Clinical Pharmacology Review

PRODUCT (Generic Name):	Rizatriptan benzoate
PRODUCT (Brand Name):	MAXALT-MLT®
sNDA:	20-865/-020
DOSAGE FORM:	Oral Disintegrating Tablet (ODT)
DOSAGE STRENGTHS:	5 mg and 10 mg
INDICATION:	Migraine with or without aura in pediatrics 12 yr and above
NDA TYPE:	supplemental NDA for PWR
SUBMISSION DATE:	3/25/2011
SPONSOR:	Merck Co.
CP REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

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1.0 EXECUTIVE SUMMARY

Rizatriptan, a selective 5-hydroxytryptamine $(5\text{-HT})_{1B/1D}$ agonist, has been approved on June 29, 1998, for the acute treatment of migraine attacks with or without aura in adults at a therapeutic dose of 10 mg or 5 mg. Two formulations of rizatriptan benzoate are available: solid tablets (MAXALT™, NDA 20-864) and orally disintegrating tablets (MAXALT-MLT™, NDA 20-865).

This application was submitted as a supplement to NDA 20-865 (Maxalt-MLT™, orally disintegrating tablet, ODT) for the acute treatment of migraine in patients from 12 through 17 years of age. A body weight-based dosing regimen is proposed: <40 kg (88 lb), 5 mg single dose will be prescribed; ≥ 40 kg (88 lb), 10 mg single dose will be administered. Efficacy and safety of more than one dose within 24 hours have not been evaluated.

This sNDA fulfills the requirements described in the amended Pediatric Written Request (PWR) issued on January 13, 2010, which requested three types of studies: safety/tolerability/pharmacokinetic study, pediatric efficacy study and pediatric long-term safety study in pediatric migraineurs 12 to 17 years of age with a history of migraine headaches. The sponsor has conducted three clinical studies in pediatric migraineurs: a single-dose PK study (083), an acute efficacy and safety study (082) and a long-term safety study (086), all using the ODT formulation and the same body weight-based dosing regimen as proposed above in the labeling.

In addition, data from several previously conducted pediatric studies in which the tablet formulation was used provide additional supportive PK, safety and efficacy information for this application. These studies include 2 PK studies (048 and 062), 2 efficacy studies (054 and 059) and 2 safety studies (059 extension and 061).

The Overall Clinical Pharmacology Summary is provided in Section 1.3.

1.1 RECOMMENDATION

The sNDA is acceptable from a Clinical Pharmacology perspective provided the agreement is reached for the Labeling recommendations with the sponsor. With this sNDA, the sponsor has fulfilled the requirements described in the amended Pediatric Written Request dated January 13, 2010.

1.2 PHASE IV COMMITMENT

No PMR/PMC.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

- The dose-normalized $AUC_{0\text{-}inf}$ and C_{max} of rizatriptan after a single dose of ODT were lower in heavier pediatric patients, indicating that a higher dose is needed in these patients to maintain the same level of exposure as in patients with lower weights.
- Results of PK study 083 supported a body weight cut-off at 40 kg, i.e, for patients ≥ 40kg, 10 mg ODT is administered; for patients < 40kg, 5 mg ODT is given. With such body weight-based dose adjustment, both weight groups had similar C_{max} compared to the historical data in adults receiving 10 mg ODT. The $AUC_{0\text{-}inf}$ in subgroup ≥ 40kg was 17% higher than that in adults, while the $AUC_{0\text{-}inf}$ in subgroup < 40kg was 15% lower. However, considering that rizatriptan is used as acute treatment, its C_{max} may be more relevant to the effectiveness.

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2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

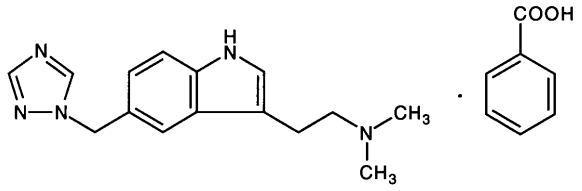
Dosage Form/Strengths/Route: Oral Disintegrating Tablet (ODT), 5 and 10 mg, Oral

Indication: Migraine with or without aura in pediatrics aged 12 years and above

Dosage and administration (Sponsor's Proposed):
Pediatric patients 12 to 17 years: <40 kg (88 lb), 5 mg single dose; ≥40 kg (88 lb), 10 mg single dose; efficacy and safety of more than one dose within 24 hours have not been evaluated.

Pharmacologic Class: Selective 5-$HT_{1B/1D}$ receptor agonist

Chemical Name: *N*,*N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate,
Mol Wt: 269.4 (free base)



Other Names: MK-0462

Physical Characteristics: White to off-white, crystalline solid

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

Mechanism of action: Rizatriptan binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} receptors. Rizatriptan has weak affinity for other 5-HT_1 receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT_7 receptor, but has no significant activity at 5-HT_2, 5-HT_3, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

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.

Formulation: Orally disintegrating tablet

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

Three clinical studies were submitted under this sNDA to fulfill the requirements described in the amended Pediatric Written Request (PWR) dated January 13, 2010. Body weight-based dosing regimen was applied in all the 3 studies, i.e, 5 mg ODT for patients <40kg and 10 mg ODT for patients ≥40 kg.

PK study – 083 (6-17 yr migraineurs)
Efficacy study – 082 (12-17 yr migraineurs)
Safety study – 086 (12-17 yr migraineurs)

In addition, there are 5 studies done earlier in 12-17 yr pediatric patients and may provide some supportive evidence.

PK studies – 048 (single dose Tablet, 10 mg)
– 062 (single dose ODT and Tablet, 5 mg)
Efficacy studies – 054 and 059 (Tablet 5 mg)
Safety studies – 059 extension and 061 (Tablet and ODT)

Clinical Pharmacology Study:
Study 083 was a randomized, double-blind, placebo-controlled, parallel panel, single-dose study involving 6 to 17 year old migraineurs. The study was performed between acute migraine attacks. It had three panels.

Subject	Panel A	Panel B
n = 3	Placebo	placebo
n = 9	5 mg rizatriptan	10 mg rizatriptan

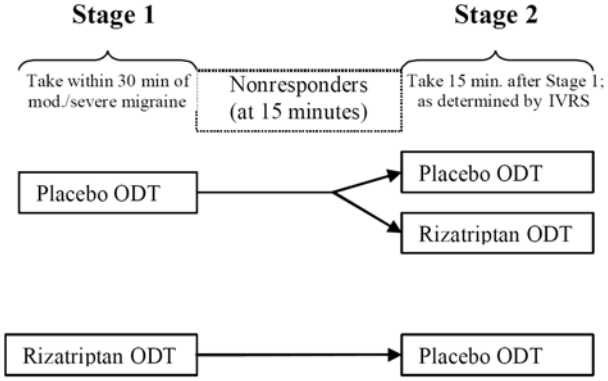
Subject	Panel C
n = 1	placebo
n = 5	5 mg or 10 mg rizatriptan

In Panel A, subjects weighted 20-39 kg and thus received a 5 mg dose of rizatriptan ODT (or placebo). In Panel B, subjects weighted 40 kg or above and received a 10 mg ODT (or placebo). Study drug was administered in the fasted state without liquid. The only difference

from the above table is that eventually 13 subjects were enrolled in Panel B, with 10 subjects receiving rizatriptan and 3 subjects receiving placebo.

Amendment 01: Panel C was added to the study by amendment in order to increase the number of male subjects in the 12-17 year old group. In Panel C, subjects weighing 20-39.9 kg received a 5 mg ODT (or placebo) and subjects weighing 40 kg and above received a 10 mg ODT (or placebo). Six subjects were randomized to rizatriptan or placebo in a ratio of 5:1. Study drug was administered as in Panels A and B.

Efficacy Trial:
Study 082 was a randomized, double-blind, placebo-controlled, parallel group study, using the same body weight-based dosing as study 083.



Stage 1 was designed to identify and exclude placebo responders from the primary efficacy analysis. Patients were randomized in 20:1 ratio to placebo or rizatriptan to treat a single migraine attack during Stage 1. After 15 minutes, patients who reported mild or no pain (i.e., responders) were instructed to take no further study medication. Patients who reported moderate or severe pain (i.e., non-responders) during Stage 1 were instructed to take study medication in Stage 2.

During Stage 2, non-responders who received placebo in Stage 1 were randomized in a 1:1 ratio to rizatriptan or placebo, with randomization stratified based on age (6 to 11 years old vs. 12 to 17 years old) and migraine intensity reported at 15 minutes post Stage 1 dose (moderate vs. severe). The migraine intensity reported at 15 minutes post Stage 1 dose was used as the Stage 2 baseline pain severity. Non-responders who received rizatriptan in Stage 1 were allocated to receive placebo in Stage 2.

Analysis of efficacy data was based on the Full Analysis Set (FAS) population, which only included patients who did not respond to placebo at Stage 1 and were randomized to Stage 2.

Reviewer's Comment: The purpose of this enrichment design is to reduce the high placebo response observed in two previous efficacy trials in pediatrics (054 and 059). Neither of the trials showed superiority of 5 mg rizatriptan tablet to placebo.

The failure may be due to high placebo response rate. For the endpoint of pain relief at 2 hr post-dose, the placebo response rate was 56-69% in trials 054 and 059, much higher than the one seen in adults trials (23-40%), while the drug effects were similar (66-68% in 054 and

059 vs. 60-63% in adults trials). For the endpoint of pain free at 2 hr post-dose, the placebo response was 28-31% in adolescents (054 and 059), also much higher than the one observed in adults trials (around or <10%), while the drug effects were similar (32-39% in 054 and 059 vs. 25-33% in adults) [Please refer to the current labeling of MAXALT for efficacy results of the adults trials]. The higher placebo response in pediatrics may be due to shorter duration of migraine in children. Typically, in children, migraines last less than 4 hours (vary from 30 minutes to 48 hours). In adults, migraine attacks last from 4 to 72 hours. The attacks in adults are typically 4 hours or more.

As shown in the Table below, the run-in phase (Stage 1) utilized in the new efficacy trial 082 helped reduce the placebo response rate, compared to studies 054 and 059. However, the placebo response is still higher than adult trials.

Table 1. Summary of Primary and Secondary Endpoints in 12-17 Year-Old Age Group in Study 082 (FAS Approach)

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)		
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 5mg or 10mg.
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.

Another difference between study 082 and the previous trials 054 and 059 is that 082 enrolled patients who have not, historically, achieved satisfactory response to treatment with non-steroidal analgesics (NSAIDs) or acetaminophen (APAP). Simple analgesics such as acetaminophen and NSAIDs are successful in 40-70% of migraine patients.

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

Primary efficacy endpoint in study 082 was pain freedom at 2 hr post-dose, defined as a reduction in headache severity from Face 5/4/3 (moderate or severe) at Stage 2 baseline to Face 1 (no pain). Patients were asked to complete a paper migraine diary at pre-specified time points to evaluate efficacy and tolerability. Migraine pain intensity was assessed using a 5-Face Pain Scale in which children and adolescents are asked to mark on the face that best represents their pain intensity level, ranging from "no pain" to "very bad pain".

Face 1 = no pain; Face 2 = mild pain; Face 3 to 4 = moderate pain; Face 5 = severe pain.

Secondary efficacy endpoint was pain relief at 2 hr post-dose, defined as a reduction in headache severity from Face 5/4/3 (moderate or severe) at Stage 2 baseline to Face 2/1 (no or mild pain). Pain relief was also assessed using the 5-Face Pain Scale.

Reviewer's Comment:
Selection of the primary endpoint
In the previous adult trials and study 059, pain relief at 2 hr was used as the primary endpoint. In study 054, pain freedom was utilized as the primary endpoint. According to the sponsor, pain freedom was used as the primary endpoint in study 082, because

1. Proposed new International Headache Society (IHS) guidelines recommended the use of pain-free as primary endpoint in future clinical trials with investigational migraine compounds.
2. Adolescents might find it difficult to differentiate between grades of pain, due to confounding non-headache symptoms. It was expected to be easier for them to determine that their headache had completely gone. This may lead to less placebo effect compared to the case where pain relief is used as primary endpoint.

In addition, based on the 2 failed pediatric trials, 059 almost showed superiority of rizatriptan treatment to placebo in terms of pain freedom ($p = 0.053$).

As shown in the Table 1 above, study 082 demonstrated superiority of rizatriptan ODT to placebo as measured by the proportion of patients reporting pain freedom at 2 hr post-dose but not pain relief. The results suggest that besides the enrichment study design to remove placebo responders, the selection of the primary endpoint is also critical.

Method used to measure the endpoints
In the previous adults efficacy trials and 2 failed adolescents trials, 4-point scale was used to measure headache pain intensity, 0 = no headache; 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Pain freedom was defined as a reduction of headache severity from Grades 2 or 3 (moderate or severe) at baseline to Grade 0 (no headache). Pain relief was defined as a reduction of headache severity from Grades 2/3 at baseline to Grades 0/1 (no headache/mild pain).

In the new efficacy trial 082, 5-Face Pain Scale was used. It is intended to present a scale similar to the four-point, verbal categorical rating scale used in adults. According to the sponsor, the 5-Face Scale is acceptable to the younger as well as older age group and will allow for the pooling of data across the 6 to 17 year old population and planned statistical analyses. It should be noted that the target population covered under the original PWR dated

on March 6th, 2009 is pediatrics across 6-17 yr old. Although this was changed to adolescents (12-17 yr) by the amended PWR issued on January 13, 2010, the efficacy study in 6 -11 yr children is still ongoing as part of the study 082 and may be the subject of a future sNDA.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

The exposure-effectiveness relationship has not been explored, since no PK samples were taken during the efficacy trial 082.

Reviewer's Comment:
Dosing regimen of efficacy trial 082
Rizatriptan was approved in adults at dose levels of 5 mg and 10 mg for both tablet and ODT formulations, while 2.5 mg was not different from placebo. 10 mg has slightly greater effect than 5 mg. [Please refer to the current labeling of MAXALT and MAXALT-MLT for efficacy results of the adults trials].

The two failed pediatric efficacy trials 054 and 059 used 5 mg tablet. The failure may be partially due to inadequate exposure of rizatriptan especially in heavier subjects. Therefore, the new efficacy trial 082 targeted on a higher dose and a body weight-based dosing regimen was applied trying to match the exposure of 10 mg rizatriptan in adults, i.e, for patients ≥40 kg, 10 mg ODT was administered; for patients <40kg, 5 mg ODT was given.

