CLINICAL REVIEW

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Established Name	Almotriptan
(Proposed) Trade Name	Axert
Therapeutic Class	Triptan
Applicant	Johnson and Johnson
Priority Designation	S
Formulation	Almotriptan malate tablets
Dosing Regimen	12.5 mg
Indication	Migraine
Intended Population	Adolescents (12 - 17 years)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval for almotriptan for both 6.25 and 12.5 mgs doses in adolescent migraine patients 12 – 17 years of age. The sponsor complied with the terms of the written request and the trial efficacy data support this approval.

1.2 Risk Benefit Assessment

The review indicates the risks/benefits of almotriptan in adolescents 12 – 17 years of age mirrors that of adults and no new safety considerations are apparent in this population

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendations for other Post Marketing Study Commitments

None.

2 Introduction and Regulatory Background

AXERT® (almotriptan malate) is a selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist. AXERT for oral administration contains almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan.

AXERT tablets (N 21-001) was originally approved on 5/7/01 for oral tablets of 6.25 mg and 12.5 mg strengths to treat acute migraine with or without aura in adults. Development of almotriptan tablets was performed under IND 053854. The sponsor now seeks an indication for acute treatment of migraine with or without aura in adolescent patients 12 to 17 years of age. On 10/31/08, the sponsor submitted a supplemental NDA to fulfill the requirement of the written request (WR), for the approved drug product to support the amended labeling regarding the use of this drug product in the pediatric population (12 to 17 years).

The sponsor submitted proposed draft label in PLR format. The amended labeling includes changes to the "USE IN SPECIFIC POPULATIONS, Pediatric use and CLINICAL PHARMACOLOGY, Pharmacokinetics section of the full prescribing information. In their proposed labeling they also added data not yet reviewed by the Agency.

The sponsor submitted the following pediatric clinical study reports according to their pediatric plan in order to fulfill the required pediatric study commitments for PREA (Pediatric Research Equity Act):

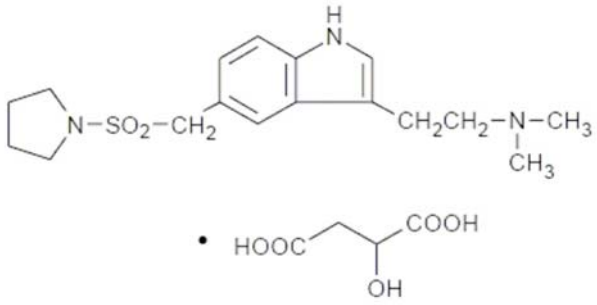
- One single dose pediatric PK study (12.5 mg, study: 638-CNS-0059-014)
- One efficacy dose ranging study (6.25 – 25 mg, study: 638-CNS-0059-015)
- One long term safety study (12.5 mg, study: CAPSS-368)

2.1 Product Information

Almotriptan malate, the active ingredient in AXERT® Tablets, belongs to the triptan class of drugs that function as selective 5-hydroxytryptamine (5-HT) agonists predominantly at the 5-HT1B/1D receptor. Its chemical name is 1-[[[3-[2-(Dimethylamino)-ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate (1:1) and its empirical formula is C17H25N3O2S-C4H6O5.

The chemical structure is shown below:

Figure 1: Almotriptan Malate Structure



2.2 Table of Currently Available Treatments for Proposed Indications

The following table summarizes medications used to treat migraine. However, most are not FDA-approved for the indication.

Table 1: Migraine Acute Therapies

Group 1 [b]	Group 2 [c]	Group 3 [d]	Group 4 [e]	Group 5 [f]
Specific Naratriptan PO Rizatriptan PO Sumatriptan SC, IN, PO Zolmitriptan PO Dihydroergotamine SC, IM, IV, IN Dihydroergotamine IV, plus antiemetic **Non-Specific** Acetaminophen, aspirin, plus caffeine, PO Aspirin PO Butorphanol IN Ibuprofen PO Naproxen sodium PO Prochlorperazine IV	Acetaminophen plus codeine PO Butalbital, aspirin, caffeine, plus codeine PO Butorphanol IM Chlorpromazine IM, IV Diclofenac K, PO Ergotamine plus caffeine, plus pentobarbital plus Bellafoline® PO Flurbiprofen PO Isometheptene CPD, PO Keterolac IM Lidocaine IN Meperedine IM, IV Methadone IM Metoclopramide IV Naproxen PO Prochlorperazine IM, PR	Butalbital, aspirin, plus caffeine PO Ergotamine PO Ergotamine plus caffeine PO Metoclopramide IM, PR	Acetaminophen PO Chlorpromazine IM Granisetron IV Lidocaine IV	Dexamethasone IV Hydrocortisone IV

[a] Table adapted from: Silberstein, SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55;754-762.Proven, pronounced statistical and clinical benefit (at least two double-blind, placebo-controlled studies and clinical impression of effect).

[b] Moderate statistical and clinical benefit (one double-blind, placebo-controlled study and clinical impression of effect).

[c] Statistically but not proven clinically or clinically but not proven statistically effective (conflicting or inconsistent evidence).

[d] Proven to be statistically or clinically ineffective (failed efficacy versus placebo).

[e] Clinical and statistical benefits unknown (insufficient evidence available).

The following are FDA-approved medications used for treating migraine:

Table 2: FDA Approved Migraine Medications

Brand Name	Generic Name	Manufacturer/Distributor	Indication for Adults*
Amerge tablets	naratriptan hydrochloride	GlaxoSmithKline	acute treatment of migraine attacks
Axert tablets	almotriptan malate	Ortho-McNeil Neurologics Inc.	acute treatment of migraine attacks
Frova tablets	frovatriptan succinate	Endo Pharmaceuticals	acute treatment of migraine attacks
Imitrex tablets, injection, nasal spray	sumatriptan succinate	GlaxoSmithKline	acute treatment of migraine attacks
Maxalt tablets and Maxalt-MLT orally disintegrating tablets	rizatriptan benzoate	Merck	acute treatment of migraine attacks
Zomig tablets, nasal spray; and Zomig-ZMT orally disintegrating tablets	zolmitriptan	AstraZeneca	acute treatment of migraine
Relpax tablets	eletriptan hydrobromide	Pfizer	acute treatment of migraine
Migranal nasal spray	dihydroergotamine mesylate	Valeant	acute treatment of migraine headache
Topamax tablets, sprinkle capsules	topiramate	Ortho-McNeil Neurologics Inc.	prevention of migraine headache
Depakote ER tablets	divalproex sodium	Abbott Laboratories	prevention of migraine headache
Blocadren tablets	timolol maleate	Merck	prevention of migraine headache
Inderal tablets, capsules	propranolol hydrochloride	AstraZeneca	prevention of migraine headache
Over-the-Counter Products			
Excedrin Migraine tablets, caplets	acetaminophen, aspirin, caffeine	Novartis Consumer Health	treatment of migraine
Advil Migraine capsules	ibuprofen	Wyeth Consumer Healthcare	treatment of migraine
Motrin Migraine Pain caplets	ibuprofen	McNeil Consumer & Specialty Pharmaceuticals	treatment of the pain of migraine headache

Source: FDA Consumer Magazine, 2006

The majority of FDA-approved migraine products are the triptans, (summarized in Table 3), including Axert (almotriptan), the subject of this review:

Table 3: Triptan Therapies Approved for Acute Migraine Treatment in the US

Trade (generic) Name	NDA	Date of FDA Approval	Route of Delivery
IMITREX Injection (sumatriptan)	20-080	December 28, 1992	Subcutaneous injection
IMITREX® Tablets (sumatriptan)	20-132	June 1, 1995	Tablet
IMITREX® Nasal Spray (sumatriptan)	20-626	August 26, 1997	Nasal spray
Zomig® (zolmitriptan)	20-768	November 25, 1997	Tablet
Amerge® (naratriptan)	20-763	February 10, 1998	Tablet
Maxalt® / Maxalt-MLT® (rizatriptan)	20-864/20-865	June 29, 1998	Tablet/orally dissolving tablet
Zomig-ZMT® (zolmitriptan)	21-231	February 13, 2001	Orally dissolvable tablet
Axert® (almotriptan)	21-001	May 7, 2001	Tablet
Frova® (frovatriptan)	21-006	November 8, 2001	Tablet
Relpax® (eletriptan)	21-016	December 26, 2002	Tablet
Zomig® (zolmitriptan)	21-450	September 30, 2003	Nasal spray

2.3 Availability of Proposed Active Ingredient in the United States

Axert, almotriptan, was approved for adult use in May 2001. The 5-HT1 receptor subtypes activated by triptan products mediate vasoconstriction in cranial arteries and in the vasculature of human dura mater. Besides their vasoconstrictor effects, triptans also stimulate 5-HT1 receptors on the peripheral terminals of the trigeminal neurons innervating cranial blood vessels where they induce peripheral neuronal inhibition through second-order neurons of the trigeminocervical complex. The actions appear to inhibit the effects of activated nociceptive trigeminal afferents and may contribute to the anti-migraine effect of triptans in humans.

These observations have led to the extensive triptan product development globally. The ingredient is widely available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The almotriptan (and other triptan) safety profile in adult patients with a clear diagnosis of migraine or cluster headache has been established and is summarized here. This sNDA, however, reviews safety and effectiveness of almotriptan in the adolescent population (12 – 17 years of age). At this time, no triptan is approved for migraine in adolescents.

While generally recognized as safe and effective, there have been class concerns raised since almotriptan's adult approval regarding, in particular, cardiac complaints. There have been fatalities within the triptan class due to cardiac causes. While perhaps vasospastic origin, it remains clearly undefined. Cerebrovascular events and fatalities have also been described, but this relationship is confounded by the presence of these complications in the migraine population in general. Other (non-coronary artery) vasospasm-type events have been described with triptan use including peripheral vascular and colonic ischemia and (rarely) transient and permanent blindness. A precise, clear relationship of these complications to the therapy, accompanied by an understanding of the pathophysiology, remains elusive, again reflecting the background migraine condition. The incidence of all of these disorders remains low, when the widespread use of triptans is considered.

Nevertheless because of the risk of myocardial ischemia and/or infarction and other adverse cardiac events, the almotriptan label clearly states that almotriptan should not be given to patients with documented ischemic or vasospastic CAD. Similarly almotriptan should not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation reveals satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The current label acknowledges the sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. The conclusion is that if, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, almotriptan should not be administered.

Still further, in patients whose risk factors predict CAD but who have a satisfactory cardiovascular evaluation, the almotriptan label strongly recommends first administration of almotriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. As a further safeguard, acknowledging cardiac ischemia can occur in the absence of clinical symptoms, the label suggests consideration be given to obtaining an electrocardiogram (ECG) during the interval immediately following the first use of almotriptan in these patients with risk factors.

The current label recommends patients who are intermittent long-term users of almotriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use the drug. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including AXERT, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Other issues that have been described include Cerebrovascular Events and Fatalities With 5-HT1 Agonists (cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events) which may be aggravated since migraine patients are already at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). 5-HT1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT1 agonists. Increases in blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT1 agonists. Problematic preclinical issues include binding to melanin-containing tissues and corneal opacities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The AXERT pediatric program, submitted to this NDA, includes 3 clinical studies (Table 4). The Pediatric Exclusivity Board, in conjunction with the Division, concluded they sponsor complied with all the criteria listed in the Pediatric Exclusivity Determination Checklist and granted exclusivity on 1/13/09.

The Phase I Study is reviewed in detail by the Clinical Pharmacology Reviewer and is mentioned in this review briefly.

Table 4: Table of Studies

Attacks in Adolescents

Protocol	Study Description	Study Treatments	No. of Subjects (Safety Population)
638-CNS-0059-014	Phase 1, single-center, open-label, single-oral-dose, parallel-group design to compare the pharmacokinetics and safety of almotriptan in adolescent (12-17 years) and adult (18-55 years) subjects with or without a history of migraine	Almotriptan 12.5 mg Oral / Single dose	18 adolescents 18 adults
638-CNS-0059-015	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging design to evaluate efficacy and safety of almotriptan for migraine attack in adolescent (12-17 years) subjects with a history of migraine with or without aura	Placebo Almotriptan 6.25 mg Almotriptan 12.5 mg Almotriptan 25 mg Oral / Single dose	172 180 182 186
CAPSS-368	Phase 3b, multicenter, open-label design to evaluate the long-term (12 months) safety of almotriptan in the treatment of multiple migraine episodes in adolescent (12-17 years) subjects with a history of migraine headache with or without aura. Efficacy was assessed as a secondary objective.	Almotriptan 12.5 mg Oral / Single doses for multiple migraine attacks over 12 months	420

The PK study 638-CNS-0059-014 (sNDA Review Study 1) was initiated and completed by Pharmacia (the IND and NDA holder at the time) between 10 November and 12 December 2001.

The double-blind, placebo-controlled efficacy trial 638-CNS-0059-015 (sNDA Review Study 2) was initiated by Pharmacia on 22 July 2003 and completed by OMJPI on 29 April 2005.

The open-label, long-term safety study CAPSS-368 (sNDA Review Study 3) was conducted by OMJPI between 23 December 2005 and 19 December 2007.

The sponsor reports all clinical studies included in this submission were conducted in accordance with principles of Good Clinical Practices (GCP).

Requirements for the PK study 638-CNS-0059-014 were specified in the original PWR issued to Pharmacia & Upjohn Co. on 15 October 2001 (Mod1.6.3\PWR\15October2001). Requirements for the efficacy study and long-term safety study were specified in the amended PWR issued to Ortho-McNeil Pharmaceuticals, Inc. (now OMJPI) on 01 February 2005. These requirements have all been reviewed and presented by the Division to the Pediatric Exclusivity Board last month. The Division confirmed to the Board that the sponsor had met all of the requirements.

By way of historical review, the efficacy study 638-CNS-0059-015 did not meet the usual FDA-required efficacy criteria for treatment of acute migraine (positive on the 4 co-primary endpoints: headache pain relief and presence of nausea, photophobia, and phonophobia at 2 hours postdose). At the 29 August 2006 SPA (Special Protocol Assessment) Advice meeting, the Division agreed that the study provided evidence supporting the efficacy of almotriptan on the relief of migraine pain in adolescents, but noted that the evidence supporting efficacy on the relief of associated symptoms appeared insufficient to meet regulatory approval.

The Division acknowledged the difficulty in showing efficacy on associated symptoms in the adolescent population, but felt studies could be designed to address these difficulties. At the 16 April 2008 Type B pre-sNDA meeting, the Division encouraged the sponsor to make the case that available data support a pediatric claim, noting that the acceptability of the argument would be a review issue. We noted we would consider the entirety of the evidence in the submission taking into consideration the characteristics of migraine in the pediatric population and the fact that AXERT has already been established as an effective medication for acute treatment of migraine in the adult population.

2.6 Other Relevant Background Information

The previous triptan migraine clinical trials in the pediatric/adolescent population over the years failed to demonstrate efficacy for primary endpoint, pain.

In the past, two controlled clinical trials evaluating sumatriptan *nasal spray* (5 to 20 mg) in pediatric patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents in terms of pain relief, the primary endpoint. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single-attack studies, 3 multiple-attack studies) evaluating *oral sumatriptan* (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies also did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents for pain relief. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents.

Postmarketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Please see Review Sections 8 Postmarketing Experience and 9.1 Literature Review/References for details of the pediatric experience with sumatriptan and almotriptan.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is acceptable and of good quality.

3.2 Compliance with Good Clinical Practices

The sponsor appears to have complied with Good Clinical Practices. Ortho-McNeil-Janssen Pharmaceuticals, Inc., Johnson & Johnson Pharmaceutical Research & Development, LLC certified it did not and would not use, in any capacity internally or externally, the services of any debarred persons under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with the Written Request for Pediatric Studies, supplemental NDA 21-001 AXERT (almotriptan malate) Tablets.

3.3 Financial Disclosures

The sponsor has provided a financial disclosure statement for 638-CNS-0059-015, the only Phase 3 efficacy study for this sNDA, as agreed to at the pre-NDA meeting on April 15, 2008. No financial disclosure information for clinical investigators involved in the conduct of the phase 1 pharmacokinetic study 638-CNS-0059-014 or the open-label safety study CAPSS-368 since these were not studies used to establish efficacy, in accordance with the FDA *Guidance for Industry: Financial Disclosure by Clinical Investigators, March 2001*.

The list of clinical investigators who participated in study 638-CNS-0059-015 was reviewed. The investigators in the 015 study do not appear to hold the disclosable financial arrangements with Ortho-McNeil-Janssen Pharmaceuticals, Inc. (previously Janssen-Ortho, LLC) .and Almirall Prodesfarma, as defined in 21 CFR 54.2 (a), (b), (c) and (t). Complete financial disclosure information was not available for 15 sub-investigators in this study as no forwarding information could be found. Financial disclosure information was available for all primary investigators, however.

Two investigators, who enrolled a total of (b) (6) patients out of 866, revealed significant payments as reported to the NDA. The sponsor did not exclude these patients because of the small number of patients involved.

The sponsor reports Dr. (b) (6) received $56,750.00 in total for (b) (6) (b) (6) and took no steps taken to minimize bias in this instance as follows:

> The investigator participated in a multicenter trial, which included 93 sites. In total, 1207 subjects were screened for the study and 866 subjects were enrolled. Dr (b) (6) enrolled (b) out of the 866 subjects. Because of the small number of subjects, the sponsor took no specific steps to minimize bias in this instance.

Dr. (b) (6) owned equity interest greater than $50,000 in Johnson & Johnson. The sponsor no steps to minimize bias:

> The investigator participated in a large multicenter trial, which included 93 sites. In total, 1207 subjects were screened for the study and 866 subjects were enrolled. Dr. (b) (6) enrolled (b) (6) out of the 866 subjects. Again, because of the small number of subjects involved, the sponsor took no specific bias-minimizing steps.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This submission does not contain Chemistry, Manufacturing and Controls (CMC) or Nonclinical Pharmacology and Toxicology information, as this information remains unchanged from that in the approved NDA. The sponsor cross-references the AXERT NDA 21-001 and DMF (b) (4) for any relevant CMC or nonclinical information. The Division agreed at the pre-sNDA meeting that this submission would not contain Modules 3 or 4.

4.2 Clinical Microbiology

See above.

4.3 Preclinical Pharmacology/Toxicology

See above.

4.4 Clinical Pharmacology

Here I briefly discuss the PWR specified single PK study. Please see the Clinical Pharm Review for detailed review as well as Section 5.3.2 of this review for an overview. The dose selected, the sponsor claims, was based on available evidence suggesting that almotriptan 12.5 mg has the best efficacy/tolerability ratio. This has been established in adults.

4.4.1 Mechanism of Action

No new data was acquired for this sNDA.

4.4.2 Pharmacodynamics

No PD study was done since a sponsor's comparative review of the pharmacokinetics and pharmacodynamics of triptans provided no scientific data supporting a difference in pharmacokinetics between healthy subjects and subjects with a history of migraine outside of an attack.

4.4.3 Pharmacokinetics

Please see Dr. Mada's and Dr. Tandon's (Office of Clinical Pharmacology) review for further details. Here I abstract their review. In general, almotriptan is well absorbed after oral administration (absolute bioavailability about 70%) with peak plasma levels 1 to 3 hours after administration; food does not affect pharmacokinetics. Almotriptan has a mean half-life of 3 to 4 hours. It is eliminated primarily by renal excretion (about 75% of the oral dose). Almotriptan is minimally protein bound (approximately 35%) and the mean apparent volume of distribution is approximately 180 to 200 liters.

The NDA's pharmacokinetic study, 638-CNS-0059-014 was conducted in adolescents. The study was designed to compare the pharmacokinetics of single dose almotriptan 12.5 mg in adolescents and adults as specified by the original PWR. It was conducted in male and female adolescent (ages 12-17 years) and adult (ages 18-55 years) subjects with or without a history of migraine. Thirty-six (36) subjects were enrolled in the study: 18 adolescents and 18 adults.

Subjects received a single oral dose of almotriptan 12.5 mg after an overnight fast. Urine and blood samples were collected over a 24-hour period for pharmacokinetic assessment. The primary pharmacokinetic endpoints include plasma almotriptan C_{max} and AUC. The secondary endpoints include plasma almotriptan T_{max}, λ_z, $T_{1/2}$, CL_{po}, CL_R, V_{ss}/F, F_e% (fraction drug recovered in urine). Spontaneous and observed AEs were recorded during this period. The ratio of the geometric means (adolescents vs. adults) of pharmacokinetic parameters for almotriptan and 90% confidence intervals were obtained and evaluated based on the bioequivalence limits of 80-125%.

The tabular summary of derived almotriptan PK parameters following a single oral dose of almotriptan 12.5 mg is presented in Table 5 from the submission:

Table 5: Adult and Adolescent Comparative PK

Parameter	Adolescents	Adults	*P* value[a]	Point Estimate	90% CI[b]
$AUC_{0-\infty}$ (ng·h/mL)					
Mean ± SD	320.4 ± 76.8	350.8 ± 56.3	0.184	90.0	80.2 - 101
Range	187.7 - 500.2	274.5 - 457.6			
AUC_{0-24} (ng·h/mL)					
Mean ± SD	312.4 ± 75.4	339.2 ± 54.3	0.229	90.7	80.8 - 102
Range	182.1 - 496.2	263.1 - 442.3			
C_{max} (ng/mL)					
Mean ± SD	55.3 ± 19.0	52.4 ± 8.4	0.564	102	89.3 - 117
Range	32.0 - 113	39.2 - 70.3			
t_{max} (h)					
Mean ± SD	1.9 ± 0.7	1.9 ± 0.7	0.818[c]	104	80.4 - 135
Range	0.5 - 3.0	0.5 - 3.0			
λ_z (h^{-1})					
Mean ± SD	0.147 ± 0.046	0.139 ± 0.025	0.539	103	89.5 - 118
Range	0.082 - 0.277	0.095 - 0.192			
$t_{1/2,z}$ (h)					
Mean ± SD	5.1 ± 1.5	5.1 ± 0.9	0.978	NC	NC
Range	2.5 - 8.5	3.6 - 7.3			
CL_{PO} (L/h)					
Mean ± SD	41.2 ± 10.2	36.5 ± 5.8	0.099	111	99.1 - 125
Range	25.0 - 66.6	27.3 - 45.5			
CL_{PO} (L/h/kg)					
Mean ± SD	0.672 ± 0.127	0.518 ± 0.144	0.002	132	116 - 151
Range	0.466 - 0.916	0.301 - 0.795			
CL_R (L/h)[d]					
Mean ± SD	15.5 ± 5.7	14.4 ± 2.9	0.462	90.7	68.4 - 120
Range	9.3 - 31.7	9.2 - 19.8			
CL_R (L/h/kg)[d]					
Mean ± SD	0.261 ± 0.115	0.200 ± 0.043	0.041	108	80.2 - 145
Range	0.136 - 0.641	0.125 - 0.276			
V_z/F (L/kg)[e]					
Mean ± SD	3.71 ± 0.78	3.36 ± 0.84	0.200	NC	NC
Range	2.63 - 4.95	2.21 - 5.45			
Fe%[f]					
Mean ± SD	36.5 ± 4.6	36.6 ± 9.3	0.982	NC	NC
Range	29.6 - 43.7	19.2 - 52.9			

Abbreviations: CI=confidence interval; NC=not calculated

[a] *P* values for between group difference were derived by analysis of variance (GLM).

[b] 90% CI for Ln-transformed parameters; adult=reference.

[c] *P* value was incorrectly presented as 0.828 in Table 2 of the clinical study report for 638-CNS-0059-014 (see Mod5.3.3.1\638-CNS-0059-014\Appendix2.2\page332).

[d] Renal clearance estimates were based on cumulative almotriptan urinary excretion during the 0- to 8-hour postdose period due to incomplete urine collections from 9 adolescent subjects during the 8- to 24-hour postdose period; adolescent N=17.

[e] In the clinical study report for 638-CNS-0059-014, volume of distribution was designated Vss/F or volume of distribution (steady state) in error. Steady state does not apply to this single-dose study.

[f] 24-hour cumulative excretion; adolescent N=9.

Please see the OCP Review for detailed summary information presented here, from the Executive Summary of that review:

Over all the mean pharmacokinetic parameters in adolescents was similar to that in adults as described below:

• Almotriptan mean C_{max} following administration of 12.5 mg almotriptan tablets in adolescents was higher by 2%, compared to adults.
• The mean AUC_{0-24} following administration in adolescents was lower by 9%, compared to adults. The AUC of three adolescents were lower than in adults. These three subjects also exhibited higher clearance. The clinical significance of this decrease in exposure in high body weight subjects was evaluated by the Review Statistician. Body weight did not impact the effectiveness analysis in the adolescents.
• The mean AUC_{0-inf} following administration in adolescents was lower by 10%, compared to adults.
• No change in the T_{max} and $T_{1/2}$ following administration of 12.5 mg almotriptan tablets in adolescents and adults.
• The oral clearance (CLPO) following oral administration of 12.5 mg almotriptan tablets in adolescents was 11% higher compared to adults.
• No change in the fraction of almotriptan excreted in the urine (Fe %) following administration of 12.5 mg almotriptan tablets in adolescents and adults, with about 36% of the dose excreted via urine during the first 24 hour period. In general about 40-50% of the almotriptan dose is recovered unchanged in urine via active tubular secretion.

For safety, 12 adverse events were reported by the sponsor in 8 subjects which I reviewed. Of these 8 subjects, 3 subjects were adolescents and 5 were adults. All AEs were considered mild in intensity, except for 1 occurrence of headache NOS (not otherwise specified) in an adolescent subject and 1 occurrence of migraine NOS in an adult subject, both of which were assessed as moderate in intensity and unrelated to study medication. The investigator attributed only 1 of the AEs (dry mouth in an adult subject) as possibly related to study medication.

There were no deaths or other serious adverse events reported in this study, and no subjects discontinued the study due to an adverse event. One 16-year-old healthy male (Subject 3) experienced a brief episode of ventricular extrasystole 3 hours after dosing with almotriptan. The event manifested as multiple individual premature ventricular contractions (PVCs). The subject was asymptomatic, conscious, and mentally alert during the event, and all vital signs were normal. Follow-up by a pediatric cardiologist revealed that the arrhythmia (frequent PVCs) was a preexisting condition. There were no clinically relevant findings from laboratory safety tests (hematology, serum chemistry, and urinalysis) or vital signs.

Based our FDA review of the trial data, adolescents had lower body weights, but no statistically significant differences from adults in almotriptan exposure (AUC and C_{max}). Based on this data, J & J wants to revise the PI stating the pharmacokinetics study of almotriptan in adolescents (12 to 17 years) and adults (18 to 55 years) with or without a history of migraine showed no differences in the rate or extent of absorption of almotriptan in adolescents compared with adults.

5 Sources of Clinical Data

The sources of Clinical Data within this marketing application are listed in the Tables of Clinical Studies below. There were no other sources of data external to the NDA such as other trials conducted by the sponsor, their designees, NIH, literature reports, or foreign marketing safety data.

5.1 Table of Clinical Studies

Three clinical studies were performed for this sNDA for almotriptan treatment of migraine attacks in adolescents are shown in Table 4. The two clinical studies providing sponsor's efficacy data for this sNDA are shown in Table 6, below. Dr. Massie and I reviewed the only controlled trial (Review Study 2) for efficacy.

Table 6: Clinical Studies Conducted for Efficacy in This sNDA

Study No. No. Study Sites[a] Country Study Period (Start / End Date) Subjects Planned / Subjects Enrolled	Study Design Study Objective Diagnosis	Treatment Dosage Route Duration	No. Subjects Evaluable for Efficacy (ITT) Overall (By treatment group) By gender: M/F Mean Age, yrs (range)	Primary Endpoint
638-CNS-0059-015 93 study sites Argentina, Colombia, Mexico, USA 22 July 2003 / 29 April 2005 924 / 866	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging Efficacy and safety Migraine with or without aura as defined by IHS criteria	Placebo; Almo 6.25, 12.5, or 25 mg Oral Single dose for single migraine attack	714 Placebo (170) M/F: 62/108 14.4 (12-17) Almo 6.25 mg (177) M/F: 75/102 14.4 (12-17) Almo 12.5 mg (181) M/F: 80/101 14.2 (12-17) Almo 25 mg (186) M/F: 71/115 14.4 (12-17)	4 coprimary endpoints: 2-hour pain relief plus presence of nausea, photophobia, and phonophobia
CAPSS-368 53 study sites USA 23 December 2005 / 19 December 2007 450 / 447	Phase 3b, multicenter, open-label Long-term safety Migraine with or without aura as defined by IHS criteria	Almo 12.5 mg Oral Single doses for multiple migraine attacks, with an optional second dose if needed 12 months	420 M/F: 187/233 14.4 (12-17)	Efficacy was a secondary objective; no primary or secondary endpoints

Abbreviations: AE = adverse event; Almo = almotriptan; ECG = electrocardiogram; F = female; ITT = intent-to-treat; IHS = International Headache Society; M = male; yrs = years.
[a] Study sites that enrolled subjects

The studies providing safety data with almotriptan treatment in adolescents are tabulated here:

Table 7: Overview of Company-sponsored Clinical Studies Providing Safety Data Relevant to Almotriptan Rx of Adolescent Migraine Attacks

Study No. Country Study Period (Start / End Date)	Study Type Study Design	No. Subjects Evaluable for Safety Overall (By treatment group)	Treatment Dosage / Route / Duration	Safety Evaluation
638-CNS-0059-014 USA 10 November 2001 / 12 December 2001	Pharmacokinetic Phase 1, single-center, open-label, single-dose, parallel-group	36 Adolescents (18) Adults (18)	Almo 12.5 mg/ Oral / Single dose	• AEs • Laboratory tests • Vital signs • ECGs
638-CNS-0059-015 Argentina, Colombia, Mexico, USA 22 July 2003 / 29 April 2005	Efficacy and safety Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging	720 Placebo (172) Almo 6.25 mg: (180) Almo 12.5 mg: (182) Almo 25 mg (186)	Placebo; Almo 6.25, 12.5, or 25 mg/ Oral / Single dose for single migraine attack	• AEs • Laboratory tests • Vital signs • ECGs
CAPSS-368 USA 23 December 2005 / 19 December 2007	Long-term safety Phase 3b, multicenter, open-label	420	Almo 12.5 mg/ oral / single doses for multiple migraine attacks over 12 months	• AEs • Laboratory tests • Vital signs • ECGs

Abbreviations: AE = adverse event; Almo = almotriptan; ECG = electrocardiogram.

