CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-001

MEDICAL REVIEW

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Axert**
Generic Name:	**almotriptan malate**
Sponsor:	**Pharmacia & Upjohn**
Indication:	**migraine**
NDA Number:	**21-001**
Original Receipt Date:	**12/17/99**
Clinical Reviewers:	**Armando Oliva, M.D.**
Review Author:	**Armando Oliva, M.D.**
Review Completed:	**8/18/00**

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1. Review Sources

The NDA for almotriptan malate for the acute treatment of migraine was submitted on 12/17/99. The archival record contains both paper and electronic material. The case report forms and case report tabulations were provided electronically. All other material (draft labeling, NDA summary, clinical section, etc.) was provided in paper volumes. Table 1 shows the portion of the NDA which I used in my review.

Table 1: Review Sources

Source	Submission Date	Material
Vol. 1.2	12/17/99	Item 2 Draft Labeling
Vol. 1.3	12/17/99	Item 3 NDA Summary
Vol. 1.96-1.204	12/17/99	Item 8 Clinical Section
Electronic CRT	12/17/99	Item 11 Case Report Tabulations
Electronic CRF	12/17/99	Item 12 Case Report Forms
Safety Update	6/15/00	Four-month Safety Update

2. Background

2.1 Indication

Almotriptan is intended for the acute treatment of migraine attacks with or without aura in adults.

2.2 Important Information from pharmacologically related agents

Almotriptan is pharmacologically similar to sumatriptan and other -triptans. Because of the potential for this class of compounds (5-$HT_{1D/1B}$ agonists) to cause coronary vasospasm, they should not be used in patients with coronary artery disease (CAD).

2.3 Administrative History

[redacted] Ownership of the IND was transferred to Pharmacia & Upjohn in 3/98. The pre-NDA meeting was held on 6/23/98. During that meeting, the Division described the requirements for the long-term safety database. We also expressed concern regarding the QTc prolongation seen in preclinical studies and stated that the sponsor must investigate the potential for QTc prolongation in humans based on the preclinical data. We also suggested they model the proposed labeling on currently approved triptans.

2.4 Proposed Labeling

2.4.1 Description

Almotriptan is manufactured in 6.25 and 12.5mg tablets for oral use.

2.4.2 Pharmacology

Almotriptan is a selective $5HT_{1B/1D}$ agonist.

2.4.3 Pharmacokinetics

T_{max} is 1-3 hours. $T_{1/2}$ is approximately 3-4 hours. Absolute bioavailability is 70%. There is no significant effect of food or presence of a migraine attack. Renal clearance is 75% (40% unchanged). Serum protein binding is 35%. Main enzyme for metabolism is MAO (27%) and CYP P450 3A4 and 2D6 (12%).

2.4.4 Indication

Almotriptan is indicated for the treatment of migraine attacks with or without aura in adults.

2.4.5 Dosing

The recommended dose is one 6.25mg or 12.5mg tablet at the onset. A repeat dose after 2 hours is permitted, up to a maximum of 50mg in 24 hours. The safety of treating more than 3 headaches per month is not established.

2.4.6 Contraindication, Warnings, and Precautions

Almotriptan should not be given to patients with documented coronary artery disease (CAD), coronary artery vasospasm, uncontrolled hypertension, hemiplegic or basilar migraine, or those hypersensitive to the drug.

2.4.7 Drug Interactions

Concomitant use with another 5-HT_1 agonist or an ergot medication is not recommended.

2.4.8 Carcinogenesis, Mutagenesis, Fertility

Almotriptan is not carcinogenic, mutagenic, clastogenic, or genotoxic based on the results of animal and in vitro studies. Fertility in female rates was decreased. Pregnancy class C.

2.4.9 Special Populations

Insufficient data are available for the elderly and no data are available for pediatric patients. Clearance is decreased by approximately 65% in patients with severe renal impairment. Clearance in hepatic disease has not been studied.

2.4.10 Adverse Events

The most commonly reported AE was nausea, occurring in 2% of patients.

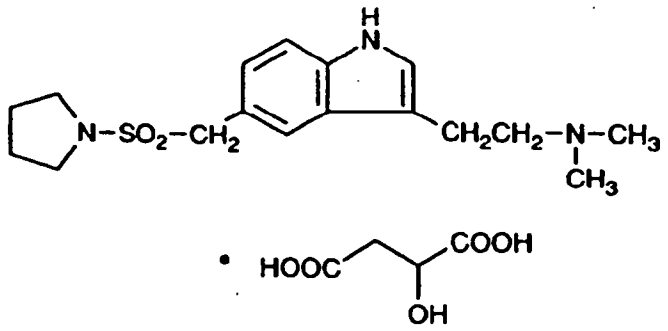
2.5 Foreign Marketing

As of September 1999, almotriptan is not registered anywhere in the world.

3. Chemistry, Manufacturing and Controls

Generic Name:	**almotriptan malate**
Trade Name:	**Axert**
Chemical Name:	**1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine hydroxybutanedioate**
Molecular Formula:	**$C_{17}H_{25}N_3O_2S \bullet C_4H_6O_5$**
Molecular Weight:	**469.56**

Figure 1: Chemical Structure



Almotriptan is manufactured as 6.25mg and 12.5mg (free base) tablets, corresponding to 8.75 and 17.5 mg of almotriptan malate. The sponsor has 12-18 months stability data.

4. Animal Pharmacology & Toxicology

4.1 Pharmacology

Almotriptan belongs to the –triptan class of drugs, which are specific for 5-HT_1 receptor subtypes. Almotriptan is a selective agonist at $5HT_{1B}$ and $5HT_{1D}$ receptors, and has very low affinity for $5HT_{1A}$ and $5HT_7$ subtypes, and no significant affinity or pharmacological activity at $5HT_2$, $5HT_3$, $5HT_4$, or $5HT_6$. It also has no affinity at adrenergic, adenosine, dopamine, endothelin, and tachykinin binding sites.

In vivo efficacy has been suggested in animal models by inhibiting plasma protein extravasation in a guinea pig model and by increasing vascular resistance in cat and dog carotid vasculature.

Almotriptan is widely metabolized in animals and in humans with qualitatively similar profiles across species. All metabolites observed in humans were also observed in animals.

4.2 Toxicology

Single oral doses at 2000 mg/kg in both mice rats caused mortality, but 1000 mg/kg was a non-lethal dose. Clinical signs included ptosis, tremors, abnormal gait, mydriasis, clonic convulsions which generally preceded death.

In repeat dose studies, the primary effects were observed in the central nervous system and cardiovascular system. CNS signs were noted in rats at oral doses of 100 mg/kg/day or greater, but were seen in dogs at 2 mg/kg/day or greater.

Cardiovascular findings in both male and female dogs were increases in heart rate and a trend toward prolongation of the QTc interval (Bazett correction) within 1 hour after dosing by oral, subcutaneous, and intravenous routes. The QTc interval trend was observed in the 5 and 12.5 mg/kg/day groups. The data were highly variable and comparisons were not statistically significant. Nevertheless, these data were viewed as a possible signal of effects on ventricular repolarization in dogs. The ECG and heart rate

changes recovered to baseline within 24 hours after dosing in all repeat dose studies. Of note, one high dose female (12.5mg/kg/day) had a sudden, unexplained death at 39 weeks in a 52 week oral dog study. A cardiovascular etiology was postulated but not proven.

Doses of 100 and 400 mg/kg/day produced parental toxicity in males and females and prolonged estrous cycles in female rats. A decrease in fertility and prolonged gestation length was seen in 400 mg/kg/day females. F1 offsprings had slightly reduced initial growth, but no developmental or reproductive effects.

There was no evidence of teratogenicity observed in any of the rat or rabbit embryotoxicity studies. Maternal toxicity seen in rats produced delays in ossification and reductions in fetal body weight. The NOEL for developmental toxicity in rats was 125 mg/kg/day. Increase in preimplantation and postimplantation losses were seen in rabbits only at maternally toxic doses, but no maternal or developmental effects were seen at 20 mg/kg/day.

There was no evidence of genotoxicity *in vitro* or *in vivo* and there was no evidence of oncogenic potential in rats or mice after lifetime doses of 20 to 38 times, respectively, the exposure at the human MRDD of 50mg.

A summary of the pivotal toxicology studies are shown in Table 2 (sponsor table 1, Vol. 1 page 62).

Table 2: Pivotal Toxicology Studies

Study (doses in mg/kg/day)	NOAEL (mg/kg/day)	Effect Defining NOAEL	AUC (µg.h/mL)	Comparison to Human MRDD (50 mg/day)
26-wk oral rat (20, 100, 500)	20	Foamy histiocytes in lungs	2.8	2.5
26-wk oral dog (2, 5, 12.5)	2	Increases in QRS, QTc, decrease in QT	1.3	1.2
52-wk oral dog (2, 5, 12.5)	5	Female death	3.8	3.5
Rat teratology (125, 250, 500, 1000)	125	Decreases in maternal and fetal weights and delays in ossification	48.5	44

5. Clinical Data Sources

5.1 Overview of Clinical Studies

The almotriptan clinical program consists of 28 human studies: twenty phase 1, three phase 2, and five phase 3 studies (Table 3, sponsor table 1, Item 3: Summary Vol. 1 page 145). A total of 4691 unique subjects were treated. Nineteen of the studies were sponsored by [redacted] thirteen phase 1, three phase 2, and three phase 3 studies. All of the [redacted] sponsored studies were conducted in [redacted] (including

the 3 pivotal efficacy trials). All of the Pharmacia and Upjohn studies were conducted in the U.S. with the exception of one phase 1 study that was conducted in the United Kingdom. The [redacted] studies listed in the table below all begin with the letters "CL" and the Pharmacia and Upjohn studies all begin with "00." All studies are completed and there were no ongoing studies at the time of submission. I describe the clinical studies briefly following Table 3 below (adapted from sponsor tables 1-4, Item 3, Vol. 1, pages 145-159).

Table 3: Almotriptan Clinical Studies

Study Type	No. of Studies	Study	Location	N Almotriptan	PBO	Sumatriptan	Total
Phase 1							
Basic PK	2	CL09	UK	7			18
		CL18	UK	11			
Factors Affecting PK	9	CL04	Spain	16			177
		CL06	UK	32			
		CL07	Germany	24			
		CL16	UK	8			
		CL20	UK	17			
		CL27	UK	25			
		CL29	Germany	16			
		CL01N	Germany	13			
		0009	USA	26			
Drug Interaction	5	0002	USA	16			67
		0003	UK	14			
		0004	USA	12			
		0005	USA	13			
		0006	USA	12			
Safety and Tolerance	4	CL01	UK	22			89
		CL02	UK	23			
		CL28	UK	24			
		0007	USA	20			
Phase 1 Total	20			351			351
Phase 2							
Oral	2	CL11	PL, H	138	31		911
		CL12	Europe	662	80		
Subcutaneous	1	CL10	Germany	91	32		123
Phase 2 Total	3			891	143		1034
Phase 3							
Placebo controlled	2	CL13	Europe	375	99	194	1578
		CL14	Europe	734	176		
Active controlled	1	0008	USA	591		582	1173
Long-term	2	CL25	Europe	761*			1346
		0011	USA	585			
Phase 3 Total	5			3046**	275	776	4097#
Total All studies	**28**			**4288****	**418**	**776**	**5482#**

* 521 of these were enrolled in CL14
** totals should have 423 subtracted from them to obtain number of unique patients treated
# totals should have 521 subtracted from them to obtain number of unique patients treated
PL=Poland, H=Hungary

In the two long-term studies (CL25 and 0011), 1346 patients were treated with almotriptan. Of these, 464 patients treated at least 2 headaches per month for 6 months and 169 patients treated at least 2 headaches per month for 1 year (section 7.1.3.4, Item 3: Summary, Vol. 1 page 161).

5.2 Phase 1 Studies

In the 20 phase 1 studies, a total of 351 subjects were exposed to almotriptan in doses ranging from 0.5mg to 200mg. Almotriptan was administered via oral, subcutaneous, sublingual, intranasal, and intravenous routes. The studies included basic PK studies, drug interactions, safety and tolerability.

There were two basic pharmacokinetic studies (CL09 and CL18). Study CL09 examined the excretion pathways and protein binding characteristics, as well as identification of metabolites after oral administration of 25mg of radiolabeled drug. Study CL18 evaluated the relative bioavailability of four different almotriptan 10mg intranasal formulations compared with a 10mg subcutaneous dose.

Nine studies were conducted to assess factors possibly affecting the PK of almotriptan. These included the bioequivalence of different formulations, the route of drug administration, patient age, renal impairment, and the influence of food.

Comparison of the bioequivalence of different oral formulations was evaluated in studies CL20 and 0009. Various routes of administration were investigated in studies CL16 (subcutaneous and sublingual), CL27 (intravenous, subcutaneous, and oral) and CL01N (three intranasal formulations). The PK of 12.5mg in the young and elderly males and females were compared in study CL06. The effect of renal impairment was studied in study CL07. Study CL29 evaluated the PK during and outside a migraine attack. Study CL04 investigated the PK under fasting and fed conditions.

Five drug interaction studies were conducted to evaluate the PK and safety after coadministration with an SSRI and CYP 2D6 inhibitor (fluoxetine – study 0002), MAO (moclobemide – study 0003), ergotamine (study 0004), a beta blocker (propranolol – study 0005), and a calcium channel blocker and weak inhibitor of CYP 3A4 (verapamil – study 0006). At the request of the Division, they conducted a sixth drug interaction study, which used the potent CYP 3A4 inhibitor ketoconazole. The results of this study were submitted at the 4-month safety update (see section 8.15, Four-Month Safety Update, page 78).

Four studies were conducted to evaluate the safety and tolerance of almotriptan. Two of the four were dose escalation studies using escalating subcutaneous doses ranging from 0.5 to14 mg (study CL01) and oral doses ranging from 5 to 200mg (study CL02). The two other studies assessed the safety and tolerance of 12.5mg in hypertensive patients (study 0007) and to determine the possible cardiovascular effects of almotriptan in a four-way crossover study of doses from 12.5mg to 50mg (study CL28).

5.3 Phase 2 Studies

Three phase 2 studies evaluated the safety and efficacy of almotriptan. A total of 1034 patients were treated either with placebo (n=143) or with a single dose of almotriptan (n=891).

Studies CL11 and CL12 were both randomized, double blind, placebo-controlled, parallel group studies using oral doses ranging from 2 to 150mg. Of the 911 patients in these studies, 800 received almotriptan and 111 received placebo. The primary efficacy endpoint was the 2-hour headache response rate.

Study CL10 was also a randomized, double blind, placebo-controlled, parallel group study using a subcutaneous formulation in doses of 2, 6, or 10mg. Of the 123 patients in this study, 91 received almotriptan and 32 received placebo. The primary endpoint again was the 2-hour headache response rate.

5.4 Phase 3 Studies

Five phase 3 studies evaluated the safety and efficacy of almotriptan. A total of 4097 patients were treated with either almotriptan (n=3046, of which 2525 were unique), placebo (n=275), and sumatriptan (n=776).

Studies CL13 and CL14 were randomized, double blind, placebo-controlled, parallel group studies. A total of 1109 patients received almotriptan, 275 patients received placebo, and 194 received sumatriptan. Study CL13 studied doses of 12.5mg, 25mg, and sumatriptan 100mg. Study CL14 studied doses of 6.25mg and 12.5mg. As in phase 2, the primary efficacy measure in both studies was the 2-hour headache response rate. Study CL13 also evaluated the equivalence of almotriptan 12.5mg and 25mg and sumatriptan 100mg with respect to the 2-hour response rate. In study CL14, the total number of headache responses and complete relief at 1 and 2 hours were evaluated over the course of 3 migraine attacks.

Study 0008 was an active control study which evaluated the quality of life and health economics, in addition to safety and efficacy, in patients treated with either almotriptan 12.5mg or sumatriptan 50mg. This was a randomized, double blind, active control, parallel group study in 591 patients treated with almotriptan and 582 treated with sumatriptan. The primary efficacy endpoint was the 2-hour headache response rate.

Studies CL25 and 0011 were uncontrolled, long-term studies. Safety and efficacy data were collected in study CL25 for one year and in study 0011 for six months. The primary efficacy endpoint was again the 2-hour headache response rate. In study CL25, 761 patients received at least one dose of almotriptan. Of this number, 597 received treatment for 6 months, and 480 received treatment for one year. Study 0011 treated 585 patients for 6 months.

6. Human Pharmacokinetics

I summarize the sponsor's review of the human pharmacokinetics. A more detailed review of these data is available in the biopharmaceutics review.

6.1 Dose Proportionality

Healthy volunteers received almotriptan as single oral doses from 1 to 200mg. The results indicated that, over a wide range of doses, the PK of almotriptan are approximately linear with respect to dose. This was also confirmed in a cardiovascular safety study in 24 healthy volunteers using doses of 12.5mg to 50mg.

6.2 ADME

6.2.1 Absorption

At least 75% of an oral dose is absorbed in man. It does not appear to undergo substantial first pass metabolism. T_{max} of the oral tablet is about 1-3 hours.

6.2.2 Distribution

The mean volume of distribution following i.v. administration is 195L indication that the drug is extensively distributed in the body. Almotriptan is not highly bound to plasma proteins. The unbound fraction appears to be >60%. Plasma protein binding is not expected to be a major factor affecting the PK of almotriptan in humans.

6.2.3 Metabolism

A large portion of the drug (35-45%) is excreted unchanged in the urine. There are three primary metabolites: [1] the indole acetic acid, [2] the glucuronide conjugate, and [3] the oxidized pyrrolidine product. The two with the highest mean plasma concentrations were [1] and [3] and are inactive.

Almotriptan is primarily metabolized by MAO-A to the indole acetic acid metabolite (27% of a single dose). It is also metabolized to a moderate degree by CYP 3A4 and to a minor degree by CYP 2D6 (to the oxidized pyrrolidine product).

These data indicate that there are three major routes affecting almotriptan clearance in man:

- Renal function
- MAO-A
- CYP 3A4

6.2.4 Excretion

A single dose of almotriptan is excreted 35-45% unchanged in the urine. 12.7% appears in the feces, and the remaining appear as metabolites excreted in the urine. The mean half-life is 3-4 hours.

6.3 Special Populations

Food had no effect on the PK of almotriptan.

Severe renal impairment caused decline in almotriptan clearance with a 2-fold increase in C_{max} and 3-fold increase in $AUC_{0\rightarrow\infty}$. As a result, the lowest dose of almotriptan should be used in this population and the total daily dose should not exceed 25mg.

The effects of hepatic impairment have not been studied. Since hepatic metabolism accounts for approximately 50% of almotriptan elimination, plasma levels could be

expected to increase by 2-fold if hepatic mechanisms were eliminated completely. This assumes renal function would be unaffected. Therefore, the lowest dose of almotriptan should be used in patients with moderate to severe hepatic dysfunction. The total daily dose should not exceed 25mg.