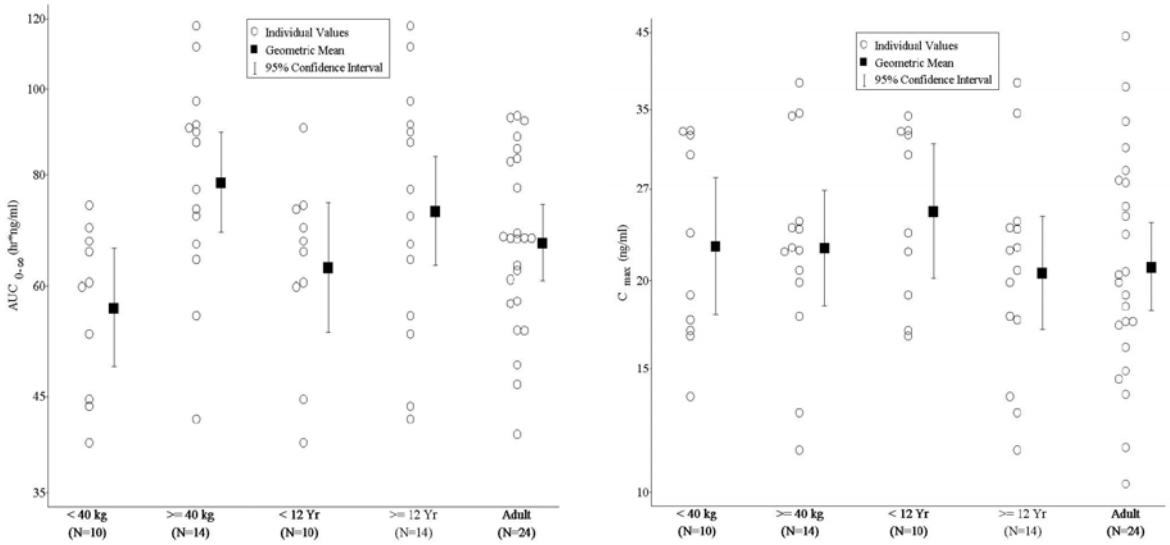
The body weight-based dose adjustment was supported by
1. **Off-label use:** 73% of the adolescents (age 11-18) were prescribed a 10 mg dose. The 5mg dose was most commonly prescribed for children <11 years old (69%) [from previous medical officer, Dr. Teresa A. Podruchny's review under IND 40,458]. Based on the growth charts released by CDC in 2000, 40-42 kg is the median value of body weight for 12 yr children.

2. **Literature report**: The same body weight-based dosing strategy was applied for pediatrics (6-17 yr) in a literature study, where a significant treatment effect was demonstrated for both doses (Ahonen K, et.al. Neurology. 2006 Oct 10;67(7):1135-40). (It should be noted that the efficacy endpoint is headache relief by two grades on a five-grade face scale at 2 hours, different from study 082).

3. **PK study 083:** The same body weight-based dosing regimen was used for pediatrics (6-17 yr). As shown in the figures below, in the <40 kg group dosed with 5 mg ODT, $AUC_{(0-\infty)}$ values were 15% lower than in adults dosed with 10 mg ODT (historical data from study 070), but the C_{max} values were similar. In the ≥40 kg group dosed with 10 mg rizatriptan, $AUC_{(0-\infty)}$ values were 17% higher than in adults dosed with 10 mg, but the C_{max} values were similar. As acute treatment, C_{max} of rizatriptan may be more relevant to its effectiveness than $AUC_{(0-\infty)}$.

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 (Protocol 070)



Universal dose of 10 mg vs. Body weight-based dosing regimen

The age range of the target population under this submission is 12-17 yr old. Very few subjects in this age group have body weight less than 40kg. There were discussions about whether it is appropriate to administer the same dose 10 mg to everyone rather than use the body weight-based dose adjustment. The universal dosing regimen seems to be supported by the findings from study 082 where the subgroup < 40kg did not show significant drug treatment effect against placebo as measured by pain freedom.

Table 2. Number (%) of Patients Reporting Pain Freedom at 2 Hours Post Stage 2 Dose for the 12-17 Year Age Group FAS Approach

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

However, the failure for this subgroup <40kg is due to much higher placebo effect (38.1%) than the subgroup ≥40 kg instead of less drug effect. Thus, it may not be helpful by simply increasing the dose from 5 mg to 10 mg for the subgroup < 40kg. Actually, the effect in drug treatment arm was slightly higher in the subgroup < 40kg than ≥40 kg subgroup, indicating that enough exposure of drug has been achieved in these lighter patients. This is also supported by the results for the secondary endpoint – pain relief.

Table 3. Number (%) of Patients Reporting Pain Relief at 2 Hours Post Stage 2 Dose for the 12-17 Year Age Group FAS Approach

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

It should also be noted that the number of subjects in the subgroup < 40kg is very limited.

In addition, 10 mg was never tested in patients < 40kg in the studies conducted by the sponsor. Though most of the patients in study 082 had body weight ≥ 40 kg or close to, there were still a few subjects with body weight away from 40 kg, e.g, 7 subjects enrolled in U.S. sites having body weight between 30 to 33 kg. Based on the results of PK study 083, it is expected that, for these patients, an increase of dose from 5 mg to 10 mg may lead to exposure (AUC and C_{max}) falling beyond the upper limit of current known range (refer to Section 2.3.1.7 and Figure 6). Thus, the safety profile is unknown with 10 mg rizatriptan ODT administered to this less weighted subgroup.

Whether 5 mg dose has effect in adolescent patients?
Two previous efficacy trials using 5 mg tablet failed to demonstrate effectiveness of rizatriptan in adolescent migraineurs. 5 mg dose was not re-tested in study 082. Considering that there are a number of changes in study 082 compared to those two trials, including adopting enrichment design, choosing pain freedom as the primary endpoint and using different measurement scale of pain intensity, it is possible that 5 mg dose may also has better efficacy than placebo if it were tested in trial 082. In adults, both 10 mg and 5 mg were effective. However, caution needs to be taken when extrapolating the findings in adults to pediatric migraineurs. There are several differences between adult and pediatric migraine symptoms, inducing a shorter duration of migraine attack in pediatric patients. Therefore, without clinical results it is difficult to conclude whether 5 mg rizatriptan has efficacy in pediatrics.

In summary, the body weight-based dosing regimen proposed by the sponsor is acceptable.

Formulation used in efficacy trial 082
Rizatriptan tablet was used in the previous pediatric trials 054 and 059. This sNDA submission is for rizatriptan ODT. Some migraine suffers may experience difficulty swallowing liquids during a migraine attack. ODT dissolves rapidly in the mouth and can be taken without liquids, and may be advantageous in pediatrics. Per the IMS Health National Prescription Audit (NPA) Plus database (2009), for off-label use of rizatriptan in pediatrics patients, the ODT formulation accounts for slightly more than half of the prescriptions.

2.2.4 What are the characteristics of exposure-safety relationships?

The relationship between exposure and safety for rizatriptan has not been explored, since no PK samples were collected from efficacy and safety trials.

Treatment with rizatriptan was generally well tolerated in adolescent patients. The incidences of adverse events were generally comparable between rizatriptan and placebo. The most

common adverse events were somnolence, nausea, fatigue, abdominal pain, and dizziness. No patient was discontinued due to an adverse event.

Table 4. Number (%) of Patients with Specific Adverse Events (Within 24 Hours Post-dose) by System Organ Class (Count ≥ 4 in One or More Treatment Groups) for the 12 to 17 Year Age Group All Patients as Treated

	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.

2.2.7 What are the general ADME characteristics of rizatriptan?

Please refer to the labeling of MAXALT and MXALT-MLT for the ADME characteristics of rizatriptan. The key features of rizatriptan ODT taken without water in pediatrics are summarized below:

- The median T_{max} values range from 0.8 to 1.7 hr, similar to adults.
- Tablet (5 mg) is bioequivalent ($AUC_{(0-\infty)}$ and C_{max}) to ODT (5 mg) taken without liquid.
- The terminal half-life ($t_{1/2}$) is about 1.6 hr, similar to adults.

2.2.8 What are the basic pharmacokinetic parameters of Rizatriptan after single and multiple doses?

Single Dose Pharmacokinetics:

Single dose PK of rizatriptan was assessed for 5 and 10 mg ODT taken without liquid and also 5 mg tablet in PK studies 062 and 083. The PK of ODT taken with water is not characterized in pediatrics.

Study 062 is a crossover study conducted in adolescents aged 12 -17 yr old and weighted > 40kg except one male subject (38kg, 12 yr).

Table 5. Summary Statistics for Rizatriptan Pharmacokinetic Parameters Following Single Dose Administration of Rizatripatan ODT 5 mg (study 062 adolescents, without water), Tablet 5 mg (study 062 adolescents), or ODT 10 mg (study 070 adults, without water)

Formulation	N	$AUC_{(0-\infty)}$† (hr•ng/mL)	C_{max}† (ng/mL)	T_{max}‡ (hr)	Apparent $t_{1/2}$§ (hr)
MK-0462 PN062 ODT (5mg)	34	30.46 (27.34, 33.93)	9.97 (8.83, 11.25)	0.8 (0.3, 3.0)	1.6 (0.3)
Female	19	34.48 (11.42)	11.27 (4.24)	1.5 (0.3, 3.0)	1.6 (0.3)
Male	15	29.12 (9.16)	9.54 (2.28)	0.8 (0.5, 3.0)	1.6 (0.3)
MK-0462 PN062 Tablet (5mg)	34	30.40 (27.29, 33.87)	10.66 (9.44, 12.03)	0.8 (0.5, 3.0)	1.5 (0.3)
Female	19	35.48 (11.97)	12.17 (4.68)	0.8 (0.5, 3.0)	1.6 (0.3)
Male	15	28.20 (9.45)	10.46 (3.84)	0.8 (0.5, 1.8)	1.5 (0.3)
MK-0462 PN070 ODT (10mg)	24	67.04 (58.96, 76.24)	20.94 (18.13, 24.18)	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)

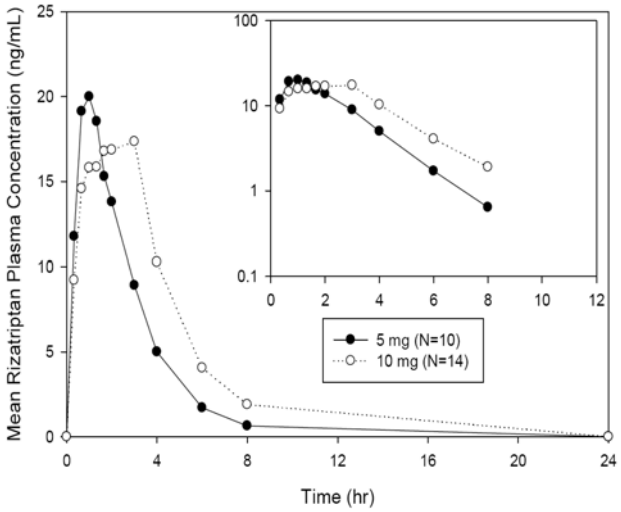
† Geometric mean back-transformed from log scale (95% CI). Mean and SD for Female and Male groups
‡ Median (Minimum, Maximum).
§ Harmonic mean (Jackknife SD).

- ODT taken without water has similar PK to Tablet regardless of gender.
- $AUC_{(0-\infty)}$ and C_{max} in adolescents were about half of the corresponding values in adults receiving 10 mg ODT (also taken without water).

Study 083 was conducted in pediatric patients aged 6 – 17 yr with body weight-based dosing regimen.

As mentioned in section 2.2.3 and also shown in the table below, C_{max} achieved in pediatrics weighted < 40kg and receiving 5 mg ODT and patients ≥ 40kg and administered with 10 mg ODT was similar to that in adults taking 10 mg ODT (historical data, study 070). $AUC_{(0-\infty)}$ was 17% higher in subgroup ≥ 40kg than adults and 15% lower in subgroup < 40kg. ODT was taken without water.

Figure 2. Mean Plasma Concentration-Time Profile of Rizatriptan Following Administration of a Single Oral Rizatriptan ODT Dose (without water) in Migraineurs Aged 6 to 17 Years (Panel A, Panel B and Panel C)‡ (Insert: Semi-Log Scale)



‡ Panel A: Single oral 5 mg rizatriptan ODT dose in patients weighing 20-39 kg;
Panel B: Single oral 10 mg rizatriptan ODT dose in patients weighing 40 kg and above;
Panel C: Single oral 5 mg rizatriptan ODT dose in patients weighing 20-39 kg or single oral 10 mg rizatriptan ODT dose in patients weighing 40 kg and above

Table 6. Summary Statistics for Rizatriptan Pharmacokinetic Parameters 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 (Protocol 070)

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 ODT dose, without water).

‖ 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 mixed 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.

The exposure of rizatriptan in pediatrics was also compared to adults in terms of age groups. For subgroup ≥ 12 yr, the $AUC_{(0-\infty)}$ and C_{max} were similar to adults. For subgroup < 12 yr, $AUC_{(0-\infty)}$ was similar, while C_{max} was slightly higher than adults.

Multiple Dose Pharmacokinetics:
Not relevant.

2.2.9 Do the pharmacokinetic parameters change with time following chronic dosing?

Rizatriptan is for acute treatment of migraine. Chronic dosing is not relevant. The $t_{1/2}$ of rizatriptan is very short (~ 1.6 hr).

2.2.10 What is the variability in the PK data?

The CV% of C_{max} and $AUC_{(0-\infty)}$ of rizatriptan was around 30% in pediatrics for ODT (without water) and tablet formulations.

Table 7. Summary Statistics for Rizatriptan $AUC_{(0-\infty)}$ and C_{max} (Arithmetic Mean, Standard Deviation, and Coefficient of Variation) Following Single Dose Administration of Rizatriptan ODT 5 mg or 10 mg in Pediatric Migraineurs Ages 6 to <12 Years and 12 – 17 Years (study 083), and in Healthy Adult Subjects (study 070)

Population	N	$AUC_{(0-\infty)}$(hr•ng/mL)			C_{max} (ng/mL)		
		Mean	SD	CV%	Mean	SD	CV%
Adult	24	68.73	15.36	23.31	22.35	8.45	37.99
Children < 12 yr	10	64.52	14.55	24.52	26.02	7.08	29.42
Children ≥12 yr	14	76.38	23.79	33.35	21.66	7.52	34.90

Mean: Arithmetic Mean; SD: Standard Deviation; Coefficient of Variation (CV%) is calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale.

