Review and Evaluation of Clinical Data

NDA (Serial Number):	**20,865/S-020**
Sponsor:	**Merck**
Drug:	**Maxalt MLT (rizatriptan benzoate)**
Proposed Indication:	**Acute Treatment of Pediatric Migraine**
Material Submitted:	**120-Date Safety Update Report**
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Reviewer:	**Nushin Todd, M.D., Ph.D., Medical Reviewer, DNDP, ODE I**

1 Introduction

On March 25, 2011, the sponsor submitted a supplemental New Drug Application (sNDA, supplement number S-020) for Maxalt-MLT™ (rizatriptan benzoate). Maxalt is a 5-$HT_{1B/1D}$ receptor agonist (triptan) approved for the acute treatment of migraine in adults. With the sNDA submission, the sponsor requested a new indication for Maxalt: for the acute treatment of migraine in pediatric patients.

Originally, the sponsor was to have submitted the sNDA for patients 6 to 17 years of age. Due to operational challenges, an agreement was reached for the sNDA to only include data for patients 12 to 17 years of age, with the understanding that results for younger patients (aged 6 to 11 years) would be submitted later. The sNDA thus provided efficacy and safety results from studies in pediatric patients aged 12-17 years and blinded data in pediatric patients aged 6 to 11 years.

Pursuant to the sNDA, the sponsor submitted a 4-month Safety Update Report (SUR) on July 22, 2011. The SUR provided final results of pediatric studies that were described in the sNDA. This included new data for the 6 to 11 year old patient population as well as cumulative results for 6 to 17 year old patients in the acute efficacy study, Protocol 082 (P082). The SUR also provided updated results for the long term safety study, Protocol 086 (P086). Review of the final data from these studies is presented below.

2 120-Day Safety Update Report of the Efficacy Study (P082)

2.1 Background

The acute efficacy study, P082, enrolled 2 pediatric age groups: 12-17 and 6-11 year olds. By the time of the sNDA submission, final results were complete for patients aged 12-17 years. Enrollment was still ongoing for the 6-11 year olds and only blinded adverse events data were presented in the sNDA.

The 4-month SUR provided the final complete results for study P082, including cumulative data for the 6 to 17 year old patient population as well as results for the 6 to 11 year old patients. The data submitted in the SUR has been reviewed and is presented below.

Results are first presented for the 6 to 17 year old population and then for the 6 to 11 year old group. Where applicable, results for the 12 to 17 year old population are reported and compared to these groups.

Additionally, Dr. Xiang Ling, from the Division of Biometrics at the FDA conducted a statistical analysis for study P082 in the SUR submission. Applicable portions of her efficacy review have been referenced and incorporated below.

2.2 Overview of Efficacy Endpoints

There was one primary efficacy endpoint in study P082: pain freedom (PF) in patients 12 to 17 years of age. There were three secondary efficacy endpoints in the study: Pain relief (PR) in patients 12 to 17 years of age; PF in patients 6 to 17 years of age; and PR in patients 6 to 17 years of age. Exploratory endpoints in the study included PF and PR in the 6 to 11 year old population. All endpoints were at 2 hours post stage 2 dosing.

Pain freedom was defined as a reduction of migraine pain from moderate or severe pain (Faces 3 to 5) to no pain (Face 1) based on a 5 Face Pain Scale. Pain relief was defined as a reduction of baseline migraine pain from moderate or severe (faces 3, 4, or 5) to mild or no pain (faces 1 or 2) based on a 5 Face Pain Scale.

2.3 Patient Disposition and Baseline Characteristics (P082)

6 to 17 Year Old Population

A total of 1,382 patients, 6 to 17 years of age, were randomized to treatment in study P082. Of the randomized patients, 977 patients (71%) were treated with study medication in either stage 1 or stage 2, or both stages. Four hundred and five (405) patients (29%) were not treated in the study. Lack of a qualifying migraine was the most common reason (64%) why these patients did not enter the study. Of the 977 treated patients, 894 (92%) completed the study. The primary reason for study discontinuation was due to protocol violation (89%). Complete patient disposition data is presented in the table below.

Table 1 Patient Disposition Data for the 6 to 17 Year Age Group in Efficacy Study (P082)

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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-4)

Demographic characteristics of patients aged 6 to 17 years in study P082 were typical of a migraine trial. There were more female than male patients overall and more white patients than other races. White patients comprised 61% of the study population. Majority of the patients (76%) were from the US.

Distribution of patients by age revealed the largest age population to be the 15 to 17 year age group, comprising 37% of the patients in the study. The 12 to 14 year olds comprised the next largest group with 35% of the study population. The 6 to 11 year old patients made up 28% of the patients in the study. At screening, 75% of the subjects weighed ≥40 kg and were stratified to the 10 mg rizatriptan dose group. The demographic data is presented in the table below.

