80mg). Accumulation does occur after multiple dosing (40mg tid, 80mg bid) over seven days. AUC is reduced by 30% and T_{max} is increased to 2.8 hours during a migraine attack. AUC and C_{max} were increased 20-30% after a high fat meal. The $T_{1/2}$ is approximately 4 hours. The volume of distribution is 138L. It is 85% protein bound. Mean total plasma clearance is 36 L/h after i.v. administration.

Non-renal clearance accounts for 90% of total clearance. The n-demethylated metabolite is the only known active metabolite and is equipotent to eletriptan in animal models. Plasma concentrations are 10-20% of parent drug and is therefore not expected to contribute significantly to the therapeutic action.

Eletriptan is primarily metabolized by cytochrome P450 CYP3A4. This is substantiated by increased plasma concentrations of eletriptan following co-administration with erythromycin, a known specific P450 CYP3A4 inhibitor. There is a small involvement of 2D6 although clinical studies do not indicate any evidence of polymorphism with regard to this enzyme.

PK is generally unaffected by age, gender, race, or menstrual cycle. Renal failure resulted in increased blood pressure more than in matched healthy subjects. Mild to moderate liver impairment resulted in increased AUC (34%) and $T_{1/2}$. C_{max} was also increased 18%, though not statistically significant. No dose adjustment is recommended. It has not been studied in severe hepatic impairment.

Minor increases in blood pressure were seen with Cafergot. The use of Cafergot within 24 hours is not recommended. Inderal caused an increase in C_{max} and AUC by 10% and 33%, respectively. There was no increase in vital signs or AE's. Erythromycin caused a 2-fold increase in C_{max} and a 4-fold increase in AUC. T_{max} was increased to 7.1 hours (this finding is also mentioned in Precautions).

2.4.4 Clinical Studies

Eletriptan relieved migraine headache and its associated symptoms in 6 randomized, double-blind, placebo-controlled studies. All six used the 40mg and 80mg doses. Two of the six also included a 20mg dose.

All six were outpatient studies. Patients were predominantly female (85%) and white (94%) with a mean age of 40 years. Headache response was assessed up to 4 hours after dosing. Maintenance of the response was assessed up to 24 hours post dose. A second dose of eletriptan was allowed 2-24 hours after the initial dose for both persistent and recurrent headaches. Four of the six studies assessed 3 attacks. In all six studies, the percent responders at 2 hours was significantly greater than placebo at all doses. Eletriptan also reduced associated symptoms.

2.4.5 Contraindication

Eletriptan should not be given to patients with ischemic cardiac, cerebrovascular, or peripheral vascular diseases, uncontrolled hypertension, hemiplegic or basilar migraine. It should not be used within 24 hours of another 5-HT_1 agonist, ergot containing medications, or methysergide.

2.4.6 Warnings

Class labeling for myocardial ischemia, cerebrovascular events, other vasospasm related events, and increased blood pressure is included.

2.4.7 Precautions

Class labeling for chest pain is included. Precautions concerning melanin binding, corneal opacities, and drug interactions with other ergots and 5-HT_1 agonists, and to CYP 3A4 inhibitors such as erythromycin are included. Eletriptan is not a substrate for MAO so no interaction with MAO inhibitors are expected. Carcinogenicity, mutagenicity studies were negative. There was no impairment of animal fertility. Proposed pregnancy category is B. Eletriptan is excreted in human breast milk. Eletriptan was safely administered to 274 adolescents. Elderly patients experienced increased blood pressure compared to young subjects. Doses above 40mg should be administered with caution to this population.

2.4.8 Adverse Reactions

The most common AE's reported are similar to those seen with other -triptans. They were asthenia and dizziness (>5% and twice the placebo rate). Also common were paresthesias, chest pain/pressure, nausea/vomiting, dizziness. Discontinuations were low (1.8%), although the opportunity to discontinue was also low due to the short term nature of the trials (1-3 attacks).

2.4.9 Dosage and Administration

Single doses of 20, 40, or 80mg are effective, with the 40mg and 80mg more effective than the 20mg dose, but also carrying a higher risk of AE's. A second dose for recurrence within 24 hours may be taken. The maximum daily dose is 160 mg. The safety of treating more than 3 headaches in a 30 day period has not been established.

2.5 Foreign Marketing

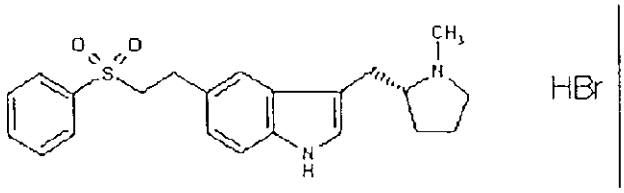
Eletriptan is not currently marketed elsewhere.

3. Chemistry, Manufacturing and Controls

Eletriptan is a white to pale colored powder which is readily soluble in water. The oral tablets contain 20, 40, or 80mg of eletriptan.

Generic Name:	**eletriptan hydrobromide**
Trade Name:	**Relpax™**
Chemical Name:	**(R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1H-indole hydrobromide**
Alternative Name:	**UK-116,044**
Molecular Formula:	**$C_{22}H_{26}N_2O_2S_2 \bullet HBr$**
Molecular Weight:	**463.43**

Figure 1: Chemical Structure – Eletriptan Hydrobromide



Eletriptan tablets stored for up to 12 months show good stability over the wide range of packaging alternatives and conditions evaluated.

4. Animal Pharmacology & Toxicology

4.1 Pharmacology

Eletriptan is a $5HT_{1B/1D}$ receptor agonist. It also has high affinity for $5HT_{1F}$ receptors. It is positive in both the carotid blood flow and the dural plasma protein extravasation animal migraine models.

4.2 Toxicology

In single dose toxicology studies, 1000 mg/kg was lethal in rats and mice. Clinical signs included convulsions, dyspnea, increased activity and tremors, salivation, mydriasis, tremors, and reduced body temperatures. There were no clinical signs nor mortality at 100 mg/kg in both species.

Repeated dose studies in rats and mice produced clinical signs similar to those seen in the single dose studies. Isolated deaths were seen above 200 mg/kg. From 25 mg/kg, increased liver weight with centrilobular hypertrophy was seen. Thyroid follicular hypertrophy was seen from 5 mg/kg upward.

Eletriptan did not cause mortality in dogs. Typical signs were hindlimb incoordination, hyperthermia, and barking. Transient corneal opacities were observed during the first days of studies lasting up to1 month but not in the 6 and 12 month studies. Dose related increased systolic BP was seen. A minimal to mild myocardial fibrosis was diagnosed histologically in two dogs at 5 mg/kg after 1 month and in 1 dog at 7.5 mg/kg after 2 weeks, but was not observed in the 6- and 12-month studies.

Analysis of ECGs showed inversion of negative T-waves to a more normal positive morphology in a number of studies including the 6-month study, where control dogs were also affected. In the 12-month study only increase in the height of the T-wave was recorded. There was no prolongation of the QT-segment in the ECG. In the 6- and 12-month studies dosing was reduced to ½ during the first week and, thus the severity of clinical signs and heart rate/blood pressure changes was significantly diminished.

In the 6-month study, 1/8 dogs each at 2.5 and 5 mg/kg had chronic peptic stomach ulcers. This was felt to be the result of high local concentrations of eletriptan released from the experimental capsule formulation of dry powder. No mucosal changes were seen in the subsequent 12-month study when the tablet (clinical) formulation was used.

In reproduction studies, no effects on fertility and no teratogenic effects were observed despite evidence of maternal toxicity. Pre- and postnatal development of the offspring was not affected.

Eletriptan was subjected to a complete battery of mutagenicity tests in which no genotoxic or clastogenic potential was detected. Eletriptan was not carcinogenic in rats and mice.

5. Clinical Data Sources

5.1 Study Type

The clinical development program consisted of 34 clinical pharmacology studies (Table 1, adapted from NDA summary, page 8, and ISE pages 5-6) and 18 phase 2/3 studies (Table 2). Of the 18 phase 2/3 studies, 2 were intravenous phase 2 studies (301, 303) and the remaining 16 were oral phase 2/3 trials. Three (3) of the 16 oral phase 2/3 studies were long term extensions of other trials. Table 3 shows how 12 of the phase 2/3 studies contributed patients to the three long-term extension studies (adapted from NDA summary, page 10).

Table 1: Phase 1 Studies

Type	Study Number
12 PK/PD studies	001, 004, 201, 202, 202A, 205, 208, 230, 299, 701, 701A, 703
9 bioavailability/bioequivalence studies	203, 204, 214, 225, 227, 228, 231, 232, 702
3 interaction studies	215, 222, 226
6 special population studies	002, 003, 211, 215, 220, 229
1 radiolabel study	207
2 formulation pilot studies	213, 224
1 program support study	212

Table 2: Phase 2/3 Studies

Study	Description
Double-blind, placebo-controlled, oral headache treatment studies	
102	Three attack, 20, 40, 80mg
103	Two attack, 40, 80mg
104	Three attack, 40mg, 80mg; sumatriptan 25, 50mg
105	Single attack, 40mg; in adolescents
302	Single attack, 5, 20, 30mg; inpatient
305	Three attack, 40, 80mg
307	Single attack, 40, 80mg; Cafergot 2 tablets
314	Single attack, 20, 40, 80mg; sumatriptan 100mg
318	Three attack, 40, 80mg, sumatriptan 50, 100mg
Double-blind, placebo-controlled, oral headache prevention study	
306	80mg used during a migraine aura
Other oral efficacy studies	
101	Open label, crossover, efficacy and PK during and without an attack
302A	Multiple attack extension of 302; 5, 20, 30mg

Study	Description
302C	Multiple attack extension of 302; 5, 20, 30mg; sumatriptan 100mg
Intravenous Studies	
301	Single attack, 16.7, 50, 102 µg/kg i.v.
303	Two period crossover, 102 µg/kg i.v.
Long-Term Studies	
108	Open label, 1 year study
316	Open label, 1 year study (ongoing)
317	Open label, 1 year study

Table 3: Phase 2/3 Oral Studies Contributing to Extension Studies

Extension Study (Total N)	Parent Studies Contributing to Extension	Total Number of Subjects in Parent Study	No. of Subjects Contributing to Extension Study
108 (N = 885)	102	1190	670
	103	632	184
	104	818	0
	105	274	31
Total			885
317 (N = 702)	305	1153	614
	306	87	8
	307	733	44
	314	692	20*
	318	774	15
Total			701**
316 (N = 411)	302***	365	24
	302A	8	3
	302C	213	44
	314	692	340
Total			411

* The 20 subjects moving from 314 to 317 were all from Australia
**One subject moved from extension study 316 to extension study 317
*** The 8 subjects in 302A and 213 subjects in 302C were from 302
Not shown is study 101 which did not contribute patients to an extension

All controlled clinical trials of the tablet were conducted in an outpatient setting with the exception of study 302. Headache severity was measured on a traditional four point scale (none, mild, moderate, severe) and was assessed at multiple time points. All second doses were optional (*i.e.*, given as needed) for recurrence or persistent pain with the exception of the 2nd and 3rd attacks in study 305. In this study, patients who responded to the first dose were required to take a second dose between 8 and 16 hours to assess the potential for preventing recurrence.

All uncomplicated migraineurs with or without aura were eligible for study. Subjects over 65 years of age were included in the majority of studies and a wide range of concomitant medications were allowed (including but not limited to beta-blockers, methysergide, selective serotonin reuptake inhibitors (SSRI's), tricyclic antidepressants (TCA's), and monoamine oxidase inhibitors (MAOI's)). Those with known coronary artery disease, significant arrhythmias, heart failure, uncontrolled hypertension, clinically significant active renal, hepatic, gastrointestinal, neurological including epilepsy, endocrine, metabolic or psychiatric disease were excluded from phase 2/3 studies.

The designs of the studies were kept as similar as possible. In addition, several studies were prospectively designed to provide data for a meta-analysis to determine the efficacy of a second dose to treat headache recurrence and non-response during one attack using placebo control (102, 104, 305, 307, and 318). In all of these studies where eletriptan was taken as the first dose, the second dose was randomized 50:50 to drug or placebo. When placebo or active comparator was the first dose, the second dose was usually the same, except in 102 and 107 where the second dose after placebo was randomized 50:50 to eletriptan or placebo in order to get data on the effects of delayed dosing.

Most of the phase 2/3 studies tested 40 and 80mg doses. The adolescent study (105) tested 40mg and the migraine aura study (306) tested 80mg alone. Lower doses were tested mostly in phase 2 studies. Study 302 and its short-term multiple attack extensions 302A and 302C tested 5, 20, and 30mg. Studies 102, 314, and 316 tested 20mg as well as 40 and 80mg (316 also tested 60mg). Study designs were generally double-blind, parallel group except for the long term safety studies 108 and 317.

5.2 Demographics

A total of 5053 individuals received eletriptan in phase 2/3 studies. Subjects ranged in age from 11 to 78 years and in weight from 30 to 211 kg. As is typical of other migraine studies, 84.7% were female. Eletriptan and placebo treated subjects were similar with respect to age, gender, race, and weight. The totals in Table 4 (adapted from tables 2.8.2.4 and 2.8.2.5 of the NDA summary) differ from the total number exposed due to missing demographic information in some patients.

Table 4: Demographics in Phase 2/3 Studies

Demographic Characteristics	All phase 2/3		1st attack - short term studies	
	Eletriptan (N=5032)	Placebo (N=1053)	Eletriptan (N=4596)	Placebo (N=988)
Sex				
Male	769 (15.3%)	198 (18.8%)	696 (15.1%)	186 (18.8%)
Female	4263 (84.7%)	855 (81.2%)	3900 (84.9%)	802 (81.2%)
Age				
Mean	39.6	37.5	39.5	37.3
Min	11	12	11	12
Max	78	69	78	66
Race				
White	4786 (95.1%)	997 (94.7%)	4368 (95%)	939 (95%)
Black	154 (3.1%)	36 (3.4%)	150 (3.3%)	33 (3.3%)
Asian	28 (0.6%)	7 (0.7%)	26 (0.6%)	5 (0.5%)
Other	58 (1.2%)	13 (1.2%)	52 (1.1%)	11 (1.1%)
Not collected	6 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (kg)				
Mean	68.7	67.1	68.7	67.1
Min	30	34	30	34
Max	211	141	211	141

5.3 Extent of Exposures

Table 5 (adapted from sponsor table 2.8.2.D.1, page 9 of the NDA summary) shows the number of subjects treated throughout phases 1/2/3.

Although 6419 subjects received eletriptan in phase 2/3 studies, the number of unique individuals was 5033, since patients enrolled in more than one study (*e.g.*, parent and extension) are counted more than once in the former total. There were 1054 unique placebo patients in phase 2/3 trials, and 1373 received active comparator agents.

Table 5: Number of Subjects in the Clinical Development Program

	Eletriptan	Placebo	Sumatriptan	Cafergot	POT
Grand Total	6950*	1273	892	203	278
Clinical Pharmacology	531	219			
IV	*106*	*48*			
Oral	*401*	*159*			
Other (SL, solution)	*24*	*12*			
Phase 2/3	6419**	1054	892	203	278
Single Attack	*1371*	*361*	*129*	*203*	*0*
Multiple Attacks	*3473*	*667*	*712*	*0*	*0*
Active Comparator	*1638*	*335*	*841*	*203*	*0*
Long Term Phase 3	*1309*	*0*	*0*	*0*	*278*

*Total by country: USA=2230; Canada=205, Other=4515; POT = physician optimized treatment

**The total number of subjects in the phase 2/3 total is lower than those in the individual categories because of overlap between the active comparator group and other study groups. Furthermore, all subjects enrolled in open-label extension studies were initially enrolled in a placebo-controlled study and are not counted twice in the total.

The mean number of attacks treated by all subjects in all phase 2/3 studies was 6. Table 6 shows the mean number of attacks treated by all subjects and the mean dose range of eletriptan used to treat the attacks (adapted from NDA summary, page 12)

Table 6: All Phase 2/3 Studies – Mean number of attacks treated, by Dose Range

Mean dose range of eletriptan per attack	Mean number of attacks treated with doses within the range	Number of subjects treating attacks with doses within the range
< 20mg	2.3	597 (9.3%)
> 20mg to < 40mg	2.2	1816 (28.3%)
> 40mg to < 80mg	5.9	2765 (43.1%)
> 80mg to < 120mg	13.3	633 (9.9%)
> 120mg to < 160mg	14.0	608 (9.5%)

In the long-term phase 3 studies, a total of 1309 patients had received eletriptan where treatment allocation was known at database cutoff (4/30/98). The long-term exposures are shown in Table 7 (adapted from sponsor table 2.8.2.13 in the NDA summary). One can see that exposures at the high dose comply with ICH and Division guidelines for 1 year exposures (≥100 patients exposed for one year, each treating ≥2 attacks/month) however the database falls short for 6 months exposures at the high dose (272 actual vs. ≥300 patients requested). However, an additional 98 were receiving blinded therapy at the time.

Table 7: Long Term Exposure (sponsor table 2.8.2.13)

	Freq	Treated	Visit at 6 mo.	Visit at 12 mo.
Eletriptan 40 mg	All attacks	390	309	133
	≥2 /month	262	212	96
Eletriptan 80 mg	All attacks	486	352	122
	≥2 /month	357	272	108
POT	All attacks	278	141	61
	≥2 /month	148	87	43
Blinded Therapy	All attacks	411	184	67
	≥2 /month	249	98	40

POT = physician optimized therapy

6. Human Pharmacokinetics

A single oral dose of eletriptan is rapidly and well absorbed across the gastrointestinal tract (approximately 81%). The mean T_{max} is independent of dose and occurs approximately 1.5h (1.3 - 2.1h). The absolute oral bioavailability of eletriptan across both males and females is approximately 50%. The pharmacokinetics of eletriptan are approximately linear between 20-80mg. Mean $T_{1/2}$ is approximately 4h (range: 3.6 - 3.8h) over the 20 to 80mg clinical dose range.