Table 8. Summary Statistics for Rizatriptan $AUC_{(0-\infty)}$ and C_{max} (Arithmetic Mean, Standard Deviation, and Coefficient of Variation) Following Single Dose Administration of Rizatriptan ODT 5 mg (without water) or Tablet 5 mg in Pediatric Migraineurs Ages 12-17 Years (study 062)

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

2.2.11 How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients?

Study 062 and 083 were conducted in pediatric patients between acute migraine attacks. Per the labeling of MAXALT and MAXALT-MLT, the presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan in adults.

2.2.12 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

According to the Clinical Pharmacology review documented by Dr. Ta-chen Wu for IND 40,458, plasma levels of rizatriptan increased slightly more than dose-proportional in adults. Due to the limited number of subjects aged 12-17 yr in study 083 and the nature of cross-study comparison between 083 and 062, it is difficult to make definite conclusion, though it appears that the exposure in adolescents increased more than dose-proportional, especially for $AUC_{(0-\infty)}$.

Table 9. Comparisons of $AUC_{(0-\infty)}$ and C_{max} of rizatriptan following a single dose of 10 mg ODT (without water) to pediatric patients aged 12-17 yr in Study 083 and a single dose of 5 mg ODT (without water) to pediatric migraineurs aged 12-17 yr in Study 062.

PK parameter	Female (≥ 12 yr)			Male (≥ 12 yr)		
	083 (n=5)	062 (N=19)	Ratio	083 (n=7)	062 (N=15)	Ratio
AUC0-∞ (hr•ng/ml)	81.48±21.19	34.48±11.42	2.36	80.71±24.82	29.12±9.16	2.77
Cmax (ng/ml)	24.46±8.05	11.27±4.24	2.17	21.37±7.69	9.54±2.28	2.24

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

2.3.1.3 Effect of age:

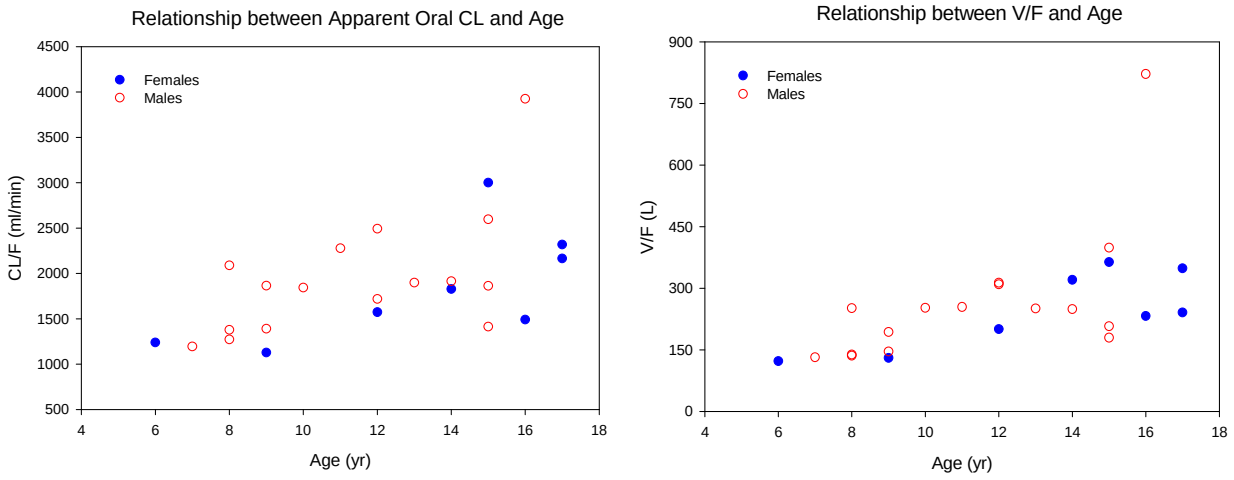
There is a trend that CL/F and V/F increase along with age. This may be due to the increase of body weight.

Table 10. Summary Pharmacokinetic Parameters (CL/F and V/F) Following Administration of a Single Oral 5 mg Rizatriptan ODT Dose or a Single Oral 10 mg Rizatriptan ODT Dose in Pediatric Migraineurs Ages 6 - <12 Years

6 to <12 years old (n = 10)	Apparent CL (CL/F) (mL/min)	Apparent V (V/F) (L)
AM (SD), Total	1567.30 (413.13)	175.67 (56.54)
AM (SD), Male	1663.53 (407.01)	187.97 (56.93)
AM (SD), Female	1182.38 (78.06)	126.46 (5.41)
AM: Arithmetic Mean; SD: Standard Deviation		

12 to 17 years old (n = 14)	Apparent CL (CL/F) (mL/min)	Apparent V (V_z/F) (L)
AM (SD), Total	2156.87 (680.47)	316.90 (159.57)
AM (SD), Male	2227.65 (788.20)	341.29 (205.82)
AM (SD), Female	2062.49 (561.64)	284.38 (68.39)
AM: Arithmetic Mean; SD: Standard Deviation		

Figure 3. Relationship between CL/F or V/F and age based on individual data from study 083 where 5 or 10 mg ODT was administered to pediatric patients < 40kg or ≥ 40kg, respectively.



Dosage adjustment is not based on age but rather on body weight.

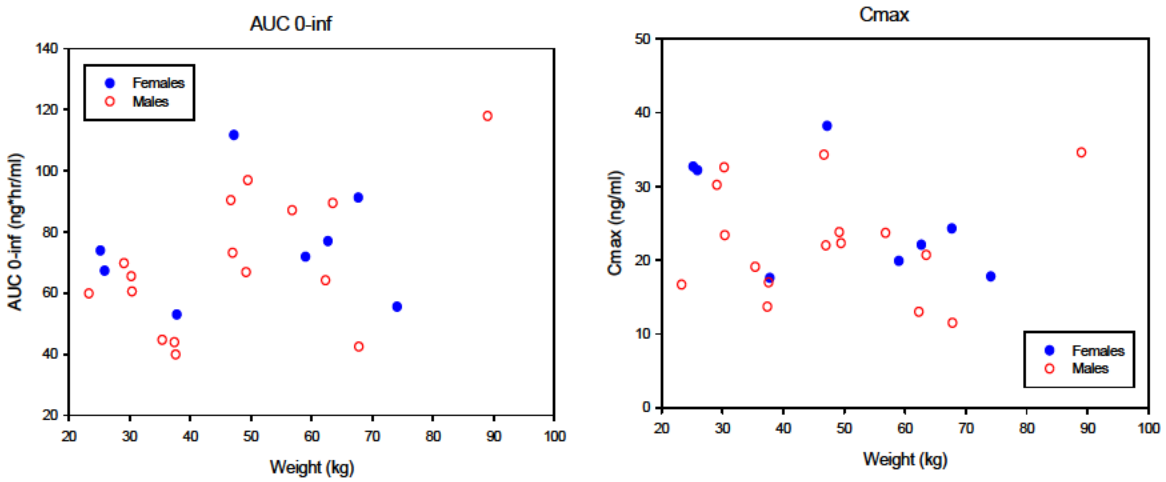
2.3.1.4 Effect of Gender:

The exposure of rizatriptan was about 20% higher in females than males. This is similar to that observed in adults where females have 30% higher $AUC_{(0-\infty)}$ and 11% higher C_{max} than males.

In study 062, the $AUC_{(0-\infty)}$ and C_{max} of rizatriptan following a single dose of 5 mg ODT was about 18% higher in females than males (refer to Table 7 under section 2.2.10).

In study 083, for the subgroup < 40kg and receiving 5 mg ODT, the $AUC_{(0-\infty)}$ and C_{max} of rizatriptan were 18% and 26% higher in females than in males, respectively. For the subgroup ≥ 40kg and administered with 10 mg ODT, the exposure is similar between females and males. However, it should be noted the number of subjects is limited especially for female sub-categories (Refer to Table 5 under section 2.28 and the Figure below).

Figure 4. Distribution of $AUC_{(0-\infty)}$ and C_{max} along with weight in female and male pediatric migraineurs aged 6 – 17yr and received 5 or 10 mg rizatriptan ODT (study 083)



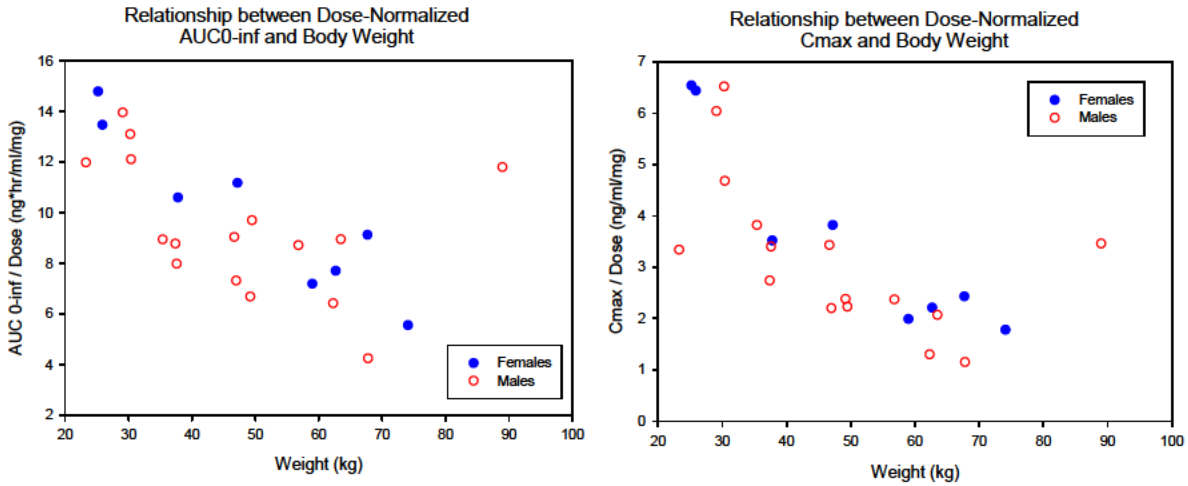
Higher exposure of rizatriptan in females was also observed following administration of tablet formulation. In study 062, the $AUC_{(0-\infty)}$ and C_{max} of rizatriptan following a 5 mg dose were 26% and 16% higher in females as compared to males, respectively. In study 048, a single dose of 10 mg tablet was administered to adolescent patients (12-17 yr) and females had about 50% higher $AUC_{(0-\infty)}$ and 28% higher C_{max} than males.

Dose adjustment: No. The ~20% increase of exposure in females has no significant clinical impact.

2.3.1.7 Body Weight:

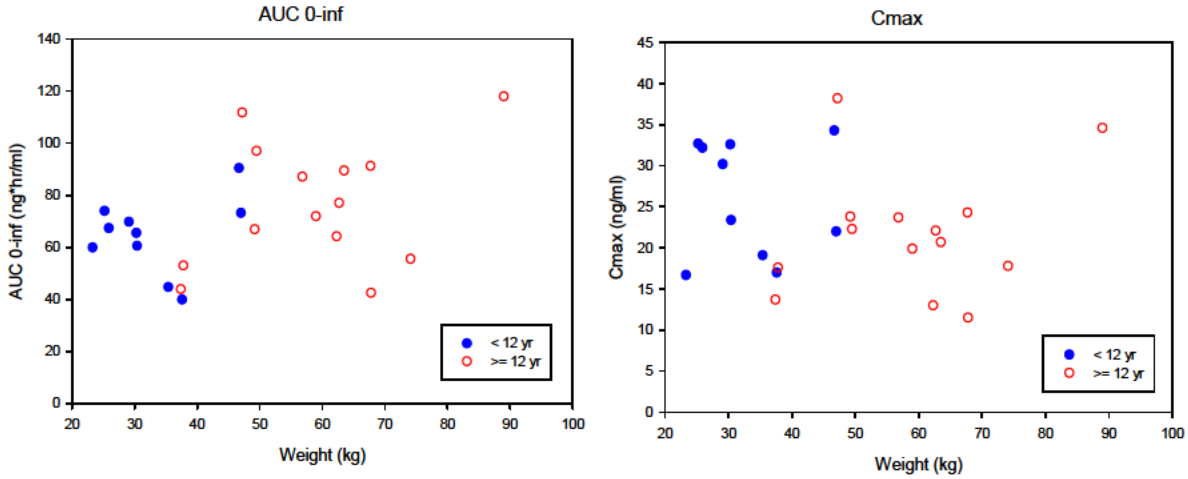
An inverse relationship between exposure (dose normalized $AUC_{(0-\infty)}$ or C_{max}) and weight was observed and more apparent at lower body weights. Lower $AUC_{(0-\infty)}$/Dose at larger weights may be due to increase of oral clearance (CL/F) of rizatriptan along with increase of body weight.

Figure 5. Relationship Between Dose-Normalized $AUC_{(0-\infty)}$ or Dose-Normalized C_{max} and Weight Following Administration of Rizatriptan ODT to Pediatric Patients Aged 6 to 17 Years (Study 083)



Dose Adjustment: The relationship between rizatriptan exposure and body weight suggests that a lower dose is needed in patients with lower body weights to match the exposure in patients with higher weights. As shown in the figures below, the PK results of study 083 supports a body weight cut-off of 40 kg, i.e, for patients ≥40 kg, 10 mg ODT will be administered; for patients < 40kg, 5 mg ODT will be prescribed.

Figure 6. Relationship Between $AUC_{(0-\infty)}$ or C_{max} and Weight Following Administration of Rizatriptan ODT to Pediatric Patients Aged 6 to 17 Years (Study 083)



The $AUC_{(0-\infty)}$ is 28% lower in patients < 40kg than patients ≥40 kg. However, as acute treatment, efficacy of rizatriptan may be more relevant with its C_{max}, which is similar between the < 40kg and ≥40 kg groups. As shown in Figure 1 under Section 2.2.3, the C_{max} in either weight group is similar to the historical data in adults receiving 10 mg ODT.

In conclusion, the body weight-based dosing regimen proposed by the sponsor is acceptable.

2.4 EXTRINSIC FACTORS

2.5 GENERAL BIOPHARMACEUTICS

2.5.2 Is the proposed to-be-marketed formulation of Rizatriptan bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

Rizatriptan ODT is the to-be-marketed product for pediatric migraineurs. ODT was used in PK study 083, Efficacy study 082 and Safety study 086.

