U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	20-865/S-020
Drug Name:	MAXALT MLT™ (rizatriptan benzoate)
Indication(s):	Adolescent Migraine
Applicant:	Merck Sharp & Dohme Corp.
Date(s):	Submission date: 03/25/2011
	PDUFA Date: 9/23/11
Review Priority:	Priority Review
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Keywords: Logistic Regression, Sample Size Re-estimation

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1. EXECUTIVE SUMMARY

The data and analysis of the pivotal study P082 support the sponsor's efficacy claim that Rizatriptan is effective in the acute treatment of migraine with or without aura in 12 to 17 year old patients. Rizatriptan is demonstrated to be statistically superior to placebo as measured by the proportion of patients reporting pain freedom at 2 hours post dose (primary endpoint). The magnitude of the treatment effect is modest. The secondary endpoint of pain relief at 2 hours post dose numerically favors Rizatriptan, but is not statistically significant (Table 8).

There was a planned interim analysis for sample size re-estimation or early termination for efficacy. The result of the interim analysis was sample size increase by 100. Results with or without the additional 100 subjects are consistent.

Results are consistent across subgroups with sufficient sample size. For the subgroup of patients weighing < 40 kg and the subgroup of patients with severe baseline pain severity, there appears to have a treatment effect in pain relief (secondary endpoint) but not pain freedom (primary endpoint). However, no conclusions can be drawn due to limited sample size of the two subgroups.

2. INTRODUCTION

2.1 Overview

Two formulations of MAXALT™, solid tablets (NDA 20-864) and Orally Disintegrating Tablets (ODT; also referred to as MAXALT-MLT™, NDA 20-865), were both approved on June 29, 1998 for the treatment of migraine attacks with or without aura. The sponsor submitted this sNDA for MAXALT ODT formulation to update labeling based on the results of the pediatric clinical program conducted to address the requirements of the Pediatric Written Request. The original Pediatric Written Request (dated March 6, 2009) required evaluation of patients 6-17 years of age in three clinical studies (Clinical PK Study, Acute Efficacy and Safety Study and Long-Term Safety Study). The final amended Written Request (Amendment 1, dated January 13, 2010), changed the requirement to evaluate only patients 12-17 years of age. Development of rizatriptan for pediatric patients has occurred under IND 40,458. A pre-sNDA teleconference was held on September 16, 2010.

The pivotal efficacy data for this sNDA was based on Protocol 082. This study was a randomized, doubleblind, placebo-controlled study. It used a weight-based dosing strategy for rizatriptan, whereby children weighing ≥20 and <40 kg receive a 5-mg dose and children weighing 40 kg or more receive a 10-mg dose. This trial was conducted in patients who had not achieved a satisfactory response with prior acetaminophen or NSAID treatment. A two-stage double-randomization design was used to attempt to exclude placebo responders. A total of 1010 subjects were randomized at 134 sites in the United States and 57 sites internationally.

Two previous trials (Protocols 054 and 059) conducted in adolescents aged 12 to 17 failed to demonstrate a statistically significant treatment effect. The sponsor stated that it was possibly due to insufficient exposures based on weight for the older and heavier children and high placebo response rate. All patients were dosed with 5 mg rizatriptan, regardless of weight. In addition, patients were not required to be non responders to acetaminophen or non-steroidal anti-inflammatory drug (NSAID) treatment in the two studies.

2.2 Data Sources

The analysis datasets are located in the following directory:
\\Cdsesub1\evsprod\NDA020865\0034\m5\datasets\p082\analysis
\\Cdsesub1\evsprod\NDA020865\0039\m5\datasets\p082\analysis\datasets

The raw datasets are located in the following directory:
\\Cdsesub1\evsprod\NDA020865\0034\m5\datasets\p082\tabulations\age12to17
\\Cdsesub1\evsprod\NDA020865\0039\m5\datasets\p082\analysis\datasets\raw\xpt

The study reports are located in the following directory:
\\Cdsesub1\evsprod\NDA020865\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\p082

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

During the review process, this reviewer was able to reproduce the primary analysis dataset and trace how the primary endpoint was derived.

3.2 Evaluation of Efficacy

Study 082 is the only pivotal efficacy study in this submission.

The study was initiated on December 01, 2009 and the last subject (12 to 17 year old) completed the primary therapy period on October 22, 2010. The last protocol amendment was dated September 22, 2010. The database lock was on November 29, 2010.

The study protocol was amended five times. Amendment 082-01 was applicable to Germany only. Amendment 082-02 (April 15, 2010) was applicable worldwide except for Germany; amendment 082-03 (April 28, 2010) was applicable to Germany only. In amendment 082-02 and 082-03, the sample size and randomization were revised according to the amended Written Request. Amendment 082-04 (applicable worldwide except for Germany) and amendment 082-05 (Germany only) were issued on September 22, 2010 to change sample size for the 6-11 year old and the trigger for the interim analysis (IA).