Elderly patients experience a slight increase in C_{max} (25mg dose: 56.8 vs. 46.2 ng/mL), slight increase in $AUC_{0\rightarrow\infty}$ (405 vs. 325 ng.h/mL) and slight delay in $T_{1/2}$ (3.7 vs. 3.2 h). The majority of these changes can be explained by age related decrease in renal clearance. Given the modest effect on C_{max}, no dosage adjustment is recommended.

There were minor gender differences noted in almotriptan PK but none sufficient to warrant any dose adjustments. The only significant gender difference was $T_{1/2}$ was 3.4 hours in young men and 3.0 hours in women, only a 13% difference. Elderly females also tended to have higher C_{max} compared to elderly males (65.7 vs. 48).

6.4 Drug Interactions

Almotriptan C_{max} was approximately 18% higher after administration with fluoxetine (a potent inhibitor of CYP 2D6). Differences in clearance and $AUC_{0\rightarrow\infty}$ were borderline statistically significant but were <10%. Clinically, the coadministration was well tolerated.

Almotriptan clearance was decreased by 27% in the presence of moclobemide (an MAO-A inhibitor). Clinically, the coadministration had no effect on vital signs or ECG intervals. Based on these results, the lowest level of almotriptan should be used in patients receiving MAO inhibitors.

Almotriptan T_{max} was significantly longer with coadministration with ergotamine. Median C_{max} values were similar in both groups. Clinically, mild and moderate AE's were reported, consisting of nausea, and dizziness. None was serious. No significant effects on vital signs were noted except for supine diastolic blood pressure at 30 minutes. ECG and Holter results were normal.

Propranolol does not appear to have any effect on the PK of almotriptan.

Verapamil (a weak CYP 3A4 inhibitor *in vivo*) modestly inhibited almotriptan clearance by about 20%. No clinically relevant pharmacodynamic interaction was seen. No reduction in almotriptan dose is recommended.

A drug interaction study with the potent CYP 3A4 inhibitor ketoconazole is pending.

6.5 Migraine Attack

A PK study in 16 migraine patients during and between migraine attacks showed little difference in the PK of almotriptan.

7. Integrated Review of Efficacy

7.1 Controlled Efficacy Trials – Study Design

The efficacy of oral almotriptan was studied in three phase 3 studies (CL13, CL14, 008) and in two phase 2 studies (CL11 and CL12). All but study 008 were placebo controlled. Study 008 used an active control (sumatriptan). CL13 also included a sumatriptan arm.

All but study CL14 treated a single migraine attack. Study CL14 evaluated the effects of study medication across three migraine attacks.

Of the 4 placebo-controlled studies, three of them (CL12, 13, 14) studied the planned marketed doses of 6.25mg and 12.5mg. These three studies are adequate and well-controlled by design to determine the efficacy of the planned marketed doses. The fourth study, CL11, was also adequate and well-controlled, but it studied doses of [redacted]

In each study, patients were instructed to take one dose of study medication at the onset of a moderate to severe migraine attack. Rescue medication was permitted after two hours. A second dose was permitted after 2 hours, but within 24 hours, for the treatment of a recurrence, defined as a response (grade 0, 1) at 2 hours followed by return of pain to grade 2, or 3 within 24 hours of the initial dose. Efficacy data were recorded in a patient diary at specified intervals during the 24 hours following initial treatment.

7.2 Dose Selection

The dose-ranging phase 1 study CL02 examined single oral doses of 5-200mg. The study showed that single doses up to 150mg were well tolerated but there was a dose dependent increasing incidence of adverse events. In the phase 2 efficacy study CL12, doses of 2 to 25mg were assessed, and almotriptan 6.25mg was determined to be the minimum effective dose based on the 2-hr headache response rate. Data from studies CL12, 13, and 14 suggested that 12.5mg had the best efficacy/safety ratio among the doses examined, according to the sponsor. Therefore, 6.25mg and 12.5mg were chosen as the safest and most effective doses for marketing.

7.3 Inclusion and Exclusion Criteria

Patients enrolled in the efficacy studies had been diagnosed with acute migraine meeting IHS guidelines, with or without aura, but were otherwise healthy. They must have been between the ages of 18-65. Those with specific cardiovascular diseases (*e.g.*, cardiac ischemia, atherosclerosis, cardiac arrhythmia, or uncontrolled hypertension) were excluded. They must have been younger than 50 years at the time of migraine onset, and have had a minimum migraine history of 1 year. They must have normally experienced 1-6 migraines per month, with at least a 24 hour headache-free period between attacks. Women must have been either postmenopausal or have had a negative serum pregnancy test and had used a reliable method of contraception for the previous 6 months.

7.4 Study Drug Administration

In studies CL12 and CL14, study drug was supplied as tablets. Placebo tablets were identical, both in appearance and taste, to almotriptan tablets. In study CL13, almotriptan, sumatriptan, and placebo were supplied as tablets inside capsules to maintain the blind.

In all three studies, patients were given two doses of study medication (one for initial treatment, the second for treatment of recurrence). In study CL14, patients returned to clinic following the first attack and received medication for a 2nd and 3rd attack. This was identical to the medication dispensed for the first attack.

7.5 Efficacy Analyses

Pain severity was assessed at protocol-specific times according to a four-point scale (0=none, 1=mild, 2=moderate, 3=severe). The primary efficacy endpoint in each study was pain response at 2 hours. A response (called "relief" in the NDA) was defined as a decrease in migraine severity, ranging from moderate to severe at baseline to mild or no pain at the time of assessment.

Primary efficacy analyses used Fisher's exact test to compare almotriptan to placebo, and was based on the intent-to-treat (ITT) population, defined as all patients randomized who received study medication and had at least one efficacy measurement.

Secondary endpoints included:

- Response at 0.5, 1, 1.5 hours
- Pain-free at 0.5, 1, 1.5, 2 hours
- Use of escape medication
- Presence of nausea, vomiting, photophobia, phonophobia at 1 and 2 hours
- Recurrence between 2 and 24 hours
- Sustained pain response (*i.e.*, response at 2 hours with no recurrence)
- Sustained complete relief (*i.e.*, complete relief at 2 hours with no recurrence)
- Estimated probability of remedication
- Estimated time to remedication

Two study-specific analyses were also performed. In study CL13, the equivalence of almotriptan and sumatriptan with respect to the 2-hr response rate was analyzed. In study CL14, the total number of positive responses and complete relief at 1 and 2 hours (across all 3 attacks) were evaluated.

The sponsor used a last (post-baseline) observation carried forward (LOCF) approach for missing data. If all post-baseline data were missing, then all assessments remained missing and the patient was excluded from the ITT. Also, if a patient's baseline headache pain was mild or missing, they were also excluded from the analyses.

Subgroup analyses included sex, age (≤45 vs. >45 years), and weight (≤65 vs. >65 kg), baseline pain (moderate vs. severe), aura (present vs. absent), use of oral contraceptives (yes, no). In addition, the use of escape medication and sustained pain response and sustained complete relief were analyzed by baseline pain severity only.

7.6 Patient Disposition

Across CL12, CL13, and CL14, 2318 patients received study medication. Of these, 1770 received various doses of almotriptan, 355 received placebo, and 193 received sumatriptan 100mg (study CL13).

The numbers of patients in each treatment group in each of the three pivotal studies are shown in Table 4 (sponsor table 6, Item 8/10, Vol. 91, page 24).

Table 4: Studies CL12, 13, 14 – Number of Patients, by Treatment Group

Study	PBO	Almotriptan				Sumatriptan 100mg	Total
		2mg	6.25mg	12.5mg	25mg		
CL12	80	170	167	164	161		742
CL13	99			183	191	193	666
CL14	176		360	374			910
Total	**355**	**170**	**527**	**721**	**352**	**193**	**2318**

7.7 Extent of Exposure

In all three placebo-controlled short-term efficacy studies, patients took one dose of study medication for the initial treatment of a moderate or severe migraine headache. A second dose was permitted after 2 hours for recurrence. Studies CL12 and CL13 were single attack studies. Study CL14 permitted treatment of three migraine attacks.

Across all studies, between 80-83% of placebo patients took one dose of study medication and the remaining 17-20% took 2 doses. For the almotriptan groups, 74-80% took one dose, and 20-27% took 2 doses.

In study CL13, approximately 69% of sumatriptan patients took one dose, and 31% took 2 doses.

As it turned out, the recurrence rate was independent of both headache pain severity at baseline and the study medication administered. The higher rate of second dose use among almotriptan patients (compared to placebo) can be explained on the basis that only patients who achieved a response could take a second dose. Since response rates were higher for almotriptan, compared to placebo, a higher number of patients were eligible to take the second dose.

7.8 Demographics and Baseline Characteristics

The demographic and baseline characteristics for the three pivotal trials are shown in Table 5 (sponsor tables 7, 8, and 9, Item 8/10, Vol. 91, pages 25, 26, 27). For attack-dependent measures, only data from attack 1 in study CL14 are presented. Approximately 85% of the patient population in the three pivotal studies were female, and >98% were white. The mean ages of patients with a treatment group varied between 39 and 43 years across all studies.

Table 5: Studies CL12, 13, 14 – Demographic and Baseline Characteristics

Characteristic Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	Almotriptan 12.5mg n/N (%)	Sumatriptan 100mg n/N (%)
Female				
CL12	69/80 (86)	144/167 (86)	137/164 (84)	
CL13	88/99 (89)		157/183 (86)	161/193 (83)
CL14	144/176 (82)	322/360 (89)	323/374 (86)	
Male				
CL12	11/80 (14)	23/167 (14)	27/164 (16)	
CL13	11/99 (11)		26/183 (86)	32/193 (17)
CL14	32/176 (18)	38/360 (11)	51/374 (14)	
Mean Age (yrs)				
CL12	39.4	40.9	41.3	
CL13	40.7		43.3	44
CL14	40.3	40.6	40.9	
Mean Weight (kg)				
CL12	64.1	66.1	65.5	
CL13	65.9		69.4	
CL14	40.3	40.6	40.9	
Baseline Pain				
Severe				
CL12	31/80 (39)	68/166 (41)	65/164 (40)	
CL13	32/99 (32)		90/183 (49)	82/193 (42)
CL14	64/176 (36)	133/360 (37)	151/374 (40)	
Moderate				
CL12	49/80 (61)	98/166 (59)	99/164 (60)	
CL13	67/99 (68)		93/183 (51)	111/193 (58)
CL14	112/176 (64)	227/360 (63)	223/374 (60)	
Aura				
CL12	21/80 (26)	34/170 (20)	34/164 (21)	
CL13	21/99 (21)		41/183 (22)	38/193 (20)
CL14	32/176 (18)	78/360 (22)	64/374 (17)	
Use Oral Contraceptives				
CL12	18/80 (22)	21/167 (13)	20/164 (12)	
CL13	16/99 (16)		24/183 (13)	21/193 (11)
CL14	33/176 (19)	62/360 (17)	68/374 (18)	
Use Migraine Prophylaxis				
CL12	1/80 (1)	0/167 (0)	0/164 (0)	
CL13	9/99 (9)		24/183 (13)	22/193 (11)
CL14	16/176 (9)	39/360 (11)	35/374 (9)	
Nausea				
CL12	52/80 (65)	105/166 (63)	118/164 (72)	
CL13	67/99 (68)		125/183 (68)	
CL14	117/176 (66)	246/360 (68)	251/373 (67)	
Vomiting				
CL12	11/80 (14)	16/166 (10)	21/164 (13)	
CL13	13/99 (13)		36/183 (20)	27/193 (14)
CL14	25/176 (14)	41/360 (11)	50/373 (13)	
Photophobia				
CL12	60/80 (75)	118/166 (71)	121/164 (74)	
CL13	58/99 (59)		110/183 (60)	107/193 (55)
CL14	132/176 (75)	252/360 (70)	259/373 (69)	
Phonophobia				
CL12	43/80 (54)	91/166 (55)	88/164 (54)	
CL13	52/99 (52)		84/183 (46)	92/193 (48)
CL14	96/176 (55)	206/360 (57)	208/373 (56)	

Unlike demographics, patients were less balanced with regard to baseline migraine characteristics. The difference in migraine prophylaxis use can be explained, in part, because patients taking prophylactic medications were excluded from CL12, but not from the other two studies.

Baseline pain severity was "severe" in 32-41% of attacks, with the exception of the 12.5mg group in study CL13, which reported 49% severe attacks. These data are higher than the generally regarded estimate that 1/3 of migraine attacks are severe. Approximately 2/3 to 3/4 of the patients had photophobia at baseline, and about half had phonophobia at baseline.

7.9 Primary Endpoint – 2-Hr Headache Response

The 2-hour headache response rates for studies CL12, 13, and 14 are shown in Table 6 (sponsor table 10, Item 8/10, Vol. 91, page 28).

Table 6: Studies CL12, 13, 14 – Two-Hour Headache Response Rates

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
CL12	27/80 (33.8)	92/166 (55.4)	0.002	96/164 (58.5)	<0.001	[redacted]	
CL13[1]	42/99 (42.4)	[redacted]		104/183 (56.8)	0.025[2]	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.

Each comparison between almotriptan and placebo in all three studies showed statistically higher 2-hr response rates in the almotriptan-treated groups. The response rates to 12.5mg were numerically, but not statistically, higher than the response rates to the 6.25mg in studies CL12 and CL14 (the two studies that used the two doses).

The sponsor also studied a 2mg dose in study CL12, and the 5mg dose in study CL11. The 2-hr headache response rate for the 2mg dose was 30.8% (vs. 33.8% for placebo, p=0.663), and for the 5mg dose was 65.7% (vs. 41.9% for placebo, p=0.083) (sponsor table ISE 1.2.1, Item 8/10, Vol. 91, page 101).[3]

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[1] The inspection of the Dr. Zintsch site (Dresden, Germany) indicated several irregularities, including evidence that the investigator had completed entries in patient diaries. This is a clear and serious violation of the protocol. I asked that Dr. Chen repeat the primary efficacy analysis for this study with the Zintsch site excluded. His re-analysis indicates that the study remains positive, and in fact, the p-value was even smaller. I refer the reader to Dr. Chen's biostatistical review for more details of this re-analysis.

[2] This is the reported p-value in the ISE. I note that the sponsor reports a different (non-significant) result for this analysis in the actual study report for CL13 (sponsor table 4.2.1.1.A, Item 8/10, Vol 15, page 35). The result is reported using 95% confidence intervals, and there is overlap in the interval between almotriptan (both doses) and placebo. It is this table which our biostatistician, Dr. Chen, quotes in his review on page 7.

[3] Reviewer's note: the reason the 5mg dose failed to reach nominal significance in study CL11 may very well be due to a power issue because of the small group/sample sizes in this study. The number of responders at 5mg were 23/35 and for placebo were 13/31.

The sponsor evaluated the 2-hour headache response rate in various subgroups: baseline pain intensity, sex, age, and weight.

Almotriptan was effective against both moderate and severe pain. The analyses reached nominal significance for 6.25mg against severe pain in the two studies in which it was used, and against moderate pain in one of the two studies. The 12.5mg was nominally significantly superior against moderate pain in the 3 studies, and against severe pain in 2 of the 3 studies (Table 7, sponsor table 11, Item 8/10, Vol. 91, page 29). It is noted that the studies were not powered to detect statistically significant differences in this subgroup.

Table 7: Studies CL12, 13, 14 – Two-Hour Headache Response Rates, by Baseline Pain

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
Severe							
CL12	5/31 (16.1)	32/68 (47.1)	0.004	30/65 (46.2)	0.006		
CL13	11/32 (34.4)			37/90 (41.1)	0.54	41/82 (50)	0.15
CL14	13/64 (20.3)	61/133 (45.9)	0.001	76/148 (51.4)	<0.001		
Moderate							
CL12	22/49 (44.9)	60/98 (61.2)	0.078	82/111 (73.9)	<0.001		
CL13	31/67 (46.3)			67/93 (72.0)	0.002	82/111 (73.9)	<0.001
CL14	45/112 (40.2)	139/227 (61.2)	<0.001	164/222 (73.9)	<0.001		

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

Efficacy was also unaffected by sex, age (≤45, >45), or weight (Table 8, Table 9, Table 10, sponsor tables ISE 1.2.4-7,10,11, Item 8/10, Vol. 91, pages 107-114, 117-120). The response rates were all numerically in favor of almotriptan, and many comparisons reached nominal significance.

Table 8: Studies CL12, 13, 14 – Two-Hour Headache Response Rates, by Sex

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
Female							
CL12	26/69 (37.7)	78/143 (54.5)	0.028	78/137 (56.9)	0.012		
CL13	38/88 (43.2)			88/157 (56.1)	0.062	99/161 (61.5)	0.008
CL14	46/144 (31.9)	179/322 (55.6)	<0.001	209/319 (65.5)	<0.001		

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
Male							
CL12	1/11 (9.1)	14/23 (60.9)	0.008	18/27 (66.7)	0.003	[redacted]	
CL13	4/11 (36.4)	[redacted]		16/26 (61.5)	0.279	24/32 (75.0)	0.031
CL14	12/32 (37.5)	21/38 (55.3)	0.157	31/51 (60.8)	0.045	[redacted]	

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

Table 9: Studies CL12, 13, 14 – Two-Hour Headache Response Rates, by Age

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
≤45 years							
CL12	18/52 (34.6)	60/113 (53.1)	0.030	53/101 (52.5)	0.041	[redacted]	
CL13	27/70 (38.6)	[redacted]		56/96 (58.3)	0.018	72/118 (61.0)	0.004
CL14	38/116 (32.8)	123/233 (52.8)	<0.001	157/245 (64.1)	<0.001	[redacted]	
>45 years							
CL12	9/28 (32.1)	32/53 (60.4)	0.020	43/63 (68.3)	0.002	[redacted]	
CL13	15/29 (51.7)	[redacted]		48/87 (55.2)	0.831	51/75 (68.0)	0.173
CL14	20/60 (33.3)	77/127 (60.6)	0.001	83/125 (66.4)	<0.001	[redacted]	

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

Table 10: Studies CL12, 13, 14 – Two-Hour Headache Response Rates, by Weight

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
≤65 kg							
CL12	15/49 (30.6)	56/93 (60.2)	0.001	50/90 (55.6)	0.007	[redacted]	
CL13	26/57 (45.6)	[redacted]		49/83 (59.0)	0.125	52/91 (57.1)	0.181
CL14	27/94 (28.7)	102/186 (54.8)	<0.001	111/171 (66.1)	<0.001	[redacted]	
>65kg	[redacted]						
CL12	12/31 (38.7)	36/73 (49.3)	0.392	46/74 (62.2)	0.033	[redacted]	
CL13	16/42 (38.1)	[redacted]		55/100 (55.0)	0.097	71/101 (70.3)	0.001
CL14	31/82 (37.8)	98/174 (56.3)	0.007	129/202 (63.9)	<0.001	[redacted]	

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

Efficacy was also unaffected by the presence of aura, use of migraine prophylaxis, or use of oral contraceptives (not shown here, sponsor tables ISE 1.2.8,9,12-15)

7.10 Secondary Endpoints

7.10.1 Migraine-Associated Symptoms

The sponsor analyzed the incidence of nausea, vomiting, photophobia, and phonophobia at 2 hours in all three studies. Both 6.25mg and 12.5mg were effective in providing relief from nausea, photophobia, and phonophobia, achieving nominally significantly superior results compared to placebo in at least 2 studies in each category. For vomiting, only 6.25mg beat placebo in study CL12, and 12.5mg beat placebo in study CL13.[4]

The results of the migraine-associated symptoms analysis is shown in Table 11 (sponsor table 18, Item 8/10, Vol. 91, page 38).