The plasma protein binding of eletriptan is moderate (83 to 88%) and unaffected by hepatic impairment or renal impairment. Multiple dose regimens of oral eletriptan result in steady state levels of eletriptan within 2 to 4 days. In healthy male subjects, accumulation of both C_{max} and AUC, following multiple dose eletriptan (20mg every 8 hours for 7 days) is as predicted based on the dosing interval and single dose pharmacokinetics. Mean T_{max}, k_{el} and $T_{1/2}$ are similar to values obtained in single oral dose studies.

The rate and extent of absorption of eletriptan is decreased during a migraine attack. During a migraine attack, the AUC, and C_{max} were reduced by approximately 30% and the mean T_{max} was increased from 1.5 to 2.8h.

There are no clinically important differences in the pharmacokinetics of eletriptan between the elderly (65 to 93 years old) and the young adult. The only finding was a statistically significant difference in k_{el}, resulting in an increased eletriptan $T_{1/2}$ of 5.7h in the elderly compared to 4.4h in the young adult. Blood pressure increases associated with eletriptan may be greater in the elderly.

A meta-analysis of AUC, C_{max} and T_{max} across six oral studies and a Population Pharmacokinetic analysis indicates that there are no significant gender differences in the pharmacokinetics of oral eletriptan.

First-pass metabolism of eletriptan is apparent in the difference between an oral absorption ratio and observed oral bioavailability. For both oral and intravenous administration of [^{14}C]-eletriptan, the plasma AUC is higher and the $T_{1/2}$ is longer for total radioactivity compared to eletriptan, indicating the presence of circulating

metabolites. Four major circulating radioactive components were identified in plasma after oral dosing; eletriptan (30% of total radioactivity), the pyrrolidine N-oxide UK-234,435 (23%), the N-desmethyl metabolite UK-135,800 (7%), and what appears to be a mixture of hydroxylated metabolites accounting for 35% of the radioactivity.

The N-desmethyl metabolite UK-135,800 has activity similar to eletriptan in vitro, but its exposure is only at maximum 17% of the eletriptan exposure, with its levels not exceeding parent drug levels. After single intravenous and oral doses of [^{14}C] -eletriptan, 44 to 55% of the total radioactivity was excreted in the urine, mainly up to 24 hours post-dose, and 30 to 45% was excreted in the feces, mainly 24 to 48 hours post-dose. The mean total recovery of radioactivity in urine and feces was 85% to 89% over the 9 days post-dosing. Metabolite profiles in the excreta were qualitatively similar following both routes of administration.

Eletriptan metabolism was investigated in vitro using human liver microsomes, primary human hepatocyte cultures, and cell lines expressing specific cytochrome P450 isozymes. CYP3A4 is the predominate enzyme metabolizing eletriptan; CYP2D6 is a minor pathway. Eletriptan metabolism is reduced slightly by quinidine, a selective inhibitor of CYP2D6. Eletriptan does not inhibit CYP1A2, CYP2C9, CYP2E1 or CYP3A4 at concentrations up to 100 µM (38 µg/ml), but does inhibit CYP2D6 activity with an approximate IC_{50} of 41µM. Eletriptan concentrations up to 100µM do not induce CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1. Eletriptan moderately induces CYP3A4 in primary human hepatocytes at concentrations greater than 5 µM, but induction of CYP3A4 in vivo is unlikely since C_{max} following oral eletriptan 80mg is approximately 0.5 µM (191ng/ml), and chronic use is not indicated.

Eletriptan is not a substrate for monoamine oxidase. Eletriptan is primarily eliminated via hepatic cytochrome P450 metabolism, with CYP3A4 as the primary metabolic path. Single oral doses of eletriptan 80mg and multiple doses up to 160mg a day for 7 days appear to have little to no influence on the metabolic activity of CYP3A4 in vivo.

Exposure to eletriptan is increased (34% for AUC) in subjects with mild or moderate hepatic impairment but this does not result in a greater blood pressure response. Eletriptan has not been investigated in subjects with severe hepatic impairment.

The renal elimination of eletriptan is low, with an average 9.3% of an intravenous dose eliminated unchanged in urine during the first 24 hours post-dose. Mean CL_R of eletriptan ranges from 64 to 80ml/min (3.8 to 4.8L/h) over the clinical dose range. Multiple daily doses of eletriptan up to 160mg a day for 7 days have no significant effect on eletriptan CL_R. The pharmacokinetics of eletriptan are similar between normal subjects and subjects with mild, moderate or severe renal disease. Increases in blood pressure associated with eletriptan treatment are greater in renally impaired subjects compared to normal subjects.

Eletriptan is excreted into human breast milk. The mean total amount of eletriptan excreted into breast milk over 24 hours was only 0.02% of an 80mg oral dose. Exposure to orally administered eletriptan, as measured by AUC and C_{max}, is increased in the

presence of food by approximately 20 to 30%. Food has no significant effect on T_{max} or $T_{1/2}$ for eletriptan. Although food increases eletriptan exposure, this finding is not considered clinically relevant as it is unlikely that migraine patients would be consuming food immediately prior to treatment.

Cafergot has an additive effect on increasing blood pressure when given one or two hours following eletriptan. The transient increases in blood pressure seen with both drugs are predictable.

Propranolol, a weak inhibitor of cytochrome P-450 metabolism used in the prophylactic treatment of migraine, appears to inhibit eletriptan metabolism. A statistically significant increase in eletriptan AUC (by 33%) and decrease in k_{el} (by 7%) is observed in the presence of propranolol. While exposure to eletriptan increased, propranolol attenuated the pharmacodynamic effects of eletriptan, producing a smaller effect on SBP, DBP and PR changes than observed with placebo. Thus, the coadministration of eletriptan with propranolol does not appear to have a clinically relevant effect.

Erythromycin, a potent CYP3A4 inhibitor, has a clinically relevant effect on the pharmacokinetics and pharmacodynamics of eletriptan consistent with inhibition of eletriptan metabolism. Systemic exposure to eletriptan 80mg was significantly increased when coadministered with erythromycin (2-fold increase in C_{max} and 4-fold increase in AUC), and k_{el} was significantly reduced resulting in a 2.5h increase in T_{max}. The transient elevations in blood pressure associated with eletriptan are more pronounced in the presence of erythromycin than in the presence of placebo.

In subjects undergoing diagnostic coronary arteriography, an intravenous infusion of eletriptan (50µg/kg) was generally associated with a slight decrease in coronary artery diameter from baseline (no greater than a mean change of -3.0% of baseline), which was not considered to be clinically important. However, one subject experienced a 65% reduction in coronary artery diameter.

Eletriptan is associated with small, transient, dose-related increases in blood pressure (primarily DBP), consistent with its mechanism of action and with other 5-$HT_{1B/1D}$ agonists. The mean maximum increases in blood pressure are typically in the range of 5 to 15mmHg after single oral doses of eletriptan up to 160mg. The changes in blood pressure are not associated with any ECG changes or specific adverse events and are not altered by multiple daily dosing. There are no differences between males and females in the blood pressure effects of eletriptan. A linear PK/PD relationship has been demonstrated between eletriptan plasma concentrations and blood pressure changes. This model predicts that the average peak plasma levels will have to be increased by at least 25% following a single oral dose of 80mg before potentially clinically relevant blood pressure increases (>10% increase from baseline in DBP) are observed in healthy subjects.

Ophthalmologic slit-lamp corneal examinations indicate no clear evidence of a relationship between eletriptan treatment and the appearance of transient, minor corneal

abnormalities. Additionally, there is no evidence of eletriptan affecting thyroid activity or cognitive function following multiple dose oral eletriptan (20 or 30mg) for up to 7 days.

7. Integrated Review of Efficacy

7.1 Background

There are 13 completed oral phase 2/3 eletriptan studies that explored the efficacy of eletriptan. These are listed in Table 8 (adapted from ISE, pages 6-7). Not included are studies 301 and 303 which were i.v. studies and are not the basis of a claim. Also not included are studies 108, 316, and 317, which are the long-term safety studies.

Table 8: Completed Phase 2/3 Oral Eletriptan Efficacy Studies

Study	Description
Double-blind, placebo-controlled, headache treatment studies	
102	Three attack, 20, 40, 80mg
103	Two attack, 40, 80mg
104	Three attack, 40mg, 80mg; sumatriptan 25, 50mg
105	Single attack, 40mg; adolescents
302	Single attack, 5, 20, 30mg
305	Three attack, 40, 80mg
307	Single attack, 40, 80mg; Cafergot 2 tablets
314	Single attack, 20, 40, 80mg; sumatriptan 100mg
318	Three attack, 40, 80mg, sumatriptan 50, 100mg
Double-blind, placebo-controlled, headache prevention study	
306	80mg used during a migraine aura
Other studies	
101	Open label, crossover, efficacy and PK during and without an attack
302A	Multiple attack extension of 302; 5, 20, 30mg
302C	Multiple attack extension of 302; 5, 20, 30mg; sumatriptan 100mg

The next table (Table 9, adapted from page 8 of the ISE) provides additional dosing information. The studies varied in terms of the age of the patients, the number of attacks treated, the dose of eletriptan used, the use of a second dose to treat non-response or recurrence, the timing of the 2nd dose for the treatment of either a non-response or recurrence, and the dosage used for the second dose.

Table 9: Completed Phase 2/3 Oral Eletriptan Studies, Dosing Information

Study	Age	Total N	n	Rx[1] Attack 1 Dose 1 [Dose 2]	Timing of 2nd Dose For Non-response	Rx of Recurrence Attack 1 In Hrs[2]	Rx Attack 2 Dose 1 [Dose 2]	Rx Attack 3 Dose 1 [Dose 2]	Rescue In Hrs[4] Dose 1 [Dose 2]
Single Attack									
101	18-65	35	35	30	-	-	-	-	2.5-3
105	12-17	274	141 133	40 [40] P [40]	-	2-24	-	-	2
302	18-65	365	87 97 91 90	5 20 30 P	-	-	-	-	2
307	18-65	732	210 214 203 105	40 [40/P] 80 [80/P] C [C] P [40/80]	2 hrs	2-24	-	-	2 [2]
314	≥18	691	144 135 141 129 142	20 [20] 40 [40] 80 [80] S100 [S100] P [P]	-	4-24			
2-3 Attacks									
103	≥18	631	507 124	40 [40] P [40]	2 hrs	2-24	40 [40] 80 [80] P [40/80]	Same as Attack 1	- [2]
102	≥18	1190	290 296 312 292	20 [20/P] 40 [40/P] 80 [80/P] P [80/P]	4 hrs	4-24	Same as Attack 1	Same as Attack 1	- [2]
305	≥18	1151	452 461 238	40 [40/P] 80 [80/P] P [P]	2 hrs	2-24	40 [40/P] 80 [80/P]	Same as Attack 2	- [2]
104	≥18	818	184 180 180 181 93	40 [40/P] 80 [80/P] S25 [S25] S50 [S50] P [P]	2 hrs	2-24	Same as Attack 1	Same as Attack 1	- [2]
318	≥18	773	175 164 181 169 84	40 [40/P] 80 [80/P] S50 [S50] S100 [S100] P [P]	2 hrs	2-24	Same as Attack 1	Same as Attack 1	- [2]
Headache Prevention									
306[3]	≥18	87	43 44	80 [40] P [40]	2 hrs	-	-	-	- [2]
>3 Attacks									
302A	18-65	8	2 5 0 1	5 20 30 P	-	-	Same as Attack 1	Same as Attack 1	2
302C	18-65	213	52 58 52 51	5 20 30 S100	-	-	Same as Attack 1	Same as Attack 1	2

[1] Treatment of eletriptan in mg; P=Placebo; C=Cafergot; S=Sumatriptan
[2] Recurrence defined as return of 2/3 headache from a state of 0/1 headache achieved after study drug and within 24 hours of initial dosing
[3] This was the headache prevention study. The first dose was given during the aura, and the second dose given if the headache occurred.
[4] Earliest time rescue medication could be taken, per protocol

7.2 Efficacy Studies

7.2.1 Enrollment

The sponsor focused on the analysis of 9 of these 13 trials for their integrated efficacy analysis. Seven of the nine were adult outpatient placebo-controlled acute treatment trials (102, 103, 104, 305, 314, 307, and 318). All trials included patients over 18 years of age with the exception of study 105, which was the adolescent efficacy study (12-17 years). Subjects were generally in good health and capable of taking medication on an outpatient basis. Based on past headache histories, it was expected that each subject would suffer at least one migraine attack every six weeks. The diagnosis of migraine had to comply with International Headache Society (IHS) criteria. Both migraineurs with or without aura were enrolled. Patients were generally already under the care of a physician for migraine headaches (*i.e.*, clinic based recruitment). The one exception was study 104, where population based recruitment was used.

7.2.2 Drug Administration

All studies were outpatient except 101 and 302. For the outpatient trials, study medication was dispensed at the randomization visit and patients were instructed to treat a moderate or severe migraine headache. Most studies allowed a second dose for persistent pain (*i.e.*, inadequate response) or to treat a headache recurrence. The second dose could be taken as soon as 2 hours after the first dose in all studies except study 104 (4 hours). Rescue medication was allowed 2 hours after the first or second dose, as appropriate. A wide range of concomitant medications was permitted; however, no sumatriptan, ergotamine, or ergotamine-like agents was allowed in the 48 hours prior to dosing with eletriptan. These same medications were also not permitted to be used as rescue within 24 hours of taking study medication.

7.2.3 Efficacy Measures

Patients recorded the presence and severity of headache symptoms in headache diaries. Specific times of assessment varied somewhat among the various studies, but were generally at baseline (0), 0.5, 1, 2, 4, and 24 hours post-dose after the initial headache, and at 2, and 24 hours after treatment for any headache recurrence. The efficacy measures recorded in patient diaries are shown below (derived from ISE, page 10).

Table 10: Recorded Efficacy Measures

Efficacy Measure	Scale
Headache	None (0), mild (1), moderate (2), severe (3)
Nausea	None (0), mild (1), moderate (2), severe (3)
Vomiting	Absent or present
Photophobia	Absent or present
Phonophobia	Absent or present
Functional Impairment	Normal (0), do something (1), do little (2), requiring bed rest (3)
Acceptability of treatment	Yes or No (assessed at 24 hours only)
Recurrence	Yes or No
Time to Recurrence	Time since initial treatment
Rescue	Yes or No
Time to Rescue	Time since initial treatment

In most studies where multiple attacks were treated, the first attack was the primary focus of analysis (with the exception of study 103, which analyzed the use of 80mg on the second attack in patients who failed to respond to 40mg in attack 1. It is the one study of the seven acute outpatient trials which the sponsor does not describe in labeling). The following derived efficacy variables were used for analyses:

Table 11: Derived Efficacy Variables

Derived Efficacy Variables	Derivation
Response Rate	Proportion with 2/3 headache at baseline and 0/1 headache at specified time point
Pain Free Rate	Proportion with 2/3 headache at baseline and no headache (0) at specified time point
Incidence of nausea, vomiting, photophobia, phonophobia	Incidence at 2 hours
Functional Impairment Response Rate	Proportion with 2/3 impairment at baseline and 0/1 impairment at specified time point
Rate of rescue medication use	Incidence
Consistency of Response	In 3 attacks studies, the percentage who responded to 0, 1, 2, or all 3 attacks (taking the same regimen for all three)
Subject's treatment acceptability	Percentage answering "Yes" to treatment acceptability question
Recurrence Rate	Percentage who had a recurrence. In some studies, time to recurrence was also reported.

The primary efficacy variable for most studies (102, 105, 305, 307, 314) was the headache response rate at 2 hours. For studies 104 and 318, the primary efficacy variable was the headache response rate at 1 hour. Response rates were also determined at other time points. Secondary efficacy variables included the pain-free response at various time points, incidence of associated symptoms at two hours, functional impairment response rate at two hours, rate of rescue medication use, treatment acceptability rate at 24 hours, and the rate of headache recurrence.

Studies 103 and 306 were quite different from the other studies and deserves special mention. Study 103 was a two-attack study designed to assess the use of 80mg eletriptan to treat a migraine headache in patients who failed to achieve a pain-free state with eletriptan 40mg in a previous attack. For their second attack, subjects received 40mg or 80mg or placebo. The primary efficacy variable was the pain-free response rate at two hours in the second attack for those who received 40mg in the first attack and did not achieve a pain-free result. Data collected for the first attack are discussed with the first attack data from the other studies.

Study 306 was a migraine headache prevention study. This study enrolled only patients with migraine with aura. They were instructed to treat an aura with study medication and the primary efficacy variable was the proportion of patients who had a grade 2/3 headache at 6 hours. Secondary variables included duration of aura, median time to

headache development, and assessment of other secondary migraine symptoms. Data from this study are discussed separately.

7.2.4 Analysis Plans

The primary analysis group was the intent-to-treat population. Headache response and pain free response were calculated for all patients who had baseline and on-treatment data and had a moderate or severe headache at baseline. For study 103 (described in the previous section), the intent-to-treat population was defined as those who received 40mg for the first attack, failed to achieve a pain-free response in the first attack, and had baseline and on-treatment data for the second attack.

The evaluable patient population included all subjects who met the following criteria:

- Satisfied inclusion/exclusion criteria in the protocol
- Satisfied the intent-to-treat criteria
- Did not receive analgesics or anti-emetics during the attack or within six hours prior to the attack
- Did not receive sumatriptan, ergotamine, or ergotamine-like drugs in the 48 hours prior to the attack
- Did not have more than six hours elapse between the onset of the headache and the time of the first dose.

