CLINICAL REVIEW

Application Type	NDA 505 (B)(1)
Application Number(s)	20,865
Priority or Standard	Priority
Submit Date(s)	3/25/11
Received Date(s)	3/25/11
PDUFA Goal Date	9/23/11
Division / Office	Division of Neurology Products
Reviewer Name(s)	Nushin Todd, MD, PhD
Review Completion Date	
Established Name	Rizatriptan
(Proposed) Trade Name	Maxalt-MLT
Therapeutic Class	Triptan
Applicant	Merck
Formulation(s)	Orally Disintegrating Tablet
Dosing Regimen	10 mg
Indication(s)	Migraine
Intended Population(s)	Adolescents (12-17 years) with migraine

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of rizatriptan, for both 5 mg and 10 mg doses, in adolescent migraine patients, 12 to 17 years of age. The sponsor has complied with the terms of the pediatric written request and the trial efficacy data support this approval.

1.2 Risk Benefit Assessment

Rizatriptan, marketed in the United States for adult migraine patients since 1998, has a well characterized safety profile. No new or unexpected adverse events were discovered in the course of the development program of rizatriptan in the adolescent population. The overall risk to benefit ratio of rizatriptan in adolescents 12 to 17 years of age is therapeutically acceptable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Rizatriptan is a selective 5-hydroxytryptamine 1B/1D (5-$HT_{1B/1D}$) receptor agonist for the treatment of acute migraine headaches in adults. It is manufactured and marketed as by Merck & Co. and is available in two formulations: tablets (referred to as MAXALT™, NDA 20-864) and orally disintegrating tablets (ODT; also referred to as MAXALT-MLT™, NDA 20-865). Both formulations are available in strengths of 5 and 10 mg.

MAXALT™ and MAXALT-MLT™ were originally approved by the FDA on June 29, 1998.

The sponsor submitted a proposed draft label in PLR format. The amended labeling includes changes to the following sections of the full prescribing information: USE IN SPECIFIC POPULATIONS, Pediatric use; and CLINICAL PHARMACOLOGY, Pharmacokinetics.

In order to fulfill the required pediatric study commitments under PREA (Pediatric Research Equity Act) the sponsor conducted 3 pediatric clinical studies in pediatric migraineurs:

- One PK study (Protocol P083)
- One efficacy study (Protocol P082)
- One long term safety study (Protocol P086)

All 3 submitted studies used the ODT formulation of rizatriptan. Body weight based dosing regimen was applied in all 3 studies, i.e., rizatriptan 5 mg ODT for subjects <40 kg and rizatriptan 10 mg ODT for subjects ≥40 kg.

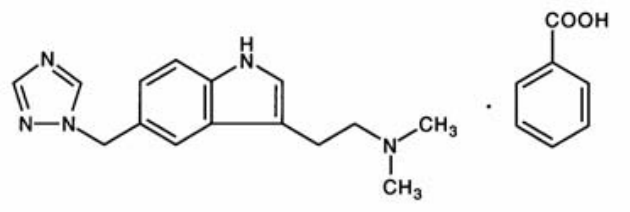
The sponsor also provided supportive data from 5 studies conducted earlier in the adolescent population (ages 12 to 17 years). These studies include to 2 PK studies (P048 and P062), 2 efficacy studies (P054 and P059), and 2 safety studies (P059 extension/P061).

2.1 Product Information

Indication:	Migraine, with or without aura, in adolescents (ages 12 to17 years)
Dosage Form/Strength:	Orally Disintegrating Tablet (ODT), 5 mg and 10 mg tablets
Proposed Dosage:	Adolescents patients, 12 to 17 years: <40 kg, 5 mg single dose; ≥40 kg, 10 mg single dose
Chemical Name:	*N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate
Pharmacologic Class:	Selective 5-HT1B/1D receptor agonist

Molecular Weight: Mol Wt: 269.4 (free base)

Structural Formula:



Physical Properties: White or off-white, crystalline solid

Solubility: Soluble in water at about 42 mg/mL (expressed as free base) at 25°C

Mechanism of Action: The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-$HT_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

2.2 Tables of Currently Available Treatments for Proposed Indications

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

Table 1 Acute Migraine Therapies in Current Use [a]

Group 1 [b]	Group 2 [c]	Group 3 [d]	Group 4 [e]	Group 5 [f]
Specific Almotriptan PO Eletriptan PO Frovatriptan PO Naratriptan PO Rizatriptan PO Sumatriptan SC, IN, PO Zolmitriptan PO, IN DHE SC, IM, IV, IN DHE IV, plus antiemetic *Nonspecific* 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 Ketorolac IM Lidocaine IN Meperidine 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 modified 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.
[b] Proven, pronounced statistical and clinical benefit (at least two double-blind, placebo-controlled studies and clinical impression of effect).
[c] Moderate statistical and clinical benefit (one double-blind, placebo-controlled study and clinical impression of effect).
[d] Statistically but not proven clinically *or* clinically but not proven statistically effective (conflicting or inconsistent evidence).
[e] Proven to be statistically or clinically ineffective (failed efficacy versus placebo).
[f] Clinical and statistical benefits unknown (insufficient evidence available).

The following are FDA approved medications used for treating migraine:

Table 2 FDA Approved Migraine Therapies in Current Use

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

Source: Adapted from Consumer Magazine, 2006

The majority of FDA approved migraine products are the triptans, summarized in Table 3.

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 12, 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 dissolving 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
Sumavel® DosePro (sumatriptan)	22-239	July 15, 2009	Subcutaneous injection

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Maxalt and Maxalt-MLT is rizatriptan. The FDA approved Maxalt and Maxalt-MLT for adult use in June 1998 (NDA 20-864 and 20-865, respectively). Rizatriptan is widely available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety profile of rizatriptan in adult patients with a clear diagnosis of migraine (b) (4) has been established. This sNDA, however, reviews safety and effectiveness of rizatriptan in the adolescent population (12-17 years of age). Currently, only one triptan, almotriptan (Axert) is approved for migraine in adolescents.

While generally recognized as safe and effective, there have been concerns regarding cardiac complaints. Fatalities have been reported within the triptan class due to cardiac causes. While perhaps vasospastic origin, the phenomenon remains pathologically 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 rizatriptan label clearly states that it should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD). Similarly it 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, triptans should not be administered.

Still further, in patients whose risk factors predict CAD but who have a satisfactory cardiovascular evaluation, the rizatriptan label strongly recommends that the first administration of rizatriptan 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 during the interval immediately following the first use of rizatriptan in these patients with risk factors.

The current label recommends patients who are intermittent long-term users of rizatriptan 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, (b) (4)

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program of rizatriptan for pediatric migraineurs was performed under investigational new drug (IND) application number 40,458. The Agency issued a Pediatric Written Request (PWR) on 6 March 2009. The PWR provided the requirements of the pediatric studies to be conducted. It was amended to its final version on 13 January 2010. The PWR is reprinted below.

Pediatric Written Request for Maxalt® (rizatriptan benzoate)

Clinical Studies

Type of studies
Study 1: Safety/Tolerability/Pharmacokinetic Study
Study 2: Pediatric Efficacy Study
Study 3: Pediatric Long-Term Safety Study

These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Objectives/rationale
Study 1: To assess the safety and tolerability of single doses of rizatriptan benzoate, and evaluate the pharmacokinetics of rizatriptan benzoate in pediatric migraineurs 12 to 17 years of age, compared to adults (historical controls).
Study 2: To evaluate the efficacy and safety of rizatriptan benzoate in the treatment of pediatric patients age 12 to 17 years of age with a history of migraine headaches.
Study 3: To evaluate the long-term safety of rizatriptan benzoate in the treatment of pediatric patients 12 to 17 years of age with a history of migraine headaches.

Indication(s) to be studied
The use of rizatriptan benzoate for the acute treatment of migraine in pediatric patients 12 to 17 years of age with a history of migraine headaches.

Study design
Study 1: Single dose, safety, tolerability and pharmacokinetic study in pediatric migraineurs 12 to 17 years of age, designed to compare the pharmacokinetic results in pediatric migraineurs with appropriate adult historical control data.
Study 2: Randomized, double-blind, placebo-controlled, parallel group outpatient study in pediatric migraineurs 12 to 17 years of age. The study design must take into account the short duration of migraine attacks, and the high placebo

response rate in pediatric patients. The dose(s) evaluated and study design must be justified based on prior rizatriptan benzoate adult and pediatric efficacy and safety studies, published literature, and the results of Study 1. The protocol must allow the use of appropriate rescue medication after a suitable post-dosing interval.
Study 3: Open label, 6-month outpatient study in pediatric migraineurs 12 to 17 years of age. This 6-month study is part of an open label 12-month outpatient study. This Written Request, however, is only requiring submission of 6-month, interim report of data by the filing date.

Age groups to be studied
Pediatric patients 12 to 17 years of age, inclusive.

Number of patients to be studied or power of the study to be achieved
Study 1: At least 12 children must be evaluated. The ages must be distributed across the age range. There must be a similar number of male and female patients.
Study 2: The study must have 80% power to demonstrate an active treatment vs. placebo difference of eleven percentage points for the proportion of patients with pain freedom at 2 hours (with a two-sided type I error rate of 0.05). Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age.
Study 3: At a minimum, 300 patients, using an effective dose, must be exposed for six months. Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age. Patients must treat, on average, approximately 1 or more headache(s) per month for the six months period. At least half of the experience must be at the highest recommended dose.

Entry criteria
Study 1: Pediatric patients between 12 and 17 years of age, with a diagnosis of migraine with or without aura, as defined by the International Headache Society (IHS) current classification.
Study 2: Pediatric patients between 12 and 17 years of age; diagnosis of migraine with or without aura, as defined by the IHS current classification; history of migraine attacks for more than 6 months; ≥ 1 to ≤ 8 moderate to severe migraine attacks per month in the 2 months prior to screening; duration of a typical untreated migraine attack (excluding sleep) of ≥3 hours.
Study 3: Pediatric patients between 12 and 17 years of age; diagnosis of migraine with or without aura, as defined by the IHS current classification; history of migraine attacks for more than 6 months; ≥ 1 to ≤ 8 moderate to severe migraine attacks per month in the 2 months prior to screening.

Clinical endpoints
Study 1: Appropriately frequent standard measures of safety (including physical examinations, vital signs, and adverse reactions monitoring). Plasma concentrations of rizatriptan must be determined. Pharmacokinetic parameters including Cmax, tmax, AUC, t ½, Cl/F and Vd must be calculated and the mean clearance and apparent volume of distribution must be estimated within a standard error of 20% or less. Covariates such as age, body weight, body surface area, gender, and concomitant medications must be studied. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under http://www.fda.gov/cder/guidance/1970dft.pdf.
Study 2: The primary efficacy endpoint must be pain freedom at 2 hours post-dose. Additional standard secondary migraine efficacy measures (including freedom from photophobia, phonophobia, or nausea, and use of rescue medication), and standard measures of safety must be included (e.g. physical examinations, vital signs, 12-lead ECG, adverse reactions monitoring, and laboratory safety tests including hematology, chemistry, urinalysis, and pregnancy test for females of childbearing potential).
Study 3: Appropriately frequent standard measures of safety (including physical examinations, vital signs, 12-lead ECG, adverse reactions monitoring, and laboratory safety tests including hematology, chemistry, urinalysis, and pregnancy test for females of childbearing potential).

Study evaluations
Study 1: Safety data as discussed above. Reports of relevant pharmacokinetic parameters.
Study 2: Safety and effectiveness data through 24 hours post-dose.
Study 3: Safety data as discussed above.

Drug information:
Dosage form: Tablet
Route of administration: oral
Regimen: To be determined by the development program.
Formulation: ODT

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under

section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Statistical information:
Study 1: Descriptive analysis of the safety data. Pharmacokinetic parameters including comparison to historic data from adults.
Study 2: Assessment of the between group difference on the primary endpoint by a pre-specified statistical methodology appropriate to the data generated. The protocol must include a plan for an interim analysis to reassess whether the study is adequately powered and must include a provision to adjust the sample size to have adequate power.
Study 3: Descriptive analysis of the safety data will be provided.

Labeling that may result from these studies:
You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that rizatriptan is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it

would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

***Format of reports to be submitted*:**
You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/cder/guidance/7087rev.htm.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before March 31, 2011. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:
Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are

declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. The type of response to the Written Request (i.e. complete or partial response);
2. The status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**"

in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

2.6 Other Relevant Background Information

In addition to the requirements for the pediatric studies outlined in the PWR (reprinted in the above section), agreement of the contents and format of the sNDA submission was reached between the Agency and the sponsor. In a pre-sNDA teleconference on 16 September 2010, consensus was reached regarding the following submission issues:

- Due to differences in study design between the PWR studies and the previously conducted pediatric studies, a pooled analysis of safety and efficacy will not be performed.
- Safety and efficacy data for pediatric subjects 6 to 11 years of age will not be required for determination of pediatric exclusivity. The sponsor plans to submit safety and efficacy results of subjects 6 to 11 years of age either in a Clinical Study Report attached to the Safety Update Report or as a separate future sNDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was acceptable. The NDA was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well-organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

The sponsor affirms that all studies in the clinical development program were approved by ethics committees or institutional review boards, in compliance with Good Clinical Practice (GCP) standards according to the International Conference of Harmonization (ICH) Guidelines and the Declaration of Helsinki, version 2004. Written informed consent was obtained for all subjects prior to any study related procedure.

The sponsor certifies it did not use the services of any investigators debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

In accordance with 21 CFR54.2, the sponsor disclosed financial agreements (form 3455) with 2 investigators:

- (b) (6) received $51,000.00 for educational program and advisory/consultant meetings regarding various drug developments.

- (b) (6) received $25,000.00 for consulting and speaking fees for MAXALT.

The payments made to (b) (6) has not influenced the trial outcomes. The number of subjects in the Full Analysis Set (FAS) was (b) (6) site and (b) (6) site.

Overall, the sponsor provided required information regarding financial disclosure and there was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of this trial.

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 Non-clinical Pharmacology and Toxicology information, as this information remains unchanged from that in the approved NDA. The sponsor cross-references the MAXALT-MLT NDA 20,865 for any relevant CMC or non-clinical information. The Agency 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

Refer to section 4.1.

4.4 Clinical Pharmacology

Here I briefly discuss the PWR specified single pharmacokinetic (PK) study, P083. Please see the Clinical Pharmacology Review for detailed review.

4.4.1 Mechanism of Action

No new data was acquired regarding mechanism of action for this sNDA.

4.4.2 Pharmacodynamics

No pharmacodynamic studies were conducted since the sponsor's comparative review of the pharmacokinetics and pharmacodynamics of triptans provided no scientific data supporting a difference between healthy subjects and subjects with a history of migraine outside of an attack.

4.4.3 Pharmacokinetics

Pharmacokinetic studies were reviewed by Xinning Yang, Ph.D., from the Office of Clinical Pharmaceutics. The reader is referred to Dr. Yang's review for details. Here, I abstract his review, summarizing the pharmacokinetic findings.

One PK study, Study P083, was submitted in the sNDA submission. In addition, the sponsor provides data from 2 PK studies conducted earlier in the pediatric development program in adolescents, ages 12 to 17 years, in support of the submitted P083 study. The 2 prior PK studies are study P048 (single dose rizatriptan 10 mg tablet) and P062 (single dose rizatriptan ODT and tablet, 5 mg).

Study P083 was a randomized, double-blind, placebo-controlled, parallel panel, single-dose study of migraineurs, 6 to 17 years of age, using a weight based dosing regimen. The study was conducted between acute migraine attacks. Subjects weighing 20-39 kg received rizatriptan 5 mg ODT or placebo, and subjects weighing ≥40 kg received rizatriptan 10 mg ODT or placebo. Study drug was administered without water. The sponsor reported that administering the study medication without water permitted a direct comparison to ODT arm conducted in adults in study P070 (historical data, study P070). The study design of P083 is presented Table 4.

Table 4 P083 Study Design

Panel A	Panel B	Panel C
Placebo (n=3)	Placebo (n=3)	Placebo (n=1)
Rizatriptan 5 mg (n=9)	Rizatriptan 10 (n=9)	Rizatriptan 5 or 10 mg (n=5)

In panel A, subjects weighed 20-39 kg and received rizatriptan 5 mg ODT. In panel B, subjects weighed ≥40 kg and received rizatriptan 10 mg ODT. Panel C was added to the protocol in order to increase the number of male subjects in the study.

Effect of Body Weight

Results of study P083 revealed the C_{max} that was achieved in pediatric subjects in study P083 weighing 20 to 39 kg and receiving rizatriptan 5 mg ODT and subjects weighing ≥40 kg and receiving rizatriptan 10 mg ODT was similar to that in adults taking rizatriptan 10 mg ODT (historical data, study P070). Please refer to Table 5 below.

Table 5 Summary Statistics for Rizatriptan Pharmacokinetic Parameter Following Single Dose Administration of Rizatriptan ODT 5 mg or 10 mg in Pediatric Migraineurs Ages 6 to 17 Years (P083, Without Water) and Rizatriptan ODT 10 mg (Without Water) in Healthy Adult Subjects (P070)

Population	N	$AUC_{(0-\infty)}$ † (hr•ng/mL)	C_{max} † (ng/mL)	T_{max} ‡ (hr)	Apparent $t_{1/2}$ § (hr)
Children < 40 kg (5 mg)	10	56.68 (48.60, 66.09)	22.39 (17.90, 28.02)	1.0 (0.3, 2.0)	1.3 (0.1)
Female	3	64.75 (10.72)	27.50 (8.58)	1.0 (0.7, 1.3)	1.3 (0.2)
Male	7	54.89 (11.83)	21.81 (7.21)	1.0 (0.3, 2.0)	1.3 (0.1)
Children ≥ 40 kg (10 mg)	14	78.49 (68.93, 89.38)	22.27 (18.43, 26.92)	1.4 (0.3, 3.0)	1.6 (0.3)
Female	5	81.48 (21.19)	24.46 (8.05)	1.0 (0.7, 3.0)	1.6 (0.3)
Male	9	80.95 (21.93)	22.88 (7.92)	1.7 (0.3, 3.0)	1.6 (0.3)
Children < 12 Yr	10	62.93 (53.22, 74.40)	25.10 (20.15, 31.26)	1.0 (0.3, 2.0)	1.3 (0.1)
Female	2	70.64 (4.66)	32.45 (0.35)	0.9 (0.7, 1.0)	1.2 (0.1)
Male	8	62.99 (16.00)	24.41 (7.05)	1.0 (0.3, 2.0)	1.3 (0.1)
Children ≥ 12 Yr	14	72.84 (63.22, 83.92)	20.53 (17.05, 24.71)	1.5 (0.7, 3.0)	1.6 (0.3)
Female	6	76.73 (22.24)	23.32 (7.73)	1.2 (0.7, 3.0)	1.6 (0.3)
Male	8	76.11 (26.41)	20.41 (7.62)	1.7 (0.7, 3.0)	1.6 (0.3)
Adult #	24	67.04 (60.71, 74.04)	20.94 (18.12, 24.20)	1.3 (0.3, 4.0)	1.7 (0.2)
Female	19	72.48 (14.32)	23.25 (8.43)	1.3 (0.3, 4.0)	1.7 (0.2)
Male	5	54.46 (10.61)	18.90 (8.53)	1.3 (1.0, 3.0)	1.7 (0.2)

Comparison	$AUC_{(0-\infty)}$ ‖ (hr•ng/mL)	C_{max} ‖ (ng/mL)
Weight < 40 kg Vs. Adult ¶	0.85 (0.73, 0.98)	1.07 (0.86, 1.34)
Weight ≥ 40 kg Vs. Adult ¶	1.17 (1.02, 1.34)	1.06 (0.87, 1.30)
Age < 12 Yr Vs. Adult ¶	0.94 (0.79, 1.11)	1.20 (0.96, 1.49)
Age ≥ 12 Yr Vs. Adult ¶	1.09 (0.94, 1.26)	0.98 (0.81, 1.19)

† Geometric mean back-transformed from log scale (95% CI). Mean and SD for Female and Male groups.

‡ Median (Minimum, Maximum).

§ Harmonic mean (Jackknife SD).

Historical data from MK-0462 Protocol 070 (10 mg dose, ODT formulation).

‖ GMR (90% CI).

¶ rMSE for $AUC_{0-\infty}$ = 0.241 and rMSE for C_{max} = 0.352 in weight model; rMSE for $AUC_{0-\infty}$ = 0.263 and rMSE for C_{max} = 0.345 in age model; rMSE: Square root of conditional mean squared error (residual error) from the linear fixed effect model. rMSE*100% approximates the between-subject % CV on the raw scale for $AUC_{0-\infty}$, C_{max}.

GMR = Geometric least-squares mean ratio between populations; CI = Confidence interval.

(Source: Sponsor's submission; Clinical Study Report, module 5.3.3.2.3, Table 11-1)

$AUC_{(0-\infty)}$ values were 15% lower in the subgroup of subjects weighing 20-39 kg that received rizatriptan 5 mg ODT compared to adults that received rizatriptan 10 mg ODT (historical data from study P070) but C_{max} was similar in both groups. The $AUC_{(0-\infty)}$ in subjects weighing ≥40 kg that received rizatriptan 10 mg ODT was 17% higher compared to adults taking the same dose (Figure 1).

