary, I agree with the sponsor that exclusion of the Zintsch center data did not affect the results of the 12.5mg vs. placebo comparison in this study. Exclusion of the Zintsch ceter data actually increased the observed treatment effect, since the placebo rate actually fell by 2%, whereas the almotriptan 12.5mg response rate stayed essentially unchanged.

In the approvable labeling, we had asked that the sponsor include the results of study CL13 (minus the Zintsch center data) in both Kaplan-Meier curves that displayed the time to response and time to remedication data. The sponsor provides several new graphs. They acknowledge that they did not include CL13 in the original time to response graph because this study lacked a 6.25mg treatment arm, and because response data at 0.5 and 1.5 hours were not collected. Thus, if this study is to be included in the labeling, they recommend that only 1 and 2 hour time-points be included.

They did not include CL13 in the time to remedication graph because, again, the study lacked a 6.25mg group.[2]

The next three figures show the graphs of the probability of achieving a response within 2 hours. The first one is the graph that the sponsor originally proposed in the draft labeling. It contained pooled data from studies CL12 and CL14 only. The second shows the effect of adding the data from study CL13. Note that only the 1 and 2 hour data are shown, since study CL13 did not collect data at 0.5 and 1.5 hours. The third figure shows the same pooled data minus the Zintsch center data.

[redacted]

[2] In previous triptan applications, we have not accepted this reason (the lack of representation of all dose groups in a study) as sufficient to exclude the study from the graph. We have traditionally used all the data from all the pivotal efficacy studies.

Figure 1: Probability of Response (As originally proposed, CL12 and CL14 only)

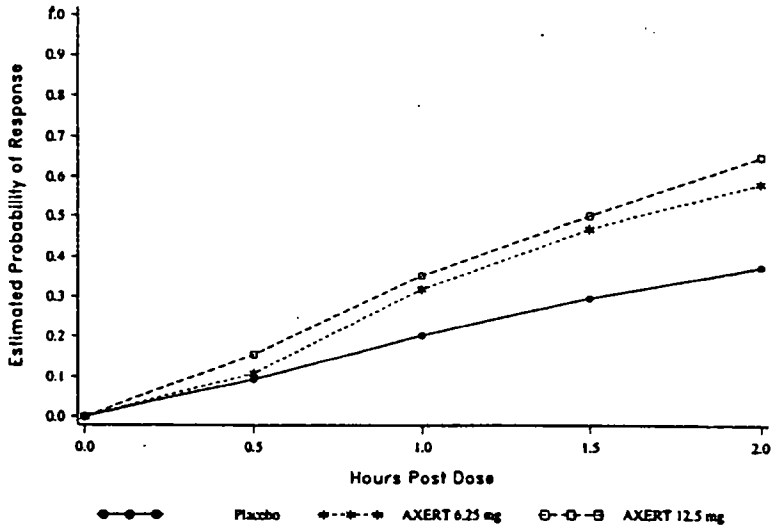

Figure 2: Probability of Response (CL12, CL13, CL14)

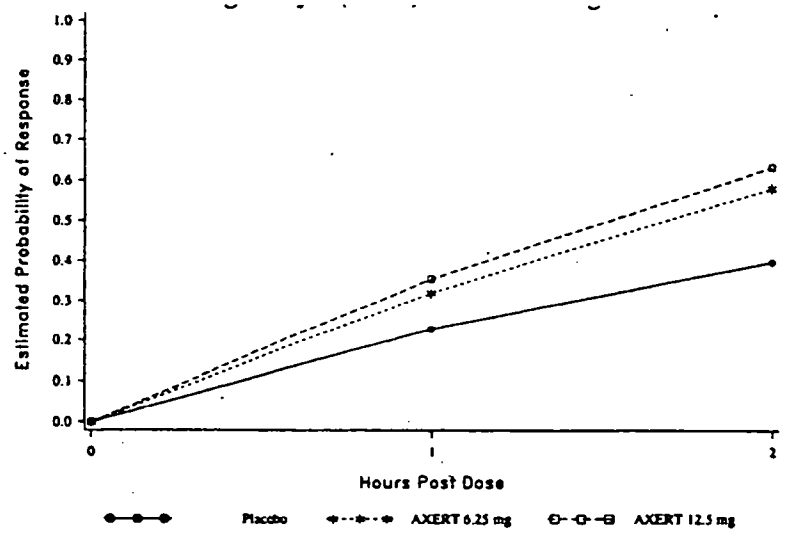

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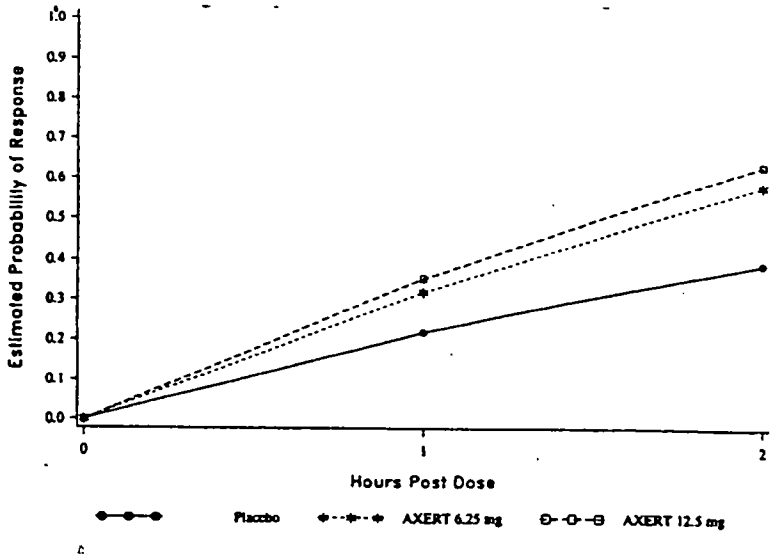
Figure 3: Probability of Response (CL12, CL13-minus Zintsch Center, CL14)



The three graphs are essentially the same. They show the 12.5mg has only a slight advantage over 6.25mg, and both are better than placebo. I recommend using Figure 3 in labeling.

The next three figures show various graphs of the probability of remedication within 24 hours. The first shows the original graph that was proposed in labeling at the original NDA submission. It containins pooled data from CL12 and CL14 only. The second shows the effect of pooling all three studies, and the third is the same as the second minus the Zintsch center data.