Table 2 Patients Demographic Characteristics by Treatment Group in Efficacy Study (P082)

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)
Ethnicity Origin						
Hispanic or Latino	17 (13.7)	2 (25.0)	51 (12.8)	54 (13.3)	5 (12.5)	129 (13.2)
Not Hispanic or Latino	107 (86.3)	6 (75.0)	349 (87.3)	351 (86.7)	35 (87.5)	848 (86.8)
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)
Body Mass Index (kg/m^2)						
Mean (SD)	21.8 (5.5)	20.7 (4.6)	21.5 (5.3)	21.8 (5.5)	22.0 (5.6)	21.7 (5.4)
Median	20.4	18.8	20.5	20.6	20.5	20.5
Range	13 to 44	17 to 31	12 to 46	10 to 44	14 to 38	10 to 46

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

(Source: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-16)

Review of migraine history of all treated subjects was similar across treatment groups. Migraineurs with aura constituted 33% of the subjects in the study. On average, there were 3.6 moderate or severe migraine attacks per month in the study population. Approximately half of all subjects (53%) reported having migraines lasting 2 to 6 hours if not treated. The most common treatment of migraine, reported by 60% of the patients, was NSAIDs. The next most common migraine treatment was acetaminophen, reported by 45% of subjects. The use of a triptan for migraine treatment was reported by 18% of subjects. The majority of subjects (81%) were not on any prophylactic therapy for their migraine. A summary of baseline migraine history of treated subjects aged 6 to 17 years is presented in the table below.

Table 3 Baseline Migraine History for the 6 to 17 Year Age Group in Efficacy Study (P082)

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)
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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-18)

6 to 11 Year Old Population

The rate of patient participation and completion of treatment in the 6 to 11 year age group was similar to the older age groups in study P082. There were 372 patients aged 6 to 11 years that were randomized in the study. Of these, 275 patients (74%) were treated with study medication. There were 97 patients (26%) in the study that were not treated. Like the older age groups, lack of a qualifying migraine was the predominant reason (54%) for not being treated. Of the 275 patients treated, 243 patients (88%) completed the study. Protocol violations constituted the largest reason for discontinuation from the study (88%). Patient disposition for the 6 to 11 year age group is presented in the table below.

Table 4 Patient Disposition Data for the 6 to 11 Year Age Group in Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=130)	Rizatriptan† / NA (N=6)	Placebo / Rizatriptan (N=111)	Placebo / Placebo (N=111)	Rizatriptan / Placebo (N=14)	Total (N=372)
	n (%)‡	n (%)‡	n (%)‡	n (%)‡	n (%)‡	n (%)‡
Patient treated	**42 (32.3)**	**1 (16.7)**	**109 (98.2)**	**109 (98.2)**	**14 (100)**	**275 (73.9)**
Treated stage 1 only	40 (95.2)	1 (100)	4 (3.7)	2 (1.8)	0 (0.0)	47 (17.1)
Treated stage 2 only	0 (0.0)	0 (0.0)	5 (4.6)	4 (3.7)	0 (0.0)	9 (3.3)
Treated both stages	2 (4.8)	0 (0.0)	100 (91.7)	103 (94.5)	14 (100)	219 (79.6)
Completed	31 (73.8)	1 (100)	96 (88.1)	101 (92.7)	14 (100)	243 (88.4)
Treated stage 1 only and completed	31 (100)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	32 (13.2)
Treated both stages and completed	0 (0.0)	0 (0.0)	96 (100)	101 (100)	14 (100)	211 (86.8)
Discontinued	11 (26.2)	0 (0.0)	13 (11.9)	8 (7.3)	0 (0.0)	32 (11.6)
Withdrawal by Subject	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)	0 (0.0)	2 (6.3)
Protocol Violation	10 (90.9)	0 (0.0)	11 (84.6)	7 (87.5)	0 (0.0)	28 (87.5)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (3.1)
Physician Decision	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Patient not treated	**88 (67.7)**	**5 (83.3)**	**2 (1.8)**	**2 (1.8)**	**0 (0.0)**	**97 (26.1)**
Discontinued	88 (100)	5 (100)	2 (100)	2 (100)	0 (0.0)	97 (100)
Withdrawal By Subject	7 (8.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (8.2)
Lost to Follow-up	21 (23.9)	2 (40.0)	2 (100)	2 (100)	0 (0.0)	27 (27.8)
Physician Decision	10 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (10.3)
Lack of Qualifying Event§	50 (56.8)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	52 (53.6)

† 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: SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-6)

In the 6 to 11 year age group, there were more male patients than female patients. Of the 275 treated patients in the 6 to 11 year age group, 56% of the patients in the study were male. In the 12 to 17 year age group, however, male patients made up 39% of the study population. There were also more black/African American patients (27%) in this age group than patients in the 12 to 17 year age group (13%). Please refer to the table below for the demographic distribution of patients in the 6 to 11 year age group.