Table 11: Studies CL12, 13, 14 – Migraine-Associated Symptoms at Two Hours

Study	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value	Sumatriptan 100mg n/N (%)	p-value
Nausea							
CL12	37/78 (47)	45/163 (28)	0.004	54/159 (34)	0.048		
CL13	43/99 (43)			59/183 (32)	0.07	60/191 (31)	0.052
CL14	81/175 (46)	122/356 (34)	0.008	103/369 (28)	<0.001		
Vomiting							
CL12	14/78 (18)	4/163 (2)	<0.001	16/159 (10)	0.098		
CL13	10/99 (10)			6/183 (3)	0.028	15/191 (8)	0.52
CL14	15/175 (9)	21/356 (6)	0.27	20/369 (5)	0.19		
Photophobia							
CL12	38/78 (49)	43/163 (26)	0.001	42/159 (26)	0.001		
CL13	37/99 (37)			48/183 (26)	0.058	48/191 (25)	0.041
CL14	83/175 (47)	121/356 (34)	0.003	101/369 (27)	<0.001		
Phonophobia							
CL12	31/78 (40)	33/163 (20)	0.002	35/159 (22)	0.005		
CL13	33/99 (33)			36/183 (20)	0.014	34/191 (18)	0.005
CL14	73/175 (42)	103/356 (29)	0.004	78/369 (21)	<0.001		

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

[4] Demonstration of nominal p-values for vomiting has traditionally been difficult for other triptans as well due, in part, to the small numbers of patients who report vomiting at baseline.

7.10.2 Equivalence to Sumatriptan

Study CL13 included a sumatriptan 100mg arm. In that study, sumatriptan 100mg was numerically superior to almotriptan 12.5mg (63.7% vs. 56.8%, Table 6, page17); however, a higher percentage of almotriptan patients had severe pain at baseline (49% vs. 42%, Table 5, page 16). When adjusted for the baseline imbalance, almotriptan 12.5mg was equivalent to sumatriptan 100mg in providing a headache response at 2 hours. This analysis used a 90% confidence interval of the differences in the percentages of patients with pain relief between −15% and +15% to show equivalence.

7.10.3 Headache Response Rates At Other Time Points

Almotriptan 6.25mg was compared with placebo at 0.5, 1, and 1.5 hours in studies CL12 and CL14. In both studies, the 6.25mg dose provided nominally significantly superior headache responses over placebo at 1 and 1.5 hours.

The 12.5mg dose was compared with placebo at 0.5, 1, and 1.5 hours in studies CL12 and CL14, and at 1 hour in study CL13 (pain was not assessed at 0.5 or 1.5 hours in this study). In both CL12 and CL14, the 12.5mg dose provided nominally significantly superior headache responses over placebo at 1 and 1.5 hours (and at 0.5 hours for study CL12 only). In study CL13, neither the 12.5mg dose nor sumatriptan 100mg provided nominally significant results over placebo at 1 hour, although they were positive at 2 hours (as described in section 7.9).

The headache response rates for each time point is shown in Table 12 (sponsor table 12, Item 8/10, Vol. 91, page 31).

Table 12: Studies CL12, 13, 14 – Headache Response Rates at Various Time Points

Study	Time (Hours)							
	0.5		1		1.5		2	
Treatment	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value
CL12								
PBO (n=80)	4 (5)		15 (19)		25 (31)		27 (34)	
6.25mg (n=166)	16 (10)	0.32	56 (34)	0.016	82 (49)	0.009	92 (55)	0.002
12.5mg (n=164)	25 (15)	0.021	59 (36)	0.007	80 (49)	0.013	96 (58)	<0.001
CL13								
PBO (n=99)	[redacted]		29 (29)		[redacted]		42 (42)	
12.5mg (n=183)			65 (36)	0.35			104 (57)	0.025
SMT 100mg (n=193)			73 (38)	0.16			123 (64)	0.001
CL14								
PBO (n=176)	20 (11)		35 (20)		47 (27)		58 (33)	
6.25mg (n=360)	41 (11)	1.00	108 (30)	0.013	157 (44)	<0.001	200 (56)	<0.001
12.5mg (n=370)	58 (16)	0.19	126 (34)	0.001	180 (49)	<0.001	240 (65)	<0.001

7.10.4 Complete Pain Relief at Various Time Points

Pain-free was assessed at 0.5, 1, 1.5, and 2 hours in studies CL12 and CL14, and at 1 hour in study CL13. Almotriptan 6.25mg did not provide effective complete pain relief at any time point prior to 2 hours in any study. In studies CL12 and CL14, the 12.5mg was nominally significantly superior to placebo at 1.5 and 2 hours. At each evaluation, 12.5mg was numerically superior to 6.25mg.

The complete headache relief rates for each time point is shown in Table 13 (sponsor table 12, Item 8/10, Vol. 91, page 31).

Table 13: Studies CL12, 13, 14 – Complete Relief Rates at Various Time Points

Study	Time (Hours)							
	0.5		1		1.5		2	
Treatment	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value
CL12								
PBO (n=80)	1 (1)		2 (2)		7 (9)		9 (11)	
6.25mg (n=166)	2 (1)	1.00	7 (4)	0.72	28 (17)	0.12	48 (29)	0.002
12.5mg (n=164)	3 (2)	1.00	19 (12)	0.016	44 (27)	0.001	63 (38)	<0.001
CL13								
PBO (n=99)	[redacted]		5 (5)		[redacted]		15 (15)	
12.5mg (n=183)			9 (5)	1.00			51 (28)	0.018
SMT 100mg (n=193)			15 (8)	0.47			65 (34)	0.001
CL14								
PBO (n=176)	1 (1)		14 (8)		18 (10)		27 (15)	
6.25mg (n=360)	6 (2)	0.44	29 (8)	1.00	60 (17)	0.051	104 (29)	0.001
12.5mg (n=370)	11 (3)	0.11	48 (13)	0.12	88 (24)	<0.001	145 (39)	<0.001

7.10.5 Use of Escape Medication

The use of escape medication (or "rescue") was permitted in the studies after the 2 hour time point. The percentages of patients using escape medication were consistently higher among those in the placebo group, with decreasing use of escape medication with increasing dose of almotriptan. The use of escape medication is shown in Table 14 (adapted from sponsor table 14, Item 8/10, Vol. 91, page 33).

Table 14: Studies CL12, 13, 14 – Use of Escape Medication

Study	PBO	Almotriptan 6.25mg		Almotriptan 12.5mg		Sumatriptan 100mg	
	n/N (%)	n/N (%)	p-value	n/N (%)	p-value	n/N (%)	p-value
CL12	47/77 (61)	64/160 (40)	0.003	58/157 (37)	0.001	[redacted]	
CL13	53/99 (54)	[redacted]		70/183 (38)	0.017	65/193 (34)	0.002
CL14	96/175 (55)	138/360 (38)	<0.001	99/373 (26)	<0.001	[redacted]	

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

7.10.6 Recurrence Rates

The interpretation of recurrence rates has traditionally been fraught with difficulty. This is because the manner in which a recurrence is defined. A recurrence was defined as any moderate or severe headache that occurred within 24 hours of initial treatment in a patient who achieved a response at 2 hours. The presence of a recurrence is contingent upon first having a response. The incidence of recurrence (*i.e.*, "recurrence rate") is calculated using a non-randomized subgroup of the original study population in the denominator.

Recurrence rates were similar across studies, regardless of treatment group. No nominally significant differences were seen in any treatment group in any study (Table 15, adapted from sponsor table 15, Item 8/10, Vol. 91, page 34).

Table 15: Studies CL12, 13, 14 – Recurrence 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	7/26 (27)	25/91 (28)	1.00	23/94 (24)	0.80		
CL13	8/42 (19)			19/103 (18)	1.00	17/121 (14)	0.46
CL14	15/58 (26)	47/199 (24)	0.73	68/237 (29)	0.75		

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

7.10.7 Treatment of Recurrence

In all three studies, patients could take a second dose of study medication for the treatment of a recurrence. In two of the three studies (CL 12 and CL13), the second dose was the same as the initial dose. In study CL14, the report does not specifically say that it was the same as the first dose, but there is also no mention that the second dose was randomized in this study, so I assume that, just as in the other two studies, it was the same as the first dose.

Migraine pain severity was evaluated at 2 hours after the administration of the second dose. Although the numbers were small, more than 70% of patients taking 6.25mg or 12.5mg as a second dose for recurrence reported a response at 2 hours, and more than 50% reported being pain free at 2 hours. The placebo recurrence response rates ranged from approximately 25% (CL13 and CL14) to 86% (CL12).

No conclusions regarding the efficacy of a second dose to treat recurrence are possible because the second dose was not randomized, and because of the small sample sizes in each group (ranging from 7-15 for placebo groups, and 19-67 for almotriptan groups (sponsor table 16, Item 8/10, Vol. 91, page 35, not shown here).

7.10.8 Probabilities of Remedication

The estimated probabilities of remedication (either rescue or a second dose) were calculated for each treatment group for each study separately using Kaplan-Meier survival methods. Patients were censored at 24 hours. The probabilities of remedication within 24 ~~hours~~ were consistently lower for either dose of almotriptan compared to placebo (Table 16, Table 17, Table 18, sponsor figure ISE 1.5.9-11, Item 8/10, Vol. 92, page 315-317).

Table 16: Study CL12 – Estimated Probability of Remedication

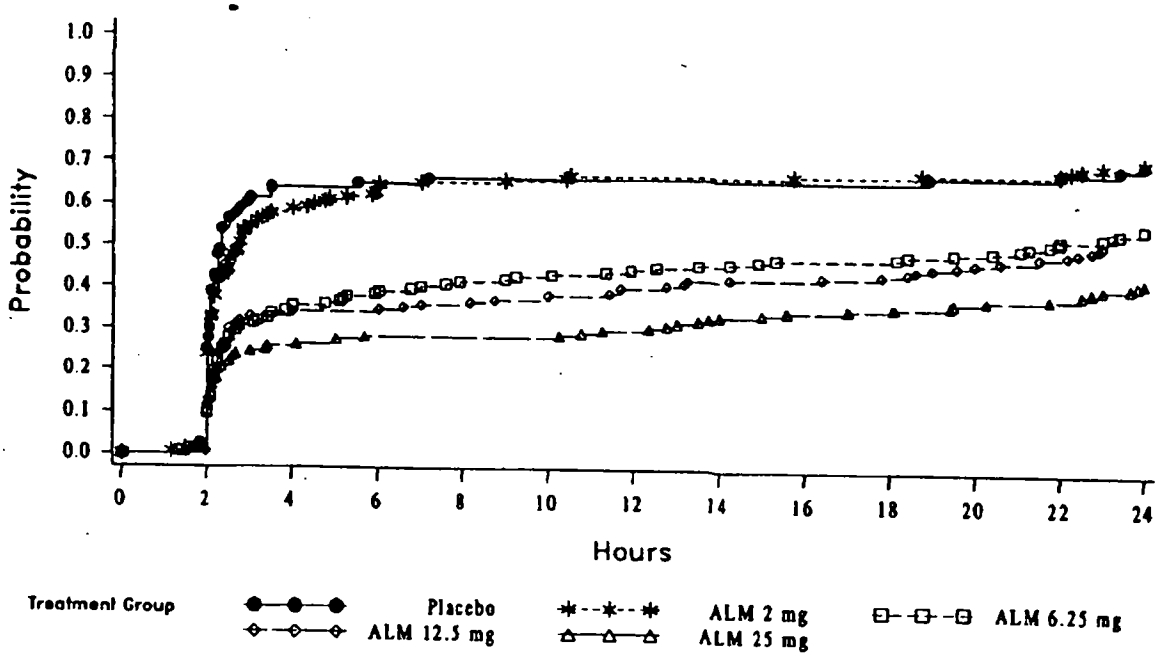


Table 17: Study CL13 – Estimated Probability of Remedication

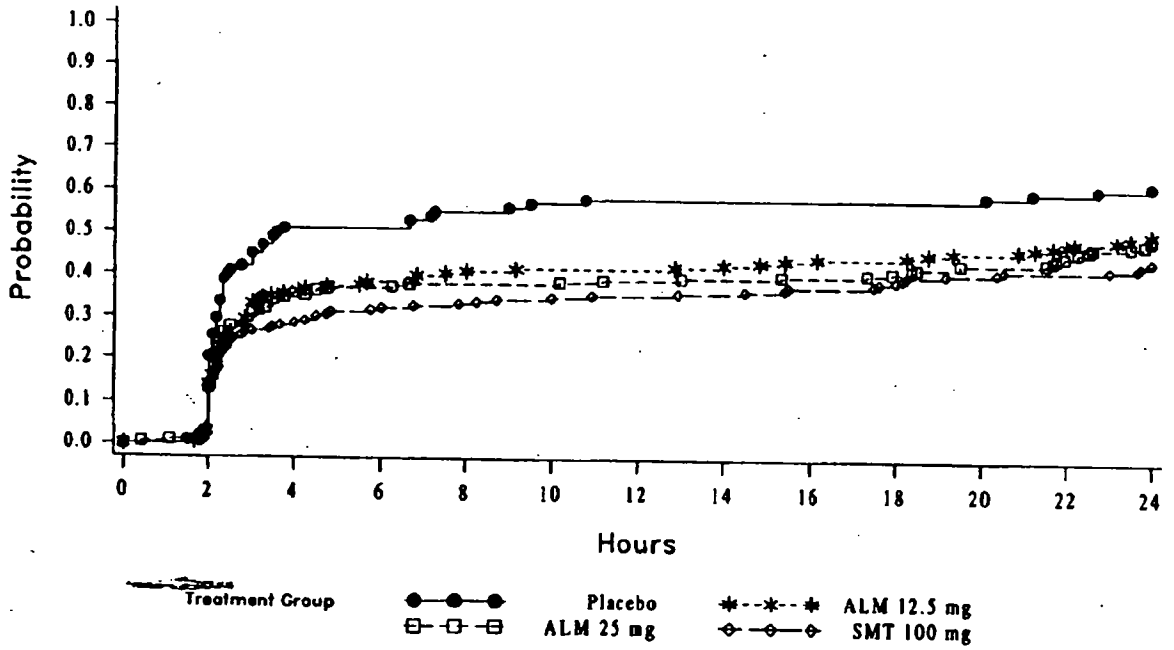
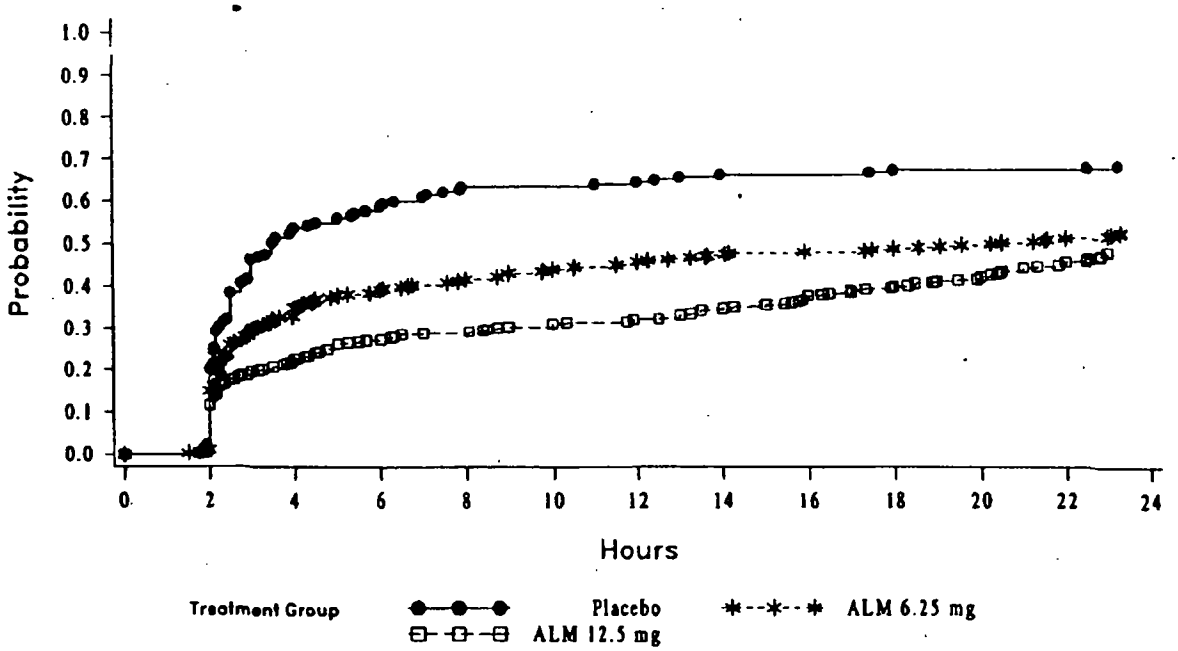


Table 18: Study CL14 – Estimated Probability of Remedication (Attack 1)



7.10.9 Sustained Response and Sustained Pain-Free Rates

A sustained response was defined as a response at 2 hours without a recurrence within 24 hours of initial treatment. Sustained pain-free was similarly defined as pain-free at 2 hours without a recurrence within 24 hours of initial treatment.[5] Both almotriptan 6.25mg and 12.5mg were nominally significantly better than placebo in both sustained response and sustained pain-free rates (Table 19, adapted from sponsor table 17, Item 8/10, Vol. 91, page 36).

Table 19: Studies CL12, 13, 14 – Sustained Response and Pain-Free 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
Sustained Response							
CL12	20/80 (25)	67/166 (40)	0.023	73/164 (44)	0.003		
CL13	34/99 (34)			85/183 (46)	0.058	106/193 (55)	0.001
CL14	43/176 (24)	153/360 (42)	<0.001	172/370 (46)	<0.001		
Sustained Pain-Free							
CL12	6/80 (8)	36/166 (22)	0.006	45/164 (27)	<0.001		
CL13	12/99 (12)			45/183 (25)	0.013	55/193 (28)	0.002
CL14	20/176 (11)	81/360 (22)	0.002	102/370 (28)	<0.001		

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

[5] I note that this definition is slightly different that one that we have used in the past, which includes the additional requirement that no remedication occur within the observation period.