Figure 4: Probability of Remedication (As originally proposed, CL12 and CL14 only)

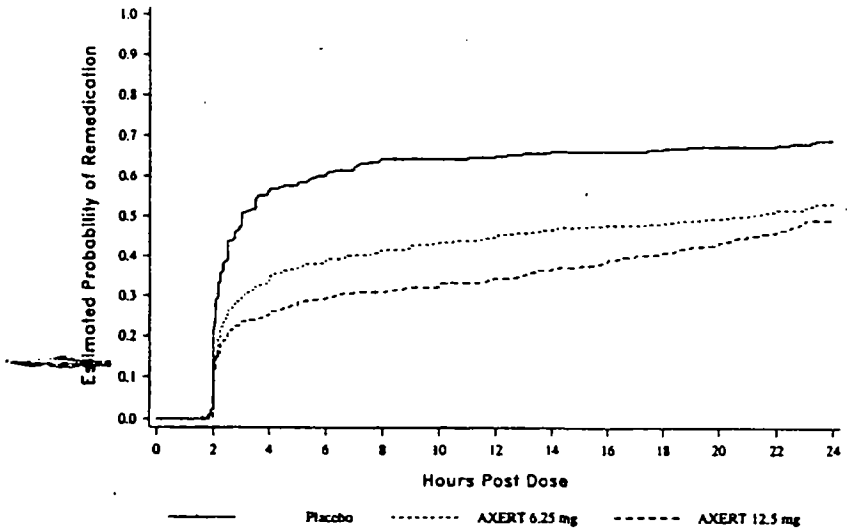


Figure 5: Probability of Remedication (CL12, CL13, CL14)

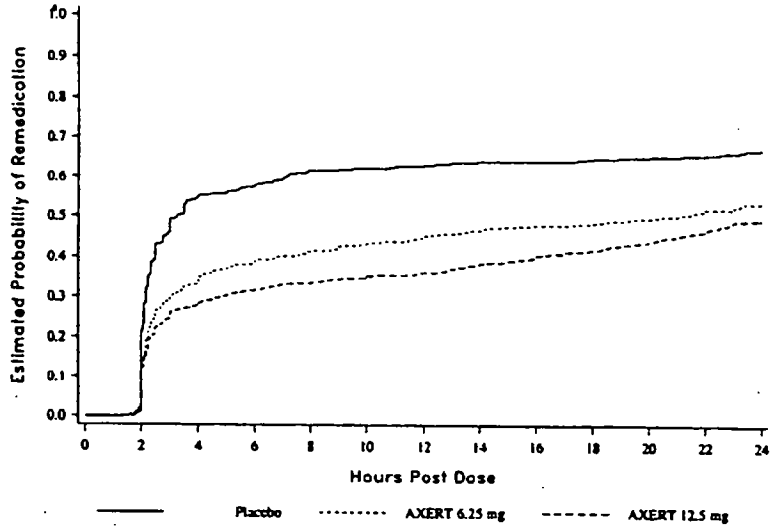
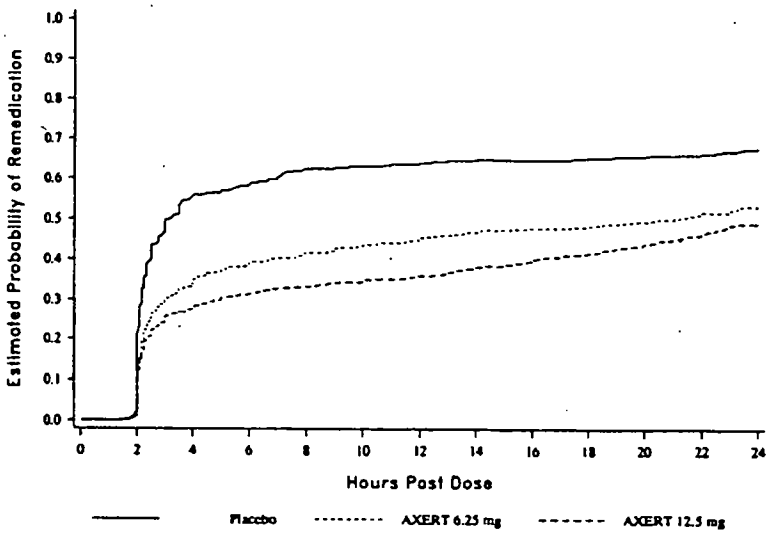


Figure 6: Probability of Remedication (CL12, CL13-minus Zintsch, CL14)



The three graphs are essentially identical. I recommend using Figure 6 in labeling.

One final note, the sponsor noted that the clinical trials section in labeling reported that 85% of the patients in the trials were female. They determine that this was incorrect, and the correct value is 86% (and is the same whether the Zintsch data are included or not). This has been corrected in their latest version of labeling.

2.3 Additional Patient Information

In the approvable letter, we requested additional clinical information on subject 756 from the European open-label long-term study CL25. This man developed clinically significant elevation in hepatic transaminases (AST/ALT) and total bilirubin while on chronic-intermittent almotriptan therapy. We requested a narrative summary, patient profile, and the case report form.

The sponsor reports that this was a 47 year old male (Coburg, Germany) who entered treatment with almotriptan 12.5mg in this long-term study on 7/30/97. His medical history included daily alcohol intake of 40 g/day. The patient returned for regular visits on 9/17/97 and 10/15/97. Up until the 10/15 visit, he had taken a total of 20 doses of study medication and presented no changes in health or laboratory analysis.

Four months into the study (11/26/97), and during which time he had taken a total of 25 doses of almotriptan, he returned to the clinic for his third regular visit. The investigator noted elevated AST, ALT, total bilirubin, and uric acid levels, outside the normal ranges. The patient was asymptomatic and the investigator took no action.

On 12/9/97, the patient returned to the clinic and was withdrawn from the study due to suspected heroin abuse. A physical examination revealed weight loss and "skin punctures" (translated from the German). Laboratory analysis revealed persistently elevated AST, ALT, total bilirubin, and uric acid levels. On 3/12/98, the patient returned to the clinic for follow-up. The abnormalities described were no longer present and the levels were in the normal range. He was not re-challenged with study medication. The pertinent lab data are shown in Table 6 (sponsor table 3, Vol. 1, page 12).

Table 6: Study CL25 – Pertinent Laboratory Data For Subject 756

Reviewer note: I reviewed the case report form and patient profile and did not uncover any additional pertinent information. Specifically, no additional tests were documented to investigate the cause of the laboratory abnormalities. I found no laboratory tests for viral hepatitis. From the available information, I would have to conclude that the laboratory abnormalities are possibly related to study drug. However, given the history of alcohol intake and suspected drug abuse, an unrelated hepatitis (alcohol, viral) remains possible as well.

2.4 Incidence of Adverse Events

In the approvable letter, we noted that the incidence of adverse events reported in the one-year long-term European trial (CL25) was lower than the AE incidences reported in the 6-month U.S. trial (0011). This is despite the fact that the European trial was twice as long and the opportunity to develop and report adverse events was greater (I reproduce table 36, page 41 of my original NDA review in Table 7 below, which illustrates these

differences between the two studies). We requested they submit a detailed description of the methodology used for the collection and reporting of AE data between the domestic and European experiences.

