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

ADDENDUM STATISTICAL REVIEW AND EVALUATION (ADDENDUM)

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: 12/23/11
Review Priority:	Priority Review
Biometrics Division:	Division I, Office of Biometrics (HFD -710)
Statistical Reviewer:	Xiang Ling, Ph.D.
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1. Summary

This addendum pertains to submission SN#0042, which contains the final clinical study reports and associated data for pediatric studies which were ongoing at the time of the submission of the original sNDA. Specifically for the pivotal study 082, enrollment for the 12-17 year-old population was complete to address the final amended Written Request (WR). However, enrollment for the 6-11 year-old population (which was included in the original WR but not the final WR) was still ongoing at the time of the original sNDA data cut off. The final CSR for Protocol 082 includes unblinded safety and efficacy data from both the 6-11 and 12-17 year old population.

The raw datasets are located in the following directory:
\\Cdsesub1\evsprod\NDA020865\0042\m5\datasets\p082\tabulations

The analysis datasets are located in the following directory:
\\Cdsesub1\evsprod\NDA020865\0046\m5\datasets\p082\analysis\datasets

The study report is located in the following directory:
\\Cdsesub1\evsprod\NDA020865\0042\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\p082

Tables in the original statistical review were updated to include 6-11 year old population. The conclusion in the original review still holds.

2. Patient Disposition, Demographic and Baseline Characteristics

A total of 1382 patients were randomized to treatment (1010 patients 12-17 years of age and 372 patients 6-11 years of age). The lack of a qualifying event was the primary reason (261/405, 64.4%) for the failure of patients to treat with study medication. Of the 977 patients who treated with study medication, 894 (91.5%) completed the study. Among patients who treated with study medication, the primary reason for study discontinuation was due to a protocol violation (74/83, 89.2%) because they did not follow/complete the required study procedures (Table 1).

Table 1. Patient Accounting by Treatment for the 6 to 17 Year Age Group

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=492)	Rizatriptan† / NA (N=31)	Placebo / Rizatriptan (N=409)	Placebo / Placebo (N=410)	Rizatriptan / Placebo (N=40)	Total (N=1382)
	n (%)‡	n (%)‡	n (%)‡	n (%)‡	n (%)‡	n (%)‡
Patient treated	**124 (25.2)**	**8 (25.8)**	**400 (97.8)**	**405 (98.8)**	**40 (100)**	**977 (70.7)**
Treated stage 1 only	117 (94.4)	8 (100)	8 (2.0)	6 (1.5)	0 (0.0)	139 (14.2)
Treated stage 2 only	0 (0.0)	0 (0.0)	7 (1.8)	7 (1.7)	0 (0.0)	14 (1.4)
Treated both stages	7 (5.6)	0 (0.0)	385 (96.3)	392 (96.8)	40 (100)	824 (84.3)
Completed	87 (70.2)	5 (62.5)	377 (94.3)	385 (95.1)	40 (100)	894 (91.5)
Treated stage 1 only and completed	87 (100)	5 (100)	0 (0.0)	0 (0.0)	0 (0.0)	92 (10.3)
Treated both stages and completed	0 (0.0)	0 (0.0)	377 (100)	385 (100)	40 (100)	802 (89.7)
Discontinued	37 (29.8)	3 (37.5)	23 (5.8)	20 (4.9)	0 (0.0)	83 (8.5)
Withdrawal by Subject	2 (5.4)	0 (0.0)	3 (13.0)	0 (0.0)	0 (0.0)	5 (6.0)
Protocol Violation	34 (91.9)	3 (100)	19 (82.6)	18 (90.0)	0 (0.0)	74 (89.2)
Lost to Follow-up	0 (0.0)	0 (0.0)	1 (4.3)	2 (10.0)	0 (0.0)	3 (3.6)
Physician Decision	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Patient not treated	**368 (74.8)**	**23 (74.2)**	**9 (2.2)**	**5 (1.2)**	**0 (0.0)**	**405 (29.3)**
Discontinued	368 (100)	23 (100)	9 (100)	5 (100)	0 (0.0)	405 (100)
Adverse Event	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Withdrawal By Subject	23 (6.3)	2 (8.7)	2 (22.2)	0 (0.0)	0 (0.0)	27 (6.7)
Protocol Violation	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Lost to Follow-up	53 (14.4)	4 (17.4)	7 (77.8)	5 (100)	0 (0.0)	69 (17.0)
Pregnancy	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Physician Decision	37 (10.1)	4 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)	41 (10.1)
Lack of Qualifying Event§	248 (67.4)	13 (56.5)	0 (0.0)	0 (0.0)	0 (0.0)	261 (64.4)