In the amendment 082-02 and 082-03, the IA was to take place when approximately 350 evaluable patients between 12 and 17 years of age were available. However, the interim analysis was conducted for 250 patients on July 23, 2010, before the amendment 082-04 and 082-05 were issued. Per sponsor's response to the reviewer's request for clarification, the reason for adjusting the timing of the IA was to avoid enrollment pause as full enrollment would be finished before the IA on the 350 evaluable patients could be completed.

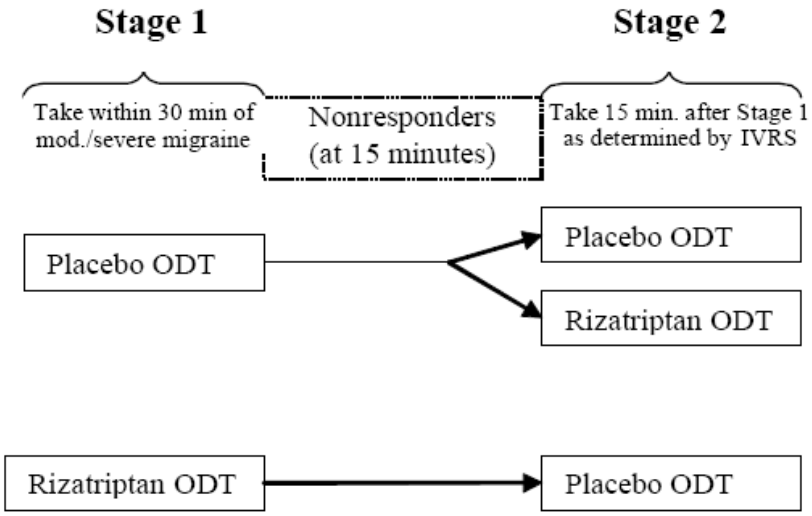
Study Design and Endpoints

Study 082 was a worldwide, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of rizatriptan ODT 5 mg and 10 mg, for the treatment of an acute migraine attack in pediatric migraineurs with and without aura, aged 6 to 17 years. Using weight-based dosing, patients weighing < 40 kg were randomized to rizatriptan 5 mg or matching placebo, and patients weighing ≥ 40 kg were randomized to rizatriptan 10 mg or a matching placebo. This study was conducted in patients who had not achieved a satisfactory response with prior Nonsteroidal anti-inflammatory drugs (NSAIDS) or Acetaminophen/ paracetamol (APAP) treatment.

A two-stage double-randomization design was used to attempt to exclude placebo responders. Patients (randomized in a 20:1 ratio to placebo or rizatriptan), treated a single migraine attack

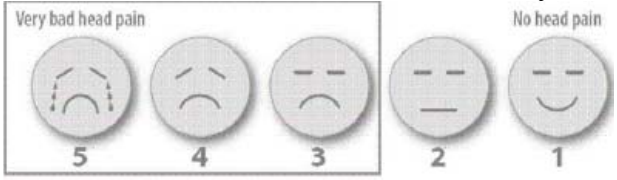
during Stage 1. Patients administered study medication within 30 minutes of onset of a qualifying migraine attack, i.e. an attack of moderate or severe intensity. After 15 minutes, patients called into the Interactive Voice Response System (IVRS) to report their pain intensity level. Patients who reported mild pain or no pain (i.e., responders) were instructed to take no further study medication. Non-responders who received placebo in Stage 1 were randomized in Stage 2 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 (Figure 1).

Figure 1. Study Treatment Procedures



Patients completed a paper migraine diary at prespecified time points to evaluate efficacy and tolerability. If a patient did not treat a qualifying migraine within 4 months, or 2 months following randomization of the last participant in his/her age group, whichever was earlier, the patient could be discontinued from the study. Patients were permitted to use their own headache medication to treat any continued migraine pain after 2 hours from administration of study medication.

The primary efficacy endpoint was pain freedom (PF) at 2 hours post Stage 2 dose. Pain intensity was assessed using a Five-Face Pain Scale with migraine pain intensity defined as follows: Face 1 = no pain; Face 2 = mild pain; Face 3 to 4 = moderate pain; Face 5 = severe pain. PF was defined as a reduction in headache severity from Face 5/4/3 at Stage 2 baseline to Face 1.



The Secondary Efficacy Endpoint was pain relief (PR) at 2 hours post Stage 2 dose, with PR defined as a reduction in headache severity from Face 5/4/3 at Stage 2 baseline to Face 2/1.

Exploratory Measures were:

- Absence of Photophobia
- Absence of Phonophobia
- Absence of Nausea
- Sustained Pain Freedom (SPF) from 2-24 hours and from 2-48 hours.