Figure 1 Individual Values, Geometric Means and 95% CIs for Rizatriptan AUC $_{(0-\infty)}$ and C_{max} Following Single Dose Administration of Rizatriptan ODT 5 mg or 10 mg in Pediatric Migraineurs Ages 6 to 17 Years (Protocol 083, Without Water) and Rizatriptan ODT 10 mg (Without Water) in Healthy Adult Subjects (P070)

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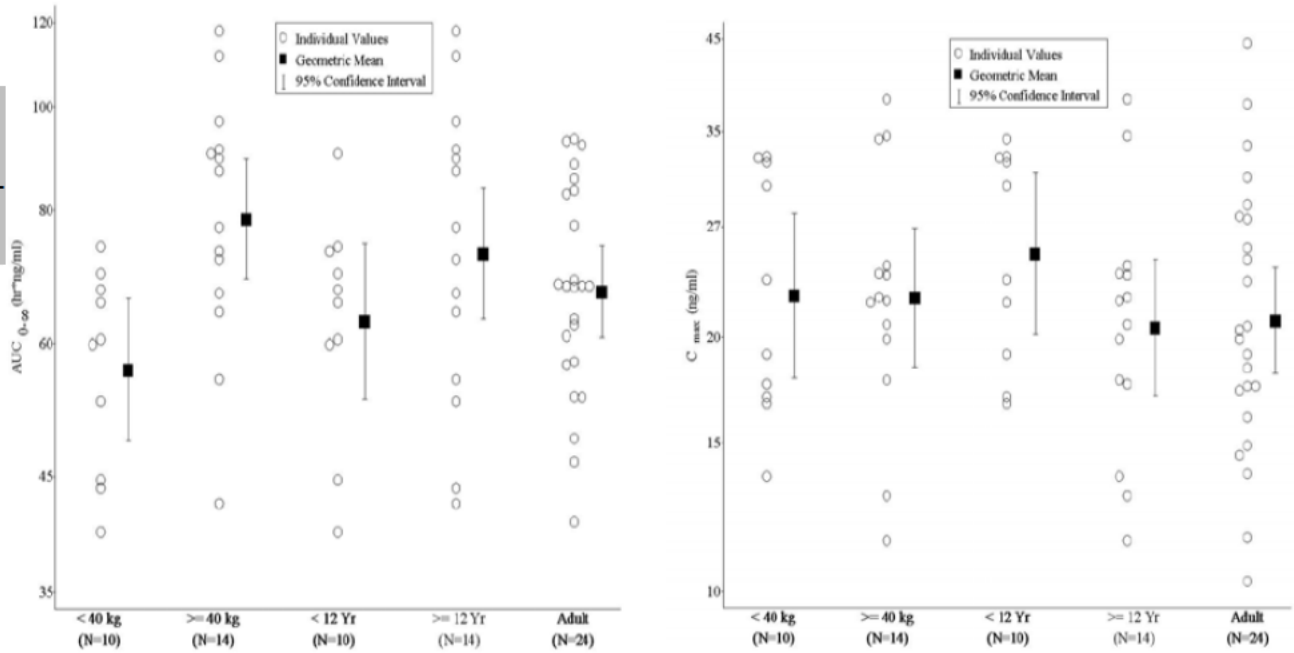


(Source: Clinical Pharmacology Review, Figure 1)

Considering that rizatriptan is used as acute treatment, its C_{max} may be more relevant to effectiveness than the AUC. The C_{max} in subjects weighing <40 kg is similar to the C_{max} in subjects weighing ≥40 kg. Also, the C_{max} in both weight groups was similar to adults dosed with rizatriptan 10 mg ODT (Table 5 above).

Effect of Gender

The exposure of rizatriptan in female pediatric subjects was approximately 20% higher than in male pediatric subjects. This is a similar pattern to that observed in adults. As reported in the current labeling for MAXALT ® and MAXALT-MLT®, adult females have 30% higher AUC $_{(0-\infty)}$ and 11% higher C_{max} than adult males.

In study P062, the AUC $_{(0-\infty)}$ and C_{max} of rizatriptan after a single dose of 5 mg ODT was about 18% higher in females than males. Please refer to the table below.

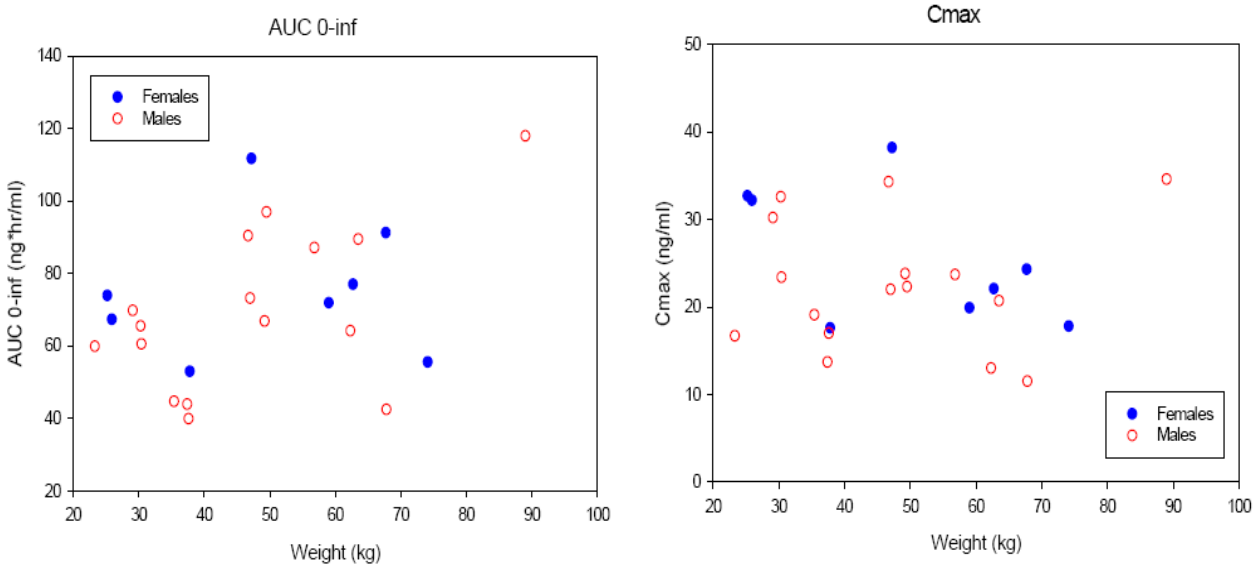
Table 6 Summary Statistics for Rizatriptan AUC (0-∞) and Cmax Following Single Dose Administration of Rizatriptan ODT 5 mg (Without Water) or Tablet 5 mg in Pediatric Migraineurs Ages 12-17 Years (P062)

Formulation (5 mg)	Gender	N	AUC0-∞ (hr•ng/ml)			Cmax (ng/ml)		
			Mean	SD	CV%	Mean	SD	CV%
ODT	Female	19	34.48	11.42	33.12	11.27	4.24	37.62
ODT	male	15	29.12	9.16	31.46	9.54	2.28	23.90
Tablet	Female	19	35.48	11.97	33.74	12.17	4.68	38.46
Tablet	male	15	28.2	9.45	33.51	10.46	3.84	36.71

(Source: Clinical Pharmacology Review, Table 7)

In study P083, for the subgroup of adolescents that were <40 kg receiving rizatriptan 5 mg ODT, the AUC $_{(0-\infty)}$ and C_{max} were 18% and 26% higher in females than in males, respectively (Dr. Yang, Clinical Pharmacology Review). The exposure was similar between females and males in subjects weighing ≥40 kg (Figure 2).

Figure 2 Distribution of $AUC_{(0-\infty)}$ and C_{max} with Weight in Female and Male Subjects Aged 6 to 17 Years and Receiving Rizatriptan 5 mg or 10 mg ODT (P083)



(Source: Clinical Pharmacology Review, Figure 4)

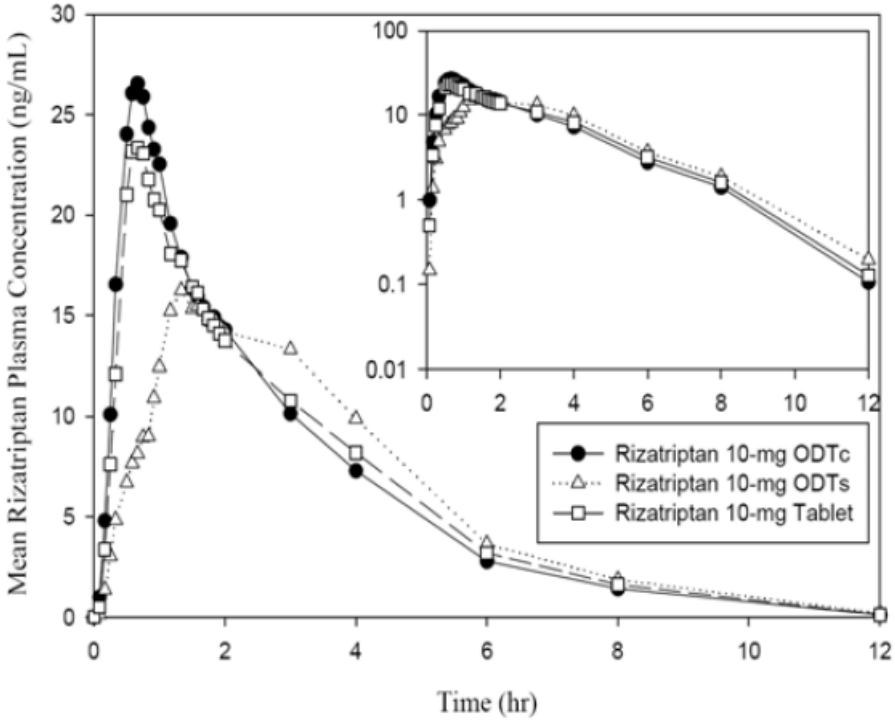
Review of P062 and P048 studies reveals that female subjects had similarly higher AUC $_{(0-\infty)}$ and C_{max} following administration of the tablet formulation of rizatriptan. Overall, the approximately 20% increase of exposure in females has no significant clinical impact.

Effect of Water

In the submitted PK study (P083), rizatriptan ODT was administered without water. It is not certain whether the PK of rizatriptan ODT will be altered in the adolescent population when it is taken with water. The efficacy and long term safety studies (P082 and P086, respectively) submitted in the sNDA did not specify whether rizatriptan ODT should be taken with or without water.

The impact of water on absorption of rizatriptan ODT was examined in adults (study P070). The absorption rate of rizatriptan ODT is faster when taken with water (Figure 3).

Figure 3 Mean Plasma Concentration-Time Profile of Rizatriptan Following Administration of a Single Oral 10 mg Rizatriptan ODTc (With Water), ODTs (Without Water) and Tablet Doses to Healthy Subjects (Insert: Semi-Log Scale) (P070)



(Source: Clinical Pharmacology Review, Figure 7)

The clinical pharmacology reviewer, Dr. Yang, presents the potential impact of rizatriptan ODT when taken with water and without water. His discussion is reprinted here.

"Since rizatriptan is used as acute treatment, it is possible that accelerated absorption of rizatriptan when ODT is taken with water may enhance its efficacy. However, this has not been formally studied. It is unknown whether ODT was taken with or without water in the previous adults trials used to support the approval of ODT. Considering the following two reasons, majority of the patients likely took ODT without water.

1. Purpose of developing ODT formulation. According to the Clinical review for the original NDA 20865, the sponsor developed the ODT formulation with the notion that some migraine sufferers experience difficulty swallowing liquids during a migraine attack; therefore, an orally administered dosage form that does not require liquids for administration would be desirable.

2. Patient information about MAXALT and MAXALT-MLT states '…. place the (ODT) tablet on your tongue. The tablet will dissolve rapidly and be swallowed with your saliva. No liquid is needed to take the ODT.'

The efficacy trial 082 under the current submission did not specify whether ODT was taken with or without water, either. Based on a proposed Pediatric Study Request (PPSR) submitted on Oct 25, 2007, patients and parents/caregivers will be instructed that MLT study drug should be placed directly on the tongue where it will dissolve and be swallowed with saliva. Administration with liquid is not necessary, but is allowed. [Please refer to the Clinical Pharmacology review documented by Dr. Ta-Chen Wu under IND 40,458]. However, none of the several versions of study 082 protocol submitted under this sNDA had the instruction about administration of water or not. Based on the same reasons as mentioned above, majority of the patients are likely just placed the tablet on the tongue without water. This may also be the case for the safety trial 086.

Assuming that ODT taken with water has faster absorption and thus higher Cmax and AUC0-2hr of rizatriptan, this may lead to higher risk of side effects besides potentially better efficacy. It seems that rizatriptan in adolescents has comparable safety profile as adults. It is expected that exposure in adolescents will be similar to the exposure in adults with the body weight-based dosing regimen. The current labeling for MAXALT-MLT in adults does not restrict the use of water for ODT administration. Overall, it is considered appropriate to keep the same instruction, i.e., (ODT) administration with liquid is not necessary.

5 Sources of Clinical Data

All documents and datasets reviewed for this sNDA submission are in electronic form. The path to this information in the CDER Electronic Document Room is:

\\CDSESUB1\EVSPROD\NDA020865\020865.enx

5.1 Tables of Studies/Clinical Trials

The following are a listing of clinical studies contributing to efficacy and safety data. The table below is reproduced from the sponsor's sNDA submission.

Table 7 Listing of Clinical Studies

Pediatric Clinical Pharmacology Studies with Rizatriptan:

Study	Design/Objective	Dose and Formulation	Total N (riza N)	Results
Protocol 048	Open label, single dose pharmacokinetic study in adolescent (12 to 17 years of age) migraineurs	Riza. 10 mg tablet	12 (12)	$AUC_{(0-\infty)}$ and C_{max} of rizatriptan were statistically significantly (marginally for C_{max}) higher in adolescent females than in adult females but not statistically significantly different between adolescent males and adult males. However, comparing adolescents to a pooled historical control data for adults, the $AUC_{(0-\infty)}$ of rizatriptan was not statistically significantly different between adolescents and adults, regardless of gender.
Protocol 062	Open-label, single-dose, balanced randomized, 2-period crossover study in adolescent migraineurs to determine the bioequivalence of a 5 mg rizatriptan tablet compared to 5 mg rizatriptan orally disintegrating tablet	Riza. 5 mg ODT (without water) and tablets	37 (37)	5 mg rizatriptan dose resulted in $AUC_{(0-\infty)}$ and C_{max} that were about half those obtained with 10 mg in adults. In this study, the $AUC_{(0-\infty)}$ was also more elevated in female than male adolescents [For the 5 mg ODT formulation in P062 (adolescents), geometric mean total $AUC_{(0-\infty)}$ = 30.5 , males = 29.1, females = 34.5 h•ng/mL, For the 10 mg ODT formulation in P070 (adults) geometric mean total $AUC_{(0-\infty)}$ = 67.0, males = 54.5, females = 72.5 h•ng/mL] [Ref. 5.3.1.2: P062].
Protocol 083	Randomized, double-blind, placebo-controlled study to assess safety, tolerability, and single-dose pharmacokinetics of MK-0462 in migraneurs aged 6 to 17 years	Riza. 5mg ODT (without water) and 10mg ODT (without water)	31 (24)	The mean plasma concentration-time profile following administration of rizatriptan ODT to pediatric migraineurs is similar to the mean profiles previously observed in adults where rizatriptan ODT was administered with or without water. Rapid absorption of rizatriptan ODT is apparent with a median T_{max} of 1.0 to 1.5 hrs post-dose with little variability given the weight range for a given dose. The exposures following single dose administration of 5 mg rizatriptan ODT to migraineurs weighing 20-39 kg, or 10 mg rizatriptan ODT to migraineurs weighing > 40 kg were similar to those observed following single dose administration of 10 mg rizatriptan ODT to adults. In a meta-analysis combining the pharmacokinetic results from this study and results from a previous study in which 10 mg rizatriptan ODT was administered to adolescents (MK-0462-062), an inverse relationship between exposure (dose normalized $AUC_{0-\infty}$) and weight was apparent at lower weights.

Phase 3 Pediatric Clinical Trials with Rizatriptan:

Protocol	Study Name	Endpoints (as Defined in the Protocol)	Duration	Treatment Arms and Randomization Ratio	Enrollment
Supportive Studies					
054 P054 Acute Efficacy in Adolescents	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Groups, Outpatient Study to Examine the Safety, Tolerability, and Efficacy of Rizatriptan 5 mg P.O. for the Acute Treatment of Migraine in Adolescents	Efficacy: Proportion of patients who had pain freedom at 2 hours post initial dose. Safety: Review of adverse events, laboratory values, ECG, and vital signs	Single Attack	**Treatment:** Initial Dose/Additional Doses: • Rizatriptan 5 mg tablet • Placebo Patients were allocated to receive the same treatment for recurrence as they received for their initial attack. Study medication was provided as follows: 5 mg rizatriptan tablets or matching placebo tablets. **Randomization**: 1:1 placebo or rizatriptan tablets	360 enrolled (179 on rizatriptan 5 mg, 181 on placebo); 296 treated (149 with rizatriptan and 147 with placebo)
059 P059 Acute Efficacy in Adolescents	A Randomized, Double-Blind, Placebo-Controlled, Parallel Groups, Outpatient Study to Examine the Safety, Tolerability, and Efficacy of Rizatriptan 5 mg P.O. for the Acute Treatment of Migraine in Adolescents	Efficacy: Proportion of patients who had pain relief defined as a reduction of headache severity from Grade 2 or 3 (moderate/severe) at baseline to Grade 0 or 1 (mild or no pain) at 2 hours post initial dose. Safety: Review of adverse events, laboratory values, ECG, and vital signs	Single Attack	**Treatment:** Initial Dose/Additional Doses: • Rizatriptan 5 mg tablet • Placebo Patients were allocated to receive the same treatment for recurrence as they received for their initial attack. Study medication was provided as follows: 5 mg rizatriptan tablets or matching placebo tablets. **Randomization:** 1:1 placebo or rizatriptan tablets	686 enrolled (341 on rizatriptan 5 mg, 345 on placebo; 476 treated (234 with rizatriptan and 242 with placebo).

Protocol	Study Name	Endpoints (as Defined in the Protocol)	Duration	Treatment Arms and Randomization Ratio	Enrollment
059 extension/ 061 P059 Extension/P061 Long Term Safety in Adolescents	Long-Term Safety and Tolerability of Rizatriptan 5-mg Tablet and 5-mg Orally Disintegrating Tablet in Adolescent Migraine Patients (Combined Protocols 059 Extension, 061)	Efficacy: Proportion of patients who had pain relief for all migraine attacks that had moderate or severe headache intensity at baseline. Safety: Review of adverse events, laboratory values, ECG, and vital signs	12 months	**Treatment:** Initial Dose/Additional Doses: • Rizatriptan 5 mg tablet • Rizatriptan 5 mg ODT • Standard care Patients were allocated to receive the same treatment for recurrence as they received for their initial attack. Patients treated up to 6 mild, moderate, or severe migraine attacks per month with rizatriptan 5-mg tablets, rizatriptan 5-mg ODT, or standard care. **Randomization:** 2:2:1 rizatriptan 5-mg tablets, rizatriptan 5-mg orally disintegrating tablets, or standard care	757 patients enrolled, 686 treated (273 rizatriptan 5 mg tablet, 281 on rizatriptan 5 mg ODT, 132 on std care)

Protocol	Study Name	Endpoints (as Defined in the Protocol)	Duration	Treatment Arms and Randomization Ratio	Enrollment
Pivotal Studies					
082 P082 Pediatric Acute Efficacy and Safety Study	A Worldwide, Randomized, Double Blind, Placebo-Controlled, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Rizatriptan for the Acute Treatment of Migraine in Children and Adolescents	Efficacy: Proportion of patients between 12 and 17 years of age who had pain freedom at 2 hours post Stage 2 dose. Safety: Review of adverse events, laboratory values, ECG, and vital signs.	Single Attack	**Treatment:** The dose of rizatriptan that patients receive is determined by body weight at screening (Visit 1); patients weighing < 40 kg receive a 5 mg dose and patients ≥ 40 kg receive a 10 mg dose. Study medication is provided as follows: 5 mg or 10 mg rizatriptan orally disintegrating tablets (ODT) or matching placebo ODT that is identical in appearance to the rizatriptan ODT. **Randomization:** Stage 1: 20:1 placebo or rizatriptan ODT Stage 2 (non-responders): Non-responders who received placebo in Stage 1 are randomized in a 1:1 ratio to rizatriptan or placebo. Patients who received rizatriptan in Stage 1 and did not respond receive placebo in Stage 2	12-17 Year Old PWR Population: 1010 enrolled; 702 treated with study medication: 337 treated with rizatriptan (29 on 5 mg, 308 on 10 mg), 365 only treated with placebo 6-11 Year Old Population: 137 enrolled 6-11 Year Old enrollment is ongoing.
086 P086 Pediatric Acute Efficacy and Safety Study	A Worldwide, Open Label, Clinical Trial to Examine the Long Term Safety and Tolerability of Rizatriptan in Pediatric Migraineurs for the Treatment of Migraine With or Without Aura	Efficacy: Proportion of patients who had pain freedom at 2 hours. Safety: Review of adverse events, laboratory values, ECG, and vital signs	12 months (study is ongoing)	**Treatment:** The dose of rizatriptan that patients receive is determined by body weight at screening (Visit 1); patients weighing < 40 kg receive a 5 mg dose and patients ≥ 40 kg receive a 10 mg dose. Study medication was provided as 5 mg or 10 mg orally disintegrating tablets (ODT).	Interim Population: 674 enrolled (28 on rizatriptan 5 mg, 646 on rizatriptan 10 mg) PWR Population: 373 enrolled (18 on rizatriptan 5 mg, 355 on rizatriptan 10 mg)

(Source: Sponsor's submission; Clinical Overview, module 2.5, Tables 2.5:1, 2.5:2)

5.2 Review Strategy

The efficacy review is based on one randomized, double-blind, placebo-controlled phase 3 trial: Protocol 082 (P082). Details of study P082 including a discussion of the study design are provided below. A review of the efficacy findings are presented in Section 6, Review of Efficacy.

Another phase 3 trial, Protocol 086 (P086), was an uncontrolled study and therefore was not evaluated for efficacy. Details of study P086 including the study design are provided below. A full review of the safety findings of study P086 as well as study P082 is presented in Section 7, Review of Safety.

Dr. Xiang Ling from the Biostatistics Division of the Agency performed the statistical analysis for this submission. Applicable portions of her efficacy review have been referenced and incorporated in Section 6, Review of Efficacy.

5.3 Discussion of Individual Studies/Clinical Trials

Three studies were submitted in the sNDA:

- Protocol P083; (PK study) is reviewed in detail by Dr. Xinning Yang from the Division of Clinical Pharmacology and the findings are presented in Section 4.4 of this document under Clinical Pharmacology

- Protocol P082; (efficacy study) is described in this section and results are reviewed in Section 6 of this document

- Protocol 086; (long term safety study) is described in this section and results are presented in Section 7 of this document

P083 (PK Study)
Please see the Clinical Pharmacology Review, Section 4.4 above, for a review and summary analysis of this study.