Table 7: Long-Term Studies – 2% Adverse Event Incidence Table

Adverse Event	CL25 12.5mg N=761 n (%)	0011 12.5mg N=585 n (%)
Body		
Back Pain	34 (4.5)	30 (5.1)
Chest Pain	11 (1.4)	17 (2.9)
Environmental Allergy	2 (0.3)	13 (2.2)
Flu syndrome	44 (5.8)	70 (12.0)
Headache	17 (2.2)	44 (7.5)
Localized Pain	23 (3.0)	29 (5.0)
Migraine	5 (0.7)	25 (4.3)
Neck Pain	14 (1.8)	12 (2.1)
Reaction Unavailable	13 (1.7)	12 (2.1)
Trauma	29 (3.8)	57 (9.7)
Upper Respiratory Infection	39 (5.1)	118 (20.2)
Digestive		
Diarrhea	15 (2.0)	18 (3.1)
Dyspepsia	11 (1.4)	16 (2.7)
Gastritis	15 (2.0)	1 (0.2)
Gastroenteritis	13 (1.7)	21 (3.6)
Nausea	23 (3.0)	30 (5.1)
Vomiting	32 (4.2)	18 (3.1)
Musculoskeletal		
Myalgia	14 (1.8)	17 (2.9)
Nervous		
Dizziness	22 (2.9)	26 (4.4)
Neuropathy	27 (3.5)	1 (0.2)
Respiratory		
Bronchitis	44 (5.8)	20 (3.4)
Cough	3 (0.4)	19 (3.2)
Pharyngitis	36 (4.7)	41 (7.0)
Rhinitis	20 (2.6)	30 (5.1)
Sinusitis	26 (3.4)	79 (13.5)
Special Senses		
Otitis Media	7 (0.9)	13 (2.2)
Urogenital		
Cystitis	20 (2.6)	1 (0.2)
Dysmenorrhea	5 (0.7)	27 (4.6)
Urinary Tract Infection	12 (1.6)	14 (2.4)

The sponsor reviewed the methodologies employed in the collection and reporting of adverse events in both studies 0011 and CL25. Overall, there were no differences in the methodologies used. In both studies, patients were instructed at the beginning of the study (in the informed consent) to report changes in their health or illnesses which occurred during the study. In both studies, patients were given a diary to facilitate the documentation of illnesses between clinic visits. In both studies, the definition, reporting,

and specifications were comparable. A summary of the methodologies used in each study is shown in Table 8 (modified from sponsor table in Appendix 4, Vol. 1, page 212).

Table 8: Studies 0011 and CL25 – AE Collection and Reporting Procedures

	0011	CL25
Definition	An AE is any untoward medical occurrence in a patient or trial subject administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have a causal relationship with the treatment or usage. A serious AE was either fatal or life-threatening, permanently or substantially disabling, or resulted in permanent impairment of function or permanent damage to a body structure, required intervention to prevent permanent impairment or damage, required prolonged hospitalization, or was a congenital anomaly or birth defect	An AE is an undesirable or unusual experience occurring in a patient concomitantly with receipt of an investigational drug in a clinical trial, whether or not considered related to the drug. Serious AE's are events associated with death, life-threatening, permanent or significant disability, hospitalization or prolongation of hospitalization and, also, congenital anomalies or cancer. Unexpected AE's are events which do not agree in nature, severity, frequency and specificity with the description of AE's in the investigator's brochure for the countries concerned. Life-threatening AE's are events for which it is necessary to take appropriate treatment in order to avoid the death of the subject.
Reporting	Nonserious and serious AE's were reported on an AE Report (AER) form, which was submitted to P&U as specified in the case report submission procedure for this protocol.	All AE's, signs and symptoms, reported or observed at any time during the study must be recorded in detail in the appropriate part of the CRF.
Reporting Period	Began at the initiation visit and ended with the final clinic visit; however, posttreatment follow-up was scheduled as appropriate.	Began at the patient enrollment to patient final visit.
Specifications	Description Start / Change Date (Time) Stop Date (Time) Intensity Seriousness Outcome Causality Action Taken	Description Start / Change Date (Time) Stop Date (Time) Intensity Seriousness Frequency Temporal sequence Outcome Causality Action Taken
Frequency	During the schedule visits, patients communicated AE's to the investigator. Scheduled visits occurred at 4, 12, 20, and 24 weeks	During the control visits, patients communicated AE's to the investigator (spontaneous and after requesting). Control visits occurred either after four treated migraine attacks or three months if the number of attacks was less than four, until one year of being enrolled in the study.
Informed Consent Instructions	"During the study, you will be asked to record medications and changes in your health on forms provided by the study doctor. "Study personnel will inquire about any changes since your last visit. "Study personnel will document the appropriate information obtained from your self-assessment booklet."	"You will need to tell your doctor at every visit if you were suffering from any illness at the time of the migraine attack. "If you do feel unwell or notice anything unusual during the study please write it down in your symptom booklet and tell your doctor at the next visit."

	0011	CL25
Diaries	A self-assessment booklet was maintained by the patient between the visits. Patients were instructed to write down all changes in their health in the booklet.	A symptom booklet was maintained by the patient between the visits. Patients were instructed to write down all untoward or adverse effects in the symptom booklet.

There was a difference in the frequency of patient visits. In CL25 (Europe), patients returned to the clinic either after four treated migraine attacks or after three months, whichever came first. In study 0011 (U.S.), patients returned for scheduled visits at 4, 12, 20, 24 weeks (*i.e.*, a patient in study 0011 would visit the clinic at fixed intervals which were independent of the number of treated attacks).

In my opinion, there still remains no easily identifiable explanation why the incidence of AE's differed in the two studies, but the fact remains that the incidence of AE's were generally lower in the European experience. This is again despite the fact that study 0011 was a six-month study and study CL25 was a year-long. One would expect that because the opportunity to report AE's in the European study was twice as long, the incidence of AE's in that study would be higher, not lower. This information provides evidence to suggest that the European study population was not entirely comparable to the domestic population, at least with regard to adverse event reporting.

I went back and examined the controlled trial AE data in more detail. There were five controlled trials available for analysis. This list included the three pivotal trials (CL12, CL13, CL14), as well as an early phase 2 dose-ranging European study (CL11) which used doses of placebo, 5mg, 25mg, 100mg, 150mg, and the lone U.S. study: 0008. This U.S. trial was a randomized, double-blind, active-controlled study that compared almotriptan 12.5mg or sumatriptan 50mg for the treatment of an acute migraine. It had a standard design, similar to other migraine efficacy studies. Since it did not have a placebo arm, it cannot be considered pivotal. However, the adverse events reported in this study do provide some useful insight into the potential differences between the U.S. and European populations. For this analysis, I used the electronic datasets that the sponsor provided for each study. I used the demographics datasets to determine the denominator for the purposes of adverse events incidence calculations. Each demographics dataset included all patients screened for each study in each dataset. The sponsor flagged each patient that was included in the safety population. From this information, I calculated number of patients analyzed for safety in each study (Table 9).