5.2 Review Strategy

For this review, the three clinical trials above were reviewed for efficacy and safety as presented in the review. Literature was relied upon where appropriate to support both the safety and efficacy information applicable to adolescents.

The following Reviewers from other disciplines contributed to the review:

- Charlie Thompson, Ph.D. (PT),
- Lois Freed, Ph.D. (PT)
- Nallaperum Chidambaram, Ph.D. (OPS/ONDQA/DPE,)
- Vaneeta Tandon, Ph.D. (OTS/OCP/DCPI)
- Sirpal Mada, Ph.D. (OTS/OCP/DCPI)
- Kun Jin, Ph.D., (Biostatistics)
- Tristan Massie, Ph.D. (Biostatistics)

Dr. Massie performed the efficacy statistical analysis. His review is incorporated jointly into this review in italicized font in Review Section 6.

5.3 Discussion of Individual Studies

Three studies were submitted to this sNDA as mentioned. Study 1 is **638-CNS-0059-014**, the PK study and will be reviewed by the Clinical Pharmacology in detail. **Study 2** is **638-CNS-0059-015**, an efficacy study, and **Study 3** is **CAPSS-368**, a long-term safety study. Before discussing the individual studies, an overview of the extent of exposure is presented.

5.3.1 Overall Extent of Exposure in the 3 Trials

The number of adolescent subjects exposed to study medication in each of the 3 company-sponsored studies conducted in adolescents is presented in Table 8. All subjects who received at least 1 dose of study medication were evaluated for safety.

In total, 1158 adolescent subjects received study treatment in these 3 studies: 172 received placebo and 986 received almotriptan (any dose).

Table 8: Number of Adolescent Subjects Evaluated for Safety in the 3 Trials

	Study Medication[a]					
	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg	Almotriptan 12.5 mg[b]	Total
638-CNS-0059-014			18			18
638-CNS-0059-015	172	180	182	186		720
CAPSS-368					420	420
Studies combined	172	180	200	186	420	1158

[a] Subjects received a single oral dose of study medication, except where indicated.
[b] Subjects took single oral doses for multiple migraine episodes for up to 12 months.

Cross-reference: Mod5.3.3.1\638-CNS-0059-014\Section7.1.1; Mod5.3.5.1\638-CNS-0059-015\Table4; Mod5.3.5.2\CAPSS-368\Table3.

For the remainder of this Review Section I review the pertinent study features for Studies 2 and 3. The results of these 2 studies are presented in Review Sections 6 and 7 below and cross-referenced.

5.3.2 Study 1 (638-CNS-0059-014):

Please see the Biopharmaceutics Review of this study and the summary analysis in Review Section 4.4.3 above. Summarized, Study 638-CNS-0059-014 was designed to compare the pharmacokinetics of almotriptan 12.5 mg in male and female adolescents (ages 12 to 17 years) and adults (ages 18 to 55 years) with or without a history of migraine. As noted, The 12.5 mg dose was selected based on the efficacy results shown previously in adult migraineurs and has been used in an efficacy study in adolescents using an oral formulation of almotriptan. The design features of the pediatric studies are summarized above in Table 7.

5.3.3 Study 2 (638-CNS-0059-015)

The overview of this trial reveals 866 subjects with a history of migraine with or without aura were enrolled and randomized in approximately equal numbers (range of 209 to 226) to the 4 treatment groups . Of the 866 subjects randomized, 720 (83.1%) took a single oral dose of study medication for treatment of a single migraine attack: 172 (82.3%) took placebo, 180 (85.3%) took almotriptan 6.25 mg, 182 (80.5%) took almotriptan 12.5 mg, and 186 (84.5%) took almotriptan 25 mg. Six hundred ninety-nine (80.7%) subjects completed the study: placebo, 166 (79.4%); almotriptan 6.25 mg, 174 (82.5%); almotriptan 12.5 mg, 178 (78.8%); and almotriptan 25 mg, 181 (82.3%). Of 167 patients who did not complete the study, the main reasons for early termination were failure to take study medication (range of 74.4% to 87.5% across treatment groups) and protocol violations (range of 4.2% to 15.4% across treatment groups).

5.3.3.1 Study 2 Design and Treatment Regimen

This was a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled acute treatment trial in adolescent subjects 12 to 17 years of age:

- The *primary objective* of the study was to evaluate the efficacy of almotriptan versus placebo at 2 hours postdose.
- *Secondary objectives* were to evaluate:
  - (1) the efficacy of almotriptan versus placebo at 0.25, 0.5, 1, 1.5, and 24 hours postdose,
  - (2) the occurrence of associated symptoms at 0.25, 0.5, 1, 1.5, and 2 hours postdose for vomiting and at 0.25, 0.5, 1, and 1.5 hours postdose for nausea, photophobia, and phonophobia,
  - (3) the incidence of headache recurrence and use of rescue medication within 2 to 24 hours after administration of almotriptan versus placebo, and
  - (4) the safety of almotriptan versus placebo.

Potential subjects assented to participate voluntarily in the study and their parent(s) or legal guardian(s) signed a written informed consent form before any screening procedures were performed. Eligible subjects were male or female, 12 to 17 years of age who would not reach their 18th birthday during their time of involvement in the study.

Subjects had a >1-year history of migraine with or without aura as defined by IHS criteria and a ≥6-month history of moderate or severe intensity migraine attacks. Subjects had a monthly frequency of at least 1 to 6 moderate intensity attacks during the 2 months preceding study enrollment; these attacks had to persist for >4 hours when untreated and occur at intervals >24 hours between attacks. Subjects had to verbalize the ability to distinguish migraine attacks from other types of headaches.

The trial included a *30-day run-in period* beginning at screening (visit 1), during which subjects were permitted to use their usual migraine medication and the frequency and severity of attacks

were documented. Subjects who did not have at least 1 headache or had more than 6 moderate or severe migraine attacks during the run-in period were not eligible for the study.

At the end of the run-in period (visit 2), eligible subjects were *randomized (1:1:1:1) to 4 treatment arms within 2 age strata (12 to 14 years and 15 to 17 years)* using block sizes of 8 for each age group. Subjects received 1 dose of almotriptan 6.25 mg, almotriptan 12.5 mg, almotriptan 25 mg or placebo.

During the treatment period (42 days), subjects were instructed to treat their first migraine headache with their single oral dose of study medication as soon as possible and no more than 4 hours after onset of moderate-to-severe headache pain. Rescue medication of the investigator's choice could be used if the subject's moderate-to-severe headache continued to persist ≥ 2 hours after taking study medication or if the subject experienced pain relief 2 hours after taking study medication followed by a recurrence (i.e., a return of moderate or severe pain) within 24 hours. Ergotamine-containing drugs and other triptans were not allowed to be used for rescue medication and no second dose of study medication was available.

Subjects recorded safety and efficacy information in a patient diary. Subjects returned for the final visit 2 to 14 days after the migraine attack was treated with study medication. Subjects who did not experience a migraine attack within 42 days after visit 2 returned to the clinic for a final visit and returned their study medication.

5.3.3.2 Study 2 Endpoints

There were 4 co-primary endpoints:

- *Headache pain relief 2 hours postdose*, defined as a decrease in headache pain intensity from either moderate or severe intensity to mild or no pain, plus
- *Presence of nausea, photophobia, and phonophobia at 2 hours postdose*.

Secondary efficacy endpoints included:

- *Headache pain relief* at 0.25, 0.5, 1.0, and 1.5 hours postdose
- *Presence of nausea, photophobia, and phonophobia* at 0.25, 0.5, 1.0, and 1.5 hours postdose
- *Presence of vomiting at 0.25, 0.5, 1.0, 1.5, and 2.0 hours* postdose
- *Headache pain-free response*, defined as a decrease in headache pain intensity from moderate or severe to none, at 0.25, 0.5, 1.0, 1.5, and 2.0 hours postdose
- *Headache recurrence*, defined as significant worsening of headache pain intensity from none or mild to moderate or severe, within 2 to 24 hours postdose in responders, where responders were subjects with headache pain relief 2 hours postdose
- *Time to recurrence*
- *Use of rescue medication* 2 to 24 hours postdose

• *Sustained pain relief*, defined as headache pain relief at 2 hours postdose with no recurrence of moderate or severe pain and no use of rescue medication 2 to 24 hours postdose
• *Sustained pain-free response*, defined as headache pain free at 2 hours postdose with no recurrence of pain and no use of rescue medication 2 to 24 hours postdose

Safety assessments included adverse events (AEs), clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), physical examinations, use of concomitant medications, and pregnancy testing. No formal comparisons of the safety parameters between treatment groups were performed.

5.3.3.3 Study 2 Statistical Methods

Sample size assumed a placebo response rate of 45% and an almotriptan response rate of 60%, across both baseline headache pain intensity subgroups (moderate or severe). The sponsor determined a sample size of 173 subjects in each of the 4 treatment groups would provide 0.80 power at the 2-sided alpha level of 0.05 to detect a 0.15 difference between almotriptan and placebo. The sample size was initially determined using the Bonferroni method but was subsequently changed to the step-down method, ordering the hypotheses (comparisons) in sequence, following correspondence with the Division and a Type A FDA meeting

Efficacy analyses were based on the *intent-to-treat (ITT)* population, defined as *all randomized subjects who took a dose of study medication and had ≥1 postdose efficacy assessmen*t.

For the primary efficacy analysis, treatment-group comparisons followed a step-down procedure to adjust for multiple comparisons. The order of the hypotheses was based on an assumed dose-response relationship of almotriptan efficacy supported by a previous meta-analysis of randomized, double-blind, placebo-controlled trials in adults, where response rates for headache pain relief 2 hours postdose were 35.3%, 55.5%, 61.3%, and 63.9%, for placebo, almotriptan 6.25 mg, almotriptan 12.5 mg, and almotriptan 25 mg respectively.

According to the step-down procedure, if almotriptan 25 mg was shown to be statistically significantly better than placebo on all 4 primary endpoints (each tested at the 0.05 alpha level), then the comparison of almotriptan 12.5 mg versus placebo could be performed. If almotriptan 12.5 mg was shown to be statistically significantly better than placebo on all 4 endpoints, then the comparison of almotriptan 6.25 mg versus placebo could be performed. If almotriptan 25 mg was not superior to placebo on all 4 primary endpoints, the step-down procedure would be terminated and the study would conclude that none of the 3 almotriptan doses was superior to placebo on all 4 primary endpoints.

Any subsequent comparisons of almotriptan 12.5 mg and 6.25 mg versus placebo would be considered exploratory with no adjustment for multiplicity. The primary efficacy analysis for comparison between treatment groups was performed using the Cochran-Mantel-Haenszel (CMH) test adjusted for baseline pain intensity (moderate or severe). A likelihood ratio chi-

square test was used as a secondary analysis for treatment group comparisons not adjusted for baseline pain intensity.

Safety analyses were summarized by treatment group for the safety population, defined as all subjects who took study medication. There were no formal comparisons of the safety parameters between treatment groups. The number and percentage of subjects with AEs were summarized. For clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, and ECG data, descriptive statistics for continuous parameters and number and percentage of subjects in each category for categorical parameters were calculated for each scheduled assessment. Observed values and change-from-baseline values were evaluated.

5.3.3.4 Study 2 Subject Disposition and Baseline Characteristics

Subjects were enrolled at 93 study sites in the United States (81 sites), Argentina (6 sites), Colombia (3 sites), and Mexico (3 sites).

In total, 1207 subjects were screened for the study and 866 subjects were enrolled and randomized to the 4 treatment groups:

- placebo, 209;
- almotriptan 6.25 mg, 211;
- almotriptan 12.5 mg, 226; and
- almotriptan 25 mg, 220.

Of the 866 subjects randomized:

- 720 (83.1%) took a single oral dose of study medication for treatment of a single migraine attack (safety population)
- 172 (82.3%) took placebo,
- 180 (85.3%) took almotriptan 6.25 mg,
- 182 (80.5%) took almotriptan 12.5 mg, and
- 186 (84.5%) took almotriptan 25 mg.

Seven hundred fourteen (714) of the 866 subjects randomized (82.4%) were analyzed for efficacy (ITT population):

- placebo, 170 (81.3%);
- almotriptan 6.25 mg,
- 177 (83.9%); almotriptan 12.5 mg, 181 (80.1%); and almotriptan 25 mg, 186 (84.5%)

The Patient Disposition Data are tabulated in Table 9:

Table 9: Patient Disposition Data

	Statistic	Placebo	Almotriptan		
			6.25 mg	12.5 mg	25 mg
Number of Patients Screened	N=1207				
Number of Patients Randomized	N	209	211	226	220
Number of Patients Who Took Study Drug and are in the Safety Population[1]	n (%)	172 (82.3)	180 (85.3)	182 (80.5)	186 (84.5)
Number of Patients in the ITT Population	n (%)	170 (81.3)	177 (83.9)	181 (80.1)	186 (84.5)
Reasons for Exclusion[2]					
Did not take study medication	n (%)	37 (94.9)	31 (91.2)	44 (97.8)	34 (100)
Did not have a post-Baseline efficacy assessment	n (%)	0	0	0	0
Patients from Dr. Leon's Site[3]	n (%)	2 (5.1)	3 (8.8)	1(2.2)	0
Number of Patients in the PP Population	n (%)	136 (65.1)	152 (72.0)	155 (68.6)	144 (65.5)
Reasons for Exclusion[4]					
Did not satisfy inclusion/exclusion criteria	n (%)	4 (5.5)	3 (5.1)	2 (2.8)	11 (14.5)
Had a serious protocol violation	n (%)	31 (42.5)	22 (37.3)	25 (35.2)	31 (40.8)
Number of Patients Who Completed the Study[1]	n (%)	166 (79.4)	174 (82.5)	178 (78.8)	181 (82.3)
Reasons for Early Termination[5]					
Adverse Event	n (%)	0	0	0	0
Protocol Violation	n (%)	5 (11.6)	3 (8.1)	2 (4.2)	6 (15.4)
Consent Withdrawn	n (%)	0	0	0	0
Lost to Follow-up	n (%)	3 (7.0)	2 (5.4)	2 (4.2)	1 (2.6)
Sponsor's Decision	n (%)	3 (7.0)	3 (8.1)	2 (4.2)	1 (2.6)
Did not Take Study Drug	n (%)	32 (74.4)	29 (78.4)	42 (87.5)	31 (79.5)

[1]Percentages are based on the number of randomized patients in each treatment group.
[2]Percentages are based on the number of patients excluded from the ITT Population in each treatment group.
[3]Because of methodological deficiencies as well as GCP non-compliance aspects seen at Dr. Leon's site (Site 10128), the patients from this site were excluded from the ITT Population.
[4]Percentages are based on the number of patients excluded from the PP Population in each treatment group. Note that Patients 151294 (Placebo) and 156482 (12.5 mg) were excluded for both reasons of 'Did not satisfy the inclusion/exclusion criteria' and 'Had a serious protocol violation'.
[5]Percentages are based on the number of patients with available data who did not complete the study in each treatment group; percentage may add up to more than 100%.
Data Source: Tables P-1.1 and P-3.1

Six hundred ninety-nine (699) of the 866 subjects randomized (80.7%) completed the study:

- placebo, 166 (79.4%);
- almotriptan 6.25 mg, 174 (82.5%);
- almotriptan 12.5 mg, 178 (78.8%); and
- almotriptan 25 mg, 181 (82.3%).

Of 167 patients who did not complete the study, the main reasons for early termination were failure to take study medication (range of 74.4% to 87.5% across treatment groups) and protocol violations (range of 4.2% to 15.4% across treatment groups)

Demographic and baseline characteristics were well balanced across the 4 treatment groups in both the ITT and safety populations as shown in the tables below (Table 10 and Table 11).

Overall, these were typical of a migraine trial, with more females than males, and more whites than other races. There were more females (60%) than males (40%). There was a slightly higher percentage of subjects in the 12-14 year age group (54%) relative to the 15-17 year age group (46%). Approximately 75% of subjects were white, 15% were black (African heritage or African American), and 10% were of other races; approximately 25% were Hispanic or Latino. Median weights ranged from 102 to 127 pounds and median heights ranged from 63 to 64 inches across treatment groups.

All subjects had experienced at least 1 moderate or severe migraine during the 2 months prior to study start.

Table 10: Safety Population Demographic and Baseline Characteristics

		ALMOTRIPTAN MALATE				
	STATISTICS	6.25 mg	12.5 mg	25 mg	PLACEBO	P-VALUE
Number of Patients in the Safety Population	N	180	182	186	172	
Ethnicity						
Hispanic or Latino	n (%)	53 (29.4)	44 (24.2)	40 (21.7)	48 (28.2)	0.307
Not Hispanic or Latino	n (%)	127 (70.6)	138 (75.8)	144 (78.3)	122 (71.8)	
Weight (pounds)	n	180	182	186	172	0.315
	Mean	125.62	124.80	129.07	128.67	
	SD	27.54	26.10	26.46	25.85	
	25th Percentile	105.0	108.0	109.2	110.2	
	Median	120.20	120.00	127.30	125.00	
	75th Percentile	144.8	139.0	143.3	144.8	
	Min., Max.	62.2, 227.0	70.4, 217.8	72.5, 215.0	64.0, 217.0	
Height (inches)	n	180	182	186	172	0.451
	Mean	63.59	63.42	63.80	64.03	
	SD	3.97	3.55	3.68	3.75	
	25th Percentile	61.0	61.0	61.4	61.5	
	Median	63.15	63.00	64.00	63.70	
	75th Percentile	66.1	66.0	66.0	66.5	
	Min., Max.	39.9, 73.0	53.5, 74.0	49.0, 72.1	48.0, 73.4	

[1] Not included in the p-value calculation.
Notes: Percentages are based on the number of patients with available data in the Safety Population in each treatment group.
For sex, age group and ethnicity, the p-value is from an uncorrected chi-squared test.
For age, weight and height, the p-value is from an ANOVA model with treatment groups.
For race the p-value is from a Likelihood Ratio Chi-Square test.

Table 11: ITT Population Demographic and Baseline Characteristics

		ALMOTRIPTAN MALATE				
	STATISTICS	6.25 mg	12.5 mg	25 mg	PLACEBO	P-VALUE
Number of Patients in the Intent-to-Treat Population	N	177	181	186	170	
Sex						
Male	n (%)	75 (42.4)	80 (44.2)	71 (38.2)	62 (36.5)	0.416
Female	n (%)	102 (57.6)	101 (55.8)	115 (61.8)	108 (63.5)	
Age (years)	n	177	181	186	170	0.544
	Mean	14.4	14.2	14.4	14.4	
	SD	2	2	2	2	
	25th Percentile	13.0	13.0	13.0	13.0	
	Median	14	14	14	14	
	75th Percentile	16.0	15.0	16.0	16.0	
	Min., Max.	12, 17	12, 17	12, 17	12, 17	
Age Group						
12 to 14 years	n (%)	92 (52.0)	99 (54.7)	98 (52.7)	95 (55.9)	0.877
15 to 17 years	n (%)	85 (48.0)	82 (45.3)	88 (47.3)	75 (44.1)	
Race						
American Indian or Alaska Native	n (%)	3 (1.7)	5 (2.8)	5 (2.7)	5 (3.0)	0.884
Asian	n (%)	1 (0.6)	0	1 (0.5)	0	
Black, of African Heritage or African American	n (%)	33 (18.9)	26 (14.4)	34 (18.4)	28 (16.7)	
Native Hawaian or Other Pacific American	n (%)	0	0	0	0	
White	n (%)	132 (75.4)	142 (78.9)	136 (73.5)	129 (76.8)	
Not Listed[1]	n (%)	0	0	0	0	
Not Allowed to Ask Per Local Regulations[1]	n (%)	0	0	0	0	
White; American Indian or Alaska Native	n (%)	6 (3.4)	6 (3.3)	9 (4.9)	5 (3.0)	
White; Black, of African Heritage or African American	n (%)	0	1 (0.6)	0	1 (0.6)	

[1] Not included in the p-value calculation.
Notes: Percentages are based on the number of patients with available data in the Intent-to-Treat (ITT) Population in each treatment group.
For sex, age group and ethnicity, the p-value is from an uncorrected chi-squared test.
For age, weight and height, the p-value is from an ANOVA model with treatment groups.
For race the p-value is from a Likelihood Ratio Chi-Square test.

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	STATISTICS	ALMOTRIPTAN MALATE 6.25 mg	ALMOTRIPTAN MALATE 12.5 mg	ALMOTRIPTAN MALATE 25 mg	PLACEBO	P-VALUE
Number of Patients in the Intent-to-Treat Population	N	177	181	186	170	
Ethnicity						
Hispanic or Latino	n (%)	50 (28.2)	43 (23.8)	40 (21.7)	46 (27.4)	0.446
Not Hispanic or Latino	n (%)	127 (71.8)	138 (76.2)	144 (78.3)	122 (72.6)	
Weight (pounds)	n	177	181	186	170	0.276
	Mean	125.32	124.95	129.07	128.97	
	SD	27.68	26.09	26.46	25.50	
	25th Percentile	105.0	108.0	109.2	110.2	
	Median	120.00	120.00	127.30	125.00	
	75th Percentile	144.5	139.0	143.3	145.0	
	Min., Max.	62.2, 227.0	70.4, 217.8	72.5, 215.0	73.0, 217.0	
Height (inches)	n	177	181	186	170	0.460
	Mean	63.58	63.43	63.80	64.04	
	SD	4.00	3.56	3.68	3.77	
	25th Percentile	60.9	61.0	61.4	61.5	
	Median	63.00	63.00	64.00	63.70	
	75th Percentile	66.1	66.0	66.0	66.5	
	Min., Max.	39.9, 73.0	53.5, 74.0	49.0, 72.1	48.0, 73.4	

[1] Not included in the p-value calculation.
Notes: Percentages are based on the number of patients with available data in the Intent-to-Treat (ITT) Population in each treatment group.
For sex, age group and ethnicity, the p-value is from an uncorrected chi-squared test.
For age, weight and height, the p-value is from an ANOVA model with treatment groups.
For race the p-value is from a Likelihood Ratio Chi-Square test.

Usual headache pain intensity was moderate for 52% of subjects and severe for 48% of subjects. The mean duration of migraine attacks ranged from 10.5 to 11.5 hours across treatment groups. The safety population data is summarized in Table 12, below.

Table 12: Safety Population Migraine History

	Statistic	Placebo	Almotriptan		
			6.25 mg	12.5 mg	25 mg
Number of Patients in the Safety Population	N	172	180	182	186
Time Since Diagnosis of Migraine (months)[1]	n	172	180	182	186
	Mean	46.8	43.0	45.5	43.0
	SD	32.7	29.2	34.2	29.5
	Median	36.4	35.0	35.1	34.9
	Minimum	0	0	0	0
	Maximum	165	146	173	163
Frequency of Severe or Moderate Migraine During the Last 2 Months					
1-6	n (%)	171 (99.4)	178 (98.9)	181 (99.5)	186 (100)
>6	n (%)	1 (0.6)	2 (1.1)	1 (0.5)	0
Usual Pain Intensity					
Moderate	n (%)	90 (52.3)	99 (55.0)	97 (53.3)	88 (47.3)
Severe	n (%)	82 (47.7)	81 (45.0)	85 (46.7)	98 (52.7)
Duration (hours)	n	172	180	182	186
	Mean	10.7	10.7	10.5	11.5
	SD	10.2	10.9	10.9	12.4
	Median	6.0	6.0	6.0	7.0
	Minimum	3	3	2	3
	Maximum	72	72	72	72

[1]If the day of diagnosis was missing, the first day of the month was used. If month and day of the month were missing, January 1 was used.
Note: Percentages are based on the number of patients diagnosed with a migraine in the Safety Population in each treatment group.
Data Source: Table P-6.1

The ITT population data is presented next.

Table 13: ITT Population Migraine History Summary

		ALMOTRIPTAN MALATE			
	STATISTICS	6.25 mg	12.5 mg	25 mg	PLACEBO
Number of Patients in the Intent-to-Treat Population	N	177	181	186	170
Time Since Diagnosis of Migraine (months)[1]	n	177	181	186	170
	Mean	42.6	45.6	43.0	46.9
	SD	29.1	34.2	29.5	32.8
	25th Percentile	20.9	21.9	23.5	23.5
	Median	34.3	35.1	34.9	36.5
	75th Percentile	58.1	57.7	56.8	59.8
	Min., Max.	0, 146	0, 173	0, 163	0, 165
Frequency of Severe or Moderate Migraine During the Last 2 Months					
None	n (%)	0	0	0	0
1-6 per month	n (%)	175 (98.9)	180 (99.4)	186 (100)	169 (99.4)
>6 per month	n (%)	2 (1.1)	1 (0.6)	0	1 (0.6)
Usual Pain Intensity					
MILD	n (%)	0	0	0	0
MODERATE	n (%)	97 (54.8)	97 (53.6)	88 (47.3)	90 (52.9)
SEVERE	n (%)	80 (45.2)	84 (46.4)	98 (52.7)	80 (47.1)
Usual Duration (hours) (If Untreated or Treated Unsuccessfully)	n	177	181	186	170
	Mean	10.8	10.5	11.5	10.8
	SD	11.0	10.9	12.4	10.2
	25th Percentile	5	4	5	5
	Median	6.0	6.0	7.0	6.0
	75th Percentile	12	12	12	12
	Min., Max.	3, 72	3, 72	3, 72	3, 72

[1] If the day of Diagnosis was missing then the first day of the month was used. If the month and the day of Diagnosis was missing then January 1st were used.
Note: Percentages are based on the number of patients diagnosed with a migraine in the Intent-to-Treat (ITT) Population in each treatment group.

The mean time since diagnosis of migraine was similar across the 4 treatment groups (range of 43.0 to 46.8 months). All patients had experienced a moderate or severe migraine during the past 2 months; all but 4 patients had experienced a moderate or severe migraine during the past 1 to 6 months. The mean duration of migraine was also similar across the 4 treatment groups (range of 10.5 to 11.5 hours).

Results for the ITT Population were very similar or identical to those for the Safety Population. Previous medications used to treat migraine in patients in the Safety Population are presented in Table 14, below.

Table 14: Medications Used Previously to Treat Migraine

PATIENT NUMBER	ITT POPULATION	LIST OF MEDICATION USED PREVIOUSLY TO TREAT MIGRAINE (NOT CODED)
151001	Yes	TYLENOL
151006	Yes	ADVIL 200 MG PO 2 TABS TYLENOL PM 1 PO AT HS
151011	Yes	MOTRIN 2 TABS PRN TYLENOL 4 TABS PRN
151016	Yes	ACETAMINOPHEN EXCEDRIN IBUPROFEN SUMATRIPTAN NASAL SPRAY
151033	Yes	IBUPROFEN TYLENOL
151037	Yes	
151038	Yes	IBUPROFEN TYLENOL
151058	Yes	AMITRIPTYLINE EXTRA STRENGTH EXCEDRIN IMITREX

Note: Information based on p.5 of the CRF.

5.3.3.5 Time between Study Visits for Study 2

The time between study visits for patients in the Safety Population and in the ITT Population is presented in Table 15 and Table 16, below.

Table 15: Safety Population Time between Study Visits

	Statistic	Placebo	Almotriptan		
			6.25 mg	12.5 mg	25 mg
Number of Patients in the Safety Population	N	172	180	182	186
Screening Period[1]					
<30 days	n (%)	4 (2.3)	6 (3.3)	6 (3.3)	5 (2.7)
30-37 days	n (%)	142 (82.6)	149 (82.8)	157 (86.3)	161 (86.6)
38-50 days	n (%)	21 (12.2)	23 (12.8)	15 (8.2)	14 (7.5)
>50 days	n (%)	5 (2.9)	2 (1.1)	4 (2.2)	6 (3.2)
Treatment Period[2]					
<10 days	n (%)	65 (37.8)	64 (35.6)	63 (34.6)	72 (38.7)
10-20 days	n (%)	43 (25.0)	43 (23.9)	44 (24.2)	44 (23.7)
21-30 days	n (%)	22 (12.8)	33 (18.3)	28 (15.4)	25 (13.4)
31-42 days	n (%)	35 (20.3)	35 (19.4)	39 (21.4)	38 (20.4)
43-60	n (%)	5 (2.9)	3 (1.7)	5 (2.7)	7 (3.8)
>60 days	n (%)	2 (1.2)	2 (1.1)	3 (1.6)	0
Final Visit[3]					
<2 days	n (%)	3 (1.7)	8 (4.4)	4 (2.2)	0
2-14 days	n (%)	153 (89.0)	157 (87.2)	160 (87.9)	161 (86.6)
15-40	n (%)	15 (8.7)	12 (6.7)	15 (8.2)	23 (12.4)
>40 days	n (%)	1 (0.6)	3 (1.7)	3 (1.6)	2 (1.1)

[1]Time between Screening and randomization (Visit 2).
[2]Time between randomization and onset of migraine.
[3]Time between onset of migraine and Final Visit.
Note: Percentages are based on the number of patients with available data in the Safety Population in each treatment group.
Data Source: Table P-8.1

Table 16: ITT Population Time Between Study Visits

	STATISTICS	ALMOTRIPTAN MALATE 6.25 mg	ALMOTRIPTAN MALATE 12.5 mg	ALMOTRIPTAN MALATE 25 mg	PLACEBO
Number of Patients in the Intent-to-Treat Population	N	177	181	186	170
Screening Period[1]					
< 30 days	n (%)	6 (3.4)	6 (3.3)	5 (2.7)	4 (2.4)
30 - 37 days	n (%)	146 (82.5)	156 (86.2)	161 (86.6)	140 (82.4)
38 - 50 days	n (%)	23 (13.0)	15 (8.3)	14 (7.5)	21 (12.4)
> 50 days	n (%)	2 (1.1)	4 (2.2)	6 (3.2)	5 (2.9)
Treatment Period[2]					
< 10 days	n (%)	64 (36.2)	63 (34.8)	72 (38.7)	63 (37.1)
10 - 20 days	n (%)	41 (23.2)	43 (23.8)	44 (23.7)	43 (25.3)
21 - 30 days	n (%)	33 (18.6)	28 (15.5)	25 (13.4)	22 (12.9)
31 - 42 days	n (%)	34 (19.2)	39 (21.5)	38 (20.4)	35 (20.6)
43 - 60 days	n (%)	3 (1.7)	5 (2.8)	7 (3.8)	5 (2.9)
> 60 days	n (%)	2 (1.1)	3 (1.7)	0	2 (1.2)
Final Visit[3]					
< 2 days	n (%)	8 (4.5)	4 (2.2)	0	3 (1.8)
2 - 14 days	n (%)	155 (87.6)	159 (87.8)	161 (86.6)	151 (88.8)
15 - 40 days	n (%)	11 (6.2)	15 (8.3)	23 (12.4)	15 (8.8)
> 40 days	n (%)	3 (1.7)	3 (1.7)	2 (1.1)	1 (0.6)

[1] Time between screening (Visit 1) and Visit 2 (randomization).
[2] Time between Visit 2 (randomization) and onset of migraine.
[3] Time between onset of migraine and Visit 3 (final visit).
Note: Percentages are based on the number of patients with available data in the Intent-to-Treat (ITT) Population in each treatment group.