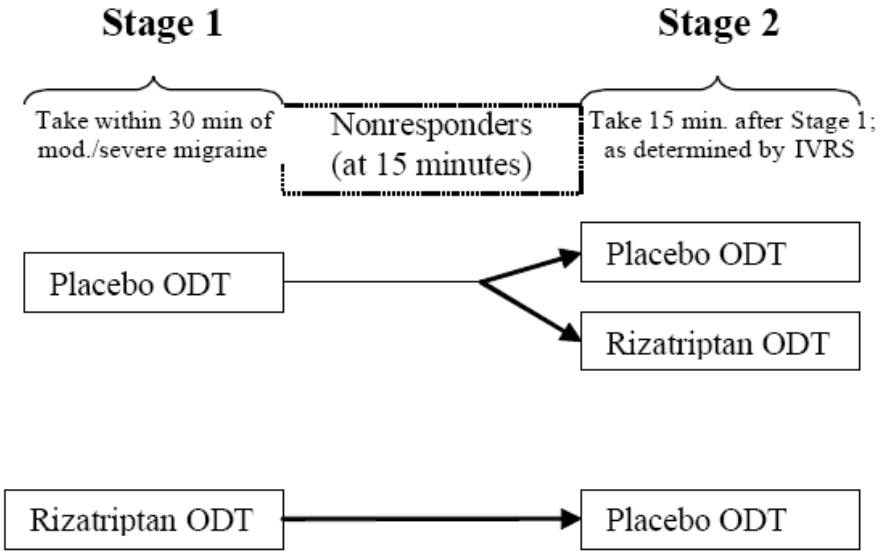
P082 (Efficacy Study)

Title
A Worldwide, Randomized, Double Blind, Placebo-Controlled, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Rizatriptan for the Acute Treatment of Migraine in Children and Adolescents

Study Design
This was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy of rizatriptan ODT, 5mg or 10 mg (based on weight), in children and adolescents aged 6 to 17 years with migraine with or without aura. A weight-based dosing regimen was employed such that subjects weighing < 40 kg were randomized to rizatriptan 5 mg ODT or matching placebo ODT. Subjects weighing $\geq$ 40 kg were randomized to rizatriptan 10 mg ODT or matching placebo ODT. The study was conducted in subjects who had not responded to prior treatment with acetaminophen or NSAIDS. Patients treated a single migraine attack in two stages. Stage 1 was designed to identify placebo responders and exclude them from the remainder of the study. Placebo non-responders from Stage 1 were then randomized into Stage 2 portion of the study in which rizatriptan was compared to placebo for efficacy.

In Stage 1, subjects were randomized in 20:1 ratio to placebo or rizatriptan. Randomization was stratified based on age (6-11 years old and 12-17 years old). Within 30 minutes of a qualifying migraine, subjects administered study medication

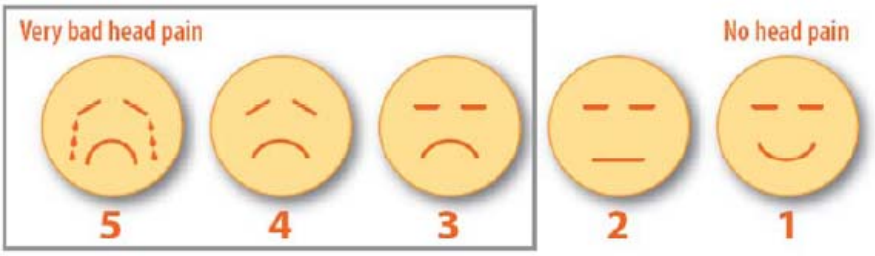
using weight based dosing regimen as described above. A qualifying migraine was defined as migraine of moderate or severe intensity. Fifteen minutes after taking Stage 1 treatment, subjects called into an Interactive Voice Response System (IVRS) to report headache pain intensity level. Subjects who reported improvement of their migraine pain to mild or no pain were classified as responders and were instructed to take no further study medication. Subjects who had moderate or severe headache pain were classified as non-responders and were instructed to take study medication in Stage 2. The non-responders to placebo in Stage 1 were randomized in 1:1 ratio to rizatriptan or placebo. Randomization was again stratified based on age (6-11 years old and 12-17 years old). Non-responders to rizatriptan in Stage 1 received placebo in Stage 2. No subject received more than one dose of rizatriptan in the study. Please refer to the diagram below for schematic representation of the study design in the pivotal efficacy study, P082.



(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3)

A paper migraine diary was completed by subjects at set time periods to assess efficacy and tolerability. Subjects who did not have adequate relief of migraine pain 2 hours after administration of Stage 2 study medication could treat their headache pain with their own headache medication. However, use of 5-HT_1 agonists and ergot derivates was prohibited for 24 hours following last dose of any study medication.

The severity of headache pain was assessed using a 5-Face Pain Scale shown below. Face 1 = no pain; Face 2 = mild pain; Faces 3 and 4 = moderate pain; Face 5 = severe pain. This scale is similar to the 4-point verbal scale used in adults. Moderate or severe migraine pain was defined as faces 3 to 5.



(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3)

Primary Efficacy Endpoint

- Pain freedom at 2 hours post Stage 2 dose

Secondary Efficacy Endpoint

- Pain relief at 2 hours post Stage 2 dose (pain relief was defined as a reduction of headache severity from Face 5/4/3 at Stage 2 baseline to Face 2/1)

Exploratory Endpoints

- Absence of photophobia, phonophobia, nausea, and vomiting at 0.5, 1, 1.5, 2, 24, and 48 hours post Stage 2 dose
- Sustained pain freedom from 2 to 24 hours and from 2 to 48 hours post Stage 2 dose
- Pain freedom and pain relief at 0.5, 1, 1.5, 24, and 48 hours post Stage 2 dose
- Functional disability rating of "as usual" at 0.5, 1, 1.5, 2, 24, and 48 hours post Stage 2 dose
- Use of rescue medications between 2 and 24 hours after Stage 2 study dose

Safety Endpoints

- Incidence of adverse events (AEs)
- Laboratory values
- Vital signs
- Electrocardiograms (ECGs)

Key Inclusion Criteria

- Male and female migraineurs aged 12 to 17 years and weighing ≥ 20 kg
- Diagnosis of migraine headache, with or without aura, as defined by International Headache Society (IHS Cephalalgia 2004:24[Suppl. 1]; 1-160) and meets following criteria:
  - Unilateral or bilateral migraine headache, with or without aura
  - Migraine attacks for more than 6 months
  - ≥ 1 to ≤ 8 moderate or severe migraine attacks per month in the 2 months prior to screening
  - Duration of untreated migraine attack (excluding sleep) is ≥ 3 hours
- No satisfactory relief of migraine pain with NSAIDs or acetaminophen
- Agrees to maintain true abstinence from sexual intercourse or uses effective method of birth control

Key Exclusion Criteria

- No satisfactory relief of migraine pain from prior treatment with 2 or more courses of $5HT_1$ agonists
- History of cardiovascular disease, congenital heart disease, cerebrovascular pathology or other systemic disease
- Female who is pregnant or breastfeeding
- Abnormal lab test parameters, vital signs or electrocardiogram

Study Visits

Each subject completed 2 study visits: screening and randomization (visit 1) and post-treatment (visit 2). The table below depicts the schedule of study events as well as schedule of procedures during the trial.

Table 8 Schedule of Study Events in Efficacy Study (P082)

Procedures/Assessments	Screening/ Randomization†	Treatment Day									Post-treatment‡
	(Visit 1)¶	Migraine Onset¶¶	Stage 1	Stage 1 / Stage 2§§	Stage 2						(Visit 2)
Specific timing (min., hr.) relative to treatment stage	Up to 4 months prior		0 min	15 min / 0 min. (+ 15 mins.)	½ hr	1 hr	1½ hr	2 hr	24 hr	48 hr	Up to 2 weeks
Medical history	X										
Headache history and symptomatology	X										
Consent§ and assent‖ form	X										
Inclusion/exclusion criteria	X										
Adolescent migraine background questionnaire	X										
Parent (guardian) background questionnaire	X										
Physical examination	X										
Laboratory assessments¥	X										X
Serum pregnancy test#	X										X
12-Lead ECG	X										X
Vital signs*	X										X
Practice diary and instructions on administration of medication and study procedures (refers to instructions on pages 2 thru 7 in the patient diary)	X¶										
Dispense study medication	X										
Administer study medication			X (Rx #1)	X (Rx #2)††							
IVRS patient called				X☎							
Complete efficacy assessments in migraine diary (pain intensity , associated symptoms, functional disability)		X	X	X	X	X	X	X	X	X	
Rescue therapy (if needed)‡‡								X---------- -X			
24 hour adolescent migraine questionnaire‖‖									X		
24 hour caregiver migraine questionnaire##									X		
Adverse event monitoring	X ---------- X										

Procedures/Assessments	Screening/ Randomization†	Treatment Day									Post-treatment‡
	(Visit 1)¶	Migraine Onset¶¶	Stage 1	Stage 1 / Stage 2§§	Stage 2						(Visit 2)
Specific timing (min., hr.) relative to treatment stage	Up to 4 months prior		0 min	15 min / 0 min. (+ 15 mins.)	½ hr	1 hr	1½ hr	2 hr	24 hr	48 hr	Up to 2 weeks
Review diary											X
Discuss monthly update calls conducted by site**	X										

† Screening evaluations were performed within the 4 months of treatment and could have been repeated once if necessary. Study treatment was not to have been administered for 3 days following the prestudy visit to allow for the receipt and review of screening safety assessments.
‡ The post-treatment visit was conducted within 14 days following administration of study treatment.
¶ Instructions were presented to and reviewed with patients and caregivers regarding administration of study medication, completion of the migraine diary, and other study procedures.
§ Consent form was signed by parent or legal guardian.
‖ Assent form was signed by adolescent.
Females of childbearing potential
☎ 15 minutes following administration of Stage 1 treatment (Rx #1), the patient called IVRS and provided treatment response to determine if patient continued into Stage 2 and to obtain dosing instructions for Stage 2 treatment (Rx #2).
* Included weight and height measurements.
†† Stage 2 treatment (Rx #2) was only taken if directed by IVRS.
‡‡ Rescue medication could have been taken 2 hours after Stage 2 dosing if pain relief was not sufficient.
§§ Stage 1 ended after the IVRS response at approximately 15 minutes post dose; Stage 2 began once Stage 2 treatment was administered.
¶¶ The migraine diary was completed when the migraine intensity became moderate; treatment was not administered until the migraine became moderate to severe.
‖‖ Completed by adolescent patients only 24 hours following administration of study medication.
Completed by the parent/guardian 24 hours following patient's administration of study medication.
** Site personnel were to contact parents/caregivers of patients who have not yet returned for Visit 2 on a monthly basis to address potential questions.
¥ Estimated total blood drawn is listed in Appendix 6.5 of the protocol [16.1.1].
Note: ECG=electrocardiogram; hr=hour; IVRS=interactive voice response system; min=minute; RX #1=Stage 1 study medication; RX #2=Stage 2 study medication

(Source: Sponsor's submission; Clinical Study Report, module 5.3.5.1.3, Table 9-1)

Statistical Methods

A sample size of 548 subjects (12-17 years of age) was needed to achieve 80% power (2-sided type 1 error rate of 0.05) to demonstrate that rizatriptan was superior to placebo for pain freedom at 2 hours post Stage 2 dose. The sample size assumed a treatment difference of 11 percentage points (36% versus 25%). It was expected that approximately 900 subjects needed to enter the study in order to yield 548 evaluable subjects.

One interim efficacy analysis was conducted on the primary endpoint of pain freedom at 2 hours post Stage 2 dose for subjects 12-17 years of age. Depending on the interim analysis results, the study could have continued as planned, discontinued due to overwhelming efficacy, or an additional 100 subjects between 12-17 years of age were needed to maintain adequate study power. Outcome of the interim efficacy analysis was to increase the sample size by 100 subjects for a total of 1,000 subjects. To maintain the overall alpha level of 0.05 for the primary endpoint, the critical alpha level for the final analysis was adjusted to 0.0477.

A logistic regression model was used to compare treatment groups with respect to the primary endpoint, pain freedom at 2 hours post Stage 2 dose. The model employed factors for treatment group (rizatriptan versus placebo), baseline headache severity (moderate or severe), and region (US or abroad).

A similar approach to analyzing the primary endpoint was utilized for analyzing the secondary endpoint, pain relief at 2 hours post Stage 2 dose. Other efficacy analyses were considered supportive and/or exploratory. The absence of photophobia, phonophobia, nausea, vomiting, and sustained pain freedom (SPF) were analyzed in the same manner as that used for analyze the primary endpoint, pain freedom at 2 hours.

Full Analysis Set (FAS) population was the primary population for analysis of efficacy data. Only subjects who were randomized to Stage 2 (placebo non-responders) were included in the FAS. Subjects randomized to rizatriptan in Stage were not included in the FAS analysis. The minimum requirement for inclusion in the FAS population was that subjects had to have taken study medication in Stage 2, had a moderate or severe baseline headache severity measurement, and had at least one post Stage 2 dose efficacy measurement prior to or including the 2 hour time point.

Missing data for headache severity, functional disability ratings, and associated symptoms in the FAS analysis were imputed by applying the Last Observation Carried Forward (LOCF) method. Baseline values missing for Stage 2 were imputed via LOCF by carrying forward the Stage 1 baseline value. Baseline values, however, were not carried forward to impute missing date post Stage 2 treatment.

The statistical methods employed for the efficacy analyses are presented in the table below.

Table 9 Analytical Methods Employed for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Pain Freedom – Proportion of patients between 12 and 17 years of age who had PF at 2 hours post Stage 2 dose	Logistic regression model†	FAS‡	LOCF
Secondary:			
Pain Relief – Proportion of patients between 12 and 17 years of age who had PR at 2 hours post Stage 2 dose	Logistic regression model†	FAS‡	LOCF

† Model included terms for treatment (rizatriptan vs. placebo), Stage 2 baseline pain severity (moderate vs. severe), and region (US vs. non-US).
‡ Only patients who did not respond to placebo at Stage 1 and were randomized to Stage 2 were included in the FAS for the efficacy analysis. Patients randomized to rizatriptan in Stage 1 were not included in the FAS. For each 2-hour endpoint, the minimum requirement for inclusion in the FAS population was that patients had administered the Stage 2 study medication, had a moderate or severe Stage 2 baseline headache severity measurement, and had at least one post Stage 2 dose efficacy measurement prior to, or including, the 2 hour time point.

(Source: adapted from Clinical Study Report, module 5.3.5.1.3, Table 9-4)

Safety analyses were conducted on all randomized subjects who received at least one dose of study treatment. Subjects who only participated in Stage 1 were also included in the safety analysis. Any subject that took rizatriptan during the study (in either Stage 1 or 2) was included in the active treatment group. 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 also calculated.

Subject Disposition, Demographic and Baseline Characteristics
Subjects were enrolled at 191 centers worldwide. The study had 134 centers in the United States and 57 internationally. Enrollment of subjects at each center varied from 1 to 72 subjects.

A total of 1,010 adolescent migraineurs, 12-17 years of age, were randomized to treatment in study P082. Of the 1,010 subjects randomized, 702 subjects were treated with study medication in either Stage 1 or Stage 2, or both Stages. Three hundred and eight (308) subjects (30.5%) were not treated in the study. Lack of a qualifying migraine was the most common reason (67.9%) why these subjects did not enter the study. Of the 702 subjects who were treated with study medication, 651 (92.7%) completed the study. The primary reason for study discontinuation was due to protocol violation (90.2%). Subject disposition data is tabulated in the table below.

Table 10 Subject Disposition Data in Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=362) n (%)‡	Rizatriptan† / NA (N=25) n (%)‡	Placebo / Rizatriptan (N=298) n (%)‡	Placebo / Placebo (N=299) n (%)‡	Rizatriptan / Placebo (N=26) n (%)‡	Total (N=1010) n (%)‡
Patient treated	**82 (22.7)**	**7 (28.0)**	**291 (97.7)**	**296 (99.0)**	**26 (100)**	**702 (69.5)**
Treated stage 1 only	77 (93.9)	7 (100)	4 (1.4)	4 (1.4)	0 (0.0)	92 (13.1)
Treated stage 2 only	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.0)	0 (0.0)	5 (0.7)
Treated both stages	5 (6.1)	0 (0.0)	285 (97.9)	289 (97.6)	26 (100)	605 (86.2)
Completed	56 (68.3)	4 (57.1)	281 (96.6)	284 (95.9)	26 (100)	651 (92.7)
Treated stage 1 only and completed	56 (100)	4 (100)	0 (0.0)	0 (0.0)	0 (0.0)	60 (9.2)
Treated both stages and completed	0 (0.0)	0 (0.0)	281 (100)	284 (100)	26 (100)	591 (90.8)
Discontinued	26 (31.7)	3 (42.9)	10 (3.4)	12 (4.1)	0 (0.0)	51 (7.3)
Withdrawal by Subject	2 (7.7)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	3 (5.9)
Protocol Violation	24 (92.3)	3 (100)	8 (80.0)	11 (91.7)	0 (0.0)	46 (90.2)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	2 (3.9)
Patient not treated	**280 (77.3)**	**18 (72.0)**	**7 (2.3)**	**3 (1.0)**	**0 (0.0)**	**308 (30.5)**
Discontinued	280 (100)	18 (100)	7 (100)	3 (100)	0 (0.0)	308 (100)

(Source: adapted from Clinical Study Report, module 5.3.5.1.3, Table 10-2)

Demographic characteristics were typical of a migraine trial with more female than male subjects and more white subjects than other races. Sixty-one percent (61%) of the subjects in the study were female. White subjects comprised 64.5% of the study population. Majority of subjects (73.2%) were from the US. The demographic data is presented in the table below.

Table 11 Subject Demographic Characteristics by Treatment Group in Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=82)	Rizatriptan† / NA (N=7)	Placebo / Rizatriptan (N=291)	Placebo / Placebo (N=296)	Rizatriptan / Placebo (N=26)	Total (N=702)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender						
Female	47 (57.3)	3 (42.9)	176 (60.5)	190 (64.2)	12 (46.2)	428 (61.0)
Male	35 (42.7)	4 (57.1)	115 (39.5)	106 (35.8)	14 (53.8)	274 (39.0)
Age (Years)						
12-14	42 (51.2)	5 (71.4)	148 (50.9)	136 (45.9)	7 (26.9)	338 (48.1)
15-17	40 (48.8)	2 (28.6)	143 (49.1)	160 (54.1)	19 (73.1)	364 (51.9)
Mean (SD)	14.4 (1.7)	13.9 (1.8)	14.5 (1.7)	14.6 (1.7)	15.2 (1.7)	14.5 (1.7)
Median	14.0	14.0	14.0	15.0	16.0	15.0
Range	12 to 17	12 to 17	12 to 17	12 to 17	12 to 17	12 to 17
Study Region						
US	55 (67.1)	6 (85.7)	205 (70.4)	225 (76.0)	23 (88.5)	514 (73.2)
Non-US	27 (32.9)	1 (14.3)	86 (29.6)	71 (24.0)	3 (11.5)	188 (26.8)
Racial Origin						
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.3)
Black or African American	8 (9.8)	2 (28.6)	36 (12.4)	40 (13.5)	3 (11.5)	89 (12.7)
Native Hawaiian or Other Pacific Islander	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
White	50 (61.0)	5 (71.4)	180 (61.9)	200 (67.6)	18 (69.2)	453 (64.5)
Asian	18 (22.0)	0 (0.0)	59 (20.3)	40 (13.5)	3 (11.5)	120 (17.1)
Multi-Racial	5 (6.1)	0 (0.0)	16 (5.5)	14 (4.7)	2 (7.7)	37 (5.3)
Ethnicity Origin						
Hispanic or Latino	13 (15.9)	1 (14.3)	38 (13.1)	38 (12.8)	4 (15.4)	94 (13.4)
Not Hispanic or Latino	69 (84.1)	6 (85.7)	253 (86.9)	258 (87.2)	22 (84.6)	608 (86.6)
Weight (at screening)						
< 40 kg	11 (13.4)	1 (14.3)	26 (8.9)	21 (7.1)	1 (3.8)	60 (8.5)
≥ 40 kg	71 (86.6)	6 (85.7)	265 (91.1)	275 (92.9)	25 (96.2)	642 (91.5)
Body Mass Index (kg/m^2)						
Mean (SD)	22.0 (4.9)	21.0 (4.9)	22.6 (5.2)	22.8 (5.5)	24.0 (5.7)	22.6 (5.3)
Median	21.3	19.1	21.8	21.4	21.6	21.4
Range	13 to 38	17 to 31	13 to 46	12 to 44	17 to 38	12 to 46

Age is based on date of enrollment.
† Patients randomized at Stage 1 but not at Stage 2.
Patient was counted only once across treatment groups.
Rizatriptan group refers to Rizatriptan 5mg or 10mg.
N = Number of treated patients.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-5)

There was a relatively even distribution of subjects with respect to age groups. The 12-14 year olds comprised 48.1% of the study population and the 15-17 year olds comprised 51.9% of the study population. At screening, 91.5% of the subjects weighed ≥40 kg and were stratified to the 10 mg dose group. Distribution of age and gender in the treatment groups is presented in Table 12.

Table 12 Age and Gender Distribution in Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA			Rizatriptan† / NA			Placebo / Rizatriptan			Placebo / Placebo			Rizatriptan / Placebo			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Patients in Population																		
	35	47	82	4	3	7	115	176	291	106	190	296	14	12	26	274	428	702
Age (Years)																		
12-14	19	23	42	4	1	5	71	77	148	66	70	136	3	4	7	163	175	338
15-17	16	24	40	0	2	2	44	99	143	40	120	160	11	8	19	111	253	364
Mean	14.2	14.5	14.4	13.3	14.7	13.9	14.0	14.8	14.5	14.1	14.8	14.6	15.1	15.3	15.2	14.1	14.8	14.5
SD	1.7	1.8	1.7	1.0	2.5	1.8	1.7	1.6	1.7	1.7	1.6	1.7	1.7	1.7	1.7	1.7	1.6	1.7
Median	14.0	15.0	14.0	13.5	15.0	14.0	14.0	15.0	14.0	14.0	15.0	15.0	16.0	16.0	16.0	14.0	15.0	15.0
Min	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Max	17	17	17	14	17	17	17	17	17	17	17	17	17	17	17	17	17	17

† Patients randomized at Stage 1 but not at Stage 2.
Patient was counted only once across treatment groups.
Rizatriptan group refers to Rizatriptan 5mg or 10mg.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-6)

Review of migraine history of all treated subjects was similar across treatment groups. Migraineurs with aura constituted 36.8% of the subjects in the study. On average, there were 3.6 moderate or severe migraine attacks per month in the study population. Approximately half of all subjects (49.4%) reported having migraines lasting 2 to 6 hours if not treated. The most common treatment of migraine used by subjects was NSAIDs. A total of 62.1% of subjects used NSAIDs for their migraine attacks. The next most common migraine treatment was acetaminophen, reported by 42.7% of subjects. The use of a triptan for migraine treatment was reported by 30.1% of subjects. The majority of subjects (80.5%) were not on any prophylactic therapy for their migraine. A summary of baseline migraine history of treated subjects is presented in the table below.