Table 9 (RA*): Studies CL12, CL13, CL14, 0008 – Safety Population

Study	PBO	2mg	5mg	6.25mg	12.5mg	25mg	100mg	150mg	suma 50mg	suma 100mg	Total
CL11	31	-	35			35	33	35	-	-	169
CL12	80	170	-	167	164	161	-	-	-	-	742
CL13	99	-	-	-	184	191	-	-	-	194	668
CL14	176	-	-	360	374	-	-	-	-	-	910
0008	-	-	-	-	591	-	-	-	582	-	1173
Total	**386**	**170**	**35**	**527**	**1313**	**387**	**33**	**35**	**582**	**194**	**3662**

*RA = reviewer analysis

Using the adverse events datasets for each study, I then calculated the incidences of all adverse events for the pooled safety dataset (US + European experience). I only included treatment emergent adverse events (and only adverse events for attack 1 in study CL14, just as the sponsor had done).

The pooled AE safety dataset included information on 1501 adverse events across all five studies. Of these, 115 were associated with the treatment of attack 2 in study CL14 and an additional 78 were associated with treatment of attack 3 in the same study. I removed these from the analysis. There were an additional 232 AE's that were not considered "treatment-emergent." The sponsor defined a treatment-emergent AE as one that was recorded during the post-treatment assessment period. This period varied according to the study. The post-assessment period lasted 3-5 days in study CL11, 2-6 days in studies CL12, CL13, CL14 and 4 days in study 0008. When these were removed, there remained total of 1076 adverse events for analysis.

The U.S. study used a single dose of almotriptan: 12.5mg. The only other studies that had a 12.5mg arm were CL12, CL13, and CL14. The incidence of adverse events in the 12.5mg arm across all studies is shown in Table 10.

Table 10 (RA): Incidence of Adverse Events in the Almotriptan 12.5mg Group

study	Almotriptan 12.5mg		
	N	n	%
U.S. (0008)	591	90	15.2
Foreign	722	112	15.5
CL12	*164*	*30*	*18.3*
CL13	*184*	*16*	*8.7*
CL14	*374*	*66*	*17.6*

In study 0008, 15.2% of patients treated with 12.5mg in study 0008 reported an adverse events. This was comparable with the overall incidences reported in the three European studies (15.5%). This analysis alone does not support the hypothesis that adverse events were underreported in Europe.

This most commonly occurring Adverse Events (≥ 0.5% incidence in any group) are shown in Table 11. I only show the placebo, 6.25mg, and 12.5mg groups. Those that occur with an equal or higher incidence in the placebo group are highlighted in gray.

Table 11 (RA): Safety Population – Adverse Events Incidence Table* (≥ 0.5%)

AE	PBO n=386	%	6.25mg n=527	%	12.5mg n=1313	%
NAUSEA	5	1.3	4	0.8	26	2.0
DIZZINESS	7	1.8	7	1.3	22	1.7
SOMNOLENCE	4	1.0	3	0.6	17	1.3
PARESTHESIA	2	0.5	6	1.1	16	1.2
HEADACHE	4	1.0	4	0.8	15	1.1
DIARRHEA	3	0.8	3	0.6	10	0.8
ASTHENIA	3	0.8	4	0.8	9	0.7
DRY MOUTH	2	0.5	6	1.1	9	0.7

AE	PBO n=386	%	6.25mg n=527	%	12.5mg n=1313	%
VASODILATION	0	0.0	2	0.4	9	0.7
LOCALIZED PAIN	1	0.3	1	0.2	8	0.6
VOMITING	6	1.6	1	0.2	8	0.6
ABD PAIN GEN	1	0.3	3	0.6	7	0.5
CHILLS	1	0.3	5	0.9	4	0.3
DIAPHORETIC	2	0.5	3	0.6	4	0.3
PALPITATION	2	0.5	4	0.8	3	0.2
NECK PAIN	2	0.5	3	0.6	2	0.2
VERTIGO	2	0.5	3	0.6	2	0.2
TREMOR	1	0.3	4	0.8	1	0.1
RESTLESSNESS	1	0.3	3	0.6	0	0.0

* adverse events with incidences ≥0.5% in any almotriptan group, and greater than placebo

Those that occur with an incidence of at least 1% and greater than placebo are: nausea, somnolence, paresthesia, headache, and dry mouth. When the incidences are rounded off to the nearest integer, then only **nausea, dry mouth**, and **paresthesia** occur with an incidence of at least 1% and greater than placebo. These are the ones that are listed in table 2 of proposed labeling (the 1% AE table).

I then repeated the same analysis and subgrouped the data according to data source (U.S. vs. European). I only examined the 12.5mg group since this is the only group that was common to both the U.S. and European studies. I present the most commonly occurring AE's (at least 0.5% incidence) in either the U.S. and/or European experience in Table 12.

Table 12 (RA): Adverse Events Incidence Table* (≥ 0.5%) – U.S. vs. European Source

AE	Almotriptan 12.5mg European* (N=722)		US** (N=591)	
	n	%	n	%
NAUSEA	13	1.8	13	2.2
DIZZINESS	10	1.4	12	2.0
HEADACHE	7	1.0	8	1.4
SOMNOLENCE	9	1.2	8	1.4
PARESTHESIA	9	1.2	7	1.2
DIARRHEA	4	0.6	6	1.0
VASODILATION	3	0.4	6	1.0
FLU SYNDROME	0	0.0	4	0.7
VOMITING	4	0.6	4	0.7
DRY MOUTH	6	0.8	3	0.5
FATIGUE	2	0.3	3	0.5
LOCALIZED PAIN	5	0.7	3	0.5
URI	1	0.1	3	0.5
ABD PAIN GEN	5	0.7	2	0.3
ASTHENIA	8	1.1	1	0.2
PHARYNGITIS	5	0.7	1	0.2
BACK PAIN	5	0.7	0	0.0

* studies CL12, CL13, CL14
** study 0008

This summary table shows that, following exposure to almotriptan 12.5mg, Americans tended to report adverse events in the controlled trials at slightly higher incidences compared to Europeans (exceptions: dry mouth, localized pain, abdominal pain, pharyngitis, back pain), but these differences were not clinically significant. In both groups, the numbers of patients reporting a particular adverse event in each treatment group are small.

I conclude that adverse event reporting incidences in the controlled trials from U.S. and Europe are similar, and this is in contrast with the incidences reported in the long-term studies.

Since the absolute AE incidences in the controlled trials are still lower than what we traditionally have seen with other triptans, I wondered whether this observation holds true for adverse events incidences following sumatriptan use. For this analysis, I compared the observed AE incidences for sumatriptan in the sponsor's development program with historical controls (I used sumatriptan approved labeling for the comparison).