The sample size of 548 was selected to achieve 80% power to demonstrate that rizatriptan is superior to placebo with respect to the proportion of patients with pain freedom at 2 hours (with a two-sided type I error rate of 0.05), if the underlying treatment difference is 11 percentage points (36% versus 25%). It was expected that approximately 900 patients between 12 and 17 years of age would be needed to enter the study in Stage 1 to yield 548 evaluable adolescent patients in Stage 2.

One interim efficacy analysis was planned in this study for patients between 12 and 17 years of age. Depending on the interim analysis results, the study may continue as planned, discontinue due to overwhelming efficacy, or an additional 100 patients between 12 and 17 years of age may be added to maintain adequate study power. Table 1 displays the range of rizatriptan response rates that may be observed at the time of interim analysis which will result in various decisions to the trial based on the calculated conditional powers (CP), under different observed placebo response rates.

Table 1. Interim Analysis Decision Rules (with 250 Evaluable subjects)

Observed Placebo Response Rate	0.1	0.2	0.3	0.4	Decision Criteria	Outcome
Observed Rizatriptan Response Rate (approximate)	< 0.164	< 0.281	< 0.391	< 0.495	CP ≤ 65%	No change
	(0.164, 0.175)	(0.281, 0.294)	(0.391, 0.404)	(0.495, 0.508)	65% < CP < 78%	Add 100 patients
	(0.175, 0.245)	(0.294, 0.365)	(0.404, 0.475)	(0.510, 0.580)	CP ≥ 78% and p-value ≥ 0.005	No change.
	≥ 0.245	≥ 0.365	≥ 0.475	≥ 0.580	p-value < 0.005	Stop for efficacy

Patient Disposition, Demographic and Baseline Characteristics

A total of 1010 patients 12 to 17 years of age were randomized and 702 were treated with study medication in either Stage 1 or Stage 2 or both Stages. The lack of qualifying event was the primary reason (209/308, 67.9%) for the failure of patients to treat with study medication. Of the 702 treated patients, 651 (92.7%) completed the study; the primary reason for study discontinuation was due to protocol violation (46/51, 90.2%) (Table 2).

Table 2. Patient Accounting by Treatment

Stage 1 Treatment / Stage 2 Treatment	Placebo[†] / NA (N=362)	Rizatriptan[†] / NA (N=25)	Placebo / Rizatriptan (N=298)	Placebo / Placebo (N=299)	Rizatriptan / Placebo (N=26)	Total (N=1010)
	n (%)[‡]	n (%)[‡]	n (%)[‡]	n (%)[‡]	n (%)[‡]	n (%)[‡]
Patient treated	**82 (22.7)**	**7 (28.0)**	**291 (97.7)**	**296 (99.0)**	**26 (100)**	**702 (69.5)**
Treated stage 1 only	77 (93.9)	7 (100)	4 (1.4)	4 (1.4)	0 (0.0)	92 (13.1)
Treated stage 2 only	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.0)	0 (0.0)	5 (0.7)
Treated both stages	5 (6.1)	0 (0.0)	285 (97 9)	289 (97.6)	26 (100)	605 (86.2)
Completed	56 (68.3)	4 (57.1)	281 (96.6)	284 (95.9)	26 (100)	651 (92.7)
Treated stage 1 only and completed	56 (100)	4 (100)	0 (0.0)	0 (0.0)	0 (0.0)	60 (9.2)
Treated both stages and completed	0 (0.0)	0 (0.0)	281 (100)	284 (100)	26 (100)	591 (90.8)
Discontinued	26 (31.7)	3 (42.9)	10 (3.4)	12 (4.1)	0 (0.0)	51 (7.3)
Withdrawal by Subject	2 (7.7)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	3 (5.9)
Protocol Violation	24 (92.3)	3 (100)	8 (80.0)	11 (91.7)	0 (0.0)	46 (90.2)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	2 (3.9)
Patient not treated	**280 (77.3)**	**18 (72.0)**	**7 (2.3)**	**3 (1.0)**	**0 (0.0)**	**308 (30.5)**
Discontinued	280 (100)	18 (100)	7 (100)	3 (100)	0 (0.0)	308 (100)
Adverse Event	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Withdrawal By Subject	16 (5.7)	1 (5.6)	2 (28.6)	0 (0.0)	0 (0.0)	19 (6.2)
Protocol Violation	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Lost to Follow-up	32 (11.4)	2 (11.1)	5 (71.4)	3 (100)	0 (0.0)	42 (13.6)
Pregnancy	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Physician Decision	27 (9.6)	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	31 (10.1)
Lack of Qualifying Event[§]	198 (70.7)	11 (61.1)	0 (0.0)	0 (0.0)	0 (0.0)	209 (67.9)

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

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

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

Patient was counted only once across treatment groups.

Rizatriptan group refers to Rizatriptan 5mg or 10mg.

N = Number of randomized patients.

Source: CSR page 73.