2.5.3 Has relative bioavailability been established with any other formulation? If yes, are they bioequivalent?

Pediatric Study:
Study 062 was an open-label, single-dose, balanced, randomized, 2-period crossover study in adolescent migraineurs (12 – 17 yr) to determine the bioequivalence of a 5 mg rizatriptan tablet compared to 5 mg rizatriptan ODT (taken without water). The sponsor did not conduct a formal BE analysis for this study. As discussed under section 2.2.8, tablet has similar PK to ODT. It appears that the two formulations are bioequivalent. The geometric mean ratio (GMR) of ODT to tablet and its 90% CI in females is: 97.84% [92.12, 103.92] for $AUC_{(0-\infty)}$ and 94% [80.60, 109.63] for C_{max}. The corresponding values in males are: 103.06% [95.72, 110.96] for $AUC_{(0-\infty)}$ and 92.7% [81.90, 104.92] for C_{max}. However, rizatriptan tablet is not proposed for prescription in pediatric patients.

Adult Study 042:
The finding in study 062 is similar to that of a previous study in adults, where 5 mg and 10 mg ODT (without water) and tablet were administered to 12 female subjects in a crossover manner.

Table 11. Pharmacokinetic Parameters ($AUC_{(0-\infty)}$, C_{max}) for Rizatriptan 5-mg Tablet and RAPIDISC™ (Orally Disintegrating Tablet, without water) in Adult Females (N=12) (Study 042)

	Geometric Mean		Geometric Mean Ratio (RAPIDISC™/ Tablet)	90% Confidence Interval	p-Value
	Rizatriptan 5-mg Tablet	Rizatriptan 5-mg RAPIDISC™			
$AUC_{(0-\infty)}$ (ng•hr/mL)[a]	32.37	31.86	0.98	(0.91, 1.07)	0.743
C_{max} (ng/mL)[a]	9.75	10.39	1.07	(0.92, 1.23)	0.460
[a] Potency-normalized.					

The extent and rate of absorption were also similar between 10 mg ODT (without water) and Tablet.

PK parameter (Mean ± SD)	Tablet (5 mg)	ODT (5mg)	Tablet (10 mg)	ODT (10 mg)
AUCinf (ng•hr/ml)	34.5 ± 13.0	33.2 ± 9.8	73.9 ± 23.4	75.9 ± 24.7
Cmax (ng/ml)	10.4 ± 3.9	11.1 ± 4.7	21.3 ± 6.9	20.3 ± 7.9
Tmax (hr)	1.0 ± 0.6	1.6 ± 0.8	1.5 ± 0.8	2.5 ± 1.4

Adult Study 070:

However, ODT taken without water was shown to have lower C_{max} than tablet and thus did not meet BE criteria in another adult study (070, Swan S, et al. J Clin Pharmacol. 2006 Feb; 46(2):172-8). The GMR of ODT (without water) to tablet for C_{max} and its 90% CI are 0.77 [0.69, 0.86]. Instead, ODT taken with liquid was demonstrated to be BE to tablet in that study.

Figure 7. 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) (Study 070)

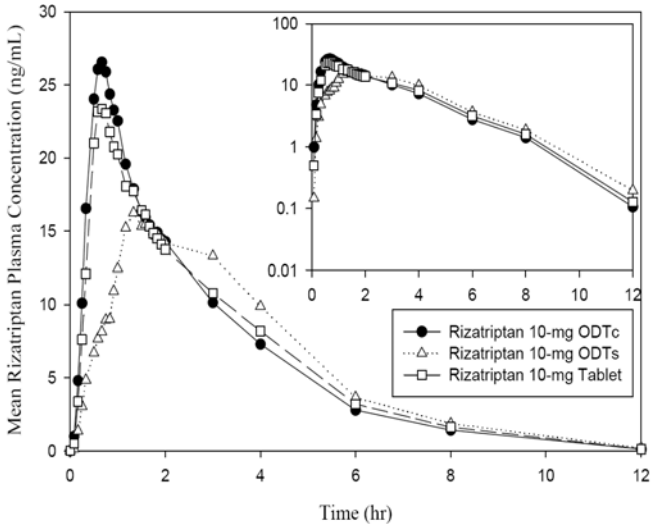


Table 12. Overall Pharmacokinetic Summary of Study 070

Endpoints	Rizatriptan 10-mg (N=24) ODTc	ODTs	Tablet	ODTc/ODTs Ratio (90% CI)	ODTc/Tablet Ratio (90% CI)
Primary					
Geometric Mean† (hr*ng/mL)					
AUC 0-1 hour	17.07	2.92	13.32		1.28 (0.79, 2.09)
AUC 0-2 hours	33.84	18.83	30.03	1.80‡ (1.53, 2.12)	
Secondary					
T_{max} (hours)					
Median	0.67	1.33§	0.67		
Mean	0.74	1.58	0.84		
Exploratory					
Geometric Mean† (ng/mL)					
$AUC_{0-\infty}$ (hr*ng/mL)	69.94	66.13	69.88	1.06†† (1.01, 1.10)	1.00 (0.96, 1.04)
C_{max} (ng/mL)	29.07	20.94	27.29	1.39‡ (1.24, 1.56)	1.07 (0.95, 1.20)

† Analysis of variance least square mean after adjusting for subject (random effect), dosing regimen, and period.

‡ ODTc vs. ODTs , p<0.001 based on analysis of variance.

§ ODTc vs. ODTs, p<0.001 based on signed-rank test.

†† ODTc vs. ODTs, p=0.031 based on analysis of variance.

ODTc = ODT with water

ODTs = ODT without water

APPEARS THIS WAY ON ORIGINAL

The GMR of ODTc/ODTs for AUC_{0-1hr} and its 90% CI is 5.85 (3.60, 9.53).
The GMR of ODTc/Tablet for AUC_{0-2hr} and its 90% CI is 1.13 (0.96, 1.33).
The GMRs of ODTs/Tablet for AUC_{0-1hr}, AUC_{0-2hr}, $AUC_{0-\infty}$ and their 90% CI are 0.22 (0.13, 0.36), 0.63 (0.53, 0.74) and 0.95 (0.91, 0.99).

Comparison between study 042 and 070:

Both 042 and 070 studies used crossover design. Study 042 was conducted in 12 females, and 070 was performed in 24 subjects with majority of them being females (n=19). Both 5 mg and

10 mg ODT or Tablet were evaluated in study 042, while only 10 mg ODT and tablet were administered in study 070.

The main difference between the two studies is on the PK sample collection time-points. Blood samples were extensively collected in study 070 at pre-dose, 5, 10, 15, 20, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 95, 100, 105, 110, 115 min and 2, 3, 4, 6, 8 and 12 hr post-dose. Fewer PK samples were collected in study 042 at pre-dose, 30, 50, 70, 80, 90, 100, 110 min and 2, 3, 4, 6 and 8 hr post-dose. Due to the extensive sampling at early phase, study 070 might capture C_{max} more accurately. Study 062 used a similar sampling schedule as study 042: pre-dose, 15, 30, 50, 70, 80, 90, 100, 110 min and 2, 3, 4, 6, 8, 10, 12 and 24 post-dose.

Though studies 042 and 070 were inconsistent in terms of BE in C_{max} of ODT taken without water compared to tablet, the two studies shared similarity in the change of T_{max}. In study 070, the mean T_{max} of ODT taken without water was delayed by 0.74 hr (45 min) on average compared to tablet. In study 042, the mean T_{max} was prolonged from 1 to 1.6 hr (5 mg) or 1.5 to 2.5 hr (10 mg) when ODT taken without water was compared to tablet. The explanation lies presumably in the fact that the tablet reaches the small intestine faster on average than the solution of rizatriptan that is formed when ODT is placed on a mucosal surface in the oral cavity.

2.5.5 What is the effect of water on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of rizatriptan in relation to water?

Pediatric Study:
ODT was administered without water in the PK studies (062 and 083) conducted in pediatric migraineurs. It has not been evaluated whether the PK of rizatriptan will change in pediatric patients when ODT is taken with water. In the pediatrics efficacy study – 082 and safety study – 086 conducted in 12-17 yr migraineurs, there is no specific instruction on the administration of rizatriptan with or without water.

Adult Study:
The impact of water on rizatriptan absorption following ODT dose was investigated in adults. Study 070 was an open label, randomized, single-dose, 3-period crossover study to compare the PK profiles of rizatriptan 10 mg tablet, 10 mg ODT administered with water (ODTc) and 10 mg ODT administered without water (ODTs) in healthy males and females. As shown in the above Figure 7 and Table 11, it is obvious that the absorption rate of rizatriptan is faster when ODT is taken with water. The GMR of ODTc to ODTs for C_{max} and $AUC_{0\text{-}2hr}$ was 1.39 and 1.80, respectively. The C_{max} was achieved ~0.84 hr (50 min) earlier when ODT was administered with water. In contrast, the GMR for $AUC_{0\text{-}inf}$ is around 1.0, indicating that the extent of absorption is not altered.

Potential Impact:
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 C_{max} and $AUC_{0\text{-}2hr}$ 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.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

A LC-MS/MS assay, P845.00, was developed to quantitiate the concentrations of MK-0462 in plasma samples collected from the PK studies. The assay validation for these methods is acceptable.

Table 13. Validation Assay Performance Summary for Rizatriptan

Report Title	Quantitation of Rizatriptan in Human Plasma via HPLC with
	MS/MS Detection Quantitation of Rizatriptan in Human Plasma
Used in Clinical Study	083
Lab/Project Code (year)	PPD/ P845.00 (2006)
Analyte Names	Rizatriptan
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC/MS/MS
Extraction Method	Liquid/liquid
QC concentrations	0.2, 0.6, 1.5, 6, 25, and 150 ng/mL
Standard Curve Concentrations	0.2, 0.4, 0.8, 3, 12, 50, 160, 200 ng/ml
Lower Limit of Quantitation	0.2 ng/ml
Upper Limit of Quantitation	200 ng/ml
Range of Recovery (%)	74.6-79.9%
Average Recovery of IS (%)	73.6 %
QC Intra-day Precision (CV%)	1.3-4.4 %
QC Intra-day Accuracy	98.6-110.0 %
QC Inter-day Precision (CV%)	3.3-12.4 %
QC Inter-day Accuracy	96.1-104.7 %
Stock solution solvent	methanol
Stability of rizatriptan	
in methanol solution	at least 637 days at -20°C
in post-preparative extract	up to 81 hr at RT
in thawed matrix	up to 29.75 hr at RT
Short-term in frozen matrix	up to 3 day at -20°C
Long-term in frozen matrix	at least 638 days at -20°C
Stress-test Stability in methanol solution	at least 25.5 hr at RT
Freeze/thaw stability	3 cycles at -20°C
Specificity	No significant interfering peaks

3.0 LABELING RECOMMENDATIONS

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (TS/CCI) immediately following this page

4.0 APPENDIX I

4.1 INDIVIDUAL STUDIES REVIEW

1.2 PK in Pediatric Patients:

Study 062: An Open-Label, Randomized, Single-Dose, 2-Period Crossover Study to Investigate the Bioequivalence of MAXALT™ and MAXALT-MLT™ Tablets in Adolescent (12 to 17 Years of Age) Patients With Migraine

Primary Objectives:

- To assess the bioequivalence of a 5-mg rizatriptan orally disintegrating tablet (ODT) compared to a 5-mg rizatriptan conventional tablet as assessed by $AUC_{0-\infty}$ and C_{max}
- To investigate the relative difference in apparent absorption rates (T_{max}) for the conventional tablet and orally disintegrating tablet.
- To assess the tolerability of a 5-mg rizatriptan orally disintegrating tablet and a 5-mg rizatriptan conventional tablet when administered as a single dose to adolescent migraine patients.

<table>
<tr><td>Study Design</td><td>This is an open-label, single-dose, randomized, 2-period crossover study at 3 to 6 centers in adolescent migraineurs, during a headache-free interval.
<table>
<tr><th>No. of Patients</th><th>Period 1</th><th>Period 2</th></tr>
<tr><td>15
15</td><td>Treatment A
Treatment B</td><td>Treatment B
Treatment A</td></tr>
</table>
A: 5 mg ODT; B; 5 mg Tablet
The 2 treatment periods was separated by at least 3 days.</td></tr>
<tr><td>Study Population</td><td>Adolescent migraineurs (12-17 yr) who were migraine free on days of study drug administration.

ENTERED: Total 37
Male (age range) 15 (12 to <15 yr: 7; 15 to < 18 yr: 8)
Female (age range) 22 (completers 19, 12 to <15 yr: 6; 15 to <18 yr: 13)
COMPLETED: 34
Body Weight: > 40 kg except one male subject with 38.1 kg.
DISCONTINUED: Total 3 (all females)
Adverse clinical experience 0
Adverse laboratory experience 1
Other 2</td></tr>
<tr><td>Dosage and Administration</td><td>5 mg ODT or tablet was to be administered in the fasting state.
Tablet is taken with ~8 ounces of water.
Patients were instructed to place the ODT directly onto the tongue without touching it and without water. Water will not be permitted for 2 hours after taking the ODT.</td></tr>
<tr><td>Sampling</td><td>To determine plasma concentrations of rizatriptan, blood samples were collected at pre-dose, 15, 30, 50, 70, 80, 90, 100, 110 minutes and 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose.</td></tr>
<tr><td>Analysis</td><td>Rizatriptan concentrations were measured using HPLC/APCI/MS/MS.
(APCI: atmospheric pressure chemical ionization)
LLOQ: 0.5 ng/ml</td></tr>
</table>

	Calibration: 0.5, 1, 2, 5, 10, 20, 50 and 100 ng/ml Range: 0.5 – 100.0 ng/ml QC: 1.5, 8 and 80 ng/ml Highest Dilution QC Concentration: 500 ng/ml Accuracy: 95.6% – 100% Precision: 2.45 – 5.19%
PK Assessment	$AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
Safety Assessment	Physical examination, laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, ECG, adverse events (AEs)

Pharmacokinetic Results:

The PK parameters of rizatriptan are shown in the following table.