The mean times between Screening and randomization, between randomization and onset of migraine, and between onset of migraine and Final Visit were similar across the 4 treatment groups. More than 80% of patients were randomized within 30 to 37 days after Screening and all but 27 patients had a migraine within 42 days after being randomized. Approximately 90% of patients had their Final Visit within 14 days after onset of their migraine.

5.3.3.6 Study 2 Treatment Compliance

Treatment compliance for patients in the Safety Population is presented in Table 17. As can be seen, overall compliance was good. Approximately 95% of patients took their study medication within 4 hours after the onset of their migraine.

The median time between the onset of migraine and study medication intake ranged from 15 to 23 minutes across treatment groups.

Table 17: Safety Population Compliance

PARAMETER	STATISTICS	ALMOTRIPTAN MALATE 6.25 mg	ALMOTRIPTAN MALATE 12.5 mg	ALMOTRIPTAN MALATE 25 mg	PLACEBO
Number of Patients in the Safety Population	N	180	182	186	172
Time Between Onset of Migraine and Study Medication Intake					
<= 4 Hours	n (%)	170 (94.4)	174 (95.6)	181 (97.3)	166 (96.5)
> 4 Hours and <= 4 Hours and 15 Minutes	n (%)	1 (0.6)	1 (0.5)	0	2 (1.2)
> 4 Hours and 15 Minutes	n (%)	8 (4.4)	5 (2.7)	3 (1.6)	4 (2.3)
	n	179	180	184	172
	Mean	1:00	0:48	0:43	0:52
	SD	1:55	1:42	1:04	1:17
	25th Percentile	0:07	0:05	0:02	0:06
	Median	0:20	0:18	0:15	0:23
	75th Percentile	1:00	0:45	0:55	1:00
	Min., Max.	00:00, 14:45	00:00, 17:55	00:00, 6:46	00:00, 8:45

Note: Percentages are based on the number of patients in the Safety Population in each treatment group.

5.3.4 Study 3 (CAPSS-368) Long-term Safety Study

The study overview reveals subjects with a history of migraine with or without aura took single oral doses of almotriptan 12.5 mg for treatment of multiple migraine attacks for up to 12 months. 447 subjects enrolled, 420 (94.0%) were included in the safety population and 319 (71.4%) completed the study. Subjects treated each migraine episode with 1 or 2 doses of study medication. The average dose per headache was 15 mg and the average number of doses per headache was 1.2.

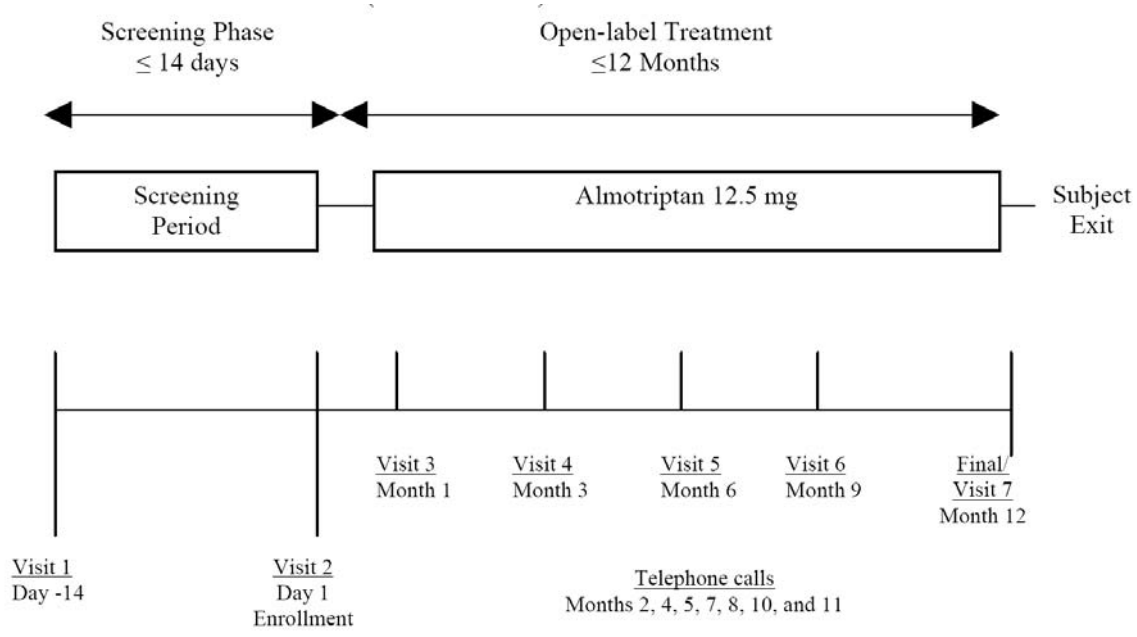
A total of 302 (67.6%) subjects treated at least 6 headaches in the first 180 days of the study, and 227 (50.8%) subjects treated at least 12 headaches and participated in the study for at least 350 days. 50.7% of the treated subjects were in the 12 to 14 year age group and 49.3% were in the 15 to 17 year age group.

5.3.4.1 Study 3 Design and Treatment Regimen

This was a phase 3b, multicenter, open-label study of adolescent subjects 12 to 17 years of age. The primary objective of the study was to evaluate the long-term safety of oral administration of almotriptan 12.5 mg in the treatment of multiple migraine episodes over a period of up to 12 months. Efficacy was assessed descriptively as a secondary objective of the study.

The study flow diagram, below, depicts the schedule of events for this trial:

Figure 2: Study Flow Diagram CAPPS-368, Long-term Safety Study (Review Study 3)



As in Study 2, before any screening procedures were performed, potential subjects signed an assent form and their parents or legal guardians signed a written informed consent form

indicating that they understood the purpose of and procedures required for the study and were willing to have their child participate in the study.

Eligible subjects were male or female between the ages of 12 and 17 years with a history of migraine with or without aura, defined by HIS criteria. Subjects had to have a history of 1 to 14 migraines and <15 headache days per month for at least 6 months before study enrollment, and headaches had to occur at intervals of >24 hours between attacks. Approximately equal numbers of subjects 12 to 14 years of age and 15 to 17 years of age were to be enrolled. To achieve this goal, study enrollment logs and the number of subjects in each age group were tracked during enrollment.

The study included a screening visit (visit 1) to determine subject eligibility to participate in the study and an open-label treatment phase that was to begin (visit 2) within 14 days following visit 1. At visit 2, eligible subjects were instructed to self-dose orally with 1 almotriptan (12.5 mg) tablet soon after the onset of migraine headache pain, preferably within an hour of onset. Study medication and headache records were dispensed.

During the open-label treatment phase, subjects were to treat all migraine episodes with almotriptan 12.5 mg for up to 12 months. Allowable rescue medication, which included antiemetics and a second dose of study medication, was permitted at any time; however, subjects were encouraged to wait a minimum of 2 hours after taking study medication. Subjects recorded medication use and migraine information on their medication and headache record.

Study visits occurred at months 1, 3, 6, 9 and 12. Following visit 3 (month 1), telephone contacts were initiated by site staff each month when there was no study visit scheduled (months 2, 4, 5, 7, 8, 10, and 11) to address subject and/or parent/caregiver concerns and to inquire about AEs.

5.3.4.2 Study 3 Evaluation Criteria

Since this was a long-term safety study, efficacy was not defined in terms of primary and secondary endpoints. The following parameters, however, were defined:

- *Pain relief*: decrease in baseline pain intensity from severe or moderate to mild or no pain at 2 (or 24) hours after a dose of almotriptan without the use of a second dose or other supplemental pain or antiemetic medication
- *Sustained pain relief*: pain relief at 2 hours and at 24 hours after a first dose of almotriptan without the use of a second dose or other supplemental pain or antiemetic medication
- *Pain free*: decrease in baseline pain intensity from severe, moderate, or mild to no pain at 2 (or 24) hours after a first dose of almotriptan without the use of a second dose or other supplemental pain or antiemetic medication
- *Sustained pain free*: pain free at 2 hours and at 24 hours after the first dose of almotriptan malate without use of a second dose or other supplemental pain or antiemetic medication

• *Occurrence of migraine symptoms* (photophobia, phonophobia, and nausea) and occurrence of vomiting at 2 hours and 24 hours postdose
• *Use of rescue medication*, defined as supplemental pain medication and/or antiemetic medication including a second dose of almotriptan, within 24 yours of the first dose of almotriptan

Safety evaluations included AEs, brief physical examinations, brief neurological examinations, clinical laboratory tests, ECG recordings, vital signs, and pregnancy testing. The following table of events outlines the chronology of this data collection:

Table 18: Long-term Safety Study (Study 3) TOE Table

Procedures	Screening Phase	Open-label Phase						
	Visit 1 Day –14	Baseline Visit 1 Day 1	Visit 3[a] Month 1	Phone calls[b]	Visit 4 Month 3	Visit 5 Month 6	Visit 6 Month 9	Final/ Visit 7[c] Month 12
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Medical, medication, and migraine history	X							
Brief physical examination	X					X		X
Brief neurological examination	X							X
Electrocardiogram	X							X
Vital signs[d]	X	X	X		X	X	X	X
Clinical labs[e]	X					X		X
Urine drug screen	X							
Pregnancy test[f]	X	X	X		X	X	X	X
Record concomitant medication	X	X	X	X	X	X	X	X
Dispense headache record[g]		X	X		X	X	X	
Record adverse events		X	X	X	X	X	X	X
Dispense study medication[h]		X	X		X	X	X	
Review headache record			X		X	X	X	X
Study medication return			X		X	X	X	X

[a] If subjects did not treat a migraine with study medication before Visit 3, they were to be discontinued and Final Visit procedures were to be completed. Subjects who treated a migraine with study medication had their headache records reviewed and adverse events discussed.
[b] Following Visit 3, telephone contacts were initiated by site staff each month when there was no study visit scheduled (Months 2, 4, 5, 7, 8, 10 and 11) for the purpose of addressing subject and/or parent/caregiver concerns and inquiring about adverse events and concomitant medications.
[c] Procedures listed in this column were performed at the subject's last visit, either after 12 months or at Early Termination.
[d] Oral temperature, sitting pulse, respiratory rate, blood pressure, and weight. Height at Visits 1, 5 and 7 only.
[e] Screening, Visit 5 and final laboratory assessments included hematology, serum chemistry, and urinalysis.
[f] A pregnancy test was required at Visit 2 if it was more than 7 days since the screening visit. Urine pregnancy tests were conducted on all female subjects of childbearing potential at each visit. Urine pregnancy testing was also conducted at each visit on female subjects who developed menses after enrollment in the study.
[g] All information regarding migraine headaches was collected at baseline and 2 and 24 hours after dosing. Rescue medication use was also collected on the headache record.
[h] In addition to scheduled visits, subjects could have visited the clinic if the need for extra study medication arose. The first dose of study medication had to be taken within 1 month of study entry.

5.3.4.3 Study 3 Statistical Methods

Sample size was determined by requirements for a long-term safety study specified in the amended PWR and was not based on statistical considerations. They estimated that approximately 450 subjects would need to be enrolled to obtain 6 months of safety data for at least 200 subjects and 12 months of safety data for at least 75 subjects, with a similar number of subjects in the 12 to 14 year and 15 to 17 year age groups.

Descriptive statistics were used for the analyses of safety and efficacy data. No formal statistical comparisons were planned for safety or efficacy analyses. Safety analyses were summarized for the *safety population, defined as all subjects who took study medication according to the headache record*. The number and percentage of subjects with AEs were summarized.

For clinical laboratory tests (hematology, serum chemistry, and urinalysis) and vital signs data, descriptive statistics for continuous parameters and number and percentage of subjects in each category for categorical parameters were calculated for each study visit. Observed values and change-from-baseline values were evaluated. For ECG assessments, changes from baseline to the final visit were summarized descriptively for heart rate, PR interval, QRS interval, heart-rate corrected QT interval (QTc)-Bazett, and QTc-Fredericia.

Efficacy analyses were based on the intent-to-treat (ITT) population, defined as all subjects who took a dose of study medication and had ≥1 postdose efficacy assessment. Efficacy data included headache pain intensity and symptom intensity. The number and percentage of headache events that achieved pain-free status, achieved pain relief, were associated with occurrence of migraine (photophobia, phonophobia, and nausea) and occurrence of vomiting at 2 hours and 24 hours post-dosing, achieved sustained pain-free status, and achieved sustained pain relief were calculated. The number and percentage of headache events associated with the use of supplemental pain medication and/or antiemetic medication were also summarized.

5.3.4.4 Study 3 Subject Disposition and Baseline Characteristics

Subjects were enrolled at 53 sites in the United States. In total, 447 subjects were enrolled with a similar number of subjects in the 12 to 15 year age group (226) and 15 to 17 year age group (221). The following table illustrates the frequency and timing for the safety, efficacy, and other assessments.

Of the 447 subjects enrolled, 420 (94.0%) subjects took at least 1 dose of study drug according to the headache record and were included in the safety population. Three hundred two (302) of the 447 subjects enrolled (67.6%) treated at least 6 headaches in the first 180 days of the study, and 227 (50.8%) subjects treated at least 12 headaches and participated in the study for more than 350 days.

Three hundred nineteen (319) of the 447 subjects enrolled (71.4%) completed the 12-month study as shown in the following table:

Table 19: Study 3 Enrolled Population Subject Disposition

	12-14 yr Age Group N = 226	15-17 yr Age Group N = 221	Overall N = 447
Number (%) subjects who completed the study	166 (73.5%)	153 (69.2%)	319 (71.4%)
Number (%) subjects who discontinued early	60 (26.5%)	68 (30.8%)	128 (28.6%)
Reason for early discontinuation			
Lost to follow-up	23 (10.2%)	30 (13.6%)	53 (11.9%)
Subject choice	13 (5.8%)	21 (9.5%)	34 (7.6%)
Lack of efficacy	9 (4.0%)	2 (0.9%)	11 (2.5%)
Other	3 (1.3%)	8 (3.6%)	11 (2.5%)
Limiting adverse event	7 (3.1%)	3 (1.4%)	10 (2.2%)
No headache treated with study medication within 30 days of Baseline Visit	5 (2.2%)	4 (1.8%)	9 (2.0%)

Note: Percentages were calculated using the number of enrolled subjects in each age group.
Cross-reference: Attachment 1.2; Section 10.

One hundred twenty-eight (28.6%) subjects discontinued from the study early. Reasons for early discontinuation were lost to follow-up (11.9%), subject choice (7.6%), lack of efficacy (2.5%), other (2.5%), limiting adverse event (2.2%), and no headache treated with study medication within 30 days of the Baseline Visit (2.0%).

The 'other' reasons for discontinuation included but were not limited to lack of drug accountability, non-compliance with protocol, pregnancy, and lack of migraines. The percentages of subjects who were enrolled and who completed the study were similar in both age groups. The most common reasons for early discontinuation were lost to follow-up (53 subjects [11.9%]) and subject choice (34 subjects [7.6%]).

Analysis of the subject populations in those enrolled is shown in this table:

Table 20: Study 3 Subject Populations of those Enrolled.

Population	12-14 yr Age Group	15-17 yr Age Group	Overall
Enrolled subjects[a]	226	221	447
Safety subjects[b]	213 (94.2%)	207 (93.7%)	420 (94.0%)
Intent-to-Treat subjects[c]	213 (94.2%)	207 (93.7%)	420 (94.0%)
Treated 6 headaches in first 180 days	154 (68.1%)	148 (67.0%)	302 (67.6%)
Treated at least 12 headaches and were in study for more than 350 days	113 (50.0%)	114 (51.6%)	227 (50.8%)

Note: Percentages were calculated using the number of enrolled subjects in each age group dispensed study medication.
[a] Subjects who met entry criteria, agreed to participate, and were dispensed study medication.
[b] Subjects who took at least one dose of study medication according to the Headache Record.
[c] Subjects who took at least one dose of study medication and had at least one post-dose efficacy assessment.
Cross-reference: Attachment 1.3; Section 10.

The ages appear evenly split, as do the number of headaches over each interval.

Enrollment exceeded the requirements of the long-term safety study specified in the amended PWR. The median number of tablet doses taken per headache was 1.2 (range 1 – 2). All 420 subjects in the safety population also had at least 1 postdose efficacy assessment and were included in the ITT population.

There were more females (55.5%) than males (44.5%) in the study. Mean age was 14.4 years (range, 12 to 17 years). Approximately 82% of subjects were white, 16% were black, and 2% were of other races; approximately 11% were Hispanic or Latino.

The percentage of male subjects was higher in the 12 to 14 year group compared with the 15 to 17 year group (55.4% vs. 33.3%). A higher percentage of subjects in the 12 to 14 year group were white compared with the 15 to 17 year group (87.3% vs. 78.0%) and a higher percentage of subjects were black in the 15 to 17 year group compared with the 12 to 14 year group (21.0% vs. 11.3%). Mean BMI of the younger age group was less than the older group (21 kg/m2 vs. 23 kg/m2). The following table summarizes both the demographic and the baseline characteristics of the subjects:

Overall, 72% of subjects took at least 1 concomitant medication. The most common concomitant medications were systemic antihistamines (24.5%), nonsteroidal anti-inflammatory/anti-rheumatic agents (21.7%), other analgesics and antipyretics (20.5%), and beta-lactam antibacterials (13.8%).

In total, 334 (79.5%) subjects took rescue medication for 1 or more of their headaches during their participation in the study. Of these 334 subjects, 306 (72.9%) took a second dose of almotriptan. The most common supplemental pain medications and/or antiemetic medications were nonsteroidal anti-inflammatory/anti-rheumatic products (25.7%) and other analgesics and antipyretics (20.0%).

Table 21: Study 3 Baseline Demographics and Characteristics

Demographic/Baseline Characteristic	12-14 yr Age Group N = 213	15-17 yr Age Group N = 207	Overall N = 420
Age (years)			
Mean (SD)	13.0 (0.83)	15.8 (0.77)	14.4 (1.61)
Median	13	16	14
Range	12, 14	15, 17	12, 17
Sex, n (%)			
Male	118 (55.4%)	69 (33.3%)	187 (44.5%)
Female	95 (44.6%)	138 (66.7%)	233 (55.5%)
Race, n (%)			
White	186 (87.3%)	160 (78.0%)	346 (82.4%)
Black	24 (11.3%)	43 (21.0%)	67 (16.0%)
Asian	2 (0.9%)	1 (0.5%)	3 (0.7%)
American Indian or Alaska Native	0	1 (0.5%)	1 (0.2%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0	1 (0.2%)
Other	0	2 (1.0%)	2 (0.5%)
Ethnicity			
Hispanic or Latino	22 (10.3%)	25 (12.1%)	47 (11.2%)
Not Hispanic or Latino	191 (89.7%)	182 (87.9%)	373 (88.8%)
Weight (lbs)			
Mean (SD)	118.6 (27.13)	138.0 (26.32)	128.2 (28.42)
Median	115	135	126
Range	66, 190	89, 254	66, 254
Height (in)			
Mean (SD)	62.9 (3.85)	65.7 (3.80)	64.3 (4.05)
Median	63	65	64
Range	51, 72	51, 76	51, 76
BMI (kg/m^2)			
Mean (SD)	20.9 (3.56)	22.5 (3.80)	21.7 (3.76)
Median	20.5	21.8	21.3
Range	15.3, 31.6	16.4, 46.0	15.3, 46.0
Oral temperature (°F)			
Mean (SD)	97.8 (0.74)	97.7 (0.76)	97.8 (0.75)
Median	97.9	97.7	97.9
Range	95.4, 100.9	93.0, 99.2	93.0, 100.9
Pulse (bpm)			
Mean (SD)	77.4 (10.89)	75.7 (11.00)	76.6 (10.97)
Median	78	74	76
Range	50, 108	51, 114	50, 114
Respiratory rate (breaths/min)			
Mean (SD)	17.4 (2.66)	17.4 (2.49)	17.4 (2.58)
Median	18	17	18
Range	12, 26	10, 26	10, 26
Systolic blood pressure (mm Hg)			
Mean (SD)	106.2 (11.18)	109.3 (11.25)	107.8 (11.31)
Median	105	110	108
Range	70, 139	80, 141	70, 141
Diastolic blood pressure (mm Hg)			
Mean (SD)	65.3 (7.77)	67.5 (7.77)	66.4 (7.84)
Median	64	68	66
Range	40, 84	48, 88	40, 88

Abbreviations: BMI = body mass index; bpm= beats per minute; SD = standard deviation
Note: Percentages were calculated using the number of Safety subjects with non-missing values in each age group. BMI was calculated using the following formula: 703 * Weight (lbs)/Height^2 (in^2)
Cross-reference: Attachment 1.4.2; Section 10.

5.3.4.5 Study 3 Extent of Exposure

The safety population's study medication exposure is shown here:

Table 22: Study Medication Exposure: Study CAPSS-368 (Safety Population)

	Almotriptan 12.5 mg (N=420)
Total dose per subject (mg)	
Mean (SD)	291.6 (248.91)
Range	12.5 – 1337.5
Average dose per headache (mg)	
Mean (SD)	15.1 (2.67)
Range	12.5 – 25.0
Average number of doses per headache	
Mean (SD)	1.2 (0.21)
Range	1 – 2

Abbreviations: SD = standard deviation

Cross-reference: Mod5.3.5.2\CAPSS-368\Attachment1.9.

6 Review of Efficacy

To assist in review, the efficacy trial overview is reproduced here in Table 23. Note that the long-term safety study, CAPPS-368, was uncontrolled and is not reviewed in this section. Only study 015, the controlled efficacy trial is analyzed in this section.

Table 23: Overview of Company-sponsored Clinical Studies Providing Efficacy Data Relevant to Migraine

Study No. No. Study Sites[a] Country Study Period (Start / End Date) Subjects Planned / Subjects Enrolled	Study Design Study Objective Diagnosis	Treatment Dosage Route Duration	No. Subjects Evaluable for Efficacy (ITT) Overall (By treatment group) By gender: M/F Mean Age, yrs (range)	Primary Endpoint
638-CNS-0059-015 93 study sites Argentina, Colombia, Mexico, USA 22 July 2003 / 29 April 2005 924 / 866	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging Efficacy and safety Migraine with or without aura as defined by IHS criteria	Placebo; Almo 6.25, 12.5, or 25 mg Oral Single dose for single migraine attack	714 Placebo (170) M/F: 62/108 14.4 (12-17) Almo 6.25 mg (177) M/F: 75/102 14.4 (12-17) Almo 12.5 mg (181) M/F: 80/101 14.2 (12-17) Almo 25 mg (186) M/F: 71/115 14.4 (12-17)	4 coprimary endpoints: 2-hour pain relief plus presence of nausea, photophobia, and phonophobia
CAPSS-368 53 study sites USA 23 December 2005 / 19 December 2007 450 / 447	Phase 3b, multicenter, open-label Long-term safety Migraine with or without aura as defined by IHS criteria	Almo 12.5 mg Oral Single doses for multiple migraine attacks, with an optional second dose if needed 12 months	420 M/F: 187/233 14.4 (12-17)	Efficacy was a secondary objective; no primary or secondary endpoints

Abbreviations: AE = adverse event; Almo = almotriptan; ECG = electrocardiogram; F = female; ITT = intent-to-treat; IHS = International Headache Society; M = male; yrs = years.
[a] Study sites that enrolled subjects

As a prelude to the detailed efficacy review, a study drug tabular overview of the results (headache pain relief and migraine-associated symptoms 2 hours post-dose by age group) is presented from the only double-blinded, placebo-controlled efficacy study (Review Study 2, 638-CNS-0059-015 (ITT Population)). This trial is the basis for the efficacy review.

Upon completion of Review Study 2, the sponsor chose the 12.5 mg dose for its long-term safety study (CAPSS-368, Review Study 3), and this is the proposed marketed drug's dose in the adolescent population.

Efficacy Summary

The sponsor presents all available information relevant to the efficacy of almotriptan in subjects ≤17 years of age. Virtually all aspects of these trials were developed with the Division over the course of development, including the components of the original PWR. Sources of efficacy data include the 2 company-sponsored clinical studies in subjects 12 to 17 years of age as specified by the amended PWR as noted in Mod1.6.3\PWR\01February2005) and by agreements with the Division contained in (Mod1.6.3\FDA SPA Letter\28January2005, (Mod1.6.3\MeetingMinutes\29August2006).

As noted, there were studies submitted to the NDA:

- Efficacy study 638-CNS-0059-015 (corresponding to Study 1 in the PWR and referred to in the Review as Study 2), detailed in this section, and
- Long-term safety study CAPSS-368 (corresponding to Study 2 in the PWR and Study 3 in this Review), detailed in the section following efficacy.

This summary also includes a review of the literature pertinent to efficacy of almotriptan in pediatric patients. Since Study 3, the long-term safety study, is uncontrolled, the efficacy data for that trial is not analyzed in this review section.

For details of these trials, including their descriptions along with their primary and important secondary endpoints, please see Discussion of Individual Studies, Section 5.3 above. Note pooling of efficacy data across the 2 company-sponsored studies was not performed due to differences in study designs, study populations, and treatment regimens. This was by prior agreement between the sponsor and the Division. The controlled study was of adequate duration and was adequately sized and well-controlled. The entry criteria were appropriate for the adolescent migraine population.

Again, Review Study 2, (aka PWR Study 1 and Sponsor Study 638-CNS-0059-015) is the basis of this efficacy review since it is the only controlled trial with analysis of the 4 co-primary endpoints. This was a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled acute treatment trial in adolescent subjects 12 to 17 years of age.

Please see Review Section 5.3.3 above for details of the trial. Briefly, the primary objective of the study was to evaluate the efficacy of almotriptan versus placebo at 2 hours postdose for the 4 co-primary endpoints:

• Headache pain relief 2 hours postdose, defined as a decrease in headache pain intensity from either moderate or severe intensity to mild or no pain, plus
• Presence of nausea, photophobia, and phonophobia at 2 hours postdose.

The choice of endpoints reflects the 4 primary co-endpoints chosen by the Division and used for all current migraine trials: headache relief at 2 hours postdose, as well as relief of the migraine associated symptoms of nausea, phonophobia, and photophobia. These endpoints have been

well-established over the years and are well-known to sponsors. The Division requirement was for analysis in the 12 – 17 year age group. The sponsor, however, performed an additional analysis stratified by age (12 – 14 and 15 – 17). Patients maintained the standard diaries of their headache frequency, presence of associated symptoms, etc., which were the sources of data for the trials.

Secondary objectives were:

- Headache pain relief at 0.25, 0.5, 1.0, and 1.5 hours postdose
- Presence of nausea, photophobia, and phonophobia at 0.25, 0.5, 1.0, and 1.5 hours postdose
- Presence of vomiting at 0.25, 0.5, 1.0, 1.5, and 2.0 hours postdose
- Headache pain-free response, defined as a decrease in headache pain intensity from moderate or severe to none, at 0.25, 0.5, 1.0, 1.5, and 2.0 hours postdose
- Headache recurrence, defined as significant worsening of headache pain intensity from none or mild to moderate or severe, within 2 to 24 hours postdose in responders, where responders were subjects with headache pain relief 2 hours postdose
- Time to recurrence
- Use of rescue medication 2 to 24 hours postdose
- Sustained pain relief, defined as headache pain relief at 2 hours postdose with no recurrence of moderate or severe pain and no use of rescue medication 2 to 24 hours postdose
- Sustained pain-free response, defined as headache pain free at 2 hours postdose with no recurrence of pain and no use of rescue medication 2 to 24 hours postdose and

No formal comparisons of the safety parameters between treatment groups were performed. Efficacy analyses were based on the intent-to-treat (ITT) population, defined as all randomized subjects who took a dose of study medication and had ≥1 postdose efficacy assessment.

In the adolescent population, the Division requires efficacy to be demonstrated on pain relief at 2 hours, as noted. The Division's current standard does not require efficacy demonstration for associated symptoms in the pediatric population if efficacy has already been established in adults.

6.1 Indication

Acute treatment of migraine with or without aura in adolescent patients 12 to 17 years of age.

6.1.1 Methods

Please see above, Discussion of Individual Studies Section 5.3 of the Review. For the efficacy clinical review, Review Study 2 (PWR Study 1) was the only controlled trial and thus is the only one reviewed in detail in this section.

6.1.2 Demographics

Please see above, Discussion of Individual Studies Section 5.3 of the Review.

6.1.3 Patient Disposition

Please see above, Discussion of Individual Studies Section 5.3 of the Review.

6.1.4 Analysis of Primary Endpoint(s)

For the analysis of primary endpoints, I first present the sponsor's analyses and conclusions, and follow with the FDA analyses as recorded by Dr. Tristan Massie of Biostatistics. Many of the sponsor's analyses were exploratory and not corrected for multiplicity, thus precluding a firm conclusion from the analyses.

The sponsor found the percentage of subjects with headache pain relief at 2 hours postdose was statistically significantly higher in the almotriptan 25 mg group compared with the placebo group (66.7% vs.55.3%; *P*=0.022). But they report no statistically significant differences between the almotriptan 25 mg and placebo groups in the percentage of subjects with the presence of nausea, photophobia, and phonophobia at 2 hours postdose.

Therefore, in accordance with the analytical method predefined in the statistical analysis plan, the sponsor terminated the step-down procedure was terminated and concluded none of the 3 almotriptan doses was superior to placebo on all 4 primary endpoints.

The sponsor performed exploratory analyses without adjustment for multiplicity assessing the efficacy of all almotriptan doses for each of the 4 primary endpoints. Discarding multiple comparisons renders their conclusions at minimum, questionable. As will be seen below, the FDA statistical analysis showed the only primary endpoint, when corrected for multiplicity, which achieved statistical significance, was headache relief at two hours.