Sumatriptan was used in two controlled trials: CL13 (100mg) and 0008 (50mg). The most commonly occurring AE's associated with sumatriptan use in these two studies are shown in Table 13. In general, sumatriptan treated patients had higher reported adverse events incidences than almotriptan-treated patients, so I used a 1% cutoff for the analysis. For comparison, I used the approved sumatriptan tablet labeling. This comparison was limited to the fact that the labeling used a 2% cutoff for reporting of adverse events, and the terms used do not exactly match the terms used in the almotriptan development program.

Table 13 (RA): Adverse Events Incidence Table (≥ 1%) - Sumatriptan

	Almotriptan Program				Sumatriptan Labeling	
	Suma 50mg (N=582)		Suma 100mg (N=194)		50mg	100mg
	n	%	n	%	%	%
ASTHENIA/FATIGUE	3	0.5	14	7.3	2*	3*
PARESTHESIA	5	0.9	5	2.6	5	3
DIZZINESS	10	1.7	4	2.1	<1**	2**
SOMNOLENCE	11	1.9	4	2.1		
ABD PAIN LOC	1	0.2	2	1.0		
CHEST PAIN	13	2.2	4	2.0	2	2
DYSPNEA	4	0.7	2	1.0		
HEADACHE	9	1.5	2	1.0		
PALPITATION	0	0.0	2	1.0		
RESTLESSNESS	1	0.2	2	1.0		
TREMOR	1	0.2	2	1.0		
URI	4	0.7	2	1.0		
NAUSEA	20	3.4	1	0.5		
VASODILATION	8	1.4	1	0.5		

* mapped to "malaise/fatigue" in approved labeling
** mapped to term "vertigo" in approved labeling

Nonetheless, the few items that can be compared show no systematic underreporting among the sumatriptan-treated patients in the almotriptan development program, based on historical controls.

It remains unanswered why the incidences of almotriptan-associated adverse events in the long-term European experience are lower compared to the long-term U.S. experience. Nonetheless, the proposed AE table proposed in labeling is accurate and does adequately reflect U.S. short-term controlled trial data.

2.5 Outlier Analysis

In the approvable letter, we requested that the sponsor conduct an outlier analysis of blood pressure data from appropriate phase 1/2 studies. In a subsequent teleconference, I further clarified this request to include an outlier analysis of blood pressure and heart rate data from placebo-controlled studies that measured these parameters shortly after study drug administration (*i.e.* during the first 24 hours of treatment). The studies that provided appropriate data for analysis were studies CL02, CL28, 0007, and CL11.[3]

CL02 and CL28 were phase 1 studies conducted in normal, healthy volunteers, 0007 was conducted in patients with hypertension controlled with medication, and CL11 was a phase 2 dose-ranging study. CL28 and 0007 were crossover studies by design, and CL02 and CL11 used a parallel design. The number of subjects exposed to study medication in each study is given in Table 14 (modified from sponsor table 4, Vol. 1, page 14).

Table 14: Studies CL02, CL28, 0007, CL11 – Study Population

Study	PBO	5mg	6.25mg	10mg	12.5mg	25mg	50mg	100mg	150mg	200mg
CL02	14	6		6		6	6	6	12	6
CL28	24				24	24	24			
0007	20				20	20				
CL11	31	35				35		33	35	
Total	**89**	**41**		**6**	**44**	**85**	**30**	**39**	**47**	**6**

The protocols did not pre-specify a set of criteria to identify outliers. Consequently, I recommended, and they used, the following definition in their post-hoc analysis of the vital signs data.[4]

Table 15: Definition of Outliers for Blood Pressure and Heart Rate Analysis

Systolic Blood Pressure	Absolute Value ≤ 90 mmHg
	Absolute Value ≥ 180 mmHg
	Increase ≥ 20 mmHg from baseline
	Decrease ≥ 20 mmHg from baseline
Diastolic Blood Pressure	Absolute Value ≤ 50 mmHg
	Absolute Value ≥ 105 mmHg
	Increase ≥ 15 mmHg from baseline

[3] the "CL" designator in the study name was used to identify European studies, and those studies beginning with "00" were domestic studies.
[4] This was the same definition used in the zolmitriptan NDA to identify vital signs outliers.

Heart Rate	Decrease ≥ 15 mmHg from baseline
	Absolute Value ≤ 50 bpm
	Absolute Value ≥ 120 bpm
	Increase ≥ 15 bpm from baseline
	Decrease ≥ 15 bpm from baseline

2.5.1 Systolic Blood Pressure

There were only two cases of absolute systolic blood pressure measurements ≥ 180 mmHg. One occurred in a subject who received 150mg (180 mmHg), and another occurred in a subject with controlled hypertension who received 25mg (182 mmHg).

There were 16 patients who had a total of 30 measurements of systolic BP ≤ 90 mmHg. The lowest systolic blood pressure recorded was 80mmHg. The measurements were scattered 0-16 hours post-dose. The distribution of abnormalities was as follows: PBO 3.4% (3/89); 5mg 2.4% (1/41); 10mg 0% (0/6), 12.5mg 6.8% (3/44); 25mg 5.9% (5/85); 50mg 10% (3/30); 100mg 2.5% (1/39); 150mg 0 (0/47); 200mg 0% (0/6). The numbers are small and difficult to interpret. Compared to placebo, patients exposed to 12.5mg, 25mg, and 50mg had incidence of low systolic blood pressure that were higher, but this trend was not seen at doses higher than 50mg. There was no clear dose-response relationship.

Changes from baseline exceeding 20 mmHg are shown in Table 16 (sponsor table 5, Vol. 1, page 15).

Table 16: Systolic Blood Pressure Changes from Baseline ≥ 20 mmHg

			Increase ≥ 20 mmHg from Baseline		Decrease ≥ 20 mmHg from Baseline	
Study	TRT	N	n	%	n	%
CL02	PBO	14	4	28.6	2	14.3
	5mg	6	2	33.3	1	16.7
	10mg	10				
	25mg	6	4	66.7	1	16.7
	50mg	6	3	50	1	16.7
	100mg	6	3	50		
	150mg	12	9	75	1	8.3
	200mg	6	6	100		
CL28	PBO	24	8	33.3		
	12.5mg	24	10	41.7	1	4.2
	25mg	24	6	25	1	4.2
	50mg	24	10	41.7	1	4.2
0007	PBO	20	2	10	3	15
	12.5mg	20	7	35	3	15
	25mg	20	12	60	4	20
CL11	PBO	31	2	6.5	6	19.4
	5mg	35	1	2.9	10	28.6
	25mg	35	5	14.3	12	34.3
	100mg	33	5	15.2	1	3
	150mg	35	3	8.6	5	14.3

The sponsor concludes that there is no clear dose-related increase in the incidence of outliers of systolic blood pressure increases of ≥20 mmHg in healthy volunteers, although in hypertensive patients (study 007), the incidence was increased in the 12.5mg and 25mg groups relative to placebo. In study CL02, there also seemed to be a dose-related increased incidence of outliers with systolic blood pressure ≥ 20 mmHg from baseline.