Table 5 Patients Demographic Characteristics for the 6 to 11 Year Age Group by Treatment Group in Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=42)	Rizatriptan† / NA (N=1)	Placebo / Rizatriptan (N=109)	Placebo / Placebo (N=109)	Rizatriptan / Placebo (N=14)	Total (N=275)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender						
Female	14 (33.3)	1 (100)	51 (46.8)	48 (44.0)	8 (57.1)	122 (44.4)
Male	28 (66.7)	0 (0.0)	58 (53.2)	61 (56.0)	6 (42.9)	153 (55.6)
Age (Years)						
6-11	42 (100)	1 (100)	109 (100)	109 (100)	14 (100)	275 (100)
Mean (SD)	9.4 (1.6)	10.0 ( )	9.1 (1.4)	9.2 (1.5)	9.0 (1.4)	9.2 (1.5)
Median	10.0	10.0	9.0	10.0	9.0	9.0
Range	6 to 11	10 to 10	6 to 11	6 to 11	6 to 11	6 to 11
Study Region						
US	40 (95.2)	1 (100)	85 (78.0)	93 (85.3)	6 (42.9)	225 (81.8)
EU	2 (4.8)	0 (0.0)	19 (17.4)	12 (11.0)	7 (50.0)	40 (14.5)
Other	0 (0.0)	0 (0.0)	5 (4.6)	4 (3.7)	1 (7.1)	10 (3.6)
Racial Origin						
Black or African American	14 (33.3)	1 (100)	23 (21.1)	34 (31.2)	1 (7.1)	73 (26.5)
White	21 (50.0)	0 (0.0)	61 (56.0)	57 (52.3)	5 (35.7)	144 (52.4)
Asian	2 (4.8)	0 (0.0)	19 (17.4)	12 (11.0)	8 (57.1)	41 (14.9)
Multi-Racial	5 (11.9)	0 (0.0)	6 (5.5)	6 (5.5)	0 (0.0)	17 (6.2)
Ethnicity Origin						
Hispanic or Latino	4 (9.5)	1 (100)	13 (11.9)	16 (14.7)	1 (7.1)	35 (12.7)
Not Hispanic or Latino	38 (90.5)	0 (0.0)	96 (88.1)	93 (85.3)	13 (92.9)	240 (87.3)
Weight (at screening)						
< 40 kg	24 (57.1)	1 (100)	80 (73.4)	71 (65.1)	10 (71.4)	186 (67.6)
≥ 40 kg	18 (42.9)	0 (0.0)	29 (26.6)	38 (34.9)	4 (28.6)	89 (32.4)
Body Mass Index (kg/m^2)						
Mean (SD)	21.3 (6.6)	18.4 ( )	18.7 (4.4)	19.0 (4.5)	18.3 (3.0)	19.2 (4.8)
Median	18.8	18.4	17.4	18.2	18.3	17.9
Range	14 to 44	18 to 18	12 to 35	10 to 40	14 to 23	10 to 44

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: SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-21)

Migraine characteristics in the 6 to 11 year old population differed slightly compared to the older patients in the study. Migraines that were preceded by aura occurred less often in the 6 to 11 year age group than patients aged 12-17 in the study (22% versus 37%, respectively). Also, migraine duration was shorter in the younger age group than the older patients in the study. Migraines lasted 2 to 6 hours in 63% of patients aged 6 to 11 years compared to 50% in patients aged 12 to 17 years.

There were, however, many similarities of migraine characteristics in younger patients, aged 6 to 11 years, compared to older patients, aged 12 to 17 years in the study. Similar to the older age groups in the study, the most common treatment of migraine, reported by 55% of patients in the 6 to 11 year age group, was NSAIDS. Also similar to the older age group, the use of a triptan for migraine treatment was reported by 18% of patients in this age group (compared to 20% in the 12 to 17 year age group). Most 6 to 11 year old patients (84%) were not on migraine prophylactic therapy. This was similar to the 12 to 17 year age group (where 81% of patients

were not on migraine prophylactic therapy). Please refer to the table below for baseline migraine history in the 6 to 11 year age group.

Table 6 Baseline Migraine History for the 6 to 11 Year Age Group in Efficacy Study (P082)

Stage 1 Treatment / Stage 2 Treatment	Placebo† / NA (N=42)	Rizatriptan† / NA (N=1)	Placebo / Rizatriptan (N=109)	Placebo / Placebo (N=109)	Rizatriptan / Placebo (N=14)	Total (N=275)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Migraine Usually Preceded by Aura						
Yes	10 (23.8)	1 (100)	25 (22.9)	23 (21.1)	2 (14.3)	61 (22.2)
No	32 (76.2)	0 (0.0)	84 (77.1)	86 (78.9)	12 (85.7)	214 (77.8)
Typical Duration of Migraine (Untreated)						
2-6 hours	25 (59.5)	1 (100)	68 (62.4)	67 (61.5)	13 (92.9)	174 (63.3)
7-24 hours	16 (38.1)	0 (0.0)	33 (30.3)	38 (34.9)	1 (7.1)	88 (32.0)
>24 hours	1 (2.4)	0 (0.0)	8 (7.3)	4 (3.7)	0 (0.0)	13 (4.7)
Usual Migraine Treatment						
None	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.4)
NSAID	24 (57.1)	1 (100)	59 (54.1)	61 (56.0)	5 (35.7)	150 (54.5)
Acetaminophen/Paracetamol (APAP)	19 (45.2)	0 (0.0)	52 (47.7)	58 (53.2)	6 (42.9)	135 (49.1)
Aspirin	1 (2.4)	0 (0.0)	5 (4.6)	7 (6.4)	0 (0.0)	13 (4.7)
Triptan	4 (9.5)	0 (0.0)	18 (16.5)	16 (14.7)	4 (28.6)	42 (15.3)
Opiate or Opiate Combination	0 (0.0)	0 (0.0)	2 (1.8)	2 (1.8)	0 (0.0)	4 (1.5)
Barbiturate Combination	1 (2.4)	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	3 (1.1)
Caffeine Containing Medications	2 (4.8)	0 (0.0)	2 (1.8)	1 (0.9)	1 (7.1)	6 (2.2)
Other	3 (7.1)	0 (0.0)	6 (5.5)	12 (11.0)	1 (7.1)	22 (8.0)
Prophylactic Migraine Treatment						
Without	39 (92.9)	1 (100)	87 (79.8)	94 (86.2)	9 (64.3)	230 (83.6)
With‡	3 (7.1)	0 (0.0)	22 (20.2)	15 (13.8)	5 (35.7)	45 (16.4)
Antidepressants	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	0 (0.0)	2 (4.4)
Antiepileptics	0 (0.0)	0 (0.0)	2 (9.1)	1 (6.7)	0 (0.0)	3 (6.7)
All other therapeutic products	3 (100)	0 (0.0)	21 (95.5)	14 (93.3)	5 (100)	43 (95.6)