Table 13 Baseline Migraine History in Efficacy Study (P082)

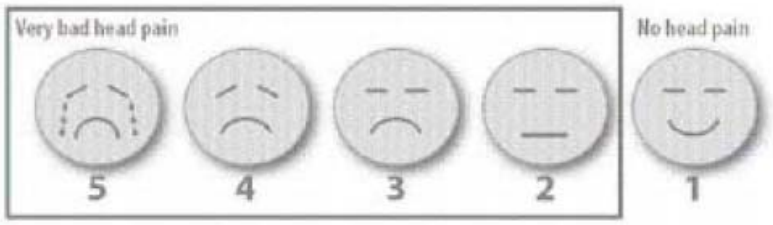
Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=82)	Rizatriptan† / NA (N=7)	Placebo / Rizatriptan (N=291)	Placebo / Placebo (N=296)	Rizatriptan / Placebo (N=26)	Total (N=702)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Migraine Usually Preceded by Aura						
Yes	29 (35.4)	2 (28.6)	108 (37.1)	111 (37.5)	8 (30.8)	258 (36.8)
No	53 (64.6)	5 (71.4)	182 (62.5)	185 (62.5)	18 (69.2)	443 (63.1)
Missing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Average Number of Moderate or Severe Migraine Attacks per Month Over the Last 3 Months						
N	82	7	291	296	26	702
Mean	3.8	3.4	3.7	3.5	3.7	3.6
SD	1.9	2.4	1.8	1.8	1.7	1.8
Median	3.5	3.0	3.0	3.0	3.0	3.0
Range	1 to 8	1 to 8	1 to 8	1 to 8	1 to 7	1 to 8
Typical Duration of Migraine (Untreated)						
2-6 hours	49 (59.8)	4 (57.1)	140 (48.1)	140 (47.3)	14 (53.8)	347 (49.4)
7-24 hours	28 (34.1)	2 (28.6)	108 (37.1)	114 (38.5)	9 (34.6)	261 (37.2)
>24 hours	5 (6.1)	1 (14.3)	43 (14.8)	42 (14.2)	3 (11.5)	94 (13.4)
Usual Migraine Treatment						
None	1 (1.2)	0 (0.0)	8 (2.7)	7 (2.4)	0 (0.0)	16 (2.3)
NSAID	48 (58.5)	4 (57.1)	182 (62.5)	183 (61.8)	19 (73.1)	436 (62.1)
Acetaminophen/Paracetamol (APAP)	34 (41.5)	5 (71.4)	125 (43.0)	127 (42.9)	9 (34.6)	300 (42.7)
Aspirin	10 (12.2)	0 (0.0)	16 (5.5)	25 (8.4)	4 (15.4)	55 (7.8)
Triptan	15 (18.3)	1 (14.3)	56 (19.2)	61 (20.6)	4 (15.4)	137 (19.5)
Opiate or Opiate Combination	0 (0.0)	1 (14.3)	1 (0.3)	8 (2.7)	0 (0.0)	10 (1.4)
Barbiturate Combination	0 (0.0)	0 (0.0)	3 (1.0)	4 (1.4)	1 (3.8)	8 (1.1)
Ergot or Ergot Combination	1 (1.2)	0 (0.0)	3 (1.0)	1 (0.3)	1 (3.8)	6 (0.9)
Caffeine Containing Medications	7 (8.5)	1 (14.3)	22 (7.6)	29 (9.8)	4 (15.4)	63 (9.0)
Other	6 (7.3)	1 (14.3)	33 (11.3)	27 (9.1)	4 (15.4)	71 (10.1)
Prophylactic Migraine Treatment						
Without	62 (75.6)	6 (85.7)	221 (75.9)	254 (85.8)	22 (84.6)	565 (80.5)
With‡	20 (24.4)	1 (14.3)	70 (24.1)	42 (14.2)	4 (15.4)	137 (19.5)
Antidepressants	3 (15.0)	0 (0.0)	16 (22.9)	12 (28.6)	1 (25.0)	32 (23.4)
Antiepileptics	0 (0.0)	0 (0.0)	23 (32.9)	10 (23.8)	2 (50.0)	35 (25.5)
Beta blocking agents	0 (0.0)	0 (0.0)	4 (5.7)	0 (0.0)	0 (0.0)	4 (2.9)
Hormonal contraceptives	0 (0.0)	0 (0.0)	4 (5.7)	1 (2.4)	0 (0.0)	5 (3.6)
All other therapeutic products	20 (100)	1 (100)	69 (98.6)	41 (97.6)	3 (75.0)	134 (97.8)

(Source: adapted from Clinical Study Report, module 5.3.5.1.3, Table 10-7)

P086 (Long Term Safety Study)

Title
A Worldwide, Open Label, Clinical Trial to Examine the Long Term Safety and Tolerability of Rizatriptan in Pediatric Migraineurs for the Treatment of Migraine with or without Aura

Study Design
In this open label study, adolescents aged 12 to 17 years, treated a qualifying migraine attack with rizatriptan ODT (5 mg or 10 mg) for up to 12 months. Subjects could treat up to 8 qualifying migraines a month. Doses of rizatriptan were based on subject's body weight at screening (Visit 1). Subjects weighing < 40 kg treated their migraine with rizatriptan 5 mg ODT. Subjects weighing ≥ 40 kg treated their migraine with rizatriptan 10 mg ODT. A qualifying migraine was defined as a migraine of mild, moderate, or severe pain intensity and was rated by the subject on a validated 5-Face Pain Scale. The faces in the box of the schematic below depict the qualifying migraine pain that could be treated.



(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-6)

Inclusion and Exclusion Criteria
As in Study P082, 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 and female between the ages of 12 to 17 years with a history of migraine, with or without aura, defined by the HIS criteria. Subjects had to have a history of 1 to 8 migraines per month for at least 6 months before study enrollment. Approximately equal number of subjects 12 to 14 years of age and 15 to 17 years of age were to be enrolled. Additionally, subjects had to weight ≥20 kg and agree to sexual abstinence or use birth control measures to prevent conception.

Female subjects who were pregnant or breastfeeding were excluded from the trial. Subjects were also excluded if they had any of the following: no satisfactory relief of migraine pain from prior treatment with 2 or more courses of $5HT_1$ agonists; had

abnormal lab test parameters, vital signs or ECG; or had a history of cardiovascular disease, congenital heart disease, cerebrovascular pathology or other systemic disease.

Documentation in a migraine diary was required by all subjects. Prior to taking study medication and 2 hours after taking study medication, subjects logged the following information in the migraine diary: migraine pain severity; associated symptoms; and degree of functional disability. The migraine diary also included questions regarding the use of rescue medications and adverse events.

Subjects who did not obtain adequate relief of their migraine pain after 2 hours of taking study medication could treat their migraine pain with usual care. Subjects, however, were not allowed the use of $5HT_1$ agonists and ergot derivatives for 24 hours following administration of study medication.

Study Visits

The study included a screening visit (Visit 1) to determine subject eligibility to participate in the study. Subjects returned to the study site on months 1, 2, 3, 4, 6, 9, and 12 after Visit 1 (+/- 7 days). Study visits consisted of safety monitoring evaluations, review of migraine diary, review of concomitant and rescue medications, and dispensing of study medications.

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

Table 14 Schedule of Study Visits in Long Term Safety Study (P086)

Visit Number	1	2	3	4	5	6	7	8	9
		Clinic Visits (Months)							
Procedures	Screening	1	2	3	4	6	9	12	Post-study‡
Variance permitted per visit in days		+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Consent and assent form§	X								
Review inclusion/exclusion criteria	X								
Collect/update medical and migraine history	X								
Update medical history		X	X	X	X	X	X	X	
Train patient using practice diary (paper)	X								
Review concomitant medication	X	X	X	X	X	X	X	X	
Perform physical exam	X							X	
Collect vital signs including weight and height at each visit	X	X	X	X	X	X	X	X	
Collect blood and urine for safety testing*	X	X		X		X	X	X	
Perform (serum) pregnancy test#	X							X	
Perform 12-Lead ECG	X	X		X		X	X	X	
Provide study diary	X	X	X	X	X	X	X		
Patient doses with study medication (up to 8x per month)		X	X	X	X	X	X	X	
Patient records headache severity, associated symptoms in the diary‡‡		X	X	X	X	X	X	X	
Rescue Medication§§		X	X	X	X	X	X	X	
Perform study medication count and review of completed diary		X	X	X	X	X	X	X	
Review adverse experiences	X----------X								
Telephone Contact – Reminder Calls**		Prior to each study visit							

† Patients who continued into this protocol within 30 days of the final visit of Protocol 082 did not repeat lab (except for pregnancy testing), electrocardiogram, physical exam, and migraine-history procedures. If the patient completed the final visit of the previous study, procedures required for this protocol were consent/assent, review of inclusion/exclusion criteria, review of interim medical history and concomitant medications, pregnancy testing for females of childbearing potential, and patient diary training.

‡ Phone contact was at least 14 days post-treatment to assess adverse experiences.

§ Assent form was signed by child/adolescent and Consent form was signed by parent or caregiver.

* Patients were instructed to refrain from taking study medication for 3 days following the Screening Visit (Protocol 82 final visit) or longer as instructed by the investigator, unless they received a phone call from the site indicating eligibility. This timeframe allowed for the processing and review of laboratory and ECG results.

Serum β-hCG test was conducted at screening and Month 12 visits. Females were instructed to conduct a urine pregnancy test at home if they believed that they might be pregnant. The results were documented in the migraine diary.

‡‡ Patients recorded all assessments in a paper diary immediately prior to dosing with study medication and the at specified time points.

§§ Non-study rescue medication was allowed for non-responding headache or headache recurrence beginning 2 hours after taking study medication. Use of rescue medication was required to conform to the local product label and the restriction of this protocol.

** Patients were contacted via telephone to remind them of their next scheduled visit and to answer any questions they had about the study.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 9-1)

Statistical Methods

Sample size for the long term safety study was determined by requirements specified in the amended PWR and was not based on statistical considerations. It was estimated that approximately 630 subjects would need to be enrolled to obtain 6 months of safety data for at least 300 subjects and 12 months of safety data for at least 100 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 performed on the All-Patients-as-Treated (APaT) population, defined as all subjects who were enrolled and administered at least one dose of study medication. The number and percentages of adverse events (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 study visits. Observed values and change-from-baseline values were evaluated. For ECG assessments, changes from baseline to the final visit were summarized (PR interval, QRS interval, QT interval, QTc interval Bazett, QTc interval Fridericia, ventricular rate).

Subject Disposition, Demographic and Baseline Characteristics
Subjects were enrolled at 146 centers in the US, Finland, Sweden and the Netherlands. The majority of the subjects (96.9%), however, were from the US. As discussed earlier, this study is currently on-going. The sponsor has submitted an interim analysis of the study which provides data for the PWR. The PWR required submission of 6 month data on a minimum of 300 subjects exposed to rizatriptan. The analyzed populations in the PWR were subjects who had completed their 6 month visit by September 30, 2010. The sponsor plans on submitting data on at least 100 subjects treated for 1 year in the long term study (P086) in a Safety Update Report (SUR) in July 2011.

By the data cut-off date of November 19, 2010, a total of 674 subjects were enrolled in the long term study (P086). The PWR population (those that have completed 6 months of the study) consisted of 373 subjects. As yet, only 14 subjects (3.8%) have been in the long term study for 9 months or longer and no subject has completed the study. Subjects treated an average of 2.2 migraines a month in the long term study (Table 15).

Table 15 Duration of Study Participation in PWR Population of Long Term Safety Study (P086)

Duration of Participation†	Rizatriptan 5 mg (N=18)		Rizatriptan 10 mg (N=355)		Total (N=373)	
	n	(%)	n	(%)	n	(%)
Completed ≥3 months	18	(100.0)	355	(100.0)	373	(100.0)
Completed ≥6 months	18	(100.0)	355	(100.0)	373	(100.0)
Completed ≥9 months	0	(0.0)	14	(3.9)	14	(3.8)
Completed ≥12 months	0	(0.0)	0	(0.0)	0	(0.0)

Summary Statistics on Patient-Level Average Number of Treated Attacks per Month for the First 6 Months ‡						
N	Mean	SD	Median	Q1 - Q3	Min	Max
373	2.2	1.4	1.8	1.2 - 2.8	0.2	7.8

† Period between Visit 1 and Last Study visit for the interim analysis. For each row completed means patient completed at least the visit in the row.

‡ Average monthly number of treated attacks over first 6 months is calculated for each patient who completed ≥ 6 months. Summary statistics are then calculated on these values.

N = number of patients.

SD = standard deviation.

Q1 = First quartile, Q3 = Third quartile.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-13)

Of the 373 subjects in the PWR population treated with rizatriptan, 366 (98.1%) are continuing in the study. Seven subjects (1.9%) discontinued. The primary reason for study discontinuation was due to subject withdrawal. Subject disposition data for PWR population is presented in the table below.

Table 16 Subject Disposition in PWR Population of Long Term Safety Study (P086)

	Rizatriptan 5mg (N=18)	Rizatriptan 10mg (N=355)	Total (N=373)
	n (%)	n (%)	n (%)
Patients treated	**18 (100.0)**	**355 (100.0)**	**373 (100.0)**
Completed	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing	17 (94.4)	349 (98.3)	366 (98.1)
Discontinued†	1 (5.6)	6 (1.7)	7 (1.9)
Withdrawal by Patient	1 (100.0)	3 (50.0)	4 (57.1)
Protocol Violation	0 (0.0)	2 (33.3)	2 (28.6)
Lost to Follow Up	0 (0.0)	1 (16.7)	1 (14.3)

† Patients counted only once across sub-categories. Percents of sub-category levels are calculated using the total number in that sub-category as the denominator.
N = Number of enrolled patients

(Source: Clinical Study Report, module 5.3.5.1.3, Table 14-5)

The discontinuation of subjects in the PWR population shown above includes only those subjects who discontinued on or after the 6 month visit. The sponsor reports that since subjects were required to complete at least 6 months of treatment to be included in the PWR population, discontinuations were counted on or after the 6 month visit.

There were 605 subjects that were enrolled and treated overall in Study P086, long term safety study. Of the 605 subjects treated with study medication, 113 of them (18.7%) discontinued. Subject withdrawal was the primary reason for discontinuation from the study (37/113, 32.7%). Subjects that were lost to follow up accounted for the next largest subset of discontinuations (33/113, 29.7%). Overall subject disposition in Study P086 is presented in Table 17.

Table 17 Disposition of All Enrolled Subjects in the Long Term Safety Study (P086)

	Rizatriptan 5mg (N=28)	Rizatriptan 10mg (N=646)	Total (N=674)
	n (%)	n (%)	n (%)
Patients treated	**23 (82.1)**	**582 (90.1)**	**605 (89.8)**
Completed	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing	21 (91.3)	471 (80.9)	492 (81.3)
Discontinued†	2 (8.7)	111 (19.1)	113 (18.7)
Adverse Event	0 (0.0)	11 (9.9)	11 (9.7)
Withdrawal by Patient	2 (100.0)	35 (31.5)	37 (32.7)
Protocol Violation	0 (0.0)	8 (7.2)	8 (7.1)
Lost to Follow Up	0 (0.0)	33 (29.7)	33 (29.2)
Lack of Efficacy	0 (0.0)	11 (9.9)	11 (9.7)
Study Terminated by Sponsor	0 (0.0)	1 (0.9)	1 (0.9)
Pregnancy	0 (0.0)	2 (1.8)	2 (1.8)
Physician Decision	0 (0.0)	9 (8.1)	9 (8.0)
Lack of Qualifying Event‡	0 (0.0)	1 (0.9)	1 (0.9)
Patients not treated	**5 (17.9)**	**64 (9.9)**	**69 (10.2)**
Discontinued†	5 (100.0)	64 (100.0)	69 (100.0)

(Source: adapted from Clinical Study Report, module 5.3.5.1.3, Table 10-2)

Demographic characteristics in the PWR population revealed that 60.9% of the subjects were female, 85.8% were white and 98.1% were from the US. At enrollment, 95.2% of subjects weighed ≥40 kg. Subject demographics in the PWR population are presented in Table 18. Close to half of the subjects (45.8%) were 12 to 14 years of age, and 54.2% were 12 to 17 years of age.

Table 18 Subject Demographic Characteristics by Treatment Group in Long Term Safety Study (PWR Population)

	Rizatriptan 5mg (N = 18) n (%)	Rizatriptan 10mg (N = 355) n (%)	Total (N = 373) n (%)
Gender			
Female	6 (33.3)	221 (62.3)	227 (60.9)
Male	12 (66.7)	134 (37.7)	146 (39.1)
Age (Years)			
12-14	16 (88.9)	155 (43.7)	171 (45.8)
15-17	2 (11.1)	200 (56.3)	202 (54.2)
Mean (SD)	13.0 (1.4)	14.7 (1.7)	14.6 (1.7)
Median	12.5	15.0	15.0
Range	12 to 17	12 to 17	12 to 17
Study Region			
US	18 (100.0)	348 (98.0)	366 (98.1)
EU	0 (0.0)	7 (2.0)	7 (1.9)
Racial Origin			
American Indian or Alaska Native	1 (5.6)	2 (0.6)	3 (0.8)
Asian	0 (0.0)	1 (0.3)	1 (0.3)
Black or African American	1 (5.6)	37 (10.4)	38 (10.2)
Multi-racial	0 (0.0)	11 (3.1)	11 (2.9)
White	16 (88.9)	304 (85.6)	320 (85.8)
Ethnicity Origin			
Hispanic or Latino	3 (16.7)	36 (10.1)	39 (10.5)
Not Hispanic or Latino	15 (83.3)	319 (89.9)	334 (89.5)
Weight (at screening)			
< 40 kg	18 (100.0)	0 (0.0)	18 (4.8)
≥ 40 kg	0 (0.0)	355 (100.0)	355 (95.2)

N = Number of patients enrolled.
Age is based on date of enrollment.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-8)

Distribution of subjects based on age, gender and dosage of study medication is presented in Table 19. Of the 355 subjects treated with rizatriptan 10 mg in the long term study, 221 (62.3%) were females.

Table 19 Age and Gender Distribution in PWR Population of Long Term Safety Study (P086)

	Rizatriptan 5mg (N = 18)			Rizatriptan 10mg (N = 355)			Total (N = 373)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Patients in Population	12	6	18	134	221	355	146	227	373
Age (years)									
12-14	11	5	16	69	86	155	80	91	171
15-17	1	1	2	65	135	200	66	136	202
Mean	13.0	13.0	13.0	14.5	14.9	14.7	14.4	14.8	14.6
SD	1.5	1.3	1.4	1.7	1.7	1.7	1.7	1.7	1.7
Median	12.5	12.5	12.5	14.0	15.0	15.0	14.0	15.0	15.0
Range	12-17	12-15	12-17	12-17	12-17	12-17	12-17	12-17	12-17

SD = Standard deviation.
N=Number of treated patients.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-9)

The mean number of doses of study medication taken by the 373 subjects in the long term study (PWR population) was 14.1. Study medication exposure (rizatriptan 5 mg and 10 mg) in the PWR population of study P086 is presented below.

Table 20 Study Medication Exposure in PWR Population of Long Term Safety Study (P086)

Total Number of Doses Taken	Rizatriptan 5mg (N = 18)	Rizatriptan 10mg (N = 355)	Total (N = 373)
Mean	17.2	14.0	14.1
SD	12.2	9.5	9.6
Median	13.0	12.0	12.0
Q1 - Q3	10 - 20	7 - 19	7 - 19
Min - Max	5 - 54	1 - 63	1 - 63

SD = Standard Deviation
Q1 = First quartile, Q3 = Third quartile.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-8)

6 Review of Efficacy

Efficacy Summary

Study P082 was a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled acute treatment of migraine trial in adolescent subjects 12 to 17 years of age. The study evaluated the efficacy of rizatriptan ODT 5 mg or 10 mg (based on weight) compared to placebo in adolescent migraineurs who have not achieved a satisfactory response to prior treatment with NSAIDs or acetaminophen. The primary endpoint was pain freedom at 2 hours after taking study medication. Secondary endpoint evaluated pain relief at 2 hours after taking study medications. Exploratory endpoints assessed the efficacy of rizatriptan compared to placebo with regards to: freedom from photophobia, phonophobia, and nausea at 2 hours post dose; sustained pain freedom from 2 to 24 hours post dose; and sustained pain freedom at 2 to 48 hours post dose.

Results of the efficacy study revealed that rizatriptan demonstrated a statistically significantly higher response rate compared to placebo for the primary efficacy endpoint of pain freedom at 2 hours post treatment dose compared to placebo (30.6% versus 22.0% respectively, p-value=0.025). The secondary endpoint of pain relief at 2 hours post treatment dose numerically favored rizatriptan over placebo, but was not statistically significant (58.8% versus 51.4% respectively, p-value=0.080).

The positive efficacy result of the primary endpoint is likely attributable to the following factors employed in study P082 which were not applied to prior adolescent studies conducted by the sponsor:

- **Non-randomization of placebo responders.** This study design treated a single migraine attack in 2 stages. Stage 1 was a placebo challenge and only non-responders to stage 1 were randomized into stage 2. In prior adolescent studies conducted by the sponsor there was no placebo challenge dosing to exclude placebo responders.
- **Use of weight based dosing.** Subjects weighing <40 kg received 5 mg of rizatriptan or placebo and subjects weighing ≥40 kg received 10 mg of rizatriptan or placebo. Previous efficacy studies conducted by the sponsor dosed adolescent subjects with 5 mg of rizatriptan or placebo, irrespective of their weight.

Virtually all aspects of the trials in the sNDA submission were developed with the Agency, including the components of the original PWR. In the adolescent population, the Agency required efficacy to be demonstrated on pain freedom at 2 hours. The Agency's current standard does not require efficacy demonstrations for associated symptoms (photophobia, phonophobia or nausea) in the pediatric population *if* efficacy has already been established in adults.

The sponsor has presented all available information relevant to the efficacy of rizatriptan in subjects 12 to 17 years of age. As noted, there were 2 Phase 3 studies submitted in the sNDA:

- Efficacy study, P082, detailed in this section and
- Long-term safety study, P086, detailed in Section 7, Review of Safety.

For details of both trials, P082 and P086, including their descriptions, please see Discussion of Individual Studies, Section 5.3 above. Note pooling of efficacy data across the 2 studies was not performed due to differences in study design. Study P086, was an open-label, uncontrolled study so data from that trial is not analyzed in this review section.

Again, Study P082 is the basis of this efficacy review as this is the only controlled trial. While the study enrolled subjects aged 6 to 17 years, this review focuses only on the adolescent population (ages 12-17 years). Subjects aged 6 to 11 years have not been included in this review as the aim of the PWR was the adolescent population. Also, the study is on-going in the 6 to 11 year old population and data is not yet available for analysis.

6.1 Indication

Acute treatment of migraine, with or without aura, in adolescent 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, Study P082 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 Subject Disposition

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

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was the proportion of adolescents aged 12 to 17 years who were migraine pain free at 2 hours post Stage 2 dose. Pain freedom at 2 hours

was defined as a reduction of baseline migraine severity of moderate or severe pain to no pain (from faces 3 to 5 to face 1) on the 5-Face Pain Scale. Face 1 is no pain, face 2 is mild pain, faces 3 and 4 are moderate pain, and face 5 is severe pain on the 5-Face Pain Scale.