There was no dose-related pattern with respect to decreases from baseline.

2.5.2 Diastolic Blood Pressure

Absolute diastolic blood pressure measurements ≥ 105 mmHg were observed in six subjects in the phase 2 study CL11. Only one observation occurred at a dose less than 25mg. These are shown in Table 17 (sponsor table VS 2.2, Vol. 1, page 238).

Table 17: Absolute Diastolic Blood Pressure Measurements ≥ 105 mmHg

Study	Dose	Patient	Age/Sex	Hour	DBP MmHg	Δ from baseline
CL11	5mg	72	41/F	1 hr	105	15
	25mg	16	24/F	Baseline	105	
	25mg	73	49/F	1 hr	110	15
	25mg	211	53/M	2 hr	110	10
	150mg	2	48/F	2 hr	105	35
	150mg	104	44/F	1 hr	110	25

Absolute diastolic blood pressures ≤ 50 mmHg were very common in this generally healthy population. The incidence of outliers were as follows: placebo 12.3% (11/89); 5mg 9.8% (4/41); 12.5mg 30% (13/44); 25mg 12.9% (11/85); 50mg 37% (11/30); 100mg 0% (0/39); 150mg 8.5% (4/47); 200mg 0% (0/6). There was no clear dose-response relationship.

The incidences of subjects having changes from baseline diastolic pressure ≥ 15 mmHg in either direction are summarized in Table 18 (sponsor table 6, Vol. 1, page 16).

Table 18: Diastolic Blood Pressure Changes from Baseline ≥ 15 mmHg

			Increase ≥ 15 mmHg from Baseline		Decrease ≥ 15 mmHg from Baseline	
Study	TRT	N	n	%	n	%
CL02	PBO	14	1	7.1	1	7.1
	5mg	6			1	16.7
	10mg	6	1	16.7	1	16.7
	25mg	6	1	16.7		
	50mg	6	1	16.7		
	100mg	6	4	66.7		
	150mg	12	8	66.7		
	200mg	6	4	66.7		
CL28	PBO	24	6	25	5	20.8
	12.5mg	24	7	29.2	7	29.2
	25mg	24	9	37.5	4	16.7
	50mg	24	11	45.8	6	25
0007	PBO	20	1	5	1	5

Study	TRT	N	Increase ≥ 15 mmHg from Baseline n	%	Decrease ≥ 15 mmHg from Baseline n	%
	12.5mg	20	2	10	2	10
	25mg	20	6	30	2	10
CL11	PBO	31	3	9.7	2	6.5
	5mg	35	2	5.7	4	11.4
	25mg	35	5	14.3	6	17.1
	100mg	33	5	15.2		
	150mg	35	4	11.4	3	8.6

There seemed to be a dose-related increasing incidence of outliers having an increase in diastolic blood pressure from baseline in three of the four studies (CL02, CL28, and 0007), but this was not seen in CL11, and it occurred generally at doses 25mg or higher. There was no trend noted in decreases from baseline.

2.5.3 *Heart Rate*

No heart rates ≥ 120 bpm were observed. Heart rates ≤ 50 bpm were common in these studies, regardless of the treatment administered. The incidence of subjects having at least one heart rate measurement ≤ 50 bpm were: PBO 28% (25/89); 5mg 7% (3/41); 10mg 67% (4/6); 12.5mg 50% (22/44); 25mg 21% (18/85); 50mg 43% (13/30); 100mg 5% (2/39); 150mg 6% (3/47); 200mg 17% (1/6). There was no clear dose-response relationship.

Incidences of outliers with changes from baseline ≥ 15 bpm in either direction are summarized in Table 19 (sponsor table 7, Vol. 1, page 17).

Table 19: Heart Rate Changes from Baseline ≥ 15 bpm

Study	TRT	N	Increase ≥ 15 bpm from Baseline n	%	Decrease ≥ 15 bpm from Baseline n	%
CL02	PBO	14	5	35.7	1	7.1
	5mg	6			1	16.7
	10mg	6	2	33.3		
	25mg	6	3	50	1	16.7
	50mg	6	3	50	1	16.7
	100mg	6	2	33.3		
	150mg	12	8	66.7		
	200mg	6	4	66.7		
CL28	PBO	24	17	70.8	1	4.2
	12.5mg	24	17	70.8	1	4.2
	25mg	24	16	66.7	1	4.2
	50mg	24	16	66.7	3	12.5
0007	PBO	20			7	35
	12.5mg	20			5	25
	25mg	20	1	5	6	30
CL11	PBO	31			5	16.1
	5mg	35	2	5.7	4	11.4
	25mg	35			2	5.7
	100mg	33	2	6.1	6	18.2
	150mg	35			4	11.4

There was no obvious dose-related effects on the incidence of subjects having significant increases or decreases in heart rate from baseline.

The sponsor concludes that based on the outlier analyses, almotriptan does not affect heart rate and has modest effects on blood pressure at therapeutically relevant doses. I agree that the effects on blood pressure seen generally occur at doses higher than the highest planned marketed dose of 12.5mg.

2.6 Safety Update

The sponsor reports no new studies have been completed that have not already been reported to the Agency in the NDA. The sponsor asserts that:

- No new data from completed studies are available
- No new safety trends or patterns have been identified from the existing data
- No other indications have been studied

The sponsor is not conducting any ongoing studies.

The European sponsor, [redacted] is, however, conducting a post-authorization study (study T.E.A.). This is an open-label observational, multicenter study over a 3-month monitoring period. It is intended to evaluate the tolerability and effectiveness of the treatment under study for all the acute migraine attacks that a patient suffers over a 3-month period. It plans to enroll 1500 patients. As of 11/21/2000, 1285 patients have been enrolled, and 2730 migraine attacks have been treated under protocol. There was one serious adverse event reported (described below). No patients have discontinued or died as of this safety cutoff date.

The sole SAE was in a 27 year-old woman. She reported abdominal and lumbar pain with nausea and vomiting on 7/28/2000. She had experienced a migraine attack on 7/24/2000 and took one almotriptan 12.5mg tablet. She had also taken [redacted] Her previous migraine was 2 days before the described attack, during which she had taken two almotriptan tablets. One day following the onset of her attack, on 7/25/2000, the migraine persisted and she took a dose of zolmitriptan (unknown dose). She developed the abdominal and lumbar pain on 7/28/2000 and received an intramuscular injection of [redacted] in the hospital and was discharged. On 7/29/2000 she returned with the feeling that she was "urinating sand" and was hospitalized after laboratory analysis revealed an elevated BUN (66 mg/dl) and creatinine (2.3 mg/dl). The clinical picture suggested renal colic. She recovered and was discharged on 8/7/2000. According to the investigator and the monitor, any relationship to study drug seemed unlikely. The patient has continued to take almotriptan after her hospitalization without reporting any adverse reactions or events.