Nevertheless, based on their analysis without multiple comparison adjustments, as shown in Table 24 and illustrated in Figure 3, they sponsor concluded the percentage of subjects with headache pain relief at 2 hours postdose was statistically significantly higher in all 3 almotriptan dose groups (6.25 mg, 12.5 mg, 25 mg) relative to the placebo group (71.8%, 72.9%, 66.7% vs. 55.3%). Their analysis of the presence of migraine-associated symptoms at 2 hours postdose showed a statistically significantly lower percentage of subjects with photophobia and with phonophobia in the almotriptan 12.5 mg group relative to the placebo group (photophobia: 24.7% vs. 40.6%; phonophobia: 21.9% vs. 34.5%). I believe this is an incorrect conclusion since there were no adjustments for multiple comparisons.

There were also lower percentages of subjects with photophobia and phonophobia in the almotriptan 6.25 mg and almotriptan 25 mg groups relative to the placebo group, although the differences did not reach the nominal significant level. Differences between each almotriptan dose group and the placebo group in the percentage of subjects with nausea 2 hours postdose

were not statistically significant. Again, absent adjustments for multiple comparisons, these analyses are questionable, but are presented here for the reader's consideration.

Table 24: Headache Pain Relief and Migraine-associated Symptoms at 2 Hours Postdose – Exploratory Analyses – 638-CNS-0059-015, Review Study 2

	Placebo (N=170)	Almotriptan 6.25 mg (N=177)	Almotriptan 12.5 mg (N=181)	Almotriptan 25 mg (N=186)
2-Hour pain relief				
n	170	177	181	186
x (%)	94 (55.3%)	127 (71.8%)	132 (72.9%)	124 (66.7%)
Adjusted *P* value		0.001	0.001	0.022
Unadjusted *P* value		0.001	<0.001	0.028
Presence of nausea				
n	165	174	178	179
x (%)	26 (15.8%)	24 (13.8%)	30 (16.9%)	37 (20.7%)
Adjusted *P* value		0.610	0.774	0.245
Unadjusted *P* value		0.610	0.784	0.238
Presence of photophobia				
n	165	174	178	179
x (%)	67 (40.6%)	58 (33.3%)	44 (24.7%)	62 (34.6%)
Adjusted *P* value		0.161	0.002	0.238
Unadjusted *P* value		0.165	0.002	0.253
Presence of phonophobia				
n	165	173	178	179
x (%)	57 (34.5%)	46 (26.6%)	39 (21.9%)	55 (30.7%)
Adjusted *P* value		0.111	0.013	0.429
Unadjusted *P* value		0.112	0.009	0.450

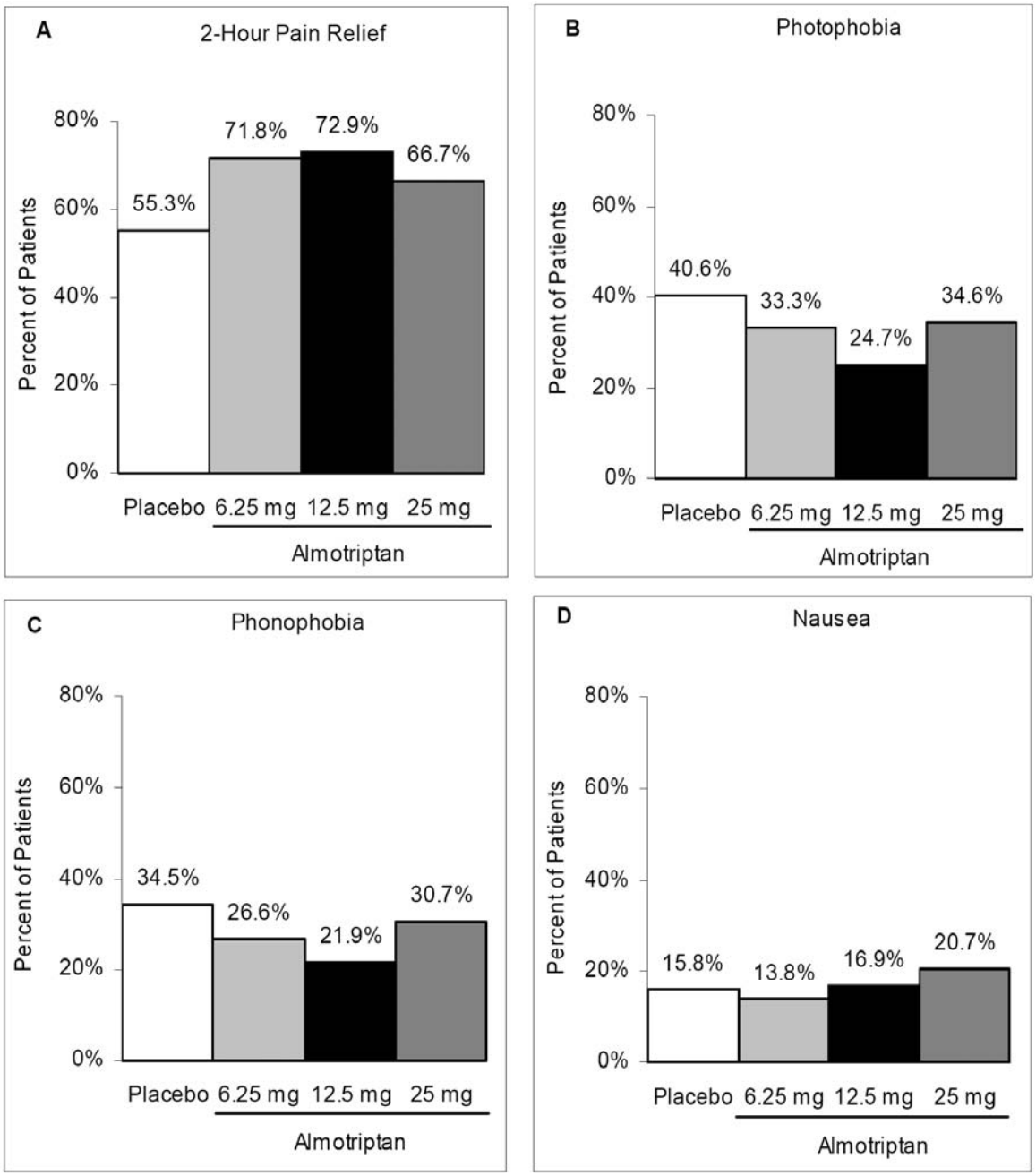
n = number of subjects with available data; x = number of subjects with the effect; percentages based on the number of subjects with available data in each treatment group.
Adjusted *P* values from Cochran-Mantel-Haenszel (CMH) test to assess treatment group differences (almotriptan vs. placebo) adjusting for baseline headache pain intensity.
Unadjusted *P* values from likelihood ratio chi-square test to assess treatment group differences (almotriptan vs. placebo).

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableE-2.1.5, \TableE-3.1.1, \TableE-3.1.2, Appendix1.7\TableE-4.2.1, Appendix1.8\TableE-4.2.2, Appendix1.9\TableE-4.2.3.

Of interest in the above table is the dose-dependent increase in nausea. It is difficult, also, to understand the presence of photophobia observations since the 6.25 mg dose (below the 12.5 mg dose) and the 25 mg dose (above the 12.5 mg dose) aren't consistent and do not trend as one might expect. And, after correcting for multiple comparisons, only headache relief achieved significance as stated at the outset.

The following figures show all this exploratory information graphically:

Figure 3: Summary of Headache Pain Relief and Migraine-associated Symptoms at 2 Hours Postdose: for the ITT Population in Efficacy Study 638-CNS-0059-015, Review Study 2, Exploratory Analyses



(A) 2-hour pain relief; (B) presence of photophobia 2 hours postdose; (C) presence of phonophobia 2 hours postdose; (D) presence of nausea 2 hours postdose.

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableE-3.1.1, \TableE-3.1.2.

The sponsor also explored the efficacy results at other time points in the trial. Their exploratory analysis found the percentage of subjects with headache pain relief at 1.5 hours postdose was higher for each of the 3 almotriptan dose groups (6.25 mg, 12.5 mg, 25 mg) relative to the

placebo group (54.2%, 55.2%, 52.2% vs. 44.1%), although the difference from placebo was statistically significant only for the 12.5 mg dose (*P*=0.059, *P*=0.037, *P*=0.130; from likelihood ratio chi-square test unadjusted for baseline severity).

While these are all exploratory analyses, I provide their results are displayed as shown in Table 10 of the trial's Clinical Study Report, reproduced here:

Table 25: Headache Pain Relief at 0.25, 0.5, 1, 1.5, and 2 Hours Post-dose and at 0.25, 0.5, 1, and 1.5 Hours Post-dose with and without Adjusting for Baseline Pain Intensity

Parameter			Almotriptan		
	Statistics	Placebo	6.25 mg	12.5 mg	25 mg
Number of Patients in the ITT Population	N	170	177	181	186
Number of Patients with Pain Relief at:					
0.25 Hours	n (%)	4 (2.4)	8 (4.5)	5 (2.8)	5 (2.7)
	Unadjusted p-value		0.265	0.808	0.840
	Adjusted p-value		0.267	0.904	0.832
0.5 Hours	n (%)	30 (17.6)	21 (11.9)	25 (13.8)	27 (14.5)
	Unadjusted p-value		0.128	0.323	0.421
	Adjusted p-value		0.118	0.200	0.458
1 Hours	n (%)	55 (32.4)	55 (31.1)	59 (32.6)	56 (30.1)
	Unadjusted p-value		0.798	0.961	0.648
	Adjusted p-value		0.795	0.795	0.708
1.5 Hours	n (%)	75 (44.1)	96 (54.2)	100 (55.2)	97 (52.2)
	Unadjusted p-value		0.059	0.037*	0.130
	Adjusted p-value		0.051	0.062	0.104
2 Hours	n (%)	94 (55.3)	127 (71.8)	132 (72.9)	124 (66.7)
	Unadjusted p-value		0.001**	<0.001**	0.028*

Data Source: Tables E-2.1.1.1 to E-2.1.5

The sponsor concludes that their exploratory analyses demonstrated no other statistically significant differences in headache pain relief between almotriptan and placebo treatments occurred at other earlier time points. Statistically significant differences between almotriptan 12.5 mg and placebo treatments were observed for phonophobia at 1.5 hours (34.1% vs. 45.8%; *P*=0.043.

Again, these are exploratory analyses, and therefore firm conclusions are not possible. For comparative purposes, the baseline data from Table 11 of the clinical study report are presented below:

Table 26: Occurrence of Nausea, Vomiting, Photophobia, and Phonophobia Immediately Prior to Taking Study Medication (Baseline) without Adjusting for Baseline Pain Intensity (Exploratory Analyses)

Parameter			Almotriptan		
	Statistics	Placebo	6.25 mg	12.5 mg	25 mg
Number of Patients in the ITT Population	N	170	177	181	186
Number of Patients with Associated Symptoms Immediately Before Taking Study Medication					
Nausea	n (%)	82 (48.2)	78 (44.1)	75 (41.1)	81 (43.5)
	Unadjusted p-value		0.436	0.200	0.375
	Adjusted p-value		0.429	0.292	0.358
Vomiting	n (%)	14 (8.2)	12 (6.8)	12 (6.6)	11 (5.9)
	Unadjusted p-value		0.607	0.566	0.392
	Adjusted p-value		0.601	0.665	0.368
Photophobia	n (%)	138 (81.2)	132 (74.6)	143 (79.0)	159 (85.5)
	Unadjusted p-value		0.138	0.611	0.275
	Adjusted p-value		0.124	0.854	0.296
Phonophobia	n (%)	127 (74.7)	125 (70.6)	133 (73.5)	142 (76.3)
	Unadjusted p-value		0.393	0.793	0.719
	Adjusted p-value		0.380	0.930	0.766

The sponsor observes no other statistically significant differences in the presence of phonophobia or photophobia were observed between almotriptan and placebo treatments at any other earlier time points in these exploratory analyses. The percentage of subjects with the presence photophobia and phonophobia in the almotriptan 6.25 mg and 12.5 mg groups was lower than that in the placebo group at 0.5, 1 and 1.5 hours postdose, but the difference did not reach statistical significance. In the almotriptan 25 mg group, the percentage of subjects with the presence of photophobia and phonophobia was generally higher than that in the placebo group. But as has been repeatedly mentioned, any firm conclusions are not possible for the reasons given.

The sponsor shows percentage of subjects with the presence of nausea 1 hour postdose was statistically significantly higher in the almotriptan 25 mg group compared with the placebo group (34.8% vs. 24.0%; *P*=0.028). This would argue against approving the 25 mg dose in adolescents.

As discussed in 1 Review Section 5.2, Dr. Tristan Massie of Biostatistics performed an analysis of the primary and secondary endpoints, which have been incorporated into this portion of the sNDA review. For the Primary Endpoint, he verified the sponsor's analysis as recorded here in italic font and states the following:

"Each of the three Almotriptan groups was nominally significantly better in terms of pain relief than the placebo group at 2 hours post-dose. However, none of the Almotriptan groups was better than placebo in terms of the presence of nausea at 2 hours postdose. In fact, most were numerically worse in terms of the presence of nausea at 2 hours postdose. If the requirement to win on the associated symptoms was removed based on clinical judgment in this pediatric setting and the testing of pain relief started with the high dose and worked down (conditional on

significance), as specified in the protocol, then we would conclude that each Almotriptan group was significantly better than placebo in terms of pain relief at 2 hours post-dose.

The treatment group differences in headache pain relief at 2 hours postdose between Almotriptan and placebo were relatively consistent across investigators and excluding any one investigator from the analysis would not change the conclusions."

6.1.5 Analysis of Secondary Endpoints(s)

Recall, the sponsor collected data on these exploratory secondary endpoints:

- *Headache pain relief* at 0.25, 0.5, 1.0, and 1.5 hours postdose
- *Presence of nausea, photophobia, and phonophobia* at 0.25, 0.5, 1.0, and 1.5 hours postdose
- *Presence of vomiting at 0.25, 0.5, 1.0, 1.5, and 2.0 hours* postdose
- *Headache pain-free response*, defined as a decrease in headache pain intensity from moderate or severe to none, at 0.25, 0.5, 1.0, 1.5, and 2.0 hours postdose
- *Headache recurrence*, defined as significant worsening of headache pain intensity from none or mild to moderate or severe, within 2 to 24 hours postdose in responders, where responders were subjects with headache pain relief 2 hours postdose
- *Time to recurrence*
- *Use of rescue medication* 2 to 24 hours postdose
- *Sustained pain relief*, defined as headache pain relief at 2 hours postdose with no recurrence of moderate or severe pain and no use of rescue medication 2 to 24 hours postdose
- *Sustained pain-free response*, defined as headache pain free at 2 hours postdose with no recurrence of pain and no use of rescue medication 2 to 24 hours postdose

An overview of the results of the study's secondary efficacy parameters is presented below in Table 27 along with graphic representation of the data, Figure 4, from the clinical study report.

Table 27: Sponsor's Analyses of Secondary Efficacy Parameters: 638-CNS-0059-015 (ITT Population)

	Placebo (N=170)	Almotriptan 6.25 mg (N=177)	Almotriptan 12.5 mg (N=181)	Almotriptan 25 mg (N=186)
Sustained pain relief[a]				
n (%)	89 (52.4%)	119 (67.2%)	121 (66.9%)	120 (64.5%)
Adjusted *P* value		0.004	0.008	0.016
Unadjusted *P* value		0.005	0.006	0.020
Headache pain free at 2 hours postdose				
n (%)	58 (34.1%)	63 (35.6%)	74 (40.9%)	75 (40.3%)
Adjusted *P* value		0.771	0.233	0.205
Unadjusted *P* value		0.773	0.191	0.226
Sustained pain free[b]				
n (%)	56 (32.9%)	61 (34.5%)	71 (39.2%)	73 (39.2%)
Adjusted *P* value		0.763	0.258	0.198
Unadjusted *P* value		0.764	0.220	0.216
Headache recurrence[c]				
n (%)	5 (5.3%)	8 (6.3%)	11 (8.3%)	4 (3.2%)
Adjusted *P* value		0.750	0.402	0.456
Unadjusted *P* value		0.758	0.377	0.444
Use of rescue medication 2 to 24 hours postdose[d]				
n (%)	11 (6.5%)	5 (2.8%)	9 (5.0%)	6 (3.2%)
Adjusted *P* value		0.106	0.521	0.156
Unadjusted *P* value		0.102	0.545	0.150
Presence of vomiting 2 hours postdose[e]				
n	165	173	178	179
x (%)	1 (0.6%)	3 (1.7%)	1 (0.6%)	6 (3.4%)
Adjusted *P* value		0.326	0.957	0.057
Unadjusted *P* value		0.338	0.956	0.074

n (%) = number of subjects with the event; percentages based on the number of subjects in the ITT population in each treatment group

[a] Sustained pain relief = subjects with headache pain relief at 2 hours postdose that continued for 24 hours with no use of rescue medication.

[b] Sustained pain free = subjects who were headache pain free at 2 hours postdose that continued for 24 hours with no use of rescue medication.

[c] Headache recurrence = subjects with headache pain relief at 2 hours postdose who experienced a recurrence within 24 hours.

[d] Use of rescue medication for subjects with and without pain relief at 2 hours is presented.

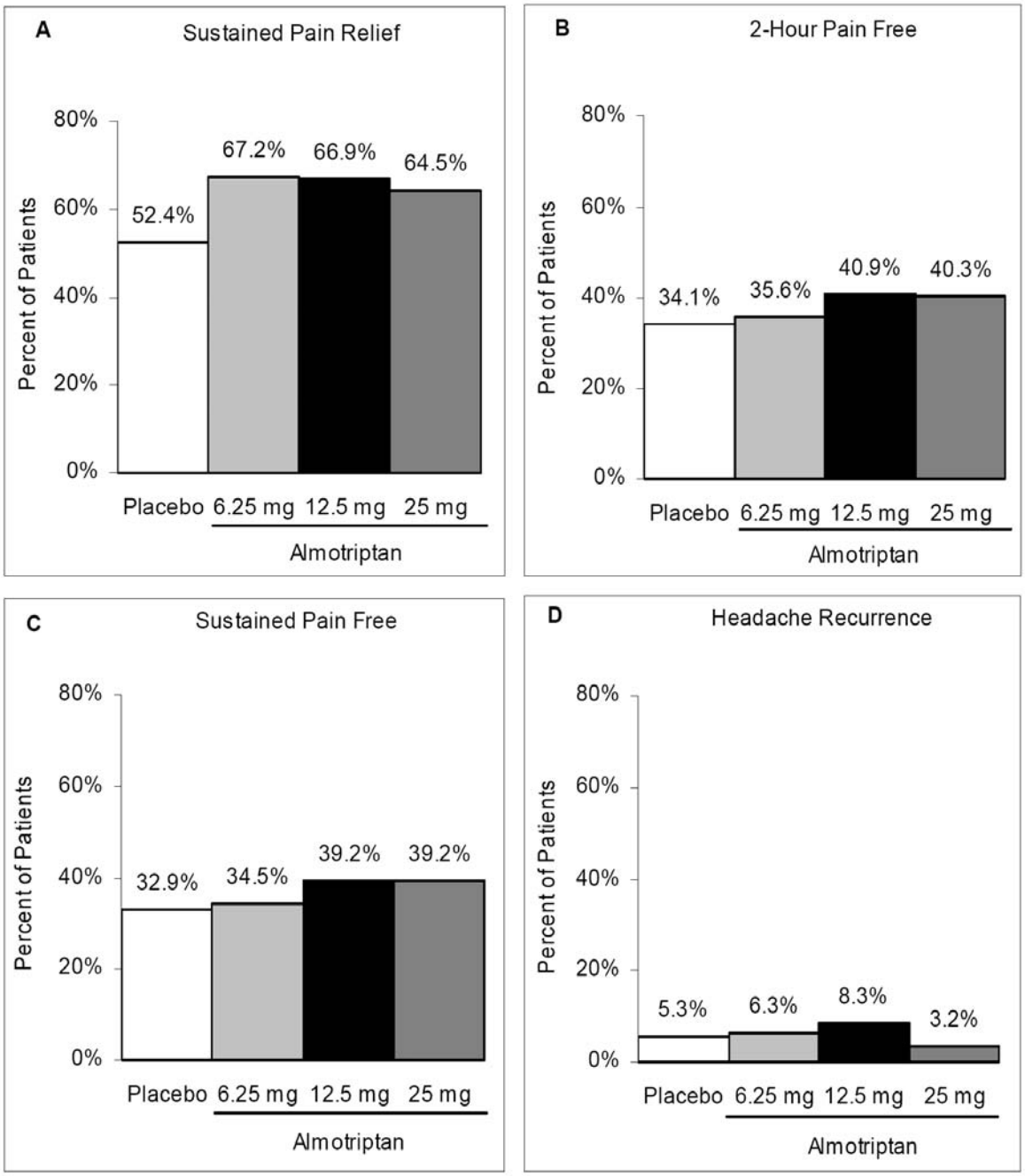
[e] n = number of subjects with available data; x = number of subjects with the presence of vomiting; percentages based on the number of subjects with available data in each treatment group.

Adjusted *P* values from Cochran-Mantel-Haenszel (CMH) test to assess treatment group differences (almotriptan vs. placebo) adjusting for baseline headache pain intensity.

Unadjusted *P* values from likelihood ratio chi-square test to assess treatment group differences (almotriptan vs. placebo)

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableE-2.5.1, TableE-2.5.2, \TableE-2.3.5.1, \TableE-2.3.5.2, \TableE-2.6.1, \TableE-2.6.2, \TableE-2.4.1, \TableE-2.4.2, \TableE-2.7.1, \TableE-2.7.2, \TableE-2.2.6.1, \TableE-2.2.6.2.

Figure 4: Sponsor's Summary of Secondary Efficacy Parameters: 638-CNS-0059-015 (ITT Population)



(A) sustained pain relief 2 to 24 hours postdose; (B) 2-hour pain free; (C) sustained pain free 2 to 24 hours postdose; (D) headache recurrence.

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableE-2.5.1, \TableE-2.3.5.1, \TableE-2.6.1, \TableE-2.4.1.

The sponsor's analyses are all exploratory, and thus are of limited use. Nevertheless, they found the percentage of subjects with *sustained pain relief 2 to 24 hours postdose* was statistically

significantly higher for each of the 3 almotriptan dose groups (6.25 mg, 12.5 mg, 25 mg) relative to the placebo group. But when these data are corrected for multiple comparisons, there is no statistical significance.

The percentage of subjects with a *2-hour headache pain-free response* in the almotriptan 6.25, 12.5, and 25 mg dose groups was higher than that for the placebo group, but differences between the almotriptan and placebo groups were not statistically significant. The 2-hour headache pain-free response is an IHS recommended primary endpoint for migraine trials. The fact they did not achieve statistical significance is an indicator of the response's lack of robustness in this trial.

In the sponsor's analyses, between-group differences (almotriptan vs. placebo) in *headache pain-free* rates were not statistically significant at any of the time points (0.25, 0.5, 1.0, 1.5, and 2 hours) as displayed in this table from the study report:

Table 28: Headache Pain Free at 0.25, 0.5, 1, 1.5 and 2 Hours Post-dose with and without Adjusting for Baseline Pain Intensity

Parameter			Almotriptan		
	Statistics	Placebo	6.25 mg	12.5 mg	25 mg
Number of Patients in the ITT Population	N	170	177	181	186
Number of Patients Who Were Headache Pain Free at:					
0.25 Hours	n (%)	1 (0.6)	0	2 (1.1)	2 (1.1)
	Unadjusted p-value		0.232	0.595	0.611
	Adjusted p-value		0.308	0.629	0.621
0.5 Hours	n (%)	2 (1.2)	3 (1.7)	6 (3.3)	7 (3.8)
	Unadjusted p-value		0.684	0.169	0.109
	Adjusted p-value		0.686	0.197	0.118
1 Hours	n (%)	13 (7.6)	14 (7.9)	17 (9.4)	14 (7.5)
	Unadjusted p-value		0.927	0.558	0.966
	Adjusted p-value		0.926	0.617	0.988
1.5 Hours	n (%)	29 (17.1)	27 (15.3)	32 (17.7)	32 (17.2)
	Unadjusted p-value		0.648	0.878	0.971
	Adjusted p-value		0.648	0.986	0.923
2 Hours	n (%)	58 (34.1)	63 (35.6)	74 (40.9)	75 (40.3)
	Unadjusted p-value		0.773	0.191	0.226
	Adjusted p-value		0.771	0.233	0.205

Data Source: Tables E-2.3.1.1 to E-2.3.5.2

Similarly, they observed no statistically significant differences between the almotriptan and placebo treatment groups in the percentage of subjects with a *sustained pain-free response*.

Headache recurrence rates within 24 hours in subjects with pain relief at 2 hours were low, and no statistically significant differences between almotriptan and placebo treatments were observed.

Rates of rescue medication use between 2 and 24 hours were also low, and no statistically significant differences between almotriptan and placebo treatments were observed.

At 2 hours postdose, there were no statistically significant differences between almotriptan and placebo treatments in the occurrence of vomiting as shown above in Table 27. However, the sponsor found the *occurrence of vomiting* at 1 hour and 1.5 hours postdose was statistically significantly higher in the almotriptan 6.25 mg and 25 mg dose groups compared with the placebo group, while no difference was observed between almotriptan 12.5 mg and placebo treatments at any time points. This information is shown in Table 29, from NDA Mod5.3.5.1\638-CNS-0059-015\Table11.

Table 29: Occurrence of Nausea, Vomiting, Photophobia, and Phonophobia Immediately Prior to Taking Study Medication and at 0.25, 0.5, 1, and 1.5 Hours Post-dose with and without Adjusting for Baseline Pain Intensity

Parameter	Statistics	Placebo	Almotriptan		
			6.25 mg	12.5 mg	25 mg
Number of Patients in the ITT Population	N	170	177	181	186
Number of Patients with Associated Symptoms Immediately Before Taking Study Medication					
Nausea	n (%)	82 (48.2)	78 (44.1)	75 (41.1)	81 (43.5)
	Unadjusted p-value		0.436	0.200	0.375
	Adjusted p-value		0.429	0.292	0.358
Vomiting	n (%)	14 (8.2)	12 (6.8)	12 (6.6)	11 (5.9)
	Unadjusted p-value		0.607	0.566	0.392
	Adjusted p-value		0.601	0.665	0.368
Photophobia	n (%)	138 (81.2)	132 (74.6)	143 (79.0)	159 (85.5)
	Unadjusted p-value		0.138	0.611	0.275
	Adjusted p-value		0.124	0.854	0.296
Phonophobia	n (%)	127 (74.7)	125 (70.6)	133 (73.5)	142 (76.3)
	Unadjusted p-value		0.393	0.793	0.719
	Adjusted p-value		0.380	0.930	0.766
Number of Patients with Associated Symptoms at 0.25 Hour Post-dose					
Nausea	n (%)	78 (45.9)	79 (44.6)	77 (42.5)	81 (43.8)
	Unadjusted p-value		0.815	0.529	0.691
	Adjusted p-value		0.812	0.651	0.672
Vomiting	n (%)	12 (7.1)	9 (5.1)	8 (4.4)	8 (4.3)
	Unadjusted p-value		0.440	0.286	0.264
	Adjusted p-value		0.436	0.396	0.247
Photophobia	n (%)	138 (81.2)	133 (75.1)	136 (75.1)	160 (86.5)
	Unadjusted p-value		0.173	0.171	0.173
	Adjusted p-value		0.154	0.291	0.185
Phonophobia	n (%)	126 (74.1)	118 (66.7)	122 (67.4)	136 (73.5)
	Unadjusted p-value		0.128	0.167	0.897
	Adjusted p-value		0.115	0.298	0.846
Number of Patients with Associated Symptoms at 0.5 Hour Post-dose					
Nausea	n (%)	62 (36.7)	68 (38.6)	66 (36.5)	76 (41.1)
	Unadjusted p-value		0.709	0.966	0.397
	Adjusted p-value		0.701	0.925	0.403
Vomiting	n (%)	4 (2.4)	10 (5.7)	5 (2.8)	8 (4.3)
	Unadjusted p-value		0.113	0.802	0.304
	Adjusted p-value		0.114	0.669	0.320
Photophobia	n (%)	128 (75.7)	120 (68.2)	128 (70.7)	149 (80.5)
	Unadjusted p-value		0.118	0.289	0.274
	Adjusted p-value		0.112	0.417	0.287
Phonophobia	n (%)	109 (64.5)	106 (60.6)	111 (61.3)	122 (65.9)
	Unadjusted p-value		0.452	0.539	0.775
	Adjusted p-value		0.460	0.805	0.813

Data Source: Tables E-2.2.1.1 to E-2.2.5.2

Parameter	Statistics	Placebo	Almotriptan		
			6.25 mg	12.5 mg	25 mg
Number of Patients with Associated Symptoms at 1 Hour Post-dose					
Nausea	n (%)	40 (24.0)	50 (28.2)	48 (26.8)	64 (34.8)
	Unadjusted p-value		0.364	0.541	0.026*
	Adjusted p-value		0.364	0.474	0.028*
Vomiting	n (%)	1 (0.6)	7 (4.0)	2 (1.1)	9 (4.9)
	Unadjusted p-value		0.028*	0.596	0.009**
	Adjusted p-value		0.039*	0.572	0.017*
Photophobia	n (%)	106 (63.5)	104 (58.8)	110 (61.5)	128 (69.6)
	Unadjusted p-value		0.370	0.698	0.227
	Adjusted p-value		0.365	0.860	0.241
Phonophobia	n (%)	93 (55.7)	98 (55.4)	89 (49.7)	110 (59.8)
	Unadjusted p-value		0.952	0.266	0.438
	Adjusted p-value		0.959	0.403	0.465
Number of Patients with Associated Symptoms at 1.5 Hours Post-dose					
Nausea	n (%)	35 (21.1)	35 (20.1)	39 (22.2)	46 (25.6)
	Unadjusted p-value		0.825	0.809	0.326
	Adjusted p-value		0.825	0.844	0.331
Vomiting	n (%)	1 (0.6)	6 (3.4)	1 (0.6)	7 (3.9)
	Unadjusted p-value		0.051	0.970	0.030*
	Adjusted p-value		0.065	0.969	0.045*
Photophobia	n (%)	83 (50.0)	81 (46.6)	82 (46.6)	95 (52.8)
	Unadjusted p-value		0.525	0.528	0.605
	Adjusted p-value		0.513	0.605	0.637
Phonophobia	n (%)	76 (45.8)	77 (44.3)	60 (34.1)	86 (47.8)
	Unadjusted p-value		0.777	0.027*	0.710
	Adjusted p-value		0.764	0.043*	0.761

Data Source: Tables E-2.2.1.1 to E-2.2.5.2

The sponsor found that differences in the occurrence of nausea, vomiting, photophobia, phonophobia, or any symptom immediately before taking study medication were not statistically significant (unadjusted or adjusted for Baseline intensity) for any of the 3 Almotriptan dose groups compared with placebo in this exploratory endpoint analysis. The occurrence of nausea at 1 hour post-dose was statistically significantly (unadjusted or adjusted for Baseline intensity) higher in the Almotriptan 25 mg dose group (34.8%) compared with placebo (24.0%).