Table 1. Summary Statistics for Rizatriptan Pharmacokinetic Parameters Following Single Dose Administration of Rizatripatan ODT 5 mg (PN062 adolescents), Tablet 5 mg (PN062 adolescents), or ODT 10 mg (PN070 adults, historical data)

Formulation	N	$AUC_{(0-\infty)}$† (hr•ng/mL)	C_{max}† (ng/mL)	T_{max}‡ (hr)	Apparent $t_{1/2}$§ (hr)
MK-0462 PN062 ODT (5mg)	34	30.46 (27.34, 33.93)	9.97 (8.83, 11.25)	0.8 (0.3, 3.0)	1.6 (0.3)
Female	19	34.48 (11.42)	11.27 (4.24)	1.5 (0.3, 3.0)	1.6 (0.3)
Male	15	29.12 (9.16)	9.54 (2.28)	0.8 (0.5, 3.0)	1.6 (0.3)
MK-0462 PN062 Tablet (5mg)	34	30.40 (27.29, 33.87)	10.66 (9.44, 12.03)	0.8 (0.5, 3.0)	1.5 (0.3)
Female	19	35.48 (11.97)	12.17 (4.68)	0.8 (0.5, 3.0)	1.6 (0.3)
Male	15	28.20 (9.45)	10.46 (3.84)	0.8 (0.5, 1.8)	1.5 (0.3)
MK-0462 PN070 ODT (10mg)	24	67.04 (58.96, 76.24)	20.94 (18.13, 24.18)	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)

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

‡ Median (Minimum, Maximum).

§ Harmonic mean (Jackknife SD).

1. The sponsor did not conduct a formal BE analysis, although the study was designed to investigate the BE between ODT and tablet in adolescent migraineurs. It appears that the two formulations are bioequivalent. The geometric mean ratio (GMR) of ODT to tablet and its 90% CI is:

All subjects: 100.19% [95.82, 104.76] for $AUC_{(0-\infty)}$ and 93.52% [84.97, 102.92] for C_{max}.
Females: 97.84% [92.12, 103.92] for $AUC_{(0-\infty)}$ and 94% [80.60, 109.63] for C_{max}.
Males: 103.06% [95.72, 110.96] for $AUC_{(0-\infty)}$ and 92.7% [81.90, 104.92] for C_{max}.

2. AUC_{0-inf} and C_{max} in adolescents receiving 5 mg ODT or tablet were about half of the corresponding values in adults receiving 10 mg ODT (historical data, ODT also taken without water). The terminal half-life was similar between adolescents and adults.

3. AUC_{0-inf} tends to decrease as body weight increases, while the trend is not observed for C_{max}. This is somewhat different from the findings in study 083 where both AUC_{0-inf} and C_{max} decrease as body weight increases. The difference may be due to a wider range of body weight in study 083 which included 10 subjects with body weight less than 40 kg, while there was only one male subject in study 062 having body weight of 38.1 kg.

Figure 1. Individual Values for Body Weight versus Rizatriptan $AUC_{(0-\infty)}$ and C_{max} Following Single Dose Administration of Rizatriptan ODT 5 mg (PN062 Adolescents)

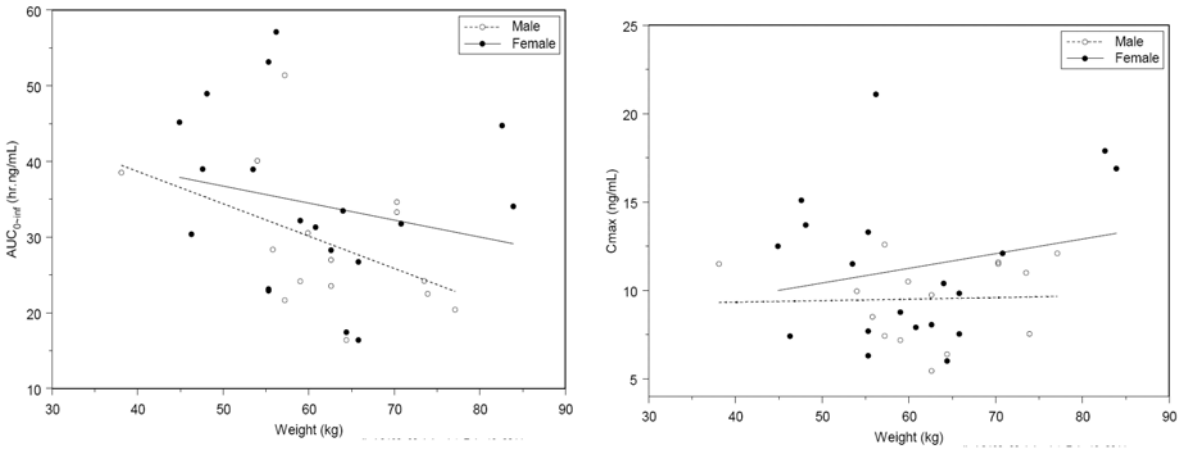
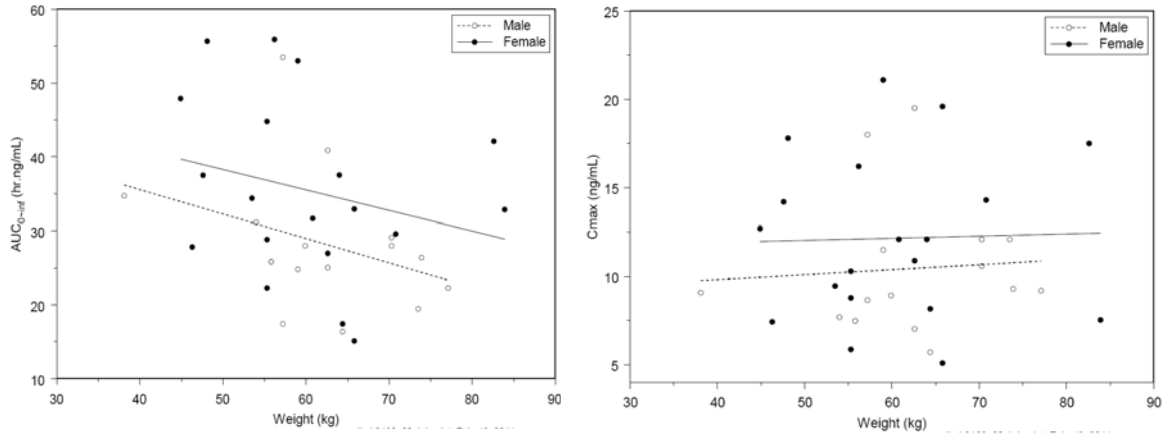


Figure 2. Individual Values for Body Weight versus Rizatriptan $AUC_{(0-\infty)}$ and C_{max} Following Single Dose Administration of Rizatriptan Tablet 5 mg (PN062 Adolescents)



4. Exposure of rizatriptan is higher in females than males. $AUC_{(0-\infty)}$ and C_{max} of rizatriptan following 5 mg ODT was about 18% higher in females than males. After a tablet dose, $AUC_{(0-\infty)}$ and C_{max} of rizatriptan were 26% and 16% higher in females as compared to males, respectively.

5. The PK of rizatriptan when ODT is taken with water has not been evaluated in adolescent migraineurs.

Safety:

5 mg rizatriptan ODT and Tablet appears generally well tolerated in adolescent migraineurs.

Conclusion:

ODT taken without water has similar $AUC_{(0-\infty)}$ and C_{max} with tablet in adolescent migraineurs regardless of gender.

Study 083: A Randomized, Double-Blind, Placebo-Controlled, Study to Assess Safety, Tolerability, and Single-Dose Pharmacokinetics of MK-0462 in Migraneurs Aged 6 to 17 Years

Objectives:

Primary Objectives

- To assess the safety and tolerability of single doses of rizatriptan Orally Disintegrating Tablets (ODT) in pediatric migraineurs ages 6-17 years.
- To obtain preliminary plasma pharmacokinetic data (e.g., AUC, C_{max}, T_{max}, and terminal $t_{1/2}$), following single dose administration of rizatriptan ODT in pediatric migraineurs ages 6-17 years

Exploratory Objectives

- To estimate preliminary plasma pharmacokinetic data following single dose administration of rizatriptan in migraineurs ages 6-17 years, and to compare with that obtained historically in adults.

Study Design

The study was performed in 6 to 17 year old migraineurs between acute migraine attacks.

Subject	Panel A	Panel B
n = 3	Placebo	placebo
n = 9	5 mg rizatriptan	10 mg rizatriptan

Subject	Panel C
n = 1	placebo
n = 5	5 mg or 10 mg rizatriptan

Panel A: subjects weighing 20-39 kg received a 5 mg ODT (or placebo).
Panel B: subjects weighing ≥40 kg received a 10 mg ODT (or placebo).
Panel C: subjects weighing 20-39 kg received a 5 mg ODT (or placebo) and subjects weighing ≥40 kg received a 10 mg ODT (or placebo).
(Panel C was added in Amendment 01 in order to increase the number of male subjects in the 12-17 year old group.)

Eventually, 13 subjects were enrolled in Panel B in which 10 subjects received rizatriptan and 3 subjects received placebo.

Study Population

	PN 083-00	PN 083-01	Total
RANDOMIZED:	25	6	31
Male (age range): (7 to 17years)	12	6	18
Female (age range): (6 to 17years)	13	0	13
COMPLETED:	25	6	31
DISCONTINUED:	0	0	0

Baseline demographics (12 – 17 yr)

	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

Baseline demographics (6 – 11 yr)

	<table><tr><th></th><th>Age (yr)</th><th>Height (cm)</th><th>Weight (kg)</th><th>Body Surface Area (m^2)†</th></tr><tr><td>Male N</td><td>9</td><td>9</td><td>9</td><td>9</td></tr><tr><td>Male Range</td><td>7 - 11</td><td>122 - 151.5</td><td>23.3 - 47</td><td>0.91 - 1.41</td></tr><tr><td>Male Arithmetic Mean</td><td>8.8</td><td>136.1</td><td>35.5</td><td>1.15</td></tr><tr><td>Female N</td><td>4</td><td>4</td><td>4</td><td>4</td></tr><tr><td>Female Range</td><td>6 - 9</td><td>124.5 - 136</td><td>25.2 - 34.5</td><td>0.95 - 1.14</td></tr><tr><td>Female Arithmetic Mean</td><td>8</td><td>129.5</td><td>28.0</td><td>1.0</td></tr><tr><td>Overall Total N</td><td>13</td><td>13</td><td>13</td><td>13</td></tr><tr><td>Overall Total Range</td><td>6 - 11</td><td>122 - 151.5</td><td>23.3 - 47</td><td>0.91 - 1.41</td></tr><tr><td>Overall Total Mean</td><td>8.5</td><td>134.1</td><td>33.2</td><td>1.1</td></tr></table>
Dosage and Administration	Study drug was administered in the fasted state without water. Up to 240 mL of Gatorade, Sprite, or A&W Root beer was permitted to be administered upon waking but not less than 2 hours prior to dosing, if desired. Water will be restricted for 1 hour prior to dosing, but will be made available at the time of dosing. Water will be permitted at the time of dosing if desired. (*Reviewer's Comment:* In the dataset, no information is available in terms of water taken or not at the time of dosing. In the study report of 083 and summary of clinical pharmacology submitted by the sponsor, the data obtained in study 083 were consistently labeled as 'without water' and always compared to adult data where ODT was taken without water).
Sampling	To determine plasma concentrations of rizatriptan, blood samples were collected at pre-dose, 20, 40, 60, 80, and 100 min, and 2, 3, 4, 6, 8, and 24 hours post-dose.
Analysis	Rizatriptan concentrations were measured using HPLC/MS/MS. LLOQ: 0.2 ng/ml Calibration: 0.2, 0.4, 0.8, 3, 12, 50, 160 and 200 ng/ml Range: 0.2 – 200 ng/ml QC: 0.6, 1.5, 6, 25, and 150 ng/mL Highest Dilution QC Concentration: 500 ng/mL Accuracy: 97.3% – 102.9% (Within-day); 98% - 103.3% (Inter-day) Precision: 2.26 – 4.96% (Within-day); 1.51 – 3.50% (Inter-day)
PK Assessment	$AUC_{0-\infty}$, AUC_{0-2hr}, C_{max}, T_{max}, $t_{1/2}$
Safety Assessment	Physical examination, laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, ECG, adverse events (AEs)

Pharmacokinetic Results:

The PK profile and parameters of rizatriptan are shown in the following figure and table.

Figure 3. Mean Plasma Concentration-Time Profile of Rizatriptan Following Administration of a Single Oral Rizatriptan ODT Dose in Pediatric Migraineurs Ages 6 to 17 Years (Panel A, Panel B and Panel C) (Insert: Semi-Log Scale)

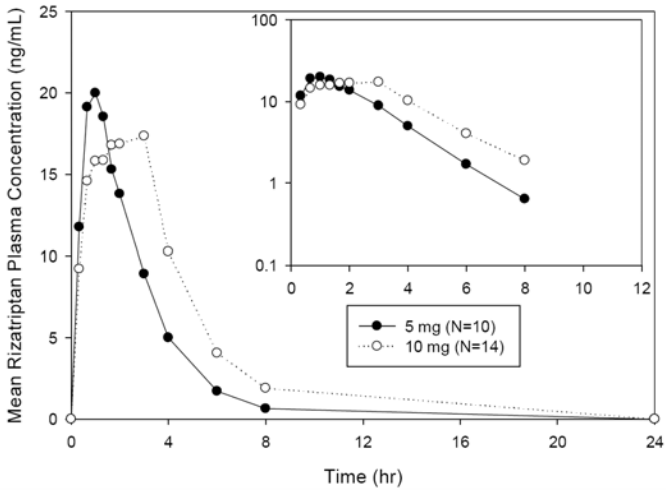


Table 2. Summary Statistics for Rizatriptan Pharmacokinetic Parameters Following Single Dose Administration of Rizatriptan ODT 5 mg or 10 mg in Pediatric Migraineurs Ages 6 to 17 Years and in Healthy Adult Subjects

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).