Almotriptan is currently only marketed in Spain under the trade names "Almogran" 12.5mg tablets (marketing authorization approved 12/23/99) and "Amignul" 12.5mg tablets (marketing authorization approved 3/14/2000). It was actually launched in Spain on 9/18/2000. It is estimated that a total of [redacted] have been dispensed in that country.

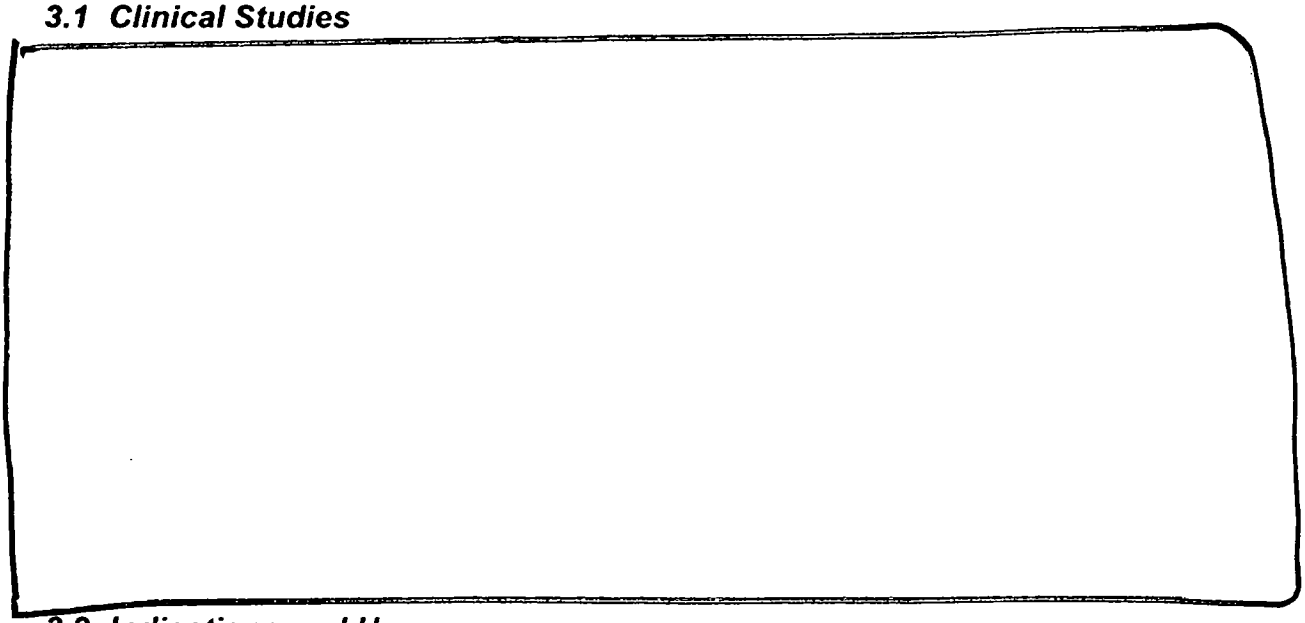
2.7 Pediatric Development Plan

The sponsor plans to submit their pediatric development plan within 120 days of the 12/20/2000 approval letter.

3. Labeling Review

The sponsor has proposed additional changes to the labeling that accompanied the approvable letter. I limit my discussion to the clinical portion of the labeling, beginning with the clinical trials section.

3.1 Clinical Studies



3.2 Indications and Usage

The sponsor accepts the language in the approvable labeling.

3.3 Contraindications

The sponsor accepts the language in the approvable labeling.

3.4 Warnings

The sponsor makes minor editorial changes, which are acceptable.

The section describing increases in blood pressures has been modified to describe mean changes in blood pressure, as requested in the approvable labeling, and focuses on the changes seen with the therapeutically relevant doses. These changes are acceptable.

3.5 Precautions

There are numerous changes to the preclinical section of Precautions. I defer comment to the pharm/tox reviewer.

The subsection on MAO inhibitors now includes a quantitation of the increase in C_{max} seen with moclobemide co-administration, as requested in the approvable labeling. This is acceptable.

The sponsor has combined the two subsections on ketoconazole and other CYP3A4 inhibitors into one subsection. This change is acceptable. However, they delete reference to the Dosage and Administration section since they do not believe that dose adjustment is necessary. They reference the fact that coadministration with ketoconazole results in a 60% increase in C_{max} and AUC. In their review of other triptan labeling, they found only one other instance of a dose reduction recommended in the setting of a less than 100% increase in exposure. This was rizatriptan-propranolol interaction, which results in a 70% increase in AUC of rizatriptan. The interaction between cimetidine-zolmitriptan, the sponsor argues, results in a doubling of AUC and half-life, yet no dose reduction is recommended. They argue that the ketoconazole-almotriptan interaction is lower and less variable than the rizatriptan-propranolol interaction, and also less than the cimetidine-zolmitriptan interaction, and therefore no dose adjustment should be necessary.

I will defer to the biopharmaceutics review regarding the PK data on this issue, but from a pure clinical standpoint, the exposures obtained with a 60% increase in C_{max} and AUC would be less than that obtained with a single dose of almotriptan 25mg, a dose which was studied rather extensively in clinical development Although there was a dose-dependent increase in adverse events seen, there were no major safety concerns with its use. I refer the reader to my original NDA review, tables 31 and 32 which I reproduce below. They compare the adverse event profiles of 6.25mg, 12.5mg, and 25mg doses from the controlled trials database (Table 20 and Table 21).

Table 20 (orig. rev. Table 31): Controlled Studies – Adverse Events by Body Systems

System	PBO N=386 n (%)	6.25mg N=527 n (%)	12.5mg N=1313 n (%)	25mg N=387 n (%)	Sumatriptan 50mg N=582 n (%)
Body (General)	12 (3.1)	25 (4.7)	78 (5.9)	33 (8.5)	48 (8.2)
Cardiovascular	3 (0.8)	9 (1.7)	16 (1.2)	11 (2.8)	9 (1.5)
Digestive	14 (3.6)	16 (3.0)	56 (4.3)	20 (5.2)	32 (5.5)
Hemic and Lymphatic	0	0	1 (0.1)	1 (0.3)	0
Metabolic and Nutritional	1 (0.3)	0	6 (0.5)	0	0
Musculoskeletal	1 (0.3)	4 (0.8)	5 (0.4)	4 (1.0)	2 (0.3)
Nervous	17 (4.4)	26 (4.9)	68 (5.2)	27 (7.0)	38 (6.5)
Respiratory	7 (1.8)	4 (0.8)	23 (1.8)	3 (0.8)	18 (3.1)
Skin	6 (1.6)	5 (0.9)	11 (0.8)	5 (1.3)	3 (0.5)
Special Senses	4 (1.0)	11 (2.1)	11 (0.8)	6 (1.6)	3 (0.5)
Urogenital	2 (0.5)	2 (0.4)	5 (0.4)	4 (1.0)	3 (0.5)