† 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 Table 10-4.

Of the 977 treated patients in the 6 to 17 year old population, 56.3% were female, 61.1% were White, 75.6% were from the US, and 74.8% weighed ≥ 40 kg (Table 2).

Table 2. Baseline Demographic Characteristics for the 6 to 17 Year Age Group

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=124)	Rizatriptan† / NA (N=8)	Placebo / Rizatriptan (N=400)	Placebo / Placebo (N=405)	Rizatriptan / Placebo (N=40)	Total (N=977)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender						
Female	61 (49.2)	4 (50.0)	227 (56.8)	238 (58.8)	20 (50.0)	550 (56.3)
Male	63 (50.8)	4 (50.0)	173 (43.3)	167 (41.2)	20 (50.0)	427 (43.7)
Age (Years)						
6-11	42 (33.9)	1 (12.5)	109 (27.3)	109 (26.9)	14 (35.0)	275 (28.1)
12-14	42 (33.9)	5 (62.5)	148 (37.0)	136 (33.6)	7 (17.5)	338 (34.6)
15-17	40 (32.3)	2 (25.0)	143 (35.8)	160 (39.5)	19 (47.5)	364 (37.3)
Mean (SD)	12.7 (2.9)	13.4 (2.1)	13.0 (2.9)	13.1 (2.9)	13.1 (3.4)	13.0 (2.9)
Median	13.0	13.5	13.0	13.0	14.0	13.0
Range	6 to 17	10 to 17	6 to 17	6 to 17	6 to 17	6 to 17
Study Region						
US	95 (76.6)	7 (87.5)	290 (72.5)	318 (78.5)	29 (72.5)	739 (75.6)
EU	23 (18.5)	0 (0.0)	78 (19.5)	52 (12.8)	10 (25.0)	163 (16.7)
Other	6 (4.8)	1 (12.5)	32 (8.0)	35 (8.6)	1 (2.5)	75 (7.7)
Racial Origin						
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.2)
Black or African American	22 (17.7)	3 (37.5)	59 (14.8)	74 (18.3)	4 (10.0)	162 (16.6)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
White	71 (57.3)	5 (62.5)	241 (60.3)	257 (63.5)	23 (57.5)	597 (61.1)
Asian	20 (16.1)	0 (0.0)	78 (19.5)	52 (12.8)	11 (27.5)	161 (16.5)
Multi-Racial	10 (8.1)	0 (0.0)	22 (5.5)	20 (4.9)	2 (5.0)	54 (5.5)
Weight (at screening)						
< 40 kg	35 (28.2)	2 (25.0)	106 (26.5)	92 (22.7)	11 (27.5)	246 (25.2)
≥ 40 kg	89 (71.8)	6 (75.0)	294 (73.5)	313 (77.3)	29 (72.5)	731 (74.8)

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

Source: CSR Table 10-16.

A total of 32.7% 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 60.0% and 44.5% of patients, respectively. The average number of moderate to severe migraine attacks per month over the last 3 months was 3.6. Most patients (81.4%) were not on migraine prophylactic therapy (Table 3).