Of the 702 treated patients, 61.0% were female, 64.5% were white, 73.2% were from the US, 17.5% were from the EU, 91.5% weighed ≥40 kg, 48.1% were 12 to 14 years of age, and 51.9% were 15 to 17 years of age (Table 3).

Table 3. Baseline Demographic Characteristics

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=82)	Rizatriptan† / NA (N=7)	Placebo / Rizatriptan (N=291)	Placebo / Placebo (N=296)	Rizatriptan / Placebo (N=26)	Total (N=702)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender						
Female	47 (57.3)	3 (42.9)	176 (60.5)	190 (64.2)	12 (46.2)	428 (61.0)
Male	35 (42.7)	4 (57.1)	115 (39.5)	106 (35.8)	14 (53.8)	274 (39.0)
Age (Years)						
12-14	42 (51 2)	5 (71.4)	148 (50.9)	136 (45.9)	7 (26.9)	338 (48.1)
15-17	40 (48.8)	2 (28.6)	143 (49.1)	160 (54.1)	19 (73.1)	364 (51.9)
Mean (SD)	14.4 (1.7)	13.9 (1.8)	14.5 (1.7)	14.6 (1.7)	15.2 (1.7)	14.5 (1.7)
Median	14.0	14.0	14.0	15.0	16.0	15.0
Range	12 to 17	12 to 17	12 to 17	12 to 17	12 to 17	12 to 17
Study Region						
US	55 (67 1)	6 (85.7)	205 (70.4)	225 (76.0)	23 (88.5)	514 (73.2)
Non-US	27 (32.9)	1 (14.3)	86 (29.6)	71 (24.0)	3 (11.5)	188 (26.8)
Racial Origin						
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.3)
Black or African American	8 (9.8)	2 (28.6)	36 (12.4)	40 (13.5)	3 (11.5)	89 (12.7)
Native Hawaiian or Other Pacific Islander	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
White	50 (61.0)	5 (71.4)	180 (61.9)	200 (67.6)	18 (69.2)	453 (64.5)
Asian	18 (22.0)	0 (0.0)	59 (20 3)	40 (13.5)	3 (11.5)	120 (17.1)
Multi-Racial	5 (6.1)	0 (0.0)	16 (5.5)	14 (4.7)	2 (7.7)	37 (5.3)
Weight (at screening)						
< 40 kg	11 (13.4)	1 (14.3)	26 (8.9)	21 (7.1)	1 (3.8)	60 (8.5)
≥ 40 kg	71 (86.6)	6 (85.7)	265 (91.1)	275 (92.9)	25 (96.2)	642 (91.5)

Source: CSR page 78.

The baseline migraine history for all treated patients was similar across groups (Table 4). A total of 36.8% of patients reported migraines usually preceded by aura. The two most common usual migraine treatments at baseline were NSAIDs and APAP reported by a total of 62.1% and 42.7% of patients, respectively. The average number of moderate to severe migraine attacks per month was 3.6. The majority of patients (80.5%) were not on prophylactic migraine therapies.