Studies CL11, CL12, CL13, CL14 (1st attack only), and 0008

Table 21 (orig. rev. Table 32): Controlled Studies – 1% Adverse Event Incidence Table

Adverse Event	PBO N=386 n (%)	6.25mg N=527 n (%)	12.5mg N=1313 n (%)	25mg N=387 n (%)	Sumatriptan 50mg N=582 n (%)
Body					
Asthenia	3 (0.8)	4 (0.8)	9 (0.7)	10 (2.6)	2 (0.3)
Chest Pain	1 (0.3)	1 (0.2)	3 (0.2)	5 (1.3)	13 (2.2)
Headache	4 (1.0)	4 (0.8)	15 (1.1)	3 (0.8)	9 (1.5)
Cardiovascular					
Palpitation	2 (0.5)	4 (0.8)	3 (0.2)	7 (1.8)	0
Vasodilation	0	2 (0.4)	9 (0.7)	4 (1.0)	8 (1.4)

Adverse Event	PBO N=386 n (%)	6.25mg N=527 n (%)	12.5mg N=1313 n (%)	25mg N=387 n (%)	Sumatriptan 50mg N=582 n (%)
Digestive					
Dry Mouth	2 (0.5)	6 (1.1)	9 (0.7)	4 (1.0)	4 (0.7)
Nausea	5 (1.3)	4 (0.8)	26 (2.0)	6 (1.6)	20 (3.4)
Nervous					
Dizziness	7 (1.8)	7 (1.3)	22 (1.7)	8 (2.1)	10 (1.7)
Paresthesia	2 (0.5)	6 (1.1)	9 (0.7)	4 (1.0)	4 (0.7)
Somnolence	4 (1.0)	3 (0.6)	17 (1.3)	9 (2.3)	11 (1.9)

Studies CL11, CL12, CL13, CL14 (1st attack only), and 0008

3.6 Adverse Reactions

The section contains minor editorial changes, which are acceptable.

3.7 Drug Abuse and Dependence

The sponsor accepts the language in the approvable labeling.

3.8 Overdosage

The sponsor accepts the language in the approvable labeling.

3.9 Dosage and Administration

The sponsor makes minor editorial changes, which are acceptable. They make a reference to the clinical studies section of labeling when discussing the dose. This is present in other triptan labeling and is acceptable.

They eliminated the dose adjustment for ketoconazole and CYP3A4 inhibitors, which I believe is acceptable, for reasons described previously.

3.10 Patient Information

As we requested, they have added a paragraph in the "Can I take Axert with other medications?" section that alerts the users to inform their doctor if they are taking a CYP3A4 inhibitor (even though no dose adjustment may be necessary). Even though no dose adjustment may be necessary, this statement is similar to the statement already present in this section regarding MAO inhibitors.

4. Comments

The sponsor had adequately addressed the requests for clinical information contained in the approvable letter. I recommend approval of the NDA.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. _____

ao 4/5/01
cc:
HFD-120
NDA 21-001

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21-001**
Sponsor:	**Pharmacia & Upjohn**
Drug:	**almotriptan**
Proposed Indication:	**migraine**
Material Submitted:	**PPSR and Peds Dev Plan**
Correspondence Date:	**3/28/01**
Date Received / Agency:	**3/29/01**
Date Review Completed	**4/16/01**
Reviewer:	**Armando Oliva, MD**

1. Introduction

In the approvable letter, dated 12/20/00, we requested that the sponsor submit their proposed pediatric development plan in order to fulfill the requirements of the pediatric rule. This submission responds to that request, and is itself a proposed pediatric study request to support pediatric exclusivity pursuant to section 505A of the Act.

2. Proposed Pediatric Development Plan

The sponsor proposes to conduct the following studies:

1. Adolescent efficacy and safety study: This is an acute study entitled "A randomized, double-blind, placebo-controlled study of oral almotriptan in the treatment of acute migraine in adolescents.
2. Adolescent pharmacokinetic study: This is entitled "Almotriptan: Comparison of the Pharmacokinetics in healthy adolescents and adults.

They provide a brief synopsis of each protocol, which I describe below.

3. Acute Efficacy/Safety Study

The primary objective of this study is to evaluate the efficacy of almotriptan 6.25mg and 12.5mg compared to placebo in the treatment of a moderate to severe migraine attack in adolescents 12-17 years of age.

The design will be a randomized, double-blind, parallel-group, placebo-controlled acute migraine treatment trial. Patients will receive a single oral dose of 6.25mg, 12.5mg or placebo at the onset of a moderate or severe migraine headache.

The planned sample size is 210 patients in each of three groups (N=630). This is powered (80%) to detect a 15% difference in 2-hour response rates between placebo and either almotriptan group. Each comparison will be at the α=0.025 level, to maintain the overall α level at 0.05.

The primary endpoint will be the 2-hour headache response rate. Multiple standard secondary migraine endpoints are planned. Standard safety monitoring is planned.

4. Pharmacokinetic Study

The objective of this study is to compare the PK of almotriptan between adolescents (12-17) and adults.

The design will be an open label, parallel-group, single dose study in adolescents and adults. A single dose of 12.5mg will be given. Plasma and urine concentrations of almotriptan will be collected at various time points.

The planned sample size is 20 subjects in each group (N=40). This is powered (80%) to detect an 18% difference in AUC between groups, using α=0.05.

5. Comments

1. The sponsor will also need to conduct a year-long safety study in adolescents. This study should be large enough to provide long-term safety data on at least 300 adolescents who each treat two or more migraines per month for six months, and at least 100 adolescents who each treat two or more migraines per month for one year.
2. The studies should enroll an equal number of younger (12-14) and older (15-17) adolescents. The sponsor should consider stratifying the randomization in the planned efficacy study by the these two age groups.
3. The efficacy study should not begin until the results of the PK study are known. Should it result that exposures in adolescents are substantially higher than those seen in adults, then either a dose adjustment (*i.e.*, reduction) for the efficacy study might be necessary, or initial exposures to study drug in the efficacy trial may need to be performed under in-house conditions for safety reasons.
4. We may have additional comments once we receive the actual protocols.
5. A biopharm consult is recommended.
6. I recommend we send our standard migraine pediatric study request letter, in which we request the results of 3 studies in adolescents: PK, efficacy, long-term safety.
7. Please convey comments 1-4 to the sponsor.

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. _____

ao 4/16/01
cc:
HFD-120
NDA 21-001