† 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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-23)

2.4 Analysis of Pain Freedom

6 to 17 Year Old Population

The primary efficacy endpoint for study P082 was PF at 2 hours post treatment in 12 to 17 year old migraineurs. Results of the primary endpoint in this age group revealed a statistically significantly higher response rate with rizatriptan compared to placebo (30.6% versus 22.0%, respectively; p-value=0.025). The reader is referred to the Clinical Review of sNDA for details of the primary efficacy endpoint results.

Pain freedom at 2 hours post treatment for the 6 to 17 year old population was the second secondary efficacy endpoint in the efficacy study. Table 7 displays the results of PF at 2 hours post treatment in the 6 to 17 year old population. There was a nominally significantly higher response rate with rizatriptan compared to placebo (33.0% versus 24.2%, respectively; p-value=0.010).

Table 7 Pain Freedom at 2 Hours Post Dose for the 6 to 17 Year Age Group in Efficacy Study (P082)

				Observed Response Rate	Comparison (Rizatriptan vs. Placebo)	
Timepoint	Treatment	m	n	% (95% CI)†	Odds Ratio (95% CI)‡	p-Value‡
2 hr	Rizatriptan	382	126	33.0 (28.3, 37.9)	1.52 (1.10, 2.10)	0.010
	Placebo	388	94	24.2 (20.0, 28.8)		

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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 11-2)

6 to 11 Year Old Population

Pain freedom at 2 hours post treatment for the 6 to 11 year old population was an exploratory efficacy endpoint in study P082. There was a higher response rate for PF in the rizatriptan group compared to the placebo group, but this difference was not nominally significant (39.8% versus 30.4%, respectively; p-value-0.269). Table 8 displays the results of PF at 2 hours post treatment in the 6 to 11 year old population.

Table 8 Pain Freedom at 2 Hours Post Dose for the 6 to 11 Year Age Group in Efficacy Study (P082)

				Observed Response Rate	Comparison (Rizatriptan vs. Placebo)	
Timepoint	Treatment	m	n	% (95% CI)†	Odds Ratio (95% CI)‡	p-Value‡
2 hr	Rizatriptan	98	39	39.8 (30.0, 50.2)	1.41 (0.77, 2.60)	0.269
	Placebo	102	31	30.4 (21.7, 40.3)		

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). 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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 11-3)

2.5 Analysis of Pain Relief

6 to 17 Year Old Population

The secondary efficacy endpoint in study P082 was PR at 2 hours post treatment in 12 to 17 year old migraineurs. Results of PR in the 12-17 year age group revealed a higher response rate for rizatriptan compared to placebo but this difference was not statistically significant (58.8% versus 51.4% respectively; p-value=0.080). The reader is again referred to the Clinical Review of sNDA for details regarding the secondary efficacy endpoint results.

Pain relief at 2 hours post treatment for the 6 to 17 year old population was the third secondary efficacy endpoint in the efficacy study. Results of PR in the 6 to 17 year old population revealed a higher response for rizatriptan compared to placebo, but this difference was not statistically significant (57.6% vs 52.6%, respectively; p-value=0.178). Results are presented in Table 9.

Table 9 Pain Relief at 2 Hours Post-Dose for the 6 to 17 Year Age Group in Efficacy Study (P082)

				Observed Response Rate	Comparison (Rizatriptan vs. Placebo)	
Timepoint	Treatment	m	n	% (95% CI)†	Odds Ratio (95% CI)‡	p-Value‡
2 hr	Rizatriptan	382	220	57.6 (52.5, 62.6)	1.22 (0.91, 1.63)	0.178
	Placebo	388	204	52.6 (47.4, 57.6)		

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). 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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 11-5)

6 to 11 Year Old Population

Pain relief at 2 hours post treatment for the 6 to 11 year old population was an exploratory endpoint in the efficacy study. There was no significant difference between rizatriptan and placebo (54.1% versus 55.9%, respectively; p-value=0.666) for PR at 2 hours post treatment for the 6 to 11 year old population. These results are presented in Table 10.

Table 10 Pain Relief at 2 Hours Post-Dose for the 6 to 11 Year Age Group in Efficacy Study (P082)

Timepoint	Treatment	m	n	Observed Response Rate % (95% CI)†	Comparison (Rizatriptan vs. Placebo) Odds Ratio (95% CI)‡	p-Value‡
2 hr	Rizatriptan	98	53	54.1 (43.7, 64.2)	0.88 (0.49, 1.58)	0.666
	Placebo	102	57	55.9 (45.7, 65.7)		

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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 11-6)

2.6 Summary of Subgroup Analysis of Pain Freedom

Overall, the treatment effect of PF response was consistent across the subgroup levels of age, gender, race and region. Interestingly, for the subgroup of patients weighing < 40 kg, there appeared to be a smaller treatment effect in PF, indicating that a 5 mg dose of rizatriptan may not be sufficient. As mentioned by Dr. Ling in her review, logistic regressions indicated that there was an effect of weight on PF (p-value = 0.086 for weight group (<40 kg vs ≥ 40 kg) and 0.005 for weight as a continuous variable). Table 11 provides a summary of subgroup analysis of PF in the various age groups in study P082.