The occurrence of phonophobia at 1.5 hours post-dose was statistically significantly (unadjusted or adjusted for Baseline intensity) lower in the Almotriptan 12.5 mg dose group (34.1%) compared with placebo (45.8%). Once more the sponsor does not comment and does not indicate the results were not corrected for multiple comparisons.

The occurrence of any symptoms at 0.5 hour post-dose was statistically significantly higher in the Almotriptan 25 mg dose group (91.9%) compared with placebo (85.2%) unadjusted (p=0.047) or adjusted (p=0.049) for Baseline pain intensity when this exploratory endpoint was analyzed by the sponsor.

Dr. Massie analyzed the secondary endpoints as well. As noted in italic font he, "*verified the sponsor's results for the following secondary analyses:*

• Headache pain relief at 0.25, 0.5, 1.0, and 1.5 hours postdose
• Presence of nausea, photophobia, and phonophobia at 0.25, 0.5, 1.0, and 1.5 hours postdose
• Presence of vomiting at 0.25, 0.5, 1.0, 1.5, and 2.0 hours postdose"

6.1.6 Other Endpoints

No other endpoints were studied or analyzed.

6.1.7 Subpopulations

The efficacy study 638-CNS-0059-015 evaluated evaluate efficacy outcomes, including headache pain relief and presence of migraine-associated symptoms (nausea, photophobia, and phonophobia) 2 hours postdose, in subgroups of adolescent subjects stratified by:

- age group (this stratification was not requested as part of the PWR)
  - 12-14 years,
  - 15-17 years,
- gender (male, female), and
- race (white, black).

The sponsor found no clinically meaningful differences in efficacy outcomes by age group, gender, or race in the trial. The subpopulation data are displayed in the following tables from the CSR (Table 30, Table 31, and Table 32).

Table 30 shows that the response rates by age group (12-14 years; 15-17 years) for headache pain relief and the presence of migraine-associated symptoms 2 hours after treatment with almotriptan or placebo in Review Study 2 (638-CNS-0059-015). The Division did not ask for this subgroup analysis as part of the PWR. All 3 almotriptan dose groups (6.25 mg, 12.5 mg, 25 mg) appear associated with higher rates of 2-hour headache pain relief relative to the placebo group in subjects 15 to 17 years of age.

I agree with the sponsor's conclusion that the 2-hour pain-relief rates after almotriptan treatment (all 3 doses) were not statistically different from placebo in subjects 12 to 14 years of age. Interestingly, the placebo rate for 2-hour pain relief was higher in the 12-14 year group (62.9%) compared with the 15-17 year group (46.9%), consistent with previous findings demonstrating an increase in placebo rates with decreasing age. The sponsor suggests the high placebo rate in the 12-14 year group confounded both the comparative analysis and the ability to demonstrate a statistically significant separation of this efficacy measure between treatment groups. I believe this is probably correct, but experience with other triptans in adolescents indicates this is difficult to gauge in younger patients.

The sponsor notes almotriptan 12.5 mg was associated with reduced rates for presence of photophobia and phonophobia in subjects aged 15 to 17 years and of photophobia in subjects aged 12 to 14 years. No other differences between the almotriptan and placebo treatment groups in migraine-associated symptoms were observed.

Table 30: Headache Pain Relief and Migraine-associated Symptoms 2 Hours Postdose by Age Group: 638-CNS-0059-015 (ITT Population)

	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg
Age 12 to 14 years	(N=89)	(N=87)	(N=96)	(N=94)
2-Hour pain relief				
n	89	87	96	94
x (%)	56 (62.9%)	66 (75.9%)	73 (76.0%)	62 (66.0%)
Adjusted *P* value		0.079	0.066	0.656
Unadjusted *P* value		0.062	0.052	0.668
Presence of nausea				
n	86	86	93	92
x (%)	14 (16.3%)	11 (12.8%)	14 (15.1%)	21 (22.8%)
Adjusted *P* value		0.555	0.855	0.252
Unadjusted *P* value		0.516	0.822	0.271
Presence of photophobia				
n	86	86	93	92
x (%)	32 (37.2%)	24 (27.9%)	20 (21.5%)	31 (33.7%)
Adjusted *P* value		0.234	0.023	0.660
Unadjusted *P* value		0.192	0.020	0.624
Presence of phonophobia				
n	86	85	93	92
x (%)	24 (27.9%)	20 (23.5%)	19 (20.4%)	28 (30.4%)
Adjusted *P* value		0.581	0.289	0.675
Unadjusted *P* value		0.512	0.242	0.711
Age 15 to 17 years	(N=81)	(N=90)	(N=85)	(N=92)
2-Hour pain relief				
n	81	90	85	92
x (%)	38 (46.9%)	61 (67.8%)	59 (69.4%)	62 (67.4%)
Adjusted *P* value		0.002	0.005	0.005
Unadjusted *P* value		0.006	0.003	0.006
Presence of nausea				
n	79	88	85	87
x (%)	12 (15.2%)	13 (14.8%)	16 (18.8%)	16 (18.4%)
Adjusted *P* value		0.882	0.550	0.563
Unadjusted *P* value		0.940	0.536	0.582
Presence of photophobia				
n	79	88	85	87
x (%)	35 (44.3%)	34 (38.6%)	24 (28.2%)	31 (35.6%)
Adjusted *P* value		0.338	0.036	0.231
Unadjusted *P* value		0.458	0.032	0.254
Presence of phonophobia				
n	79	88	85	87
x (%)	33 (41.8%)	26 (29.5%)	20 (23.5%)	27 (31.0%)
Adjusted *P* value		0.069	0.016	0.132
Unadjusted *P* value		0.099	0.012	0.150

N=number of subjects in the intent-to-treat (ITT) population; n = number of subjects with available data;
x = number of subjects with the effect; percentages based on the number of subjects with available data in each treatment group.
Adjusted *P* values from Cochran-Mantel-Haenszel (CMH) test to assess treatment group differences (almotriptan vs. placebo) adjusting for baseline headache pain intensity.
Unadjusted *P* values from likelihood ratio chi-square test to assess treatment group differences (almotriptan vs. placebo)

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableE-3.3.1.1.1.1, \TableE-3.3.1.1.1.2, \TableE-3.3.1.1.2.1, \TableE-3.3.1.1.2.2, \TableE-3.3.1.2.1.1, \TableE-3.3.1.2.1.2, \TableE-3.3.1.2.2.1, \TableE-3.3.1.2.2.2.

In Table 31, the sponsor summarizes response rates by gender for pain relief and presence of migraine-associated symptoms 2 hours after treatment with almotriptan or placebo in Review Study 2 (638-CNS-0059-015).

In both male and female subjects almotriptan 12.5 mg appears associated with higher rates of 2-hour headache pain relief relative to placebo. In females, almotriptan 6.25 mg was associated with a higher rate of 2-hour headache pain relief relative to placebo. In females, the almotriptan 12.5 mg dose group showed reduced rates for presence of photophobia and phonophobia relative to placebo. No other differences between almotriptan and placebo are recorded by the sponsor in males or females.

Table 31: Headache Pain Relief and Migraine-associated Symptoms 2 Hours Postdose by Gender: 638-CNS-0059-015 (ITT Population)

	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg
Male	(N=62)	(N=75)	(N=80)	(N=71)
2-Hour pain relief				
n	62	75	80	71
x (%)	36 (58.1%)	55 (73.3%)	60 (75.0%)	50 (70.4%)
Adjusted *P* value		0.064	0.038	0.065
Presence of nausea				
n	60	75	77	67
x (%)	7 (11.7%)	9 (12.0%)	13 (16.9%)	9 (13.4%)
Adjusted *P* value		0.938	0.347	0.887
Presence of photophobia				
n	60	75	77	67
x (%)	21 (35.0%)	23 (30.7%)	25 (32.5%)	18 (26.9%)
Adjusted *P* value		0.648	0.769	0.249
Presence of phonophobia				
n	60	75	77	67
x (%)	14 (23.3%)	16 (21.3%)	16 (20.8%)	19 (28.4%)
Adjusted *P* value		0.804	0.735	0.568
Female	(N=108)	(N=102)	(N=101)	(N=115)
2-Hour pain relief				
n	108	102	101	115
x (%)	58 (53.7%)	72 (70.6%)	72 (71.3%)	74 (64.3%)
Adjusted *P* value		0.009	0.013	0.135
Presence of nausea				
n	105	99	101	112
x (%)	19 (18.1%)	15 (15.2%)	17 (16.8%)	28 (25.0%)
Adjusted *P* value		0.547	0.748	0.217
Presence of photophobia				
n	105	99	101	112
x (%)	46 (43.8%)	35 (35.4%)	19 (18.8%)	44 (39.3%)
Adjusted *P* value		0.184	<0.001	0.556
Presence of phonophobia				
N	105	98	101	112
x (%)	43 (41.0%)	30 (30.6%)	23 (22.8%)	36 (32.1%)
Adjusted *P* value		0.104	0.008	0.211

N=number of subjects in the intent-to-treat (ITT) population; n = number of subjects with available data; x = number of subjects with the effect; percentages based on the number of subjects with available data in each treatment group.
Adjusted *P* values from Cochran-Mantel-Haenszel (CMH) test to assess treatment group differences (almotriptan vs. placebo) adjusting for baseline headache pain intensity.

Cross-reference: Appendix2.1.1, Appendix2.1.2, Appendix2.1.5, Appendix2.1.6.

Table 32 summarizes response rates by race (white, black) for pain relief and presence of migraine-associated symptoms 2 hours after treatment with almotriptan or placebo in

Review Study 2. The sponsor observes the total number of subjects of all other races combined (N=54) was too small for meaningful comparison with white (N=539) and black (N=121) races, even if it assumed combining all other races into a single group (ie, Other) for comparison is valid.

Table 32: Headache Pain Relief and Migraine-associated Symptoms 2 Hours Postdose by Race: 638-CNS-0059-015 (ITT Population)

	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg
White	(N=129)	(N=132)	(N=142)	(N=136)
2-Hour pain relief				
n	129	132	142	136
x (%)	63 (48.8%)	91 (68.9%)	97 (68.3%)	87 (64.0%)
Adjusted *P* value		0.001	0.002	0.009
Presence of nausea				
n	124	129	139	129
x (%)	23 (18.5%)	21 (16.3%)	29 (20.9%)	31 (24.0%)
Adjusted *P* value		0.673	0.621	0.303
Presence of photophobia				
n	124	129	139	129
x (%)	55 (44.4%)	47 (36.4%)	37 (26.6%)	48 (37.2%)
Adjusted *P* value		0.222	0.003	0.219
Presence of phonophobia				
n	124	128	139	129
x (%)	49 (39.5%)	34 (26.6%)	34 (24.5%)	45 (34.9%)
Adjusted *P* value		0.033	0.012	0.408
Black	(N=28)	(N=33)	(N=26)	(N=34)
2-Hour pain relief				
n	28	33	26	34
x (%)	23 (82.1%)	28 (84.8%)	25 (96.2%)	26 (76.5%)
Adjusted *P* value		0.548	0.162	0.587
Presence of nausea				
n	28	33	26	34
x (%)	2 (7.1%)	2 (6.1%)	1 (3.8%)	3 (8.8%)
Adjusted *P* value		0.888	0.483	0.832
Presence of photophobia				
n	28	33	26	34
x (%)	8 (28.6%)	7 (21.2%)	3 (11.5%)	10 (29.4%)
Adjusted *P* value		0.376	0.123	0.947
Presence of phonophobia				
n	28	33	26	34
x (%)	5 (17.9%)	8 (24.2%)	3 (11.5%)	6 (17.6%)
Adjusted *P* value		0.631	0.647	0.978

N=number of subjects in the intent-to-treat (ITT) population; n = number of subjects with available data;
x = number of subjects with the effect; percentages based on the number of subjects with available data in each treatment group.
Adjusted *P* values from Cochran-Mantel-Haenszel (CMH) test to assess treatment group differences (almotriptan vs. placebo) adjusting for baseline headache pain intensity.

Cross-reference: Appendix2.1.3, Appendix2.1.4, Appendix2.1.7, Appendix2.1.8.

White subjects (N=539) showed a pattern similar to that of the whole study population, i.e., all

3 almotriptan doses were associated with higher rates for 2-hour headache pain relief relative to placebo, while the almotriptan 12.5 mg dose group, in addition, showed reduced rates for presence of photophobia and phonophobia relative to placebo. There were no differences between any almotriptan doses and placebo in 2-hour pain relief or presence of migraine-associated symptoms in black subjects; however, the number of subjects in each treatment group was small (N=26 to N=34). In all of these analyses, it does not appear multiple comparisons are taken into account.

Dr. Massie performed a confirmatory analysis of the above. He "*confirmed the sponsor's exploratory analyses of gender, race, and age. The treatment effect on pain relief at 2 hours postdose was reasonably consistent across gender groups, race groups, and age groups. In other words, there was no compelling evidence that the treatment effect on pain relief at 2 hours post-dose varied significantly by gender, race, or age group category.*

The FDA statistical reviewer also verified the sponsor's exploratory analyses of the presence of nausea at 2 hours postdose in the subgroup that had nausea at baseline, as well as in the group that did not have nausea at baseline. Similar analyses corresponding to the other associated symptoms were also verified. These subgroup results for the presence of associated symptoms were reasonably consistent with those in the overall ITT population. For example, in the subgroup of patients that had nausea at baseline, none of the Almotriptan groups was nominally significantly better than placebo in terms of the presence of nausea at 2 hours postdose.

The following table is provided for this review:

Table 33 Presence of Nausea at 2 Hours Post-Dose by Nausea at Baseline (ITT)

	Treatment Group															
	PLACEBO				ALMO 6.25MG				ALMO 12.5MG				ALMO 25 MG			
	Nausea				Nausea				Nausea				Nausea			
	No		Yes		No		Yes		No		Yes		No		Yes	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Baseline Nausea																
No	77	91.67	7	8.33	95	97.94	2	2.06	94	90.38	10	9.62	92	89.32	11	10.68
P-value* vs. Placebo								0.057				0.861				0.612
Yes	62	76.54	19	23.46	55	71.43	22	28.57	54	72.97	20	27.03	50	65.79	26	34.21
P-value* vs. Placebo								0.462				0.612				0.139

* p-values are exploratory (unadjusted for multiplicity) and are from a Cochran-Mantel-Haenszel (CMH) test to assess the significance of treatment group difference (Almotriptan group total vs. placebo total) adjusting for the baseline headache pain intensity"

These data suggest that baseline nausea is not improved by the drug and there is no benefit administering 12.5 mg or 25.0 mg for nausea developing as a consequence of the migraine.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy study of almotriptan for acute treatment of migraine in adolescents (12 to 17 years) in Review Study 2 did not demonstrate efficacy on all 4 co-primary endpoints using the pre-specified step-down approach to adjust for multiple comparisons (discussed in detail by Dr. Massie, the statistical reviewer).

The sponsor's exploratory analyses, without adjustments for multiple comparisons, showed all 3 almotriptan doses (6.25 mg, 12.5 mg, and 25 mg) were associated with statistically significantly greater 2-hour headache pain relief compared to placebo, and secondary analyses showed that all

3 almotriptan doses were associated with statistically significantly greater sustained pain relief up to 24 hours postdose compared with placebo. This is difficult to interpret conclusively absent a satisfactory multiple comparison adjustment. Almotriptan 12.5 mg was also associated with statistically significantly lower percentages of subjects with the presence of photophobia and phonophobia at 2 hours postdose compared with placebo.

By *retrospective examination of data*, the sponsor suggests that a dose-response relationship was not the appropriate assumption on which to order the hypotheses for the step-down analyses of multiple comparisons that started with the almotriptan 25 mg dose then followed with the 12.5 mg and 6.25 mg doses, respectively. Although the difference from placebo for 2-hour headache pain relief was statistically significant for all 3 almotriptan doses, the highest response rate was observed with the 12.5 mg dose (72.9%), not the 25 mg dose (66.7%) (See Table 24).

The response rate for sustained pain relief showed a similar pattern (12.5 mg, 66.9%; 25 mg, 64.5%) as shown in the table below, reproduced from the sponsor's Table 3 of the Efficacy summary. Note that the sustained relief for the 6.25 mg dose was statistically better than for the other 2 doses for this exploratory endpoint.

Since the lower 6.25 mg dose is also superior to placebo for the primary end-point, pain relief at 2 hours, I believe this dose should be added in the label's dosing and administration recommendation. The sponsor has not suggested that dose in draft labeling for unclear reasons.

Table 34: Analyses of Secondary Efficacy Parameters: 638-CNS-0059-015 (ITT Population)

	Placebo (N=170)	Almotriptan 6.25 mg (N=177)	Almotriptan 12.5 mg (N=181)	Almotriptan 25 mg (N=186)
Sustained pain relief[a]				
n (%)	89 (52.4%)	119 (67.2%)	121 (66.9%)	120 (64.5%)
Adjusted *P* value		0.004	0.008	0.016
Unadjusted *P* value		0.005	0.006	0.020
Headache pain free at 2 hours postdose				
n (%)	58 (34.1%)	63 (35.6%)	74 (40.9%)	75 (40.3%)
Adjusted *P* value		0.771	0.233	0.205
Unadjusted *P* value		0.773	0.191	0.226
Sustained pain free[b]				
n (%)	56 (32.9%)	61 (34.5%)	71 (39.2%)	73 (39.2%)
Adjusted *P* value		0.763	0.258	0.198
Unadjusted *P* value		0.764	0.220	0.216
Headache recurrence[c]				
n (%)	5 (5.3%)	8 (6.3%)	11 (8.3%)	4 (3.2%)
Adjusted *P* value		0.750	0.402	0.456
Unadjusted *P* value		0.758	0.377	0.444
Use of rescue medication 2 to 24 hours postdose[d]				
n (%)	11 (6.5%)	5 (2.8%)	9 (5.0%)	6 (3.2%)
Adjusted *P* value		0.106	0.521	0.156
Unadjusted *P* value		0.102	0.545	0.150
Presence of vomiting 2 hours postdose[e]				
n	165	173	178	179
x (%)	1 (0.6%)	3 (1.7%)	1 (0.6%)	6 (3.4%)
Adjusted *P* value		0.326	0.957	0.057
Unadjusted *P* value		0.338	0.956	0.074

n (%) = number of subjects with the event; percentages based on the number of subjects in the ITT population in each treatment group

[a] Sustained pain relief = subjects with headache pain relief at 2 hours postdose that continued for 24 hours with no use of rescue medication.

[b] Sustained pain free = subjects who were headache pain free at 2 hours postdose that continued for 24 hours with no use of rescue medication.

[c] Headache recurrence = subjects with headache pain relief at 2 hours postdose who experienced a recurrence within 24 hours.

[d] Use of rescue medication for subjects with and without pain relief at 2 hours is presented.

[e] n = number of subjects with available data; x = number of subjects with the presence of vomiting; percentages based on the number of subjects with available data in each treatment group.

Adjusted *P* values from Cochran-Mantel-Haenszel (CMH) test to assess treatment group differences (almotriptan vs. placebo) adjusting for baseline headache pain intensity.

Unadjusted *P* values from likelihood ratio chi-square test to assess treatment group differences (almotriptan vs. placebo)

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableE-2.5.1, TableE-2.5.2, \TableE-2.3.5.1, \TableE-2.3.5.2, \TableE-2.6.1, \TableE-2.6.2, \TableE-2.4.1, \TableE-2.4.2, \TableE-2.7.1, \TableE-2.7.2, \TableE-2.2.6.1, \TableE-2.2.6.2.

The sponsor also observes the dose-response effect for migraine-associated photophobia and phonophobia followed a similar pattern: namely, treatment with the 12.5 mg dose of almotriptan was associated with the lowest percentages of subjects with the presence of these migraine-associated symptoms at 2 hours postdose and statistically significant differences in these measures relative to those observed with placebo treatment. While I agree with these observations, they are all unadjusted for multiplicity, and thus may not be conclusive.

The sponsor describes, in the almotriptan 6.25 mg and 25 mg dose groups, the percentages of subjects with the presence of photophobia and phonophobia 2 hours postdose were lower than those observed in the placebo group, although the differences did not reach statistical significance for either dose. At 0.5, 1 and 1.5 hours postdose, the percentages of subjects with the presence of photophobia and phonophobia in the almotriptan 6.25 mg and 12.5 mg groups were numerically lower than those in the placebo group. In the almotriptan 25 mg group, the percentages of subjects with photophobia and phonophobia 0.5, 1 and 1.5 hours postdose were generally higher than those in the placebo group. Of the 3 almotriptan doses, the 25 mg dose had the least beneficial effect on photophobia and phonophobia relative to placebo. This appears correct, given the limits of analysis on data uncorrected for multiplicity.

Differences between almotriptan and placebo in the percentage of subjects with migraine-associated nausea 2 hours postdose were not statistically significant for any dose. The reasons are unknown, perhaps, the sponsor says, since little is known about the underlying mechanism of reported triptan related improvement of migraine-associated nausea or the interrelationship between nausea, migraine clinical course, and migraine treatment.

As shown in Table 24: Headache Pain Relief and Migraine-associated Symptoms at 2 Hours Postdose – Exploratory Analyses – 638-CNS-0059-015, Review Study 2, the percentage of subjects with nausea 2 hours postdose increased in a dose-related manner across the 3 almotriptan dose groups (13.8%, 16.9%, and 20.7% for the 6.25 mg, 12.5 mg, and 25 mg doses, respectively), while the percentage of subjects with nausea at baseline was similar across treatment groups (48.2%, 44.1%, 41.1%, and 43.5% for the placebo, 6.25 mg, 12.5 mg, and the 25 mg treatment groups, respectively). Relative to the placebo group (15.8%), the percentage of subjects with nausea 2 hours postdose was numerically (but not statistically) lower in the almotriptan 6.25 mg dose group (13.8%), similar in the 12.5 mg dose group (16.9%), and higher in the 25 mg dose group (20.7%).

To explain this observation, the sponsor cites literature from previous studies by Linde, and others, noting the anti-migraine action of triptans can be preceded by an exacerbation of migraine pain intensity and allodynia prior to providing pain relief and evidence showing a direct association between intensity of migraine pain and presence of nausea. If, the sponsor purely speculates, the association between pain intensity and nausea infers triptan-associated exacerbation of nausea as well as pain, it is possible that triptan treatment has opposing effects on nausea, i.e., inducing new onset nausea or exacerbating already present nausea prior to a therapeutic reduction of nausea associated with the migraine attack. They buttress this speculation from additional literature reports from Cipolla, et. al, that the 5-HT1B/1D receptor

agonist sumatriptan reduced gastric motility and delayed gastric emptying in the same dose range used in the treatment of migraine.

Bottom Line: the underlying etiology of the effect of triptan treatment on nausea is unknown, and any attempt by the sponsor to explain the effect is speculative. The simple fact is that headache can decrease but nausea can simultaneously increase.

A statistically significant beneficial effect of almotriptan on nausea was not demonstrated in this study. The sponsor believes it unlikely that a beneficial effect of almotriptan on nausea would be demonstrated even with a study of different design. The 638-CNS-0059-015 study results for migraine-associated symptoms were confounded by the fact that not all subjects had nausea, photophobia, and/or phonophobia at baseline.

The sponsor makes these conclusions: Almotriptan 25 mg provided no additional benefit compared with almotriptan 12.5 mg and in some subjects may be associated with exacerbation of migraine pain, migraine-associated symptoms, or both prior to affecting benefit. Additionally, almotriptan 12.5 mg provided the best overall efficacy for acute treatment of migraine in adolescents 12 to 17 years of age, i.e., pain relief (2-hour relief and sustained relief up to 24 hours). However, the sponsor does not mention that 6.25 mg was just as good for pain relief and did not cause increased nausea. While there was reduction in the incidence of migraine-associated photophobia and phonophobia, this did not occur with nausea.

My conclusion, based on my review of the data, notes the 6.25 mg dose also is effective in headache relief. Since it did not increase nausea this dose should also be recommended in the label. The sponsor did not make this recommendation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence and/or tolerance of almotriptan efficacy in adolescents were not assessed in Review Study 2, the efficacy study. This was assessed by the sponsor, instead, by a post hoc analysis of data from the uncontrolled long-term safety study (Review Study 3, CAPSS-368). Headache pain relief 2 hours post-treatment with almotriptan 12.5 mg was evaluated over 3 migraine attacks (first, second, and last) (Table 35), below.

Table 35: Summary of Results Related to Persistence of Almotriptan Efficacy: CAPSS-368 (ITT Population, N=420)

	Predose Pain Intensity		
	Moderate	Severe	Total
First attack			
Sample size	290	91	381
Pain relief in 2 hours, n (%)	217 (74.8%)	42 (46.2%)	259 (68.0%)
Second attack			
Sample size	242	139	381
Pain relief in 2 hours, n (%)	189 (78.1%)	67 (48.2%)	256 (67.2%)
Last attack			
Sample size	255	126	381
Pain relief in 2 hours, n (%)	188 (73.7%)	56 (44.4%)	244 (64.0%)
	Predose Nausea or Vomiting		Total
	Yes	No	
First attack			
Sample size	159	222	381
Pain relief in 2 hours, n (%)	102 (64.2%)	157 (70.7%)	259 (68.0%)
Second attack			
Sample size	162	219	381
Pain relief in 2 hours, n (%)	99 (61.1%)	157 (71.7%)	256 (67.2%)
Last attack			
Sample size	183	198	381
Pain relief in 2 hours, n (%)	110 (60.1%)	134 (67.7%)	244 (64.0%)

Abbreviations: ITT = intent-to-treat

Notes: Sample size = subjects who treated at least 3 severe or moderate migraine attacks during the study
Percentages calculated using sample size in each category (baseline intensity, predose nausea or vomiting).
Headache pain relief = decrease in baseline pain intensity from severe or moderate to mild or no pain at 2 hours after the first dose of almotriptan without the use of a second dose or other supplemental pain or antiemetic medication.

Cross-reference: Appendix3.1, Appendix3.2.

As shown just above, almotriptan provided similar rates of 2-hour pain relief in the first, second, and last migraine attack (68.0%, 67.2%, and 64.0%). 2-hour pain relief rates were similar across migraine attacks for subjects with moderate pain intensity (74.8%, 78.1%, and 73.7%) and severe pain intensity (46.2%, 48.2%, and 44.4%) headaches, as well as subjects with pre-dose nausea or vomiting (64.2%, 61.1%, and 60.1%) and those without pre-dose nausea or vomiting (70.7%, 71.7%, and 67.7%).

An analysis of 2-hour headache pain relief for each of the 4 strata (moderate headache with nausea or vomiting, moderate headache without nausea or vomiting, severe headache with nausea or vomiting, and severe headache without nausea or vomiting) also showed very similar pain relief rates across the 3 headache attacks (Appendix3.3).

From this data the sponsor concludes 2-hour headache pain relief data in Review Study 3, the long-term safety study, CAPSS-368, the almotriptan effect persists over multiple migraine attacks in adolescents who treated their migraines with almotriptan 12.5 mg. They detected no evidence of tolerance to almotriptan.

6.1.10 Additional Efficacy Issues/Analyses

No pre-specified efficacy issues or analyses were performed; however the sponsor performed numerous post-hoc analyses as documented in their appendices looking at efficacy outcomes of Review Study 2, a variety of subgroup analyses from that trial, and persistence analyses of Review Study 3.

7 Review of Safety

Safety Summary

The Division and the sponsor had agreed to the content and format of the safety information in the adolescent population for this sNDA. To introduce this Review section, the following brief review of the trials is presented.

Across the 3 adolescent studies, a total of 1158 adolescent subjects received at least 1 dose of study medication and were evaluated for safety: 172 received placebo and 986 received almotriptan (any dose) distributed as shown in this safety exposure table from the sponsor:

Table 36: Number of Adolescent Subjects Evaluable for Safety in Adolescent Clinical Studies

	Study Medication[a]					
	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg	Almotriptan 12.5 mg[b]	Total
638-CNS-0059-014			18			18
638-CNS-0059-015	172	180	182	186		720
CAPSS-368					420	420
Studies combined	172	180	200	186	420	1158

[a] Subjects received a single oral dose of study medication, except where indicated.
[b] Subjects took single oral doses for multiple migraine episodes for up to 12 months.

Cross-reference: Mod5.3.3.1\638-CNS-0059-014\Section7.1.1; Mod5.3.5.1\638-CNS-0059-015\Table4; Mod5.3.5.2\CAPSS-368\Table3.

In the PK study 638-CNS-0059-014, (Review Study 1, reviewed by Biopharmaceutics) 18 adolescent subjects (12 to 17 years of age) and 18 adult subjects (18 to 53 years of age) with or without a history of migraine received a single oral dose of almotriptan 12.5 mg and completed the study. Demographic and baseline characteristics of the study population are summarized above in Review Section 5.3.