For the integrated discussion, the 2 hour headache response rate was also calculated according to:

- Age: 18-40; 41-64; ≥65 years
- Gender: male; female
- Race: white; black; oriental; other
- Onset of menses: females who treated a migraine one day prior up to 4 days after the onset of menstruation
- Concomitant oral contraceptive/estrogen use
- Migraine prophylaxis treatment: patients were included in this group if they were taking beta blockers, tricyclic antidepressants, SSRI's, valproic acid, calcium channel blockers, flunarizine, methysergide, or MAOI's.

Statistical tests of significance were conducted at the 5% level and were two-sided unless specified in the individual study reports. Where the primary comparison was eletriptan vs. placebo or eletriptan vs. comparator, a pre-specified step-down procedure was used, with no further adjustments being made for multiple comparisons. No statistical tests were performed for active comparator vs. placebo.

Analysis of covariance (logistic regression with treatment dose as factor) was used to make treatment comparisons. In the statistical model, main effects treatment and baseline were fitted and retained in the model regardless of statistical significance. Other main effects (*e.g.*, age, gender, race) were fitted and retained if significant at the 5% level. Interaction effects were then fitted and were retained if significant at the 10% level. Significance was based on the Wald chi-square test.

A prospectively defined meta-analysis was performed incorporating data from five phase 3 studies: 102, 104, 305, 307, and 318. The objectives of the meta-analysis were to determine whether there was any effect of using a second dose of eletriptan to treat either initial non-response or to treat headache recurrence in a single migraine attack. A meta-analysis was prospectively planned for these studies since preliminary statistical investigations indicated that approximately 5,000 patients would otherwise be required to receive two doses of study medication within a single study to achieve enough statistical power.

There were certain analyses which were performed specifically for the integrated summary of efficacy which were not performed for the individual study reports. These included:

- Response rates at 30 minutes
- Pooled vomiting analysis from the 7 outpatient adult placebo-controlled migraine studies (since the number of patients with vomiting in each individual study was small)
- Pooled subgroup analyses of: effects of migraine prophylaxis, age, gender, race, concomitant oral contraceptive/estrogen therapy, menses.
- Pooled dose-response analysis from the 7 outpatient adult placebo-controlled studies to assess the 2 hour headache response rate.
- Pooled dose-response analysis from the 7 outpatient adult placebo-controlled studies to assess effects of a second dose for headache recurrence.
- Pooled cumulative headache response within 4 hours was plotted using data from the 7 outpatient adult placebo-controlled studies. No distinction whether patient took 2nd dose or rescue prior to 4 hours was made in this analysis.

7.3 Results

The efficacy results focused on the effects of the first dose used to treat the first attack in the various efficacy studies.

7.3.1 Baseline Data

Table 12 (adapted from sponsor table on page 15 of the ISE) shows the number of patients assessed in the ITT and evaluable populations for the primary efficacy analysis. The data include the 7 adult outpatient efficacy trials and the one adolescent trial (105).

Table 12: Primary Efficacy Studies – ITT and Evaluable Population

Study	ITT	Evaluable	% Evaluable
102	1182	898	76.0%
103	625	444	71.0%
104	813	722	88.8%
105	270	223	82.6%
305	1151	950	82.5%
307	730	597	81.8%
314	691	635	91.9%
318	772	671	86.9%
Total	6234	5140	82.5%

The main reasons for a patient being non-evaluable were taking a concomitant medication that was not allowed in the protocol (63%), and taking study medication too late (>6 hours) after the onset of a migraine (24%).

Patients were to treat a moderate or severe headache at baseline. Among the 8 studies, the percentages of subjects with a moderate headache varied somewhat among the studies, with moderate headache being most prevalent in all cases. Overall, approximately 64% had a moderate headache at baseline (range 55% - 74% in studies 314 and 102, respectively). There were very few that treated a grade 0/1 headache in the studies, ranging from 0-3 (0% - 2.2%) in any treatment group in any study (sponsor table 2.8.4.1.1, not shown here).

7.3.2 Efficacy of 5 mg Dose

Although the 5mg dose is not described in the Integrated Summary of Efficacy, it was used in 3 efficacy studies: 302, which was a phase 2 inpatient study, and its two short-term extension studies 302a and 302c.

Study 302 had 4 treatment arms: 5mg, 20mg, 30mg, and placebo. Patients treated a single migraine attack in an in-clinic setting. The primary efficacy measure was the 2-hour headache response rate. The results of this study are shown in Table 13 (study report 302, pages 21-22). The 2-hour response rate for 5mg was numerically superior to placebo (38.3% vs. 33.7%) but it failed to achieve statistical significance.

Table 13: Study 302 – Efficacy Results

	5mg n=86	20mg n=97	30mg n=91	PBO n=89
2-hour response	33 (38.3%) p=0.5207	45 (46.3%) p=0.0791	43 (47.2%) p=0.0652	30 (33.7%)
2-hour pain-free	10 (12.1%) p=0.5665	18 (19.1%) p=0.0652	18 (20.9%) p=0.0295	8 (9.3%)

p-values compared to placebo

Study 302a, while placebo controlled, only enrolled 8 patients (2 at 5mg, 5 at 20mg, and 1 placebo) and did not provide meaningful efficacy data due to its small size.

Study 302c was not placebo controlled but rather used an active control, sumatriptan 100mg, along with eletriptan 5mg, 20mg, 30mg. Each patient treated 9 attacks. The primary efficacy measure was the 2-hour headache response rate for attack 1. The study treated approximately 50 patients per treatment arm (49 with 5mg, 56 with 20mg, 49 with 30mg and 50 with sumatriptan 100mg). The 2-hour response rates for attack 1 were 30.6%, 51.8%, 71.4%, and 60% for 5mg, 20mg, 30mg, and sumatriptan 100mg, respectively. Without a placebo arm, one cannot say that the 5mg had any treatment effect at all, but all the other doses were numerically better than 5mg.

In summary, the only study in which a substantial number of patients were exposed to 5mg and placebo showed that the 2 hour headache response rate for the 5mg dose was numerically, but not statistically, higher than the placebo rate.

7.3.3 Efficacy of 20 mg Dose

Efficacy of the 20 mg dose is supported by data from studies 102 and 314. The primary time points were two hours post-dose for these studies. A summary of data for headache response and pain-free response up to 2 hours is shown in Table 14 (ISE page 16).

Table 14: Efficacy of the 20 mg Dose

	0.5 Hour			1 Hour			2 Hours		
	20mg	PBO	p-value	20mg	PBO	p-value	20mg	PBO	p-value
102	n=285	n=279		n=287	n=279		n=273	n=276	
Response	5 3%	3.9%	0.4614	23.7%	14.7%	0.0069	47.3%	21.7%	<0.0001
Pain-free	0 4%	0	0.2427	3.8%	1.1%	0.0480	14.3%	4.0%	0.0001
314	n=143	n=136		n=135	n=132		n=129	n=126	
Response	6 3%	5.9%	0.9398	24.4%	12.1%	0.0133	54.3%	23.8%	<0.0001
Pain-free	0	0	1. 0	2.2%	1.5%	0.6714	19.4%	5.6%	0.0018

Both studies demonstrated a statistically significant difference in the headache response rate at 2 hours in favor of eletriptan 20mg. This was the primary endpoint for both studies. Response rate was also nominally significantly lower in both studies at 1 hour. Response rates at 30 minutes were numerically, but not statistically, in favor of drug in both studies, but were almost equal in study 314. Pain-free rates were nominally positive in favor of drug at two hours in both studies, and at 1 hour for study 102 only (but numerically in favor of drug in the other study). No real trend in pain-free rates was evident at 30 minutes.

The 20mg dose was also evaluated in the early, relatively small inpatient phase 2 study (study 302, Table 13, page 22). In this study, the 2-hour response rates for 20mg and placebo were 46.3% and 33.7% (p=0.0791, n=97 and 89, respectively). Although not statistically significant, a numerical trend in favor of drug is evident with response rates comparable to those seen in the later studies.

7.3.4 Efficacy of 40 mg Dose

All seven adult outpatient efficacy studied the 40mg dose (102, 103, 104, 305, 307, 314, 318). The primary time point was two hours post-dose, except studies 104 and 318, where it was 1 hour. A summary of the data for headache response and pain-free response up to 2 hours for the 40mg dose is shown in Table 15 (ISE page 17).

All seven studies demonstrated a statistically significant difference in the headache response rate at 2 hours in favor of eletriptan 40mg. Response rates at 1 hour were also statistically higher for drug in 6 of the 7 studies (all except 104, where it was numerically slightly in favor of placebo). Of the two studies where 1 hour was the primary time point, study 314 was positive and study 104 was negative. Response rates at 30 minutes were determined for 6 of the 7 studies. Thirty minute response rates were nominally significant in favor of drug in two studies (102 and 305), numerically in favor of drug in two other studies (103 and 318) and numerically in favor of placebo in two other studies (104 and 314).

Table 15: Efficacy of the 40 mg Dose

	0.5 Hour			1 Hour			2 Hours		
	40mg	PBO	p-value	40mg	PBO	p-value	40mg	PBO	p-value
102	n=291	n=279		n=285	n=279		n=281	n=276	
Response	8.6%	3.9%	0.0254	34.0%	14.7%	<0.0001	61.9%	21.7%	<0.0001
Pain-free	0.7%	0	0.1006	6.7%	1.1%	0 0027	27.0%	4.0%	<0 0001
103	n=493	n=121		n=491	n=122		n=492	n=122	
Response	11.0%	5.0%	0.0953	32.8%	14.8%	0.0006	57.5%	29.5%	<0.0001
Pain-free	0.8%	0	0.9999	5.7%	2.5%	0.1704	24.2%	4.9%	<0.0001
104	n=178	n=88		n=176	n=89		n=175	n=86	
Response	7.9%	11.4%	0.3301	21.6%	22.5%	0.8183	62.3%	39.5%	0.0007
Pain-free	1.1%	0	0.2064	5.1%	2.2%	0 2897	19.4%	9.3%	0.0417
305	n=437	n=233		n=436	n=234		n=430	n=232	
Response	8.0%	1.7%	0.0031	33.3%	9 0%	<0.0001	61.6%	19.0%	<0.0001
Pain-free	0.7%	0	0.1109	5.7%	0	<0 0001	31.6%	2.6%	<0.0001
307	--	--		n=205	n=102		n=206	n=102	
Response	--	--	--	29.3%	12.7%	0 0017	53.9%	20.6%	<0.0001
Pain-free	--	--	--	5.9%	1.0%	0 0813	28 2%	4.9%	<0.0001
314	n=125	n=136		n=124	n=132		n=117	n=126	
Response	4.8%	5.9%	0.7347	37.9%	12.1%	<0.0001	65.0%	23.8%	<0.0001
Pain-free	0	0	1 0	8.1%	1.5%	0 0266	29.1%	5.6%	<0.0001
318	n=175	n=82		n=172	n=82		n=169	n=80	
Response	7.4%	2.4%	0.1282	30.2%	12.2%	0.0021	63.9%	31.3%	<0.0001
Pain-free	0	0	1. 0	5.8%	1.2%	0.1295	30.8%	3.8%	0.0001

Pain-free rates were nominally positive in favor of drug at two hours in all seven studies, and in three studies at one hour (102, 305, and 314). The other 4 studies were numerically in favor of drug at one hour. There were really no trends evident in pain-free rates at 30 minutes in the 6 studies in which they were determined.

7.3.5 Efficacy of 80 mg Dose

Six studies employed the 80mg dose (102, 104, 305, 307, 314, and 318). The primary time point was 2 hours for all studies except 104 and 318, where it was 1 hour. A summary of the data for headache response and pain-free response up to 2 hours for the 40mg dose is shown in Table 16 (ISE page 19).

All six studies demonstrated a statistically significant difference in the headache response rate at 2 hours in favor of eletriptan 80mg. Response rates at 1 hour were also statistically lower for drug in all six studies, including 104 and 314 where this was the primary time point. Response rates at 30 minutes were determined for 5 of the 6 studies. Thirty minute response rates were nominally significant in favor of drug in three studies (102, 305, and 318), and were numerically in favor of drug in study 314 but was numerically in favor of placebo in study 104.

Pain-free rates were nominally positive in favor of drug at 2 hours in all six studies, and in five of the six studies at one hour (and numerically in favor of drug in the sixth). Two studies at 30 minutes showed nominally positive pain-free rates in favor of drug at 30 minutes (305 and 314), but the numbers were small and lack real clinical meaning. The other three studies which determined 30 minute pain-free rates showed slight numerical trends favoring drug, but again the numbers were too small to have clinical meaning.

Table 16: Efficacy of the 80 mg Dose

	0.5 Hour			1 Hour			2 Hours		
	80mg	PBO	p-value	80mg	PBO	p-value	80mg	PBO	p-value
102	n=300	n=279		n=297	n=279		n=290	n=276	
Response	9.3%	3.9%	0.0096	31.6%	14.7%	<0.0001	58.6%	21.7%	<0 0001
Pain-free	0.7%	0	0.1032	10.4%	1.1%	0.0001	27.2%	4.0%	<0.0001
104	n=176	n=88		n=174	n=89		n=170	n= 86	
Response	6.3%	11.4%	0.1722	35.1%	22.5%	0.0287	70.0%	39.5%	<0.0001
Pain-free	1.1%	0	0.1972	5.7%	2.2%	0.2067	26.5%	9.3%	0.0021
305	n=451	n=233		n=441	n=234		n=446	n=232	
Response	11.1%	1.7%	0.0002	33.3%	9.0%	<0.0001	64.6%	19.0%	<0.0001
Pain-free	2.2%	0	0.0039	12.2%	0%	<0.0001	34.3%	2.6%	<0.0001
307	--	--		n=206	n=102		n=209	n=102	
Response	--	--	--	38.8%	12.7%	<0.0001	67.9%	20 6%	<0 0001
Pain-free	--	--	--	14.1%	1.0%	0.0063	37.8%	4.9%	<0.0001
314	n=137	n=136		n=128	n=132		n=118	n=126	
Response	12.4%	5.9%	0.0682	40.6%	12.1%	<0.0001	77.1%	23.8%	<0.0001
Pain-free	2 2%	0	0.0421	17 2%	1.5%	0.0005	37.3%	5.6%	<0.0001
318	n=159	n=82		n=157	n=82		n=160	n=80	
Response	13.2%	2.4%	0.0170	36.9%	12.2%	0.0001	66.9%	31.3%	<0.0001
Pain-free	0.6%	0	0.3653	12.7%	1.2%	0.0172	36.9%	3.8%	<0.0001

7.3.6 Eletriptan vs. Active Comparators

Oral sumatriptan was used as a positive control in studies 104 (25mg, 50mg), 314 (100mg), 318 (50mg, 100mg). Cafergot (2 tablets each with ergotamine 1mg tartrate/ caffeine 100mg) was used as an active comparator in study 307. All of these studies had a placebo arm. The results are described below.

7.3.6.1 Eletriptan vs. Sumatriptan

Three studies compared eletriptan with sumatriptan: 104, 314, and 318. In reviewing the protocols for each of these studies, I note that patients who previously used sumatriptan (any formulation) were excluded from enrollment in studies 104 and 318. This was not an exclusion criterion in study 314.

Study 104 used a step-down procedure to make treatment comparisons. This method of performing multiple comparisons maintained the family-wise significance level at 0.5%. The method assumed that response rates increased (or decreased) monotonically with dose. The first "family" of comparisons was 80mg vs. sumatriptan 25mg. If significant at the 0.05 level, the second contrast was performed between 40mg and sumatriptan 25mg and between 80mg and sumatriptan 50mg. Each was conducted at the 0.25% level. If either was significant then the third contrast was performed between 40mg and sumatriptan 50mg, and so on. Finally, the analysis compared both doses of eletriptan with placebo. Study 314 was designed to demonstrate equivalence between 80mg and sumatriptan 100mg. Study 318 used a similar step-down procedure as was used in study 104. For more details on the statistical analysis plan, I refer the reader to Dr. Flyer's biometrics review.

The 20mg dose was compared with sumatriptan 100mg in Study 314. The response rates were similar between the two at all three time points. At 0.5, 1, and 2 hours, the eletriptan 20mg response rates were 6.3, 24.4, and 54.3%, respectively. For sumatriptan 100mg they were 9.5, 19.8, and 54.8%, respectively. None of the comparisons was nominally significant. Pain-free rates were also similar between the two.

The 40mg dose was compared to sumatriptan 25mg and 50mg in study 104, and with 50mg and 100mg in study 314. A summary data table for headache response at 0.5, 1, and 2 hours is shown below (Table 17, ISE page 21). In study 104, sumatriptan 25mg and 50mg were numerically superior to eletriptan 40mg at 0.5 and 1 hour, but this reversed at 2 hours with eletriptan 40mg numerically better than the other two. None of these analyses reached nominal significance.

Table 17: Efficacy of Eletriptan 40mg vs. Sumatriptan

Study	Time Point	Response Rates				p-value		
		40mg	S25mg	S50mg	S100mg	vs. S25	vs. S50	vs. S100
104	0.5	7.9%	9.2%	8.4%	--	0.5909	0.7936	--
	1	21.6%	24.4%	27.1%	--	0.4580	0.1973	--
	2	62.3%	52.6%	56.0%	--	0.0899	0.2477	--
314	0.5	4.8%	--	--	9.5%	--	--	0.1636
	1	37.9%	--	--	19.8%	--	--	0.0021
	2	65.0%	--	--	54.8%	--	--	0.0532
318	0.5	7.4%	--	7.9%	9.0%	--	0.8935	0.5769
	1	30.2%	--	24.3%	26.7%	--	0.1805	0.4714
	2	63.9%	--	50.0%	53.1%	--	0.0079	0.0474

In study 314, sumatriptan 100mg was numerically better than eletriptan 40mg at 0.5 hours, but this reversed at 1 and 2 hours with eletriptan 40mg numerically better at both later time points. This reached nominal significance at 1 hour and almost reached nominal significance at 2 hours.