Table 4. Baseline Migraine History

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=82)	Rizatriptan† / NA (N=7)	Placebo / Rizatriptan (N=291)	Placebo / Placebo (N=296)	Rizatriptan / Placebo (N=26)	Total (N=702)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Migraine Usually Preceded by Aura						
Yes	29 (35.4)	2 (28.6)	108 (37.1)	111 (37.5)	8 (30.8)	258 (36.8)
No	53 (64.6)	5 (71.4)	182 (62.5)	185 (62.5)	18 (69.2)	443 (63.1)
Missing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Typical Duration of Migraine (Untreated)						
2-6 hours	49 (59.8)	4 (57.1)	140 (48.1)	140 (47.3)	14 (53.8)	347 (49.4)
7-24 hours	28 (34.1)	2 (28.6)	108 (37.1)	114 (38.5)	9 (34.6)	261 (37.2)
>24 hours	5 (6.1)	1 (14.3)	43 (14.8)	42 (14.2)	3 (11.5)	94 (13.4)
Usual Migraine Treatment						
None	1 (1.2)	0 (0.0)	8 (2.7)	7 (2.4)	0 (0.0)	16 (2.3)
NSAID	48 (58.5)	4 (57.1)	182 (62.5)	183 (61.8)	19 (73.1)	436 (62.1)
Acetaminophen/Paracetamol (APAP)	34 (41.5)	5 (71.4)	125 (43.0)	127 (42.9)	9 (34.6)	300 (42.7)
Aspirin	10 (12.2)	0 (0.0)	16 (5.5)	25 (8.4)	4 (15.4)	55 (7.8)
Triptan	15 (18.3)	1 (14.3)	56 (19.2)	61 (20.6)	4 (15.4)	137 (19 5)
Opiate or Opiate Combination	0 (0.0)	1 (14.3)	1 (0.3)	8 (2.7)	0 (0.0)	10 (1.4)
Barbiturate Combination	0 (0.0)	0 (0.0)	3 (1.0)	4 (1.4)	1 (3.8)	8 (1.1)
Ergot or Ergot Combination	1 (1.2)	0 (0.0)	3 (1.0)	1 (0.3)	1 (3.8)	6 (0.9)
Caffeine Containing Medications	7 (8.5)	1 (14.3)	22 (7.6)	29 (9.8)	4 (15.4)	63 (9.0)
Other	6 (7.3)	1 (14.3)	33 (11.3)	27 (9.1)	4 (15.4)	71 (10.1)
Average Number of Moderate or Severe Migraine Attacks per Month Over the Last 3 Months						
N	82	7	291	296	26	702
Mean	3.8	3.4	3.7	3 5	3.7	3.6
SD	1.9	2.4	1.8	1.8	1.7	1.8
Median	3.5	3.0	3.0	3.0	3.0	3.0
Range	1 to 8	1 to 8	1 to 8	1 to 8	1 to 7	1 to 8
Prophylactic Migraine Treatment						
Without	62 (75.6)	6 (85.7)	221 (75.9)	254 (85.8)	22 (84.6)	565 (80 5)
With‡	20 (24.4)	1 (14.3)	70 (24.1)	42 (14.2)	4 (15.4)	137 (19.5)
Antidepressants	3 (15.0)	0 (0.0)	16 (22.9)	12 (28.6)	1 (25.0)	32 (23.4)
Antiepileptics	0 (0.0)	0 (0.0)	23 (32.9)	10 (23.8)	2 (50.0)	35 (25.5)
Beta blocking agents	0 (0.0)	0 (0.0)	4 (5.7)	0 (0.0)	0 (0.0)	4 (2.9)
Hormonal contraceptives	0 (0.0)	0 (0.0)	4 (5.7)	1 (2.4)	0 (0.0)	5 (3.6)
All other therapeutic products	20 (100)	1 (100)	69 (98.6)	41 (97.6)	3 (75.0)	134 (97.8)

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

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

Source: CSR page 81-85.

Baseline migraine characteristics were relatively balanced between patients who received rizatriptan and placebo in Stage 2 baseline. Of the patients treated with Stage 2 medication, 83.5% reported moderate headaches and 16.8% reported severe headaches at baseline. Most patients reported photophobia and phonophobia at baseline, with 76.5% and 78.5% of patients reporting these symptoms, respectively. A total of 39.8% of patients reported nausea at Stage 2 baseline (Table 5).

Table 5. Patient Stage 2 Baseline Migraine Characteristics (All Patients Treated with Stage 2 Medication)

Stage 1 Treatment / Stage 2 Treatment	Placebo / Rizatriptan (N=287)	Placebo / Placebo (N=292)	Rizatriptan / Placebo (N=26)	Total (N=605)
	n (%)	n (%)	n (%)	n (%)
Baseline Severity				
Moderate	240 (83.6)	243 (83.2)	22 (84.6)	505 (83 5)
Severe	47 (16.4)	49 (16.8)	4 (15.4)	100 (16.5)
Presence of Phonophobia				
Yes	209 (72.8)	232 (79.5)	22 (84.6)	463 (76.5)
No	78 (27.2)	59 (20.2)	4 (15.4)	141 (23.3)
Missing	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Presence of Photophobia				
Yes	217 (75.6)	237 (81.2)	21 (80.8)	475 (78.5)
No	70 (24.4)	54 (18.5)	5 (19.2)	129 (21.3)
Missing	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Presence of Nausea				
Yes	117 (40.8)	114 (39.0)	10 (38.5)	241 (39.8)
No	169 (58.9)	177 (60.6)	16 (61.5)	362 (59.8)
Missing	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.3)
Presence of Vomiting				
Yes	17 (5.9)	10 (3.4)	0 (0.0)	27 (4.5)
No	269 (93.7)	281 (96.2)	26 (100)	576 (95.2)
Missing	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.3)
Ability to Perform Daily Activities				
As Usual	5 (1.7)	5 (1.7)	0 (0.0)	10 (1.7)
Some	46 (16.0)	49 (16.8)	9 (34.6)	104 (17.2)
A Little	118 (41.1)	127 (43.5)	12 (46.2)	257 (42.5)
Not at All	118 (41.1)	110 (37.7)	5 (19.2)	233 (38.5)
Missing	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)

Rizatriptan group refers to Rizatriptan 5mg or 10mg.
N = Number of treated patients.

Source: CSR Table 10-9.