Table 3. Baseline Migraine History for the 6 to 17 Year Age Group

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=124)	Rizatriptan† / NA (N=8)	Placebo / Rizatriptan (N=400)	Placebo / Placebo (N=405)	Rizatriptan / Placebo (N=40)	Total (N=977)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Migraine Usually Preceded by Aura						
Yes	39 (31.5)	3 (37.5)	133 (33.3)	134 (33.1)	10 (25.0)	319 (32.7)
No	85 (68.5)	5 (62.5)	266 (66.5)	271 (66.9)	30 (75.0)	657 (67.2)
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	74 (59.7)	5 (62.5)	208 (52.0)	207 (51.1)	27 (67.5)	521 (53.3)
7-24 hours	44 (35.5)	2 (25.0)	141 (35.3)	152 (37.5)	10 (25.0)	349 (35.7)
>24 hours	6 (4.8)	1 (12.5)	51 (12.8)	46 (11.4)	3 (7.5)	107 (11.0)
Usual Migraine Treatment						
None	1 (0.8)	0 (0.0)	9 (2.3)	7 (1.7)	0 (0.0)	17 (1.7)
NSAID	72 (58.1)	5 (62.5)	241 (60.3)	244 (60.2)	24 (60.0)	586 (60.0)
Acetaminophen/Paracetamol (APAP)	53 (42.7)	5 (62.5)	177 (44.3)	185 (45.7)	15 (37.5)	435 (44.5)
Aspirin	11 (8.9)	0 (0.0)	21 (5.3)	32 (7.9)	4 (10.0)	68 (7.0)
Triptan	19 (15.3)	1 (12.5)	74 (18.5)	77 (19.0)	8 (20.0)	179 (18.3)
Opiate or Opiate Combination	0 (0.0)	1 (12.5)	3 (0.8)	10 (2.5)	0 (0.0)	14 (1.4)
Barbiturate Combination	1 (0.8)	0 (0.0)	4 (1.0)	5 (1.2)	1 (2.5)	11 (1.1)
Ergot or Ergot Combination	1 (0.8)	0 (0.0)	3 (0.8)	1 (0.2)	1 (2.5)	6 (0.6)
Caffeine Containing Medications	9 (7.3)	1 (12.5)	24 (6.0)	30 (7.4)	5 (12.5)	69 (7.1)
Other	9 (7.3)	1 (12.5)	39 (9.8)	39 (9.6)	5 (12.5)	93 (9.5)
Average Number of Moderate or Severe Migraine Attacks per Month Over the Last 3 Months						
N	124	8	400	405	40	977
Mean	3.7	3.4	3.6	3.7	3.4	3.6
SD	1.8	2.2	1.7	1.8	1.7	1.8
Median	3.0	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	101 (81.5)	7 (87.5)	308 (77.0)	348 (85.9)	31 (77.5)	795 (81.4)
With‡	23 (18.5)	1 (12.5)	92 (23.0)	57 (14.1)	9 (22.5)	182 (18.6)
Antidepressants	3 (13.0)	0 (0.0)	18 (19.6)	12 (21.1)	1 (11.1)	34 (18.7)
Antiepileptics	0 (0.0)	0 (0.0)	25 (27.2)	11 (19.3)	2 (22.2)	38 (20.9)
Beta blocking agents	0 (0.0)	0 (0.0)	4 (4.3)	0 (0.0)	0 (0.0)	4 (2.2)
Hormonal contraceptives	0 (0.0)	0 (0.0)	4 (4.3)	1 (1.8)	0 (0.0)	5 (2.7)
All other therapeutic products	23 (100)	1 (100)	90 (97.8)	55 (96.5)	8 (88.9)	177 (97.3)

† 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.
Patient was counted only once across treatment groups.
Rizatriptan group refers to Rizatriptan 5mg or 10mg.

Source: CSR Table 10-18.