Rizatriptan demonstrated a statistically significantly higher response rate compared to placebo for the primary efficacy endpoint (30.6% versus 22.0%, p-value=0.025). Two hours after treatment in Stage 2, 87 out of 284 subjects (30.6%) in the rizatriptan group experienced pain freedom, while 63 out of 286 subjects (22.0%) achieved pain freedom in the placebo group. Table 21 displays the efficacy findings for the primary endpoint.

Table 21 Primary Efficacy Endpoint

Endpoint	Treatment	N	n/m	Observed Response Rate % (95% CI)[†]	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)[‡]	p-Value[‡]
Primary						
Pain Freedom at 2 hours post dose	Rizatriptan	285	87/284	30.6 (25.3, 36.4)	1.55(1.06, 2.26)	0.025*
	Placebo	289	63/286	22.0 (17.4, 27.3)		

An odds ratio >1 is in favor of the Rizatriptan group.

[†] Exact confidence intervals.

[‡] Computed using a logistic model adjusting for Stage 2 baseline pain severity (moderate vs. severe) and region (US vs. ex-US).

* Statistically significant at α=0.0477 level, which accounts for the interim sample size adjustment.

Treatment refers to Stage 2 treatment group.

Rizatriptan group refers to Rizatriptan 5 mg or 10 mg.

N = Number of patients who did not respond to placebo in Stage 1 and treated with Stage 2 dose.

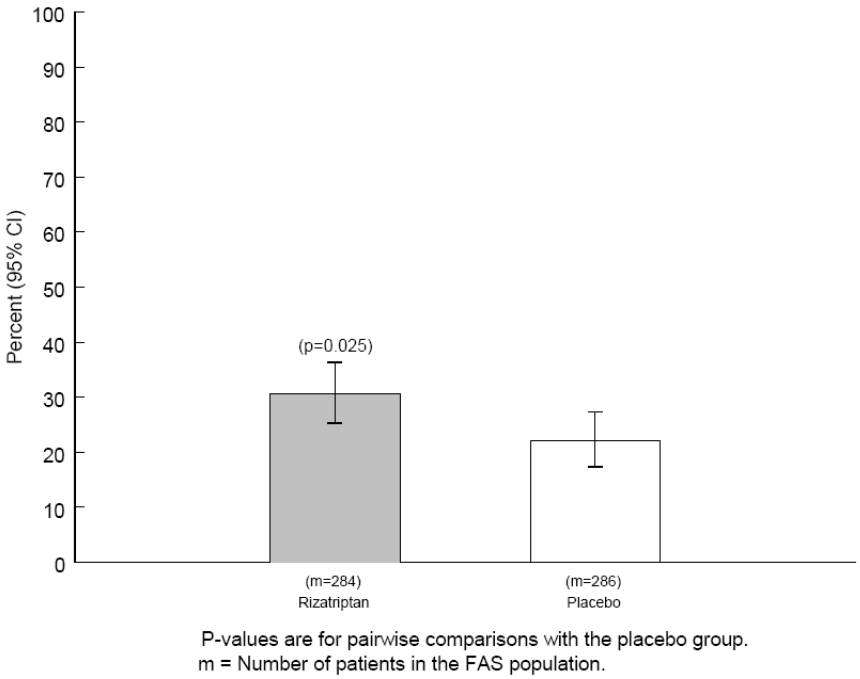
n = Number of evaluable patients with Pain Freedom or Pain Relief (reported or carried forward) at 2 hours post Stage 2 dose.

m = Number of evaluable patients in FAS population.

(Source: adapted from Clinical Summary, module 2.7.3, Table 2.7.3-pedmigraine: 12)

The observed percentages of subjects with pain freedom at 2 hours post Stage 2 dose by treatment group and the p-value from the comparison of the rizatriptan group to placebo (FAS approach) are presented in the figure below.

Figure 4 Observed Response Rate and 95% Confidence Intervals for Pain Freedom at 2 Hours Post Stage 2 Doses (FAS Approach)



(Source: Clinical Study Report, module 5.3.5.1.3, Figure 11-1)

6.1.5 Analysis of Secondary Endpoint

The secondary efficacy endpoint was pain relief at 2 hours post Stage 2 dose in adolescents aged 12 to 17 years. Pain relief was defined as a reduction of baseline migraine pain from moderate or severe (faces 3, 4, or 5) to mild or no pain (faces 1 or 2).

Rizatriptan demonstrated a higher response compared to placebo for pain relief at 2 hours post Stage 2 dose (58.8% versus 51.4%). This difference, however, was not statistically significant (p-value=0.080). Pain relief was reported in 167 out of 284 subjects (58.8%) in the rizatriptan group 2 hours after Stage 2 dosing. In the placebo group, 147 out of 286 subjects (51.4%) reported pain relief 2 hours after Stage 2 treatment. Table 22 displays the efficacy findings for the secondary endpoint.

Table 22 Secondary Efficacy Endpoint

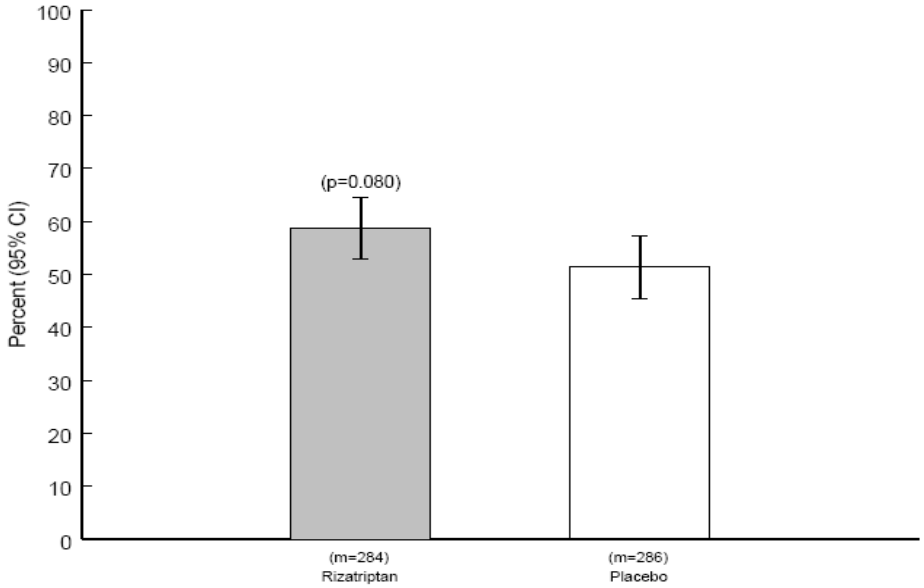
Endpoint	Treatment	N	n/m	Observed Response Rate % (95% CI)†	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡
Secondary						
Pain Relief at 2 hours post dose	Rizatriptan	285	167/284	58.8 (52.8, 64.6)	1.35(0.96, 1.90)	0.080
	Placebo	289	147/286	51.4 (45.4, 57.3)		

An odds ratio >1 is in favor of the Rizatriptan group.
† Exact confidence intervals.
‡ Computed using a logistic model adjusting for Stage 2 baseline pain severity (moderate vs. severe) and region (US vs. ex-US).
* Statistically significant at α=0.0477 level, which accounts for the interim sample size adjustment.
Treatment refers to Stage 2 treatment group.
Rizatriptan group refers to Rizatriptan 5 mg or 10 mg.
N = Number of patients who did not respond to placebo in Stage 1 and treated with Stage 2 dose.
n = Number of evaluable patients with Pain Freedom or Pain Relief (reported or carried forward) at 2 hours post Stage 2 dose.
m = Number of evaluable patients in FAS population.

(Source: adapted from Clinical Summary, module 2.7.3, Table 2.7.3-pedmigraine: 12)

The observed percentages of subjects with pain relief at 2 hours post Stage 2 dose by treatment group and the p-value from the comparison of the rizatriptan group to placebo (FAS approach) are presented in the figure below.

Figure 5 Observed Response Rate and 95% Confidence Intervals for Pain Relief at 24 Hours Post Stage 2 Dose (FAS Approach)



(Source: Clinical Study Report, module 5.3.5.1.3, Figure 11-3)

6.1.6 Other Endpoints

Some exploratory endpoints included in the efficacy study (P082) were the following:

- Absence of photophobia, phonophobia, nausea, and vomiting at 0.5, 1, 1.5, 2, 24, and 48 hours post Stage 2 dose
- Sustained pain freedom from 2 to 24 hours and from 2 to 48 hours post Stage 2 dose
- Pain freedom and pain relief at 0.5, 1, 1.5, 24, and 48 hours post Stage 2 dose
- Functional disability rating of "as usual" at 0.5, 1, 1.5, 2, 24, and 48 hours post Stage 2 dose
- Use of rescue medications between 2 and 24 hours after Stage 2 study dose

The sponsor's analyses are exploratory, and thus are of limited use. This is especially true of data from time points later than 2 hours post Stage 2 dose as subjects were permitted to use rescue medication for their migraine symptoms 2 hours post Stage 2 dosing. The data submitted by the sponsor did not distinguish whether or not subjects had taken rescue medication. Therefore, exploratory analyses of events that may be influenced by rescue medication are not included in this review.

The exploratory endpoints of absence of migraine associated symptoms of photophobia, phonophobia, nausea and vomiting at 2 hours post Stage 2 was evaluated (Table 23). Rizatriptan was nominally statistically superior to placebo for the symptoms of nausea and vomiting (p=0.013 and p=0.026, respectively) but not for the symptoms of photophobia (p=0.26) and photophobia (p=0.11).

Table 23 Absence of Migraine Associated Symptoms at 2 Hours Post Treatment

Timepoint	Treatment	N	n/m	Observed Response Rate % (95% CI)†	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡
Absence of Photophobia						
2 hr	Rizatriptan	285	167/284	58.8 (52.8, 64.6)	1.21 (0.87, 1.70)	0.257
	Placebo	289	152/286	53.1 (47.2, 59.0)		
Absence of Phonophobia						
2 hr	Rizatriptan	285	182/284	64.1 (58.2, 69.7)	1.32 (0.94, 1.85)	0.111
	Placebo	289	164/286	57.3 (51.4, 63.1)		
Absence of Nausea						
2 hr	Rizatriptan	285	246/283	86.9 (82.4, 90.6)	1.77 (1.13, 2.77)	0.013
	Placebo	289	224/286	78.3 (73.1, 83.0)		
Absence of Vomiting						
2 hr	Rizatriptan	285	280/283	98.9 (96.9, 99.8)	4.25 (1.19,15.23)	0.026
	Placebo	289	273/286	95.5 (92.4, 97.6)		

An odds ratio >1 is in favor of the Rizatriptan group.

† Exact confidence intervals.

‡ Computed using a logistic model adjusting for Stage 2 baseline pain severity (moderate vs. severe) and region (US vs. ex-US).

Treatment refers to Stage 2 treatment group.

Rizatriptan group refers to Rizatriptan 5 mg or 10 mg.

N = Number of patients who did not respond to placebo in Stage 1 and treated with Stage 2 dose.

n = Number of evaluable patients with desired response (reported or carried forward) at 2 hours post Stage 2 dose.

m = Number of evaluable patients in FAS population.

(Source: Clinical Summary, module 2.7.3, Table 2.7.3-pedmigraine: 13)

6.1.7 Subpopulations

The efficacy study, P082, evaluated the treatment effect of pain freedom and pain relief 2 hours post dose, in subgroups of adolescent subjects stratified by:

- Age
  - 12-14 years
  - 15-17 years
- Gender
  - Female
  - Male
- Race
  - Caucasian
  - Non-Caucasian
- Region
  - US
  - Non-US

Dr. Xiang Ling, from the Division of Biometrics at the FDA, conducted subgroup analyses based on age, gender, race and region for the primary and secondary endpoints (pain freedom and pain relief at 2 hours post treatment dose, respectively). Treatment effects with regards to pain freedom and pain relief responses were consistent across the subgroups. Table 24 and Table 25 (reproduced from Dr. Ling's review) are presented below.

Table 24 Summary of Subgroup Analysis of Pain Freedom

Subgroup	Rizatriptan (N=285)		Placebo (N=289)	
	n/m	(%)	n/m	(%)
Age (Years)				
12-14	49/144	34.0	36/129	27.9
15-17	38/140	27.1	27/157	17.2
Gender				
Female	53/173	30.6	37/185	20.0
Male	34/111	30.6	26/101	25.7
Racial				
Caucasian	55/176	31.3	39/192	20.3
Non-Caucasian	32/108	29.6	24/ 94	25.5
Region				
US	60/198	30.3	46/215	21.4
Non-US	27/ 86	31.4	17/ 71	23.9

n (%) = Number (percent) of evaluable patients with pain freedom at 2 hours post-dose.
m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 11-5, confirmed by Dr. Ling)

Table 25 Summary of Subgroup Analysis of Pain Relief

Subgroup	Rizatriptan (N=285)		Placebo (N=289)	
	n/m	(%)	n/m	(%)
Age (Years)				
12-14	89/144	61.8	72/129	55.8
15-17	78/140	55.7	75/157	47.8
Gender				
Female	93/173	53.8	93/185	50.3
Male	74/111	66.7	54/101	53.5
Racial				
Caucasian	107/176	60.8	104/192	54.2
Non-Caucasian	60/108	55.6	43/ 94	45.7
Region				
US	120/198	60.6	112/215	52.1
Non-US	47/ 86	54.7	35/ 71	49.3

n (%) = Number (percent) of evaluable patients with pain relief at 2 hours post-dose.
m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 11-6, confirmed by Dr. Ling)

The efficacy study, P082, evaluated the treatment effect of pain freedom and pain relief 2 hours post dose, in subgroups of adolescent subjects stratified by:

- Baseline weight
  - <40 kg
  - ≥40 kg

- Baseline migraine severity
  - Moderate
  - Severe

The majority of the patients in the efficacy study (P082) weighed ≥40 kg and had moderate baseline migraine pain. For these two subgroups, Dr. Ling reports that the difference in pain freedom and pain response rates between rizatriptan and placebo groups were consistent with the primary results (Tables 26 and 27 below).

Dr. Ling also reports that for subjects weighing <40 kg and the subgroup of patients with severe baseline migraine pain severity, there appeared to be a treatment effect with regards to pain relief (secondary endpoint) but not pain freedom (primary endpoint).

However, no conclusions could be drawn due to limited sample size of the two subgroups (Table 26 and Table 27).

Table 26 Summary of Subgroup Analysis on Pain Freedom by Subject Weight

Subgroup	Rizatriptan (N=285)		Placebo (N=289)	
	n/m	(%)	n/m	(%)
Baseline Weight				
< 40 kg	9/ 26	34.6	8/ 21	38.1
≥ 40 kg	78/258	30.2	55/265	20.8
Stage 2 Baseline Pain Severity				
Moderate	81/238	34.0	56/237	23.6
Severe	6/ 46	13.0	7/ 49	14.3
n (%) = Number (percent) of evaluable patients with pain freedom at 2 hours post-dose. m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.				

(Source: Clinical Study Report, module 5.3.5.1.3, Table 11-5, confirmed by Dr. Ling)

Table 27 Summary of Subgroup Analysis on Pain Relief by Subject Weight

Subgroup	Rizatriptan (N=285)		Placebo (N=289)	
	n/m	(%)	n/m	(%)
Baseline Weight				
< 40 kg	15/ 26	57.7	10/ 21	47.6
≥ 40 kg	152/258	58.9	137/265	51.7
Stage 2 Baseline Pain Severity				
Moderate	149/238	62.6	133/237	56.1
Severe	18/ 46	39.1	14/ 49	28.6
n (%) = Number (percent) of evaluable patients with pain relief at 2 hours post-dose. m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.				

(Source: Clinical Study Report, module 5.3.5.1.3, Table 11-6, confirmed by Dr. Ling)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The weight based dosing regimen used in the sNDA was derived from information obtained from the following sources:

- PK finding in study P083
- Post-hoc analyses from previously conducted adolescent studies, studies P054 and P059
- Published findings of Ahonen et al (Neurology 2006;67:1135–1140)

Results of PK study (P083) revealed the pharmacokinetic profile of the pediatric population treated with rizatriptan using a weight based approach is similar to the PK profile of adults. The details of these findings are presented in Section 4.4, Clinical Pharmacology, as well as the pharmacology review conducted by Dr. Xinning Yang.

Post-hoc analysis of prior acute efficacy studies in adolescents, P054 and P059 showed that 5 mg rizatriptan trended to be more efficacious in adolescents with a lower body weight. Overview of these studies is presented in Table 7 in Section 5.1, Tables/Studies of Clinical Trials.

Additionally, a study conducted in Finland by Ahonen on pediatric migraineurs employed a weight based dosing regimen. The study was a double blind, placebo controlled, 3 way crossover trial in children ages 6-17 years. Children were dosed by weight; those weighing $\geq$20 kg and <40 kg received 5 mg of rizatriptan, and those weighing $\geq$40 kg received 10 mg of rizatriptan. Results of the study revealed significant efficacy of headache relief in subjects treated with rizatriptan based on weight.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Due to the short term nature of this trial, no comment may be made upon persistence of therapeutic efficacy or tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

No additional pre-specified efficacy issues or analyses were performed.

7 Review of Safety

Safety Summary

No new or unexpected adverse events were discovered in the course of the development program of rizatriptan in adolescent migraineurs aged 12 to 17 years. Additionally, the sponsor complied with all the safety requirements set forth in the amended PWR.

I identified no significant deficiencies in the sNDA safety submission. The sponsor submitted all necessary summaries and supporting data. There were no notable inconsistencies between the data sources. The routine clinical safety testing seemed appropriate and capable of identifying major safety signals of rizatriptan.

There was one death reported in the submitted clinical trials. The death was due to a traffic accident and unrelated to study medication. There were no dropouts or discontinuations in the PK study (P083). In the efficacy study (P082), 51/702 treated subjects (7.3%) discontinued from the study. Protocol violations constituted the major reason for discontinuations (46/51, 90.2%). In the long term efficacy study (P086), 113/605 subjects in the interim population (18.7%) discontinued from the study. Subject withdrawal (37/113, 32.7%) and loss to follow up (33/113, 29.2%) constituted the major reasons for subject discontinuations.

No serious adverse events (SAEs) were reported in the PK or efficacy studies. There were 4 SAEs reported in the PWR population of the long term safety study. The 4 SAEs were adverse events (AEs) associated with an overdose of study drug. An overdose occurred if a subject took a second dose of study drug within 24 hours of the first dose. The AE associated with an overdose was reported as serious even if no other criteria for SAEs were met. The 4 SAEs in the long term safety study were: dyspnea (1 subject), abdominal discomfort (2 subjects), and abdominal discomfort and fatigue (1 subject).

In the efficacy study (P082), the incidence of drug related AEs were similar between the rizatriptan and placebo groups (11.6% versus 10.7%, respectively). Common AEs, reported by ≥2% of subjects in the rizatriptan treatment group consisted of somnolence (3.3%), nausea (3.0%), and fatigue (2.4%).

In the PWR population of the long term safety study (P086), the incidence of drug related AEs was 20.6% (77/373 subjects). Common AEs, reported by ≥2% of subjects, were somnolence (6.5%), dizziness (6.5%), nausea (4.8%) and fatigue (4.2%). All of these AEs occurred in the rizatriptan 10 mg dose group.

Review of lab data, vital signs data, and ECG data collected during the clinical trials did not reveal any new or unexpected adverse events.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data analyzed in this review were derived primarily from the 3 clinical studies submitted by the sponsor in the sNDA:

- PK Study (P083)
- Efficacy Study (P082)
- Long Term Safety Study (P086)

Additionally, prior pediatric studies conducted by the sponsor were reviewed for safety information that may have differed or deviated from the safety results reported in the submitted clinical trials. These studies, along with the submitted clinical studies analyzed for safety, are presented in Table 7, Section 5.1 Table of Studies/Clinical Trials.

7.1.2 Categorization of Adverse Events

Adverse event categorization and preferred terms used in coding were referenced to the Medical Dictionary for Regulatory Activities (MedDRA®), version 13.0 and provided in the transport file. During the review, I audited the case report forms, the narratives of SAEs and overdoses. No systematic errors in coding were detected.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of safety data across the 3 adolescent studies in the sNDA submission was not performed due to differences in study design. In accordance to prior agreement with the Agency on 16 September 2010, the sponsor did not conduct a pooled analysis of safety between previously conducted pediatric studies and the PWR studies submitted in the current sNDA. This was also due to study design issues.

Additionally, unblinded safety data for 6 to 11 year old subjects are not pooled or included in this submission. Subjects aged 6 to 11 years were still being enrolled in the study (P082) at the time of data cut off for the application. The Agency confirmed that for determination of pediatric exclusivity, data for the 6 to 11 year old population is not required.

7.2 Adequacy of Safety Assessments

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.

The sponsor and the Agency jointly met over the course of responding to the Agency's PWR. As documented in the various reviews, meeting minutes, and the request for pediatric trials evaluating Maxalt, the sponsor responded satisfactorily to all Agency 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 adequate and complete.

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

The sponsor has conformed to the amended PWR requirements set forth on 13 January 2010 regarding overall exposure and duration to study medication as well as demographics of the adolescent population being evaluated. Treatment exposure and population demographics of the 3 individual trials are presented below.

PK Study (P083)
The PWR requirement for the PK study was for at least 12 adolescent subjects, ages 12 to 17 years, to be distributed across the age range. Similar numbers of male and female subjects were required.

The PWR population of the PK study enrolled 18 adolescent subjects (of the 31 total subjects). The 18 adolescent subjects comprised of 8 subjects in 12-14 year old age group and 10 subjects in the 15-17 year old age group. There were 9 males and 9 females in the PWR population. A summary of the baseline demographic characteristics of the PK study is presented in Table 28.

Table 28 Summary Baseline Demographic Characteristics of PK Study (PWR Population)

	Age (yr)	Height (cm)	Weight (kg)	Body Surface Area (m^2)†
Male N	9	9	9	9
Male Range	12 - 17	147.3 - 182.9	37.4 - 89.0	1.24 - 2.12
Male Arithmetic Mean	14.3	167.4	60.9	1.68
Female N	9	9	9	9
Female Range	12 - 17	152.0 - 170.0	37.8 - 77.5	1.27 - 1.87
Female Arithmetic Mean	15.1	161.0	60.0	1.63
Overall Total N	18	18	18	18
Overall Total Range	12 - 17	147.3 - 182.9	37.4 - 89.0	1.24 - 2.12
Overall Total Arithmetic Mean	14.7	164.2	60.4	1.65

AN = Allocation Number
†BSA calculated using the Mosteller formula: BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)^{½}

(Source: Summary of Clinical Pharmacology Studies, module 2.7.2, Table 2.7.2:9)

Efficacy Study (P082)

The PWR requirement for the efficacy study was for reasonable efforts be made to enroll similar number of subjects in the 12-14 and 15-17 year old age groups. Also, at least one third of the enrolled subjects must be between 12 and 14 years of age.