In the efficacy study 638-CNS-0059-015 (Review Study 2, the efficacy study), 866 subjects were randomized and 720 subjects with a history of migraine with or without aura took a single oral dose of study medication for treatment of a single migraine attack: 172 received placebo, 180 received almotriptan 6.25 mg, 182 received almotriptan 12.5 mg, and 186 received almotriptan 25 mg (Review Section 5.3.3). Demographic and baseline characteristics of the study population are summarized in that same section. The following table briefly presents the subjects' dispositions:

Table 37: Subject Disposition: 638-CNS-0059-015 (Review Study 2, Efficacy Study)

	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg
Patients screened (N=1207)				
Patients randomized	209	211	226	220
Patients who took study drug (safety population)[a]	172 (82.3%)	180 (85.3%)	182 (80.5%)	186 (84.5%)
Patients who completed the study[a]	166 (79.4%)	174 (82.5%)	178 (78.8%)	181 (82.3%)
Reasons for early termination[b]				
Adverse event	0	0	0	0
Protocol violation	5 (11.6%)	3 (8.1%)	2 (4.2%)	6 (15.4%)
Lost to Follow-up	3 (7.0%)	2 (5.4%)	2 (4.2%)	1 (2.6%)
Sponsor's decision	3 (7.0%)	3 (8.1%)	2 (4.2%)	1 (2.6%)
Did not take study drug	32 (74.4%)	29 (78.4%)	42 (87.5%)	31 (79.5%)

[a] Percentages based on the number of randomized patients in each treatment group.
[b] Percentages based on the number of patients with available data who did not complete the study in each treatment group; percentage may add up to more than 100% due to rounding.

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableP-1.1, \TableP-3.1.

In the long-term safety study CAPSS-368, subjects with a history of migraine with or without aura took single oral doses of almotriptan 12.5 mg for treatment of multiple migraine attacks for up to 12 months. The following 2 tables summarize the subject disposition and exposure:

Table 38: Subject Disposition: Study CAPSS-368 (Review Study 3, Long-term Safety)

	Almotriptan 12.5 mg
Enrolled subjects[a]	447
Safety subjects[b]	420 (94.0%)
Subjects who completed the study[c]	319 (71.4%)
Subjects who discontinued early	128 (28.6%)
Reason for early discontinuation	
Lost to follow-up	53 (11.9%)
Subject choice	34 (7.6%)
Lack of efficacy	11 (2.5%)
Other	11 (2.5%)
Limiting adverse event	10 (2.2%)
No headache treated with study medication within 30 days of baseline visit	9 (2.0%)

Note: Percentages based on the number of enrolled subjects.
[a] Subjects who met entry criteria, agreed to participate, and were dispensed study medication.
[b] Subjects who took at least one dose of study medication according to the headache record.
[c] Subjects completed the study if they treated migraines with study medication throughout the trial and completed all assessments at Month 12.

Cross-reference: Mod5.3.5.2\CAPSS-368\Attachment1.2, \Attachment1.3.

Table 39: Study Medication Exposure: Study CAPSS-368 (Safety Population)

	Almotriptan 12.5 mg (N=420)
Total dose per subject (mg)	
Mean (SD)	291.6 (248.91)
Range	12.5 – 1337.5
Average dose per headache (mg)	
Mean (SD)	15.1 (2.67)
Range	12.5 – 25.0
Average number of doses per headache	
Mean (SD)	1.2 (0.21)
Range	1 – 2

Abbreviations: SD = standard deviation

Cross-reference: Mod5.3.5.2\CAPSS-368\Attachment1.9.

It can be seen that of the 447 subjects enrolled, 420 (94.0%) took at least 1 dose of study medication and 319 (71.4%) completed the study. Subjects treated each migraine episode with 1 or 2 doses of study medication. Additional features:

- The average dose per headache was 15 mg and the average number of doses per headache was 1.2.
- A total of 302 (67.6%) subjects treated at least 6 headaches in the first 180 days of the study, and
- 227 (50.8%) subjects treated at least 12 headaches and participated in the study for at least 350 days.

The sponsor is quick to point out the study exceeded the sample size requirements of the long-term safety study specified in the PWR. Demographic and baseline characteristics of the study population have been previously summarized above in Review Section 5.3.

These data, further suggests almotriptan is safe for clinical use and is generally well tolerated in adolescents 12 to 17 years of age. I agree with the sponsor's bottom line conclusion: By direct data comparison and by clinical opinion, the safety and tolerability profiles of almotriptan in the treatment of multiple migraine attacks for up to 12 months in adolescents are similar to the profiles observed in adult populations.

7.1 Methods

Three sources of data were used to evaluate safety in pediatric subjects ≤ 17 years of age:

- 3 company-sponsored clinical studies in adolescent subjects (12 to 17 years of age) (see Table 7: Overview of Company-sponsored Clinical Studies Providing Safety Data Relevant to Almotriptan Rx of Adolescent Migraine Attacks),
- literature reports of pediatric exposure to almotriptan, and
- Postmarketing spontaneous safety reports in pediatric patients from the date of first authorization of almotriptan in December 1999 through 30 June 2008.

The safety of almotriptan versus placebo was assessed by the following assessments:

- adverse events (AEs),
- clinical laboratory evaluations,
- vital signs,
- electrocardiograms (ECGs),
- physical examinations, use of concomitant medications, and
- Pregnancy testing.

7.1.1 Clinical Studies Used to Evaluate Safety

The studies used to evaluate safety are shown above in Table 7: Overview of Company-sponsored Clinical Studies Providing Safety Data Relevant to Almotriptan Rx of Adolescent Migraine Attacks.

7.1.2 Adequacy of Data

The adequacy of exposure as a function of both the size of the safety database and the duration of exposure was acceptable. It met the pre-specified requirements outlined in the PWR. Adverse events were coded using MedDRA, v6.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

By prior agreement with the Division in April 2008, pooling of safety data across the 3 adolescent studies was not performed due to differences in drug exposure, study populations, and treatment regimens. The only common almotriptan dose across the 3 studies is the 12.5 mg dose. The study population in 638-CNS-0059-014 (subjects with or without migraine) differed from that in 638-CNS-0059-015 and CAPSS-368 (subjects with a history of migraine attacks). The study duration and extent of exposure differed between 638-CNS-0059-015 (a single dose) and CAPSS-368 (multiple doses for up to 1 year).

Given there is no common study drug exposure across these 3 studies, the sponsor and DNP agreed an integrated summary of safety data would not provide meaningful information. The

sponsor therefore summarized the safety data for each study separately and then compared them descriptively. Since integrated safety tables, figures, and datasets were not generated and since this summary of clinical safety is sufficiently detailed (while still meeting the suggested size limitations for Module 2), the sponsor did not provide a separate integrated summary of safety in eCTD Module 5.3.5.3. In its responses to the Briefing Document, the Division agreed with the sponsor's plan for the content and format of safety information for this sNDA.

7.2 Adequacy of Safety Assessments

The sponsor and the Division jointly met over the course of responding to the Division's Pediatric Written Request. As documented in the various reviews, various meeting minutes, and the request for pediatric trials evaluating Axert, the sponsor responded satisfactorily to all Division suggestions regarding overall numbers of patients and demography. The standard appropriate migraine trial tests in the exposed population were conducted without incident. The quality of the sponsor's safety data is good and it was complete. The Pediatric Exclusivity Board agreed and granted the firm exclusivity.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

An overview is presented above in Table 10: Safety Population Demographic and Baseline Characteristics. Here, the overall exposure and demographics are displayed by individual trial, from the sponsor's study reports:

Table 40: Demographic and Baseline Characteristics: 638-CNS-0059-014 PK (Safety Population), Review Study 1

	Adolescents (N=18)	Adults (N=18)
Age (years)		
Mean (SD)	14.9 (1.6)	37.0 (9.1)
Range	12.6 – 17.6	18.2 – 53.4
Gender, n (%)		
Male	9 (50%)	9 (50%)
Female	9 (50%)	9 (50%)
Race, n (%)		
White	10 (56%)	14 (78%)
Black	4 (22%)	1 (6%)
Asian	0	1 (6%)
Not reported	4 (22%)	2 (11%)
Weight (kg)		
Mean (SD)	62.0 (13.2)	73.5 (14.0)
Range	35.9 – 89.5	53.1 – 94.0
Height (cm)		
Mean (SD)	165.9 (10.7)	173.6 (10.4)
Range	140.0 – 182.9	156.2 – 193.0
BMI (kg/m^2)		
Mean (SD)	22.3 (3.3)	24.1 (2.5)
Range	17.9 – 27.0	20.4 – 28.7
History of migraine, n (%)	2 (11%)	3 (17%)

Abbreviations: BMI = body mass index; SD = standard deviation

Cross-reference: Mod5.3.3.1\638-CNS-0059-014\Table1a, \Table1b, \Appendix3.4.1.

There were 36 subjects in the above PK study (638-CNS-0059-014): 18 adolescents and 18 adults (Table 40). There was an equal number of males (N=9) and females (N=9) subjects in the study. The majority of subjects were white (56% of adolescents; 78% of adults). The adolescent group was equally distributed between those in the 12-14 year age group (N=9) and those in the 15-17 year age group (N=9). As expected, mean body weight, height, and body mass index (BMI) were lower in the adolescent group relative to the adult group.

Two subjects took concomitant medications during the study. One subject used and continued to use hydrocortisone cream for eczema throughout the study. The other subject took extra strength acetaminophen for a headache approximately 9.5 hours post-almotriptan dose. Use of these concomitant medications was approved by the investigator.

For the efficacy study, Review Study 2, Table 41 below displays the essential information. It can be seen the demographic and baseline characteristics were balanced across the 4 treatment groups in the efficacy study (638-CNS-0059-015) (Table 41):

- Overall, there were more females (60%) than males (40%).
- There was a slightly higher proportion of subjects in the 12-14 year age group (54%) relative to the 15-17 year age group (46%).
- Approximately 75% of subjects were white, 15% were black (African heritage or African American), and 10% were of other races; approximately 25% were Hispanic or Latino.
- Mean duration of prior migraine attacks was similar across treatment groups (10.5 to 11.5 hours).

More than 90% of subjects in each of the 4 treatment groups used a concomitant medication. (90.1% to 94.2%) Of the concomitant medications used by ≥5% of subjects in any of the treatment groups, all were medications used to treat pain. The 3 most common concomitant medications across all 4 treatment groups were Advil (16.1% to 21.5%), Ibuprofen (18.3% to 24.7%), and Tylenol (16.7% to 21.1%).

Table 41: Demographic and Baseline Characteristics: 638-CNS-0059-015 (Safety Population), Review Study 2 Efficacy

	Placebo (N=172)	Almotriptan 6.25 mg (N=180)	Almotriptan 12.5 mg (N=182)	Almotriptan 25 mg (N=186)
Age (years)				
Mean (SD)	14.4 (2)	14.4 (2)	14.2 (2)	14.4 (2)
Range	12 – 17	12 – 17	12 – 17	12 - 17
Age group, n (%)				
12 to 14 years	96 (55.8%)	94 (52.2%)	100 (54.9%)	98 (52.7%)
15 to 17 years	76 (44.2%)	86 (47.8%)	82 (45.1%)	88 (47.3%)
Gender, n (%)				
Male	63 (36.6%)	76 (42.2%)	80 (44.0%)	71 (38.2%)
Female	109 (63.4%)	104 (57.8%)	102 (56.0%)	115 (61.8%)
Race, n (%)				
White	129 (75.9%)	132 (74.2%)	142 (78.5%)	136 (73.5%)
Black, of African heritage or African American	28 (16.5%)	33 (18.5%)	26 (14.4%)	34 (18.4%)
American Indian or Alaska Native	5 (2.9%)	3 (1.7%)	5 (2.8%)	5 (2.7%)
Asian	0	1 (0.6%)	0	1 (0.5%)
Other [a]	8 (4.7%)	9 (5.1%)	8 (4.4%)	9 (4.9%)
Not reported	2 (1.2%)	2 (1.1%)	1 (0.6%)	1 (0.5%)
Ethnicity, n (%)				
Not Hispanic or Latino	122 (71.8%)	127 (70.6%)	138 (75.8%)	144 (78.3%)
Hispanic or Latino	48 (28.2%)	53 (29.4%)	44 (24.2%)	40 (21.7%)
Weight (lbs)				
Mean (SD)	128.67 (25.9)	125.62 (27.5)	124.80 (26.1)	129.07 (26.5)
Range	64.0 – 217.0	62.2 – 227.0	70.4 – 217.8	72.5 – 215.0
Height (in)				
Mean (SD)	64.03 (3.8)	63.59 (4.0)	63.42 (3.6)	63.80 (3.7)
Range	48.0 – 73.4	39.9 – 73.0	53.5 – 74.0	49.0 – 72.1
Usual migraine pain intensity				
Moderate	90 (52.3%)	99 (55.0%)	97 (53.3%)	88 (47.3%)
Severe	82 (47.7%)	81 (45.0%)	85 (46.7%)	98 (52.7%)
Migraine duration (hours)				
Mean (SD)	10.7 (10)	10.7 (11)	10.5 (11)	11.5 (12)
Range	3 – 72	3 – 72	2 – 72	3 – 72

Abbreviations: SD = standard deviation

[a] Includes white; American Indian or Alaska Native and white; black or African heritage or African American.

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableP-4.1, \TableP-6.1.

For the third trial, the long-term safety trial data displayed below in Table 42and in the accompanying study report discussion.

Salient highlights:

- There were more females (55.5%) than males (44.5%) in the long-term safety study (CAPSS-368).
- The percentage of males was higher in the 12-14 year group than the 15-17 year group (55.4% vs. 33.3%).
- The majority of subjects was white (82.4%).
- A higher percentage of subjects in the 12-14 year group was white compared with the 15-17 year group (87.3% vs. 77.3%), and
- A higher percentage of subjects was black in the 15-17 year group compared with the 12-14 year group (20.8% vs. 11.3%).
- Mean age was 14.4 years (range, 12 to 17 years).

Overall, 72% of subjects took at least 1 concomitant medication. The most common concomitant medications were:

- Systemic antihistamines (24.5%),
- Nonsteroidal anti-inflammatory/anti-rheumatic agents (21.7%),
- other analgesics and antipyretics (20.5%), and
- Beta-lactam antibacterials (13.8%).

In total, 334 (79.5%) subjects took rescue medication for 1 or more of their headaches during their participation in the study. Of these 334 subjects, 306 (72.9%) took a second dose of almotriptan. The most common supplemental pain medications and/or antiemetic medications were nonsteroidal anti-inflammatory/anti-rheumatic products (25.7%) and other analgesics and antipyretics (20.0%).

Please see the table below for details.

Table 42: Demographic Characteristics: CAPSS-368 (Safety Population), Review Study 3, Long-term Safety

	12 – 14 Years of Age (N=213)	15 – 17 Years of Age (N=207)	All Subjects (N=420)
Age (years)			
Mean (SD)	13.0 (0.83)	15.8 (0.77)	14.4 (1.61)
Range	12 – 14	15 – 17	12 – 17
Gender, n (%)			
Male	118 (55.4%)	69 (33.3%)	187 (44.5%)
Female	95 (44.6%)	138 (66.7%)	233 (55.5%)
Race, n (%)			
White	186 (87.3%)	160 (77.3%)	346 (82.4%)
Black	24 (11.3%)	43 (20.8%)	67 (16.0%)
Asian	2 (0.9%)	1 (0.5%)	3 (0.7%)
American Indian or Alaska Native	0	1 (0.5%)	1 (0.2%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0	1 (0.2%)
Other	0	2 (1.0%)	2 (0.5%)
Ethnicity, n (%)			
Not Hispanic or Latino	191 (89.7%)	182 (87.9%)	373 (88.8%)
Hispanic or Latino	22 (10.3%)	25 (12.1%)	47 (11.2%)
Weight (lbs)			
Mean (SD)	118.6 (27.13)	138.0 (26.32)	128.2 (28.42)
Range	66 – 190	89 – 254	66 – 254
Height (in)			
Mean (SD)	62.9 (3.85)	65.7 (3.80)	64.3 (4.05)
Range	51 – 72	51 – 76	51 – 76
BMI (kg/m^2)			
Mean (SD)	20.9 (3.56)	22.5 (3.80)	21.7 (3.76)
Range	15.3 – 31.6	16.4 – 46.0	15.3 – 46.0

Abbreviations: BMI = body mass index; SD = standard deviation

Cross-reference: Mod5.3.5.2\CAPSS-368\Attachment1.4.2.

7.2.2 Explorations for Dose Response

Please see Section 6.1.8, above, for complete review of the details of clinical information relevant to dosing. The sponsor tested 3 doses in Review Study 2, the efficacy study, to determine an effective dose for the long-term safety study. As related above, in Section 6.1.8, exploratory analyses demonstrated all 3 almotriptan doses (6.25 mg, 12.5 mg, and 25 mg) were associated with statistically significantly greater 2-hour headache pain relief compared with placebo, and secondary analyses showed that all 3 almotriptan doses were associated with statistically significantly greater sustained pain relief up to 24 hours postdose compared with placebo (but this comparison is not sustained statistically without adjustments for multiple comparisons).

Almotriptan 12.5 mg was also associated with statistically significantly lower percentages of subjects with the presence of photophobia and phonophobia at 2 hours postdose compared with placebo. These analyses were post-hoc with the limitations that may occur in that situation.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was conducted as part of the sNDA.

7.2.4 Routine Clinical Testing

As discussed in Section7.1, the following routine clinical testing was conducted to evaluate the drug in adolescents:

- adverse events (AEs),
- clinical laboratory evaluations,
- vital signs,
- electrocardiograms (ECGs),
- physical examinations, use of concomitant medications, and
- Pregnancy testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Section 4.4, above and the Clinical Pharmacology Review for additional details. No additional data was generated for this sNDA. No formal drug-drug interaction studies have been performed in pediatric subjects (<18 years of age).

Note: No clinically significant interactions have been observed in adults between almotriptan and the following drugs: propranolol, fluoxetine, verapamil, ergotamine, ethinyl estradiol and desogestrel, and alcohol.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Review Section 2.4, where the triptan class safety issues are presented. The sponsor's safety evaluation was done well for this sNDA.

As noted, the triptans have several areas that were identified for close monitoring in the trials. Please see Table 18 for the monitoring schedule of the long-term safety study. The events are:

> *Drug-Associated Cardiac Events and Fatalities:* These have been observed both in the Premarketing Experience and Post-marketing Experience with triptans as detailed in Section 2.4. ECG's were obtained at study entry and at exit routinely. There were no fatalities in the pediatric trials.
>
> *Drug-Associated Cerebrovascular Events and Fatalities:* Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in

patients treated with oral or subcutaneous triptan, and some have resulted in fatalities. Physical Exams were routinely conducted.

Other Vasospasm-Related Events: Triptans may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Vital Signs were routinely monitored.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with triptans, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension.

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are nearly double those obtained under other conditions.

Use in Women of Childbearing Potential: Pregnancy tests were conducted routinely during the trials.

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions were evaluated during the periodic visits, phone calls, and exams.

These events, ischemic heart disease, hepatotoxicity, hypersensitivity, cerebrovascular events, convulsive disorders, visual disturbances, and possible interactions with serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (serotonergic syndrome), have been identified by both FDA and European Union (EU) regulatory authorities for safety monitoring.

The sponsor conducted their own medical review of safety data across the 3 adolescent studies identifying 7 AEs of special interest: chest pain or discomfort in 3 subjects in Review Study 2, 638-CNS-0059-015 and 1 subject in Review Study 3, CAPSS-368, single reports of dyspnea and facial vasoconstriction in 638-CNS-0059-015, and 1 case of transient, asymptomatic ventricular extrasystole related to preexisting arrhythmia in 638-CNS-0059-014. None of the AEs of special interest was serious and all resolved without sequelae. There were no reports of seizures, or AEs suggestive of cerebrovascular events, ischemic heart disease, hepatotoxicity, hypersensitivity, visual disturbance, or serotonergic syndrome in these studies.

Patients were monitored for these potential conditions throughout the 3 trials in accordance with the PWR. The safety of oral administration of the proposed dose of 12.5 mg almotriptan malate in the treatment of multiple migraine episodes over a period of up to 12 months in an adolescent

(12 to 17 years of age) population was evaluated in the long-term safety study. This met requirements of the FDA's Pediatric Written Request, dated 07 February 2005, issued under the Best Pharmaceuticals for Children Act.

Study enrollment exceeded the requirements of a long-term safety study specified in the FDA's Written Request (i.e., each patient should treat, on average, approximately one or more headache(s) per month for 6 to 12 months. At a minimum, 200 patients, using an effective dose, must be exposed for 6 months and 75 patients must be exposed for 1 year, with a similar number of patients in the 12 to 14 and 15 to 17 year age groups).

7.3 Major Safety Results

By way of introduction to this Review Section an overview of clinical study adverse events is tabulated in this table from the sponsor's summary of clinical safety of almotriptan in adolescents:

Table 43: Overview of Adverse Events in Adolescent Subjects in Clinical Studies (Safety Population)

	638-CNS-0059-015[a]				CAPSS-368[b]	638-CNS-0059-014[c]
	Placebo	Almotriptan 6.25 mg	Almotriptan 12.5 mg	Almotriptan 25 mg	Almotriptan 12.5 mg	Almotriptan 12.5 mg
Subjects evaluable for safety	172	180	182	186	420	18
Subjects with at least 1 AE	32 (18.6%)	27 (15.0%)	43 (23.6%)	48 (25.8%)	282 (67.1%)	2 (11.1%)
Number of AEs	49	45	66	73	949	4
Subjects with at least 1 treatment-related AE[d]	10 (5.8%)	12 (6.7%)	22 (12.1%)	23 (12.4%)	32 (7.6%)	0
Number of treatment-related AEs[d]	12	18	33	32	91	0
Subjects with at least 1 moderate or marked/severe AE[e]	2 (1.2%)	5 (2.8%)	6 (3.3%)	9 (4.8%)	183 (43.6%)	1 (5.6%)
Number of moderate or marked/severe AEs[e]	2	8	7	12	475	1
Subjects who died during the study	0	0	0	0	0	0
Subjects with at least 1 SAE	0	0	0	0	8 (1.9%)	0
Number of SAEs	0	0	0	0	8	0
Subjects who discontinued due to AEs	0	0	0	0	10 (2.4%)	0

Abbreviations: AE = adverse event; SAE = serious adverse event

[a] Subjects took a single oral dose of study medication for treatment of a single migraine attack.
[b] Subjects took oral doses of almotriptan 12.5 mg for treatment of multiple migraine episodes for up to 12 months.
[c] Subjects with or without a history of migraine received a single oral dose of almotriptan 12.5 mg for pharmacokinetic analysis, not for treatment of migraine attack.
[d] As assessed by the investigator. Missing causality was imputed to treatment-related.
[e] As assessed by the investigator. Intensity rating 'severe' was used in 638-CNS-0059-014 and 638-CNS-0059-014; 'marked' was used in CAPSS-368. Missing intensity was imputed to severe in 638-CNS-0059-014 and 638-CNS-0059-014 and to marked in CAPSS-368.

Cross-reference: Mod5.3.3.1\638-CNS-0059-014\Appendix3.6.1; Mod5.3.5.1\638-CNS-0059-015\Section12.2; Mod5.3.5.2\CAPSS-368\Table18.

The sponsor makes the following introductory points:

- There were no deaths of subjects in these clinical studies.
- Among subjects who treated multiple migraines with almotriptan 12.5 mg for up to 12 months in Review Study 3,CAPSS-368, 8 (1.9%) experienced at least 1 serious adverse event (SAE) and 10 (2.4%) discontinued the study due to AEs.
- Among subjects who treated a single migraine attack in Review Study 2, 638-CNS-0059-015, AEs of any causality and AEs assessed by the investigator as treatment-related were reported more frequently in subjects receiving almotriptan 12.5 mg and 25 mg compared with subjects receiving almotriptan 6.25 mg or placebo.
- Treatment-related AEs reported among subjects in Review Study 3,CAPSS-368, however, who took almotriptan 12.5 mg for multiple migraine attacks (7.6%) were not substantially higher than those who took almotriptan 6.25 mg or placebo for a single migraine attack (6.7% and 5.8%, respectively) in 638-CNS-0059-015.

One of the common AEs in Review Study 2, 638-CNS-0059-015 was nausea (see Table 44). Nausea was also a common AE in Review Study 3, CAPSS-368 (see Table 45). Nausea has been shown to improve with triptan treatment; but it is often reported as the most frequent treatment-emergent adverse event. Determining migraine-associated nausea vs. treatment-related nausea can be challenging in any migraine therapy trial. Also please see nausea discussion in the Efficacy Review Section and Table 33.

Table 44: Summary of Common (Occurring in >2% of Subjects in Any Treatment Group) Adverse Events (All Causalities) by System Organ Class and Preferred Term: 638-CNS-0059-015 (Safety Population)

System Organ Class Preferred Term	Placebo (N=172)	Almotriptan 6.25 mg (N=180)	Almotriptan 12.5 mg (N=182)	Almotriptan 25 mg (N=186)	Product Label[a]
Nervous system disorders	10 (5.8%)	11 (6.1%)	19 (10.4%)	23 (12.4%)	
Dizziness	3 (1.7%)	7 (3.9%)	6 (3.3%)	11 (5.9%)	≥1%
Somnolence	3 (1.7%)	1 (0.6%)	9 (4.9%)	6 (3.2%)	≥1%
Gastrointestinal disorders	6 (3.5%)	5 (2.8%)	8 (4.4%)	11 (5.9%)	
Nausea	0	2 (1.1%)	5 (2.7%)	3 (1.6%)	≥1%

Note: Adverse events (AEs) coded using Medical Dictionary for Regulatory Activities (MedDRA), version 6.0. Number and percentage of subjects by system organ class includes all subjects with AEs within that class. For individual AEs, only those AEs occurring in >2% of subjects in any treatment group are included in the table.

[a] Incidence rate of AEs in subjects treated with almotriptan in adult clinical trials as listed in the AXERT® product label.[2]

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\ TableS-1.1.1.

Table 45: Summary of Common (Occurring in ≥2% of Subjects) Adverse Events (All Causalities) by System Organ Class and Preferred Term: CAPSS-368 (Safety Population)

System Organ Class Preferred Term	Almotriptan 12.5 mg (N=420)
Infections and infestations	179 (42.6%)
Nasopharyngitis	52 (12.4%)
Sinusitis	29 (6.9%)
Upper respiratory tract infection	28 (6.7%)
Pharyngitis streptococcal	18 (4.3%)
Gastroenteritis viral	15 (3.6%)
Influenzae	14 (3.3%)
Viral infection	13 (3.1%)
Pharyngitis	11 (2.6%)
Bronchitis	9 (2.1%)
Gastrointestinal disorders	65 (15.5%)
Nausea	25 (6.0%)
Vomiting	23 (5.5%)
Abdominal pain upper	10 (2.4%)
Respiratory, thoracic and mediastinal disorders	61 (14.5%)
Pharyngolaryngeal pain	27 (6.4%)
Nasal congestion	17 (4.0%)
Cough	16 (3.8%)
Injury, poisoning and procedural complications	53 (12.6%)
Joint sprain	12 (2.9%)
General disorders and administration site conditions	26 (6.2%)
Pyrexia	15 (3.6%)

Note: Adverse events (AEs) coded using Medical Dictionary for Regulatory Activities (MedDRA), version 8.1. Number and percentage of subjects by system organ class includes all subjects with AEs within that class. For individual AEs, only those AEs occurring in ≥2% of subjects in any treatment group are included in the table.

Cross-reference: Mod5.3.5.2\CAPSS-368\Attachment3.1.2.1.

The percentage of almotriptan-treated subjects who reported AEs typically associated with triptans in the 3 adolescent studies was low (e.g., atypical sensations, pain and pressure sensations, cardiovascular events, digestive events, neurologic events, and other miscellaneous events). The sponsor forcefully concludes in comparison with adult clinical studies there is little evidence that these events occurred in higher frequency in adolescents relative to adults. Upon review, I agree there is no apparent difference between adolescents and adults in the trials.

7.3.1 Deaths

There were no deaths in the 3 trials.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events (SAEs) reported in the PK study, Review Study 1, 638-CNS-0059-014 or the Review Study 2, 638-CNS-0059-015, the efficacy study.

Overall, in Review Study 3, CAPSS 368, the long-term safety study, 67.1% of the subjects participating in this study had an adverse event (all causality). Approximately 44% of the subjects participating in this study had at least one adverse event (all causality) that was reported to be of moderate or marked intensity. None of the enrolled subjects died during the study. Eight (1.9%) subjects had a serious adverse event, none of which were considered related to treatment with almotriptan malate.

Thirty-two (7.6%) subjects had at least one adverse event that was judged to be related to treatment with almotriptan malate. The most common treatment-related events were nausea (1.4%) and somnolence (1.4%). All other treatment-related adverse events were reported by less than 1% of the subjects.

Ten (2.4%) subjects withdrew from the study because of an adverse event. Seven of the 10 subjects who withdrew had adverse events that were judged to be related to treatment with almotriptan malate. These adverse events were nausea, somnolence, vomiting, upper abdominal pain, muscle spasms, and migraine.

This information is depicted in the following table from the CSR for the long-term safety study.

Table 46: Subjects With Adverse Events/Reactions

	12-14 yr Age Group N=213		15-17 yr Age Group N=207		Overall N=420	
	n	%	n	%	n	%
Subject who had at least one adverse event	142	66.7	140	67.6	282	67.1
Subjects who had at least one treatment-related adverse event [a]	17	8.0	15	7.2	32	7.6
Subjects who had at least one moderate or marked adverse event	92	43.2	91	44.0	183	43.6
Subjects who died during the study	0	0	0	0	0	0
Subjects who had a serious adverse event	3	1.4	5	2.4	8	1.9
Subjects who discontinued due to an adverse event	7	3.3	3	1.4	10	2.4

[a] Treatment-related adverse events were those that the investigator regarded as possible, probable, or very likely related to treatment or missing.

As can be seen, eight (1.9%) of the 420 subjects in the long-term safety study CAPSS-368, had a serious adverse event as shown in Table 47.

Table 47 Subject Listing of Serious Adverse Events: CAPSS-368 (Safety Population)

Subject Number	Gender/ Age (yrs)/ Race	Preferred Term	Outcome	Severity	Relationship
02007	F/17/B	Gun shot wound	Resolved	Mild	Not related
11001	F/13/W	Intussusception	Resolved	Marked	Not related
17001	M/16/W	Gastroenteritis	Resolved	Marked	Not related
32002	F/12/W	Appendicitis	Resolved	Marked	Not related
32004	M/15/W	Major depression	Resolved	Marked	Doubtful
36007	F/17/W	Appendicitis	Resolved	Marked	Not related
39013	F/15/W	Fetal bradycardia	Resolved	Moderate	Not related
52002	F/13/W	Post procedural hemorrhage	Resolved	Moderate	Not related

Abbreviations: B = black; F = female; M = male; W = white; yrs = years
Note: Subject 37019, excluded from the Safety population, had a serious adverse event (appendicitis). There is no headache record for this subject and study drug exposure cannot be determined.