7.10.10 Consistency of Response

Study CL14 studied 3 consecutive attacks. Both 6.25mg and 12.5mg were significantly superior to placebo in both the 2-hour response rates and 2-hour pain-free rates in all three attacks. This is shown in Table 20 (sponsor table 19, Item 8/10, Vol. 91, page 39).

Table 20: Study CL14 – Consistency of Response

Attack	PBO n/N (%)	Almotriptan 6.25mg n/N (%)	p-value	Almotriptan 12.5mg n/N (%)	p-value
2-Hr Response Rates					
1	58/176 (33)	200/360 (56)	<0.001	240/370 (65)	<0.001
2	55/147 (37)	185/313 (59)	<0.001	215/324 (66)	<0.001
3	49/131 (37)	173/288 (60)	<0.001	209/301 (46)	<0.001
2-Hr Pain-Free Rates					
1	27/176 (15)	104/360 (29)	0.001	145/370 (39)	<0.001
2	26/147 (18)	91/313 (29)	0.008	127/324 (39)	<0.001
3	20/131 (15)	99/288 (34)	<0.001	129/301 (43)	<0.001

p-values are Fisher's exact test vs. placebo

7.11 Other Controlled Studies

There were three other controlled studies that evaluated the efficacy of almotriptan but are not considered pivotal for various reasons described here. These studies were CL10, CL11, and 008. CL10 used a subcutaneous formulation, CL11 was oral and placebo-controlled but did not use the planned marketed doses, and 008 was not placebo-controlled, but rather used an active control with sumatriptan 50mg.

7.11.1 Study CL10

This was a randomized, double blind, placebo-controlled, parallel group study which evaluated 3 doses of subcutaneous almotriptan (2mg, 6mg, 10mg) and placebo for the acute treatment of a single migraine attack. Ninety-one (91) patients received almotriptan and 32 received placebo. The primary efficacy endpoint was the 2-hour headache response rate. Other efficacy measures included the 2-hour pain-free rate, the use of escape medication, and the recurrence rate. The key results are shown in Table 21 (sponsor table 21, Item 8/10, Vol. 91, page 43).

Table 21: Study CL10 – Key Results

Outcome	PBO (n=32) n/N (%)	2mg (n=31) n/N (%)	6mg (n=29) n/N (%)	10mg (n=31) n/N (%)
2-hr response	16 (50)	19 (61)	28 (96)	28 (90)
2-hr pain-free	8 (25)	8 (26)	17 (59)	12 (39)
Escape	11 (34)	7 (23)	0 (0)	3 (10)
Recurrence	1 (3)	3 (10)	2 (7)	3 (10)

Results in gray - p≤0.05 compared to placebo

Both the 6mg and 10mg doses were associated with significantly higher response rates, pain-free rates and lower rates of escape medication use.

7.11.2 Study CL11

This was a randomized, double blind, placebo-controlled, parallel group study which evaluated 4 doses of oral almotriptan (5mg, 25mg, 100mg, 150mg) and placebo for the acute treatment of a single migraine attack, using a single dose (recurrences were not treated with study medication). The primary endpoint was the 2-hr headache response rate. One hundred thirty-eight (138) patients received almotriptan and 31 received placebo.

Oral doses of 25mg, 100mg, and 150mg were significantly more effective than placebo in providing a headache response at 2 hours. Secondary endpoint were supportive of this conclusion. The key results are shown in Table 22 (adapted from sponsor table 22, Item 8/10, Vol. 91, page 44).

Table 22: Study CL11 – Key Results

Outcome	PBO (n=31) n (%)	5mg (n=35) n (%)	p	25mg (n=35) n (%)	p	100mg (n=33) n (%)	p	150mg (n=35) n (%)	p
2-hr response	13 (42)	23 (66)	0.083	28 (80)	0.002	23 (70)	0.043	30 (86)	<0.001
2-hr pain-free	6 (19)	15 (43)	0.063	18 (51)	0.010	17 (52)	0.010	15 (43)	0.063
Escape	15 (48)	7 (20)	0.019	6 (17)	0.009	9 (27)	0.12	6 (17)	0.009
Recurrence	2/13 (15)	7/23 (30)	0.44	2/28 (7)	0.58	10/23 (44)	0.14	2/30 (7)	0.57

p-value vs. placebo using Fisher's exact test

7.11.3 Study 008

This study was a randomized, double blind, active control, parallel group study which evaluated almotriptan 12.5mg or sumatriptan 50mg for the acute treatment of a single migraine attack. A second dose was permitted after two hours for recurrence within 24 hours. The primary endpoint was the 2-hour headache response rate. A total of 591 patients received oral almotriptan 12.5mg and 582 received oral sumatriptan 50mg. Approximately 80% took just one dose of study medication, and 20% took both doses.

The 2-hour headache response rates were similar between treatments: 58% vs. 57% for almotriptan and sumatriptan, respectively. None of the main secondary endpoints were positive with the exception that the 2-hr pain-free rate was nominally significantly higher for sumatriptan 50mg (18% vs. 25% for almotriptan vs. sumatriptan). The key results are shown in Table 23 (adapted from sponsor table 23, Item 8/10, Vol. 91, page 45).

Table 23: Study 008 – Key Results

Outcome	Almotriptan 12.5mg N=591 n (%)	Sumatriptan 50mg N=582 n (%)	p-value
2-hr response	343 (58)	333 (57)	0.81
2-hr pain-free	106 (18)	143 (25)	<0.01
Escape	217 (37)	193 (33)	0.20
Recurrence	94/343 (27)	80/333 (24)	0.32

p-values are chi-square

7.12 Sponsor's Efficacy Conclusions

Based on the results of the 3 adequate and well-controlled clinical trials CL12, CL13, and CL14, the sponsor concludes the following:

- Almotriptan provided statistically significant higher headache response rates over placebo at 2 hours, the primary efficacy endpoint in the three studies
- It generally provided nominally significant higher response rates at 1 hour
- Almotriptan was effective in providing relief from migraine associated symptoms. Relief was usually significantly better than placebo at 2 hours.
- Efficacy was unaffected by baseline pain, age, sex, weight, or baseline characteristics (aura, use of oral contraceptives, use of migraine prophylaxis)
- Almotriptan 12.5mg generally provided patients with higher rates of pain relief, for both the primary and secondary efficacy endpoints, than almotriptan 6.25mg. The effects were dose related.
- The use of escape medication was dose-dependent, with the highest rate noted for placebo and decreasing rates of use corresponding to increasing doses of almotriptan; patients using 12.5mg required escape medication least frequently. Similarly, the estimated time to remedication after treatment with either dose of almotriptan was significantly longer than for placebo.
- Recurrence rates were not significantly affected by almotriptan treatment.
- Sustained responses and sustained pain-free rates were significantly better than placebo. Both endpoints were provided more frequently by 12.5mg than by 6.25mg
- Almotriptan provided significant pain relief over the course of three consecutive migraine attacks
- Almotriptan was equivalent in efficacy to sumatriptan 100mg, based on pain response at 2 hours, after adjustment for baseline pain severity.

7.13 Reviewer's Analyses

Based on the sponsor's analyses, the evidence for efficacy of almotriptan in the acute treatment of migraine is quite robust and I chose not to repeat the analyses presented. Instead, I focus in this section on analyses that assist in the proper labeling of the product. In particular, I evaluate the time to response and the time to remedication, using pooled data from the 3 pivotal studies.

7.13.1 Time to Response

The sponsor provided important migraine attack information in files named effacl12.xpt, effacl13.xpt, and effacl14.xpt (one for each pivotal study). I pooled the data from all three studies to generate the "time to response" graph. The dataset was organized such that

there was one record for each attack treated. In the case of study CL14, where patients were allowed to treat up to three attacks with study medication, there were as many as three records for each patient. There were a total of 3,826 records in the pooled dataset. I used only records for the first attack from study CL14. This reduced the number of records to 2,318. The distribution of first attacks (records) by study and treatment group is shown in Table 24 (RA – stands for "reviewer analysis"). This is identical to the sponsor provided Table 4, on page 15 of this review.

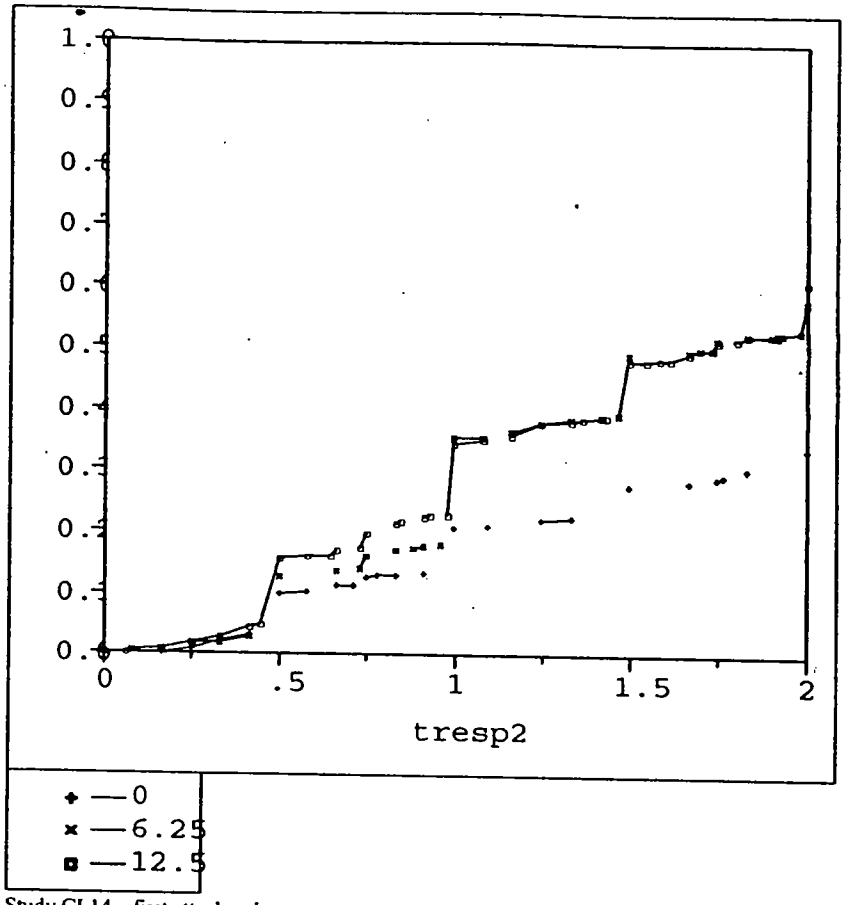
Table 24 (RA): Studies CL12, 13, 14 – Distribution of First Attack

Study	PBO	2mg	6.25mg	12.5mg	25mg	Suma 100mg	Total
12	80	170	167	164	161	0	742
13	99	0	0	183	191	193	666
14	176	0	360	374	0	0	910
Total	**355**	**170**	**527**	**721**	**352**	**193**	**2318**

The sponsor provided important date/time variables which allow analysis of a "time to response analysis: MED_DATE and MED_TIME provided the date and time that the initial dose of study medication was used to treat the attack, and LES_DATE and LES_TIME provided the time that the headache first lessened in intensity. Although the term "lessened" is not defined in the dataset or in the variable.pdf file, the study reports indicated that the sponsor collected the date and time of "amelioration of pain (mild or none)." This field is the only one submitted that could represent this variable. Therefore, I felt it was safe to assume that LES_DATE and LES_TIME coded the date/time that a response first occurred. A simple subtraction of these two date/times provided the time to response. I censored those who had missing LES_DATE/TIME fields, or whose time to response exceeded 2 hours, to two hours.

I used Kaplan-Meier survival methods in JMP Version 3.2.5 to generate the time to response graph shown in Table 25. Numerically, both the 6.25mg and 12.5mg doses are associated with a higher probability of a response within the first two hours of treatment, compared to placebo, although there is little numerical difference noted between the 6.25mg and 12.5mg doses.

Table 25 (RA): Studies CL12, 13, 14 – Time to Response



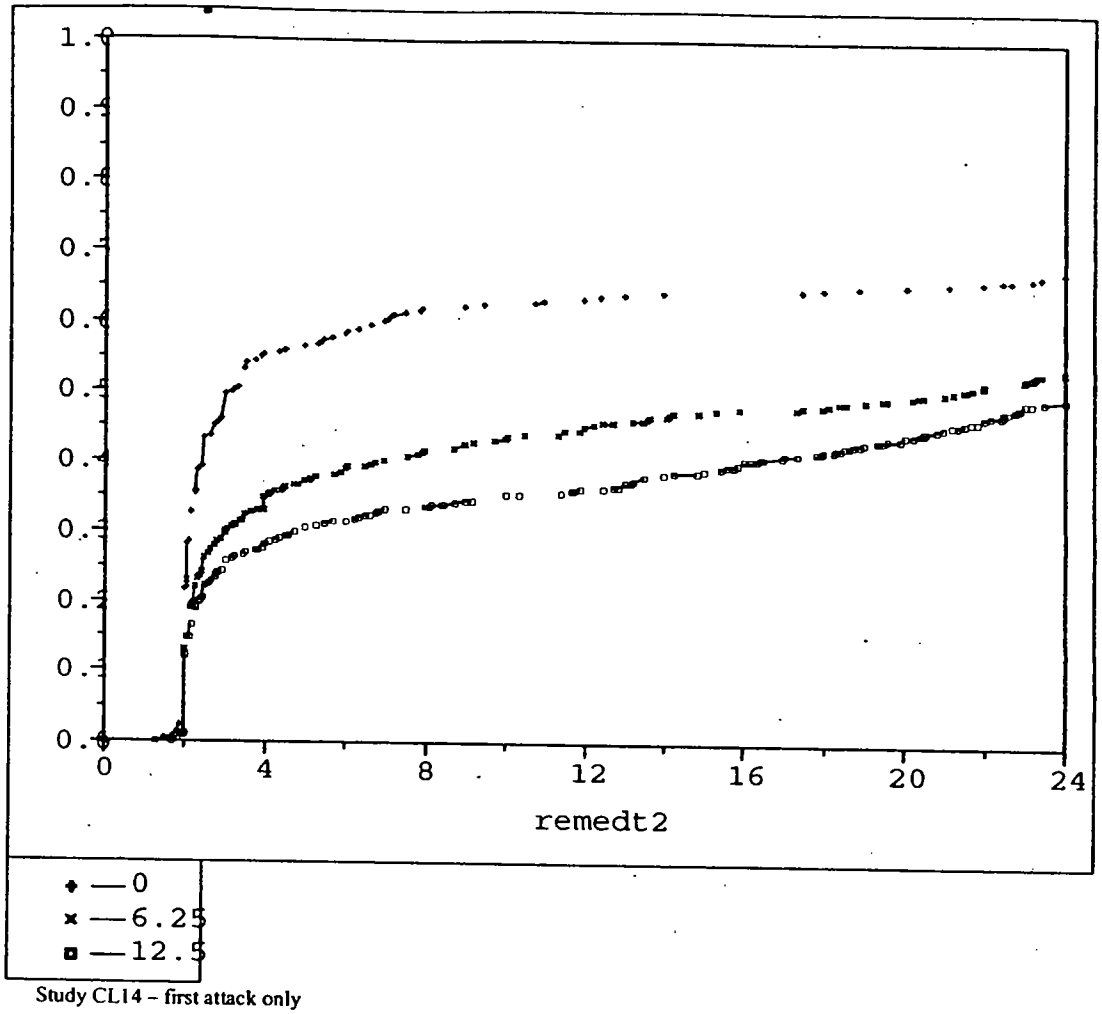
Study CL14 – first attack only

7.13.2 Time to Remedication

I used the same method described in the previous section to generate a "time to remedication graph" using the same data. In this case, the sponsor provided a separate variable called REMEDT which coded the elapsed time, in hours, when remedication occurred.

The graph of the estimated probabilities of time to remedication (using Kaplan-Meier survival methods) is shown in Table 26. Both the 6.25mg and 12.5mg doses were associated with numerically lower probabilities of remedication starting at about 2 hours. The 12.5mg dose had numerically lower probabilities compared with the 6.25mg dose.

Table 26 (RA): Studies CL12, 13, 14 – Estimated Time to Remedication



Study CL14 – first attack only

7.14 Reviewer's Efficacy Conclusions

Based on my review of the submission, I conclude that:

- 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.
- The trials did not study the safety or efficacy of more than two doses within 24 hours.

8. Integrated Review of Safety

8.1 Background

The safety database in migraine patients consists of all safety data gathered in the eight phase 2/3 studies. All studies are completed at the time of the NDA submission (Table 3, page 8). A total of 5131 migraine patients were treated with study drug (almotriptan, sumatriptan, or placebo). Of these, 4610 were unique patients, since the 521 remaining patients were treated in both CL14 and CL25.

In the controlled oral studies (CL11, CL12, CL13, CL14, and 0008), 1840 patients were treated with the recommended doses of 6.25 or 12.5mg (527 at 6.25mg and 1313 at 12.5mg). All studies involved the treatment of a single attack, except study CL14 which treated 3 attacks. In addition, 1346 patients were treated with 12.5mg in two long-term uncontrolled studies (CL25 for one year and 0011 for six month). The extent of exposure in the phase 2/3 program is shown in Table 27 (adapted from sponsor table 2, Item 8/10, Vol. 91, page 339).

Table 27: Phase 2/3 Studies – Extent of Exposures, By Dose

Study*	PBO	Dose (mg) Almotriptan 2	5	6	6.25	10	12.5	25	100	150	Sumatriptan 50	100	Total
Controlled													
CL10	32	31		29		31							**123**
CL11	31		35					35	33	35			**169**
CL12	80	170			167		164	161					**742**
CL13	89						184	191				194	**668**
CL14	176				360		374						**910**
0008							591				582		
Sub-Total	481	201	35	29	527	31	1313	387	33	35	582	194	**3785**
Uncontrolled													
CL25							761						**761**
0011							585						**585**
Sub-Total							1346						**1346**
Total	**418**	**201**	**35**	**29**	**527**	**31**	**2659**	**387**	**33**	**35**	**582**	**194**	**5131**

*all studies were p.o. except CL10 which was subcutaneous

The majority of the experience was at 12.5mg, particularly since this was the dose used in the long-term safety studies.

Finally, 351 healthy volunteers received almotriptan in the 20 phase 1 clinical studies.

For the purposes of the safety analysis, the sponsor organized the studies into 5 groupings, based on whether or not the trials were controlled, the route of administration, and special populations. These groupings are outlined below.

8.1.1 Grouping 1 – Phase 2/3 Controlled Studies – Oral Administration

This group provides controlled safety data. It is the focus of the safety analyses presented in this review. It consists of the 5 controlled oral phase 2/3 studies CL11, CL12, CL13, CL14, and 0008. CL11 was placebo-controlled but did not study the planned marketed doses, and study 0008 was not placebo-controlled but instead used an active control (sumatriptan 50mg).