In study 318, sumatriptan was again numerically better than eletriptan 40mg at 0.5 hours but this trend again reversed at 1 and 2 hours with eletriptan numerically better than either sumatriptan 50mg or 100mg. This reached nominal significance at 2 hours against both sumatriptan doses. The sponsor's analysis of pain-free rates for 40mg were similar to the response rate analysis and I don't include them here.

The 80mg dose was compared with sumatriptan 25mg and 50mg in study 104, with 50mg and 100mg in study 314, and with 100mg in study 318. A summary data table for headache response at 0.5, 1, and 2 hours is shown below (ISE page 23).

In study 104, Both doses of sumatriptan were numerically better than 80mg at 30 minutes, but this trend reversed at 1 and 2 hours with 80mg numerically better than either dose of sumatriptan. This reached nominal significance at 2 hours.

Table 18: Efficacy of Eletriptan 80mg vs. Sumatriptan

Study	Time Point	Response Rates				p-value		
		80mg	S25mg	S50mg	S100mg	vs. S25	vs. S50	vs. S100
104	0.5	6.3%	9.2%	8.4%	--	0.3184	0.4636	--
	1	35.1%	24.4%	27.1%	--	0.0241	0.0806	--
	2	70.0%	52.6%	56.0%	--	0.0007	0.0040	--
314	0.5	12.4%	--	--	9.5%	--	--	0.4860
	1	40.6%	--	--	19.8%	--	--	0.0007
	2	77.1%	--	--	54.8%	--	--	0.0002
318	0.5	13.2%	--	7.9%	9.0%	--	0.1212	0.2679
	1	36.9%	--	24.3%	26.7%	--	0.0106	0.0530
	2	66.9%	--	50.0%	53.1%	--	0.0018	0 0138

In study 314, eletriptan 80mg was numerically better than sumatriptan 100mg at all time points, and reached nominal significance at 1 and 2 hours.

In study 318, a similar pattern was seen. Eletriptan 80mg was numerically better than sumatriptan 50mg or 100mg at all three time points. It reached nominal significance at 1 hour against sumatriptan 50mg only, and at 2 hours against both sumatriptan doses. I again note that studies 104 and 318 excluded patients who previously tried sumatriptan, but this was not an exclusion criterion in study 314. The sponsor's analysis of pain-free rates for 80mg were similar to the response rate analysis and I don't include them here.

7.3.6.2 Eletriptan vs. Cafergot

Cafergot (2 tablets, each containing ergotamine tartrate 1mg and caffeine 100mg) was used as a positive control in study 307. This study also used eletriptan 40mg and 80mg, and placebo. Table 19 shows the results of the active treatment in this study (ISE page 24). Both eletriptan 40mg- and 80mg- treated patients achieved numerically higher response rates at both 1 and 2 hours, and this was nominally significant. Pain-free rates followed a similar pattern. Responses at 30 minutes were not obtained in this study.

Table 19: Study 307 – Efficacy of Eletriptan vs. Cafergot

	Time Point	Treatment			p-value	
		40mg	80mg	Cafergot	vs. 40	vs. 80
Response Rates	1 hr post-dose	29.3%	38.8%	13.3%	0.0001	<0.0001
	2 hr post-dose	53.9%	67.9%	33.0%	<0.0001	<0.0001
Pain-free Rates	1 hr post-dose	5.9%	14.1%	4.1%	0.4214	0.0011
	2 hr post-dose	28.2%	37.8%	10.2%	<0.0001	<0.0001

7.3.7 Dose-Response

The sponsor performed a pooled efficacy analysis using data collected at 0.5, 1, 2 hours for the first attack from the seven adult outpatient efficacy studies (102, 103, 104, 305, 307, 314, 318). These are shown below (ISE page 25). At two hours, the pooled analysis showed a nominally significance dose response (p=0.0001).

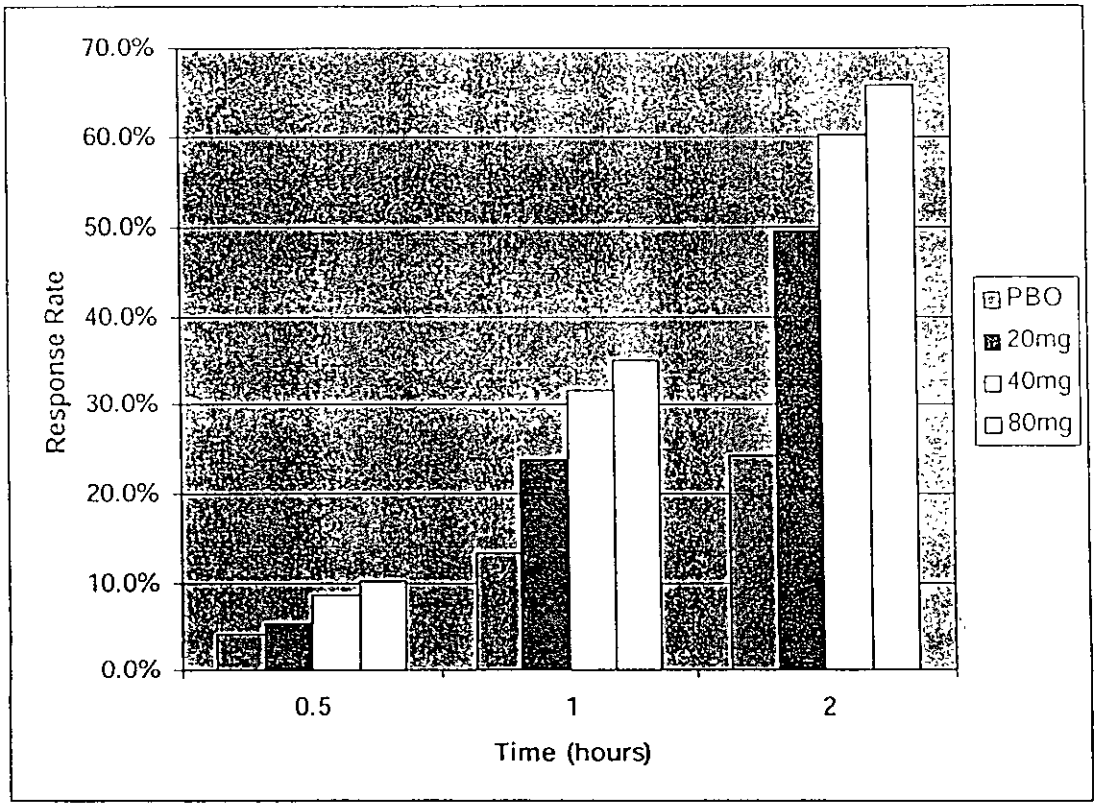
Table 20: Dose Response – Pooled Efficacy Analysis

Time point	PBO	20mg	40mg	80mg
0.5	4.3%	5.6%	8.6%	10.3%
1	13.3%	23.9%	31.7%	35.0%
2	24.4%	49.5%	60.2%	65.8%
(95% CI)		(44.6- 54.4)	(58.0- 62.4)	(63.3- 68.3)

Includes 1st attack from seven adult outpatient efficacy studies, 102, 103, 104, 305, 307, 314, 318

Pairwise comparisons between doses were nominally significant for 80mg vs. 40mg (p=0.0049) and for 40mg vs. 20mg (p=0.0001). The same data are presented graphically in Figure 2. A similar trend was seen with the pain-free response (2 hours: 4.4%, 15.9%, 27.2%, 32.9%, for placebo, 20mg, 40mg, and 80mg, respectively, no p value given).

Figure 2: Pooled Efficacy Studies – Response Rates at 0.5, 1, 2 hours



Includes 1st attack from seven adult outpatient efficacy studies, 102, 103, 104, 305, 307, 314, 318

7.3.8 Eletriptan 80mg vs. 40mg

Study 103 was specifically designed to evaluate the effects of 80mg in patients who had previously received 40mg for a migraine attack and failed to achieve a pain-free result. The study employed four treatment arms, as shown in Table 21 below. The primary endpoint for the study was the 2-hour pain-free response rate for attack two in the subgroup of patients in groups 3 and 4 who failed to achieve a 2-hour pain-free result in attack 1.

Table 21: Study 103 – Dosing Scheme

	Attack 1		Attack 2	
	Dose 1	Optional Dose 2	Dose 1	Optional Dose 2
Group 1	Placebo	E40	Placebo	E40
Group 2	Placebo	E40	Placebo	E80
Group 3	E40	E40	E40	E80
Group 4	E40	E40	E80	E80

The two-hour pain-free response for 80mg was 26.3% (total n=156) and for 40mg was 20.3% (total n=138). Although numerically in favor of the 80mg dose, it failed to reach statistical significance.

7.3.9 Recurrence

A headache recurrence was defined as the recurrence of a grade 2/3 headache within 24 hours of initial treatment in a patient who achieved a response at 2 or 4 hours (depending on the study). Most studies measured recurrence from the 2 hour time point. The recurrence rates for the 7 adult outpatient efficacy studies are shown in Table 22 (ISE page 28).

Table 22: Headache Recurrence Rates

Study	PBO	20mg	40mg	80mg
102	43.9%	28.2% *	31.6% *	23.1% *
103	39.4%	--	15.8% *	--
104	19.4%	--	6.5% *	7 5% *
305	39.6%	--	30.3%	21.0% *
307	44.4%	--	20.9% *	22.1% *
314	23.5%	28.4%	33.7%	31.7%
318	25.0%	--	19.3%	16.2%

* nominally significant vs. placebo

Recurrence rates were numerically lower for eletriptan in six of the seven studies (all but 314), and reached nominal significance for almost all eletriptan doses (20, 40, 80mg) in those six studies with the exception of the 40mg dose in study 305 (although the trend was in the right direction). Study 314 was the only study where recurrence rates were numerically higher than placebo.[1]

The sponsor performed a pooled analysis of recurrence using data from all six studies that included both the 40mg and 80mg doses (all listed in Table 22 except study 103). Recurrence rates for placebo, 20mg, 40mg, and 80mg were 35.5%, 28.2%, 23.2%, and 20.6%, respectively. (The size of the subgroups were 284, 255, 1183, 1000, respectively). A dose-response analysis on the pooled recurrence data demonstrated a nominal significant p=0.0022. Pairwise comparison of 80mg vs. 40mg was also nominally significant with p=0.0073 but not for 40mg vs. 20mg (p=0.3160). None of the

[1] Reviewer's note: It is difficult to interpret recurrence rates since they are derived from non-randomized subgroups of the original study population. Perhaps a better measure is sustained response, which includes the entire intent-to-treat population in the analysis.

comparisons of headache recurrence rates between eletriptan and comparator groups were nominally significant in any study.

7.3.10 Nausea

The sponsor analyzed baseline and post-treatment nausea in the 7 adult outpatient efficacy studies and the 1 adolescent study (study 105). The results of those analyses are shown in Table 23 (adapted from sponsor table 2.8.4.8.1). Nausea was present at baseline in approximately 60-70% of the patients. The occurrence of nausea was lower in study 104, which employed a population-based recruitment (~40%). The effect of study treatment on nausea was analyzed by examining if nausea was present two hours after treatment regardless of whether nausea was present or absent at baseline.

Table 23: Nausea at Two Hours Post-Treatment

Study	Dose	N	Nausea Present At Baseline				Nausea Absent At Baseline				p-value		
			Base line	%	2HR	%	Base line	%	2HR	%	vs. PBO	vs. low dose comparator	vs. high dose comparator
102	20mg	290	177	(65.1)	72	(40.7)	95	(34.9)	84	(88.4)	0.0001		
	40mg	296	187	(66 8)	99	(52.9)	93	(33.2)	75	(80.6)	<0.0001		
	80mg	312	190	(64 8)	83	(43 7)	103	(35.2)	81	(78.6)	0.0003		
	PBO	292	190	(69.1)	53	(27.9)	85	(30.9)	57	(67.1)			
103	40mg	507	286	(58.2)	166	(58.0)	205	(41.8)	171	(83 4)	0.0989		
	PBO	124	71	(59.2)	29	(40.8)	49	(40.8)	44	(89.8)			
104	40mg	184	68	(39 5)	38	(55.9)	104	(60.5)	89	(85.6)	0.4765	0.6357	0 9236
	80mg	180	69	(40 8)	44	(63.8)	100	(59.2)	79	(79.0)	0.5596	0.7500	0.9532
	S25mg	180	79	(47.3)	42	(53 2)	88	(52.7)	74	(84 1)			
	S50mg	181	72	(41.6)	42	(58 3)	101	(58.4)	84	(83.2)			
	PBO	93	33	(37 5)	13	(39.4)	55	(62.5)	49	(89.1)			
105	40mg	141	57	(41.3)	34	(59.6)	81	(58.7)	69	(85.2)	0.3340		
	PBO	133	62	(48.1)	38	(61 3)	67	(51.9)	62	(92.5)			
305	40mg	452	282	(65 6)	162	(57.4)	148	(34.4)	120	(81.1)	<0.0001		
	80mg	461	279	(63.4)	152	(54 5)	161	(36.6)	137	(85.1)	<0.0001		
	PBO	238	153	(66.8)	52	(34.0)	76	(33.2)	55	(72.4)			
307	40mg	210	140	(67.6)	75	(53.6)	67	(32.4)	54	(80.6)	0.0059	<0.0001	
	80mg	214	145	(69.7)	78	(53.8)	63	(30.3)	51	(81.0)	0.0050	<0.0001	
	Cafergot	203	137	(69.5)	34	(24.8)	60	(30.5)	36	(60.0)			
	PBO	105	68	(67.3)	23	(33 8)	33	(32.7)	24	(72.7)			
314	20mg	144	86	(67.2)	50	(58.1)	42	(32.8)	36	(85.7)	0.0021		0.3259
	40mg	135	74	(62.2)	38	(51.4)	45	(37.8)	38	(84.4)	0.0291		0.8885
	80mg	141	85	(72.0)	59	(69.4)	33	(28.0)	30	(90.9)	<0.0001		0.0095
	S100mg	129	74	(65.5)	36	(48.6)	39	(34.5)	34	(87.2)			
	PBO	142	82	(65.6)	31	(37.8)	43	(34.4)	31	(72.1)			
318	40mg	175	108	(64.7)	67	(62 0)	59	(35.3)	52	(88.1)	0.0003	0.0160	0.0380
	80mg	164	108	(67.9)	61	(56.5)	51	(32.1)	43	(84.3)	0.0053	0.1627	0.2851
	S50mg	181	110	(63.2)	52	(47.3)	64	(36.8)	52	(81.3)			
	S100mg	169	115	(72.3)	58	(50.4)	44	(27.7)	35	(79.5)			
	PBO	84	54	(67.5)	19	(35.2)	26	(32.5)	19	(73.1)			

Nausea at two hours was numerically less common with eletriptan use in 7 out of 8 studies, and this reached nominal significance in 5 of the 7. The one study which did not support this finding was study 105, the adolescent efficacy study. Compared to sumatriptan 50mg and 100mg in study 318, eletriptan 40mg (but not 80mg) was associated with nominally significantly less nausea compared to either dose of sumatriptan. In study 314, a nominally significantly larger proportion of patients treated

with eletriptan 80mg had no nausea at two hours compared with those treated with sumatriptan 100mg. The other sumatriptan comparator study, study 104, showed no difference between the two agents. In the Cafergot comparator study, study 307, both eletriptan 40mg and 80mg were associated with lower incidences of nausea at two hours compared to two tablets of Cafergot.

7.3.11 Vomiting

Baseline and post-treatment vomiting was summarized individually for 8 phase 2/3 studies (the 7 adult outpatient efficacy studies and the 1 adolescent study). These were the same studies that were analyzed for the nausea analysis. Vomiting at baseline was infrequent, generally well below 10% in any treatment group (range 0.6% - 15.2%), therefore the sponsor analyzed the data by pooling across studies. Only the eletriptan vs. placebo comparisons were considered. The incidence of vomiting at 2 hours was nominally significantly lower for eletriptan 40mg and 80mg compared to placebo (Table 24, sponsor table. 2.8.4.8.2.2). The 20mg was numerically better than placebo but it failed to reach nominal significance.

Table 24: Vomiting at Two Hours Post-treatment, Pooled Analysis

Dose	N	Vomiting Present At Baseline				Vomiting Absent At Baseline				p-value vs. PBO
		Base Line	%	2HR	%	Base Line	%	2HR	%	
20mg	434	13	(3.3)	8	(61.5)	387	(96.8)	374	(96.6)	0.0903
40mg	1959	108	(5 9)	80	(74.1)	1732	(94.1)	1684	(97.2)	<0.0001
80mg	1472	91	(6.6)	65	(71 4)	1280	(93.4)	1239	(96.8)	0 0006
S25mg	180	4	(2.4)	3	(75.0)	163	(97.6)	160	(98.2)	
S50mg	362	18	(5 2)	14	(77.8)	330	(94.8)	317	(96.1)	
S100mg	298	36	(13.4)	30	(83.3)	233	(86.6)	217	(93.1)	
Cafergot	203	26	(13 2)	17	(65.4)	171	(86.8)	154	(90.1)	
Placebo	1078	58	(5.7)	32	(55.2)	954	(94.3)	900	(94 3)	

7.3.12 Photophobia

Baseline and post-treatment photophobia were summarized individually for 7 studies (6 of the 7 adult outpatient efficacy trials, and the adolescent trial). Study 314 was not included in the analysis because separate photophobia and phonophobia data were not collected. The results of the analyses are shown in Table 25 (sponsor table 2.8.4.8.3). At baseline, approximately 70-80% of patients had photophobia. Compared with placebo, incidences of photophobia at 2 hours were nominally significantly lower for all doses of eletriptan regardless of dose. This was true in all studies except study 104, where the p value for 40mg vs. placebo was 0.0561. In study 318, the 40mg dose was nominally significantly better that sumatriptan 50mg but not sumatriptan 100mg. The 80mg dose was nominally significantly better than either the 50mg or 100mg sumatriptan dose. In study 104, 80mg was nominally significantly better than sumatriptan 25mg but not 50mg. The 40mg dose was similar to either sumatriptan doses. The 20mg dose was not compared to sumatriptan in either of these studies. There was a nominally significantly lower incidence of photophobia with eletriptan (either 40mg or 80mg) compared to Cafergot in study 307.