Statistical Methodologies

A logistic regression model with factors for Stage 2 treatment group (rizatriptan vs. placebo), Stage 2 baseline headache severity (moderate or severe), and region (US or ex-US) was used to compare treatment groups with respect to pain freedom (PF) at 2 hours post Stage 2 dose. As planned in the protocol, a single interim efficacy analysis on the primary endpoint was planned for sample size re-estimation (increase by 100 patients) or stop for efficacy (if p-value< 0.005). To maintain the overall alpha level at 0.05 for the primary endpoint, the critical alpha level for the final analysis was adjusted to 0.0477. Based on Chen et al (2004, Statist. Med.), increasing the sample size when the unblinded interim result is promising will not inflate the type I error rate.

The secondary endpoint, pain relief (PR) at 2 hours was analyzed in the same manner as that used to analyze the primary endpoint (PF). A sequential testing was used that the secondary endpoint was to be formally tested (α=0.05 level) only if the test of the primary hypothesis was statistically significant at α=0.0477 level.

Other efficacy analyses were considered supportive and/or exploratory. The absence of photophobia, phonophobia, nausea, vomiting and Sustained Pain Freedom (SPF) were analyzed in the same manner as that used to analyze pain freedom at 2 hours.

Analysis of efficacy data was based on the Full Analysis Set (FAS) population, which included patients who did not respond to placebo at Stage 1 and were randomized to Stage 2. Patients randomized to rizatriptan in Stage 1 were not included in the FAS. Additionally, for each 2-hour endpoint, the FAS population also required patients to have taken the Stage 2 study medication, had a moderate to severe Stage 2 baseline score, and had at least one post Stage 2 dose efficacy measurement prior to or including the 2-hour time point.

For time points after the Stage 2 dose, missing data for headache severity, ratings of functional disability, and associated symptoms in the FAS analysis were imputed by applying the Last Observation Carried Forward (LOCF) method. Missing Stage 2 baseline values were imputed via LOCF by carrying forward the Stage 1 baseline value, if available. Stage 2 baseline values were not "carried forward" to impute missing post Stage 2 treatment data.

Results and Conclusions

One interim efficacy analysis was performed in this study for patients between 12 and 17 years of age and at the time point at which a total of approximately 250 evaluable patients were available. This was conducted by an unblinded statistician who had no other responsibilities associated with the study. An external DMC reviewed the interim results and recommended to increase the sample size by 100 patients to a total of 1000 patients. The interim analysis result is in Table 6.

Table 6. Sponsor's Interim Analysis Result for the Primary Endpoint

Endpoint	Treatment	N	n/m	Observed Response Rate % (95% CI)	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡	Conditional Power %
Pain Freedom at 2 hours post Stage 2 dose	Rizatriptan	121	37 / 121	30.6 (22.5 , 39.6)	1.56 (0.88 , 2.78)	0.131	68.6
	Placebo	128	28 / 128	21.9 (15.1 , 30.0)			

† Only patients who did not respond to placebo at Stage 1 and are randomized to Stage 2 were included. Patients randomized to Rizatriptan in Stage 1 were excluded.

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

An odds ratio >1 is in favor of the Rizatriptan 5mg or 10mg group.

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

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

m = Number of evaluable patients in FAS population.

Source: Sponsor response on May 02, 2011. Submission SN# 037.

Of the 579 patients who treated with study medication at Stage 2, 570 patients are included in the FAS. Seven patients (1 in Rizatriptan group and 6 in placebo group) are excluded for absence of post Stage 2 dose data through 2 hours.

Table 7. Patient Accounting in the Analyses of the Primary and Secondary Efficacy Endpoints (All Patients Treated with Stage 2 Medication)

Stage 1 Treatment / Stage 2 Treatment	Placebo/Rizatriptan (N=287) n (%)†	Placebo/Placebo (N=292) n (%)†	Total (N=579) n (%)†
Pain Severity (PF and PR) at 2 hrs			
Patients included in FAS analysis	284 (99.0)	286 (97.9)	570 (98.4)
Patients excluded from FAS analysis‡	3 (1.0)	6 (2.1)	9 (1.6)
No post Stage 2 dose data through 2 hours	1 (33.3)	6 (100)	7 (77.8)
Not treated with Stage 1 medication	2 (66.7)	3 (50.0)	5 (55.6)

† For counts of patients included/excluded from FAS analysis, percentage based on patients treated with Stage 2 Medication. Within patients excluded from FAS analysis, subgroup percentages based on patients excluded from FAS analysis. Patients may be excluded from FAS analysis for more than one reason.

‡ Patient may be excluded from FAS analysis for more than one reason.

Rizatriptan group refers to Rizatriptan 5mg or 10mg.

N = Number of patients treated with Stage 2 medication.

FAS = Full analysis set.

Source: CSR Table 10-4.

For the primary efficacy endpoint, PF at 2 hours post dose for patients 12 to 17 years old, rizatriptan demonstrated a statistically significantly higher response rate compared to placebo (30.6% vs. 22.0%, p-value=0.025). For the secondary efficacy endpoint, PR at 2 hours post dose, rizatriptan demonstrated a higher response rate compared to placebo (58.8% vs. 51.4%) but was not statistically significant (p-value=0.080). Results for the primary and secondary endpoints are summarized in Table 8.