Table 11 Summary of Subgroup Analysis of Pain Freedom for the 6 to 17 Year Age Group

Subgroup	Rizatriptan (N=383)		Placebo (N=391)	
	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: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 11-70 and confirmed by the statistical reviewer, Dr. Ling)

2.7 Summary of Safety Findings in Study P082

No patients discontinued from the study due to an adverse event (AE). There were no serious adverse events (SAEs) reported in any age group of patients treated with rizatriptan in study P082. Triptan related AEs (e.g., chest or throat tightening, paresthesia/dysesthesias, somnolence and dizziness) profiles were similar between the various age groups and similar between rizatriptan and placebo. Review of laboratory tests, vital signs, and electrocardiograms (ECGs) revealed no clinically significant findings for the 6 to 11 year old patients or the 12 to 17 year old patients.

3 120-Day Safety Update Report of the Long Term Safety Study (P086)

3.1 Background

At the time of the sNDA submission, P086, the pediatric long term safety study was still ongoing. Interim data of the study, however, were presented in the sNDA that specifically addressed the PWR requirement regarding the number of patients to be studied (minimum of 300 patients exposed for 6 months of treatment with rizatriptan). The sNDA submission contained data on 373 patients (PWR population) who completed 6 months of study participation.

The 4-month SUR provided cumulative safety results based on the final, one year data from study P086. Updated results were presented on the 606 enrolled patients. This included safety data on 432 patients who had completed at least 12 months of treatment with rizatriptan.

3.2 Safety Results

Adequacy of Data

I identified no significant deficiencies in the SUR submission for study P086. The sponsor submitted all necessary updated summaries and supporting data. There were no notable inconsistencies between the data sources.

Overall Exposure and Demographics of Target Population

The sponsor exceeded the Agency's requirement for the size of the pediatric migraine safety database (of at least 300 patients treating an average of at least 1 migraine attack per month for 6 months, and at least 100 patients treating an average of at least 1 migraine attack per month for 12 months). By the time of the SUR submission, out of 606 patients enrolled, 499 patients had completed at least 6 months of treatment, and 432 had completed at least 12 months of treatment (Table 12). Of these, 423 patients treated at least 1 migraine per month, on average, for a 6-month duration and 339 patients treated at least 1 migraine per month, on average, for a 12-month duration.

Table 12 Number of Patients (%) by Duration of Study Participation in 3-Month Intervals (P086)

Duration of Participation[†]	Rizatriptan 5 mg (N=23)		Rizatriptan 10 mg (N=583)		Total (N=606)	
	n	(%)	n	(%)	n	(%)
Completed ≥3 months	23	(100.0)	528	(90.6)	551	(90.9)
Completed ≥6 months	21	(91.3)	478	(82.0)	499	(82.3)
Completed ≥9 months	20	(87.0)	442	(75.8)	462	(76.2)
Completed ≥12 months[§]	19	(82.6)	413	(70.8)	432	(71.3)
Completed ≥365 days[‖]	16	(69.6)	295	(50.6)	311	(51.3)

Summary Statistics on Patient-Level Average Number of Treated Attacks per Month for 12 Months[‡]						
N	Mean	SD	Median	Q1 - Q3	Min	Max
432	2.0	1.3	1.7	1.0 - 2.6	0.1	7.9

[†] Period between Visit 1 and Last Study visit. For each row completed means patient completed at least the visit in the row.
[‡] Average monthly number of treated attacks for 12 months is calculated for each patient who completed 12 months. Summary statistics are then calculated on these values.
[§] Includes 5 patients who were discontinued on their 12 month visit.
[‖] Includes 3 patients who were discontinued on their 12 month visit.
N = number of patients.
SD = standard deviation.
Q1 = First quartile, Q3 = Third quartile.

(Source: SUR; Clinical Study Report, Module 5.3.5.1.3, Table 12-7)

Distribution of patients based on age, gender and dosage of study medication in the final report submitted in SUR was consistent with the data provided in NDA for the PWR population of Study P086. Demographic data also conformed to the Agency's requirement regarding distribution of study population (reasonable effort should be made to enroll a similar number of patients in the 12 to 14 and 15 to 17 age groups; at a minimum, one third of the enrolled patients should be between 12 and 14 years of age, and, at least half of the treatment experience must be at the highest recommended dose). The table below summarizes the demographic characteristics of final study population of Study P086.