There were a total of 702 subjects treated with study medication in either Stage 1 or 2 in the efficacy study. Table 11 in Section 5.3 above depicts the essential demographic characteristics of subjects treated in the study. The demographic and baseline characteristics in the study revealed:

- Overall, there were more females (61%) than males (39%)
- There was slightly higher proportion of subjects in 15-17 year age group (51.9%) relative to the 12-14 year age group (48.1%)
- Majority of subjects weighed ≥40 kg (91.5%)
- Approximately 65% of subjects were white, 17% were Asian, 13% were black, and 5% were multi-racial; approximately 13% were of Hispanic origin

Subjects reported an average of 3.6 moderate or severe migraine attacks per month. Over a third of the subjects (36.8%) reported aura symptoms prior to migraine attacks. NSAIDs and acetaminophen were the 2 most common migraine treatments reported by subjects in study. Approximately 62% of subjects reported treating their migraines with NSAIDs and 43% of subjects used acetaminophen.

Of the 702 subjects treated in P082, 188 subjects (26.8%) used concomitant medications. NSAID and acetaminophen were the most common concomitant medications

Long term safety study (P086)
The following are the PWR requirements regarding the number of subjects to be studied in the long term safety study:

> At a minimum, 300 patients, using an effective dose, must be exposed for six months. Reasonable efforts must be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients must be between 12 and 14 years of age. Patients must treat, on average, approximately 1 or more headache(s) per month for the six months period. At least half of the experience must be at the highest recommended dose.

The interim study population constituted 605 treated adolescent subjects in the long term safety study. Of these, 373 subjects completed ≥6 months of treatment. Subjects treated an average of 2.2 migraine attacks per month for the first 6 months. There were 300 subjects who treated more than 1 migraine attack per month (284 subjects in rizatriptan 10 mg dose group and 16 subjects in the rizatriptan 5 mg dose group). Other salient highlights include:

- There were more females (60.9%) than males (39.1%)
- There was slightly higher proportion of subjects in the 15-17 year age group (54.2%) relative to the 12-14 year age group (45.8%)
- The majority of subjects weighed ≥40 kg (95.2%)
- Most of the subjects were white (85.8%)

Of the 373 subjects in the PWR population of P086, 231 subjects (61.9%) used concomitant medications. NSAID and acetaminophen were the most common concomitant medications used (24.1% and 13.1%, respectively).

Table 18 in Section 5.3 above depicts the essential demographic characteristics of these subjects.

7.2.2 Explorations for Dose Response

Please refer to section 6.1.8 regarding the weight based dosing approach utilized in the PWR studies.

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

The routine clinical safety testing seemed appropriate and capable of identifying major safety signals. The following routine clinical testing was conducted in evaluating the drug in adolescents:

- Adverse events (AEs)
- Clinical laboratory evaluations
- Vital signs
- Electrocardiograms (ECGS)
- Physical examinations
- Use of concomitant medications
- 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).

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. As noted, the triptans have several areas that have been identified for close monitoring in the trials. 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. There were no fatalities in any of the sponsor's trials. ECG findings are presented in Section 7.4.4, Electrocardiograms.
>
> *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. No reported incidences of cerebrovascular events were documented in any of the sponsor's trials.
>
> *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. Outcomes of the reported pregnancies in the clinical trials are discussed below in Section 7.6.2 (Human Reproduction and Pregnancy Data).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions were evaluated during the periodic visits 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 the FDA for safety monitoring.

7.3 Major Safety Results

7.3.1 Deaths

There was one death reported in the 3 trials. One subject in the long term safety study, P086, was involved in a road traffic accident and died. The death was reported as unrelated to the trial. I have reviewed the case report and concur. The following is a sponsor's summary report of the death.

Subject AN 20446, a 16-year-old, white female, entered the study on 29-Mar-2010 and allocated to the rizatriptan 10 mg group. The first dose of study medication was taken on 31-Mar-2010. The last dose of study medication was taken on 08-May-2010. On (b) (6) the patient was involved in a road traffic accident and died. The cause of death was road traffic accident, which was reported by the investigator as not related to the study medication.

7.3.2 Nonfatal Serious Adverse Events

The sponsor defined a serious adverse event (SAE) as any AE that resulted in one or more of the following:

- Death
- Life-threatening Event – The subject was at risk of death at the time of the event. It did not refer to the hypothetical risk of death if the AE was more severe or was to progress.
- Inpatient Hospitalization (admission or prolongation).
- Persistent or Significant Disability/Incapacity – Any AE having an outcome that was associated with a substantial disruption of the ability to carry out normal life functions.
- Congenital Anomaly/Birth Defect – In offspring of subject taking the product regardless of time to diagnosis.
- Other Medically Important Events – Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in (the bullet points) above.

Additionally, the sponsor also required collection of information for overdose or cancer.

For this submission, the sponsor defined an overdose, whether accidental or intentional, as ingestion of rizatriptan of more than 5 mg in a 24 hour period for subjects with a body weight less than 40 kg at screening and more than 10 mg in a 24 hour period for subjects with screening body weight of 40 kg or more.

PK Study (P083)
Thirty one subjects were treated in the PK study (P083). No SAEs were reported in this study.

Efficacy Study (P082)
There were a total of 702 subjects (337 subjects in the rizatriptan group and 335 subjects in the placebo group) treated in the acute efficacy study (P082). A total of 2 SAEs were reported in the study population. The SAEs, enterobacter bacteremia and migraine, occurred in 2 subjects who received placebo. These events were classified as not related to study drug. No SAEs were reported in subjects who were treated with rizatriptan.

Safety Study (P086)
There were 605 subjects in the interim evaluated population of the long term safety study (P086) who received at least one dose of study medication. Twenty SAEs were reported in 17 subjects in the interim population. Of the 20 SAEs, 4 were deemed to be related to study drug. All SAEs were in the rizatriptan 10 mg treatment group.

The 4 SAEs deemed to be related to study drug were associated with overdose of study medication. Adverse events associated with overdose were reported as serious even if no other criteria for SAE were met. The narratives of the 4 subjects experiencing an SAE are presented below.

> **Subject AN 20075 (dyspnea)**, a 14-year-old, white female, was enrolled into the study on 29-Jan-2010 and allocated to the rizatriptan 10 mg group. The first dose of study medication was taken on 03-Feb-2010. On 18-Mar-2010, the patient took a dose of study medication, and on 19-Mar-2010, less than 24 hours later a second dose of study medication was taken. **Dyspnea** was reported following the dose on 19-Mar-2010; this event resolved the same day (19-Mar-2010). The dyspnea was reported by the investigator as mild in intensity and related to study medication, and the accidental overdose with adverse event was not related to study medication. The patient was discontinued from the study on 10-May-2010 for lack of efficacy.
>
> **Subject AN 20133 (abdominal discomfort)**, a 17-year-old, black female, was enrolled into the study on 19-Feb-2010 and allocated to the rizatriptan 10 mg group. The first dose of study medication was taken on 29-Mar-2010. On 15-May-2010, the patient took a dose of study medication for a migraine and another dose less than 24 hours later on 16-May-2010 for a different migraine. The patient developed an **upset stomach** within minutes of taking study medication on both occasions, both events lasting for one hour. The patient recovered from upset stomach on 16-May-2010. The upset stomach was reported by the investigator as mild in intensity and related to study medication. Treatment with rizatriptan was continued.
>
> **Subject AN 20496 (fatigue and abdominal discomfort)**, a 16-year-old, white female, was enrolled into the study on 12-Apr-2010 and allocated to the rizatriptan 10 mg group. The first dose of study medication was taken within 24 hours on 12 Apr-2010. On 19-Apr-2010, the patient took a dose of study medication and on 20-Apr-2010, less than 24 hours later a second dose of study medication was taken. On 20-Apr-2010, the patient experienced **fatigue and abdominal discomfort** as a result of the overdose; these events resolved later the same day (20-Apr-2010). On 18-May-2010, the patient took a dose of study medication and on 19-May-2010, less than 24 hours later a second dose of study medication was taken. On 19-May-2010, the patient experienced tiredness as a result of the overdose; this event resolved on 20-May-2010. The fatigue (both

events) and abdominal discomfort were reported by the investigator as mild in intensity and related to study medication. Both events of accidental overdose with adverse effect were considered as not related to study medication. Treatment with rizatriptan was continued.

Subject AN 20583 (abdominal discomfort), a 16-year-old, white female, was enrolled into the study on 07-Apr-2010 and allocated to the rizatriptan 10 mg group. The first dose of study medication was taken on 12-Apr-2010, and a second dose was taken less than 24 hours later on 13-Apr-2010. On 13-Apr-2010, the patient experienced **abdominal discomfort** secondary to the accidental overdose; this event resolved the same day. The abdominal discomfort was reported by the investigator as mild in intensity and related to medication, and the accidental overdose with adverse effect was not related to study medication. Treatment with rizatriptan was continued.

There was one suicide attempt and 2 suicidal ideations. These 3 subjects were discontinued from the trial and the 3 events were considered by investigators not to be drug related. There was a death (discussed above) that was not related to study medication.

Additionally, there was one case of each of the following events: major depression, tibia/fibula fracture, syncope, and sinus bradycardia (discussed in ECG section). There were 2 cases of each of the following events: gastroenteritis and appendicitis. Again, these events were not considered to be drug related. I have reviewed all the cases and concur.

7.3.3 Dropouts and/or Discontinuations

PK study (P083)
There were no discontinuations or dropouts in the PK study.

Efficacy study (P082)
There were no discontinuations or dropouts in the efficacy study due to an adverse event. Of the 1010 total number of subjects that were randomized, 308 subjects (30.5%) were not treated. The most common reason why subjects were not treated was lack of a qualifying migraine (209/308 subjects, 67.9%).

Of the 702 subjects that were treated with study medication in study P082, 51 subjects (7.3%) did not complete the study. Protocol violation was the major reason why these subjects failed to complete the study (46/51, 90.2%). Subjects taking the wrong study medication in any stage during the study constituted the largest reason for protocol violations (39 subjects). Another 5 subjects took their Stage 2 study medication instead

of taking their Stage 1 study medication. An accounting of subject disposition is presented in Table 29.

Table 29 Accounting of Subjects by Treatment Group in the Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=362)	Rizatriptan† / NA (N=25)	Placebo / Rizatriptan (N=298)	Placebo / Placebo (N=299)	Rizatriptan / Placebo (N=26)	Total (N=1010)
	n (%)‡	n (%)‡	n (%)‡	n (%)‡	n (%)‡	n (%)‡
Patient treated	**82 (22.7)**	**7 (28.0)**	**291 (97.7)**	**296 (99.0)**	**26 (100)**	**702 (69.5)**
Treated stage 1 only	77 (93.9)	7 (100)	4 (1.4)	4 (1.4)	0 (0.0)	92 (13.1)
Treated stage 2 only	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.0)	0 (0.0)	5 (0.7)
Treated both stages	5 (6.1)	0 (0.0)	285 (97.9)	289 (97.6)	26 (100)	605 (86.2)
Completed	56 (68.3)	4 (57.1)	281 (96.6)	284 (95.9)	26 (100)	651 (92.7)
Treated stage 1 only and completed	56 (100)	4 (100)	0 (0.0)	0 (0.0)	0 (0.0)	60 (9.2)
Treated both stages and completed	0 (0.0)	0 (0.0)	281 (100)	284 (100)	26 (100)	591 (90.8)
Discontinued	26 (31.7)	3 (42.9)	10 (3.4)	12 (4.1)	0 (0.0)	51 (7.3)
Withdrawal by Subject	2 (7.7)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	3 (5.9)
Protocol Violation	24 (92.3)	3 (100)	8 (80.0)	11 (91.7)	0 (0.0)	46 (90.2)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	2 (3.9)
Patient not treated	**280 (77.3)**	**18 (72.0)**	**7 (2.3)**	**3 (1.0)**	**0 (0.0)**	**308 (30.5)**
Discontinued	280 (100)	18 (100)	7 (100)	3 (100)	0 (0.0)	308 (100)
Adverse Event	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Withdrawal By Subject	16 (5.7)	1 (5.6)	2 (28.6)	0 (0.0)	0 (0.0)	19 (6.2)
Protocol Violation	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Lost to Follow-up	32 (11.4)	2 (11.1)	5 (71.4)	3 (100)	0 (0.0)	42 (13.6)
Pregnancy	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Physician Decision	27 (9.6)	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	31 (10.1)
Lack of Qualifying Event§	198 (70.7)	11 (61.1)	0 (0.0)	0 (0.0)	0 (0.0)	209 (67.9)

† Patients randomized at Stage 1 but not at Stage 2.

‡ Patients counted only once across sub-categories. Percents of sub-category levels calculated using the total number in that sub-category as the denominator.

§ Patient was randomized, but did not experience a qualifying migraine during the study.

Patient was counted only once across treatment groups.

Rizatriptan group refers to Rizatriptan 5mg or 10mg.

N = Number of randomized patients.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-2)

Long term safety study (P086)

In the interim population of the long term safety study, 605 subjects enrolled and treated with study medication. Of the 605 subjects, 113 subjects (18.7%) discontinued from the study.

Withdrawal from the study and loss to follow up constituted the two main factors for discontinuation. Subject withdrawal was the most common reason for discontinuation (37/605 subjects, 6.1%). The next most common reason was loss to follow up (33/605 subjects, 5.5%). Table 30 provides an accounting of subject disposition in the long term safety study.

Table 30 Accounting of All Enrolled Subjects in the Long Term Safety Study (P086, Interim Population)

	Rizatriptan 5mg (N=28)	Rizatriptan 10mg (N=646)	Total (N=674)
	n (%)	n (%)	n (%)
Patients treated	**23 (82.1)**	**582 (90.1)**	**605 (89.8)**
Completed	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing	21 (91.3)	471 (80.9)	492 (81.3)
Discontinued†	2 (8.7)	111 (19.1)	113 (18.7)
Adverse Event	0 (0.0)	11 (9.9)	11 (9.7)
Withdrawal by Patient	2 (100.0)	35 (31.5)	37 (32.7)
Protocol Violation	0 (0.0)	8 (7.2)	8 (7.1)
Lost to Follow Up	0 (0.0)	33 (29.7)	33 (29.2)
Lack of Efficacy	0 (0.0)	11 (9.9)	11 (9.7)
Study Terminated by Sponsor	0 (0.0)	1 (0.9)	1 (0.9)
Pregnancy	0 (0.0)	2 (1.8)	2 (1.8)
Physician Decision	0 (0.0)	9 (8.1)	9 (8.0)
Lack of Qualifying Event‡	0 (0.0)	1 (0.9)	1 (0.9)
Patients not treated	**5 (17.9)**	**64 (9.9)**	**69 (10.2)**
Discontinued†	5 (100.0)	64 (100.0)	69 (100.0)
Withdrawal by Patient	3 (60.0)	16 (25.0)	19 (27.5)
Lost to Follow Up	1 (20.0)	16 (25.0)	17 (24.6)
Physician Decision	1 (20.0)	15 (23.4)	16 (23.2)
Lack of Qualifying Event‡	0 (0.0)	17 (26.6)	17 (24.6)

† Patients counted only once across sub-categories. Percents of sub-category levels are calculated using the total number in that sub-category as the denominator.

‡ Includes patients who enrolled but did not experience a qualifying migraine.

N = Number of enrolled patients

(Source: Clinical Study Report, module 5.3.5.1.3, Table 10-2)

7.3.4 Significant Adverse Events

Adverse events specific to triptan use were analyzed in the 3 clinical trials (P083, P082, and P086). The sponsor defined triptan related AE as any report of asthenia, chest discomfort, dizziness, dry mouth, fatigue, somnolence, myalgia, nausea, paresthesia, or throat tightness.

PK study (P083)
There was 1 case of "excessive sleepiness" reported of moderate intensity and lasting 1.5 hours in a 15 year old subject. The subject was in the rizatriptan 10 mg treatment group. There was also 1 case of headache of severe intensity and lasting 1.3 hours in another 15 year old subject in the rizatriptan 10 mg treatment group.

Efficacy study (P082)
Of the 702 subjects in study P082, 116 (16.5%) reported an AE within 24 hours post dose. The incidences of AEs and drug-related AEs were similar between the rizatriptan and the placebo groups. In the rizatriptan group, 39 subjects (11.6%) had a drug related AE and the placebo group had 39 subjects (10.7%). No subjects had a serious AE and no one discontinued from the study due to an AE. Table 31 displays a summary of the AEs within 24 hours after treatment with study medication in study P082.

Table 31 Summary of Adverse Events (Within 24 Hours Post Dose) in Efficacy Study (P082)

	Rizatriptan n (%)	Placebo n (%)	Total n (%)
Patients in population†	337	365	702
with no adverse event	280 (83.1)	306 (83.8)	586 (83.5)
with one or more adverse events	57 (16.9)	59 (16.2)	116 (16.5)
with drug-related‡ adverse events	39 (11.6)	39 (10.7)	78 (11.1)
with serious adverse events	0 (0.0)	2 (0.5)	2 (0.3)
with serious drug-related‡ adverse events	0 (0.0)	0 (0.0)	0 (0.0)
who died	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to adverse events	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to drug-related‡ adverse events	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to serious drug-related‡ adverse events	0 (0.0)	0 (0.0)	0 (0.0)
with one or more triptan-related	33 (9.8)	33 (9.0)	66 (9.4)

† Patients who took at least one dose of study medication.

‡ As determined by the investigator to be related to the drug.

Patients who took any Rizatriptan during the study (Stage 1 or 2) were included in the Rizatriptan treatment group and patients who only took placebo during the study were included in the placebo group. Post-dose refers to the APaT therapy dose.

Rizatriptan group refers to Rizatriptan 5mg or 10mg.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-2)

Triptan related AEs were similar in incidences between the rizatriptan treatment group and the placebo group. There were 33 subjects in each group (9.8% in rizatriptan group and 9.0% in placebo group) with triptan related AEs. Common triptan related AEs in the rizatriptan treatment group (≥2% and greater than placebo) consisted of somnolence (11/337 subjects, 3.3%), nausea (11/337 subjects, 3.0%), and fatigue (8/337 subjects, 2.4%). The sponsor reported no clinically important differences in triptan related AEs between the rizatriptan and placebo treatment groups. Distribution of triptan related AEs is presented in the table below.

Table 32 Summary of Triptan Related Adverse Events (Within 24 Hours Post Dose) in Efficacy Study (P082)

	Rizatriptan n (%)	Placebo n (%)	Total n (%)
with triptan-related adverse events	33 (9.8)	33 (9.0)	66 (9.4)
Asthenia	4 (1.2)	0 (0.0)	4 (0.6)
Dizziness	5 (1.5)	12 (3.3)	17 (2.4)
Dry mouth	2 (0.6)	3 (0.8)	5 (0.7)
Fatigue	8 (2.4)	8 (2.2)	16 (2.3)
Myalgia	1 (0.3)	0 (0.0)	1 (0.1)
Nausea	10 (3.0)	10 (2.7)	20 (2.8)
Paraesthesia	1 (0.3)	2 (0.5)	3 (0.4)
Somnolence	11 (3.3)	9 (2.5)	20 (2.8)

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-15)

Long term safety study (P086)

Of the 373 subjects in the long term safety study (PWR population), 184 subjects (49.3%) reported an AE within 24 hours of taking rizatriptan. Seventy-seven subjects (20.6%) reported having a drug related AE. The rate of AEs and drug related AEs were higher in the rizatriptan 10 mg treatment group than in the rizatriptan 5 mg treatment group. Seventy-five subjects (21.1%) reported having a drug related AE in the rizatriptan 10 mg group while 2 subjects (11.1%) in the rizatriptan 5 mg group had a drug related AE.

Table 33 Summary of Adverse Events (Within 24 Hours Post Any Dose) in Long Term Safety Study (P086, PWR Population)

	Rizatriptan 5 mg		Rizatriptan 10 mg		Total	
	n (%)	(95% CI)‡	n (%)	(95% CI)‡	n (%)	(95% CI)‡
Patients in population†	18		355		373	
with no adverse event	10 (55.6)	(30.8, 78.5)	179 (50.4)	(45.1, 55.7)	189 (50.7)	(45.5, 55.9)
with one or more adverse event	8 (44.4)	(21.5, 69.2)	176 (49.6)	(44.3, 54.9)	184 (49.3)	(44.1, 54.5)
with a drug-related‡ adverse event	2 (11.1)	(1.4, 34.7)	75 (21.1)	(17.0, 25.7)	77 (20.6)	(16.6, 25.1)
with a serious adverse event	0 (0.0)	(0.0, 18.5)	3 (0.8)	(0.2, 2.4)	3 (0.8)	(0.2, 2.3)
with a serious drug-related adverse event	0 (0.0)	(0.0, 18.5)	1 (0.3)	(0.0, 1.6)	1 (0.3)	(0.0, 1.5)
who died	0 (0.0)	(0.0, 18.5)	0 (0.0)	(0.0, 1.0)	0 (0.0)	(0.0, 1.0)
who discontinued due to an adverse event	0 (0.0)	(0.0, 18.5)	0 (0.0)	(0.0, 1.0)	0 (0.0)	(0.0, 1.0)
who discontinued due to a drug-related‡ adverse event	0 (0.0)	(0.0, 18.5)	0 (0.0)	(0.0, 1.0)	0 (0.0)	(0.0, 1.0)
who discontinued due to a serious adverse event	0 (0.0)	(0.0, 18.5)	0 (0.0)	(0.0, 1.0)	0 (0.0)	(0.0, 1.0)
who discontinued due to a serious drug-related adverse event	0 (0.0)	(0.0, 18.5)	0 (0.0)	(0.0, 1.0)	0 (0.0)	(0.0, 1.0)
with one or more Triptan-related events	0 (0.0)	(0.0, 18.5)	74 (20.8)	(16.7, 25.4)	74 (19.8)	(15.9, 24.3)

† Patient took at least one dose of study medication.
‡ As determined by the investigator to be related to the drug.
‡ Exact confidence intervals.
CI = Confidence interval.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-17)

Triptan related AEs were reported by 74 subjects (19.8%). All of the triptan related AEs occurred in the rizatriptan 10 mg treatment group. In the PWR population, common triptan related AEs consisted of dizziness (6.2%), somnolence (6.2%), nausea (4.6%) and fatigue (4.0%). Distribution of triptan related AEs is presented in the table below.