Table 25: Photophobia at Two Hours Post-treatment

Study	Dose	N	Photophobia Present At Baseline				Photophobia Absent At Baseline				p-value		
			Base Line	%	2HR	%	Base Line	%	2HR	%	vs. PBO	vs. low Dose Comparator	vs. high Dose comparator
102	20mg	290	218	(79.9)	79	(36.2)	55	(20.1)	48	(87.3)	<0.0001		
	40mg	296	231	(82.2)	111	(48.1)	50	(17.8)	46	(92.0)	<0.0001		
	80mg	312	236	(81.4)	115	(48.7)	54	(18.6)	51	(94.4)	<0.0001		
	Placebo	292	225	(81.5)	35	(15.6)	51	(18.5)	41	(80.4)			
103	40mg	507	391	(79.5)	193	(49.4)	101	(20.5)	86	(85.1)	<0.0001		
	Placebo	124	96	(78.7)	24	(25.0)	26	(21.3)	21	(80.8)			
104	40mg	184	124	(72.1)	63	(50.8)	48	(27.9)	41	(85.4)	0.0561	0 6874	0.8953
	80mg	180	126	(74.6)	75	(59.5)	43	(25.4)	38	(88.4)	0.0020	0 0630	0 1098
	S25mg	180	122	(73.1)	56	(45.9)	45	(26.9)	41	(91.1)			
	S50mg	181	123	(70.7)	59	(48.0)	51	(29.3)	46	(90.2)			
	Placebo	93	61	(69.3)	24	(39.3)	27	(30.7)	20	(74.1)			
105	40mg	141	109	(79.0)	66	(60.6)	29	(21.0)	20	(69.0)	0.9336		
	Placebo	133	93	(71.5)	48	(51.6)	37	(28.5)	35	(94.6)			
305	40mg	452	299	(70.0)	158	(52 8)	128	(30.0)	123	(96 1)	<0 0001		
	80mg	461	314	(71 5)	189	(60.2)	125	(28.5)	119	(95 2)	<0.0001		
	Placebo	238	172	(75.1)	33	(19 2)	57	(24.9)	43	(75.4)			
307	40mg	210	149	(72.3)	67	(45 0)	57	(27.7)	48	(84.2)	0 0416	0 0015	
	80mg	214	160	(76 9)	99	(61.9)	48	(23.1)	44	(91.7)	<0.0001	<0 0001	
	Cafergot	203	156	(79.2)	39	(25.0)	41	(20.8)	36	(87.8)			
	Placebo	105	77	(75 5)	19	(24.7)	25	(24.5)	25	(100.0)			
318	40mg	175	132	(79.0)	70	(53.0)	35	(21.0)	30	(85 7)	0.0033	0 0463	0.1854
	80mg	164	114	(70.8)	68	(59.6)	47	(29.2)	44	(93.6)	0 0001	0 0010	0.0084
	S50mg	181	131	(75.3)	54	(41.2)	43	(24.7)	35	(81.4)			
	S100mg	169	121	(76 1)	55	(45 5)	38	(23.9)	31	(81.6)			
	Placebo	84	60	(75 0)	18	(30 0)	20	(25.0)	16	(80 0)			

7.3.13 Phonophobia

The same 7 studies used to summarize photophobia data were used to summarize the effects of study medication on phonophobia. Phonophobia was present at baseline in approximately 65-75% of patients. The incidences of phonophobia at 2 hours are shown in Table 26 (sponsor table 2.8.4.8.4). All comparisons between eletriptan (all doses) and placebo were nominally significantly positive, with the exception of 40mg in study 307 (p=0.0557). The incidence of phonophobia was either numerically or nominally significantly lower with eletriptan use compared to sumatriptan in studies 318 and to Cafergot in study 107. There were little numerical differences between 40mg or 80mg and either sumatriptan 25mg or 50mg in study 104.

Table 26: Phonophobia at Two Hours Post-treatment

Study	Dose	N	Phonophobia Present At Baseline				Phonophobia Absent At Baseline				p-value		
			Base Line	%	2HR	%	Base Line	%	2HR	%	vs. PBO	vs. low Dose Comparator	vs. high Dose comparator
102	20mg	290	177	(64.8)	76	(42.9)	96	(35.2)	89	(92.7)	<0.0001		
	40mg	296	184	(65.5)	89	(48.4)	97	(34.5)	93	(95.9)	<0.0001		
	80mg	312	193	(66.6)	105	(54.4)	97	(33.4)	90	(92.8)	<0.0001		
	Placebo	292	179	(64.9)	32	(17.9)	97	(35.1)	83	(85.6)			
103	40mg	507	325	(66.2)	177	(54.5)	166	(33.8)	148	(89.2)	<0.0001		
	Placebo	124	85	(71.4)	22	(25 9)	34	(28.6)	24	(70.6)			

Study	Dose	N	Phonophobia Present At Baseline				Phonophobia Absent At Baseline				p-value		
			Base Line	%	2HR	%	Base Line	%	2HR	%	vs. PBO	vs. low Dose Comparator	vs. high Dose comparator
104	40mg	184	109	(63.4)	58	(53.2)	63	(36.6)	57	(90.5)	0.1788	0.9531	0 7977
	80mg	180	123	(72.8)	69	(56.1)	46	(27 2)	46	(100.0)	0.0292	0.2878	0.4506
	S25mg	180	109	(65.7)	57	(52.3)	57	(34.3)	52	(91.2)			
	S50mg	181	114	(65.9)	60	(52.6)	59	(34.1)	56	(94 9)			
	Placebo	93	56	(63.6)	26	(46.4)	32	(36.4)	26	(81.3)			
105	40mg	141	87	(63.5)	49	(56.3)	50	(36.5)	47	(94.0)	0.6003		
	Placebo	133	84	(64.6)	42	(50.0)	46	(35.4)	45	(97 8)			
305	40mg	452	294	(68.7)	169	(57.5)	134	(31.3)	123	(91.8)	<0.0001		
	80mg	461	317	(72.7)	188	(59.3)	119	(27.3)	117	(98.3)	<0.0001		
	Placebo	238	160	(69.9)	35	(21.9)	69	(30 1)	56	(81 2)			
307	40mg	210	152	(73.8)	69	(45.4)	54	(26.2)	50	(92 6)	0.0557	0.0028	
	80mg	214	146	(70.9)	92	(63.0)	60	(29.1)	56	(93.3)	<0.0001	<0.0001	
	Cafergot	203	147	(75.8)	44	(29.9)	47	(24.2)	40	(85.1)			
	Placebo	105	72	(70.6)	22	(30.6)	30	(29.4)	28	(93 3)			
318	40mg	175	137	(81.5)	77	(56.2)	31	(18.5)	27	(87 1)	0.0031	0 0612	0.0330
	80mg	164	121	(75 2)	72	(59.5)	40	(24.8)	37	(92.5)	0.0005	0.0112	0 0055
	S50mg	181	134	(76.1)	58	(43.3)	42	(23.9)	38	(90 5)			
	S100mg	169	124	(78 0)	54	(43 5)	35	(22 0)	29	(82.9)			
	Placebo	84	68	(85 0)	23	(33.8)	12	(15.0)	10	(83.3)			

7.3.14 Second Dose – Meta Analysis

The use of a second dose to treat either headache recurrence or initial non-response was examined in a prospectively planned meta analysis incorporating data from five phase 3 studies: 102, 104, 305, 307, and 318. These were the only 5 studies in which the second dose was randomized to drug or placebo. Subjects could take a second dose 2 hours after the first dose in all studies except 102, where the between-dose interval was at least 4 hours. The number of subjects included in the meta analysis are summarized below (Table 27, ISE page 34). Subjects are divided according their treatment sequence (first dose, second dose).

Table 27: Second Dose Meta Analysis – Number of Subjects Analyzed

		40/40	40/P	80/80	80/P
Recurrence	ITT	96	93	75	78
	Evaluable	76	78	58	56
Non-Response	ITT	234	230	188	208
	Evaluable	135	138	117	115

The next table shows the second dose baseline and 2-hour post-treatment results for those treating a headache recurrence (Table 28, ISE table 34). This analysis shows that those patients who received a second dose of eletriptan (either 40mg or 80mg) had a significantly higher 2-hour recurrence response rate and pain-free rates compared to those who received placebo as their second dose. It is important to remember that these are non-randomized groups since entry into each group is contingent upon first achieving a response with the initial dose—as a result, baseline imbalances in recurrent headache characteristics can occur. One can see that the 40 mg groups were relatively balanced with respect to the intensity of the headache recurrence, but the 80mg group who

received placebo as a second dose had a higher percentage of severe recurrent headaches compared to those to received 80mg as their second dose. The analysis used was an analysis of covariance (ANCOVA) using, among others, baseline severity as a covariate (sponsor section 8.15, Appendix V, page 9).

The conclusion is that a second dose was effective in the treatment of a headache recurrence. The second eletriptan dose was also associated with a greater proportion of patients with no nausea, vomiting, photophobia, or phonophobia.

Table 28: Second Dose Meta Analysis for Headache Recurrence

	40/40	40/P	80/80	80/P
Moderate at baseline	67%	68%	79%	65%
Severe at baseline	31%	30%	20%	35%
Response rate	74%	33%	82%	28%
p-value	p< 0.0001	--	p< 0.0001	--
Pain-free rate	38%	13%	41%	11%
p-value	p= 0.0012	--	p< 0.0001	--

The meta analysis also examined the effects of a second dose for the treatment of a non-response to an initial dose of eletriptan. Of those who received eletriptan 40mg as initial treatment and failed to respond, 49% receiving a second dose of 40mg and 51% receiving placebo as the second dose responded to the second dose (p=0.6401). The results were similar for the 80mg dose. Of those who received eletriptan 80mg as initial treatment and failed to respond, 48% responded to a second dose of 80mg and 53% responded to placebo as the second dose (p=0.4247). The efficacy of a second dose to treat persistent pain was not demonstrated by this analysis.

7.3.15 Other Analyses

Functional impairment was assessed on a 4 point scale: 0=no disability, 1=can perform some activity, 2=can perform little activity, 3=bed rest. A functional impairment response was defined as a 2/3 at baseline and 0/1 at a particular time point. Among the eight outpatient adult and adolescent efficacy studies, over 80% had a functional impairment of 2 or 3 at baseline. Eletriptan functional impairment responses in adults were 50% or greater, with response rates generally higher in the high dose groups. Placebo functional response rates were 30.9% or less.

Eletriptan-treated patients generally used rescue medication less often than placebo patients. This was true in 7 of the 8 studies analyzed. In the last study (study 307), 22.9%, 15%, and 23.8% used rescue in the 40mg, 80mg, and placebo groups, respectively. The rescue rates seen for eletriptan were comparable to those seen in other studies, but the placebo rescue rate was unusually low. In this study, patients were allowed to take a second dose of medication for non-response after 2 hours, which in the case of placebo patients, the 2nd dose was either eletriptan 40mg or 80mg. This could explain the low need for rescue among patients who initially took placebo in this study.

Treatment acceptability among eletriptan patients was consistently higher compared to placebo treated patients.

In studies that treated three attacks (106, 305, 318, 104), the sponsor analyzed the proportion of patients who responded to at least 2 out of 3 or all 3 attacks. The results of this analysis are shown in Table 29 (ISE page 33).

Table 29: Consistency of Headache Response

Dose	102		305		318		104	
	≥2/3	3/3	≥2/3	3/3	≥2/3	3/3	≥2/3	3/3
20 mg eletriptan	68.4%	32.1%	--	--	--	--	--	--
40 mg eletriptan	77.3%	47.3%	66.2%	29.6%	63.4%	36.6%	54.1%	23.9%
80 mg eletriptan	81.8%	59.7%	64.8%	37.2%	79.0%	49.4%	63.8%	21.3%
25 mg sumatriptan	--	--	--	--	--	--	47.6%	21.4%
50 mg sumatriptan	--	--	--	--	52.8%	22.5%	44.8%	13.8%
100 mg sumatriptan	--	--	--	--	60.8%	24.1%	--	--
Placebo	15.8%	7.9%	--	--	28.6%	8.6%	34.9%	7.0%

All placebo patients in study 102, 318, and 104 received placebo as initial treatment for all three attacks. Placebo patients in study 305 received placebo for the initial attack, but received either 40mg or 80mg for attacks 2 and 3.

There was a dose-response relationship within each of the three studies that used a clinic based recruitment (102, 305, 318). That is to say, increasing doses of eletriptan were associated with increase proportion of patients who responded to at least 2 of 3 or 3/3 attacks. This pattern was seen in study 104, the population-based recruitment study, but only for those who responded to at least 2/3 attacks.

7.3.16 Adolescents

Study 105 enrolled adolescent migraineurs between the ages of 12-17. It compared 40mg to placebo in the treatment of an acute migraine. As in other studies, two-thirds had a moderate headache at baseline and one-third treated a severe headache. The response rates for 40mg at one hour and two hours were similar to that seen in the adult studies (27.3% and 57.2%); however the placebo response rates were very high (26.0%, 57.4%, at 1 and 2 hours, respectively) and there appeared to be no benefit of the 40mg dose over placebo in this study population.

There were several secondary parameters measured that indicated a possible benefit to the 40mg dose in this population. Recurrence rate in the eletriptan group was lower (9% vs. 26.7%, p=0.0059). Time to headache recurrence was longer (13.8 vs. 7.7 hrs) with the 40mg dose. Pain-free response rates at 1 and 2 hours were numerically, but not statistically, lower with the 40mg dose (4.3% vs. 3.1% at 1 hour, 22.5% vs. 14.7% at 2 hours, for 40mg and placebo, respectively). Subjects taking the 40mg dose used less rescue medication (31.9% vs. 39.1%) and also had higher rates of treatment acceptability (58.2% vs. 49.6%). These findings suggest to this reviewer that the sustained response rate may better a better primary efficacy parameter in this population in future studies.

7.3.17 Treatment of Aura for Headache Prevention

Study 306 enrolled migraine patients with aura and studied 80mg or placebo taken during an aura to measure the ability to prevent a headache. There were no statistically

significant difference between 80mg and placebo in its ability to prevent a headache in this setting. There were also no differences in the need for a second dose, treatment acceptability, or use of rescue medication. The median time to headache development between the two groups were similar (1.3 hrs and 1.0 hrs, for 80mg and placebo respectively), as was the duration of the aura symptoms (0.7 hrs and 0.8 hrs, respectively). The results showed that eletriptan was not effective in preventing the onset of a moderate or severe headache when given during the aura phase, and neither enhanced nor delayed the resolution of aura or onset of headache pain.

7.3.18 Subgroup Analyses

7.3.18.1 Age

Among the adult population, response rates were analyzed according to age strata (18-40, 41-64, and ≥65 years). Treatment response was consistent across age groups for 20mg (47.9-51.3%), 40mg (55-62.3%), and 80mg (63.8-78.6%). Placebo responses were similar for the 18-40 and 41-64 age groups (27% and 21.5%, respectively), but was much higher in the ≥65 age group (71.4%). There was a statistically significant treatment by age interaction (p-0.0134), likely due to the high placebo response rate in the elderly.

7.3.18.2 Gender

The response rates were generally consistent group by group between genders. There was neither a statistically significant treatment by gender interaction nor a statistically significant gender effect.

Table 30: Response Rates by Gender

	Male			Female		
	N	Response	%	N	Response	%
20 mg	65	38	(58.5)	337	161	(47.8)
40 mg	284	164	(57.7)	1586	962	(60.7)
80 mg	184	115	(62.5)	1209	802	(66.3)
Placebo	148	28	(18.9)	876	222	(25.3)

7.3.18.3 Race

There was no statistically significant race effect and no statistically significant treatment by race interaction among the four race groups analyzed (white, black, Asian, other).

7.3.18.4 Menstrual Migraine

The sponsor analyzed the effect of eletriptan on the treatment of a menstrual migraine in those women who treated a migraine that occurred within 1 day prior or four days after the onset of menses. There were six studies which collected such data: 102, 103, 104, 307, 314, and 318. The results are shown in Table 31 (ISE page 36). All doses of eletriptan were associated with a higher proportion of 2-hour responders compared to placebo.

Table 31: Treatment of Menstrual Migraine

Dose	N	2 Hour Response	p-value
20 mg Eletriptan	75	35 (46.7%)	0.0008
40 mg Eletriptan	274	176 (64.2%)	<0.0001
80 mg Eletriptan	194	132 (68.0%)	<0.0001
Placebo	155	40 (25.8%)	--

7.3.18.5 Oral Contraceptive/Hormonal Replacement

Response rates in all women were analyzed according to use of oral contraceptives or hormone replacement therapy (OC/HRT). Eletriptan was effective whether or not OC/HRT were used. Response rates were higher in women taking OC/HRT compared to those who did not (maximum effect seen with the 40mg dose: 65.4% with vs. 58.4% without). There was not a significant study treatment by OC/HRT interaction.

7.3.18.6 Migraine Prophylaxis

Response rates were analyzed in all patients according to the use of migraine prophylactic medications (beta blockers, tricyclic antidepressants, SSRI's, valproate, calcium channel blockers, flunarizine, methysergide). Eletriptan was effective in either group, but response rates were consistently higher in those who were not taking migraine prophylactic medications (nominal p=0.0091). There was not a statistically significant study treatment by prophylactic use interaction.