Table 13 Patient Demographic Characteristics (P086)

	Rizatriptan 5mg (N = 23) n (%)	Rizatriptan 10mg (N = 583) n (%)	Total (N = 606) n (%)
Gender			
Female	8 (34.8)	364 (62.4)	372 (61.4)
Male	15 (65.2)	219 (37.6)	234 (38.6)
Age (Years)			
12-14	21 (91.3)	252 (43.2)	273 (45.0)
15-17	2 (8.7)	331 (56.8)	333 (55.0)
Mean (SD)	12.9 (1.2)	14.7 (1.7)	14.7 (1.7)
Median	13.0	15.0	15.0
Range	12 to 17	12 to 17	12 to 17
Study Region			
US	22 (95.7)	565 (96.9)	587 (96.9)
EU	1 (4.3)	18 (3.1)	19 (3.1)
Racial Origin			
American Indian or Alaska Native	1 (4.3)	4 (0.7)	5 (0.8)
Asian	0 (0.0)	4 (0.7)	4 (0.7)
Black or African American	2 (8.7)	57 (9.8)	59 (9.7)
Multi-racial	0 (0.0)	22 (3.8)	22 (3.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.2)
White	20 (87.0)	495 (84.9)	515 (85.0)
Ethnicity Origin			
Hispanic or Latino	3 (13.0)	76 (13.0)	79 (13.0)
Not Hispanic or Latino	20 (87.0)	507 (87.0)	527 (87.0)
Weight (at screening)			
< 40 kg	23 (100.0)	0 (0.0)	23 (3.8)
≥ 40 kg	0 (0.0)	583 (100.0)	583 (96.2)

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

(Source: SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-4)

Salient demographic highlights of the 606 patients treated in the long term safety study (P086) include:

- There was slightly higher proportion of patients in the 15-17 year age group (55.0%) relative to the 12-14 year age group (45.0%)
- The majority of patients weighed ≥40 kg (96.2%), and as such, were treated with the highest recommended dose
- There were more females (61.4%) than males (38.6%)
- Most of the patients were white (85.0%)

Dropouts and Discontinuations

Final accountings of patients in the long term safety study revealed that of the 606 enrolled and treated patients, 179 patients (29.5%) discontinued from the study. Lost to follow up (64/606 patients, 10.6%) and withdrawal by patient (58/606 patients, 9.6%) were the primary reasons for study discontinuation (Table 14). The data on the interim population reported in the NDA

revealed that subject withdrawal was the most common reason for discontinuation (37/605 patients, 6.1%). The next most common reason was loss to follow up (33/605 patients, 5.5%).

Table 14 Accounting of All Enrolled Patients (P086)

	Rizatriptan 5mg (N=28)	Rizatriptan 10mg (N=646)	Total (N=674)
	n (%)	n (%)	n (%)
Patients treated	**23 (82.1)**	**583 (90.2)**	**606 (89.9)**
Completed	19 (82.6)	408 (70.0)	427 (70.5)
Discontinued†	4 (17.4)	175 (30.0)	179 (29.5)
Adverse Event	0 (0.0)	15 (8.6)	15 (8.4)
Withdrawal by Patient	2 (50.0)	56 (32.0)	58 (32.4)
Protocol Violation	0 (0.0)	10 (5.7)	10 (5.6)
Lost to Follow Up	2 (50.0)	62 (35.4)	64 (35.8)
Lack of Efficacy	0 (0.0)	13 (7.4)	13 (7.3)
Pregnancy	0 (0.0)	2 (1.1)	2 (1.1)
Physician Decision	0 (0.0)	15 (8.6)	15 (8.4)
Lack of Qualifying Event‡	0 (0.0)	2 (1.1)	2 (1.1)
Patients not treated	**5 (17.9)**	**63 (9.8)**	**68 (10.1)**
Discontinued†	5 (100.0)	63 (100.0)	68 (100.0)
Withdrawal by Patient	3 (60.0)	16 (25.4)	19 (27.9)
Lost to Follow Up	1 (20.0)	16 (25.4)	17 (25.0)
Physician Decision	1 (20.0)	15 (23.8)	16 (23.5)
Lack of Qualifying Event‡	0 (0.0)	16 (25.4)	16 (23.5)

† Patients counted only once across sub-categories. Percents of sub-category levels are calculated using the total number in that sub-category as the denominator.
‡ Includes patients who enrolled but did not experience a qualifying migraine.
N = Number of enrolled patients

(Source: SUR; Clinical Study Report, Module 5.3.5.1.3, Table 10-2)

Deaths and Nonfatal Serious Adverse Events

There were no deaths reported in the SUR. By the time of the 120-day safety update, there were an additional 5 serious adverse events (SAEs) reported from the original 20 SAEs presented in sNDA. None of the additional 5 SAEs were deemed related to study drug.

There were 2 suicide attempts reported in patients since the sNDA submission. These cases were determined not to be related to study drug and both patients continued in the study.

Triptan Related Adverse Events

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

Triptan related AEs were reported by 136 patients (22.4%) of the 606 patients in the long term safety study. Almost all of the triptan related AEs occurred in the rizatriptan 10 mg treatment group. The distribution of specific triptan related events in the SUR was the same as the pattern seen in the PWR population of the long term safety study. The common triptan related AEs consisted of dizziness (7.4%), somnolence (6.8%), nausea (5.6%) and fatigue (4.8%). Distribution of triptan related AEs is presented in the table below.