In this group, a total of 3662 patients received study medication: 169 in study CL11, 742 in study CL12, 668 in study CL13, 910 in study CL14, and 1173 in study 0008. Of these 3662 individuals, 386 received placebo, 527 received 6.25mg, 1313 receive 12.5mg, 387 received 25mg, and 582 received sumatriptan 50mg. The remaining 467 patients received other doses of almotriptan (2, 5, 100, or 150mg) or sumatriptan 100mg.

In the only multiple attack controlled trial, 910 patients were treated in study CL14. The majority treated three attacks (74.4% for placebo, 80.6% for 6.25mg, and 81% for 12.5mg).

The extent of exposures in the controlled studies is shown in Table 28 (sponsor table 7, Item 8/10, Vol. 91, page 356). Most patients took only one dose although a second dose was permitted for relapse. It's interesting to note that the placebo patients had the lowest proportion taking a second dose. The proportion patients taking a second dose were similar among the three almotriptan dose groups and the sumatriptan 50mg group (20-23%).

Table 28: Controlled Studies – Extent of Exposures

Number of Doses Taken	PBO N=386 n (%)	6.25mg N=527 n (%)	12.5mg N=1313 n (%)	25mg N=387 n (%)	Suma 50mg N=582 n (%)
One	323 (83.7)	414 (78.6)	1011 (77.0)	305 (78.8)	465 (79.9)
Two	63 (16.3)	113 (21.4)	302 (23.0)	82 (21.1)	117 (20.1)

8.1.2 Grouping 2 – Phase 3 Uncontrolled Long-Term Studies

This group forms an additional important source of safety data because it provides the long-term experience with the drug under conditions of expected use. It consists of the two long-term safety studies CL25 and 0011.

A total of 1313 patients were treated in the uncontrolled studies: 761 in study CL25, a 12-month study, and 585 in study 0011, a 6-month study. All received almotriptan 12.5mg. As in the controlled studies, patients were allowed to take a second dose in case of recurrence.

The total number of attacks treated per patient ranged 1-97 in study CL25 and 1-60 in study 0011. The mean number of attacks treated per patient was virtually the same in both studies: 18.0 and 18.2, respectively. The mean number of doses taken per attack was 1.4 and 1.3, respectively.

8.1.3 Grouping 3 – Safety Data for Patients Averaging Two Migraines per Month

This is a subset of grouping 2 and includes data from patients that meet ICH and Division guidelines for the adequate long-term safety evaluation of a new drug, *i.e.*, the safety database must include at least 300 patients treating at least 2 headaches per month for 6 months, and at least 100 patients treating at least 2 headaches a month for 1 year.

The sponsor refers to these populations as the "6-month population" and the "12-month population." Since study 0011 was a 6-month study, the 12-month population consist exclusively of patients from study CL25 only.

A total of 464 patients treated an average of at least 2 headaches per month for 6 months, and 169 patients treated an average of at least 2 headaches per month for 12 months (Table 29, adapted from Item 3, Vol. 1, page 191). One-hundred forty-nine patients (149) of the 12-month population are also included in the 6-month population. These numbers exceed ICH and Division guidelines for long-term exposure of migraine patients on chronic-intermittent therapy.

Table 29: Studies CL25 and 0011 – Number of Patients Treating ≥2 headaches/month

Duration	N	Number of Attacks	Number of Doses per Attack
6-months	464	12-60	1.4
12-months	169	24-95	1.5

The total number of attacks treated in the 6-month population ranged from 12-60, and in the 12-month population ranged from 24-95. The mean number of doses per attack was 1.4 in the 6-month population and 1.5 in the 12-month population.

8.1.4 Grouping 4 – Phase 2 Controlled Studies – Subcutaneous Administration

This grouping contains the results of study CL10. This was a small study in which 32 received placebo, 31 received 2mg, 29 received 6mg, and 31 received 10mg. All medication was given subcutaneously in the arm as a single dose. A repeat dose for recurrence or persistent pain was not permitted.

8.1.5 Grouping 5 – Phase 1 Studies

Pertinent data from the 20 phase 1 studies are included here. Of the 20 phase 1 studies, 16 of them administered oral almotriptan to 297 subjects, 4 studies administered almotriptan subcutaneously to 24 subjects, one study administered almotriptan sublingually to 8 subjects, and one study administered almotriptan intravenously to 24 subjects.

8.2 Deaths

There were no deaths reported in the almotriptan clinical development program.

8.3 Serious Adverse Events

There were four serious adverse events report in the oral controlled trials.

- CL14 (614, placebo) – 25 year-old female was hospitalized for diaphoresis, tremors, and vomiting. All were serious and considered drug-related. The events occurred on the same day medication was taken for treatment of her first attack. The patient recovered without incident. She withdrew consent from the study and failed to treat any additional attacks.
- CL12 (158, 2mg) – 58 year-old female took 2mg on 1/27/97. She had severe episode of colitis approximately 3 weeks later on 2/12/97 requiring hospitalization, and she had asthmatic respirations on 3/17/97, almost 2 months later. She had fully recovered at the time of her follow-up visit on 3/21/97.
- CL14 (79, 12.5mg) – 25 year-old female was hospitalized approximately six weeks after treatment with biliary colic. She underwent successful cholecystectomy and was fully recovered on her end of study visit.
- CL14 (1282, 6.25mg) – 47 year-old female took a total of 4 doses of 6.25mg throughout the study. On the last day of drug administration (8/6/97), she experienced nausea, vomiting, and epigastric discomfort, which was not recorded in the case report form (??). She reported these symptoms the next day at her fourth follow-up visit. An ECG showed posterolateral repolarization changes and she was hospitalized on 8/6/97 for suspected myocardial ischemia (screening ECG was negative). Cardiac enzymes were negative. Her stress test ("ergometry") was negative, and coronary angiography was also negative. This event was considered drug related.

In the long-term studies, serious adverse events were reported by 3.5% (27/761) of the patients in study CL25 and by 1.9% (11/585) of the patients in study 0011. These are listed in Table 30 (sponsor table 28, Item 3, Vol. 1, page 201). Most incidents were isolated cases. Those that were not are not likely drug related (surgical procedures, trauma, hemorrhoid, skin cancer, migraine).

Table 30: Studies CL25 and 0011 – Serious Adverse Events

Serious Adverse Event	CL25 12.5mg N=761 n (%)	0011 12.5mg N=585 N (%)
Body		
Back Pain	1 (0.1)	0
Carcinoma	1 (0.1)	0
Chest Pain	1 (0.1)*	0
Headache	1 (0.1)	0

Serious* Adverse Event	CL25 12.5mg N=761 n (%)	0011 12.5mg N=585 N (%)
Migraine	2 (0.3)	1 (0.2)
Reaction unevaluable**	6 (0.8)	0
Trauma	4 (0.5)	0
Cardiovascular		
Coronary Artery Occlusion	0	1 (0.2)
Vasovagal reaction	1 (0.1)	0
Digestive		
Carcinoma colorectal	0	1 (0.2)
Cholecystitis	0	1 (0.2)
Disorder rectal	1 (0.1)	0
Hemorrhoid	3 (0.4)	0
Neoplasm GI	1 (0.1)	0
Hemic and Lymphatic		
Lymphoma	1 (0.1)	0
Musculoskeletal		
Tenosynovitis	1 (0.1)	0
Nervous		
Cerebral ischemia	1 (0.1)	0
CNS cyst	0	1 (0.2)
Skin		
Carcinoma skin	0	2 (0.3)
Melanoma skin	0	1 (0.2)
Special Senses		
Disorder ear	1 (0.1)	0
Urogenital		
Abortion spontaneous	1 (0.1)	0
Calculus kidney	0	1 (0.2)
Menstrual disorder	1 (0.1)	0
Ovarian disorder	1 (0.1)	0
Fibroid uterus	1 (0.1)	0
Menorrhagia	0	1 (0.2)
Metrorrhagia	1 (0.1)	0
Ovarian Cyst	1 (0.1)	0
Unintended pregnancy	0	1 (0.2)

* relation to study medication unknown
** includes surgical intervention for voluntary sterilization (2), hysterectomy for myomata (1), varisectomy (1), septoplasia (1), knee arthroscopy (1)

There were no serious adverse events reported in the phase 2 subcutaneous study, and there was only one SAE in the phase 1 studies. This was patient 18 in study CL27. The event was a vasovagal episode during an intravenous infusion of almotriptan 3mg. The subject recovered after treatment with atropine. The event was probably related to venous catheter placement and not to drug.

8.4 Adverse Dropouts

Since most of the controlled trials were single attack studies (all but CL14, which treated 3 attacks), the opportunity to discontinue prematurely due to adverse events from these trials was limited. As a result, there were no adverse dropouts from the single attack studies.

There were five patients who discontinued prematurely due to adverse events in the oral controlled trials and all of them discontinued after the first attack in study CL14. All of them occurred on the same day that medication was taken. None of the events was considered serious.

- CL14 (373, 12.5mg) – headache, hypesthesia, localized pain, nausea
- CL14 (103, 6.25mg) – dizziness, drowsiness
- CL14 (354, 6.25mg) – hyperreflexia and nystagmus (later found to be pre-existing)
- CL14 (1270, 6.25mg) – syncope[6]
- CL14 (312, 6.25mg) – diarrhea, nausea, vomiting, headache

In the long-term uncontrolled studies, 4.7% (63/1346) discontinued due to adverse events (3.5% in study CL25, and 6.2% in study 0011). The most common adverse events leading to discontinuation were migraine (6), chest pain (5), QT prolongation (4), hypertension (3), depressive symptoms (3), and unintended pregnancy (3).

No patient discontinued from the subcutaneous study (CL10) due to an adverse event.

There were four ADO's in the phase 1 studies:

- 5, CL01N – withdrew due to headache after receiving a 10mg intranasal dose of almotriptan
- 6 and 12, 0003 – both withdrew due to abnormal Holter monitor at baseline. These were not due to study medication.
- 7, 0002 – withdrew due to a positive pregnancy test upon checking into the clinic for the second study period (adverse event: exposure in utero). She had undergone an elective abortion between study periods.

8.5 Adverse Events

Adverse Events in the controlled studies include those treatment-emergent events that were recorded in the post-attack assessment period (3-5 days in study CL11 and 2-6 days in studies CL12, CL13, CL14, and 4 days in study 0008).

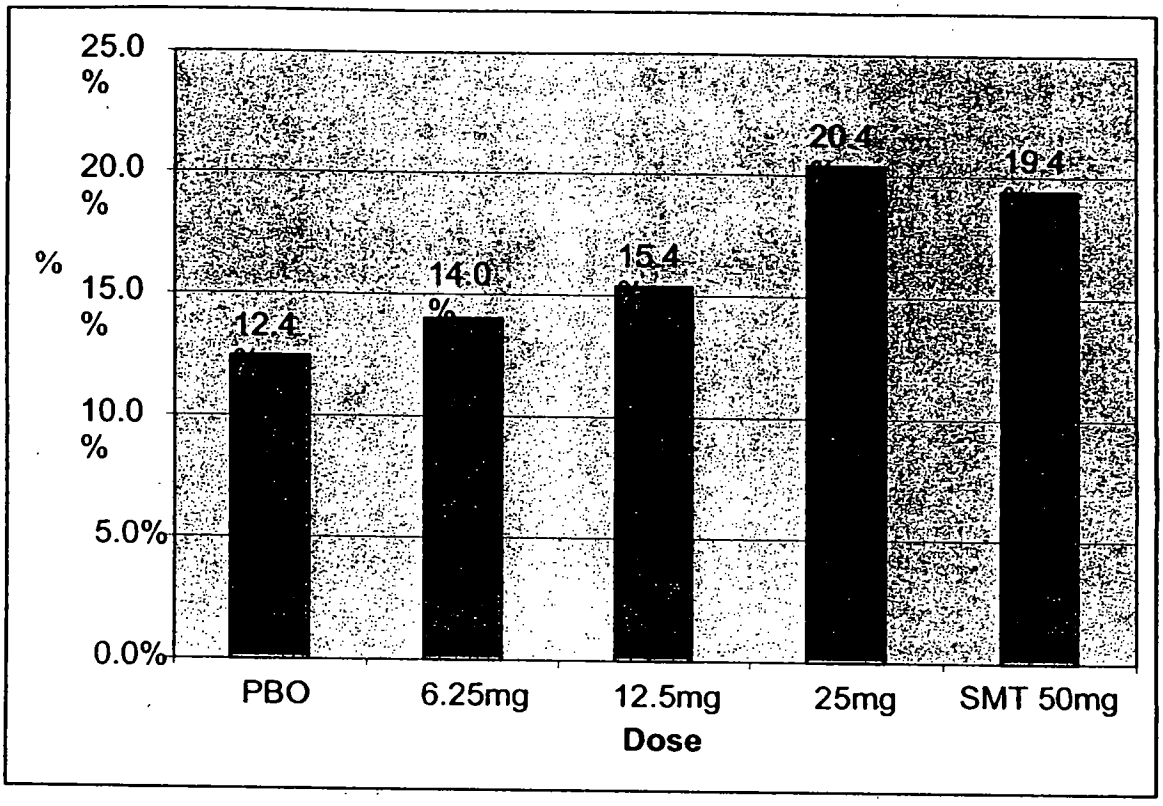
In the single attack controlled studies, patients on placebo, 6.25mg, and 12.5mg reported overall AE's incidences of 12.4%, 14.0%, and 15.4%, respectively. The overall incidences of AE's by dose is shown in Figure 2 (adapted from ISS figure 5, Item 8/10, Vol. 91, page 370).

The overall incidences of AE's in the 100mg and 150mg groups were 24.2% and 34.3%, respectively, but these are based on relatively small numbers (33 and 35 patients) and are not included in the figure. It generally shows a trend of increasing AE's with increasing

[6] No narrative of this event is provided. According to the Case Report Form, the patient experienced a "tendency to collapse" occurring 20 minutes after taking study medication. The event lasted 2 hours and 40 minutes, and the subject recovered fully. No actual loss of consciousness is described, but no additional details are available.

dose. The incidence of AE's for the 25mg group was comparable to the sumatriptan 50mg dose group in this safety population.

Figure 2 (RA): Single Attack Controlled Studies – Overall Incidences of Adverse Events



The incidences of AE's group by major body system, are shown in Table 31 (sponsor table 24, Item 3, Vol. 1, page 193).

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

The three body systems body (general), nervous, and digestive had the highest AE incidences, and there appeared to be a numerical dose-response trend.

Table 32 (sponsor table 24, Item 3, Vol. 1, page 193) lists the incidence of adverse events that occurred with at least a 1% incidence in any of the main treatment groups, and at a rate greater than placebo.

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)
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

At the recommended doses of 6.25mg and 12.5mg, the most common AE's associated with almotriptan use were nausea, somnolence, headache, dry mouth, and paresthesia. These are similar to the AE's seen with other triptans. Headache and nausea are symptoms of the underlying disease. In the case of headache, the incidence was very similar to placebo. In the case of nausea, the incidence for 12.5mg was higher than placebo, but this was not true of the 6.25mg dose.

It is interesting to note that the incidence of chest pain, at the recommended doses of 6.25mg and 12.5mg, were actually numerically lower than placebo (0.2% vs. 0.3%) and was substantially lower than the incidence for the sumatriptan 50mg group (2.2%). The incidence of nausea was also lower than sumatriptan.

It is also interesting to note that the overall incidence of adverse events is lower for almotriptan compared to other approved triptans. For example, a 2% incidence table (the standard cutoff for triptan AE tables) for almotriptan 6.25mg and 12.5mg would include just nausea (and perhaps dizziness if one rounds up), whereas for approved labeling for sumatriptan tablets includes 8 entries. I wondered if this was related to the fact that the almotriptan trials were all conducted in Europe and perhaps there was a tendency to under-report adverse events there. However, I compared the incidences reported above with the AE incidences in study 0008 (a U.S. active-controlled study), and the AE incidences were comparable (sponsor table 13, Item 8/10, Vol. 42 page 48, not shown here). I also compared the AE incidences reported for sumatriptan 50mg in these studies

with those reported in approved labeling. In general, it is difficult to compare the two tables because many of the categories are different. However, paresthesia for sumatriptan 50mg approved labeling is listed as 5% incidence, whereas in the almotriptan studies, it was only 0.7%. Chest pain in approved labeling is listed as 2% whereas in the almotriptan studies is listed as 2.2%. Vertigo in approved labeling is listed as 2% whereas in the almotriptan studies is listed as 1.7%.

Adverse events in the controlled studies were analyzed by sex, age, weight, presence of aura, use of migraine prophylaxis, and use of oral contraceptive. No clinically important differences were identified within each subgroup (shown here are effects of sex and age, Table 33, Table 34, taken from sponsor tables 25, 27, ISS, Item 8/10, Vol. 91, pages 376, 378.

Table 33: Controlled Studies – Adverse Events by Sex

	Females			Males		
	PBO N=329 n (%)	6.25mg N=466 n (%)	12.5mg N=1114 n (%)	PBO N=57 n (%)	6.25mg N=61 n (%)	12.5mg N=169 n (%)
Patients with at least one AE	41 (12.5)	67 (14.4)	170 (14.9)	7 (12.3)	7 (11.5)	32 (18.9)

Table 34: Controlled Studies – Adverse Events by Age

	≤45 years			> 45 years		
	PBO N=261 n (%)	6.25mg N=346 n (%)	12.5mg N=832 n (%)	PBO N=125 n (%)	6.25mg N=181 n (%)	12.5mg N=481 n (%)
Patients with at least one AE	30 (11.5)	50 (14.5)	136 (16.3)	18 (14.4)	24 (13.3)	66 (13.7)

Across all three attacks in study CL14, AE's were reported by 21.1% of placebo patients, 21.1% of 6.25mg patients, and by 25.7% of 12.5mg patients. The most common AE's reported were similar as those reported after an initial attack.

Table 35 shows the incidence of adverse events in each dose group according to the number of doses taken to treat the attack (sponsor table 23, ISS, Item 8/10, Vol. 91, page 374). It shows that the incidences were similar across treatment groups after one dose. It is problematic to compare the one-dose and two-dose populations since the second population is not a randomized group and consist of responders who subsequently relapsed.