7.4 Sponsor's Efficacy Conclusions

Based on the results of the eletriptan clinical program, the sponsor concludes the following (ISE, page 5):

7.4.1 Primary Efficacy Conclusions

- Eletriptan (20, 40, and 80 mg) rapidly, reliably, and effectively treated the pain and other associated symptoms of acute migraine headache in adults with or without aura
- Eletriptan relieved migraine headache pain as early as 0.5 hours after dosing and demonstrated clearly superior reduction in, or eradication of, migraine headache pain one hour and two hours after dosing compared with placebo.
- Eletriptan exhibited a dose-response relationship for the headache response rate and pain- free rate.

7.4.2 Recurrence Conclusions

- Headache recurrence rates for subjects treated with eletriptan were low (generally under 30%).
- Eletriptan exhibited a dose-response relationship for recurrence, with the lowest recurrence rate being in the 80 mg group.
- A second eletriptan dose of the same strength was shown to be effective in treating headache recurrence that occurred within 24 hours of initial treatment.

7.4.3 Comparator Conclusions

- Eletriptan demonstrated statistically superior or similar results compared with oral sumatriptan in treating the pain and other associated symptoms of acute migraine headache.
- Eletriptan was statistically significantly superior to Cafergot in relieving headache pain and associated symptoms of acute migraine headache.

7.4.4 Secondary Efficacy Conclusions

- Eletriptan treatment resulted in statistically significantly lower incidences of nausea, vomiting, phonophobia, photophobia, and functional impairment than placebo treatment.
- Eletriptan treatment was associated with rates of subject acceptability that were statistically significantly higher than placebo or comparator.
- Rescue medication use among eletriptan-treated subjects was less than in subjects treated with placebo or comparator.

7.4.5 Population Subgroup Conclusions

- Eletriptan effectively treated migraine headaches in adults regardless of age, race, gender, baseline headache severity, duration of attack, or use of concomitant migraine prophylactic medication.
- Eletriptan effectively treated migraine headaches in female adults using concomitant oral contraceptives or estrogen-based hormone replacement therapy.
- Eletriptan effectively treated female adults with a migraine headache that occurred within one day prior to and four days after menstruation.
- Eletriptan was not shown to be statistically significantly better than placebo in relieving migraine headache pain in adolescents; however, there were trends favoring eletriptan in that eletriptan-treated subjects had statistically significantly less recurrence, as well as less use of rescue medication, higher rates of pain-free response, and greater rates of acceptability than placebo-treated subjects.

7.4.6 Other Conclusions

- Eletriptan was not shown to prevent the development of migraine headache pain when given during aura.
- Among subjects who did not respond by two hours to an initial dose of eletriptan and then took either a second eletriptan dose of the same strength or placebo, approximately half the subjects achieved a response two hours later whether the second dose was eletriptan or placebo. This indicates an ongoing effect of the first eletriptan dose rather than additional benefit provided by the second eletriptan dose.

7.5 Reviewer's Analyses

The sponsor has provided the results of 7 adequate and well-controlled trials which examined the efficacy of eletriptan in the treatment of acute migraine. The evidence for efficacy of all three doses (20mg, 40mg, 80mg) is quite robust and I found little need to repeat those analyses here. Instead, I chose to focus on issues related to product labeling. Specifically, I attempted to answer the following questions:

- What is the headache response rates during the first 4 hours of treatment for each dose?

- What is the probability of requiring remedication or rescue within 24 hours of initial treatment?
- Is the 80mg dose more effective than the 40mg dose?
- Is eletriptan effective at 30 minutes?

7.5.1 Methods

I used the efficacy datasets supplied by the sponsor to perform my own analyses of the data. These were supplied as electronic case report tabulations as SAS transport files, one for each study. I included data from the seven adult outpatient acute efficacy studies (102, 103, 104, 305, 307, 314, and 318). I created a pooled efficacy dataset containing headache diary information for every attack treated at every time point. I used efficacy data for the first attack only for my analyses.

7.5.2 Demographics

I analyzed basic demographic information for patients in each study to evaluate whether the treatment groups were reasonably balanced at baseline. I compared age, sex, race, and baseline headache intensity among all the studies (Table 32). Throughout this section, I use the abbreviation (RA) to designate a table derived from a reviewer analysis. Baseline characteristics were fairly balanced across studies.

Table 32: (RA) Baseline Demographic Information

Study	Dose	N	Age Mean	Gender Male n, %	Gender Female n,%	Race White n,%	Race Black n,%	Race Asian n,%	Race Other n,%	Baseline Headache Mod n,%	Baseline Headache Sev n,%	Nausea Absent n,%
102	20	290	41 5	44 15 2	246 84.8	274 94 5	10 3.4	2 0.7	4 1.4	217 74 8	73 25.2	102 35 2
	40	296	41.7	44 14.9	252 85.1	283 95.6	9 3.0	1 0.3	3 1 0	222 75 0	74 25.0	102 34.5
	80	312	41.9	32 10.3	280 89.7	298 95.5	9 2 9	1 0.3	4 1.3	226 72.4	85 27.2	108 34.6
	P	292	41.8	35 12.0	257 88.0	275 94.2	9 3 1	2 0 7	6 2.1	215 73.6	77 26.4	92 31.5
103	40	507	40.4	70 13.8	437 86.2	482 95.1	7 1.4	4 0.8	14 2.8	358 70.6	146 28.8	209 41.2
	P	124	40.8	10 8.1	114 91.9	113 91.1	4 3.2	1 0 8	6 4.8	72 58.1	52 41.9	51 41.1
104	40	184	35.3	34 18.5	150 81.5	125 67.9	53 28.8	3 1 6	3 1.6	140 76.1	44 23.9	108 58.7
	80	180	34.1	21 11.7	159 88.3	137 76.1	39 21.7	2 1.1	2 1.1	125 69 4	55 30.6	106 58 9
	P	93	35.2	15 16.1	78 83.9	69 74.2	21 22.6	1 1.1	2 2 2	67 72.0	24 25.8	58 62.4
	S25	180	35.3	37 20.6	143 79.4	137 76.1	41 22.8	1 0.6	1 0.6	129 71.7	51 28.3	95 52 8
	S50	181	34.7	43 23.8	138 76.2	128 70.7	53 29.3	0 0.0	0 0.0	132 72.9	49 27.1	105 58.0
305	40	452	41.3	75 16.6	377 83.4	449 99.3	0 0.0	2 0.4	1 0.2	274 60.6	175 38.7	155 34.3
	80	461	42.0	70 15.2	391 84.8	455 98.7	4 0.9	2 0.4	0 0.0	273 59.2	188 40.8	169 36.7
	P	238	41.8	46 19.3	192 80.7	236 99.2	0 0.0	2 0.8	0 0.0	137 57.6	101 42.4	78 32.8
307	40	210	39.8	30 14.3	180 85.7	209 99.5	1 0.5	0 0.0	0 0 0	112 53.3	97 46.2	67 31.9
	80	214	40.1	22 10.3	192 89.7	210 98.1	1 0.5	2 0.9	1 0.5	115 53.7	98 45.8	65 30.4
	C	203	39.7	28 13.8	175 86.2	202 99 5	1 0.5	0 0.0	0 0.0	108 53.2	94 46.3	60 29.6

Study	Dose	N	Age Mean	Gender Male n, %	Gender Female n,%	Race White n,%	Race Black n,%	Race Asian n,%	Race Other n,%	Baseline Headache Mod n,%	Baseline Headache Sev n,%	Nausea Absent n,%
314	P	105	41 5	14 13.3	91 86.7	104 99.0	0 0 0	1 1.0	0 0.0	54 51.4	51 48 6	33 31.4
	20	144	40 1	26 18.1	118 81.9	143 99.3	0 0.0	1 0.7	0 0 0	82 56.9	62 43.1	51 35.4
	40	135	41.4	21 15.6	114 84.4	135 100.0	0 0.0	0 0.0	0 0.0	68 50.4	63 46.7	47 34.8
	80	141	40.2	27 19.1	114 80.9	141 100.0	0 0.0	0 0.0	0 0.0	81 57.4	60 42.6	42 29.8
	P	142	41 3	29 20 4	113 79.6	142 100.0	0 0.0	0 0.0	0 0.0	74 52.1	66 46.5	49 34 5
	S100	129	39.9	21 16.3	108 83.7	128 99.2	0 0 0	0 0.0	1 0 8	71 55.0	56 43 4	46 35 7
318	40	175	38.0	21 12 0	154 88.0	173 98.9	1 0.6	1 0.6	0 0.0	101 57.7	74 42.3	61 34.9
	80	164	39.9	22 13.4	142 86.6	163 99.4	0 0 0	0 0.0	1 0.6	97 59.1	65 39 6	55 33.5
	P	84	37.5	9 10.7	75 89.3	83 98.8	0 0 0	1 1 2	0 0.0	48 57.1	36 42.9	27 32 1
	S100	169	38.2	21 12.4	148 87.6	168 99.4	0 0.0	1 0 6	0 0 0	96 56.8	73 43.2	47 27 8
	S50	181	37 4	19 10.5	162 89 5	181 100.0	0 0 0	0 0 0	0 0.0	105 58.0	76 42.0	67 37 0

7.5.3 Time to Headache Response

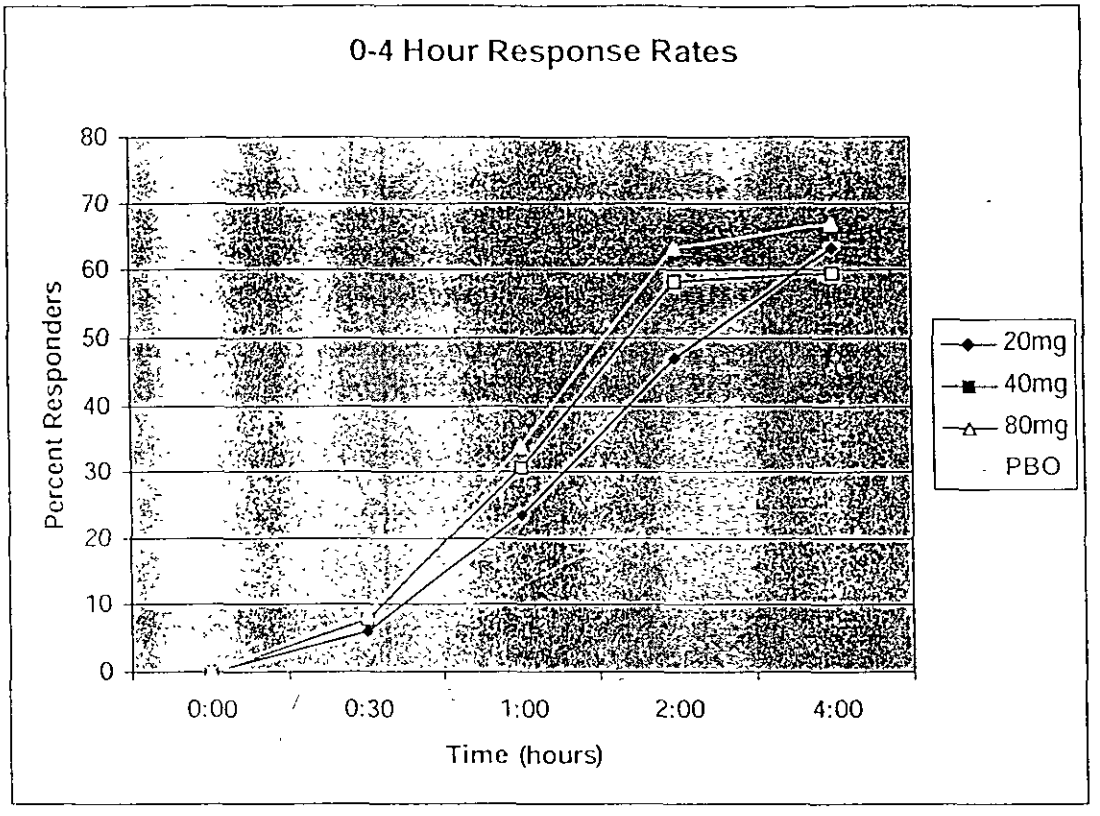
I used the efficacy data from the 7 adult outpatient studies to graph "time to response" within 4 hours. There were 5,986 patients which contributed data to this analysis. They are broken down by study and treatment in the following way:

Table 33: (RA) – Time to Headache Response – Patient Population

Study	N	20mg	40mg	80mg	PBO	Cafergot	Suma 25mg	Suma 50mg	Suma 100mg
102	1190	290	296	312	292	0	0	0	0
103	631	0	507	0	124	0	0	0	0
104	818	0	184	180	93	0	180	181	0
305	1151	0	452	461	238	0	0	0	0
307	732	0	210	214	105	203	0	0	0
314	691	144	135	141	142	0	0	0	129
318	773	0	175	164	84	0	0	181	169
Total	5986	434	1959	1472	1078	203	180	362	298

I did not perform a Kaplan-Meier survival analysis on this data because the protocols did not use a stopwatch approach. All responses are measured in 30 minute or 1 hour intervals, resulting in large and abrupt steps in the Kaplan-Meier curves. Therefore, I plotted the response rate at each time point between 0-4 hours to obtain a general trend of response rates over time. This is shown in Figure 3. I remind the reader that rescue was permitted after 2 hours in most studies (all but study 102). This figure differs from the sponsor's (Table 20, and Figure 2, page 28) in that mine includes the 4 hour time point (which admittedly is confounded by the use of rescue medication).

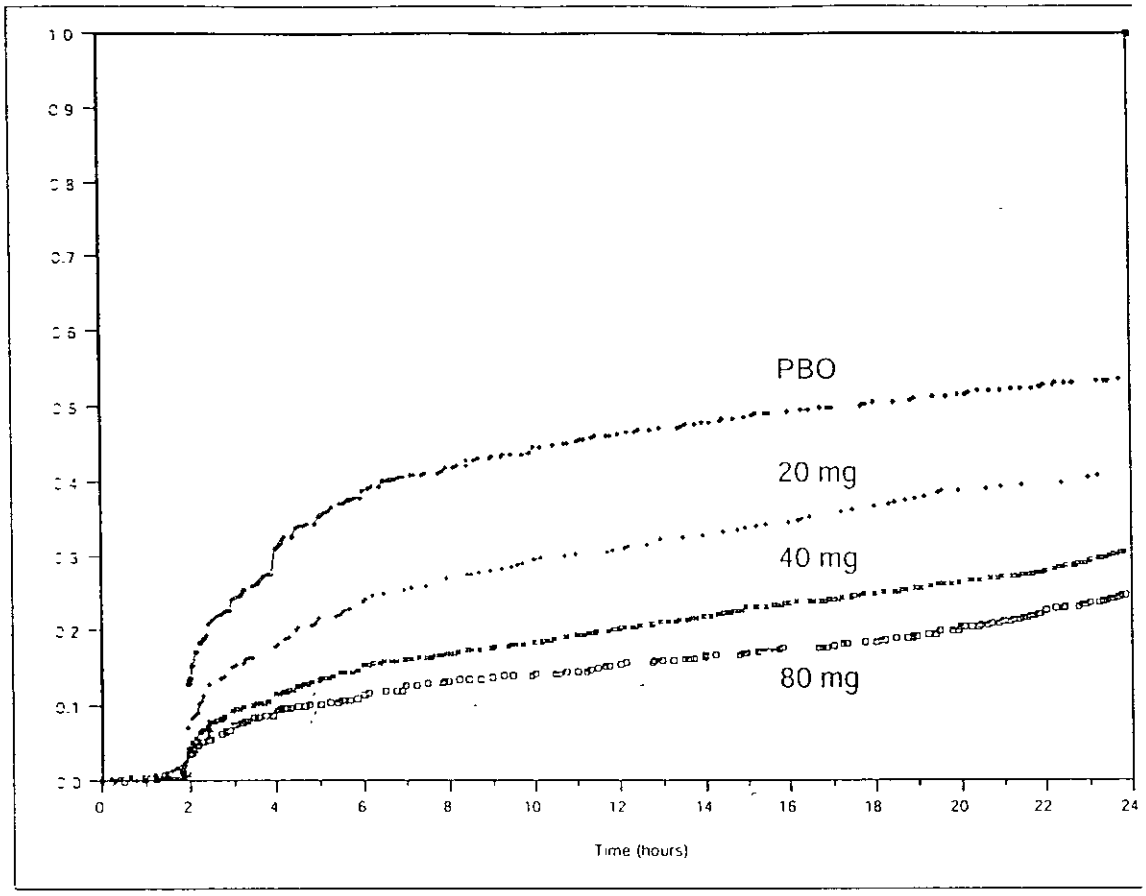
Figure 3: (RA) – 0-4 Hour Headache Response Rates



7 5.4 Time to Remedication

I used the efficacy results from the first attack of the 7 adult outpatient studies to generate a Kaplan-Meier survival plot of the probability of requiring remedication (either a 2nd dose or rescue) within 24 hours of initial treatment. The sponsor provided a variable which documented the time to rescue for each patient, and I calculated the time to the second dose (if one was taken) by subtracting the time the 2nd dose was taken minus the time the first dose was taken. I then took the smaller of the two (time to rescue vs. time to 2nd dose) to obtain a time to remedication. Anyone not taking a 2nd dose or rescue within 24 hours was censored to 24 hours. I used the same 5,986 patients which contributed efficacy data for the first attack of the 7 studies. Of these, 4,943 received eletriptan or placebo (the remaining received an active comparator, either Cafergot or sumatriptan). The probability of remedication within 24 hours is shown in Figure 4. The graph indicates that patients taking placebo had the highest probability of remedication within 24 hours and patients on eletriptan 80mg had the lowest.