Table 15 Summary of Triptan Related Adverse Events (Within 24 Hours Post Any Dose) (P086)

	Rizatriptan 5 mg		Rizatriptan 10 mg		Total	
	n (%)	(95% CI)‡	n (%)	(95% CI)‡	n (%)	(95% CI)‡
Patients in population†	23		583		606	
with no triptan-related adverse event	22 (95.7)	(78.1, 99.9)	448 (76.8)	(73.2, 80.2)	470 (77.6)	(74.0, 80.8)
with one or more triptan-related adverse events	1 (4.3)	(0.1, 21.9)	135 (23.2)	(19.8, 26.8)	136 (22.4)	(19.2, 26.0)
Asthenia	0 (0.0)	(0.0, 14.8)	6 (1.0)	(0.4, 2.2)	6 (1.0)	(0.4, 2.1)
Chest discomfort	0 (0.0)	(0.0, 14.8)	6 (1.0)	(0.4, 2.2)	6 (1.0)	(0.4, 2.1)
Dizziness	1 (4.3)	(0.1, 21.9)	44 (7.5)	(5.5, 10.0)	45 (7.4)	(5.5, 9.8)
Dry mouth	0 (0.0)	(0.0, 14.8)	9 (1.5)	(0.7, 2.9)	9 (1.5)	(0.7, 2.8)
Fatigue	1 (4.3)	(0.1, 21.9)	28 (4.8)	(3.2, 6.9)	29 (4.8)	(3.2, 6.8)
Myalgia	0 (0.0)	(0.0, 14.8)	5 (0.9)	(0.3, 2.0)	5 (0.8)	(0.3, 1.9)
Nausea	0 (0.0)	(0.0, 14.8)	34 (5.8)	(4.1, 8.1)	34 (5.6)	(3.9, 7.8)
Paraesthesia	0 (0.0)	(0.0, 14.8)	6 (1.0)	(0.4, 2.2)	6 (1.0)	(0.4, 2.1)
Somnolence	0 (0.0)	(0.0, 14.8)	41 (7.0)	(5.1, 9.4)	41 (6.8)	(4.9, 9.1)
Throat tightness	0 (0.0)	(0.0, 14.8)	4 (0.7)	(0.2, 1.7)	4 (0.7)	(0.2, 1.7)

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

(Source: SUR; Clinical Study Report, Module 5.3.5.1.3, Table 12-20)

Common Adverse Events

Similar to the data in the sNDA submission, the most common AE reported in the SUR for study P086 was accidental overdose. The sponsor defined overdose as taking a second dose of rizatriptan within 24 hours of the first dose. This conservative definition of overdose led to a large number of cases being reported in P086. Review of the reported overdose cases provided in the submission revealed no incidence of significant clinical consequence.

Of the 606 patients treated in the P086 PWR population, 151 patients (24.9%) took more than 1 dose of study medication in a 24 hour period. Overdosing of study medication occurred in 11/23 patients (47.8%) in the rizatriptan 5 mg treatment group and in 137/583 patients (23.5%) in the rizatriptan 10 mg treatment group. No subject took more than 2 doses of study medication in any 24 hour period. Please refer to Table 16 below for details.

The next most common AEs after study drug overdose, occurring in ≥ 2% of all treated patients within 24 hours post any dose, were dizziness (7.4%), somnolence (6.8%), nausea (5.6%) and fatigue (4.8%). Almost all of these AEs occurred in the rizatriptan 10 mg treatment group. Except for overdose, there were no AEs reported in >1 subject in the rizatriptan 5 mg group.

Table 16 Summary of Common Adverse Events (Occurring in ≥2% of Patients) by System Organ Class (Within 24 Hours Post Dose) (P086)