Table 35: Controlled Studies – Adverse Events by Number of Doses Taken

	One Dose			Two Doses		
	PBO N=323 n (%)	6.25mg N=414 n (%)	12.5mg N=1011 n (%)	PBO N=63 n (%)	6.25mg N=113 n (%)	12.5mg N=302 n (%)
Patients with at least one AE	42 (13.0)	51 (12.3)	146 (14.4)	6 (9.5)	23 (20.4)	56 (18.5)

In the uncontrolled studies, adverse events included those that occurred or worsened in severity. Since the period of observation was quite long (6-12 months), the opportunity to develop and report an AE was increased and the incidences are higher as a result. Fifty-three percent (53%, 403/761) of patients in study CL25 and 73% (428/585) of patients in study 0111 reported at least one AE. As in the controlled studies, the body systems with the most AE's were body (general), digestive, and nervous. In addition, relatively high rates of respiratory AE's (>10%) were also reported. There are no placebo groups for comparison. Individual AE's that occurred with an incidence of >2% in either study are shown in Table 36 (sponsor table 26, Item 3, Vol. 1, page 196). Since these were open-label, uncontrolled studies, interpretation of these results is problematic. For example, the most common AE's reported in study CL25 were flu and bronchitis. It is doubtful that these are drug related, and fewer than 10% of these were deemed treatment-related by the investigators.

Table 36: 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)

Adverse Event	CL25 12.5mg N=761 n (%)	0011 12.5mg N=585 n (%)
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 adverse events reported by the 6-month and 12-month populations were similar than those reported by all patients undergoing long-term treatment (sponsor table 27, Item 3, Vol. 1, page 198, not shown here).

In study CL10, the controlled subcutaneous phase 2 study, 28.1% (9/32) patients in the placebo group and 19.4% (6/31), 27.6% (8/29), and 29.9% (9/31) of patients in the 2, 6, and 10mg groups, respectively, reported at least one AE. The types and incidence of individual AE's were similar to those seen in the oral controlled studies.

The AE's reported in the phase 1 studies were, again, similar to those seen in the controlled phase 3 trials. The dose-limiting AE's noted in study CL01 (14mg subcutaneous dose) were vasodilation, headache, paresthesias of the face, and in study CL02 (200mg oral dose) were vasodilation, paresthesia, pressure sensations. These are known effects of $5HT_{1B/1D}$ agonists.

8.6 Laboratory Findings

Laboratory tests were collected at baseline/screening and 2 to 6 days after study drug administration in the controlled studies. Post-baseline laboratory assays were not performed in study 0008, and were optional in study CL13 (only 20/668 patients in this study had them done). Interpretation of these results is problematic given the long latency between study drug ingestion and laboratory assessment, and the lack of useful data from studies 0008 and CL13.

Very few patients (<1% in any of the main treatment groups in controlled studies) had clinically significant post-baseline laboratory findings. There was no relationship between the number or type of abnormal assay results and the dose of almotriptan administered. These are listed in Table 37 (sponsor table 55, ISS, Item 8/10, Vol. 91,

page 414). Sumatriptan 100mg is substituted for 50mg in study 0008 since no post-treatment lab values were collected in that study.

Table 37: Controlled Studies – Laboratory Abnormalities

Assay	PBO n/N (%)	6.25mg n/N (%)	12.5mg n/N (%)	25mg n/N (%)	SMT 100mg n/N (%)
Chemistry					
CK	0	0	2/525 (0.4)	0	0
Total Cholesterol	0	0	1/528 (0.2)	0	0
Triglycerides	1/280 (0.4)	0	0	0	0
Hematology					
Lymphocytes	0	0	1/524 (0.2)	0	0
Neutrophils	0	0	1/524 (0.2)	0	0
White Blood Cells	0	0	1/524 (0.2)	1/192 (0.5)	
Urinalysis					
Blood	1/281 (0.4)	0	1/520 (0.2)	0	0
Sediment	0	0	1/478 (0.2)	0	0

In the long-term studies, study CL25 performed laboratory assays at screening and 2-6 days after every fourth attack, or every 3 months, whichever occurred first. Twenty (2.6%) of 762 patients reported clinically significant laboratory assays. Six (6) patients reported hematology abnormalities (decreased hemoglobin (2), increased WBC (1), leukopenia (1), lymphopenia (1)). Nine (9) patients reported clinical chemistry abnormalities, which included elevated ALT (3), AST (2), GGT (3), CK (2), triglycerides (2), sodium (1), uric acid (1), total bilirubin (1)[7]. Five (5) patients had urinalysis abnormalities, which included altered urine sediment (4), blood in urine (2), and elevated urine protein (1). The total number of abnormalities reported exceed the number of patients because some patients had more than one abnormality. The numbers of abnormalities of any particular laboratory parameters were quite small and do not suggest a drug-related pattern.

Study 0011 performed laboratory assessments at screening/baseline, and 1, 3, 5, and 6 months after study medication was dispensed. Thirty-four (5.8%) of 585 patients reported 63 clinically significant laboratory assays. The distribution of the abnormalities is shown in Table 38 (sponsor table 17, study report 0011, Item 8/10, vol. 78, page 62). Because assays were based on time in study, rather than time since last dose, it is difficult to interpret these results since the assays have no relationship to the last dose taken. The lack of a control arm in both 0011 and CL25 makes additional interpretation of these data problematic.

[7] This subject (id 756), was the only subject that had both elevation in transaminases (AST, ALT) and bilirubin. The abnormality occurred 4 months after starting medication. This subject was discontinued from the study for suspected heroine abuse.

Table 38: Study 0011 – Clinically Significant Laboratory Assays

Lab	Assay	12.5mg Total N = 585		
		n	N	%
Chemistry	SGPT	4	579	0.7
	SGOT	1	579	0.2
	Total Bilirubin	1	579	0.2
	Calcium	1	579	0.2
	Total Cholesterol	8	574	1.4
	Creatine Kinase	5	577	0.9
	GGT	4	578	0.7
	Glucose	4	578	0.7
	Potassium	1	577	0.2
	Triglycerides	5	577	0.9
Hematology	Hematocrit	3	575	0.5
	Hemoglobin	3	575	0.5
	Platelet	2	577	0.3
	RBC	3	576	0.5
Urinalysis	Urine blood	6	572	1.0
	Urine RBC	8	574	1.4
	Urine WBC	4	573	0.7

In the subcutaneous study CL10, laboratory assessments occurred at screening and at the final visit (3-5 days after study drug administration). No clinically significant abnormalities were observed. The phase 1 studies also failed to reveal any clinically significant laboratory abnormalities.

8.7 Vital Signs

Three phase 1 studies (CL02, CL28, and 0007) allowed careful vital signs assessment shortly after treatment. The studies examined a wide range of almotriptan doses (6.25mg – 200mg), and included placebo. A summary of the results are as follows:

- Heart Rate – a dose-related increase in heart rate relative to placebo was observed only in study CL02. Maximum increases during the first 8 hours of treatment were 3 bpm for placebo, 11 bpm for 25mg, 7 bpm for 50mg, 2 bpm for 100mg, 17 bpm for 150mg, and 17 bpm for 200mg. For the two highest doses, the elevation in heart rate was seen as early as 2 hours post-dose, were maximum at 4 hours and were still present at 8 hours.

- Systolic Blood Pressure – in all three studies, there was a dose-related increase in systolic blood pressure compared to placebo. The increases began within 30 minutes after dosing and were resolved by 8 hours after dosing.

  In study CL02, the maximum increases in the first 8 hours were 3mm for placebo, 14mm for 25mg, 11mm for 50mg, 13mm for 100mg, 16mm for 150mg, and 28mm for 200mg.

  In study CL28, mean weighted increase vs. placebo 0-4 hours after dosing were 0.21mm for 12.5mg, 2.78mm for 25mg, and 4.17mm for 50mg. The increases were

statistically significant for the 25mg and 50mg doses but not for 12.5mg.

In study 0007, mean weighted changes from baseline over the first 4 hours were 1.38mm for placebo, 6.25mm for 12.5mg, and 11mm for 25mg.

- Diastolic Blood Pressure – in all three studies, there was a dose-related increase in diastolic blood pressures compared to placebo. The increases began within 30 minutes after dosing and were resolved by 8 hours post-dosing.

  In study CL02, maximum increases in the first 8 hours were 1mm for placebo, 8mm for 25mg, 9mm for 50mg, 11mm for 100mg, 15mm for 150mg, and 18mm for 200mg.

  In study CL28, mean weighted increases vs. placebo 0-4 after dosing were 1.35mm for 12.5mg, 3.77mm for 25mg, and 6.11mm for 50mg. The differences were statistically significant for the 25mg and 50mg doses, but not the 12.5mg.

  In study 0007, mean weighted changes from baseline over the first 4 hours were 1.59mm for placebo, 1.85mm for 12.5mg, and 4.84mm for 25mg.

No clinically significant vital signs abnormalities were observed in any of the other almotriptan clinical studies.

In conclusion, almotriptan was associated with dose-related increases in systolic and diastolic blood pressures in three phase 1 studies, and in heart rate in one phase 1 study. The effects were transient and most noticeable at doses higher than 12.5mg.

8.8 ECG

Due to the finding in the preclinical studies which showed evidence of effects of almotriptan on cardiac repolarization (QTc prolongation in dogs, section 4.2, page 6), the sponsor specifically assessed the drug's effect on the ECG in general, and on cardiac repolarization in particular. Eleven phase 1 and two phase 2 studies addressed specifically the effects of almotriptan on the ECG shortly after drug administration. ECG's were assessed at pre-specified times post-dosing, including assessments at or around the time of T_{max} (4 hours). The sponsor used Bazett's formula to correct the QT interval for heart rate. They felt this was appropriate because their assertion that almotriptan has no clinically important effect on heart rate. I point out that one study (study CL02, described in the previous section) did show a dose-related increase in heart rate associated with almotriptan, but admittedly not at the clinically relevant doses of 6.25-12.5mg. However, in order to assess the true affect of the drug over a wide range of doses (up to 200mg), then a correction other than the Bazett correction may be appropriate. I discuss this in more detail in my review of the ECG data, which is located in section 8.14.3, page 55 of this review.

A total of 503 subjects/patients contributed to this analysis, including normal volunteers, migraine patients during migraine attacks, and special populations (renal, hypertensives, elderly, drug-interactions). In all sub-populations studied, using doses exceeding the

highest therapeutic dose by a factor of >10, the sponsor concluded that almotriptan did not produce any dose-related effects on ECG intervals, and more importantly, no dose-related QTc prolongations were apparent.

The clinically important QTc interval data are summarized in Table 39 (sponsor table 32, Item 3, Vol. 1, page 208). The incidence of QTc intervals above 500 msec was low in each treatment group and numerically was the same between 12.5mg and placebo using pooled data.

Table 39: ECG – QTc Intervals > 500 msec

Study	PBO n/N	5mg n/N	12.5mg n/N	25mg n/N	50mg n/N	100mg n/N	150mg n/N	200mg n/N
CL02	0/14	0/6		0/6	0/6	0/6	1/12	0/6
CL06			1/32					
CL07			0/24					
CL28	0/24		0/24	0/24	0/24			
CL29 in*			1/16					
CL29 out*			0/16					
0002			0/16					
0003			0/14					
0005			0/13					
0006			0/12					
0007	1/20		0/20	0/20				
CL11	0/31	0/35		0/34		0/33	0/35	
Total	**1/89 (1.1%)**	**0/41 (0%)**	**2/187 (1.1%)**	**0/84 (0%)**	**0/30 (0%)**	**0/39 (0%)**	**1/47 (2.1%)**	**0/6 (0%)**

* in=during migraine attack; out=outside migraine attack

The following tables (sponsor tables 30 and 31, Item 3, Vol. 1, page 207) show the number of patients with changes in QTc intervals of greater than either 30msec or 60msec. The numbers fail to show a clear dose-response relationship.

Table 40: ECG – Changes in QTc intervals >30 msec

Study	PBO n/N	5mg n/N	12.5mg n/N	25mg n/N	50mg n/N	100mg n/N	150mg n/N	200mg n/N
CL02	0/14	0/6		0/6	2/6	0/6	4/12	1/6
CL06			6/32					
CL07			3/24					
CL28	2/24		0/24	1/24	0/24			
CL29 in*			2/16					
CL29 out*			2/16					
0002			1/16					
0003			4/14					
0005			0/13					
0006			0/12					
0007	3/20		4/20	0/20				
CL11	4/31	6/35		4/34		5/33	2/35	
Total	**9/89 (10.1%)**	**6/41 (14.6%)**	**22/187 (11.8%)**	**5/84 (6%)**	**2/30 (6.7%)**	**5/39 (12.8%)**	**6/47 (12.8%)**	**1/6 (16.7%)**

* in=during migraine attack; out=outside migraine attack

Table 41: ECG – Changes in QTc intervals >60 msec

Study	PBO* n/N	5mg n/N	12.5mg n/N	25mg n/N	50mg n/N	100mg n/N	150mg n/N	200mg n/N
CL02	0/14	0/6		0/6	0/6	0/6	1/12	0/6
CL06			3/32					
CL07			1/24					
CL28	0/24		0/24	0/24	0/24			
CL29 in*			1/16					
CL29 out*			0/16					
0002			0/16					
0003			0/14					
0005			0/13					
0006			0/12					
0007	0/20		0/20	0/20				
CL11	0/31	1/35		0/34				
Total	**0/89 (0%)**	**1/41 (2.4%)**	**5/187 (2.7%)**	**0/84 (0%)**	**0/30 (0%)**	**1/39 (2.6%)**	**1/47 (2.1%)**	**0/6 (0%)**

* in=during migraine attack; out=outside migraine attack

There was one clinically significant ECG finding noted in the clinical studies. In study CL14, patient number 1282 (6.25mg group) took 4 doses of study medication. The last dose was 8/4/97. On 8/5/97, the patient experienced nausea, vomiting, and epigastric discomfort. Her fourth visit was the next day, on 8/6/97, during which she had an ECG which showed abnormal posterolateral repolarization changes. She was admitted to evaluate these changes between 8/6-8/15/97. She was eventually diagnosed with "myocardial ischemia." Coronary angiography was, however, normal, as was her blood pressure and cardiac enzymes. This case was also reported as a serious adverse event, which I reviewed in section 8.3, Serious Adverse Events, page 35.

No clinically significant ST segment abnormalities were noted in any of the almotriptan clinical studies. ECG data from CL02, CL28, 0007, and CL11 were analyzed for any ST segment abnormalities. These studies were chosen because they evaluated both placebo, and clinically relevant almotriptan doses, and because ECG assessments were done at prespecified times after dosing, including at around T_{max}. One patient (184, CL11) had nonspecific ST-T wave changes 2 hours after receiving a 5mg dose of almotriptan; it was considered abnormal but not clinically significant.

In the uncontrolled 12-month study CL25, two clinically significant ECG's were noted:

- Patient number 70 had clinically significant non-specific T wave abnormality on visit 4. This was recorded as a mild adverse event, not related to study drug administration.
- Patient ~~number~~ 207 had clinically significant 1st degree AV block on visit 1, after treating 4 attacks in 1.5 months. This was recorded as a mild AE, possibly related to study medication. At a later visit, a cardiologist considered the event not clinically significant.

In the uncontrolled 6-month study 0011, a lengthening of the QTc interval was seen in 14 patients at some point during the study. However, because of the lack of a control group, or specified post-dosing assessment times, the results are difficult to interpret. In the majority of cases, the ECG's were done several days after the most recent dose of

almotriptan. Since the half-life of almotriptan is 3 hours, it seems doubtful that any QT prolongation observed 24 hours after dosing would be related to almotriptan, but rather represent individual variation. The QTc intervals were labeled as abnormal if they exceeded 450 msec for men or 470 msec for women. All values ranged between 450-500 msec, with the exception of patient 2204 with a QTc of 501 msec at three months (6 days after last dose) and patient 7605 with a QTc of 513 msec at the final sixth month visit (7 days after last dose).

8.9 Withdrawal Phenomenon and Abuse Potential

The triptans have no documented abuse potential or withdrawal effects. Withdrawal phenomena and abuse potential of almotriptan were not specifically evaluated.

8.10 Human Reproduction Data

Seven women became pregnant during the almotriptan clinical studies – six in the long-term studies and one in a phase 1 study All but one were discontinued from further study.

- Three patients in study CL25 (15, 172, and 85) became pregnant and were withdrawn from the study. All three delivered normal babies.
- Two patients in study 0011 (2300 and 2905) became pregnant and were withdrawn from the study. Both had due dates in Oct. 1999 and no additional information was available at the time of NDA filing.
- One patient in study CL25 (5) had probable miscarriage 10 days after taking a dose of almotriptan. The event was considered drug-related but the patient remained in the study.
- One subject in study 0002 was withdrawn from study following a positive pregnancy test upon checking into the clinic for the second phase of the study. It was determined that she had undergone an elective abortion between study periods. The event was considered resolved and there was no further follow-up

8.11 Overdose

No overdose data were provided. However, six normal volunteers have received single doses of 200mg (study CL02), and 47 subjects (35 were migraineurs during an attack in study CL11) received single doses as high as 150mg. These represent exposures 12-16 times the recommend highest single dose of 12.5mg. Although overall incidence of adverse events were increased at these doses, there were no serious adverse events associated with these exposures.

8.12 Summary of Key Adverse Events

Based on ~~the data~~ presented, the most common adverse events associated with almotriptan use are listed below. In the five phase 3 oral controlled trials, these were the only adverse events that occurred in either the 6.25mg or 12.5mg group at an incidence of ≥1% and greater than placebo.

- Headache
- Dry mouth
- Nausea
- Paresthesia

- Somnolence

8.13 Sponsor's Safety Conclusions

Overall, the sponsor concludes that the results of the safety analyses presented support the use of the 6.25mg and 12.5mg doses for acute use in patients with migraine. This is based on the following observations (adapted from Item 3, Vol. 1, pages 210-212):

- Overall adverse event incidences in the controlled trials were similar for placebo, 6.25mg, and 12.5mg (12.4%, 14.0%, and 15.4%, respectively).
- Individual adverse event rates were similar among placebo, 6.25mg, and 12.5mg. None occurred at a rate higher than 2% in either almotriptan group. None occurred at a rate of one percentage point or higher compared to placebo. The only adverse event that reached an incidence of 2.0% was nausea in the 12.5mg group.
- Although there was one case of myocardial ischemia (serious adverse event, in study CL14) associated with almotriptan use, this is a well known risk of $5HT_{1B/1D}$ agonists and almotriptan should not be given to patients with documented coronary artery disease.
- There were only 2 other serious adverse events in controlled trials. Both occurred at least 2 weeks after almotriptan administration, and none was considered drug-related.
- The long-term safety of almotriptan was assessed in 464 patients treating at least 2 migraines per month for 6 months and 169 patients treating at least 2 migraines per month for 12 months. No safety concerns associated with long-term use were identified.
- Cardiac safety, including ECG's, was extensively analyzed and no concerns were identified, other than the single patient with myocardial ischemia noted above. There was no evidence of dose-related QTc prolongation or ST segment changes.
- No clinically important differences in almotriptan's safety profile could be identified on the basis of sex, age, weight, presence or absence of aura, use of migraine prophylaxis, use of oral contraceptives, presence of controlled mild to moderate hypertension, presence of various degrees of renal impairment, use of fluoxetine, moclobemide, ergotamine, propranolol, or verapamil.
- There was no consistent evidence of laboratory or vital signs abnormalities associated with almotriptan use, although small, transient increases in blood pressure and heart rate were seen at doses greater than 12.5mg in some studies.
- Pregnant or lactating women should not be treated with almotriptan as there is no clinical experience in the patient population.