Cross-reference: Mod5.3.5.2\CAPSS-368\Listing2.16.

Appendicitis was the only SAE experienced by more than 1 subject in this study. All SAEs resolved and were assessed by the investigator as not related to almotriptan treatment with the exception of the event of major depression that was assessed as having a doubtful relationship to study medication.

One subject (37019), who was excluded from the safety population, had an appendectomy 7 days after being dispensed study drug. The sponsor had no headache record for this subject, so study drug exposure could not be determined and the subject was excluded.

7.3.3 Dropouts and/or Discontinuations

No subjects had AEs that resulted in withdrawal from the PK study (Review Study 1, 638-CNS-0059-014 or the efficacy study (Review Study 2, 638-CNS-0059-015.

On the other hand, a total of 10 patients withdrew, 7 of who were in the 12 – 14 yr age group, and 3 in the 15 – 17 yr group.

In the PK study (Review Study 1), a 16-year old male adolescent (Subject #3) experienced a brief episode of ventricular extrasystole 3 hours after dosing with 12.5 mg of almotriptan. The event manifested as multiple individual premature ventricular contractions (PVCs). Subject 3 was asymptomatic, conscious and mentally alert during the event, and all vital signs were normal. Although the initial medical history review failed to show the subject as having an existing history of cardiac arrhythmia or other heart disease, follow up by a pediatric cardiologist revealed that the arrhythmia (frequent PVCs) was a preexisting condition and had been documented by Holter monitoring on three different occasions as early as 1998.

Ten (2.4%) of the 420 subjects in the long-term safety study (Review Study 3, CAPSS-368) withdrew from the study due to 1 or more AEs (Table 48). With the exception of nausea and somnolence, all AEs that led to withdrawal occurred in 1 subject each. Discontinuations due to somnolence and nausea were considered related to treatment with almotriptan.

With one exception, the 13 year old with elevated serum triglycerides, the AEs resolved.

Please see Review Section 7.3.5, below, for additional details regarding AEs of special interest.

Table 48: Subject Listing of Adverse Events Leading to Withdrawal: CAPSS-368 (Safety Population)

Subject Number	Gender/ Age (yrs)/ Race	Preferred Term	Outcome	Severity	Serious	Relationship
03016	F/12/W	Syncope	Resolved	Mild	No	Doubtful
32004	M/15/W	Major depression	Resolved	Marked	Yes	Doubtful
36007	F/17/W	Nausea	Resolved	Moderate	No	Very likely
39001	M/13/W	Blood triglycerides increased	Persisting	Mild	No	Not related
39004	F/16/W	Somnolence	Resolved	Mild	No	Very likely
39008	F/12/W	Somnolence	Resolved	Mild	No	Very likely
39020	F/12/W	Vomiting	Resolved	Moderate	No	Probable
41004	M/13/W	Abdominal pain upper	Resolved	Mild	No	Possible
		Nausea	Resolved	Mild	No	Possible
49004	M/12/W	Muscle spasms	Resolved	Moderate	No	Very likely
52004	F/12/W	Migraine	Resolved	Marked	No	Very likely

Abbreviations: B = black; F = female; M = male; W = white; yrs = years.

Cross-reference: Mod5.3.5.2\CAPSS-368\Listing2.17.

Nine patients were discontinued from the Review Study 2, the efficacy study, due to "Sponsor Decision." The sponsor submitted additional information in response to our query for details on these subjects explaining as follows, "Sponsor decision" was one of the check-box options on the End of Study CRF page. The nine patients discontinued had this option selected. There was no additional information provided as a basis for this decision for any of these subjects; however, a summary of the findings are presented for each subject, which I reviewed.

Three subjects (Subjects 151343, 156640, and 156403) were randomized but did not take a dose of study drug and did not report any migraines according to their treatment group (see Response Submission Appendix 2).

The remaining 6 subjects (Subjects 151529, 156591, 151511, 151532, 156548, and 151525) were randomized and received study drug at Dr. Leon-Flores site (Site 10128). These 6 subjects were discontinued from the study because of methodological deficiencies and Good Clinical Practice (GCP) non-compliance issues observed at Dr. Leon's site, and the sponsor chose to close the investigational site. These 6 subjects were included in the safety analysis set as per the protocol but were excluded from the intent-to-treat population.

None of 9 subjects had significant protocol violations (see Response Appendix 3).

7.3.4 Significant Adverse Events

As stated, no subjects had AEs that resulted in withdrawal from the PK study (Review Study 1, 638-CNS-0059-014) or the efficacy study (Review Study 2, 638-CNS-0059-015). But 10

7.3.5 Submission Specific Primary Safety Concerns

The sponsor relates that, in their 11th PSUR Preliminary Assessment Report, the EU regulatory authorities identified events of special interest/concern, requiring safety monitoring. The list includes those events suggesting:

- A convulsive disorder
- Hepatotoxicity
- Hypersensitivity
- Myocardial ischemia
- Cerebrovascular events
- A visual disturbance
- And those associated with serotonergic syndrome

To meet this stipulation, the sponsor had all AEs reported in the 3 adolescent studies manually reviewed by a medical expert for any events that could signal safety issues as categorized above. This occurred after the clinical study reports for the PK study 638-CNS-0059-014 and the efficacy study 638-CNS-0059-015 were finalized, and was included as part of the clinical study report for the long-term safety study CAPSS-368.

In total, 7 AEs were identified and classified as AEs of special interest, which I reviewed. The sponsor notes, and I agree, none of these events was serious and all resolved without sequelae. The sponsor reports no reports of seizures, cerebrovascular events, or AEs suggestive of ischemic heart disease, hepatotoxicity, hypersensitivity, or visual disturbance in adolescents in these clinical studies.

One AE of special interest was identified in the *PK study* and was discussed above. These subjects received a single dose of almotriptan 12.5 mg for PK analysis **not** for treatment of migraine. The 16-year-old male (Subject 3) experienced a brief episode of ventricular extrasystole 3 hours after dosing with almotriptan. The event manifested as multiple individual premature ventricular contractions (PVCs). The subject was asymptomatic, conscious, and mentally alert during the event, and all vital signs were normal.

Follow-up by a pediatric cardiologist revealed that the arrhythmia (frequent PVCs) was a preexisting condition. The investigator assessed the event as unrelated to study medication.

Five AEs of special interest were identified in the *efficacy study* (Review Study 2). Subjects in this study took a single dose of study medication (placebo or almotriptan 6.25 mg, 12.5 mg or 25 mg) to treat a single migraine attack. These subjects included:

- Two subjects, both randomized to the almotriptan 6.25 mg treatment arm, experienced severe intensity chest pain.
    - Subject 151065 developed the chest pain approximately 5½ hours after taking almotriptan 6.25 mg and the event was reported resolved approximately 5 minutes after onset.
    - Subject 156577 developed the chest pain approximately 7 hours after taking almotriptan 6.25 mg and the event was reported resolved approximately 3½ hours after onset.
- One subject (156424), in the almotriptan 12.5 mg arm, experienced mild intensity chest discomfort approximately 15 minutes after taking study medication and the event was reported resolved within 20 minutes of onset.
- One subject (156545), in the almotriptan 25 mg arm, reported moderate intensity dyspnea approximately 15 minutes after taking study medication and the event was reported resolved within 15 minutes of onset.
- One subject (151198) in the almotriptan 25 mg arm experienced mild intensity facial vasoconstriction at the time of study drug administration that was reported resolved within a minute of onset.

All 5 AEs of special interest were assessed by the investigator as related to study medication.

One AE of special interest was identified in the *long-term safety study*, Review Study 3. Subjects in this study self-administered almotriptan 12.5 mg for treatment of multiple migraine episodes for up to 12 months:

- Subject 42004, a 17-year-old male, experienced mild intensity non-cardiac chest pain which resolved on the day of onset. The event occurred approximately 3 months after taking the first dose of almotriptan. He reported taking a total of 5 doses of almotriptan prior to the event of chest pain; the last almotriptan dose was reportedly taken approximately 1 month prior to the event. He completed the 12-month study and reported taking a total of 11 doses of almotriptan on 7 treatment days after the event of chest pain. There was no reported recurrence of chest pain. The chest pain was assessed by the investigator as possibly related to almotriptan treatment.

In addition to the 7 events that were identified as AEs of special interest, I reviewed the 5 cases of syncope (56003, 52005, 51007, 37008, and 03016) and 1 case of loss of consciousness (37004) in the long-term safety study CAPSS-368 which were not considered AEs of special interest. Upon review of the case histories and case report forms for these subjects, I share the sponsor's conclusion these were not associated with cardiac ischemia.

I requested all the details documenting no event had a plausible temporal relationship to administration of almotriptan, no event was assessed as severe in intensity, and no event was determined to be an SAE. This information was submitted in their response to the query. And I reviewed these details, including the additional narratives requested. All events resolved without sequelae, and all events were assessed by the investigator as not related (4 AEs) or of doubtful

relationship (2 AEs) to study medication. One subject (03016) withdrew from the study due to syncope. That narrative was reviewed and I agree with the conclusion.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Please see Review Section 7.3, above, where this information was presented as an overview. The following tables presented in that section display the data:

- Table 43: Overview of Adverse Events in Adolescent Subjects in Clinical Studies (Safety Population)
- Table 44: Summary of Common (Occurring in >2% of Subjects in Any Treatment Group) Adverse Events (All Causalities) by System Organ Class and Preferred Term: 638-CNS-0059-015 (Safety Population)
- Table 45: Summary of Common (Occurring in ≥2% of Subjects) Adverse Events (All Causalities) by System Organ Class and Preferred Term: CAPSS-368 (Safety Population)
- Table 46: Subjects With Adverse Events/ReactionsTable 47 Subject Listing of Serious Adverse Events: CAPSS-368 (Safety Population)

7.4.2 Laboratory Findings

J and J report no clinically important clinical laboratory findings in any of the 3 adolescent studies. I reviewed the data and concur.

Laboratory Safety Values reported as AEs are presented in the following Summary Tables from Review Studies 2 and 3:

Table 49: Summary of Safety Laboratory Values Reported as Adverse Events by System Organ Class and Preferred Term: 638-CNS-0059-015 (Safety Population)

System Organ Class Preferred Term	Placebo (N=172)	Almotriptan 6.25 mg (N=180)	Almotriptan 12.5 mg (N=182)	Almotriptan 25 mg (N=186)
Hematology Parameters				
Blood and lymphatic system disorders				
Eosinophilia	1 (0.6%)	1 (0.6%)	1 (0.5%)	1 (0.5%)
Anemia NOS	0	0	1 (0.5%)	0
Lymphocytosis	0	0	1 (0.5%)	0
Neutropenia	0	0	1 (0.5%)	0
Investigations				
Eosinophil count increased	1 (0.6%)	0	0	0
Monocyte count increased	0	0	0	1 (0.5%)
Platelet count decreased	1 (0.6%)	0	0	0
Red blood cell Burr cells present	1 (0.6%)	0	0	0
Clinical Chemistry				
Investigations				
Blood creatine phosphokinase increased	2 (1.2%)	0	2 (1.1%)	2 (1.1%)
Blood triglycerides increased	1 (0.6%)	0	0	0

Cross-reference: Mod5.3.5.1\638-CNS-0059-015\TableS-1.1.1, TableS-1.2.1, TableS-1.3.1.

I reviewed the sponsor's data, including shift analyses. I verified the mean values for hematology, clinical chemistry, and urinalysis parameters were within normal range and were similar across the 4 treatment groups at Screening and did not noticeably change at Final Visit. The incidence of N→L and N→H shifts were also similar across the 4 treatment groups.

Table 50: Summary of Safety Laboratory Values Reported as Adverse Events by System Organ Class and Preferred Term: CAPSS-368 (Safety Population)

System Organ Class Preferred Term	Almotriptan 12.5 mg (N=420)
Hematology Parameters	
Blood and lymphatic system disorders	
Leukopenia	2 (0.5%)
Anemia	3 (0.7%)
Investigations	
Hematocrit decreased	1 (0.2%)
Hemoglobin decreased	1 (0.2%)
Neutrophil count increased	1 (0.2%)
RBC count decreased	1 (0.2%)
WBC count increased	1 (0.2%)
Clinical Chemistry	
Investigations	
Blood glucose increased	2 (0.5%)
ALT increased	1 (0.2%)
AST increased	1 (0.2%)
Blood triglycerides increased	1 (0.2%)
Urinalysis	
Investigations	
Protein urine	2 (0.5%)
Protein urine present	2 (0.5%)
Blood urine present	1 (0.2%)
Glucose urine present	1 (0.2%)
RBCs urine	1 (0.2%)
WBCs urine positive	1 (0.2%)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RBC = red blood cell; WBC = white blood cell

Cross-reference: Mod5.3.5.2\CAPSS-368\Attachment3.1.2.1.

The sponsor performed shift analyses in the long term safety study on all abnormal labs affecting at least 5% of all subjects, regardless if they were associated with AEs. This is shown next.

Table 51: Shifts (Normal to Low or High) From Baseline to Visit 5 or Final/Visit 7 in at Least 5% of All Subjects for Serum Chemistry Laboratory Results: Safety Population

	12-14 yr Age Group N=213		15-17 yr Age Group N=207		Overall N=420	
Parameter	N to L	N to H	N to L	N to H	N to L	N to H
Cholesterol (mg/dL)						
n	125	125	121	121	246	246
Visit 5/Month 6	0	5 (4.0%)	0	8 (6.6%)	0	13 (5.3%)
n	134	134	125	125	259	259
Final/Visit 7	0	8 (6.0%)	0	14 (11.2%)	0	22 (8.5%)
Glucose (mg/dL)						
n	163	163	153	153	316	316
Visit 5/Month 6	17 (10.4%)	6 (3.7%)	13 (8.5%)	4 (2.6%)	30 (9.5%)	10 (3.2%)
n	171	171	160	160	331	331
Final/Visit 7	14 (8.2%)	5 (2.9%)	19 (11.9%)	4 (2.5%)	33 (10.0%)	9 (2.7%)
CO_2 (mEq/L)						
n	171	171	158	158	329	329
Visit 5/Month 6	6 (3.5%)	0	12 (7.6%)	0	18 (5.5%)	0
n	180	180	162	162	342	342
Final/Visit 7	5 (2.8%)	0	8 (4.9%)	0	13 (3.8%)	0
Phosphorus (mg/dL)						
n	113	113	130	130	243	243
Visit 5/Month 6	0	29 (25.7%)	0	12 (9.2%)	0	41 (16.9%)
n	121	121	135	135	256	256
Final/Visit 7	1 (0.8%)	29 (24.0%)	0	12 (8.9%)	1 (0.4%)	41 (16.0%)
Triglycerides (mg/dL)						
n	157	157	150	150	307	307
Visit 5/Month 6	0	18 (11.5%)	0	5 (3.3%)	0	23 (7.5%)
n	164	164	152	152	316	316
Final/Visit 7	0	9 (5.5%)	0	7 (4.6%)	0	16 (5.1%)

Abbreviations: CO_2 = carbon dioxide
Note: Low (L) was less than the lower normal limit; Normal (N) was within normal range; and High (H) was greater than the upper normal limit.
Percentages were calculated using the number of Safety subjects overall or in the age group within a baseline category.
Only subjects with non-missing baseline and post-baseline results for a given Visit were included.
The baseline visit was considered the latest measurement up to and including Visit 2 date (including unscheduled visits).
Cross-reference: Attachments 3.3.2.1; 3.3.2.2, 3.3.2.3, Section 10.

The above table summarizes shifts (normal to low or high) from baseline to Visit 5 and Final/Visit 7 for serum chemistry parameters in at least 5% of all subjects in the safety population. I reviewed these data and concur with the conclusions that are described. At both Visit 5/Month 6 and Final/Visit 7, approximately 16% of all subjects had a shift in phosphorus values from within the normal reference range at baseline to above the normal reference range. The percentage of subjects with shifts in phosphorus was greater in the 12 to 14 year age group compared with the 15 to 17 year age group (Visit 5/Month 6: 25.7% vs. 9.2%; Final/Visit 7

(24.0% vs. 8.9%). Shifts from within the normal reference range at baseline to above the normal reference range post-baseline in more than 5% of all subjects occurred for the following serum chemistry parameters: cholesterol: 5.3% at Visit 5/Month 6, 8.5% at Final/Visit 7; and triglycerides 7.5% at Visit 5/Month 6, 5.1% at Final/Visit 7.

Shifts from within the normal reference range at baseline to below the normal reference range post-baseline in more than 5% of all subjects occurred for the following serum chemistry parameters: glucose: 9.5% at Visit 5/Month 6, 10.0% at Final/Visit 7; and CO2: 5.5% at Visit 5/Month 6.

With the exception of a shift in phosphorus from normal to high, in general, the observed shifts in serum chemistry parameter values from baseline to post-baseline assessments were similar in both age groups.

The sponsor performed no outlier analyses of the chemistry findings above. They did analyze the individually clinically significant abnormalities, however. The table below lists these subjects:

Table 52: List of Subjects With Hematology, Serum Chemistry, or Urinalysis Test Results Reported as AEs in the Safety Population

Subject Number	Sex/ Age/ Race	Preferred Term	Outcome	Severity	Serious	Relationship
02001	M/16/B	Protein urine	Persisting	Mild	No	Not related
02007	F/17/B	Hematocrit decreased	Unknown	Mild	No	Not related
		Hemoglobin decreased	Unknown	Mild	No	Not related
		Protein urine present	Unknown	Mild	No	Not related
		RBC count decreased	Unknown	Mild	No	No related
12008	F/14/B	Leukopenia	Persisting	Mild	No	Not related
14003	F/15/W	Blood glucose increased	Persisting	Mild	No	Not related
28001	F/16/W	Leukopenia	Resolved	Moderate	No	Possible
28008	F/16/W	WBC urine positive	Resolved	Mild	No	Not related
28011	M/14/W	Blood glucose increased	Resolved	Moderate	No	Not related
		Glucose urine present	Resolved	Moderate	No	Not related
33003	M/14/W	Blood urine present	Persisting	Moderate	No	Not related
		RBCs urine	Persisting	Moderate	No	Not related
33011	F/15/W	Protein urine present	Resolved	Mild	No	Doubtful
33014	M/17/W	ALT increased	Resolved	Mild	No	Doubtful
		AST increased	Resolved	Mild	No	Doubtful
39001	M/13/W	Anemia	Resolved	Mild	No	Doubtful
		Blood triglycerides increased	Resolved	Marked	No	Possible
		Blood triglycerides increased	Persisting	Mild	No	Not related
39009	F/13/W	Neutrophil count increased	Persisting	Mild	No	Not related
		WBC count increased	Persisting	Mild	No	Not related
47005	F/15/B	Anemia	Persisting	Mild	No	Not related
47007	F/17/B	Anemia	Persisting	Mild	No	Not related
47008	F/17/W	Protein urine	Persisting	Mild	No	Not related

Cross-reference: Listing 2.15

Fifteen of 420 (3.6%) subjects in the safety population had 24 laboratory values that were reported as adverse events. These events were persisting at the end of study for 9 (60.0%) of these subjects. The single marked severity case refers to elevated triglycerides in a mildly anemic subject reported above.

Two events (leukopenia [28001, 16 yo WF] and increased blood triglycerides [39001, 13yo WM]) were regarded as possibly related to treatment with almotriptan malate. Only one event (increased blood triglycerides) was considered to be of marked intensity. Subject 39001 discontinued from the study due to the event of elevated blood triglycerides. No follow-up was given for this subject and the narrative accompanying the submission for this subject does not provide any indication it resolved.

The strict definition of potentially clinically significant deviations was not provided and no outliers are described by the sponsor. I manually reviewing the shift lab data, looking for outliers, in this small chemistry database, and concluded there was only one, the case of increased blood triglycerides in the 13 year old WM. The data do not otherwise reveal any issues of concern to me.

7.4.3 Vital Signs

The sponsor reports no clinically important vital signs shifts in any of the 3 adolescent studies. I reviewed the data and concur. There were no outliers in the vital sign data. The sponsor did define potentially clinically relevant changes in vital signs as follows:

- For systolic BP any change (increase or decrease) of $\geq$ 15 mm from the mean
- For diastolic BP, any change (increase or decrease) of $\geq$ 15 mm from the mean

For *Review Study 1,* the PK study, there were no clinically relevant findings from vital signs measurements.

For *Review Study 2*, the Efficacy Study, the sponsor reports mean vital signs measures were similar across the 4 treatment groups at all scheduled assessments. Changes in mean vital signs from baseline (visit 2) to final visit were small with no clinically meaningful differences across treatment groups, including PBO.

The percentage of subjects with a ≥15 mmHg increase or decrease from baseline to final visit in SBP ranged from 5.8% to 8.6% and from 2.9% to 4.4%, respectively. The percentage of subjects with a ≥15 mmHg increase or decrease in DBP ranged from 2.3% to 6.1% and from 2.2% to 5.4%, respectively.

I reviewed these data and agree. I verified that the mean values for vital signs and ECG results were similar across the 4 treatment groups at Screening and did not noticeably change at Final Visit; the incidence of patients who had increases or decreases of ≥15 mm Hg in their systolic or diastolic BP were also similar across the 4 treatment groups.

For *Review Study 3*, the long-term safety study, the sponsor described changes in mean vital signs from baseline to post-baseline assessments were small with no consistent trend to increase or decrease over time. These appear minor to me.

The percentage of subjects with an abnormal (≥15 mmHg) increase in SBP and DBP was ≤ 12.2% and ≤ 6.6%, respectively, across all study visits. The percentage of subjects with an abnormal (≥15 mmHg) decrease in SBP and DBP was ≤ 7.0% and ≤ 4.7%, respectively. I reviewed these study results and found them to be straightforward minor fluctuations in mean values for systolic and diastolic blood pressure, sitting pulse rate, respiratory rate, body weight, height, and oral temperature. The percentages of subjects involved with these variations are low. And, the fluctuations are not marked.

The results are summarized in this table from the CSR:

Table 53: Abnormal Increase or Decrease in Blood Pressure: Safety Population

(Study CAT 33-308)

Visit	12-14 yr Age Group N = 213	15-17 yr Age Group N = 207	Overall N = 420
Visit 3/Month 1			
Systolic blood pressure			
Increase of at least 15 mmHg	15 (7.2%)	21 (10.6%)	36 (8.9%)
Decrease of at least 15 mmHg	8 (3.9%)	12 (6.0%)	20 (4.9%)
Total non-missing results	207	199	406
Diastolic blood pressure			
Increase of at least 15 mmHg	11 (5.3%)	5 (2.5%)	16 (3.9%)
Decrease of at least 15 mmHg	7 (3.4%)	8 (4.0%)	15 (3.7%)
Total non-missing results	207	199	406
Visit 4/Month 3			
Systolic blood pressure			
Increase of at least 15 mmHg	13 (6.7%)	22 (11.7%)	35 (9.1%)
Decrease of at least 15 mmHg	9 (4.6%)	18 (9.6%)	27 (7.0%)
Total non-missing results	195	188	383
Diastolic blood pressure			
Increase of at least 15 mmHg	12 (6.2%)	9 (4.8%)	21 (5.5%)
Decrease of at least 15 mmHg	7 (3.6%)	11 (5.9%)	18 (4.7%)
Total non-missing results	195	188	383
Visit 5/Month 6			
Systolic blood pressure			
Increase of at least 15 mmHg	23 (12.7%)	16 (9.6%)	39 (11.2%)
Decrease of at least 15 mmHg	8 (4.4%)	9 (5.4%)	17 (4.9%)
Total non-missing results	181	167	348
Diastolic blood pressure			
Increase of at least 15 mmHg	8 (4.4%)	15 (9.0%)	23 (6.6%)
Decrease of at least 15 mmHg	8 (4.4%)	5 (3.0%)	13 (3.7%)
Total non-missing results	181	167	348
Visit 6/Month 9			
Systolic blood pressure			
Increase of at least 15 mmHg	17 (10.1%)	16 (10.1%)	33 (10.1%)
Decrease of at least 15 mmHg	11 (6.5%)	10 (6.3%)	21 (6.4%)
Total non-missing results	168	159	327
Diastolic blood pressure			
Increase of at least 15 mmHg	11 (6.5%)	10 (6.3%)	21 (6.4%)
Decrease of at least 15 mmHg	11 (6.5%)	5 (3.1%)	16 (4.9%)
Total non-missing results	168	159	327
Final/Visit 7			
Systolic blood pressure			
Increase of at least 15 mmHg	26 (13.7%)	18 (10.5%)	44 (12.2%)
Decrease of at least 15 mmHg	9 (4.7%)	15 (8.7%)	24 (6.6%)
Total non-missing results	190	172	362
Diastolic blood pressure			
Increase of at least 15 mmHg	10 (5.3%)	12 (7.0%)	22 (6.1%)
Decrease of at least 15 mmHg	2 (1.1%)	7 (4.1%)	9 (2.5%)
Total non-missing results	190	172	362

Abbreviations: mmHg = millimeters of mercury

Note: Percentages were calculated using the number of Safety subjects in the overall group or age group with non-missing baseline and visit results. Increase and decrease in blood pressure were assessed by comparing the post-baseline visit to baseline visit. Baseline visit was considered the latest measurement up to and including Visit 2 date (including unscheduled visits).

Cross-reference: Attachments 3.5.2.1, 3.5.2.2, and 3.5.2.3; Section 10.

7.4.4 Electrocardiograms (ECGs)

For *Review Study 1*, the PK study, One adolescent subject (Subject 3) had an abnormal ECG 3 hours post-dosing with almotriptan. This event was discussed in detail above.

For *Review Study 2*, the Efficacy Study, the sponsor indicates the incidence of subjects with abnormal significant ECG interpretations was small and similar across 4 treatment groups at screening and final visit. I reviewed these data and concur. The percentage of subjects with abnormal significant ECG interpretations ranged from 0.5% to 1.7% at screening and from 0.6% to 1.1% at final visit.

Shifts in ECG interpretation from normal to abnormal significant or abnormal insignificant to abnormal significant occurred in only 5 subjects:

- 2 in the almotriptan 6.25 mg group and
- 1 each in the placebo, almotriptan 12.5 mg, and almotriptan 25 mg groups.

No "abnormal, significant" ECG was deemed clinically significant by the investigator, but the exact criteria for what was considered clinically significant are not specified in this NDA.

Prolonged QT interval was reported as an AE in 2 subjects in the almotriptan 6.25 mg group, 1 subject in the placebo group, and 1 subject in the almotriptan 25 mg group. None of these AEs was assessed by the investigator as severe in intensity or related to study drug. I reviewed the ECG results and agree with their report.

For *Review Study 3*, the long-term safety study, the sponsor shows the changes from screening to final visit in mean quantitative ECG parameters (PR interval, QRS axis, QRS interval, QT interval, heart-rate corrected QT interval [QTc] Bazett, QTc Fredericia, heart rate, and RR interval) were small (<1.5%). The great majority of subjects had normal ECG results at both baseline and at the Final/Visit 7 assessment. Table 54, below, lists the 14 subjects whose ECG results shifted from normal at baseline to abnormal at the final visit with comments regarding each one. I reviewed the available information in the submission and concur with the conclusions of the sponsor. None were considered SAEs by the sponsor. I reviewed the ECG data and concur with the sponsor's observations and conclusions.

Table 54: List of Subjects with Overall ECG Results That Shifted From Normal at Baseline to Abnormal at the Final Visit and Were Regarded as Possibly Clinically Significant

Table 27: List of Subjects With Overall ECG Results That Shifted From Normal at Baseline to Abnormal at the Final Visit and Were Regarded as Possibly Clinically Significant (Study CAPSS-368)

Subject Number	Visit	Overall Result	Comment Recorded on ECG Tracing
09005	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal, Possibly significant	Sinus bradycardia, abnormal left axis deviation, non-specific T abnormality
10015	Visit 1/Screening	Normal	Sinus bradycardia
	Visit 7/Final	Abnormal Possibly significant	Sinus bradycardia, left atrial abnormality, LVH voltage criteria present, minor right intraventricular conduction delay
10022	Visit 1/Screening	Normal	Sinus arrhythmia
	Visit 7/Final	Abnormal Possibly significant	Prolonged QT interval
12034	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Premature ventricular systole
18013	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Left atrial abnormality
25009	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Non-specific T wave abnormality
27003	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Sinus bradycardia, LVH voltage criteria present
29001	Visit 1/Screening	Normal	Sinus bradycardia, LVH voltage criteria present, possible LVH
	Visit 7/Final	Abnormal Possibly significant	Sinus arrhythmia, LVH voltage criteria present, minor right intraventricular conduction delay
30010	Visit 1/Screening	Normal	Sinus bradycardia
	Visit 7/Final	Abnormal Possibly significant	Sinus bradycardia, intraventricular conduction delay
31004	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Bradycardia, ectopic atrial rhythm, incomplete right bundle branch block, crista pattern
34005	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Left atrial abnormality
37003	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Prolonged QT interval
39006	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Indeterminate QRS axis consistent with right ventricular hypertrophy, borderline QT interval
55005	Visit 1/Screening	Normal	NC
	Visit 7/Final	Abnormal Possibly significant	Intraventricular conduction delay

NC = no comment (was recorded on ECG tracing)
Source: ECG tracings

Fourteen subjects had a shift in their ECG interpretation from normal at baseline to abnormal, possibly clinically significant (not precisely defined) at the final assessment. Two subjects had

ECG abnormalities that were reported as AEs. One of the patients, subject 03007 (13yo WM), had the abnormality (right intraventricular conduction delay) both at baseline and at the final visit, and this was deemed to have doubtful relationship to study drug. The other, Subject 03029 (15 yo BF), had a prolonged PR interval of > 30 msec (141 at baseline, 214 msec at final visit). This PR prolongation relationship to study almotriptan was regarded as doubtful by the sponsor, but no additional details were given, other than that by 47 days following the final visit, the PR interval had returned to normal.

Again, I reviewed these data and find no discrepancies in what is reported by the sponsor above. There were no marked outliers based on my manual review of the ECG data in this small database.

7.4.5 Special Safety Studies

J and J reports the efficacy study 638-CNS-0059-015 – Review Study 2 – (N=720) and the long-term safety study CAPSS-368 – Review Study 3 – (N=420) were used to evaluate adolescent safety in special groups and situations. Their analysis of adolescent subjects in the PK study 638-CNS-0059-014 (N=18) was too small to provide a meaningful interpretation of data.