Figure 4: (RA) – Probability of Remedication 0-24 Hours



7.5.5 Efficacy of 80mg vs. 40mg

The sponsor wishes to market three doses: 20mg, 40mg, and 80mg. The 20mg and 40mg doses both appear to be quite effective. I chose to review the question whether the 80mg dose is more effective than the 40mg dose. I chose to analyze data from the studies that used both the 40mg and 80mg dose. I used the efficacy data from the first dose from the first attack of each study. There were 6 studies which used both the 40mg and 80mg doses to treat an initial attack. These were: 102, 104, 305, 307, 314, and 318. I would like to note that this was not a primary analysis in any of the studies and such an analysis presented here is merely exploratory or descriptive. The nominal p values presented have no statistical inferential meaning.

The results for the pooled analysis for each time point is shown in Table 34. The 80mg dose was numerically superior to the 40mg dose at each time point, and it reached nominal significance at all time points. Study 314 was the only study to look at a 1.5 hour

time point, and again the 80mg was numerically superior to the 40 mg (61% vs. 51%) but it failed to reach nominal significance (p=0.11), likely due to the small sample size (n=126 and 123, respectively).

Table 34: (RA) – Pooled Analysis, 80mg vs. 40mg

Time Point (hours)	80mg	40mg	nominal p*
0.5	127/1235 (10.3%)	94/1222 (7.7%)	0.025
1.0	498/1419 (35.1%)	440/1416 (31 1%)	0.023
2.0	931/1417 (65.7%)	857/1410 (60.8%)	0.007
4.0	983/1090 (90.2%)	889/1029 (86.4%)	0.007

* chi-square

The next table (Table 35) shows the 2-hour headache response rate for each individual study, comparing the 80mg vs. 40mg dose. There was a numerical advantage of 80mg over 40mg in all studies except 102, and nominal significance is seen in 2 of the 6 studies (307 and 314).

Table 35: (RA) – Two-Hour Headache Response Rates, 80mg vs. 40mg

Study	80mg	40mg	nominal p*
102	176/300 (58.7%)	176/288 (61.1%)	0 5455
104	124/177 (70.0%)	113/181 (62.4%)	0 1273
305	289/448 (64.5%)	272/443 (61.4%)	0.3366
307	142/210 (67.6%)	111/207 (53.6%)	0.0034
314	92/120 (76.7%)	76/120 (63.3%)	0.0242
318	108/162 (66.7%)	109/171 (63.7%)	0.5757

* chi-square

7.5.6 Efficacy at 30 minutes

The sponsor has a statement in draft labeling that eletriptan is effective as early as 30 minutes; therefore I chose to analyze the efficacy of the 20mg, 40mg, and 80mg doses at 30 minutes. The 30 minute time point was not a primary designated efficacy time point in any of the studies. Therefore, this analysis is exploratory only. I collected efficacy data for each patient who recorded their pain intensity at 30 minutes from all 7 adult outpatient efficacy studies. The breakdown of patients by study and treatment group is shown in Table 36. Of the 5,986 patients with efficacy data in the seven studies, 5,187 reported efficacy data at 30 minutes (one patient in study 314 taking Sumatriptan 100mg had efficacy data at 30 minutes recorded twice. I deleted the second duplicate record

from analysis). Study 307, the study using Cafergot as a comparator agent, did not collect 30 minute efficacy data and is therefore not included in this analysis.

Table 36: (RA) Efficacy at 30 Minutes – Patient Population

Study	N	20mg	40mg	80mg	PBO	Suma 25mg	Suma 50mg	Suma 100mg
102	1178	287	294	308	289	0	0	0
103	626	0	503	0	123	0	0	0
104	810	0	180	179	93	178	180	0
305	1128	0	442	452	234	0	0	0
314	679	144	131	137	138	0	0	129
318	766	0	175	161	83	0	180	167
Total	5187	431	1725	1237	960	178	360	296

The 30-minute headache response rate for the pooled population is shown in Table 37. All three doses of eletriptan were numerically superior to placebo at 30 minutes, and the response rates reached nominal significance for 40mg and 80mg. All three doses of sumatriptan were also nominally significantly better than placebo at 30 minutes. I point out, however, that response rates were numerically very small: 10% or less. Therefore, efficacy at 30 minutes is somewhat misleading because the vast majority of patients did not achieve a response at that time point, regardless of the treatment used.

Table 37: (RA) – Pooled Analysis, 30-Minute Headache Response Rate

Dose	Response Rate (%)	Nominal p* (vs. PBO)
20mg	25/431 (5.8%)	0.34
40mg	148/1721 (8.6%)	<0.001
80mg	127/1235 (10.28%)	<0.0001
PBO	44/960 (4.58%)	--
Suma 25mg	16/178 (8.99%)	0.0245
Suma 50mg	29/360 (8.06%)	0.0177
Suma 100mg	27/296 (9.12%)	0.005

*chi-square

I present the 30-minute headache response rates for each study individually in Table 38. A numerical trend in favor of eletriptan and sumatriptan over placebo is seen in most studies (with the exception of study 104, the population-based recruitment study).

Table 38: (RA) – 30-Minute Headache Response Rates

Study	20mg	40mg	80mg	PBO	Suma 25mg	Suma 50mg	Suma 100mg
102	16/287 (5.57%)	25/294 (8.5%)	29/307 (9.45%)	11/289 (3.81%)			
103		54/499 (10.82%)		7/123 (5.69%)			
104		14/180 (7.78%)	11/179 (6.15%)	12/93 (12.9%)	16/178 (8.99%)	15/180 (8.33%)	
305		35/442 (7.92%)	49/452 (10.84%)	4/234 (1.71%)			
314	9/144 (6.25%)	7/131 (5.34%)	17/137 (12 41%)	8/138 (5.8%)			12/129 (9.3%)
318		13/175 (7.43%)	21/160 (13 13%)	2/83 (2.41%)		14/180 (7.78%)	15/167 (8.98%)

7.6 Reviewer's Efficacy Conclusions

From the data presented, I conclude the following:

1. Eletriptan 20mg, 40mg, and 80mg are all effective treatment for acute migraine, based on the effects on the 2-hour headache response rates, and associated migraine symptoms.
2. The 5mg dose, although numerically superior to placebo in study 302, was not shown to be statistically superior. Nonetheless, it is possible that doses lower than 20mg (*e.g.* 10mg or even 5mg) are effective, but this would require additional studies, with sufficient power, in order to establish this possibility.
3. There is evidence to suggest that the 40mg dose is better than 20mg, and that the 80mg dose is better than the 40mg dose.
4. Eletriptan vs. Sumatriptan: in the two studies that used sumatriptan and excluded sumatriptan non-responders (104 and 318), eletriptan 40mg appeared to beat sumatriptan 50mg and 100mg in study 318 but failed to beat sumatriptan 25mg and 50mg in study 104. Eletriptan 80mg beat sumatriptan 25mg and 50mg in study 104 and beat sumatriptan 50mg and 100mg in study 318. (As I will note in my safety review below, eletriptan 80mg also has higher incidences of adverse events compared to sumatriptan 100mg).
5. Recurrence: treatment with eletriptan was generally associated with decreased incidence of recurrence within 24 hours.
6. Second dose: treatment with a second dose of eletriptan for recurrence was generally effective. However, the use of a second dose to treat persistent pain was not shown to be effective.
7. Adolescents: the efficacy of eletriptan to treat migraine in adolescents was not established in the single outpatient adolescent study (study 105). This was possibly due to a high placebo response rate (~57%).
8. Migraine Aura: Eletriptan was not effective in preventing the onset of a moderate or severe headache when given during the aura phase, and neither enhanced nor delayed the resolution of aura or onset of headache pain.

8. Integrated Review of Safety

8.1 Background

The safety database for the sponsor's integrated summary of safety contains exposure and safety data on 5,562 separate individuals who received eletriptan (5,033 in the phase 2/3 program and 529 in clinical pharmacology studies). Since many subjects participated in more than one study (*e.g.*, randomized controlled trial and also an open label long-term extension), the actual number of non-unique patients across all studies is 6,950, as shown in Table 39 (ISS page 1). The sum of all clinical pharmacology studies is greater than the sum of the oral and i.v. studies since it includes other patients who received other experimental formulations. The sum of all phase 2/3 studies is less than the sum of the four study types since there was overlap between the active comparator studies and the other groups.

*Table 39: All Studies – Number of Subjects Treated with Eletriptan**

Study Type	Total	
Oral Dosing Clinical Pharmacology	401	
Intravenous Dosing Clinical Pharmacology	106	
All Clinical Pharmacology Studies		*531*
Single Attack, Placebo Controlled Studies	1371	
Multiple Attack, Placebo Controlled Studies	3473	
Active Comparator, Placebo Controlled Studies	1638	
Long Term Phase 3 Studies	1309	
All Phase 2/3 Studies		*6419*
All Studies		*6950*

*Patients who participated in more than one study (*e.g.*, RCT and extension) are counted more than once. There were 5,562 unique patients exposed to eletriptan.

A total of 1273 subjects received placebo in the clinical development program (219 in clinical pharmacology studies, and 1054 in phase 2/3 studies). Some patients received both eletriptan in placebo. This occurred in some clinical pharmacology studies using a cross-over design. Some patients received both eletriptan and placebo in phase 2/3 studies (*e.g.*, a second dose following eletriptan could have been either eletriptan or placebo). For the purposes of patient accounting, they are counted as receiving eletriptan. The 1054 placebo patients in the phase 2/3 studies only received placebo.

The sponsor's integrated summary of safety presents the data from 48 completed studies and 3 additional studies that were ongoing at the time of the NDA submission (308, 316, 317; safety cutoff date was 4/30/98).

The phase 2/3 program contained many studies employing a wide range of designs and treatment regimens, including single attack, short term multiple attack, and long term studies. For practical reasons, there was no placebo arm in the long term studies. Sumatriptan data are available only from single attack and short term multiple attack studies. Physician optimized treatment (POT) was used in two long term studies; however the majority of POT patients received sumatriptan. The sponsor divided the phase 2/3 studies in the following manner for purposes of the safety analysis:

Table 40: Safety Protocol Sets

All Phase 2/3 studies	1101, 102, 103, 104, 105, 108, 302, 302A, 302C, 305, 306*, 307, 314, 316, 317 and 318
Double blind, placebo controlled, single attack and first of short term multiple attack studies	102, 103, 104, 105, 302, 305, 307, 314 and 318
Double blind, placebo controlled, short term multiple attack studies	102, 103, 104, 305 and 318
Placebo controlled, active comparator studies	104, 314 and 318 (all sumatriptan)
Long term Phase 3 studies	108, 316 and 317

* In study 306, patients took study medication during an aura to prevent a headache

The first group (all phase 2/3 studies) is used for general discussion of the overall phase 2/3 safety dataset. It is not used for treatment comparisons due to the multiple varying designs used in the studies. The "single attack and first of short term multiple attack" grouping provides placebo controlled safety data from acute exposures to eletriptan (and sumatriptan as well). The "short term multiple attacks" studies provide both incidence data and frequency data. The "active comparator" studies include the three sumatriptan studies. As noted in my efficacy review, patients in studies 104 and 318 were not previously exposed to sumatriptan and represent the two least-biased studies for a comparison between the two triptans. Cafergot was used in only one study (307) and a safety comparison between eletriptan and Cafergot is contained in that individual study report. The "long term phase 3 studies contain safety data from two studies of identical design (108 and 317) and blinded data from a third (316).

The safety analysis includes incidences and severity of adverse events, the proportions of subjects who discontinued prematurely, the incidence of clinically significant laboratory abnormalities, and changes in vitals signs and ECG's. Serious adverse events, including deaths, are summarized separately. Safety data are also analyzed by important demographic subgroups including age, gender, and race.

For the acute studies, two approaches were used when reporting safety data. The first one reported the initial dose of medication taken, and the second reported the total dose taken for the attack. For the long term studies, the dose presented is the stabilized dose. Laboratory data were collected at scheduled clinic visits and not at fixed times relative to study dosing. Vital signs were recorded at the study centers and entered directly on the case report form. ECG's in Europe were interpreted by a cardiologist and the interpretation sent to the sponsor for manual data entry. In the U.S., the ECG data were obtained electronically at the study sites and sent by telephone to a single company where the ECG trace was produced and interpreted by a cardiologist. Data were sent to the sponsor in files for electronic data entry. In phase 2/3 studies, vital signs and ECG's were obtained at scheduled clinic visits and not at fixed times relative to study dosing. Therefore, it is not possible to detect acute or transient effects of the drugs on vital signs and ECG's from these studies.

8.2 Deaths

There were 5 deaths in the eletriptan clinical development program across all phase 1/2/3 trials as of 4/30/98. Three of the five deaths were in patients who received eletriptan. The fourth death was a patient taking sumatriptan under physician optimized treatment (POT)

during a long term extension study. The fifth death was on blinded therapy at the time, and is characterized as such in the sponsor's summaries; however, the blind was subsequently broken and the patient was taking eletriptan. A summary table of the deaths is shown in Table 41 (ISS page 73).

Table 41: Deaths in the Clinical Development Program

	Eletriptan	PBO	Sumatriptan/ POT	Cafergot	Blinded Rx
Number of Subjects	6950	1273	1170	203	411
Duration of Observation (Subject Years)	1281.1	48.8	241.2	3. 9	220.7
Deaths:					
On Treatment or within 30 days of End of Treatment	2	0	0	0	0
>30 days after End of Treatment	1	0	1	0	1*

*later determined to be on eletriptan therapy

The mortality rates based on 100 person-years of exposures were 0.2 for eletriptan and 0.4 for sumatriptan. The reported death on "blinded treatment" (study 316) who subsequently was found to have received eletriptan is not included in this total since the duration of observation data cannot be derived while all other subjects in that study remain blinded. The five deaths are discussed individually below. The investigators did not attribute any of the deaths to study medication. I agree with that assessment.

004-95010004
This was a 22 year old female who received a single dose of eletriptan 80mg. Three days later she was involved in a car accident and she died after an additional 10 days from severe head injuries.

104-50910524
This was a 45 year old female was randomized to receive eletriptan 40mg. She subsequently died from an acute cerebral infarction. It could not be determined if any study drug had been taken prior to her death, but post-mortem analysis of body tissues revealed no detectable levels of eletriptan. The cause of the cerebral infarction was unknown.

The case report form provides little additional information. She underwent screening on 6/25/97. Medication for the first attack was dispensed on 7/14/97. She was found dead on 7/29/97. Cause of death was listed as "hemorrhagic cerebral infarction" but there is no mention how this diagnosis was made. Actual date of death was suspected to be 7/26/97, but it is not clear from the CRF why this date was suspected. There is no indication that study medication was taken.

302C-00660466
This was a 46 year old female who received five doses of eletriptan 20mg prn over a ten week period. She had a history of anxiety and depression and committed suicide four days after the last dose.

108-50580749 (sumatriptan)
This was a 61 year old female who treated four migraine attacks with sumatriptan 50mg prn over a four-month period. Two weeks after the last dose, a benign insulin producing pancreatic tumor was discovered and following its surgical removal she developed an infected pancreatic pseudocyst and pancreatitis and subsequently died of cardiac arrest.

316-00920211 (blinded therapy → eletriptan)
This was a 51 year old female who received eletriptan 20mg prn over a nine month period, then 40mg prn over a ten month period. Fifty-five days after her last dose, she committed suicide following a period of untreated depression.

8.3 Serious Adverse Events

Serious adverse events were defined as those events that were fatal, life threatening, resulted in permanent disability, required inpatient hospitalization or prolongation of a hospital stay, or resulted in congenital abnormality/birth defect. Additional events may be considered serious if they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

For the 6,950 subjects who received eletriptan in the clinical development program, there were 92 serious adverse event (SAE) cases as of 4/30/98. Six SAE's were reported from the 988 who received placebo and 20 cases were reported from the 1170 who received either sumatriptan or physician optimized therapy (POT). Table 42 (ISS page 70) summarizes the SAE's reported in phase 1/2/3 trials. The rates for SAE's are shown in Table 43. As one can see, the rates were comparable between eletriptan and sumatriptan, and lower than the rates seen in placebo treated patients.

Table 42: Summary of Serious Adverse Events

	Eletriptan	PBO	Sumatriptan/ POT	Cafergot	Blinded Rx
Number of Subjects	6950	1273	1170	203	411
Duration of Observation (Subject Years)	1281.1	48.8	241.2	3. 9	220.7
Serious Adverse Events: All Cases Reported	92	6	20	0	26
Related to Study Drug	4*	0	0	0	0

*three are related to eletriptan, 1 related to eletriptan/propranol

Table 43: Rates of Serious Adverse Events

	SAE	pt-yrs	Rate (per 100 pt-yrs)
Eletriptan	92	1281.1	7.2
Placebo	6	48.8	12.3
Sumatriptan	20	241.2	8.3
Cafergot	0	3.9	0

The most commonly reported SAE's for eletriptan treated patients were headaches, migraines, or aggravation of migraines (10 cases, vs. 1 on placebo), various neoplasms (7 cases vs. none on placebo). The seven neoplasms were basal cell carcinoma (2), breast cancer (3), unspecified (2) and medical/surgical/health service procedures (25 cases vs. 1 on placebo.

There were four eletriptan-associated SAE's that were attributed to treatment. These are described below. A complete listing off all the serious adverse events reported in all clinical studies can be found in Table 72, Appendix A - page 112.