8.14 Reviewer's Safety Analyses

The sponsor's safety review generally demonstrates that almotriptan, at the planned marketing doses of 6.25mg and 12.5mg, is reasonably safe under conditions of proposed use. I chose to limit my safety analyses to three specific areas. First, the incidence of adverse events reported in the controlled trials that used the planned marketing doses (CL12, 13, and 14) are very low – unusually low compared to other triptans. I performed my own adverse event analysis on the data provided. Second, I wished to verify that long-term exposures were adequate to meet ICH and Division guidelines. Finally, I chose to analyze the ECG data provided to evaluate the possible risk of QTc prolongation, which was seen in the animal studies.

For my analyses of the safety data, I used JMP version 3.2.5.

8.14.1 Adverse Events

The adverse event analysis presented by the sponsor included AE data obtained from patients treated in the 5 controlled oral phase 3 studies (CL11, 12, 13, 14, and 0008). CL11 did not use any of the planned marketed dose, so it only contributed 31 patients in the placebo group. Study 0008 did not include a placebo group, but instead had an active control (sumatriptan 50mg). I chose instead to perform the same AE analysis using data from the 3 placebo controlled phase 3 studies that employed the planned marketed doses (CL12, 13, 14).

The sponsor provided electronic line listings (*i.e.*, datasets) of all adverse events in studies CL12, CL13, and CL14 in files AESCL12.xpt, AESCL13.xpt, and AESCL14.xpt. Adverse events were coded whether they were treatment emergent or not. For those AE's that were coded as non-treatment emergent, the records lacked a date and time that study medication was taken. This is consistent with the fact that non-treatment emergent AE's occurred prior to medication use.

Since study CL14 included AE data from all three attacks, I only included AE's that occurred after treatment of the first attack. I then pooled all the treatment-emergent AE's from the three studies to form a single pooled dataset. This dataset contained 667 records, and each record contained information about a single adverse event.

The sponsor provided raw AE terms, and preferred terms using both COSTART and WHO coding dictionaries. For my review, I arbitrarily focused on the COSTART terms. I first examined the coding of raw terms to their corresponding COSTART terms. There were 378 unique raw terms in the dataset. I was satisfied with the coding in all but one case. Of particular interest, chest pain included all terms for chest pressure, pain, and discomfort. There was one report of [redacted] sensation (in patient ALM416.12.099.1104) which was coded as [redacted] This was the only record that I actually changed to "chest pain" so that it would be included with other reports of chest pain in the analysis.

I grouped the table by patient, treatment, and AE. I then grouped this second table by AE to get a count of the number of patients in the dataset that reported each AE. I then subgrouped by treatment group to get a count of the of the number of patients in each treatment group that reported each treatment-emergent AE. In order to calculate incidences for each treatment group, I divided these numbers by the number of patients in each treatment group, as shown in Table 27, page 32.

I then sorted the table by AE incidences by high dose (12.5mg) in descending order. The table of most commonly reported AE's in these three studies is shown in

Table 42(RA): Studies CL12, 13, 14 (first attack) – Adverse Events Reported by >0.5% of Patients in Either the Almotriptan 6.25mg or 12.5mg Group

AE	PBO (n=355)	2mg (n=170)	6.25mg (n=527)	12.5mg (n=722)	25mg (n=352)	Suma 100mg (n=194)
NAUSEA	1.4	0.0	0.8	1.8	1.4	0.5
DIZZINESS	2.0	1.2	1.3	1.4	2.0	2.1
PARESTHESIA	0.6	0.6	1.1	1.2	1.1	2.6
SOMNOLENCE	1.1	0.6	0.6	1.2	2.3	2.1
ASTHENIA	0.8	0.6	0.8	1.1	2.6	5.2
HEADACHE	0.8	1.2	0.8	1.0	0.9	1.0
DRY MOUTH	0.6	0.6	1.1	0.8	1.1	0.5
ABDOMINAL PAIN GENERALIZED	0.3	0.0	0.6	0.7	0.9	0.5
BACK PAIN	0.0	0.6	0.2	0.7	0.3	0.5
LOCALIZED PAIN	0.3	0.0	0.2	0.7	1.4	0.5
PHARYNGITIS	0.6	0.0	0.4	0.7	0.3	0.5
DIARRHEA	0.8	0.6	0.6	0.6	0.9	0.0
VOMITING	1.4	0.6	0.2	0.6	0.9	0.5
CHILLS	0.3	0.6	0.9	0.4	0.3	0.0
DIAPHORETIC	0.6	0.6	0.6	0.4	0.9	0.5

Of all the AE's that occurred with an incidence ≥1% in the almotriptan 6.25mg or 12.5mg group, only nausea, paresthesia, somnolence, asthenia, headache, and dry mouth occurred at incidence(s) greater than placebo. This list is slightly different than the sponsor's list (Table 32, page 39), which I reproduce below. In their list, the most common AE's occurring ≥1% in either group, and greater than placebo, were nausea, paresthesia, somnolence, headache, dry mouth. Asthenia is the only one that appears in my list and not in theirs.

Table 43: 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)
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

In my list, chest pain was very infrequent, and occurred with incidences of 0.3, 0.0, 0.2, 0.1, 1.7, 1.0, for placebo, 2mg, 6.25mg, 12.5mg, 25mg, and sumatriptan 100mg,

respectively. The incidences of chest pain in the planned marketed doses were comparable to the incidence of chest pain in placebo patients, and was lower than in the sumatriptan 100mg group.

8.14.2 Long-Term Exposures

The two long-term studies were CL25 (one year) and 0011 (six months). The sponsor provided exposure information in two files, admn0011.xpt, and admncl25.xpt. I pooled the data to obtain one large dataset and performed my analysis on this file.

The file contained important dosing information in the long-term studies. Each record represented the administration of a single 12.5mg dose. Important variables included patient id (PID), study start date (VISITINIT) and end date (VISFINL), and date and time of dose. Also included was a variable (INTAKE) which coded whether the dose represented the first dose or second dose. Basic demographic variables were included, as were certain derived variables such as the number of total doses of almotriptan used by each patient, etc.

My first analysis focused on determining the extent of exposures. Table 44 shows the important statistics regarding duration of participation in each study. Study 0011 was a 6 month study. The mean duration of participation was 153.3 days, and the median was 183 days. Study CL25 was a one year study and mean duration of participation was 300.9 days, and the median was 364 days.

Table 44 (RA): CL25 and 0011 – Days on Study

	Study	
	0011 N=585	CL25 N=761
Mean (Days)	153.3	300.9
S.D.	55.0	109.7
Median (Days)	183	364

The distribution of days on study for each trial is shown in Figure 3 and Figure 4.

Figure 3 (RA): CL25 – Distribution of Days on Study

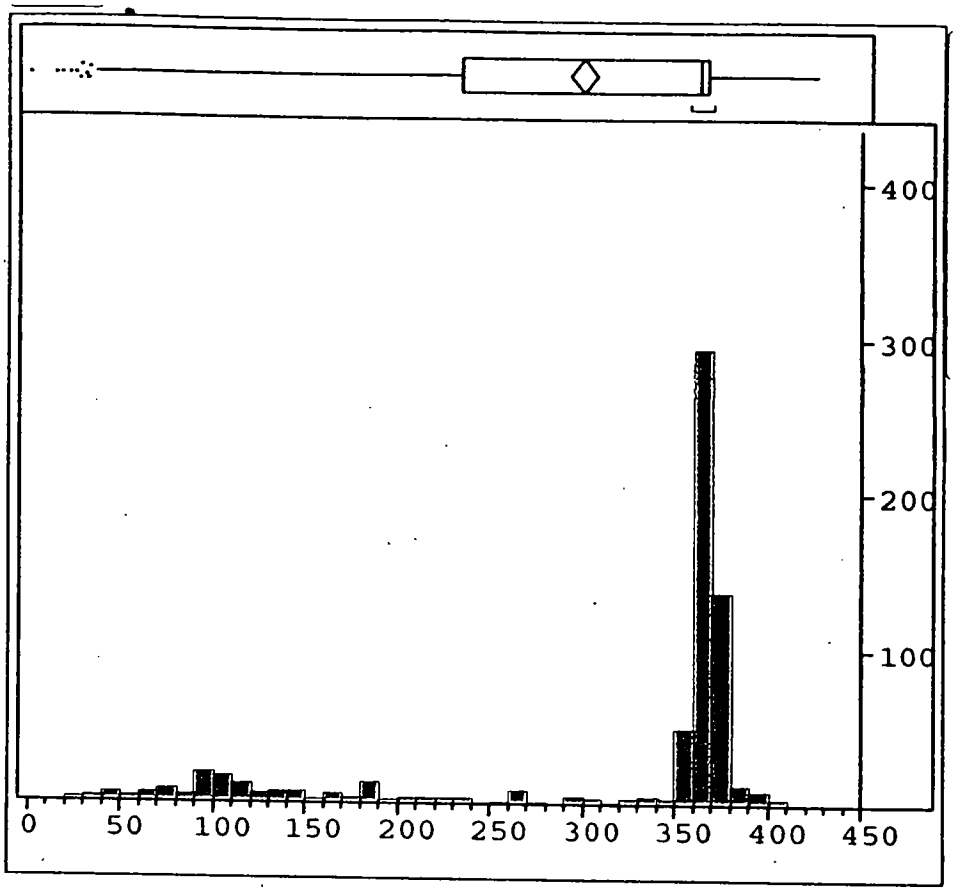
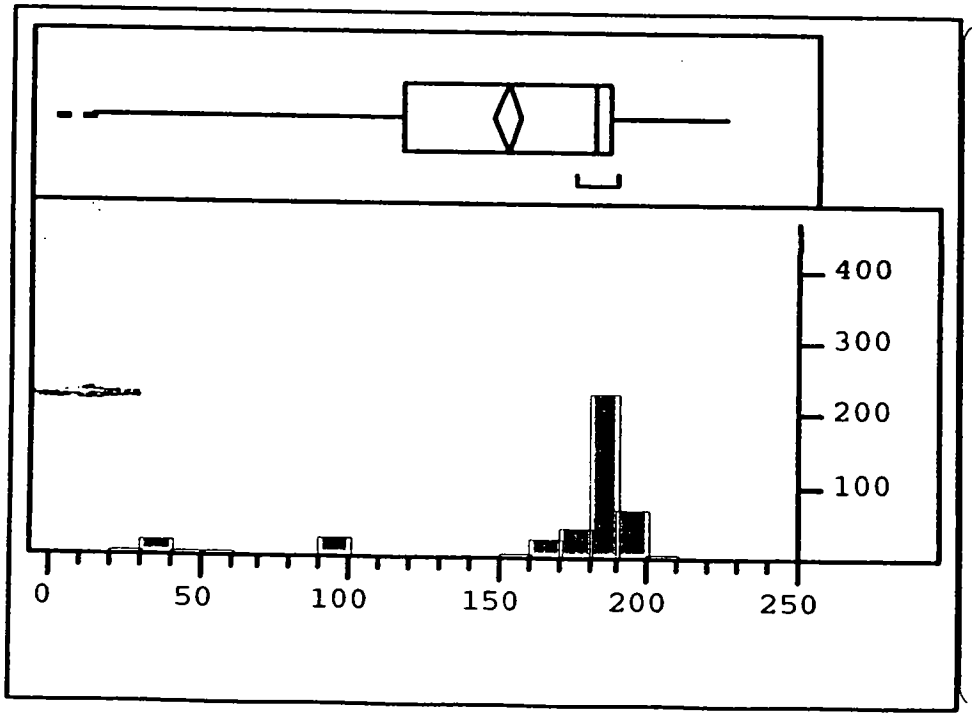


Figure 4 (RA): 0011 – Distribution of Days on Study



The 761 patients in study CL25 treated a total of 13,714 migraines, and the 585 patients in study 0011 treated a total of 11,016 migraines. The average number of migraines treated was quite similar between the two studies (18.0 and 18.8, respectively), even though one study was twice as long as the other (Table 45). This resulted in an average number of migraines treated per month of 3.7 for study 0011 and 1.8 for study CL25.

Table 45 (RA): CL25 and 0011 – Number of Migraines Treated

	Study	
	0011 N=585	CL25 N=761
Attacks	11016	13714
Mean	18.8	18.0
Mean/mo.	3.7	1.8
S.D.	12.9	12.6
Median	18	17

In study CL25, 38% of the attacks treated (5275/13714) required the use of a second dose. In study 0011, the percentage of attacks treated with a second dose was 24% (2693/11016). For both studies combined, a second dose was used in roughly one-third of the attacks (32%, 7698/24730).

The next series of analyses focus on the ICH and Division guidelines for long-term exposures. The sponsor has already reported that the safety database meet or exceed the guidelines (Table 29: Studies CL25 and 0011 – Number of Patients Treating ≥2 headaches/month, page 34). I chose to recreate that analysis.

I started with the pooled dataset containing all the exposure data for the two studies. I then flagged the records of all patients who were enrolled in each study for a period of either 6 months or 12 months. I used 180 days for the 6-month mark, and 360 days for the one year mark (using fixed 30-day months for ease of analysis). I realize the 360 day mark is actually 5 days short of the actual year mark, but I used this number for ease of analysis.

There were a total of 945 patients who participated in a long-term study for at least 6 months (611 in study CL25 and 334 in study 0011). There were a total of 464 patients who participated in a long-term study for at least 12 months (all came from study CL25, since study 0011 was a six-month study).

I calculated the attack frequency for each patient by dividing the number of attacks treated by the number of days in the study and multiplying by 30 to get a monthly rate. I then identified all patients that had attack frequencies greater than or equal to 2, 3, or 4 migraines.

I identified the 6-month population as those patients who treated at least 2 headaches per month at least 6 months. I also determined the number who treated ≥3/mo., and ≥4/mo. I did the same analysis for the 12-month population. The results are shown in Table 46. It shows that 441 patients treated at least 2 migraines per month for at least 6 months, and 147 patients treated at least 2 migraines per month for at least 12 months. The table also shows that the safety database is insufficient to support the treatment of ≥3 migraines/month since those numbers do not meet ICH and Division guidelines.

Table 46 (RA): CL25 and 0011 – Number of Patients Treating ≥2 Migraines per Month for At Least 6 Months or 12 Months

Migraine Frequency	Treatment ≥ 6 months			Treatment ≥12 months		
	≥2/mo.	≥3/mo.	≥4/mo.	≥2/mo.	≥3/mo.	≥4/mo.
Study CL25	174	56	21	147	50	20
Study 0011	267	215	139	0	0	0
Total	**441**	**271**	**160**	**147**	**50**	**20**

8.14.3 ECG Analysis

Since the phase 3 studies were conducted in an outpatient setting, the ECG's recorded were not done in the immediate post-dosing period. In order to analyze the immediate post-dosing period, one must examine the ECG's obtained during the phase 1/2 inpatient studies.

There were 20 phase 1 studies and 3 phase 2 studies, for a total of 23. Most of these studies collected ECG data shortly after dosing (*i.e.*, ≤24 hours post-dose). I reviewed the protocols for each of these studies, and the ECG monitoring program for each study is shown in Table 47. I confirmed the accuracy of my table with the sponsor and they agree that this was the correct monitoring program. Of the 23 phase 1/2 studies, three studies (CL09, 0009 and CL12) did not obtain ECG's within 24 hours of treatment. The remaining 20 studies (18 phase 1 and two phase 2 studies) included at least one pre-dose, and at least one post-dose 12-lead ECG within 24 hours.

Table 47(RA): Phase 1/2 Studies – ECG Monitoring Intervals

Study	P	minutes							hours													
		5	10	15	20	25	30	45	1	1.5	2	2.5	3	3.5	4	5	6	7	8	10	12	16	24
Phase 1																							
CL09	X																						
CL18	X			X					X														X
CL04	X							X		X			X				X				X		X
CL06	X						X		X	X	X		X		X		X		X		X		X
CL07	X						X		X		X				X		X		X	X	X	X	X
CL16	X			X					X		X				X								X
CL20	X							X		X			X				X				X		X
CL27	X	X	X	X	X	X	X	X		X			X				X				X		X
CL29	X								X		X		X		X				X		X		

		minutes							hours														
Study	P	5	10	15	20	25	30	45	1	1.5	2	2.5	3	3.5	4	5	6	7	8	10	12	16	24
CL01N	X						X		X		X				X				X		X		X
0009																							
0002	X								X				X				X						
0003	X								X				X				X						
0004	X								X				X				X						
0005	X										X				X								
0006	X										X				X								
CL01	X			X					X		X				X								X
CL02	X			X					X		X				X								X
CL28	X						X		X	X	X	X	X	X	X	X	X	X	X		X	X	X
0007	X								X				X				X						X
Phase 2																							
CL11	X										X												
CL12	X																						
CL10	X						X				X												

P= pre-dosing (screening and/or baseline)

Two studies (CL04 and CL27) did not measure ECG intervals. According the protocols, the ECG's were analyzed as either normal or abnormal. That left 18 studies (16 phase 1 and 2 phase 2 studies) with immediate post-dosing ECG interval data.

Of these remaining 18 studies (Table 48), four phase 1 studies (CL01, CL18, CL16, and CL01N) and 1 phase 2 study (CL10) used a formulation other than the oral tablet (CL01-subcutaneous, CL18-intranasal and subcutaneous, CL16-sublingual and subcutaneous, CL01N-intranasal, CL10 – subcutaneous). Interpretation of the ECG's from these studies in subjects receiving drug via the intranasal or sublingual route should consider the lower bioavailability resulting from these routes. For this reason, I concentrated on data generated from the remaining 13 oral studies, which is the intended marketing route. These 13 studies involved oral administration of either placebo or almotriptan at doses ranging from 5mg to 200mg, involving 4,446 ECG's in 391 subjects.