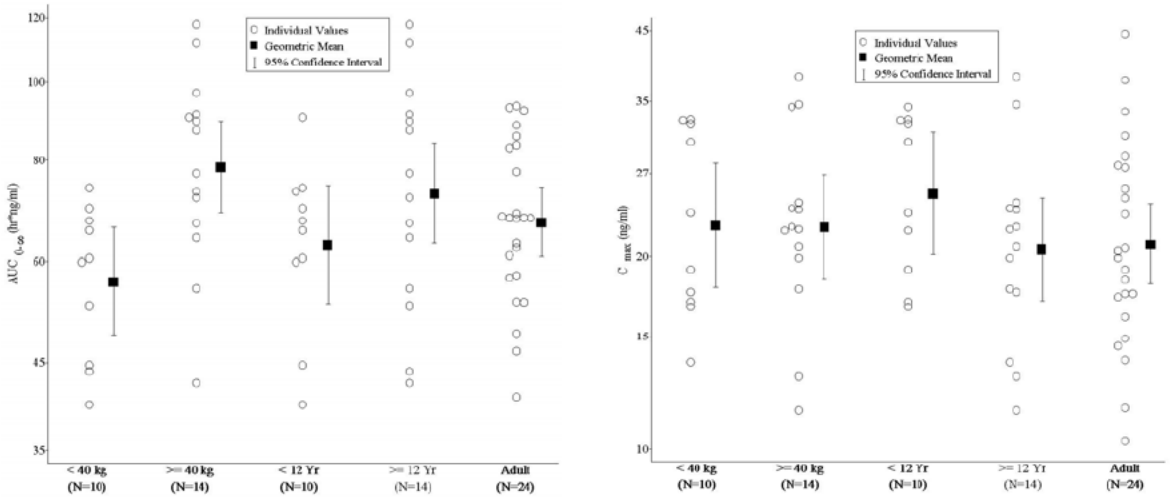
[¶] rMSE for $AUC_{0-\infty}$ = 0.241 and rMSE for C_{max} = 0.352 in weight model; rMSE for $AUC_{0-\infty}$ = 0.263 and rMSE for C_{max} = 0.345 in age model; rMSE: Square root of conditional mean squared error (residual error) from the linear fixed effect model. rMSE*100% approximates the between-subject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

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

1. In the <40kg group of pediatric migraineurs, $AUC_{0\text{-}inf}$ values were 15% lower than in adults dosed with 10 mg ODT (historical data, taken without water), but the C_{max} values were similar. In the ≥40kg group, $AUC_{0\text{-}inf}$ values were 17% higher than in adults dosed with 10 mg ODT, but the C_{max} values were similar.

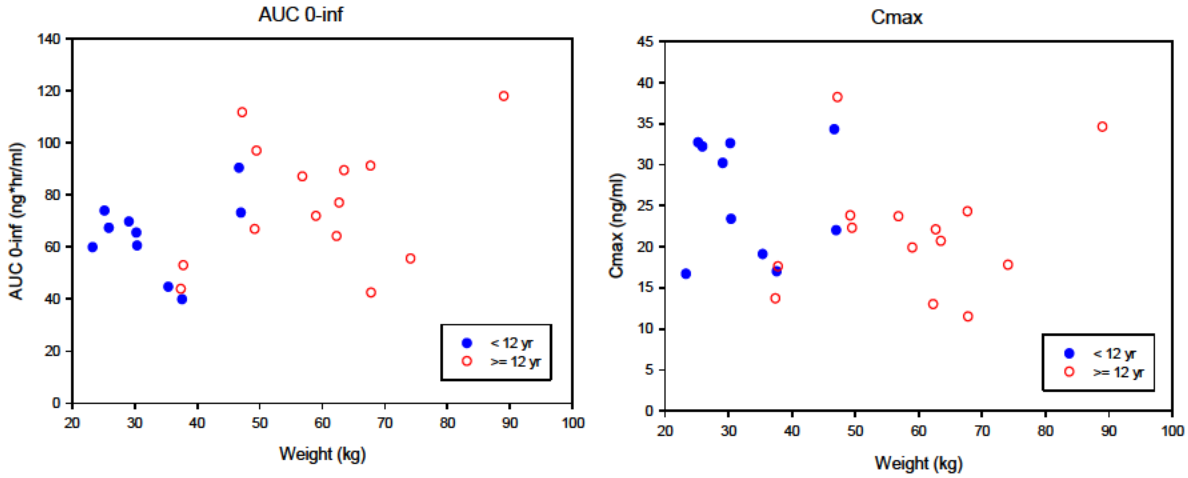
For age group ≥12 yr, the $AUC_{(0\text{-}\infty)}$ and C_{max} were similar to adults. For age group <12 yr, $AUC_{(0\text{-}\infty)}$ was similar, while C_{max} was slightly higher than adults.

Figure 4. Individual values, Geometric means and 95% CIs for Rizatriptan $AUC_{(0\text{-}\infty)}$ and C_{max} following single dose administration of Rizatriptan ODT 5 mg or 10 mg in Pediatric Migraineurs Ages 6 to 17 years (083, without water) and Rizatriptan ODT 10 mg (without water) in Healthy adult subjects (Protocol 070)



With this body weight-based dosing regimen, the $AUC_{(0\text{-}\infty)}$ is 28% lower in patients <40kg than patients ≥40 kg. However, as acute treatment, efficacy of rizatriptan may be more relevant with its C_{max}, which is similar between the <40kg and ≥40 kg groups.

Figure 5. Relationship Between $AUC_{(0\text{-}\infty)}$ or C_{max} and Weight Following Administration of Rizatriptan ODT (without water) to Pediatric Patients Aged 6 to 17 Years (Study 083)



2. The <40kg group had slightly higher $AUC_{0\text{-}2hr}$ (geometric mean: 28.48 ng•hr/ml) than the ≥40kg group (25.19 ng•hr/ml), both of which are higher than that in adults (18.83 ng•hr/ml).

Figure 6. Individual values, Geometric means and 95% CIs for Rizatriptan $AUC_{(0\text{-}2hr)}$ 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 (Protocol 070)

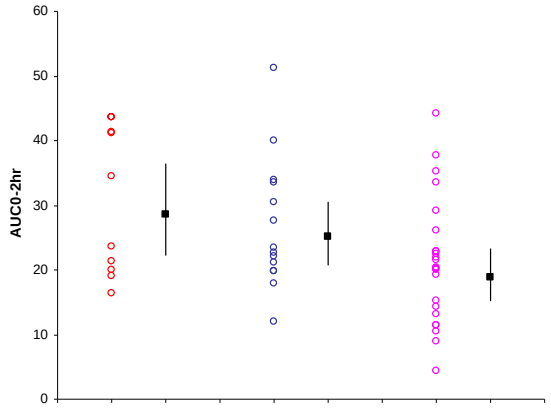
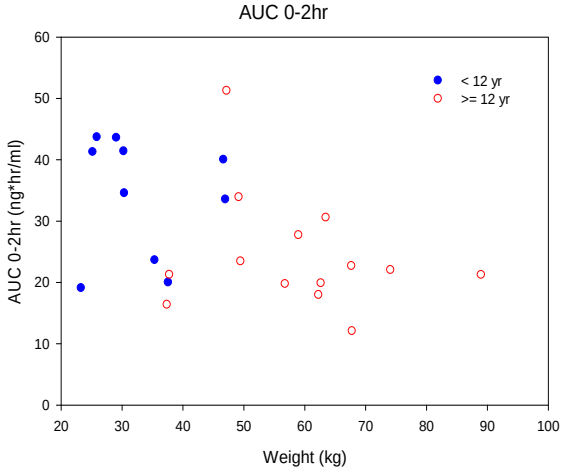
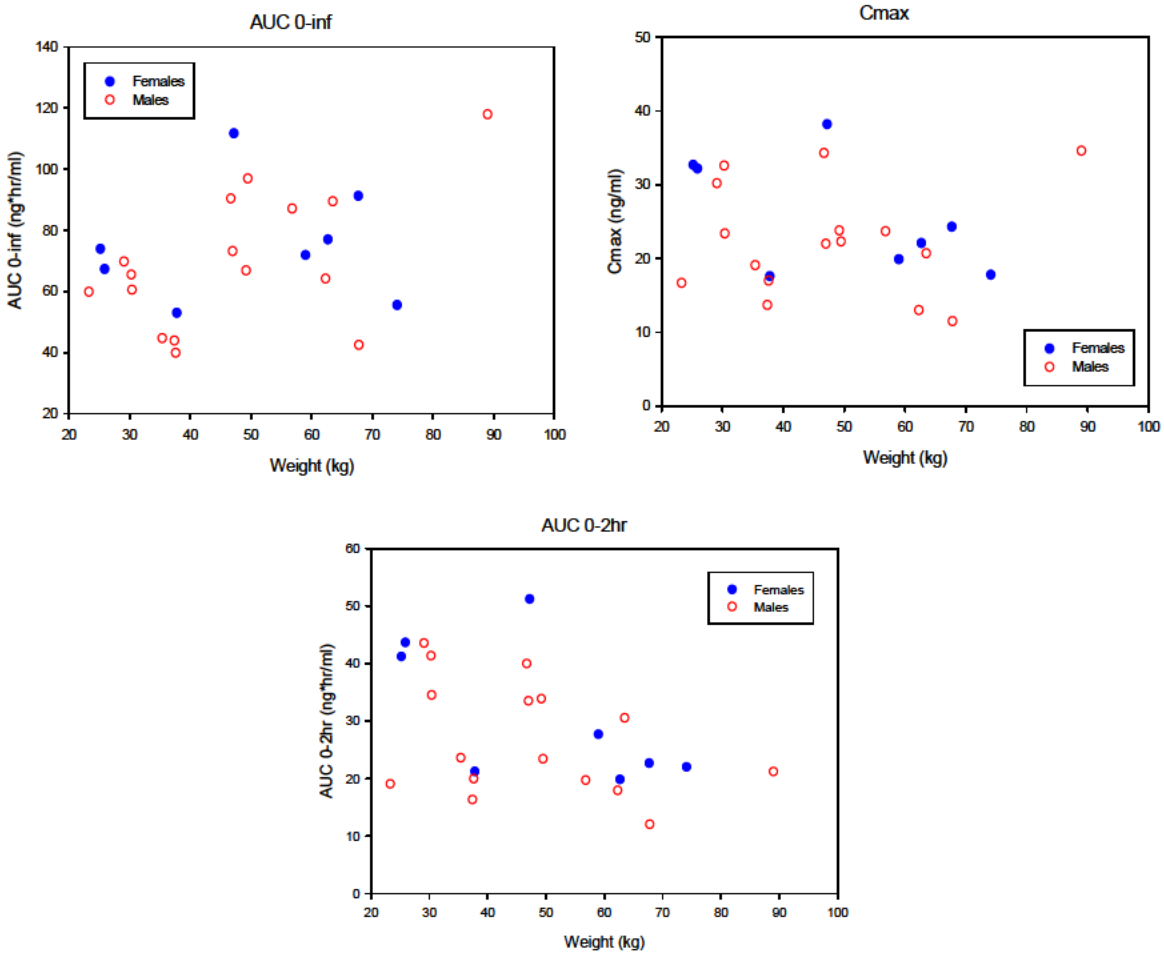


Figure 7. Relationship Between $AUC_{(0\text{-}2hr)}$ and Weight following administration of Rizatriptan ODT (without water) to Pediatric Patients Aged 6 to 17 Years (Study 083)



3. For the subgroup <40kg, $AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}2hr)}$ and C_{max} of rizatriptan were 18%, 27% and 26% higher in females than in males, respectively. For the subgroup ≥ 40kg, the exposure is similar between females and males. However, it should be noted the number of subjects is limited especially for female sub-categories.

Figure 8. Distribution of $AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}2hr)}$ and C_{max} along with weight in female and male pediatric migraineurs aged 6 – 17yr and received 5 or 10 mg rizatriptan ODT (study 083)



Safety:

Rizatriptan, administered as 5 or 10 mg ODT, are generally well tolerated in pediatric migraineurs aged 6 -17 yr.

Conclusion:

A weight-based dosing scheme in which pediatric patients ages 6 to 17 years and weighing 20 to <40 kg receive 5 mg rizatriptan ODT, and weighing ≥40 kg receive 10 mg rizatriptan generated C_{max} values that were similar to those observed in adults taking 10 mg ODT (historical data comparison). The plasma $AUC_{(0-\infty)}$ values were somewhat (~17% higher or lower) different from those in adults. However, as acute treatment, efficacy of rizatriptan may be more relevant with its C_{max}. The findings from this study supported the body weight-based dosing regimen used in the efficacy and safety trials.

Study 048: A Single-Dose Study to Investigate the Pharmacokinetics and Safety of Rizatriptan in Adolescent (12 to 18 Years of Age) Patients With Migraine

Objectives:

- To investigate the plasma concentrations of rizatriptan and L-706,248 (active N-monodesmethyl metabolite) in adolescent migraine patients (12 to 18 years of age) receiving a single 10-mg dose of rizatriptan.
- To compare plasma concentration profiles of rizatriptan and L-706,248 following administration of a 10-mg tablet in adolescent patients (12 to 18 years of age) with historical data from healthy adult subjects.
- To assess the safety and tolerability of a single dose of rizatriptan in adolescent patients.

<table>
<tr><td>Study Design</td><td>Single dose study</td></tr>
<tr><td>Study Population</td><td>Adolescent migraineurs (12-18 yr) who were not experiencing a migraine on the study day.
ENTERED: Total 12
Male (age range) 6 (13 to 18)
Female (age range) 6 (14 to 18)
Body Weight: All > 40 kg
COMPLETED: 12
DISCONTINUED: Total 0
Clinical adverse experience 0
Laboratory adverse experience 0
Other 0</td></tr>
<tr><td>Dosage and Administration</td><td>A single 10 mg Tablet administered in the fasting state with 250 ml water.</td></tr>
<tr><td>Sampling</td><td>To determine plasma concentrations of rizatriptan, blood samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose. Urine samples were collected at pre-dose, 0-2 hr, 2- 4hr, 4-6 hr, 6-8 hr, 8-12 hr and 12-24 hr.</td></tr>
<tr><td>Analysis</td><td>Plasma
<table>
<tr><td>Analyze</td><td>Rizatriptan (MK-0462)</td><td>N-monodesmethyl-rizatriptan (L-706,248)</td></tr>
<tr><td>Method</td><td colspan="2">LC/MS/MS</td></tr>
<tr><td>LOQ (ng/ml)</td><td>0.5</td><td>0.2</td></tr>
<tr><td>Calibration (ng/ml)</td><td>0.5, 1, 2, 5,10, 20, 50 and 100</td><td>0.2, 0.4, 0.8, 2, 4, 8, 20 and 40</td></tr>
<tr><td>QC (ng/ml)</td><td>1, 2, 10, 50</td><td>0.4, 0.8, 4 and 20</td></tr>
<tr><td>Accuracy</td><td>95.6-106.4%</td><td>97.2-101.9%</td></tr>
<tr><td>Precision</td><td>3.73-11.28%</td><td>3.06-8.02%</td></tr>
</table>
Urine
<table>
<tr><td>Analyze</td><td>Rizatriptan (MK-0462)</td><td>N-monodesmethyl-rizatriptan (L-706,248)</td></tr>
<tr><td>Method</td><td colspan="2">LC/MS/MS</td></tr>
<tr><td>LOQ (ng/ml)</td><td>5</td><td>2</td></tr>
<tr><td>Calibration (ng/ml)</td><td>5, 10, 25, 50, 100, 250, 500, 1000, 1250, 2500</td><td>2, 4, 10, 20, 40, 100, 200, 400, 500, 1000</td></tr>
<tr><td>QC (ng/ml)</td><td>10, 25, 250,1000</td><td>4, 10, 100 and 400</td></tr>
<tr><td>Accuracy</td><td>96.7-104.6%</td><td>93.8-100.8%</td></tr>
<tr><td>Precision</td><td>2.51-9.16%</td><td>4.09-13.42%</td></tr>
</table>
</td></tr>
</table>

PK Assessment	$AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, ke, renal clearance (CLr), and urinary excretion (Ue) of rizatriptan and L-706,248. The metabolite-to-parent ratio of $AUC_{0-\infty}$, C_{max} and Ue.
Safety Assessment	Physical examination, laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, ECG, adverse events (AEs)

Pharmacokinetic Results:

The PK parameters of rizatriptan in adolescents and adults following administration of a single 10 mg tablet are shown in the following tables and figures.