7.4.6 Immunogenicity

No immunogenicity data was gathered for this sNDA.

7.5 Other Safety Explorations

None.

7.5.1 Dose Dependency for Adverse Events

The long-term safety study used only the single dose of 12.5 mgs, so there were no analyses of adverse events vis-à-vis dosing.

7.5.2 Time Dependency for Adverse Events

These do not appear to have been explored for this sNDA.

7.5.3 Drug-Demographic Interactions

This data was reviewed by Dr. Tristan Massie, Biostatistics, whose review is incorporated above. He notes there are no differences between age, sex, race or gender.

7.5.4 Drug-Disease Interactions

No formal drug-disease interaction studies have been performed in pediatric subjects (<18 years of age) for this sNDA.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been performed in pediatric subjects (<18 years of age) for this sNDA.

7.6 Additional Safety Explorations

The sponsor did analyze their data for almotriptan effects on ability to drive or operate machinery or impairment of mental ability. Commonly reported neurocognitive AEs in adolescent clinical trials included dizziness and somnolence. Dizziness occurred in 4.4% [24/546] of subjects treated with almotriptan(6.25, 12.5 or 25 mg) in the single-dose efficacy study 638-CNS-0059-015 and 1.9% (8/420) of subjects treated with almotriptan in the long-term safety study CAPSS-368.

Somnolence occurred in 2.9% (16/548) of subjects treated with almotriptan (6.25, 12.5 or 25 mg) in 638-CNS-0059-015 and 1.4% (6/420) of subjects treated with almotriptan in CAPSS-368. Although not reported in 638-CNS-0059-015, insomnia occurred in 1.9% (8/420) subjects and syncope occurred in 1.2% (5/420) subjects in CAPSS-368. These events were generally mild or moderate in intensity and few subjects discontinued the study due to these events, according to the sponsor's data.

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted for this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

There were no reported pregnancies among adolescent subjects in the PK study 638-CNS-0059-014 or the efficacy study 638-CNS-0059-015.

Pregnancies were reported for 3 16 year old adolescent subjects during the long-term safety study CAPSS-368. These 3 pregnancies were captured in the almotriptan global postmarketing surveillance database (Mod5.3.6). No other adolescent pregnancies have been reported during postmarketing surveillance. The 3 pregnancies in CAPSS-368 are summarized below:

- *Subject 12025*, a black 16-year-old female, reported treating a total of 26 headaches each with 1 dose of almotriptan 12.5 mg over a period of approximately 10½ months (22 September 2006 to 13 August 2007) before a positive urine pregnancy test result was observed at a follow-up visit on 18 September 2007. A blood sample was taken for a serum pregnancy test to confirm the urine pregnancy test result. The subject gave birth to a healthy male on (b) (6). The infant received Bili-lite™ treatment for 1 day as

therapy for newborn jaundice. The investigator assessed the newborn jaundice as not related to treatment with study medication.

- *Subject 19004*, a white 16-year-old female, reported treating a total of 4 headaches each with 1 dose of almotriptan 12.5 mg over a period of approximately 3 weeks (14 July 2006 to 08 August 2006) before a positive urine pregnancy test result was observed at the 3-week visit on 17 August 2006. A blood sample was taken for a serum pregnancy test to confirm the urine pregnancy test result. The subject's participation in the study was terminated. The subject gave birth to a healthy male on (b) (6). The pregnancy, labor, and delivery were uneventful.
- *Subject 39013*, a white 16-year-old female, treated a total of 18 headaches with a total of 26 doses of almotriptan 12.5 mg over a period of approximately 5 months (11 August 2006 to 11 January 2007) before a positive urine pregnancy test result was observed at a follow-up visit on 05 February 2007. The subject's participation in the study was terminated. The subject was scheduled for labor induction on (b) (6). While in labor, the fetal heart rate dropped (fetal bradycardia) and the baby was delivered by caesarean section. The subject gave birth to a healthy female and remained in the hospital for routine recovery.

I reviewed the data and narratives for these 3 cases and agree with the reports.

7.6.3 Pediatrics and Effect on Growth

This sNDA is the first, if approved, for pediatric migraine. As previously described, a comprehensive review of the literature did not reveal any information regarding almotriptan use in adolescent patients that might be inconsistent with the product label for almotriptan malate. The sponsor culled the literature and only found two more case reports in the literature. It appears in adolescents, at least, there are no special pediatric concerns. The drug has not been systematically evaluated in patients younger than 12 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose have been reported in adolescent clinical trials.

A single postmarketing surveillance report of an intentional multiple-drug overdose in a suicide attempt during the reporting period (December 1999 through 30 June 2008) was found. The patient, a 16-year-old female in France, took oxetorone (1800 mg; 15-30 times [x] the therapeutic dose), almotriptan (75 mg; 6 x the therapeutic dose), and naratriptan (10 mg; 4 x the therapeutic dose). She experienced loss of consciousness and cardiac and neurologic impairment that resolved following hospitalization. The reporter assessed the events as serious and probably related to almotriptan, oxetorone, and naratriptan.

The *abuse potential* of almotriptan was not specifically examined in adolescent clinical studies, but no abuse or drug-seeking behaviors of adolescent subjects has been reported in clinical studies. Except for the 1 report (above) of intentional multiple-drug overdose in a suicide attempt

there have been no reports of abuse or drug-seeking behaviors in adolescents in postmarketing surveillance during the reporting period (December 1999 through 30 June 2008).

Withdrawal effects of almotriptan have not been specifically examined in adolescent clinical studies, but no withdrawal effects of adolescent subjects have been reported in clinical studies or postmarketing surveillance.

7.7 Additional Submissions

None.

8 Postmarketing Experience

The sponsor performed a literature search as detailed in Section 9.1 Literature Review/References. In addition to that all spontaneous reports relevant to the safety of almotriptan in the pediatric population (≤17 years of age) received by Almirall Corporate Drug Safety from worldwide sources cumulatively from the date of first authorization of almotriptan in December 1999 through 30 June 2008 were summarized. They identified 18 pediatric individual case safety reports (ICSRs) including a total of 27 adverse drug reactions (ADRs). It is not possible to estimate total almotriptan exposure in the worldwide pediatric population because almotriptan sales by patient age are not captured.

Of the 18 pediatric ICSRs, 16 were received from the US, 1 from France, and 1 from Germany. The ICSRs of pediatric patients were captured mainly from clinical trials.

The almotriptan dose taken at or around the time of the ADR was reported in 17 of the 18 ICSRs. Of those 17 ICSRs, 14 patients were taking almotriptan 12.5 mg prn for migraine attack, 2 patients were taking almotriptan 6.25 mg prn for migraine attack, and 1 patient took an intentional overdose of almotriptan (75 mg) one time. In one ICSR of lack of efficacy, information regarding almotriptan dosage and duration of exposure was not captured from the reporter (patient's mother).

The system organ classes with the most ADRs were injury, poisoning and procedural complications (8 ADRs), and general disorders and administration site conditions (6 ADRs) (Table 44). The most frequently reported ADRs were drug ineffective (4 cases) and drug exposure during pregnancy (3 cases). There was 1 ADR reported for each of the remaining preferred terms. Of the 23 ADRs where outcome was applicable (excluding the 4 lack of efficacy events), 20 ADRs resolved and 3 pregnancies resulted in normal healthy births.

No safety signal was detected in pediatric cases related to ADRs of special interest. There were no reports of seizures or ADRs suggestive of cerebrovascular events, ischemic heart disease, hepatotoxicity, hypersensitivity, or visual disturbance. Non-serious chest pain was reported in 1 patient. One patient intentionally overdosed on 3 serotonergic drugs in a suicide attempt. The

patient experienced loss of consciousness and cardiac and neurologic impairment that resolved following hospitalization.

Table 55: Postmarketing Reports of Adverse Drug Reactions in Pediatric Patients (≤17 Years of Age) by System Organ Class and Preferred Term: December 1999 through 30 June 2008

System Organ Class	Preferred Term	ADRs per Preferred Term
Cardiac disorders	Bradycardia foetal	1
	Bundle branch block	1
	Sinus tachycardia	1
Ear labyrinth disorders	Vertigo	1
Gastrointestinal disorders	Intussusception	1
	Nausea	1
General disorders and administration site conditions	Chest pain	1
	Drug ineffective	4
	Fatigue	1
Infections and infestations	Appendicitis	1
Injury, poisoning and procedural complications	Concussion	1
	Drug exposure during pregnancy	3
	Gun shot wound	1
	Ligament injury	1
	Multiple drug overdose intentional	1
	Post procedural haemorrhage	1
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	1
Nervous system disorders	Burning sensation	1
	Loss of consciousness	1
	Pyramidal tract syndrome	1
Psychiatric disorders	Major depression	1
Reproductive system and breast disorders	Breast tenderness	1

ADR = adverse drug reaction

Cross-reference: Mod5.3.6\Table1.

9 Appendices

9.1 Literature Review/References

The sponsor conducted a comprehensive literature search seeking reports of the pediatric experience with almotriptan and sumatriptan. They found 90 references in the executed search. The output was further manually screened to eliminate obvious false drops (e.g., animal studies) and additional duplicates not removed by the software (24 references). The remaining 66 references were manually screened to eliminate review articles (29 references), references pertaining to adults only (at least 18 years of age; 24 references), non-treatment studies (2 references), and meeting abstracts of studies subsequently published as a full report (2 references).

Recent reviews were screened for any additional studies not retrieved by the literature search (0 references). Nine references report on the use of almotriptan in a study population that included pediatric patients. Of these 9 references, 5 evaluated a study population that included both adults and pediatric patients (17 years of age or younger). No individual data specific to pediatric patients are reported in these 5 publications.

Literature searches identified 4 publications presenting original, unique data related to the safety and efficacy of almotriptan in patients less than 18 years of age. Of these, 2 publications reported adolescent use of almotriptan in company-sponsored clinical studies: 638-CNS-0059-014 and 638-CNS-0059-015. These studies are discussed above. The 2 reports presenting original, unduplicated data from non-company-sponsored clinical studies were reviewed. The relevant information is noted next.

In an open-label, pilot study, 15 subjects 11 to 17 years of age with a history of migraine with or without aura (14 female; 1 male) were offered almotriptan for acute treatment if headache frequency was not >4 migraine headache attacks/month and headache-free interval between attacks was >24 hours. Subjects <50 kg body weight were given almotriptan 6.25 mg (N=2); subjects >50 kg were given almotriptan 12.5 mg (N=13). There was 1 adverse event reported during the study. The subject described transient mild stiffness that was not considered to be clinically significant and did not impair school or social performance. Efficacy of almotriptan was satisfactory in this subject.

One case report described use of almotriptan 12.5 mg in the acute treatment of menstrually related migraine in a 15-year old female. She had a 7-year history of headaches, including chronic daily headaches, menstrually related migraines that occurred approximately once a month and lasted up to 48 hours (associated with nausea, photo/phonophobia, light-headedness, and occasional vision of lights of 1-minute duration), and other headaches occurring with variable frequency (associated with sinus pressure, lacrimation, sinus congestion, and drainage). Her academic performance suffered due to frequent school absenteeism. For migraine prophylaxis, the patient was prescribed topiramate 100 mg twice daily and riboflavin 400 mg daily with the addition of magnesium oxide (400 mg daily) or chelated magnesium (1,000 mg daily). Naproxen (1 to 2 tablets as needed [prn]) alone or in combination with almotriptan 12.5 mg was to be taken at onset of mild headaches. Almotriptan 12.5 mg was to be taken within 20 minutes of onset of an acute migraine attack followed by a second dose if the patient was not pain free after 2 hours. After 3 months the patient had only mild daily headaches. Treatment with fluoxetine (up to 20 mg per day) was initiated. At the 4-month follow-up, the patient complained of chronic recurrent abdominal pain and head/neck muscle soreness. The results of an esophago-gastroduodenoscopy were unremarkable. The chronic recurrent abdominal pain and head/neck muscle soreness may have been symptoms associated with the underlying headache/migraine disorder or possibly associated with almotriptan or concomitant medications. An oral contraceptive regimen containing desogestrel/ethinyl estradiol and ethinyl estradiol was prescribed and almotriptan therapy continued.

At the 22-month follow-up, the patient no longer experienced daily headaches and almotriptan reportedly provided complete relief of pain within 1 hour as well as relief from migraine-associated neck pain. The patient reported that she tolerated almotriptan better than other triptans. She rarely missed school.

Based on their search, the sponsor concluded no safety information regarding almotriptan use in adolescent patients that might be inconsistent with the product label for almotriptan is apparent.

9.2 Patient Narratives for SAEs in the 3 Trials

For Review Study 1:

In the PK study (Review Study 1), a 16-year old male adolescent (Subject #3) experienced a brief episode of ventricular extrasystole 3 hours after dosing with 12.5 mg of almotriptan. The event manifested as multiple individual premature ventricular contractions (PVCs). Subject 3 was asymptomatic, conscious and mentally alert during the event, and all vital signs were normal. Although the initial medical history review failed to show the subject as having an existing history of cardiac arrhythmia or other heart disease, follow up by a pediatric cardiologist revealed that the arrhythmia (frequent PVCs) was a preexisting condition and had been documented by Holter monitoring on three different occasions as early as 1998.

For Review Study 2:

In the Efficacy Study (Review Study 2) there were 5 cases of SAEs of special interest, discussed here.

Subject 151065 (adverse event of special interest: chest pain): This 13-year-old black female subject was randomized to almotriptan 6.25 mg on 30 September 2003. Relevant medical history included migraine diagnosis (since 1996), chronic sinusitis, and seasonal allergies.

The subject took study medication on 26 October 2003 at 15:07, approximately 1½ hours after onset of migraine attack (13:40). The subject experienced chest pain the same day at 20:30, approximately 5½ hours after taking study medication. The subject did not report taking any concomitant medications at the time of the adverse event. The chest pain was severe in intensity. The event was reported resolved the same day at 20:35, approximately 5 minutes after onset. No action was taken with the study drug as a result of this event. The subject also reported moderate stomach pain at the time of occurrence of the chest pain.

In the investigator's opinion, the chest pain was related to the study drug.

Subject 151198 (adverse event of special interest: vasoconstriction): This 14-year-old white female subject was randomized to almotriptan 25 mg on 15 December 2003. Relevant medical history included migraine diagnosis (since 2002).

The subject took study medication on 20 December 2003 at 21:20, within a minute of onset of migraine attack (21:19). The subject experienced facial vasoconstriction at the time of administration of study medication (21:20). The subject did not report taking any concomitant medications at the time of the adverse event. The vasoconstriction was mild in intensity. The event was reported resolved the same day at 21:21, within a minute of onset. No action was taken with the study drug as a result of this event. The subject developed a mild rash on the face the next day (21 December 2003) that was treated with Neosporin and resolved by 23 December 2003.

In the investigator's opinion, the vasoconstriction was related to the study drug.

Subject 156424 (adverse event of special interest: chest discomfort): This 17-year-old white female subject was randomized to almotriptan 12.5 mg on 13 August 2004. Relevant medical history included migraine diagnosis (since 1999), premenstrual syndrome, and syncope.

The subject took study medication on 24 August 2004 at 13:45, approximately 15 minutes after onset of migraine attack (13:27). The subject experienced chest discomfort the same day at 14:00, approximately 15 minutes after taking study medication. The subject did not report taking any concomitant medications at the time of the adverse event. The chest discomfort was mild in intensity. The event was reported resolved the same day at 14:20, within 20 minutes of onset.

No action was taken with the study drug as a result of this event. The subject also reported mild right ear pain at the time of occurrence of the chest discomfort. In the investigator's opinion, the chest discomfort was related to the study drug.

Subject 156545 (adverse event of special interest: dyspnea): This 16-year-old white, Hispanic/Latino, female subject was randomized to almotriptan 25 mg on 13 January 2005. Relevant medical history included migraine diagnosis (since 2003).

The subject took study medication on 28 February 2005 at 19:15, approximately 15 minutes after onset of migraine attack (19:00). The subject experienced difficulty breathing the same day at 19:30, approximately 15 minutes after taking study medication. The subject did not report taking any concomitant medications at the time of the adverse event.

The dyspnea was moderate in intensity. The event was reported resolved the same day at 19:45, within 15 minutes of onset. No action was taken with the study drug as a result of this event. The subject also reported moderate paresthesias around the mouth at the time of occurrence of the dyspnea.

In the investigator's opinion, the dyspnea was related to the study drug.

Subject 156577 (adverse event of special interest: chest pain): This 17-year-old white female subject was randomized to almotriptan 6.25 mg on 24 January 2005. Relevant medical history included migraine diagnosis (since 2002), eczema, asthma, scoliosis, sulfa allergy, and seasonal allergic rhinitis.

The subject took study medication on 07 February 2005 at 12:30, approximately 4¼ hours after onset of migraine attack (08:15). The subject experienced chest pain the same day at 17:30, approximately 7 hours after taking study medication. The subject did not report taking any concomitant medications at the time of the adverse event. The chest pain was severe in intensity. The event was reported resolved the same day at 21:00, approximately 3½ hours after of onset. No action was taken with the study drug as a result of this event.

In the investigator's opinion, the chest pain was related to the study drug.

For Review Study 3:

Please see Table 47, above. The narratives for the trials subjects experiencing an SAE follow below:

Subject 02007 (serious adverse event: gun shot wound): This 17-year-old black female subject experienced a superficial gun shot wound to her abdomen. The subject had no relevant medical history.

The subject received the first dose of study drug on 10 April 2006 and received the last recorded dose on 20 August 2006 (total of 10 recorded doses). No action was taken with the study drug. Concomitant medications at the time of the event included acetaminophen/acetylsalicylic acid/caffeine, promethazine, and meperidine.

On (b) (6), the subject experienced a superficial gun shot wound to her right upper abdomen while attending an after-school program. The subject was transported to the emergency room by ambulance and admitted for observation. A portable X-ray of the abdomen and portable chest X-ray showed no acute abnormalities and, specifically, no foreign body. No clinically significant laboratory results were observed. The subject was admitted to the hospital overnight. Treatment included naproxen, tetanus vaccine, antibiotic ointment, and cefazolin sodium.

The event was mild in severity. On (b) (6), the serious adverse event was considered resolved, but the event continued as a non-serious adverse event until 05 June 2006. On (b) (6), the subject was discharged from the hospital.

The subject treated 9 headaches (10 doses) with study drug as a participant in this study. The event occurred 7 days after the last recorded use of study drug. The subject could not account for missing study drug and was regarded irresponsible. As a result, the subject's participation in the study was terminated.

In the investigator's opinion, the event was not related to the study drug.

Subject 11001 (serious adverse event: intussusception): This 13-year-old white female subject experienced a small bowel intussusception. The subject had a history of morphine allergy.

The subject received the first dose of study drug on 22 April 2006 and received the last recorded dose on 12 May 2007 (total of 62 dose days). Study medication was temporarily stopped on 05 May 2006 and re-started with permission from the medical monitor on 24 May 2006. Concomitant medications at the time of the event included acetaminophen/ diphenhydramine, acetaminophen/acetylsalicylic acid/caffeine, and acetaminophen/caffeine/pyrilamine maleate.

On (b) (6), the subject was admitted to the hospital with complaints of intermittent, "crampy" abdominal pain that persisted for one week. A gall bladder ultrasound for the right upper quadrant pain revealed a possible polyp on the fundus of the gall bladder. The subject's mother reported that the subject had stomach aches with pain throughout childhood. The stomach pain would subside over time with the use of acetaminophen. The mother also reported that the subject had surgery to correct the small bowel growing into the large intestine.

The subject underwent an exploratory laparotomy with small-bowel enteroscopy and a biopsy of the mesenteric lymph node. A nasogastric tube and Foley catheter were maintained in place. She remained afebrile with normal, stable vital signs. The subject was ambulated on postoperative Day 1. She received prophylaxis for DVT and stress ulcers.

A CT scan of the abdomen and pelvis with contrast performed postoperatively revealed no intussusception and a few small non-specific mesenteric lymph nodes in the right lower quadrant. On (b) (6), a surgical pathology report of the mesentery node revealed intact normal architecture and sinuses that contained no abnormal infiltrates. Medication during hospitalization included hydrocodone/acetaminophen, tegaserod maleate, nitazoxanide, cefoxitin, magnesium hydroxide, meperidine, and promethazine.

The event was marked in severity. The event was considered resolved on (b) (6), and the subject was discharged from the hospital.

The subject treated 3 headaches (3 doses) with study drug before the event and 59 headaches (67 doses) after the event. There was no reported recurrence of intussusception. The subject completed the 12-month study.

In the investigator's opinion, the event was not related to the study drug.

Subject 17001 (serious adverse event: gastroenteritis): This 16-year-old white male subject experienced gastroenteritis. The subject had no relevant medical history.

At the time of the event, the subject had not received study drug. No concomitant medications were reported.

On 23 July 2006, the subject complained of abdominal pain with fever. On 26 July 2006, the subject's temperature was reported to be 102°F. On (b) (6), the subject was admitted to the hospital to rule out appendicitis, per surgery consult. The abdominal pain was in the right lower quadrant with occasional radiation to the epigastrium. The subject had one episode of vomiting. Abdominal X-rays showed nonspecific abdominal bowel gas pattern. An unremarkable enhanced CT of the abdomen and pelvis revealed no evidence of appendicitis or bowel obstruction. The symptoms were diagnosed as gastroenteritis. The event was marked in severity. Treatment included IV fluids, morphine sulfate, ondansetron, and acetaminophen.

The event was considered resolved on (b) (6), and the subject was discharged.

The subject treated the first headache with study drug after the event of gastroenteritis. He treated 19 headaches (22 doses) before experiencing viral gastroenteritis (non-serious adverse event) on 28 November 2006. He was given promethazine hydrochloride for vomiting and stomach cramps and the event was considered resolved on 29 November 2006. He treated 45 more headaches (48 doses) without recurrence of gastroenteritis, and completed the 12-month study.
In the investigator's opinion, the events of gastroenteritis and viral gastroenteritis were not related to the study drug.

Subject 32002 (serious adverse event: appendicitis): This was a 12-year-old female subject who experienced appendicitis. The subject had a medical history of frequent ear infections (pressure-equalizing tube surgery in 1998), tonsillitis (tonsillectomy and adenoidectomy in 1999), asthma, and eczema.

The subject had not received study drug prior to the onset of the event. On (b) (6) (b) (6), the subject was hospitalized for appendicitis. The event was marked in severity. On (b) (6) the subject underwent a laparoscopic appendectomy for early appendicitis and had an uneventful postoperative course. Darvocet and morphine were administered for pain.

On (b) (6) the event was considered resolved and the subject was discharged from the hospital. Also on this date, the subject experienced a rash and itching due to hydrocodone/acetaminophen, which was treated with diphenhydramine. This was perceived as an allergic reaction to hydrocodone. (The condition was recorded as a non-serious adverse event.)

The subject treated the first headache with study drug after the event of appendicitis, and treated a total of 25 headaches (34 doses) before completing the 12-month study. In the investigator's opinion, the event was not related to the study drug.

Subject 32004 (serious adverse event: major depression): This was a 15-year-old white male subject who experienced major depression. The subject had no relevant medical history.

The subject received the first dose of study drug on 16 October 2006 and received the last recorded dose on 24 January 2007 (total of 15 dose days).

Concomitant medications at the time of the event included minocycline. On (b) (6) (b) (6), the subject was admitted for in-patient psychiatric treatment for a diagnosis of schizophrenia. On admission, the subject's chief complaint was that he had an emotional breakdown and that he had been hearing voices ("good" and "evil") since about the fourth grade. He was feeling distraught and frustrated, stating that he wanted to die. The event was marked in severity. Treatment consisted of risperidone and escitalopram. His mood started to improve fairly quickly.

On (b) (6) the subject was taken off of suicide precautions and he appeared to be stable for discharge. On (b) (6) the event was considered resolved.

The subject treated 15 headaches (16 doses) with almotriptan malate before the event of major depression. The event occurred 14 days after the last recorded use of study drug. Study drug was permanently discontinued due to this event and the subject's participation in the study was terminated.

The investigator considered it doubtful that the event was related to the study medication.

Subject 36007 (serious adverse event: appendicitis; adverse event leading to discontinuation: nausea): This was a 17-year-old white female subject who experienced appendicitis and later discontinued the study due to the event of nausea. The subject had a history of otitis media and palpitations.

The subject did not receive almotriptan malate prior to the event of appendicitis. Concomitant medications at the time of the event of appendicitis included ibuprofen, rizatriptan, acetaminophen/acetylsalicylic acid/caffeine, and ketorolac. No concomitant medications were reported at the time of the event of nausea.

On (b) (6) the subject went to the emergency room with complaints of acute abdominal pain associated with some nausea. The event was marked in severity. A CT scan of the abdomen suggested early appendicitis. The subject was admitted. After a surgical consult, a laparoscopic appendectomy was performed. Operative findings were consistent with acute appendicitis. The event was considered resolved on (b) (6)

On (b) (6), the subject was in satisfactory condition and was discharged home. In the investigator's opinion, the event of appendicitis was not related to the study drug.

The subject received the first dose of study drug on 09 June 2006 after the event of appendicitis.

On 10 January 2007, the subject had a migraine with moderate pain and mild phonophobia, and experienced moderate nausea and vomiting 2 hours after taking one dose of study drug; nausea and vomiting were not reported at baseline. All headache symptoms were resolved by 24 hours. The subject had treated 14 headaches (17 doses) with study drug before the event of nausea was reported as an adverse event and 3 headaches (3 doses) after the event.

On 04 February 2007, the subject treated a migraine headache with mild pain and mild phonophobia with one dose of study drug; no symptoms of nausea or vomiting were present. On 18 February 2007, the subject treated another migraine with moderate pain and mild photophobia and phonophobia with one dose of study drug. Mild nausea was present at baseline and 2 hours after treatment with study drug. The subject was vomiting 24 hours after treatment with study drug even though other headache symptoms were not present. On 08 March 2007, the subject treated a migraine with moderate pain, mild photophobia, and mild phonophobia with one dose of study drug. Moderate nausea was reported at baseline and moderate nausea and vomiting were reported 2 hours after taking study drug. All headache symptoms were resolved at 24 hours.

Study drug was discontinued because of the event of nausea and the subject's participation in the study was terminated.

In the investigator's opinion, the event of nausea was very likely related to the study drug.

Subject 37019 (serious adverse event: appendicitis): This was a 12-year-old white female subject who experienced appendicitis. The subject had no relevant medical history.

This subject was enrolled in the study and study drug (6 tablets of almotriptan malate) was dispensed on 04 August 2006. The subject withdrew consent to participate in the study (date of withdrawal not available). There is no headache record for this subject and study drug exposure cannot be determined. Concomitant medications at the time of the event included ibuprofen.

On (b) (6), the subject was seen in the emergency room due to complaints of a stomach ache. The event was marked in severity. A CT scan of the abdomen and pelvis with contrast showed findings consistent with acute appendicitis. She was transferred and admitted to the hospital.

On (b) (6), a laparoscopic appendectomy was performed without complications. On (b) (6), the event was considered resolved and the subject was discharged. In the investigator's opinion, the event was not related to the study drug.

Subject 39013 (serious adverse event: fetal bradycardia): This 15-year-old white female subject experienced fetal bradycardia. The subject had a medical history of allergic rhinitis, appendicitis with resultant appendectomy, and joint pain (knees and hips).

The subject received the first dose of study drug on 11 August 2006 and received the last recorded dose on 11 January 2007 (total of 26 recorded doses). No information about concomitant medications at the time of the event is available.

The start date of the subject's last menses was 11 December 11 2006. The subject treated 16 headaches (23 doses) with study drug between 11 August 2006 and 15 December 2006, and she treated 2 headaches (3 doses) between 20 December 2006 and 11 January 2007.

On 05 February 5 2007, HCG total was 106768 mIU/mL, confirming pregnancy with an anticipated delivery date of 20 September 2007. All other laboratory values were within normal limits. The subject's participation in the study was terminated due to the pregnancy.

On 15 September 2007, an obstetrical ultrasound revealed the presence of a single living intrauterine fetus equal to approximately 39 weeks and 1 day gestation. The fetal heart beat was recorded at 157 bpm. A biophysical profile revealed a normal score of 8/8. On 19 September 2007, a biophysical profile was again normal at 8/8.

On (b) (6), the subject was scheduled for labor induction. While in labor, the fetal heart rate dropped (fetal bradycardia) and the baby was delivered by low flap transverse caesarean section. The subject gave birth to a normal/healthy girl with Apgar scores of 9 and 9. Findings during the cesarean section included umbilical cord around neck x 1. The subject remained in the hospital for routine recovery.
The event was considered moderate in severity and resolved on the day of onset.

In the investigator's opinion, the event was not related to study medication.

Subject 52002 (serious adverse event: post procedural hemorrhage):
This 13-year-old white female subject experienced a post-procedural hemorrhage. The subject had a medical history of chronic tonsillitis, chronic abdominal pain, and H-pylori.

The subject received the first dose of study drug on 31 May 2006 and received the last dose on 24 March 2007 (total of 24 dose days).

Concomitant medications at the time of the event included lansoprazole, sucralfate, and ondansetron.

On 08 December 2006, the subject had a tonsillectomy and adenoidectomy. On 15 December 2006 at about 6:00 pm, the subject experienced an abrupt tonsil hemorrhage that lasted for a few minutes. On (b) (6) at about 2:30 am, the subject experienced a second episode of bleeding and her parents escorted her to the emergency room. Upon arrival, the bleeding had subsided. An examination revealed that some eschar was present on the surgical site. Intravenous fluids were administered and the subject was treated with hydrocodone/acetaminophen for pain. There was a large clot in the tonsillar fossa, but no airway problem was noted. The event was moderate in severity. The subject was kept overnight for observation and she was discharged home in stable condition.

The subject treated 19 headaches (20 doses) before the event of post procedural hemorrhage and 5 headaches (5 doses) after the event. The subject completed the 12-month study without recurrence of the event of post procedural hemorrhage.

In the investigator's opinion, the event was not related to the study drug.

9.3 Labeling Recommendations

See Revised Label from DNP.

9.4 Advisory Committee Meeting

None needed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert D. Harris
4/23/2009 11:04:19 AM
MEDICAL OFFICER

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