211-01410005
This was a 54 year old female who participated in a phase 1 coronary angiography study (study 211). She had an extended hospitalization after experiencing chest tightness and coronary vasospasm after she received 50 µg/kg intravenous dose of eletriptan. The subject reported mild chest tightness soon after the eletriptan infusion and angiography documented 60-70% constriction of the right proximal coronary artery The constriction resolved spontaneously within 30 minutes, but the sensation of chest tightness continued and was not relieved by glyceryl trinitrate. ECG showed no ischemia or significant changes from baseline The patient was kept overnight for observation and discharged the following morning with no symptoms. The chest tightness was not felt to be due to vasospasm since the symptoms did not improve with nitrates and did not resolve when the vasospasm resolved. The investigator concluded that the chest tightness and vasospasm were related to eletriptan but not related to each other. The investigator considered that the coronary artery constriction was most likely due to contact with the right coronary catheter. Published data indicate that coronary spasm occurs in approximately 3% of coronary angiograms and is largely due to catheter tip irritation.

305-02040283
This was a 50 year old female with a history of cholelithiasis who was hospitalized with elevated SGOT/SGPT after presenting to the emergency department with severe tightness of the throat. The subject took four doses of eletriptan 80mg over a period of 23 days and the throat tightness started approximately four hours after the final dose Her peak AST was 129 IU/L (ULN 19 IU/L) and ALT was 304 IU/L (ULN 23 IU/L). She had concomitant increases in GGT and LDH. The severe throat tightness lasted one hour The liver enzyme abnormality resolved in approximately 2 weeks although her GGT remained moderately elevated. ECG's were all normal, hepatitis serology was negative and there was no history of alcohol intake. The Epstein-Barr antigen was positive. Concomitant medications included dimenhydrinate, estradiol, and levonorgestrel, and metoprolol. The elevated liver enzymes and throat tightness were considered drug related.

306-00030344
This was a 38 year old female who developed moderate dizziness, severe muscular weakness, severe tiredness, moderate feeling of drunkenness and moderate incoherent speech after taking eletriptan 80mg during an aura. She did not seek medical attention and the symptoms resolved spontaneously. The investigator summarized the symptoms as either complicated migraine or a transient ischemic attack and considered them serious (as they represented a hazard to the subject) and related to treatment. The same subject had taken two doses of 40mg previously without a similar episode. She had a history of slurred speech during previous migraine attacks, though less severe than this episode.

222-02120013
The fourth eletriptan-related SAE listed in Table 42 was that of a 34 year old female who received eletriptan 80mg and propranolol 160mg in a drug-drug interaction study (study 222). She suffered bronchial asthma three months after completing study treatment. The investigator considered the event was causally related to propranol treatment.

8.4 Dropouts

8.4.1 Overall Profile of Dropouts

Of the 6,419 subject who received eletriptan in phase 2/3 studies, 1,299 (20.2%) discontinued the study prematurely. Table 44 (ISS page 10) gives the reasons for discontinuations. The proportion of discontinuations for each treatment groups were comparable among eletriptan, physician optimized therapy (POT) and placebo. The proportion of discontinuations were higher for sumatriptan (40.8%) and lower for Cafergot (1%) but the numbers were very small for the latter and the data for Cafergot come generally from one acute study where the opportunity to discontinue was small.

The proportion who discontinued for reasons due study drug were higher for eletriptan and POT (4.3% and 4.8%, respectively) than for other treatments.

Table 44: Discontinuations from Phase 2/3 Studies

	Number of Subjects (%)				
	Eletriptan	Sumatriptan	Cafergot	POT	Placebo
Total Treated	6419	892	203	278	1054
Discontinued	1299 (20.2)	364 (40.8)	2 (1.0)	73 (26.3)	206 (19.5)
Related to Study Drug	273 (4.3)	29 (3.3)	2 (1.0)	13 (4.7)	28 (2.7)
Adverse Event	113 (1.8)	9 (1.0)	2 (1.0)	0 (0.0)	10 (0.9)
Laboratory Abnormality	7 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Insufficient Response	153 (2.4)	20 (2.2)	0 (0.0)	13 (4.7)	16 (1 5)
Not Related to Study Drug	1026 (16.0)	335 (37.6)	0 (0.0)	60 (21.6)	178 (16.9)
Adverse Event	52 (0.8)	9 (1.0)	0 (0.0)	3 (1 1)	4 (0.4)
Laboratory Abnormality	13 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0 2)
Other	961 (15.0)	325 (36.4)	0 (0.0)	57 (20.5)	172 (16.3)

When taking into account observation time, the rates for discontinuations per year of observation were 1.0 for eletriptan, 4.7 for placebo, 4.2 for sumatriptan, and 0.5 for both Cafergot and POT indicating that eletriptan use was not associated with an unusually high rate of discontinuation.

The discontinuation incidences among those enrolled in short term, multiple attack studies were also comparable between eletriptan and placebo. Of the 3,466 who received eletriptan in short term studies, 833 (24%) discontinued prematurely, compared with 195 of 666 placebo patients (29.3%). The incidence of discontinuations felt to be due to the study medication were also comparable between eletriptan and placebo (2.9% vs. 3.6%, respectively).

In single attack studies, discontinuations were very low as there was little chance to dropout with such a design. The dropout rates for all causes were 1.2% for eletriptan and 2.5% for placebo.

In placebo controlled, sumatriptan comparator studies (104, 304, 318), discontinuation rates for eletriptan, sumatriptan, and placebo were comparable: 28.4% (319/1124) of eletriptan treated patients discontinued prematurely, compared with 28.8% (92/319) who discontinued placebo, and 41% (345/841) who discontinued sumatriptan.

In long-term studies (108, 317, 316), data remained blinded for study 316 as of 4/30/98, the cutoff date for the NDA. This study employed a sumatriptan control arm. Studies 108 and 317 were both open label, and used physician optimized therapy (POT) as control. In these studies, patients were stabilized on doses of 40mg or 80mg after a six attack run-in period. It's important to note that these were not randomized dose groups. The majority of POT patients (245/278, or 88%) took sumatriptan. Of 1309 patients who received eletriptan in long-term studies, 351 (26.8%) discontinued prematurely, compared with 73/278 (26.3%) of those on POT. A more detailed account of these discontinuations is shown in Table 45 (ISS page 15). The table shows that the majority of discontinuations to

eletriptan occurred during the 6-headache run-in phase, during which time the eletriptan dose was not stabilized (NS). Treatment related AE's accounted for discontinuations in 43 (3.3%) of eletriptan patients, but no POT treated subject. This can be explained by the design of these studies. Investigators were instructed to discontinue any eletriptan patient who didn't tolerate therapy, whereas patients who didn't tolerate a particular POT treatment were not discontinued, but instead were switched to another form of treatment.

Table 45: Discontinuations from Long-Term Phase 3 Studies

	Eletriptan 40mg	Eletriptan 80mg	Eletriptan NS	POT
Total Treated	390	486	433	278
Discontinued	46 (11.8)	81 (16.7)	224 (51.7)	73 (26.3)
Related to Study Drug	12 (3.1)	28 (5.8)	68 (15.7)	13 (4.7)
Adverse Event	2 (0.5)	8 (1.6)	33 (7.6)	0 (0.0)
Laboratory Abnormality	1 (0.3)	2 (0 4)	2 (0.5)	0 (0.0)
Insuff. Clinical Response	9 (2.3)	18 (3.7)	33 (7.6)	13 (4.7)
Not Related to Study Drug	34 (8.7)	53 (10.9)	156 (36.0)	60 (21.6)
Adverse Event	8 (2.1)	5 (1.0)	17 (3.9)	3 (1.1)
Laboratory Abnormality	2 (0.5)	3 (0.6)	2 (0.5)	0 (0 0)
Other	24 (6 2)	45 (9.3)	137 (31.6)	57 (20.5)

NS = dose not stabilized

The sponsor also analyzed discontinuations by initial dose using the first attack data from the short term multiple attack studies. The discontinuations, by initial dose, are shown in Table 46 (ISS page 16). Discontinuations for all causes were higher for sumatriptan treated patients, but the numbers were smaller. The incidence of discontinuations due to study medication were similar for eletriptan and sumatriptan. The proportion of patients on eletriptan 80mg that discontinued due to a medication related event was twice as high as the 40mg group (3.4% vs. 1.7%), with most of the increase due to ADO's; however this was still comparable to placebo and sumatriptan 100mg groups (3.5% and 4.1%, respectively).

Table 46: Discontinuations in Short-Term Multiple Attack Studies, by Initial Dose

	PBO	Eletriptan			Sumatriptan		
		20mg	40mg	80mg	25mg	50mg	100mg
	N=627	N=290	N=1709	N=1227	N=180	N=362	N=169
Discontinued	19.8%	12.8%	18.0%	18.4%	31.7%	30.1%	32.0%
Related to Study Drug	3.5%	2.1%	1.7%	3.4%	1.7%	0.8%	4.1%
Adverse Event	1.1%	0.7%	1.0%	2.4%	1.1%	0.6%	0.6%
Insuff Clinical Response	2.1%	1.4%	0.6%	1.0%	0.6%	0.3%	3.6%
Unrelated to Study Drug	16.3%	10.7%	16.3%	15.0%	30.0%	29.3%	27.8%

Most of the clinical pharmacology studies were single dose studies and discontinuations were low, as might be expected. Of 401 eletriptan treated subjects, three (0.7%) discontinued due to AE or lab abnormality, compared with 1/159 (0.6%) for placebo patients. None was considered treatment-related.

In the two ongoing long-term safety studies that where the blind was broken by the time of the NDA submission (studies 108 and 317), the levels of discontinuations due to

laboratory abnormalities in these studies were low, with 12 eletriptan treated subjects (0.9%) and no POT treated subject discontinuing due to laboratory abnormalities. Five of the 12 eletriptan subjects (0.4%) discontinued due to laboratory abnormalities considered related to study treatment. All five were discontinued due to liver enzyme abnormalities, though not all were clinically significant. These cases are discussed in section 8.7 - Elevated , page 71.

The rates of discontinuation for insufficient clinical response in the long term studies 108 and 317 were similar for eletriptan and POT treated patients: 60/1309 (4.6%) and 13/278 (4.7%), respectively.

8.4.2 Adverse Events Associated with Dropouts

When analyzing the adverse dropouts (ADO's), the sponsor used a different algorithm to identify these patients. They used tables generated from "final status" pages of case report forms instead of those generated from adverse event pages (as was done for Table 44). The numbers generated from the "final status" pages are more accurate since they include AE's that occurred up to 7 days after treatment. This resulted in different number reported than those in Table 44. This is their explanation for the discrepancy.

Among all patients treated in all studies, 2.2% of eletriptan treated patients dropped out due to an adverse events, compared with 1.7% for sumatriptan and 1.1% for placebo (Table 47, adapted from sponsor table 2.8.6.2.3).

Table 47: Incidence of Adverse Dropouts from Phase 2/3 Studies

Treatment	n	%
Eletriptan (N=6419)	142	2.2
Placebo (N=1054)	12	1.1
Sumatriptan (N=892)	15	1.7
Cafergot (N=203)	2	1.0
POT (N=278)	1	0.4
Blinded therapy (N=411)	10	2.4

The adverse events associated with dropouts were varied and were similar to adverse events reported with triptan use in general. No single eletriptan associated ADO occurred with an incidence greater than 0.4%. The most common ADO's are shown in Table 48 (adapted from sponsor table 2.8.6.2.3). All occurred with similar incidences among the three treatment groups listed (eletriptan, placebo, sumatriptan) with the exception of chest pain. There were 17 ADO's due to chest pain for eletriptan (0.3%) but no cases for either placebo or sumatriptan (0%). A more detailed table of adverse dropouts, organized according to body system, is contained in Table 73, Appendix B - page 115.

Table 48: Most Common Adverse Dropouts in Phase 2/3 Studies

ADO	Eletriptan n, (%)	PBO n, (%)	Sumatriptan n, (%)
Nausea	28 (0.4)	3 (0.3)	6 (0.7)
Dizziness	23 (0.4)	3 (0.3)	3 (0.3)
Asthenia	17 (0.3)	1 (0.1)	1 (0.1)

ADO	Eletriptan n, (%)	PBO n, (%)	Sumatriptan n, (%)
Chest Pain	17 (0.3)	0 (0)	0 (0)
Headache	10 (0.2)	2 (0.2)	1 (0.1)
Vomiting	16 (0.2)	3 (0.3)	1 (0.1)
Hypertonia*	10 (0.2)	0 (0)	0 (0)
Paresthesia	11 (0.2)	0 (0)	1 (0.1)
Somnolence	14 (0.2)	0 (0)	1 (0.1)

* includes sensation of tightness or stiffness, mostly in the neck/whole body

In the short term multiple attack efficacy studies, ADO's due to eletriptan were slightly higher (84/3466 or 2.4%) compared to placebo (11/666 or 1.7%). The AE's most commonly leading to discontinuation in the short term efficacy studies were asthenia, chest pain (usually reported as tightness or pressure), nausea and dizziness. Discontinuations due to laboratory abnormalities were low (8/3466 or 0.2% for eletriptan patients, and 4/666 or 0.6% for placebo treated patients). As might be expected, placebo patients discontinued for insufficient clinical response at more than double the rate seen for eletriptan treated patients (2.3% vs. 1.0%).

8.5 Adverse Events

8.5.1 Methods

Since the clinical development program contained studies employing various designs, the sponsor analyzed adverse event data using a number of protocol sets, as shown in Table 40: Safety Protocol Sets, page 47. The "single attack and first of multiple attack" and "short term multiple attack" protocol sets allow comparisons between eletriptan and placebo following short-term administration (1-3 migraines). The "active comparator" set includes data from studies including both placebo and sumatriptan control (108, 304, 318). The "long-term" protocol set contains two studies of identical design (108 and 317) and blinded data from a third (316). The clinical pharmacology studies provide additional adverse event data for oral and intravenous formulations.

The sponsor performed its analyses of adverse events based on treatment-emergent AE's, *i.e.*, AE's that were either first reported during the study or that worsened relative to baseline during the study. For completeness, they also include the incidence of all AE's regardless of treatment emergence, therefore including adverse events reported before dosing or more than seven days after dosing.

Important preferred terms are used throughout this section, and it's important to describe the investigator terms underlying them. The term "hypertonia" is used by the sponsor in a non-traditional way since it includes subjective sensations of tightness or stiffness, rather than true, objective evidence of increased muscle tone. The important preferred terms, with their investigator terms, are shown below:

- Chest pain: includes mostly chest tightness or pressure
- Vasodilatation: includes sensation of warmth or flushing, affecting the whole body or face/neck
- Dysphagia: includes mostly throat tightness or constriction

- Hypertonia: includes sensation of tightness or stiffness, mostly in the neck/whole body
- Paresthesia: includes tingling or abnormal sensation, mainly affecting the head and face

8.5.2 Adverse Events in All Phase 2/3 Studies

Of the 6,419 subjects who received eletriptan in all phase 2/3 studies, 3,409 (53.1%) had at least one adverse event and 2,469 (38.5%) had at least one treatment emergent, treatment related adverse event. Severe AE's (all causality) were reported by 11.6% of eletriptan treated patients and 2.2% had AE's that resulted in discontinuation (described in section 8.4, Dropouts, page 50). Severe AE's were considered treatment related in 7.3% and 1.8% resulted in discontinuation due to treatment related AE's. The rates of treatment emergent AE's reported per year of observation were 7.2 for eletriptan, 15.0 for placebo, 9.9 for sumatriptan, 45.1 for Cafergot, and 3.2 for POT.

For eletriptan, the COSTART body systems with the most frequent reports of AE's were "body as a whole," "digestive," and "nervous" systems. A summary of the most common treatment emergent AE's is presented in Table 49 (ISS page 21). The mean dose per attack (calculated as the sum of all doses divided by the total number of migraine attacks) were 66.7mg for eletriptan and 90.9mg for sumatriptan. One can see that the most common AE's reported for eletriptan are typical of those seen with other triptans: asthenia, nausea, dizziness, somnolence, etc.

Table 49: Adverse Events (≥3%) in All Phase 2/3 Studies

Body System COSTART Term	Eletriptan (N= 6419)		Placebo (N=1054)		Sumatriptan (N=892)		Cafergot (N=203)		POT (N=278)	
	A/C	T/R	A/ C	T/R	A/C	T/R	A/C	T/R	A/ C	T/R
Body as a Whole										
Abdominal pain	3.2	1.9	1.3	0.7	2.6	1.9	1.5	1.5	2.5	0.7
Asthenia	11.1	8.7	3.1	1.9	7.2	5.8	5.9	3.9	10.1	7.2
Back pain	3.3	1.4	1.4	0.0	1.8	1.2	0.5	0.5	8.3	2.5
Chest pain	4.0	3.6	1.0	0.8	2.4	2.1	3.0	2.5	5.4	4.7
Chills	1.6	1.1	1.4	1.0	1.0	0.8	3.0	2.0	1.4	0.4
Headache	5.5	2.3	3.5	2.0	4.0	2.0	2.5	0.5	5.4	1.8
Pain	2.6	1.6	0.5	0.2	1.3	0.8	0.0	0.0	4.0	2.5
Cardiovascular										
Vasodilatation	3.1	2.7	2.3	1.5	2.4	2.4	1.5	1.5	2.9	2.2
Digestive										
Diarrhea	2.2	0.9	1.2	0.3	2.2	1.3	4.9	3.0	2.2	1.4
Dry Mouth	3.8	3.6	2.5	2.4	3.7	3.3	3.0	3.0	0.0	0.0
Dyspepsia	2.4	1.4	0.7	0.6	2.6	1.5	3.4	2.5	1.8	1.1
Dysphagia	2.9	2.9	0.3	0.2	0.8	0.8	1.0	1.0	4.7	4.7
Nausea	10.5	6.4	5.6	3.3	9.2	4.9	9.9	5.4	13.3	7.2
Vomiting	4.1	1.4	5.0	2.0	4.5	1.5	5.9	2.0	5.4	1.1
Musculoskeletal										
Arthralgia	1.8	0.8	0.5	0.1	0.6	0.2	0.0	0.0	5.0	0.7