Table 3. $AUC_{(0-\infty)}$ (Geometric Means) for Rizatriptan 10-mg Single Oral Dose

	Geometric Mean $AUC_{(0-\infty)}$ (ng•hr/mL)			Geometric Mean Ratio (Adolescents/Adults) and 90% CI	
Gender	Adolescents—Protocol 048[a,b]	Adults—Protocol 035[c]	Adults—Pooled[d]	Adults—Protocol 035[c]	Adults—Pooled[d]
Females	108.72	70.32	--	1.55 (1.27, 1.89)	--
	103.66	--	76.81	--	1.35 (0.97, 1.87)
Males	66.88	65.34	--	1.02 (0.81, 1.29)	--
	66.80	--	73.36	--	0.91 (0.67, 1.23)
Pooled	85.27	67.78	--	1.26 (1.09, 1.46)	--
	82.68	--	73.83	--	1.12 (0.84, 1.50)

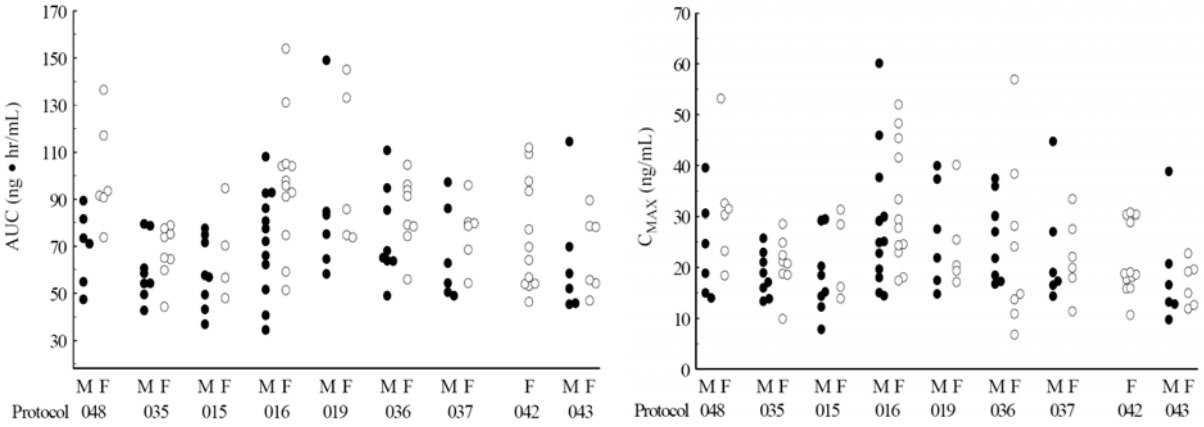
[a] N=6 males and 6 females.
[b] The geometric mean estimate for adolescents depends on the historical control group of adults.
[c] N=8 males and 8 females.
[d] N=54 males and 61 females.

Table 4. C_{max} (Geometric Means) for Rizatriptan 10-mg Single Oral Dose

	Geometric Mean C_{max} (ng/mL)			Geometric Mean Ratio (Adolescents/Adults) and 90% CI	
Gender	Adolescents—Protocol 048[a,b]	Adults—Protocol 035[c]	Adults—Pooled[d]	Adults—Protocol 035[c]	Adults—Pooled[d]
Females	30.96	20.22	--	1.53 (1.07, 2.19)	--
	35.39	--	23.48	--	1.51 (1.00, 2.28)
Males	21.80	20.12	--	1.08 (0.75, 1.56)	--
	21.37	--	23.06	--	0.93 (0.59, 1.47)
Pooled	25.98	20.17	--	1.29 (1.01, 1.64)	--
	27.21	--	22.77	--	1.19 (0.81, 1.76)

[a] N=6 males and 6 females.
[b] The geometric mean estimate for adolescents depends on the historical control group of adults.
[c] N=8 males and 8 females.
[d] N=54 males and 61 females.

Figure 9. Individual Values of $AUC_{(0-\infty)}$ (ng•hr/mL) and C_{max} (ng/mL) for Rizatriptan by Protocol and Gender Following a 10-mg Oral Dose



1. Exposure of rizatriptan in adolescent females was higher than that in adult females, with $AUC_{(0-\infty)}$ being 35-55% higher and C_{max} being 51-53% higher, while exposure in adolescent males was similar to that in adult males.

2. Within adolescents, females have higher $AUC_{(0-\infty)}$ than males with GMR (geometric mean ratio) of 1.5 (90% CI: 1.23, 1.83) and higher C_{max} with GMR of 1.28 (0.82, 1.99).

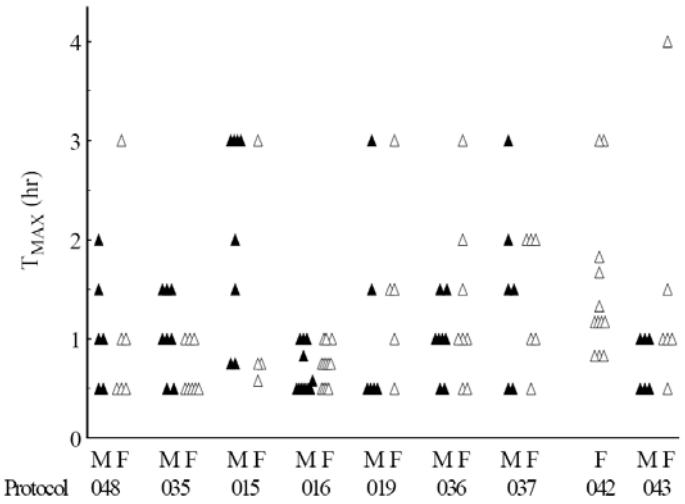
3. T_{max} was similar for adolescents and adults.

Table 5. T_{max} (Medians) for Rizatriptan 10-mg Single Dose

	Median T_{max} (hr)			Difference in Medians (Adolescents-Adults) and 90% CI	
Gender	Adolescents—Protocol 048[a]	Adults—Protocol 035[b]	Adults—Pooled[c]	Adults—Protocol 035[b]	Adults—Pooled[c]
Females	0.75	0.50	--	0.00 (-0.50, 0.00)	--
	0.75	--	1.00	--	0.08 (0.00, 0.50)
Males	1.00	1.00	--	0.00 (-0.50, 0.50)	--
	1.00	--	1.00	--	0.00 (-0.50, 0.50)
Pooled	1.00	1.00	--	0.00 (-0.50, 0.00)	--
	1.00	--	1.00	--	0.00 (0.00, 0.50)

[a] (N=6 males and 6 females).
[b] (N=8 males and 8 females).
[c] (N=54 males and 61 females).

Figure 10. Individual values of T_{max} (hr) for Rizatriptan by protocol and gender following a 10-mg Oral dose



4. $T_{1/2}$ was similar for adolescents and adults (1.7 vs. 1.8 hr).

5. Similar to the parent drug, the exposure of N-monodesmethyl-rizatriptan (L-706,248) was also higher in adolescent females than that in adult females, with $AUC_{(0-\infty)}$ being 45% higher and C_{max} being 31-34% higher, while the exposure of L-706,248 was similar in adolescent males and adult males. Though L-706,248 has activity similar to that of rizatriptan at the 5-$HT_{1B/1D}$ receptor, it is formed only to a minor degree. Plasma concentrations of L-706,248 are approximately 14% of those of parent compound, and it is eliminated at a similar rate.

Safety:

There were no serious clinical, laboratory, or other adverse experiences.

Conclusion:
Overall, the exposure of rizatriptan in adolescents is similar or higher than that in adults. Adolescent females have higher exposure than adult females, while adolescent males have exposure similar to adult males.

5.0 APPENDIX II

FILING REVIEW

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N 20-865/S020	**Brand Name**	Maxalt-MLT®
OCP Division (I, II, III)	DCP-I	**Generic Name**	Rizatriptan benzoate (MK-0462)
Medical Division	HFD-120	**Drug Class**	5-HT1B/1D agonists (triptans)
OCP Reviewer	Xinning Yang	**Indication(s)**	Acute treatment of migraine (12-17 yr of age)
OCPB Team Leader	Angela Y. Men	**Dosage Form**	Orally disintegrating tablets (ODT)
		Dosing Regimen	5 mg for patients with body weight < 40 kg; 10 mg for patients ≥ 40 kg
Date of Submission	03/25/2011	**Route of Administration**	Oral
Estimated Due Date of OCP Review	07/22/2011	**Sponsor**	Merck Co.
Division Due Date	07/29/2011	**Priority Classification**	Priority
PDUFA Due Date	09/25/2011		

Clin. Pharm. and Biopharm. Information

This application for Maxalt-MLT™ (Rizatriptan benzoate) orally disintegrating tablet (ODT) is being submitted as a supplemental submission to NDA 20-865 for the acute treatment of migraine in patients from 12 through 17 years of age. With this sNDA, the sponsor has fulfilled the requirements described in the amended Pediatric Written Request dated January 13, 2010.

Oral rizatriptan benzoate, a selective 5-hydroxytryptamine (5-HT) 1B/1D agonist, has been approved on June 29, 1998 for the acute treatment of migraine attacks with or without aura in adults at a therapeutic dose of 10 mg or 5 mg. Two formulations of rizatriptan are available: solid tablets (MAXALT™, NDA 20-864) and orally disintegrating tablets (MAXALT-MLT™, NDA 20-865), which may be taken without liquid and may be advantageous in a pediatric population.

To address the requirements of the amended PWR, the sponsor conducted three clinical studies using a weight based dosing approach: a PK study in pediatric migraineurs (083), an acute efficacy and safety study (082) and a long-term safety study (086), all using the ODT formulation. Study 083 was conducted to evaluate the single-dose PK of rizatriptan in pediatric patients aged 6 to 17 years who weighting 20 to < 40 kg received 5 mg rizatriptan ODT and who weighting ≥ 40 kg receive 10 mg ODT. The phase 3 efficacy study was performed to demonstrate effectiveness of rizatriptan in patients from 12-17 years of age, as measured by the primary endpoint of pain freedom 2 hours after taking medication.

In addition, data from several previously conducted pediatric studies in which the tablet formulation were used provide additional supportive PK, safety and efficacy information for this application. These studies include 2 PK studies (048 and 062), 2 efficacy studies (054 and 059) and 2 safety studies (059 extension and 061).

This NDA consists of

3 Phase I Single-dose PK studies:

1. 048: 10 mg rizatriptan tablet in patients (12-17 yr), compared to historical data in adults
   - $AUC_{0\text{-}inf}$ (35-55%) and C_{max} (51-53%) in adolescent females higher than adult females.
   - $AUC_{0\text{-}inf}$ and C_{max} in adolescent males similar to adult males.
   - Within adolescents, females have higher AUC than males with GMR ratio of 1.5
   - $T_{1/2}$ similar for adolescents and adults (1.7 vs. 1.8 hr).

2. 062: BE study comparing 5 mg rizatriptan ODT (without water) and tablet in patients (12-17 yr)
   - Formal BE analysis not done. $AUC_{0\text{-}inf}$ and C_{max} similar between tablets and ODT.
   - $AUC_{0\text{-}inf}$ tends to decrease as body weight increases.
   - $AUC_{0\text{-}inf}$ higher in females than males.
   - $AUC_{0\text{-}inf}$ and C_{max} in adolescents were about half of the corresponding values obtained in adults receiving 10 mg ODT (historical data, without water).

3. 083: Weight-based dosing in patients (6-17 yr), 5 mg rizatriptan ODT for patients <40kg 10 mg ODT for patients ≥ 40 kg, without water
   - In the < 40kg group, $AUC_{0\text{-}inf}$ values were somewhat lower than in adults dosed with 10 mg ODT (historical data, w/o water), but the C_{max} values were similar.
   - In the ≥ 40kg group, $AUC_{0\text{-}inf}$ values were somewhat higher than in adults dosed with 10 mg ODT (historical data, w/o water), but the C_{max} values were similar.
   - In both groups, $AUC_{0\text{-}inf}$ and C_{max} in females slightly higher than males.

3 Efficacy Studies:

1. 054 and 059: 5mg rizatriptan tablet in patients (12-17 yr)
   - Failed to demonstrate a statistically significant effect of treatment on primary endpoints (pain freedom and pain relief at 2 hours post dose, respectively).
   - A response trend observed in the lower age stratum (12-14 yr) compared to older age stratum (15-17 yr). Heavier children trended toward poorer outcomes.

2. 082: Weight-based dosing in patients (12-17 yr), 5 mg rizatriptan ODT for patients <40kg, 10 mg ODT for patients ≥ 40 kg, single dose
   - Rizatriptan was statistically superior to placebo as measured by the proportion of patients reporting pain freedom at 2 hours post dose (primary endpoint).
   - Rizatriptan was not shown to be superior compared to placebo for the secondary endpoint of pain relief at 2 hours post dose.