Table 8. Summary of Primary and Secondary Endpoints (FAS)

Endpoint	Treatment	m	n	Observed Response Rate % (95% CI)†	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡
Primary						
Pain Freedom at 2 hours post dose	Rizatriptan	284	87	30.6 (25 3, 36.4)	1.55(1.06, 2.26)	0.025
	Placebo	286	63	22.0 (17.4, 27.3)		
Secondary						
Pain Relief at 2 hours post dose	Rizatriptan	284	167	58.8 (52.8, 64.6)	1.35(0.96, 1.90)	0.080
	Placebo	286	147	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).

m = Number of evaluable patients in FAS population.

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

Source: CSR page 6.

For the exploratory endpoints of migraine associated symptoms at 2 hours post dose, rizatriptan was nominally statistically superior to placebo for the symptoms of nausea (p=0.013), and vomiting (p=0.026), but not for the symptoms of photophobia (p=0.26) and phonophobia (p=0.11) in the PWR 12 to 17 year old population (Table 9).

Table 9. Absence of Photophobia, Phonophobia, Nausea, and Vomiting at 2 hours

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

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

[†] Exact confidence intervals.

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

Treatment refers to Stage 2 treatment group.

Rizatriptan group refers to Rizatriptan 5 mg or 10 mg.

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

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

m = Number of evaluable patients in FAS population.

Source: page 57 of submission section 2.7.3

Reviewer's Analyses and Comments

The reviewer has confirmed the efficacy analysis results presented in this review.

The reviewer conducted sensitivity analyses for the primary and key secondary endpoints by including none or any 1, 2 or all 3 of the following covariates: baseline headache severity, region, weight group. The results of sensitivity analyses are consistent with the primary analysis results.

There were only 4 subjects in FAS missing observations at 2-hour post stage 2 dose, which had minimum impact on efficacy results.

Since the original planned sample size was 900, the reviewer conducted analysis on the first 900 randomized subjects. The result (Table 10) shows that estimated treatment effect is consistent with the analysis result on the FAS.

Table 10. Summary of Primary and Secondary Endpoints (First 900 Randomized subjects)

Endpoint	Treatment	m	n	Observed Response Rate % (95% CI)†	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡
Primary						
Pain Freedom at 2 hours post dose	Rizatriptan	259	80	30.9 (25 3, 36.9)	1.52(1.02, 2.27)	0.040
	Placebo	254	57	22.4 (17.5, 28.1)		
Secondary						
Pain Relief at 2 hours post dose	Rizatriptan	259	151	58.3 (52.0, 64.4)	1.32(0.92, 1.89)	0.127
	Placebo	254	131	51.6 (45.2, 57.9)		

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).

m = Number of evaluable patients in FAS population.

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

Source: FDA reviewer.

The sponsor proposed to test the secondary endpoint of Pain Relief (PR) for the 12 to 17 year old patients at level 0.05 if the test of the primary hypothesis was statistically significant. Hung et al (2007, JBS) show that under a group sequential design or an adaptive design, this testing strategy may inflate the type I error rate for the secondary hypothesis. However, the conclusion still holds that the analysis of PR is not statistically significant, although it is trending in favor of Rizatriptan.

In summary, the results are robust and support the efficacy of Rizatriptan in the acute treatment of migraine in 12 to 17 year old patients.

3.3 Evaluation of Safety

Please see the clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The treatment effect in PF and PR response appeared to be consistent across the subgroup levels of age, gender, race and region (Table 11 and Table 12).

Table 11. Summary of Subgroup Analysis of Pain Freedom (1)

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

n (%) = Number (percent) of evaluable patients with pain freedom at 2 hours post-dose.

m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.

Source: CSR Table 11-5, confirmed by the reviewer.

Table 12. Summary of Subgroup Analysis of Pain Relief (1)

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

n (%) = Number (percent) of evaluable patients with pain relief at 2 hours post-dose.

m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.

Source: CSR Table 11-6, confirmed by the reviewer.

4.2 Other Special/Subgroup Populations

Majority of the patients weigh ≥ 40 kg and had moderate baseline pain. For the two subgroups, the difference in PF and PR response rates between rizatriptan and placebo groups appeared consistent with the primary results (Table 13 and Table 14).

For the subgroup of patients weighing < 40 kg and the subgroup of patients with severe baseline pain severity, there appeared to have a treatment effect in pain relief (secondary endpoint) but not pain freedom (primary endpoint). However, no conclusions could be drawn due to limited sample size of the two subgroups (Table 13 and Table 14).