Baseline migraine characteristics were relatively balanced between patients who received rizatriptan and placebo in Stage 2. Of the patients treated with Stage 2 medication, 82.3% reported moderate headaches and 17.2% reported severe headaches at baseline. Most patients reported photophobia and phonophobia at baseline, with 72.7% and 75.8% of patients reporting these symptoms, respectively. A total of 40.2% of patients reported nausea at Stage 2 baseline (Table 4).

Table 4. Patient Stage 2 Baseline Migraine Characteristics for the 6 to 17 Year Age Group (All Patients Treated with Stage 2 Medication)

Stage 1 Treatment / Stage 2 Treatment	Placebo / Rizatriptan (N=392)	Placebo / Placebo (N=399)	Rizatriptan / Placebo (N=40)	Total (N=831)
	n (%)	n (%)	n (%)	n (%)
Baseline Severity				
No Pain	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Mild Pain	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Moderate	322 (82.1)	329 (82.5)	33 (82.5)	684 (82.3)
Severe	68 (17.3)	68 (17.0)	7 (17.5)	143 (17.2)
Missing	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Presence of Phonophobia				
Yes	269 (68.6)	305 (76.4)	30 (75.0)	604 (72.7)
No	122 (31.1)	92 (23.1)	10 (25.0)	224 (27.0)
Missing	1 (0.3)	2 (0.5)	0 (0.0)	3 (0.4)
Presence of Photophobia				
Yes	288 (73.5)	314 (78.7)	28 (70.0)	630 (75.8)
No	103 (26.3)	83 (20.8)	12 (30.0)	198 (23.8)
Missing	1 (0.3)	2 (0.5)	0 (0.0)	3 (0.4)
Presence of Nausea				
Yes	155 (39.5)	164 (41.1)	15 (37.5)	334 (40.2)
No	235 (59.9)	233 (58.4)	25 (62.5)	493 (59.3)
Missing	2 (0.5)	2 (0.5)	0 (0.0)	4 (0.5)
Presence of Vomiting				
Yes	23 (5.9)	16 (4.0)	4 (10.0)	43 (5.2)
No	367 (93.6)	381 (95.5)	36 (90.0)	784 (94.3)
Missing	2 (0.5)	2 (0.5)	0 (0.0)	4 (0.5)
Ability to Perform Daily Activities				
As Usual	6 (1.5)	5 (1.3)	0 (0.0)	11 (1.3)
Some	55 (14.0)	61 (15.3)	12 (30.0)	128 (15.4)
A Little	159 (40.6)	165 (41.4)	17 (42.5)	341 (41.0)
Not at All	171 (43.6)	166 (41.6)	11 (27.5)	348 (41.9)
Missing	1 (0.3)	2 (0.5)	0 (0.0)	3 (0.4)

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

Source: CSR Table 10-20.

3. Results and Conclusions

Family-wise Type I error was controlled through a sequential testing procedure in which, a formal evaluation of the statistical significance of the secondary hypotheses was contingent upon statistical significance for the primary hypothesis at the α=0.0477 level (adjusted to account for the interim sample size adjustment). Testing then proceeded to the secondary hypotheses that were tested sequentially in the following order: PR at 2 hours post Stage 2 dose (12 to 17 years old), PF at 2 hours post Stage 2 dose (6 to 17 years old), and PR at 2 hours post Stage 2 dose (6 to 17 years old). The primary null hypothesis was rejected, but the first secondary hypothesis failed to be rejected, and hence, formal statistical significance was not achieved for any of the secondary efficacy endpoints for the 6 to 17 year old population.

For the second secondary endpoint of PF at 2 hours post-dose for the 6 to 17 year old population, there was a nominally significantly higher response rate with rizatriptan compared to placebo (33.0% vs. 24.2%; p-value=0.010). For the exploratory endpoint of PF at 2 hours post-dose for the 6 to 11 year old population, there was a higher response rate for PF at 2 hours post Stage 2 dose compared to placebo (39.8% vs. 30.4%), but this difference though similar to that in the other age categories but was not nominally significant (p-value=0.269) (Table 5).