Table 34 Summary of Triptan Related Adverse Events (Within 24 Hours Post Any Dose) in Long Term Safety Study (P086, PWR Population)

	Rizatriptan 5 mg		Rizatriptan 10 mg		Total	
	n (%)	(95% CI)‡	n (%)	(95% CI)‡	n (%)	(95% CI)‡
Patients in population†	18		355		373	
with no triptan-related adverse event	18 (100.0)	(81.5, 100.0)	281 (79.2)	(74.6, 83.3)	299 (80.2)	(75.7, 84.1)
with one or more triptan-related adverse events	0 (0.0)	(0.0, 18.5)	74 (20.8)	(16.7, 25.4)	74 (19.8)	(15.9, 24.3)
Asthenia	0 (0.0)	(0.0, 18.5)	3 (0.8)	(0.2, 2.4)	3 (0.8)	(0.2, 2.3)
Chest discomfort	0 (0.0)	(0.0, 18.5)	5 (1.4)	(0.5, 3.3)	5 (1.3)	(0.4, 3.1)
Dizziness	0 (0.0)	(0.0, 18.5)	23 (6.5)	(4.2, 9.6)	23 (6.2)	(3.9, 9.1)
Dry mouth	0 (0.0)	(0.0, 18.5)	6 (1.7)	(0.6, 3.6)	6 (1.6)	(0.6, 3.5)
Fatigue	0 (0.0)	(0.0, 18.5)	15 (4.2)	(2.4, 6.9)	15 (4.0)	(2.3, 6.5)
Myalgia	0 (0.0)	(0.0, 18.5)	2 (0.6)	(0.1, 2.0)	2 (0.5)	(0.1, 1.9)
Nausea	0 (0.0)	(0.0, 18.5)	17 (4.8)	(2.8, 7.6)	17 (4.6)	(2.7, 7.2)
Paraesthesia	0 (0.0)	(0.0, 18.5)	4 (1.1)	(0.3, 2.9)	4 (1.1)	(0.3, 2.7)
Somnolence	0 (0.0)	(0.0, 18.5)	23 (6.5)	(4.2, 9.6)	23 (6.2)	(3.9, 9.1)
Throat tightness	0 (0.0)	(0.0, 18.5)	3 (0.8)	(0.2, 2.4)	3 (0.8)	(0.2, 2.3)

† Patient took at least one dose of study medication.
‡ Exact confidence intervals.
CI = Confidence interval.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-36)

7.3.5 Submission Specific Primary Safety Concerns

No additional submission specific safety concerns were identified during this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

PK study (P083)
In the PWR population of the PK study, there were 14 AEs reported by 10 subjects. Six of these AEs were reported to be possibly or probably related to study drug. Four of the 6 possible or probable AE cases related to study drug were determined to be mild in intensity. (The cases of severe and moderate intensity AEs have been presented in section 7.3.4). The 6 drug related AEs were headache, fatigue, visual impairment, hypersomnia, elevated blood pressure and somnolence.

Efficacy study (P082)

Common AEs reported by ≥2% of subjects within 24 hours post dose in the rizatriptan treatment group were somnolence (3.3%), nausea (3.0%), and fatigue (2.4%). The percentage of subjects experiencing AEs was similar between the rizatriptan and placebo treatment groups. Table 35 provides a summary of the common AEs reported in Study P082.

Table 35 Summary of Common Adverse Events (Occurring in ≥2% of Subjects) by System Organ Class (Within 24 Hours Post Dose) in Efficacy Study (P082)

	Rizatriptan n (%)	Placebo n (%)	Total n (%)
Patients in population†	337	365	702
with no adverse event	280 (83.1)	306 (83.8)	586 (83.5)
with one or more adverse events	57 (16.9)	59 (16.2)	116 (16.5)
Gastrointestinal disorders	**23 (6.8)**	**29 (7.9)**	**52 (7.4)**
Abdominal pain upper	5 (1.5)	8 (2.2)	13 (1.9)
Nausea	10 (3.0)	10 (2.7)	20 (2.8)
Vomiting	2 (0.6)	5 (1.4)	7 (1.0)
General disorders and administration site conditions	**14 (4.2)**	**16 (4.4)**	**30 (4.3)**
Asthenia	4 (1.2)	0 (0.0)	4 (0.6)
Fatigue	8 (2.4)	8 (2.2)	16 (2.3)
Nervous system disorders	**26 (7.7)**	**25 (6.8)**	**51 (7.3)**
Dizziness	5 (1.5)	12 (3.3)	17 (2.4)
Somnolence	11 (3.3)	9 (2.5)	20 (2.8)

Although a patient may have had two or more adverse events of the same type, the patient is counted only once for that type of adverse event.

† Patients took at least one dose of study medication.

Patients who took any Rizatriptan during the study (Stage 1 or 2) were included in the Rizatriptan treatment group and patients who only took placebo during the study were included in the placebo group. Post-dose refers to the APaT therapy dose.

Rizatriptan group refers to Rizatriptan 5mg or 10mg.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-6)

Long term safety study (P086)

The most common AE reported in study P086 was accidental overdose (subject taking 2 doses of study drug in 24 hours). Recall, the sponsor defined an overdose of study drug as ingestion of rizatriptan of more than 5 mg in a 24 hour period for subjects with a body weight less than 40 kg at screening and more than 10 mg in a 24 hour period for subjects with screening body weight of 40 kg or more.

Of the 373 subjects treated in the P086 PWR population, 77 subjects (20.6%) took more than 1 dose of study medication in a 24 hour period. Overdosing of study medication occurred in 8 subjects (44.4%) in the rizatriptan 5 mg treatment group and in 67

subjects (18.9%) in the rizatriptan 10 mg treatment group. No subject took more than 2 doses of study medication in any 24 hour period.

The sponsor attributes the large number of overdose cases on 2 reasons. The sponsor states that "reasons for overdose likely included previous experience with triptan drugs in which two doses are allowed in a 24 hour period and confusion on the difference between a 24 hour period and a calendar day".

The next most common AEs, after study drug overdose, were somnolence (6.5%), dizziness (6.5%), nausea (4.8%) and fatigue (4.2%). All of these AEs occurred in the rizatriptan 10 mg treatment group. Except for overdose, there were no AEs reported in >1 subject in the rizatriptan 5 mg group.

Table 36 Summary of Common Adverse Events (Occurring in ≥2% of Subjects) by System Organ Class (Within 24 Hours Post Dose) in Long Term Safety Study (P086, PWR Population)

	Rizatriptan 5 mg		Rizatriptan 10 mg		Total	
	n (%)	(95% CI)‡	n (%)	(95% CI)‡	n (%)	(95% CI)‡
Patients in population†	18		355		373	
with no adverse event	10 (55.6)	(30.8, 78.5)	179 (50.4)	(45.1, 55.7)	189 (50.7)	(45.5, 55.9)
with one or more adverse events	8 (44.4)	(21.5, 69.2)	176 (49.6)	(44.3, 54.9)	184 (49.3)	(44.1, 54.5)
Gastrointestinal disorders	**3 (16.7)**	**(3.6, 41.4)**	**41 (11.5)**	**(8.4, 15.3)**	**44 (11.8)**	**(8.7, 15.5)**
Frequent bowel movements	1 (5.6)	(0.1, 27.3)	0 (0.0)	(0.0, 1.0)	1 (0.3)	(0.0, 1.5)
Irritable bowel syndrome	1 (5.6)	(0.1, 27.3)	0 (0.0)	(0.0, 1.0)	1 (0.3)	(0.0, 1.5)
Nausea	0 (0.0)	(0.0, 18.5)	17 (4.8)	(2.8, 7.6)	17 (4.6)	(2.7, 7.2)
Vomiting	1 (5.6)	(0.1, 27.3)	5 (1.4)	(0.5, 3.3)	6 (1.6)	(0.6, 3.5)
General disorders and administration site conditions	**0 (0.0)**	**(0.0, 18.5)**	**30 (8.5)**	**(5.8, 11.8)**	**30 (8.0)**	**(5.5, 11.3)**
Fatigue	0 (0.0)	(0.0, 18.5)	15 (4.2)	(2.4, 6.9)	15 (4.0)	(2.3, 6.5)
Infections and infestations	**1 (5.6)**	**(0.1, 27.3)**	**15 (4.2)**	**(2.4, 6.9)**	**16 (4.3)**	**(2.5, 6.9)**
Nasopharyngitis	1 (5.6)	(0.1, 27.3)	5 (1.4)	(0.5, 3.3)	6 (1.6)	(0.6, 3.5)
Injury, poisoning and procedural complications	**8 (44.4)**	**(21.5, 69.2)**	**72 (20.3)**	**(16.2, 24.8)**	**80 (21.4)**	**(17.4, 26.0)**
Accidental overdose§	8 (44.4)	(21.5, 69.2)	67 (18.9)	(14.9, 23.3)	75 (20.1)	(16.2, 24.5)
Musculoskeletal and connective tissue disorders	**1 (5.6)**	**(0.1, 27.3)**	**20 (5.6)**	**(3.5, 8.6)**	**21 (5.6)**	**(3.5, 8.5)**
Muscle tightness	1 (5.6)	(0.1, 27.3)	4 (1.1)	(0.3, 2.9)	5 (1.3)	(0.4, 3.1)
Nervous system disorders	**0 (0.0)**	**(0.0, 18.5)**	**63 (17.7)**	**(13.9, 22.1)**	**63 (16.9)**	**(13.2, 21.1)**
Dizziness	0 (0.0)	(0.0, 18.5)	23 (6.5)	(4.2, 9.6)	23 (6.2)	(3.9, 9.1)
Migraine	0 (0.0)	(0.0, 18.5)	10 (2.8)	(1.4, 5.1)	10 (2.7)	(1.3, 4.9)
Somnolence	0 (0.0)	(0.0, 18.5)	23 (6.5)	(4.2, 9.6)	23 (6.2)	(3.9, 9.1)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**(0.0, 18.5)**	**15 (4.2)**	**(2.4, 6.9)**	**15 (4.0)**	**(2.3, 6.5)**

Although a patient may have had two or more adverse events of the same type, the patient is counted only once for that type of adverse event.
† Patient took at least one dose of study medication.
‡ Exact confidence intervals computed for those criteria with at least 1% incidence in one or more treatment groups.
§ An overdose of rizatriptan is defined as ingestion of more than 5 mg in a 24-hour period for patients with a screening body weight of less than 40 kg and more than 10 mg in a 24-hour period for patients with a screening body weight of 40 kg or more.
CI = Confidence interval.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-20)

7.4.2 Laboratory Findings

Laboratory assessments included hematology, blood chemistry, and urinalysis tests. The sponsor reported no clinically important laboratory findings in any of the 3 adolescent studies. I have reviewed the data. From the submitted clinical trials there were 3 cases of interest involving liver enzyme elevations in the long term safety studies. These spikes in enzyme levels had either normalized or decreased to levels where they no longer exceeded the predefined limits of change by the follow up laboratory assessment.

PK study (P083)
Laboratory assessments were conducted at enrollment into the study, pre-dose, 24 hours post-dose and post-study (10-14 days after last dose administration). There were no reported discontinuations or SAEs related to lab abnormalities.

Efficacy study (P082)
Laboratory assessments were conducted on the first visit (screening/randomization) and at post-treatment visit (within 14 days after treatment dose). The laboratory measurement with largest change from the predefined limits was eosinophils (7/321, 2.2% subjects in rizatriptan group and 7/354, 2% of subjects in placebo group). Overall, there were no clinically relevant differences in laboratory measurements exceeding the predefined limits between the rizatriptan and placebo treatment groups.

Table 37 Number (%) of Subjects Exceeding the Predefined Limits of Change in Laboratory Measurements in All Treated Adolescents (P082)

Laboratory Parameter	Predefined Limit of Change	Rizatriptan (N=337) n/m (%)	Placebo (N=365) n/m (%)
Hematology			
Hematocrit (Males) (%)	≤ 94.9% LLN	1/129 (0.8)	0/141 (0.0)
Hematocrit (Females) (%)	≤ 94.1% LLN	1/192 (0.5)	2/213 (0.9)
Hemoglobin (Males) (gm/dL)	≤ 90.5% LLN	1/129 (0.8)	0/141 (0.0)
Hemoglobin (Females) (gm/dL)	≤ 81.9% LLN	1/192 (0.5)	0/213 (0.0)
Leukocytes (10[3]/microL)	≤ 64.2% LLN	1/321 (0.3)	0/354 (0.0)
	≥ 149.0% ULN	1/321 (0.3)	0/354 (0.0)
Neutrophils (10[3]/microL)	≤ 37.0% LLN	0/321 (0.0)	0/354 (0.0)
Eosinophils (10[3]/microL)	≥ 147.0% ULN	7/321 (2.2)	7/354 (2.0)
Platelets (10[3]/microL)	≤ 57.7% LLN	1/309 (0.3)	2/341 (0.6)
	≥ 177.7% ULN	0/309 (0.0)	0/341 (0.0)
Hepatic Function			
Bilirubin (mg/dL)	≥ 166.7% ULN	3/328 (0.9)	1/360 (0.3)
Alkaline Phosphatase (IU/L)	≥ 300% ULN	0/326 (0.0)	0/360 (0.0)
AST (IU/L)	≥ 300% ULN	0/327 (0.0)	2/360 (0.6)
ALT (IU/L)	≥ 300% ULN	0/327 (0.0)	1/360 (0.3)
Renal Function			
Sodium (mEq/L)	≤ 94.7% LLN	0/328 (0.0)	0/359 (0.0)
	≥ 105.4% ULN	0/328 (0.0)	1/359 (0.3)
Potassium (mEq/L)	≤ 88.2% LLN	0/326 (0.0)	0/358 (0.0)
	≥ 111.1% ULN	2/326 (0.6)	4/358 (1.1)
Clinical Chemistry			
Creatinine (mg/dL)	≥ 142.9% ULN	0/328 (0.0)	0/360 (0.0)

Patients who took any Rizatriptan during the study (Stage 1 or 2) were included in the Rizatriptan treatment group and patients who only took placebo during the study were included in the placebo group.
Rizatriptan group refers to Rizatriptan 5mg or 10mg.
N = Number of patients took at least one dose of study medication.
n/m = Number of treated patients meeting the predefined limit criteria/Number of treated patients with valid postdose values of the laboratory parameters.
LLN = Lower limit of normal range; ULN = Upper limit of normal range; ALT = Alanine aminotransferase.
AST = Aspartate aminotransferase; RBC = Red blood cell.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-33)

Long term safety study (P086)

Laboratory tests were obtained at screening visit and on study visits 1, 3, 6, 9, and 12. The sponsor reported the laboratory measurements that had the largest percentage of change exceeding the predefined limits were increased eosinophils (14/367, 3.8% of subjects), decreased hematocrit (4/227, 1.8% of subjects), and increased potassium (4/373, 1.1% of subjects) in the PWR population (Table 38).

Of note, there were 3 cases of elevated liver enzymes in the interim population of the long term study. The sponsor reported treating 605 adolescent subjects in the long term safety study. Of these, 598 subjects had post-baseline hepatic laboratory results. Three subjects who received rizatriptan 10 mg had elevations of alanine aminotransferase (ALT) that exceeded the predefined limits of change for ALT (≥300% upper limit of normal, ULN). The following are the case reports of the 3 subjects with elevated liver enzymes in the long term study:

Subject AN 20053, a 17 year old, white male, took the first dose of rizatriptan on 18-Feb-2010. On 17-Apr-2010 the patient took a dose of study medication, and at the 10-May-2010 visit, the patient's ALT was 138 IU/L (baseline 26 IU/L [ULN 33 IU/L]), which exceeded the predefined limits of change; the aspartate aminotransferase (AST) (57 IU/L [baseline 21 IU/L]) was above the ULN (36 IU/L); and bilirubin and alkaline phosphatase were within normal limits (WNL). No concomitant medication was reported at the time of ALT, AST, and AST elevations. At the next clinic visit (27-Jul-2010), the ALT (21 IU/L) and AST (23 IU/L) had returned to WNL.

AN 20102, a 16 year old, white female, took the first dose of rizatriptan on 18-Feb-2010. On 03-May-2010 the patient took a dose of study medication, and at the 11-May-2010 visit, the patient's ALT was 195 IU/L (baseline 12 IU/L [ULN 35 IU/L]), which exceeded the predefined limits of change; the AST (107 IU/L [baseline 16 IU/L]) was above the ULN (41 IU/L); and bilirubin and alkaline phosphatase were WNL. The patient reported having taken olopatadine hydrochloride beginning on 10-May-2010. At the repeat laboratory assessment (18-May-2011), the ALT (84 IU/L) and AST (44 IU/L) had decreased from the previous week, and the ALT no longer exceeded the predefined limits of change. At the next scheduled visit (12-July-2010), the ALT (14 IU/L) and AST (19 IU/L) had returned to WNL.

AN 20139, a 17 year old, white male, took the first dose of rizatriptan on 27-Feb-2010. On 05-Aug-2010 and 06-Aug, 2010, the patient took a dose of study medication, and at the 16-Aug-2010 visit, the patient's ALT was 126 IU/L (baseline 25 IU/L [ULN 40 IU/L]), which exceeded the predefined limits of change; the AST (56 IU/L [baseline 28 IU/L]) was above the ULN (43 IU/L); and bilirubin and alkaline phosphatase were WNL. The patient reported having taken 800 mg ibuprofen on 16-Aug-2010. At the repeat laboratory assessment (18-Aug-2010 [last laboratory assessment in the interim database]), the ALT (95 IU/L) had decreased from the previous assessment, and it no longer exceeded the predefined limits of change; and the AST (43 IU/L) had returned to WNL.

Table 38 Number (%) of Subjects Exceeding the Predefined Limits of Change in Laboratory Measurements in Long Term Safety Study (Interim Population)

Laboratory Parameter	Predefined Limit of Change	Rizatriptan 5mg (N=23) n/m (%)	Rizatriptan 10mg (N=582) n/m (%)	Total (N=605) n/m (%)
Hematology				
Hematocrit (%)†	≤94.9% LLN	0/14 (0.0)	0/210 (0.0)	0/224 (0.0)
Hematocrit (%)‡	≤94.1% LLN	0/8 (0.0)	6/360 (1.7)	6/368 (1.6)
Hemoglobin (gm/dL)†	≤90.5% LLN	0/14 (0.0)	0/210 (0.0)	0/224 (0.0)
Hemoglobin (gm/dL)‡	≤81.9% LLN	0/8 (0.0)	1/360 (0.3)	1/368 (0.3)
Leukocytes (10[3]/microL)	≤64.2% LLN	0/22 (0.0)	1/570 (0.2)	1/592 (0.2)
	≥149.0% ULN	0/22 (0.0)	5/570 (0.9)	5/592 (0.8)
Neutrophils (10[3]/microL)	≤37.0% LLN	0/22 (0.0)	2/570 (0.4)	2/592 (0.3)
Eosinophils (10[3]/microL)	≥147.0% ULN	3/22 (13.6)	16/570 (2.8)	19/592 (3.2)
Platelet (10[3]/microL)	≤57.7% LLN	0/22 (0.0)	0/569 (0.0)	0/591 (0.0)
	≥177.7% ULN	0/22 (0.0)	0/569 (0.0)	0/591 (0.0)
Hepatic Function				
Bilirubin (mg/dL)	≥166.7% ULN	0/23 (0.0)	3/575 (0.5)	3/598 (0.5)
Alkaline Phosphatase (IU/L)	≥300.0% ULN	0/23 (0.0)	0/575 (0.0)	0/598 (0.0)
AST (IU/L)	≥300.0% ULN	0/23 (0.0)	0/575 (0.0)	0/598 (0.0)
ALT (IU/L)	≥300.0% ULN	0/23 (0.0)	3/575 (0.5)	3/598 (0.5)
Clinical Chemistry				
Sodium (mEq/L)	≤94.7% LLN	0/23 (0.0)	0/575 (0.0)	0/598 (0.0)
	≥105.4% ULN	0/23 (0.0)	1/575 (0.2)	1/598 (0.2)
Potassium (mEq/L)	≤88.2% LLN	0/23 (0.0)	1/575 (0.2)	1/598 (0.2)
	≥111.1% ULN	0/23 (0.0)	5/575 (0.9)	5/598 (0.8)
Renal Function				
Creatinine (mg/dL)	≥142.9% ULN	0/23 (0.0)	0/575 (0.0)	0/598 (0.0)

† For male.
‡ For female.
N = number of patients who took at least one dose of study medication.
n / m = Number of treated patients meeting the predefined limit criteria / number of treated patients with valid postdose values of the laboratory parameters.
LLN = Lower limit of normal range; ULN = Upper limit of normal range; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-41)

As described in the case reports above, almost all of the liver enzyme abnormalities had normalized by the repeat laboratory assessment. The exception was the ALT level in subject AN 20139 which had decreased to the point of not exceeding the predefined limits of change.

7.4.3 Vital Signs

The sponsor reports no clinically significant vital signs shifts and no trends for changes in vital signs over time in the 3 trials. I reviewed the data and concur. There was one adverse event reported (in study P083) for vital signs from the 3 clinical trials submitted. Further information regarding vital signs for the clinical trials is provided below.

Vital signs evaluated as part of the safety monitoring during the clinical trials included blood pressure, heart rate, respiratory rate, and temperature. Table 39 provides the sponsor-defined clinically relevant changes in vital signs.

Table 39 Criteria for Clinically Significant Vital Sign Abnormalities

Systolic blood pressure:	≥ 130 mm Hg and 20 mm Hg increase[†] ≤ 105 mm Hg and 20 mm Hg decrease[†]
Diastolic blood pressure:	≥ 85 mm Hg and 15 mm Hg increase[†] ≤ 65 mm Hg and 15 mm Hg decrease[†]
Pulse:	≥ 130 bpm and 15 bpm increase[†] ≤ 60 bpm and 15 bpm decrease[†]
Body temperature:	> 38°C (oral equivalent)
Respiratory rate:	> 25 or increase of 10 or < 5 or decrease[†] of 10 (per minute)
[†]Relative to baseline value	

(Source: Clinical Study Report, module 5.3.5.1.3, Table 9-4)

PK study (P083)
Subjects in the PK study had vital signs assessed at predose and every 20 minutes for the first 3 hours post-dose, then every hour until 8 hours post-dose. Respiratory rate and temperature were measured at pre- and post-study time points. One subject had an adverse event due to an increase in blood pressure. The AE was rated as mild and possibly related to study. The following in the sponsor's summary of the AE:

> In P083 Pediatric PK Study, one patient (AN201) had an increase in blood pressure during Day 1. Predose blood pressure was 120/63 and heart rate was 44 bpm. The blood pressure was the highest at 2 hours postdose when the semi-recumbent BP was 153/66 and heart rate was 57 bpm; standing BP was 138/73 with a heart rate of 60 bpm. He reported no unusual symptoms and reported feeling his usual self. While the subject had no history of high blood pressure, it was noted by the investigator that there is a history of hypertension in the families of both parents. The intensity of the adverse event was rated as mild, and the investigator considered the event as possibly due to study drug.

Efficacy study (P082)
Vital signs were obtained at Visit 1 (screening and randomization) and Visit 2 (Post-treatment). The post-treatment phase could occur anytime from 2 days to 2 weeks after treatment with study medication. No clinically significant changes in vital signs were detected in the trial.