Table 13. Summary of Subgroup Analysis of Pain Freedom (2)

	Rizatriptan (N=285)		Placebo (N=289)	
Subgroup	n/m	(%)	n/m	(%)
Baseline Weight				
< 40 kg	9/ 26	34.6	8/ 21	38.1
≥ 40 kg	78/258	30.2	55/265	20.8
Stage 2 Baseline Pain Severity				
Moderate	81/238	34.0	56/237	23.6
Severe	6/ 46	13.0	7/ 49	14.3

n (%) = Number (percent) of evaluable patients with pain freedom at 2 hours post-dose.

m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.

Source: CSR Table 11-5, confirmed by the reviewer.

Table 14. Summary of Subgroup Analysis of Pain Relief (2)

	Rizatriptan (N=285)		Placebo (N=289)	
Subgroup	n/m	(%)	n/m	(%)
Baseline Weight				
< 40 kg	15/ 26	57.7	10/ 21	47.6
≥ 40 kg	152/258	58.9	137/265	51.7
Stage 2 Baseline Pain Severity				
Moderate	149/238	62.6	133/237	56.1
Severe	18/ 46	39.1	14/ 49	28.6

n (%) = Number (percent) of evaluable patients with pain relief at 2 hours post-dose.

m = Number of evaluable patients in FAS population. Patients with a missing subgroup entry were excluded from that subgroup analysis.

Source: CSR Table 11-6, confirmed by the reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Results from the pivotal study P082 demonstrate that rizatriptan is effective in the acute treatment of migraine in adolescent patients (ages 12-17 years). For the primary efficacy endpoint, PF at 2 hours post dose for patients 12 to 17 years old, rizatriptan demonstrated a statistically significantly higher response rate compared to placebo (30.6% vs. 22.0%, p-value=0.025). For the secondary efficacy endpoint, PR at 2 hours post dose, rizatriptan demonstrated a higher response rate compared to placebo (58.8% vs. 51.4%) but was not statistically significant (p-value=0.080). Results for the primary and secondary endpoints are summarized in Table 8.

There was a planned interim analysis for sample size re-estimation or stop for efficacy. The result of the interim analysis was to increase sample size by 100. Results with or without the additional 100 subjects are consistent.

There is minimum missing data and the results are robust with respect to covariates. Results are consistent across subgroups with sufficient sample size. For the subgroup of patients weighing < 40 kg and the subgroup of patients with severe baseline pain severity, there appears to have a treatment effect in pain relief (secondary endpoint) but not pain freedom (primary endpoint). However, no conclusions can be drawn due to limited sample size of the two subgroups.

5.2 Conclusions and Recommendations

The data and analysis of the pivotal study P082 support the sponsor's efficacy claim that Rizatriptan is effective in the acute treatment of migraine with or without aura in 12 to 17 year old patients.

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification
Specify for each trial:

Protocol Number (s): 082
Protocol Title (optional):
Phase: 3
Control: Placebo Control
Blinding: Double-Blind
Number of Centers: 191
Region(s) (Country): US, Belgium, Canada, Denmark, Estonia, Finland, France, Germany, India, Italy, Latvia, Netherlands, Norway, Poland, Romania, Spain, Sweden, United Kingdom
Duration: 8 Weeks
Treatment Arms: Placebo/ Rizatriptan
Treatment Schedule: children weighing ≥20 and <40 kg received a 5-mg OD dose and children weighing 40 kg or more received a 10-mg OD dose
Randomization: Yes
Ratio: 20:1 in Stage 1 and 1:1 in Stage 2
Method of Randomization: stratification
Central via an IVRS
If stratified, then the Stratification Factors: 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)
Primary Endpoint: pain freedom at 2 hours post Stage 2 dose
Primary Analysis Population: Full Analysis Set (FAS)
Statistical Design: Superiority
Adaptive Design: Yes
Primary Statistical Methodology: logistic regression
Interim Analysis: Yes
If yes:
No. of Times: 1
Method: IA on the primary endpoint for sample size re-estimation or stop for efficacy
α Adjustment: Yes
α Spending Function: interim analysis at level 0.005 and final analysis at level 0.0477
DSMB: Yes
Sample Size: 1000
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?
Power= 0.80
Δ= 11%
α = 0.05

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? Yes
- Did the Applicant perform **Sensitivity Analyses**? No
- How were the **Missing Data** handled? LOCF
- Was there a **Multiplicity** involved? No

  If yes,

  Multiple Arms (Yes/No)?

  Multiple Endpoints (Yes/No)?

  Which method was used to control for type I error?
- **Multiple Secondary Endpoints**: Are they being included in the label? No

  If yes, method to control for type 1 error.

Were Subgroup Analyses Performed (Yes/No)? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No
- Overall, was the study positive (Yes/No)? Yes

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

/s/

XIANG LING
07/15/2011

KUN JIN
07/15/2011
I concur with this review.

HSIEN MING J J HUNG
07/15/2011