Table 5. Summary of Efficacy Endpoints (FAS)

Endpoint/Population	Treatment	m	n	Observed Response Rate % (95% CI)†	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡
Pain Freedom at 2 hours post dose						
12 to 17 year old Primary endpoint	Rizatriptan Placebo	284 286	87 63	30.6 (25.3, 36.4) 22.0 (17.4, 27.3)	1.55(1.06, 2.26)	0.025
6 to 17 year old 2nd secondary endpoint	Rizatriptan Placebo	382 388	126 94	33.0 (28.3, 37.9) 24.2 (20.0, 28.8)	1.52(1.10, 2.10)	0.010
6 to 11 year old exploratory endpoint	Rizatriptan Placebo	98 102	39 31	39.8 (30.0, 50.2) 30.4 (21.7, 40.3)	1.41(0.77, 2.60)	0.269
Pain Relief at 2 hours post dose						
12 to 17 year old 1st secondary endpoint	Rizatriptan Placebo	284 286	167 147	58.8 (52.8, 64.6) 51.4 (45.4, 57.3)	1.35(0.96, 1.90)	0.080
6 to 17 year old 3rd secondary endpoint	Rizatriptan Placebo	382 388	220 204	57.6 (52.5, 62.6) 52.6 (47.5, 57.6)	1.22(0.91, 1.63)	0.178
6 to 11 year old exploratory endpoint	Rizatriptan Placebo	98 102	53 57	54.1 (43.7, 64.2) 55.9 (45.7, 65.7)	0.88(0.49, 1.58)	0.666

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). Age group (6 to 11 years old vs. 12 to 17 years old) was added as a covariate for endpoints involving the 6-17 year old patients.

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 tables 11-1 to 11-6.

The reviewer has confirmed the efficacy analysis results presented in this review. The reviewer conducted sensitivity analyses and conclude that the above the results are robust with respect to covariates.

The treatment effect in PF response appeared to be consistent across the subgroup levels of age, gender, race and region. The study used a weight-based dosing strategy for rizatriptan, whereby children weighing <40 kg receive a 5-mg dose and children weighing 40 kg or more receive a 10-mg dose. For the subgroups of patients weighing < 40 kg, there appeared to have a smaller treatment effect in PF (Table 6), indicating that 5 mg dose may not be sufficient. Logistic regressions indicated that there was an effect of weight on Pain Freedom (p-value = 0.086 for weight group (<40 kg vs ≥ 40 kg) and 0.005 for weight as a continuous variable).

Table 6. Summary of Subgroup Analysis of Pain Freedom for the 6 to 17 Year Age Group

	Rizatriptan (N=383)		Placebo (N=391)	
Subgroup	n/m	(%)	n/m	(%)
Age (Years)				
6-11	39/ 98	39.8	31/102	30.4
12-14	49/144	34.0	36/129	27.9
15-17	38/140	27.1	27/157	17.2
Gender				
Female	70/219	32.0	51/231	22.1
Male	56/163	34.4	43/157	27.4
Racial				
Caucasian	80/232	34.5	57/247	23.1
Non-Caucasian	46/150	30.7	37/141	26.2
Region				
US	86/273	31.5	66/301	21.9
Non-US	40/109	36.7	28/ 87	32.2
Baseline Weight				
< 40 kg	39/ 99	39.4	33/ 90	36.7
≥ 40 kg	87/283	30.7	61/298	20.5
Stage 2 Baseline Pain Severity				
Moderate	116/316	36.7	81/322	25.2
Severe	10/ 66	15.2	13/ 66	19.7

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 (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 11-70, confirmed by the reviewer.

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/s/

XIANG LING
11/18/2011

KUN JIN
11/18/2011
I concur with this review.

HSIEN MING J HUNG
11/21/2011