Long term safety study (P086)
Vital signs were taken at screening visit and at all scheduled clinic visits (months 1, 2, 3, 4, 6, 9, and 12). As reported by the sponsor, the vital sign measurement with the largest number of subjects that experienced a change exceeding the predefined limits was for decreased diastolic blood pressure (54/372, 14.5% of subjects). Decrease systolic blood pressure (38/372, 10.2% of subjects) and decreased pulse (34/372, 9.1% of subjects) were the next two most common.

Table 40 Number (%) of Subjects Exceeding the Predefined Limits of Change in Vital Sign Measurements in Long Term Safety Study (PWR Population)

Vital Sign Parameter	Predefined Limit of Change	Rizatriptan 5mg (N=18) n/m (%)	Rizatriptan 10mg (N=355) n/m (%)	Total (N=373) n/m (%)
Diastolic Blood Pressure (mmHg)	Value ≤ 65 and Decrease ≥ 15	1/18 (5.6)	53/354 (15.0)	54/372 (14.5)
	Value ≥ 85 and Increase ≥ 15	0/18 (0.0)	11/354 (3.1)	11/372 (3.0)
Systolic Blood Pressure (mmHg)	Value ≤ 105 and Decrease ≥ 20	1/18 (5.6)	37/354 (10.5)	38/372 (10.2)
	Value ≥ 130 and Increase ≥ 20	1/18 (5.6)	8/354 (2.3)	9/372 (2.4)
Pulse (beats/min)	Value ≤ 60 and Decrease ≥ 15	3/18 (16.7)	31/354 (8.8)	34/372 (9.1)
	Value ≥ 130 and Increase ≥ 15	0/18 (0.0)	0/354 (0.0)	0/372 (0.0)
Respiratory Rate (breaths/min)	Value < 5 or decrease ≥ 10 or Value > 25 or increase ≥ 10	1/18 (5.6)	13/347 (3.7)	14/365 (3.8)
Temperature (C)	Value > 38 Centigrade (oral equivalent)	0/18 (0.0)	0/351 (0.0)	0/369 (0.0)

N = Patients who took at least one dose of study medication.
n = Number of treated patients meeting the predefined limit criteria.
m = Number of treated patients with valid pre- and post-treatment values of the vital signs parameter.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-43)

Overall, there were no reported adverse events related to vital signs in the long term safety study (P086).

7.4.4 Electrocardiograms (ECGs)

Electrocardiogram data were summarized by mean changes from baseline in ECG-measurements for the following parameters: PR Interval, QRS Interval, QT Interval, QTc Interval Bazett, QTc Interval Fridericia, and Ventricular Rate. The sponsor reports that

there were no clinically relevant ECG findings in the clinical trials. I reviewed the ECG data and concur with the sponsor's observations and conclusions.

PK study (P083)
Electrocardiograms were conduced at the following time points in the trial: pre-study, pre-dose, 24 hours post-dose and post-study (10-14 days after last dose administration). No AEs related to ECG findings were documented. The sponsor reported there were no consistent treatment-related changes in ECG parameters.

Efficacy study (P082)
Electrocardiograms were drawn on the first visit (screening/randomization) and at post-treatment visit (within 14 days after treatment dose). Summary statistics for ECG measurements from baseline and change from baseline in all treated adolescents are presented in Table 41. There were no clinically relevant differences between the rizatriptan group and the placebo group with regards to ECG measured parameters. Additionally, there were no AEs related to ECG findings in the acute efficacy study.

Table 41 ECG Change from Pre-Treatment Visit to Post-Treatment Visit in All Treated Adolescents (P082)

ECG Parameter	Treatment†	m	Baseline Mean (SD)	Treatment Mean (SD)	Change from Baseline Mean (SD)	Change from Baseline [Min, Max]
PR Interval (msec)	Rizatriptan	331	146.13 (19.97)	146.17 (19.69)	0.02 (12.88)	[-44.00, 58.00]
	Placebo	359	143.42 (17.69)	143.62 (18.20)	0.20 (11.40)	[-36.00, 46.00]
QRS Interval (msec)	Rizatriptan	331	86.47 (7.96)	87.18 (8.17)	0.72 (6.48)	[-24.00, 34.00]
	Placebo	359	85.83 (7.75)	86.51 (8.21)	0.69 (6.04)	[-24.00, 24.00]
QT Interval (msec)	Rizatriptan	331	381.85 (26.51)	379.85 (28.62)	-1.95 (24.55)	[-86.00, 88.00]
	Placebo	359	377.22 (26.09)	375.33 (26.38)	-1.89 (23.20)	[-56.00, 68.00]
QTcF Interval (msec)	Rizatriptan	331	399.34 (15.49)	398.77 (17.52)	-0.54 (14.78)	[-52.00, 59.00]
	Placebo	359	396.61 (15.27)	396.92 (15.48)	0.31 (14.49)	[-56.00, 55.00]
QTcB Interval (msec)	Rizatriptan	331	408.31 (18.00)	408.55 (19.20)	0.27 (16.80)	[-44.00, 46.00]
	Placebo	359	406.67 (18.76)	408.13 (18.03)	1.47 (17.87)	[-64.00, 52.00]
Ventricular Rate (beats/min)	Rizatriptan	331	69.84 (11.19)	70.69 (11.33)	0.85 (10.16)	[-37.00, 38.00]
	Placebo	359	71.10 (12.31)	72.23 (11.57)	1.13 (10.96)	[-34.00, 33.00]

† For QTcF, correction performed using Fridericia´s method. For QTcB, correction performed using Bazett´s method.
Patients who took any Rizatriptan during the study (Stage 1 or 2) were included in the Rizatriptan treatment group and patients who only took placebo during the study were included in the placebo group.
Rizatriptan group refers to Rizatriptan 5mg or 10mg.
m = Number of treated patients with valid pre and post-treatment values of the parameter. Post-treatment values were determined using the most recent value following the last dose of study medication.
SD = Standard deviation.

(Source: Clinical Study Report, module 5.3.5.1.3, Table 12-37)

Long term safety study (P086)
ECGs were obtained at screening visit and on study visits 1, 3, 6, 9, and 12. There were 2 SAEs related to ECG changes. Both AEs were deemed not to be related to study treatment.

One subject (AN 20377), a 12 year old white male, was discontinued from the study due QT prolongation on ECG. The AE was classified as mild in intensity and considered to be unrelated to study medication by the study investigator. Another subject (AN20382), a 13 year old white male, was noted to have sinus bradycardia (heart rate of 50). The patient's mother reported that the patient has a history of sinus bradycardia and has been asymptomatic. Patient was seen by his cardiologist who reported that the sinus bradycardia was normal for the patient. The AE was deemed unrelated to study drug by the investigator and the subject was not discontinued from the study.

Prior Pediatric Studies

I reviewed ECG related AEs and clinically significant changes from prior pediatric trials submitted by the sponsor. Noteworthy ECG-related AEs occurred in study P059 extension/P061 long term safety in adolescents. In this open-label study, a total of 686 subjects were treated with study medication (273 with rizatriptan 5 mg tablet, 281 with rizatriptan 5 mg ODT, and 132 with standard care).

Of the 686 treated subjects in study P059 extension/P061, 9 had ECG related AEs: 4 in the tablet, 4 in the ODT, and 1 in standard care group. One subject in the ODT group had a finding of ST segment elevation on ECG that was determined to be possibly related to study drug by the investigator. The subject was subsequently discontinued from the study. The following is a narrative of the case:

> Subject AN 0183, a 13-year old female patient at site 061035 in the ODT treatment group, had an abnormal variant of elevated ST segment. The patient had treated a total of 5 migraine attacks with 7 doses of rizatriptan ODT. Her last migraine attack was 18 days prior to the adverse experience and was treated with 2 doses of study medication. The investigator felt the adverse experience was possibly related to study medication and was a clinically significant change in the ECG. This adverse experience resulted in the early discontinuation of the patient from the study.

The other 8 ECG related AEs were deemed not to be treatment related and none of the 8 subjects discontinued from the study. Seven subjects on rizatriptan (4 in tablet group, 3 in ODT group) had the following ECG related AEs: right atrial hypertrophy, right ventricular hypertrophy, 1st degree AV block, prolonged QT interval, T-wave abnormality, sinus tachycardia, 2nd degree AV block. One subject (in the standard care group) had left ventricular hypertrophy.

There were another 3 ECG findings in this study that were classified as clinically significant change and not reported as AEs. One subject in the rizatriptan tablet group had sinus arrhythmia while another subject in the same group had sinus bradycardia. One subject in the standard care group had both sinus bradycardia and 1st degree AV block.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted for this sNDA.

7.4.6 Immunogenicity

No investigations of immunogenicity were submitted for this sNDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All clinical trials in the sNDA used rizatriptan ODT dose of either 5 mg or 10 mg based on subject weight, 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

I analyzed AEs by subgroups based on gender, age, and race for the long term safety study (P086). Adverse events by subgroups used the 24 hours and 14 days post treatment time points for analysis. The analyses revealed a consistently higher incidence of AEs occurring in females than males (in the categories of at least one AE, drug related AEs and triptan related AEs).

P086 Long Term Safety Study: Subgroup Analysis by Gender
Of the 355 subjects in the rizatriptan 10 mg group (PWR population), 221 subjects (62.3%) were female. Distribution of AEs by gender indicated a higher incidence of AEs occurring in females than males. There were 57.0% females with at least one AE compared to 37.3% of males. Drug related AE occurred at a rate of 24.9% in females compared to14.9% in males. Similarly, triptan related AEs occurred in 24.0% of females but only in 15.7% of males at 24 hours post any dose. Table 42 displays the subgroup comparison by gender at 24 hours post any dose. The pattern was similar when data were analyzed for 14 days post any dose.

Table 42 Adverse Events Summary in Rizatriptan 10 mg ODT Group (Within 24 Hours Post Any Dose) Subgroup Analysis by Gender in Study P086

Gender	Female		Male	
	n/N	(%)	n/N	(%)
With at least one AE	126/221	(57.0)	50/134	(37.3)
With a drug-related AE	55/221	(24.9)	20/134	(14.9)
With an SAE	1/221	(0.5)	2/134	(1.5)
With a drug-related SAE	1/221	(0.5)	0/134	(0.0)
Who discontinued due to an AE	0/221	(0.0)	0/134	(0.0)
With a Triptan-related AE	53/221	(24.0)	21/134	(15.7)

Although a patient may have had two or more adverse events of the same type, the patient is counted only once for that type of adverse event.
N = Patients who took at least one dose of study medication.
n = Number of patients experiencing AE category.
AE = Adverse experience. SAE = Serious adverse experience.

(Source: Clinical Study Report, module 5.3.5.1.2, Table 14-95)

P086 Long Term Safety Study: Subgroup Analysis by Age

Of the 355 subjects in the rizatriptan 10 mg group (PWR population), 155 subjects (43.7%) were between the ages of 12-14 years and 200 subjects (56.3%) were between the ages of 15-17 years. Distribution of AEs by age indicated a higher percentage of AEs occurring in the younger (12-14 year old) age group than the older (15-17 year old) age group. The proportion of subjects with at least 1 AE in the 12-14 year old group compared to the 15-17 year old group was 54.2% versus 46.0%, respectively. Drug related AE occurred in 22.6% of 12-14 year olds compared to 20.0% in the 15-17 year old group. Triptan related AEs occurred in 24.5% of subjects in the 12-14 year old group and 18.0% of subjects in 15-17 year old group. Table 43 below depicts the subgroup comparison by age at 24 hours post any dose. Results were similar when data were reviewed for AEs 14 days post any dose.

Table 43 Adverse Events Summary in Rizatriptan 10 mg ODT Group (Within 24 Hours Post Any Dose) Subgroup Analysis by Age in Study P086

Age	12 to 14 years old		15 to 17 years old	
	n/N	(%)	n/N	(%)
With at least one AE	84/155	(54.2)	92/200	(46.0)
With a drug-related AE	35/155	(22.6)	40/200	(20.0)
With an SAE	2/155	(1.3)	1/200	(0.5)
With a drug-related SAE	0/155	(0.0)	1/200	(0.5)
Who discontinued due to an AE	0/155	(0.0)	0/200	(0.0)
With a Triptan-related AE	38/155	(24.5)	36/200	(18.0)

Although a patient may have had two or more adverse events of the same type, the patient is counted only once for that type of adverse event.
N = Patients who took at least one dose of study medication.
n = Number of patients experiencing AE category.
AE = Adverse experience. SAE = Serious adverse experience.

(Source: Clinical Study Report, module 5.3.5.1.2, Table 14-84)

P086 Long Term Safety Study: Subgroup Analysis by Race

Of the 355 subjects in the rizatriptan 10 mg group (PWR population), 304 subjects (85.6%) were white. A comparison of white subjects to non-white subjects with regards to AEs revealed no meaningful difference in the groups. A similar proportion of white subjects had at least one AE compared to non-whites (49.3% versus 51.0%, respectively), a drug related AE (21.4% versus 19.6%, respectively) or a triptan related AE (21.1% versus 19.6%, respectively) in 24 hours post any dose. As with other subgroup analyses discussed above, results at 14 days post any dose was similar to the 24 hours post any dose. Table 44 depicts the subgroup comparison by race at 24 hours post any dose time point.

Table 44 Adverse Events Summary in Rizatriptan 10 mg ODT Group (Within 24 Hours Post Any Dose) Subgroup Analysis by Race in Study P086

Race	Caucasian		Non-Caucasian	
	n/N	(%)	n/N	(%)
With at least one AE	150/304	(49.3)	26/51	(51.0)
With a drug-related AE	65/304	(21.4)	10/51	(19.6)
With an SAE	2/304	(0.7)	1/51	(2.0)
With a drug-related SAE	0/304	(0.0)	1/51	(2.0)
Who discontinued due to an AE	0/304	(0.0)	0/51	(0.0)
With a Triptan-related AE	64/304	(21.1)	10/51	(19.6)

Although a patient may have had two or more adverse events of the same type, the patient is counted only once for that type of adverse event.
N = Patients who took at least one dose of study medication.
n = Number of patients experiencing AE category.
AE = Adverse experience. SAE = Serious adverse experience.

(Source: Clinical Study Report, module 5.3.5.1.2, Table 14-106)

7.5.4 Drug-Disease Interactions

No formal drug-disease interaction studies have been conducted in pediatric subjects for this sNDA. Since this NDA is a 505(b)1 application, it relies on the same recommendations and cautions as described in the package insert of the reference listed drug, MAXALT® and MAXALT-MLT®.

7.5.5 Drug-Drug Interactions

No formal drug-disease interaction studies have been conducted in pediatric subjects for this sNDA.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted for this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

A total of 4 pregnancies were reported in the 3 clinical trials that were treated with rizatriptan ODT. No conclusions can be drawn from the pregnancy outcomes due to the

relatively low numbers of documented pregnancies. These low numbers are understandable as pregnancy was an exclusionary criterion in the clinical trials. Summaries of the pregnancy cases are presented below.

PK study (P083)
No pregnancies were reported among adolescent subjects in the PK study (P083).

Efficacy study (P082)
Pregnancies were reported in 2 adolescent subjects during the short term efficacy study, P082. The following is a summary of these cases:

- Subject AN 00551, a 15 year old multi-racial female who was randomized into the study on 26 May 2010 and took both doses of study medication on 12 July 2010. At post-treatment visit on 22 July 2010, subject reported positive home pregnancy test. A pregnancy test performed in the clinic was also positive. Subject returned for a follow-visit with her parents 4 days later to discuss that she is intending on carrying the pregnancy to term. Estimated delivery date was for (b) (6). No further information regarding pregnancy outcome was available at the time of the sNDA submission.

- Subject AN 00810, a 17 year old multi-racial female who was randomized into the study on 29 June 2011. Subject took both doses of study medication on 15 August 2010. She returned to the clinic for post-treatment visit, including a pregnancy test, on 18 August 2010. The post-treatment pregnancy test was positive. Subject reported her last menstrual period was on (b) (6) Estimated delivery date was for (b) (6). No further information regarding the status of the pregnancy was available.

Long term safety study (P086)
There were 2 pregnancies reported in the long term safety study, P086. Summaries of these cases are presented here:

- Subject AN 20054, a 16 year old white female who enrolled into the study on 19 June 2010. She was stratified to the rizatriptan ODT 10 mg arm of the study. Subject took the first dose of rizatriptan on 24 January 2010. The last dose of study drug was reported to be on 10 October 2010. Subject presented to the clinic on 20 October 2010 for visit #7 and had a positive pregnancy laboratory test on evaluation. Her last menstrual period was (b) (6) and estimated delivery date was for (b) (6) No further information regarding the status of the pregnancy was available.

- Subject AN 20513, a 17 year old white female who was stratified to the rizatriptan 10 mg ODT group. Subject took her first dose of study medication on 7 April 2010. Her last menstrual period was (b) (6). Subject became aware that

she was pregnant on 13 September 2010. Her last dose of study medication was on 14 August 2010. Pregnancy test was confirmed on follow-up clinic visit on 6 October 2010. Her estimated delivery date was for (b) (6)

Additionally, there were a total of 4 pregnancies documented in adolescent subjects taking rizatriptan in the clinical trials conducted on adolescents in support of this sNDA. Again, no conclusions can be drawn from the pregnancy outcomes due to the relatively low numbers of reported cases. Summaries of pregnancy cases in the supportive trials are presented below.

Efficacy study (P059)
There was 1 pregnancy in this acute efficacy study. Subject AN 1447, a 15 year old female, treated a migraine headache with 1 dose of rizatriptan 5 mg tablet. On post-treatment visit (day 17), serum pregnancy test was positive. Subject had an elective abortion of study day 43.

Long term safety study (P059, extension 061)
There were 3 documented pregnancies in this long term study in adolescents who were treated with rizatriptan 5 mg tablet or ODT formulation. One subject (AN 0057), age 17, was randomized into the rizatriptan 5 mg tablet group. This subject had a molar pregnancy requiring a dilation and curettage.

The other 2 pregnancy cases were in the rizatriptan 5 mg ODT group. Subject AN 0030, age 17, delivered a full term healthy baby. Subject 1704 had a spontaneous abortion.

7.6.3 Pediatrics and Assessment of Effects on Growth

A comprehensive review of the literature did not reveal any information regarding rizatriptan use in adolescent subjects that might be inconsistent with the product label for rizatriptan.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
The sponsor defined overdose as taking a second dose of rizatriptan within 24 hours of the first dose. This conservative definition of overdose led to a large number of cases being reported in the long term safety study (P086). Review of the reported overdose cases provided in the submission revealed no incidence of significant clinical consequence.
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There were no cases of overdose from study drug in the PK study (P083) or the efficacy study (P082). Discussions regarding overdose from study drug have been detailed in sections 7.3.3 and 7.3.4 above.

Drug Abuse Potential
While abuse potential of rizatriptan has not been specifically examined in adolescent clinical studies, there have been no reports of drug abuse or drug-seeking behaviors of adolescent subjects in clinical studies. Additionally, postmarketing surveillance of rizatriptan has not detected any signal for abuse potential.

Withdrawal and Rebound
Even though withdrawal effects of rizatriptan have not been specifically examined in adolescent clinical studies, no withdrawal effects of adolescent subjects have been reported in clinical studies or postmarketing surveillance.

Similar to withdrawal effects, rebound effects have not been specifically evaluated in adolescents. Nonetheless, a review of the submitted adolescent clinical trials as well as postmarketing analysis of rizatriptan reveals no evidence of rebound concerns from rizatriptan in adolescents.

7.7 Additional Submissions / Safety Issues

There were no data from submissions other than those noted above.

8 Postmarket Experience

The sponsor conducted a thorough search of all spontaneous reports relevant to the safety of rizatriptan in the pediatric population ($\leq$17 years of age) through the Worldwide Adverse Experience System (WAES) database using Periodic Safety Update Report (PSUR) criteria from the date of first authorization of rizatriptan in 21 January 1998 through 31 December 2010. They identified 77 pediatric reports of which 33 were considered serious. It is not possible to estimate the total rizatriptan exposure in the worldwide pediatric population because rizatriptan sales by patient age are not captured.

Frequently reported events with rizatriptan in the pediatric population were tabulated by the sponsor and are listed in the table below.

Table 45 Frequent Adverse Events in Pediatric Population (17 Years and Younger); Postmarketing Review (21 January 1998 to 31 December 2010

17 Years and Younger	
Event (N=189)	**N (%)**
Drug administration error	10 (5.2%)
Overdose*	9 (4.7%)
Drug ineffective	8 (4.2%)
Off label use	8 (4.2%)
Somnolence*	8 (4.2%)
No adverse event	8 (4.2%)
Accidental overdose	4 (2.1%)
Asthenia*	4 (2.1%)
Dizziness*	4 (2.1%)
Erythema*	4 (2.1%)
Headache*	4 2.1%)
Syncope*	4 (2.1%)
Abdominal discomfort	3 (1.6%)
Migraine	3 (1.6%)
Nausea*	3 (1.6%)
Speech disorder	3 (1.6%)
Accidental exposure	2 (1.1%)
Confusional state	2 (1.1%)
Convulsion*	2 (1.1%)
Dysphagia*	2 (1.1%)

* Considered a listed event in the CCDS for rizatriptan benzoate

(Source: Adapted from Clinical Study Report, module 5.3.6, Table 1)

Distributions of the 77 reports by pediatric age and AEs are as follows:

- 58 reports (75%) are in 13-17 year age group. The 58 reports contained a total of 135 AEs.
- 17 reports (22%) are in the 5-12 year old group. The 17 reports contained 46 AEs.
- 2 reports (3%) are in the 1-4 year old group

In total, there were 181 AEs reported in the pediatric population from the postmarketing review. The system organ class (SOC) with the most AEs was nervous system disorder (43 out of 181 AEs). This was followed by general disorders and administration site conditions (34 out of 181 AEs) and injury, poisoning and procedural complications (32 out of 181 AEs).

Review of the AEs in the 77 reports received by the sponsor revealed no new safety signals associated with rizatriptan use in the pediatric population.

9 Appendices

9.1 Literature Review/References

The sponsor conducted a comprehensive literature search seeking reports in English of the pediatric experience with rizatriptan. They found 3 references in the executed search. Two of the references were studies conducted by the sponsor. The third study was conducted in Finland by Ahonen et al (Neurology 2006; 67:1135–1140). All 3 references have been discussed in the sponsor's submission.

Additionally, I reviewed the extensive literature citations submitted by the sponsor for this sNDA and find them to be appropriate with no data contraindicating use of this product in adolescent migraineurs.

9.2 Labeling Recommendations

See Revised Label from the Agency.

9.3 Advisory Committee Meeting

No advisory committee consideration was needed for this application.

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

/s/

NUSHIN F TODD
09/12/2011

ERIC P BASTINGS
09/12/2011