Table 48(RA): Phase 1/2 Studies – ECG's Available for QT Analysis

		minutes							hours														
Study	P	5	10	15	20	25	30	45	1	1.5	2	2.5	3	3.5	4	5	6	7	8	10	12	16	24
Phase 1																							
CL18*	X			X					X														X
CL06	X						X		X	X	X		X		X		X		X		X		X
CL07	X						X		X		X				X		X		X	X	X	X	X
CL16*	X			X					X		X				X								X
CL20	X							X		X			X				X				X		X
CL29	X								X		X		X		X				X		X		
CL01N*	X						X		X		X				X				X		X		X
0002	X								X				X				X						
0003	X								X				X				X						
0004	X								X				X				X						
0005	X										X				X								
0006	X										X				X								
CL01*	X			X					X		X				X								X
CL02	X			X					X		X				X								X

		minutes							hours														
Study	P	5	10	15	20	25	30	45	1	1.5	2	2.5	3	3.5	4	5	6	7	8	10	12	16	24
CL28	X						X		X	X	X	X	X	X	X	X	X	X	X		X	X	X
0007	X								X				X				X						X
Phase 2																							
CL11	X										X												
CL10	X						X				X												

P= pre-dosing (screening and/or baseline)
* indicated studies that did not employ the oral route

The datasets required "cleaning" in order to facilitate the analysis. I standardized the coding for the treatment received across all studies, such that each ECG was associated with a particular treatment code (*e.g.*, 12.5mg, 6mg SQ, PBO, etc.). Also, some studies were single dose, but others employed a crossover design resulting in up to 8 treatment sequences. I associated each ECG with a particular treatment sequence. I also associated each ECG with a flag which designated whether the recording occurred after active treatment (active=1) or after no active treatment (active=0, which included placebo, screening, baseline, and post-study ECG's).

I also added a comment field in order to identify ECG's performed under special conditions (*e.g.*, subcutaneous, renal impairment, during a migraine, in conjunction with a concomitant medication such as fluoxetine, Cafergot, or propranolol). I then associated each post-treatment ECG with a baseline ECG for comparison. The baseline ECG was usually the ECG taken at time 0 (baseline) of that particular treatment sequence. However, when such a baseline tracing was not available, I used the screening ECG for comparison. Finally, I pooled these modified datasets into one integrated ECG database for analysis.

I chose four analyses. The first one focused on study CL28, which was the inpatient cardiovascular safety study. I chose this study because it offered the most frequent monitoring program during the first 24 hours, and it included the 12.5mg dose (the highest dose intended for marketing) as well as 25mg and 50mg (up to 4 times the highest intended marketed dose). I then analyzed study CL02, which employed oral doses up to 200mg to investigate any possible dose-response relationships, particularly at the highest doses used in the drug development program. I then analyzed study CL11 which was a fairly large phase 2 study that using single oral doses of 5mg to 150mg during a migraine attack. Finally, I performed a pooled analysis on all the oral ECG data across all of the studies.

8.14.3.1 Study CL28

I focused my first analysis of the phase 1/2 ECG data from study CL28. This study was specifically designed to evaluate the cardiovascular safety of the drug. This was a randomized, double blind, placebo-controlled crossover study. Each patient received placebo, 12.5mg, 25mg, and 50mg as a single dose in a randomized fashion. Each dose was separated by a period of 7 days. Inpatient monitoring included physical examination, laboratory tests, vital signs, and ECG's at frequent intervals, as shown in Table 48 (including measurements around the T_{max} of 1-3 hours). Twenty-four healthy subjects (12 males and 12 females) participated in this study.

I first looked for any possible relationship between dose and heart rate. If almotriptan has an effect on heart rate, then the Bazett's correction of the QT interval for heart rate may not be appropriate.[8]

The mean heart rate for each treatment group, listed by time point, is shown in Table 49. This and all subsequent analyses were done using SAS JMP version 6.2.5.

Table 49 (RA): Study CL28 – Mean Heart Rates, by Treatment Group and Time Point

Time Point (hr)	PB0 (n=24)	12.5mg (n=24)	25mg (n=24)	50mg (n=24)	p-value*
0	59.6	57.6	56.4	56.2	0.436
0.5	56.8	54.9	55.0	54.9	0.708
1.0	57.3	55.5	55.4	57.2	0.718
1.5	58.0	55.5	56.3	46.2	0.616
2.0	59.1	57.1	58.7	57.5	0.739
2.5	65.2	65.6	64.9	64.7	0.985
3.0	56.3	64.1	64.3	67.0	0.569
3.5	66.0	64.1	63.2	66.0	0.501
4.0	66.5	64.7	63.6	64.3	0.559
5.0	69.3	67.6	67.7	66.9	0.716
6.0	66.6	64.3	66.9	66.7	0.573
7.0	65.9	63.5	65.4	66.4	0.589
8.0	63.9	63.1	64.5	64.9	0.907
12.0	60.2	60.2	60.4	59.6	0.986
16.0	57.3	46.2	58.3	56.6	0.833
24.0	62.2	59.4	58.8	59.2	0.492

*ANOVA

There were no nominally significant differences in heart rate at any time point. However, since the numbers are relatively small (only 24 per group) and because there was a baseline imbalance of 3.4 bpm between placebo and the high dose group, I repeated the analysis using change from baseline, using the patient's own baseline heart rate taken at time 0 of each ECG recording. This analysis is shown in Table 50.

Table 50 (RA): Study CL28 – Mean Change from Baseline Heart Rate, by Time Point

Time Point (hr)	PB0 (n=24)	12.5mg (n=24)	25mg (n=24)	50mg (n=24)	p-value*
0	-	-	-	-	
0.5	-2.9	-2.7	-1.4	-1.4	0.597
1.0	-2.3	-2.1	-1.0	1.0	0.295
1.5	-1.6	-2.1	-0.1	0	0.458
2.0	-0.5	-0.5	2	1.2	0.386
2.5	5.6	7.7	8.4	8.9	0.290
3.0	5.7	6.5	7.9	10.7	0.021
3.5	6.3	6.5	6.8	9.8	0.230
4.0	6.9	7.1	7.2	8.1	0.934

[8] Based on Dr. Burkhart's memo, dated 7/9/99, on correcting the QTc for heart rate. In the memo, he describes that Bazett's formula ($QTc = QT / RR^{1/2}$) overcorrects for heart rate > 60 and under corrects for heart rate < 60.

Time Point (hr)	PB0 (n=24)	12.5mg (n=24)	25mg (n=24)	50mg (n=24)	p-value*
5.0	9.7	10.0	11.2	10.7	0.873
6.0	7.0	6.7	10.5	10.4	0.114
7.0	6.3	6.0	9.0	10.1	0.137
8.0	4.3	5.5	8.0	8.6	0.107
12.0	0.6	2.7	4.0	3.4	0.332
16.0	-2.3	-1.4	1.9	0.3	0.185
24.0	2.5	1.8	2.4	2.9	0.948

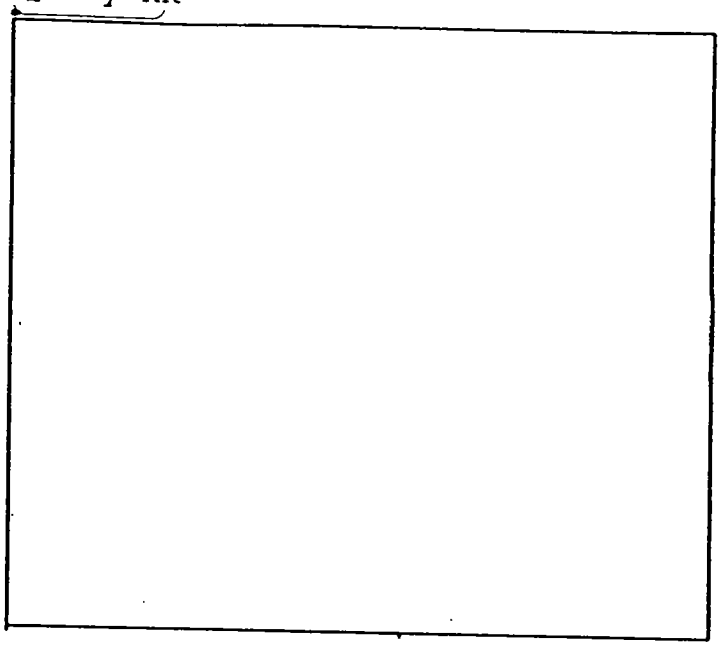
*ANOVA

This analysis shows a dose-related increase in heart rate from baseline, which is maximal (and nominally positive) at 3 hours, but also evident numerically at other time points between 2.5 – 8 hours. This finding appears to confirm the sponsor reported almotriptan-associated increase in heart rate seen in study CL02. 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 of the measured QT interval, as described in his memo.

In analyzing the QT data in this study, I used all ECG's done during placebo treatment, and during baseline (pre-treatment) with active drug to analyze the relationship between heart rate and QT interval in this study population. There were 456 such tracings available for analysis. Three-hundred sixty of these (360) were performed just prior or during placebo treatment. The remaining 72 tracings represent baseline tracings for each active treatment group (24 each for 12.5mg, 25mg, and 50mg). The relationship between QT and heart rate (using the RR interval) is shown graphically in Figure 5.

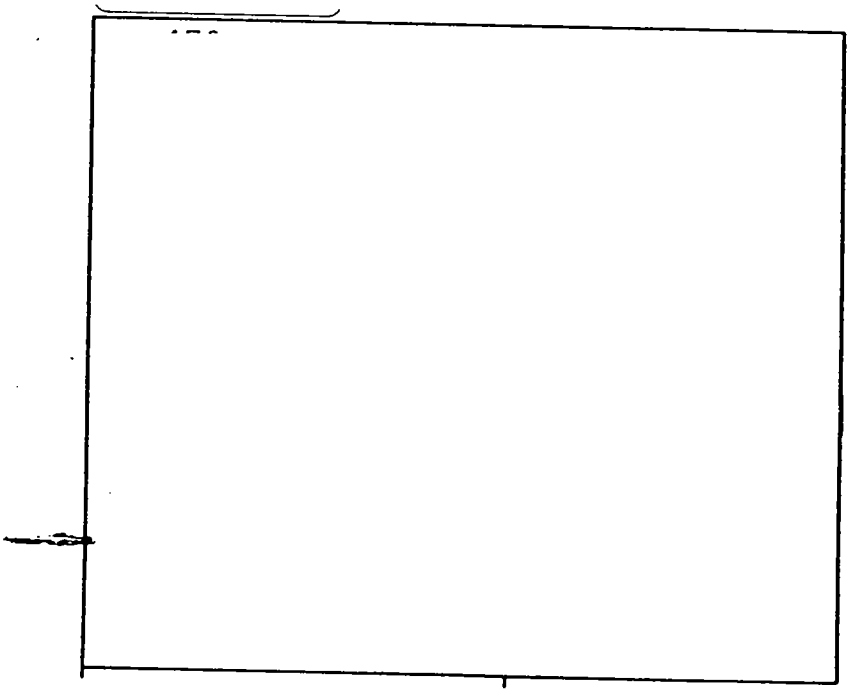
Figure 5 demonstrates what is already known about the relationship between QT and heart rate. As heart rate increases (*i.e.*, smaller RR interval), the QT decreases.

Figure 5 (RA): Study CL28 – 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 6. The formula I used is $QTc = QT / RR^{1/2}$.

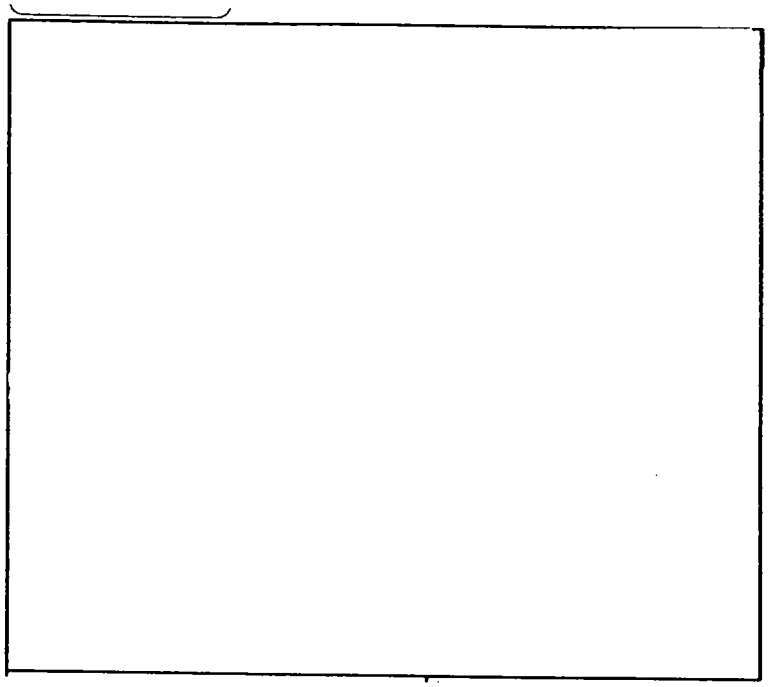
Figure 6 (RA): Study CL28 – RR vs. QTc in Placebo/Baseline ECG's (Bazett Method)



This graph shows that there is still a substantial effect of heart rate on the QTc, as corrected using Bazett's formula. The ideal correction for this population should produce a fitted line with a slope of zero (*i.e.*, a horizontal line, as described in page 3 of Dr.

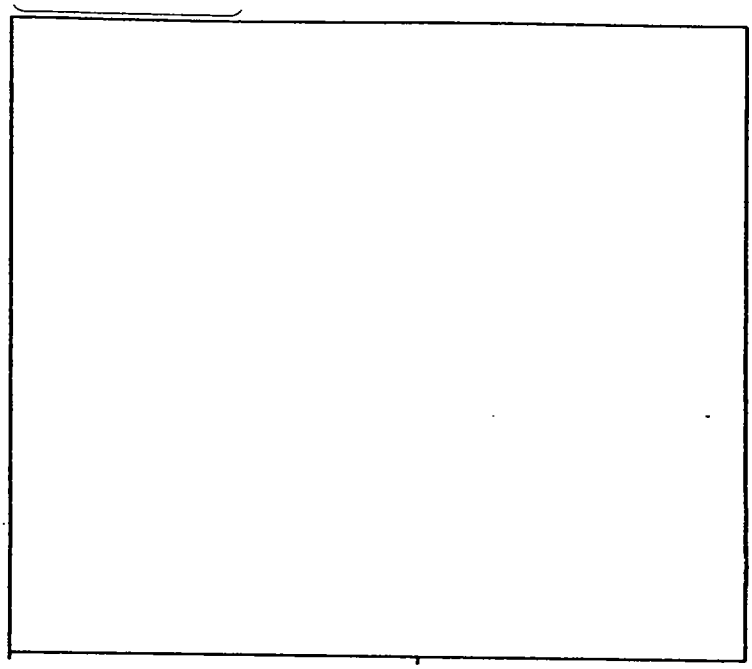
Burkhart's memo). I explored several values for the fractional exponent to the formula that might result in a slope of zero. In his memo, he suggests that the formula [redacted] results in a fitted line with almost no slope in most of the datasets that he has observed. This correction yields the following plot (Figure 7). One can see that the slope of the line is still negative, but not as steep as that seen using Bazett's correction. Therefore, it is a better formula to use for the QTc, but still not ideal.

Figure 7 (RA): Study CL28 – RR vs. QTc in Placebo/Baseline ECG's (using the correction [redacted]



I experimented with several values for the fractional exponent in the formula to try and obtain a flat slope to the fitted line. By trial and error, I found that the value of [redacted] gave almost a flat line [redacted] Therefore, I used the formula [redacted] to correct the QT intervals in this study. I use the term QTc' (QTc prime) to identify all QTc intervals calculated using this formula.

Figure 8 (RA): Study CL28 – RR vs. QTc in Placebo/Baseline ECG's (using the correction [redacted]



The relationship between QTc' and treatment group is shown in Table 51. There is no evidence for an almotriptan-associated QTc prolongation from this analysis.

Table 51 (RA): Study CL28 – Mean QTc' by Treatment Group and Time Point

Time Point (hr)	PB0 (n=24)	12.5mg (n=24)	25mg (n=24)	50mg (n=24)	p-value*
0	402	404	401	400	0.842
0.5	398	399	395	395	0.725
1.0	398	400	396	399	0.884
1.5	399	403	397	394	0.280
2.0	398	401	399	398	0.859
2.5	401	403	398	399	0.633
3.0	397	392	394	391	0.337
3.5	397	393	393	392	0.408
4.0	393	393	392	389	0.573
5.0	393	393	396	390	0.567
6.0	394	396	394	391	0.562
7.0	393	399	391	392	0.101
8.0	392	394	391	389	0.453
12.0	391	395	391	391	0.505
16.0	406	405	406	406	0.987
24.0	389	392	389	390	0.721

*ANOVA; QTc' values in msec

The mean changes in QTc' from baseline are shown in Table 52. Again, there is no evidence for treatment-related increase from baseline in QTc' from this analysis.

Table 52 (RA): Study CL28 – Mean QTc' Changes from Baseline

Time Point (hr)	PB0 (n=24)	12.5mg (n=24)	25mg (n=24)	50mg (n=24)	p-value*
0	-	-	-	-	
0.5	-4	-5	-6	-6	0.949
1.0	-4	-5	-5	-2	0.835
1.5	-3	-2	-4	-6	0.444
2.0	-4	-4	-2	-2	0.959
2.5	0	-2	-3	-2	0.857
3.0	-5	-13	-7	-10	0.147
3.5	-4	-11	-9	-9	0.231
4.0	-8	-11	-10	-12	0.823
5.0	-9	-11	-5	-10	0.453
6.0	-8	-9	-7	-10	0.888
7.0	-9	-6	-10	-9	0.641
8.0	-9	-11	-10	-12	0.919
12.0	-11	-9	-10	-10	0.978
16.0	4	1	5	5	0.622
24.0	-13	-12	-12	-11	0.962

*ANOVA; changes in QTc' values in msec

There were no QTc' intervals greater than 500 msec in the study. There were no changes from baseline of greater than 60 msec. Three subjects had changes from baseline in QTc' intervals that were greater than 30 msec. Two patients received placebo and had these changes noted at 5 and 16 hours, respectively. The third subject took 25mg and had the change noted at 5 hours.

8.14.3.2 Study CL02

I chose to analyze ECG data from study CL02 because this study exposed subjects to single doses up to 200mg and may provide important dose-response data, particularly at high doses. This was a randomized, double blind, placebo-controlled, parallel group, single dose phase 1 study. Twenty-two healthy male subjects, aged 18-50, were enrolled, treated, and analyzed. Single doses of active drug or placebo were administered orally in a step-wise fashion between two parallel groups of eight subjects each (groups A and B): 5, 10, 25, 50, 100, 150, and 200mg. A 250mg dose was planned but not given due to adverse events reported at 200mg (chest/neck heaviness, hypertension, paresthesias, lightheadedness, muscular fatigue). At each dose level, six subjects received active drug and 2 received placebo. No subject received placebo on more than one occasion. Six additional subjects (group C) received 150mg, which was the maximum tolerated dose in the previous two groups. A washout period of at least one week was allowed between doses in each subject.

Physical exams, ECG's and laboratory tests were performed within 2 weeks prior to the clinical phase, 24 hours after treatment, and within 2 weeks after the clinical phase was complete. In addition, vital signs and ECG's were recorded at regular intervals after dosing (see Table 47, page 55 for ECG intervals).

As in study CL28, I first looked for a relationship between dose and heart rate. The mean heart rate for each treatment group, listed by time point, is shown in Table 53. There was