3 Long-term Safety Studies:

1. 059 extension and 061: 5mg rizatriptan tablet or ODT in patients (12-17 yr)
2. 086: Weight-based dosing in patients (12-17 yr), 5 mg rizatriptan ODT for patients <40kg, 10 mg ODT for patients ≥ 40 kg, single dose

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	3		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting/non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	3		3 Single dose PK
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single/multi dose:	X	1		1 of 3 PK studies
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS Class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	67			
Total Number of Studies				
	3 PK + 1 Bio-analytical Assay+ literature			

Filability and QBR comments

	"X" if yes	Comments
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)	No PK sampling taken in the efficacy study 082 Very few subjects (2 out of 18) in study 083 had body weight less than 40 kg ODT was taken without water in PK study 083. It was not specified whether ODT was taken with or without water in efficacy study 082 protocol.	
Other comments or information not included above		
Primary reviewer Signature and Date	Xinning Yang	May 20th, 2011
Secondary reviewer Signature and Date	Angela Men	May 20th, 2011

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	To-be-marketed formulation used.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	x			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		No exposure-response information.

General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Xinning Yang	05/20/2011
Reviewing Clinical Pharmacologist	Date
Angela Y. Men	05/20/2011
Team Leader/Supervisor	Date

Table 5.2.1 Table of All Clinical Studies

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.3.2: P083]	Paul Winner, D.O., Premiere Research at Palm Beach Neurology, West Palm Beach, FL (Site 083-0001); Steven Linder, M.D., Dallas Pediatric Neurology Associates, Dallas, TX (Site 083-0002)	This was a randomized, double-blind, placebo-controlled, parallel panel, single-dose study involving 6 to 17 year old migraineurs. The study was performed between acute migraine attacks. Subjects were allocated to one of two panels based on body weight: 20-39 kg and 40 kg and above.	18	13	6-17 yrs	Otherwise healthy male and female subjects with a history of migraines (as defined by the Headache Classification Subcommittee of the International Headache Society), 6 to 17 years of age.	A single dose of rizatriptan was administered on Day 1.	Pharmacokinetics: Pharmacokinetic parameters, including $AUC_{(0-\infty)}$, $AUC_{(0-2h)}$, C_{max}, T_{max}, and apparent $t_{1/2}$ was be determined from rizatriptan plasma concentrations at specified time points following administration of rizatriptan. Safety: The safety and tolerability of rizatriptan was assessed by repeated clinical evaluation of physical examination, vital signs, 12-lead ECG, laboratory safety tests (hematology/blood chemistry/urinalysis) and adverse experience monitoring.	1. Single doses of rizatriptan ODT are generally sufficiently safe and well-tolerated in pediatric migraineurs ages 6 - 17 years, based on an examination of adverse experiences, to permit continued clinical investigation. 2. A weight-based dosing scheme in which pediatric patients ages 6 to 17 years and weighing 20 to <40 kg receive 5 mg rizatriptan, and weighing ≥40 kg receive 10 mg rizatriptan generated plasma rizatriptan $AUC_{(0-\infty)}$ and C_{max} values that were generally similar to those observed in adults (historical data comparison). 3. The data support further evaluation of the safety, tolerability and efficacy of this rizatriptan ODT dosing scheme in larger-scale clinical trials in the pediatric migraineur population.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.5.1: P082]	Pearlman, Eric (082-04)	Randomized, double blind, placebo-controlled, parallel group study to evaluate safety and efficacy of rizatriptan for the acute treatment of migraine in children and adolescents.	428	274	12 to 17 years	Reported 1 to 8 moderate to severe migraine attacks with or without aura per month in the 2 months prior to the screening visit and had not experienced satisfactory relief from migraine pain with non-steroidal analgesics or acetaminophen.	5 mg if < 40 kg; 10 mg if ≥ 40 kg / single dose	Rating of headache pain severity at baseline and at 2 hours post Stage 2 dose recorded in the migraine diary using a validated 5-Face Pain Scale. Presence (yes/no) of migraine associated symptoms (photophobia, phonophobia, nausea, or vomiting), and degree of functional disability at 2 hours post Stage 2 dose were recorded in migraine diary.	Interim results for patients in the Pediatric Written Request (PWR) 12 to 17 year old population: Rizatriptan was demonstrated to be statistically superior to placebo as measured by the proportion of patients in the PWR 12 to 17 year old population reporting pain freedom at 2 hours post dose (primary endpoint). Rizatriptan was not shown to be superior compared to placebo for the secondary endpoint of pain relief at 2 hours post dose. Treatment with rizatriptan was generally well tolerated for the treatment of acute migraine in the PWR patients 12 to 17 years of age.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population			Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Interim Results
			M	F	Age Range				
[Ref. 5.3.5.1: P086]	Pearlman, Eric (P086-01)	Open-label clinical trial to examine the long-term safety and tolerability of rizatriptan for the treatment of acute migraine in pediatric patients.	263	411	12 to 17 years	Reported 1 to 8 mild to severe migraine attacks with or without aura per month in the 2 months prior to the screening visit.	5 mg if < 40 kg; 10 mg if ≥ 40 kg / single dose	Rating of headache pain severity at baseline and at 2 hours post dose recorded in the migraine diary using a validated 5-Face Pain Scale. Presence (yes/no) of migraine associated symptoms (photophobia, phonophobia, nausea, or vomiting) and functional disability at 2 hours post dose as recorded in the migraine diary.	The efficacy of rizatriptan was consistently demonstrated for pain freedom at 2 hours post dose at Months 1 to 3, Months 4 to 6, and Months 7 to 9 for both populations without evidence to suggest the development of tolerance to the ability to relieve migraine pain. The majority of patients reported absence of migraine associated symptoms of photophobia, phonophobia, nausea, and vomiting at 2 hours post dose. More than half of the patients had migraine attacks associated with "as usual" functional disability at 2 hours post dose. Rizatriptan was generally well tolerated in the long-term treatment of acute migraine in pediatric patients age 12 to 17 years. No clinically important findings were observed in laboratory values, vital signs, and electrocardiograms.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population			Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
			M	F	Age Range				
[Ref. 5.3.3.2: P048]	Paul K. Winner, D.O. (048)	An open-label, single-dose study.	6	6	13 to 18	Nonsmoking male and female adolescent (from 12 to 18 years of age) patients with a history of migraine, who were otherwise healthy.	Each patient received a single 10-mg oral dose of rizatriptan.	The primary pharmacokinetic variable was $AUC_{(0-\infty)}$ of rizatriptan. C_{max} of rizatriptan, $AUC_{(0-\infty)}$ of L-706,248, and C_{max} of L-706,248 were evaluated as secondary variables. Exploratory variables included time to maximum concentration (T_{max}), half-life ($t_{½}$), elimination rate constant (k_e), renal clearance (CL_r), and urinary excretion (U_e) of rizatriptan and L-706,248. Metabolite-to-parent ratios of $AUC_{(0-\infty)}$, C_{max} and U_e were explored. Heart rate and blood pressure were measured at various time points following administration of rizatriptan. Adverse experiences and laboratory safety results were recorded.	Follow. oral admin. of a 10-mg dose of rizatriptan (RZ): (1) Geometric mean (GM) AUC and C_{max} for RZ may be 50 and 76% larger, respect., in adoles. than in adults, based on the 90% confidence intervals (CI). Differ. are > in females (F) than in males (M). (2) GM $AUC_{(0-\infty)}$ for L-706,248 is sim. bet. adoles. and adults. (3) GM C_{max} for L-706,248 may be 2.52-fold > in adoles. than in adults, based on the 90% CI. (4) Based on the safety profile of RZ, the range of obs. AUC and C_{max} values for RZ in adults and adoles., and the min. poten. contrib. of L-706,248 to the activity of RZ, the poss. of ↑ plasma conc. of RZ and L-706,248 in adoles. compared to adults is not of clin. concern. (5) With respect to a compar. bet. adolesc. M and F in this study, (a) $AUC_{(0-\infty)}$ of RZ and L-706,248 is greater in adoles. F than in adoles. M. (b) C_{max} of RZ and L-706,248 is sim. in adoles. F and M. (6) RZ 10 mg is gen. safe and well toler. in adoles. pts.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.1.2: P062]	Multicenter (062)	An open-labeled, single-dose, balanced randomized, 2-period crossover study to determine the bioequivalence of a 5-mg rizatriptan conventional tablet compared to 5-mg rizatriptan orally disintegrating tablet in adolescent migraineurs, during a headache-free interval.	15	22	(12 to 17)	Healthy male and female adolescent migraine patients between 12 and 17 years of age who were migraine free on days of study drug administration and weighed at least 40 kg.	A single 5-mg conventional tablet and a single 5-mg orally disintegrating tablet in random order.	Pharmacokinetics: Blood and urine was collected over 24 hours following each dose of rizatriptan for the determination of pharmacokinetic parameters. Area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), and time to maximum concentration (T_{max}) were calculated, where possible, for each dose. Safety: Adverse experiences and laboratory safety parameters were collected throughout the study. Vital signs and ECG measurements were taken in each period.	Rizatriptan, administered as a single 5-mg conventional tablet and a single 5-mg orally disintegrating tablet, appears generally well tolerated in adolescent migraine patients.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.5.1: P054]	Multicenter (054)	Outpatient, randomized, double-blind (with in-house blinding), placebo-controlled, parallel-groups design	98 67	 96 98 01	12 to 14 15 to 17 12 to 14 15 to 17 18 to 99	Male and female patients between 12 and 17 years of age with a history of migraine (International Headache Society [IHS] criteria) for at least 6 months prior to study start, with or without aura.	Dosage: Rizatriptan 5-mg tablet and placebo tablet (to match 5 mg). Duration: Single dose for initial migraine headache followed by up to 2 additional doses within 24 hours of the initial dose for migraine recur-rence(s).	Rating of headache severity on a 4-point scale (0 = no headache; 1 = mild pain; 2 = moderate pain; 3 = severe pain) immediately before initial dose and at 0.5, 1, 1.5, 2, 3, and 4 hours thereafter. Safety was assessed by review of the incidence of adverse experiences, laboratory values, ECG recordings, and vital signs.	1. Rizatriptan 5 mg is not statistically superior to placebo in affording patients pain-free and pain relief status at 2 hours postdose. 2. Rizatriptan 5 mg is superior to placebo in reducing functional disability at 1.5 and 2 hours postdose. 3. Rizatriptan 5 mg is well tolerated for the acute treatment of migraine in adolescent patients.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.5.1: P059]	Multicenter (059)	Outpatient, randomized, double-blind (with in-house blinding), placebo-controlled, parallel-group study. Patients treated a single moderate/severe (Grade 2/3) migrainous headache plus up to 2 recurrences with rizatriptan 5 mg or placebo.	303	383	12 to 17	Male and female patients between 12 and 17 years of age with a history of migraine (International Headache Society [HIS] criteria) for the 6 months prior to study start, with or without aura.	5 mg or placebo, up to 3 doses.	Rating of headache severity of a 4-point scale (0 = no headache, 1 = mild pain, 2 = moderate pain, 3 = severe pain) immediately before initial dose and at 0.5, 1, 1.5, 2, 3, and 4 hours thereafter. Safety was assessed by review of the incidence of adverse experiences, laboratory values, ECG recordings and vital signs.	In adolescent patients age 12-to-17 years who treated moderate or severe migraine headaches, (1) Rizatriptan 5 mg was not superior to placebo in the proportion of patients reporting relief at 2 hours after administration of test drug; (2) Rizatriptan 5 mg had a marginal effect compared to placebo in the proportion of patients reporting pain-free status at 2 hours after administration of test drug; (3) Rizatriptan 5 mg was safe and well tolerated.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population M	Study Population F	Study Population Age Range	Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
[Ref. 5.3.5.1: P059C1]	Multicenter (059 Extension, 061)	Randomized, open-label, parallel-groups, outpatient study. Patients treated up to 6 migraine attacks (mild, moderate, or severe intensity) plus 2 recurrences per month, for up to 1 year.	277	409	12 to 17	Male and female patients between the ages of 12 and 17 with a history of migraine (International Headache Society [HIS] criteria) for the 6 months prior to study start, with or without aura.	Rizatriptan 5 mg tablet, orally disintegrating tablet (wafer; [ODT]), or standard care, up to 3 doses per migraine attack, for up to 12 months.	Safety was evaluated by review of adverse experiences and periodic safety examinations, including vital signs, 12-lead ECGs, routine laboratory screens. Efficacy was determined for pain relief at 2 hours post-dose, for pain free at 2 hrs, and for the use of additional migraine medication. The criteria was a 4-point headache severity rating scale of 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain; ratings were done at onset of attack and 2 hours postdose. The use of additional migraine medication was recorded in the patient diary.	In open-label studies of 12- to-17-year-old patients with mild, moderate, or severe migraine attacks: 1) Rizatriptan 5-mg tablets and orally disintegrating tablets are generally safe and well tolerated for up to 12 months of treatment; 2) The safety of rizatriptan 5-mg tablets and orally disintegrating tablets is comparable to that of standard care migraine medications; 3) Rizatriptan 5-mg tablets and orally disintegrating tablets appear more effective than standard care for the treatment of acute migraine.

[Ref]	Primary Investigator (Prot. No.)	Methodology	Study Population			Diagnosis/ Inclusion Criteria	Dosage/ Duration	Evaluation Criteria	Results
			M	F	Age Range				
[Ref. 5.3.3.1: 814]	070-0001: Suzanne Swan, M.D./ Davita Clinical Research	This was an open label, randomized, 3-period crossover study in 24 health volunteers aged 18 to 45 years.	5	22	18-42 yrs	A total of twenty-seven (27) healthy nonsmoking male and female subjects between the ages of 18 and 42 were enrolled in this study. Female subjects could not be pregnant or breast-feeding, and female subjects of childbearing potential were required to use specified birth control measures.	This was an open-label, 3-period, single dose study. In each period, subjects received a single oral dose of rizatriptan 10-mg tablet, rizatriptan 10-mg ODTc, or rizatriptan 10 mg ODTs in a randomized, crossover manner. Each dosing was separated by a minimum of 7 days.	Pharmacokinetic: The following pharmacokinetic parameters were determined: (1) AUC 0-2 hours for the comparison between ODTc and ODTs; (2) AUC 0-1 hour for the comparison between ODTc and tablet; (3) Tmax for all 3 dosing regimens. Safety: Safety evaluations included clinical assessment of vital signs, physical examinations, laboratory safety tests, and evaluation of adverse experiences.	(1) Rizatriptan 10-mg ODT taken with water has a faster rate of absorption compared to rizatriptan 10-mg ODT taken without water as assessed by the geometric mean AUC0-2 hours for plasma concentration. . (2) Rizatriptan 10-mg ODT taken with water did not show a faster rate of absorption compared to rizatriptan 10-mg tablet as assessed by the geometric mean AUC0-1 hour plasma concentration.

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/s/

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