	Rizatriptan 5 mg		Rizatriptan 10 mg		Total	
	n (%)	(95% CI)‡	n (%)	(95% CI)‡	n (%)	(95% CI)‡
Patients in population†	23		583		606	
with no adverse event	10 (43.5)	(23.2, 65.5)	274 (47.0)	(42.9, 51.1)	284 (46.9)	(42.8, 50.9)
with one or more adverse events	13 (56.5)	(34.5, 76.8)	309 (53.0)	(48.9, 57.1)	322 (53.1)	(49.1, 57.2)
Gastrointestinal disorders	**3 (13.0)**	**(2.8, 33.6)**	**78 (13.4)**	**(10.7, 16.4)**	**81 (13.4)**	**(10.8, 16.3)**
Frequent bowel movements	1 (4.3)	(0.1, 21.9)	0 (0.0)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Irritable bowel syndrome	1 (4.3)	(0.1, 21.9)	0 (0.0)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Nausea	0 (0.0)	(0.0, 14.8)	34 (5.8)	(4.1, 8.1)	34 (5.6)	(3.9, 7.8)
Vomiting	1 (4.3)	(0.1, 21.9)	14 (2.4)	(1.3, 4.0)	15 (2.5)	(1.4, 4.0)
General disorders and administration site conditions	**1 (4.3)**	**(0.1, 21.9)**	**51 (8.7)**	**(6.6, 11.3)**	**52 (8.6)**	**(6.5, 11.1)**
Fatigue	1 (4.3)	(0.1, 21.9)	28 (4.8)	(3.2, 6.9)	29 (4.8)	(3.2, 6.8)
Infections and infestations	**3 (13.0)**	**(2.8, 33.6)**	**35 (6.0)**	**(4.2, 8.3)**	**38 (6.3)**	**(4.5, 8.5)**
Ear lobe infection	1 (4.3)	(0.1, 21.9)	0 (0.0)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)
Nasopharyngitis	1 (4.3)	(0.1, 21.9)	9 (1.5)	(0.7, 2.9)	10 (1.7)	(0.8, 3.0)
Upper respiratory tract infection	1 (4.3)	(0.1, 21.9)	5 (0.9)	(0.3, 2.0)	6 (1.0)	(0.4, 2.1)
Injury, poisoning and procedural complications	**11 (47.8)**	**(26.8, 69.4)**	**147 (25.2)**	**(21.7, 28.9)**	**158 (26.1)**	**(22.6, 29.8)**
Accidental overdose§	11 (47.8)	(26.8, 69.4)	137 (23.5)	(20.1, 27.2)	148 (24.4)	(21.1, 28.0)
Musculoskeletal and connective tissue disorders	**1 (4.3)**	**(0.1, 21.9)**	**36 (6.2)**	**(4.4, 8.4)**	**37 (6.1)**	**(4.3, 8.3)**
Muscle tightness	1 (4.3)	(0.1, 21.9)	9 (1.5)	(0.7, 2.9)	10 (1.7)	(0.8, 3.0)
Nervous system disorders	**1 (4.3)**	**(0.1, 21.9)**	**112 (19.2)**	**(16.1, 22.6)**	**113 (18.6)**	**(15.6, 22.0)**
Dizziness	1 (4.3)	(0.1, 21.9)	44 (7.5)	(5.5, 10.0)	45 (7.4)	(5.5, 9.8)
Headache	0 (0.0)	(0.0, 14.8)	13 (2.2)	(1.2, 3.8)	13 (2.1)	(1.1, 3.6)
Migraine	0 (0.0)	(0.0, 14.8)	14 (2.4)	(1.3, 4.0)	14 (2.3)	(1.3, 3.8)
Somnolence	0 (0.0)	(0.0, 14.8)	41 (7.0)	(5.1, 9.4)	41 (6.8)	(4.9, 9.1)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**(0.0, 14.8)**	**24 (4.1)**	**(2.7, 6.1)**	**24 (4.0)**	**(2.6, 5.8)**
Skin and subcutaneous tissue disorders	**1 (4.3)**	**(0.1, 21.9)**	**15 (2.6)**	**(1.4, 4.2)**	**16 (2.6)**	**(1.5, 4.3)**
Skin warm	1 (4.3)	(0.1, 21.9)	0 (0.0)	(0.0, 0.6)	1 (0.2)	(0.0, 0.9)

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

† Patient took at least one dose of study medication.

‡ Exact confidence intervals computed for those criteria with at least 2% incidence in one or more treatment groups.

§ An overdose of rizatriptan is defined as ingestion of more than 5 mg in a 24-hour period for patients with a screening body weight of less than 40 kg and more than 10 mg in a 24-hour period for patients with a screening body weight of 40 kg or more.

CI = Confidence interval.

(Source: Adapted from SUR; Clinical Study Report, Module 5.3.5.1.3, Table 12-20)

Review of Laboratory, Vital Signs, and ECG Data

The sNDA reported 3 cases of elevated liver enzymes in the interim population of study P086. The 3 patients had received rizatriptan 10 mg. Almost all of the liver enzyme abnormalities had normalized by the repeat laboratory assessment. The exception was the ALT level in one patient which returned to normal in 3 months from the initial elevated level.

The SUR had an additional patient with elevated liver enzymes. The following is the case report of the additional patient in the SUR with elevated liver enzymes in the long term study:

> **AN 20022**, 12-year-old, White male, took the first dose of rizatriptan on 20-Jan-2010. On 15-Jun-2010, the patient took a dose of study medication, and at the 24-Jun-2010 visit, the patient's ALT was 73 IU/L (baseline 46 IU/L [ULN 55 IU/L]) and aspartate aminotransferase (AST) was 48 IU/L (baseline 32 IU/L [ULN 41 IU/L]) were above the ULN; bilirubin and alkaline phosphatase were within normal limits (WNL). No concomitant medication was reported at the time of ALT and AST elevations. On 24-Sep-2010, the patient's ALT was 121 IU/L and AST was 75 IU/L, above the ULN. These values were above the ULN at the Month 12 visit on 03-Jan-2011 (ALT 121 IU/L and AST 63 IU/L). At the repeat laboratory assessment visit on 10-Mar-2011, the patient's ALT was 166 IU/L, which exceeded the predefined limits of change. The ULN for this patient's ALT changed at his unscheduled Month 12 visit based on age. The ULN for a 12 year old was 55 IU/L and the ULN for a 13 year old was 45 IU/L. At the time of this clinical study report, no further information was available, including when the patient's ALT value returned to normal.

The sponsor provided a detailed clinical follow up of the above patient in an email to the Agency on October 28, 2011. In the correspondence, the sponsor provided evidence that the subject's continued elevations and fluctuations of liver function tests were not consistent with a drug effect due to rizatriptan and could be explained by fatty infiltration of the liver due to morbid obesity (which was the conclusion reached by the subject's pediatrician and the principal investigator). I have reviewed the information and concur.

The sponsor reported no clinically relevant vital signs or ECG findings in study P086, both in the sNDA and in the SUR. I reviewed the vital signs and ECG data and concur with the sponsor's observations.

3.3 Safety Conclusions

No new or unexpected AEs were detected in the 120-day SUR in the long term safety study, P086. There were no clinically relevant findings in laboratory tests, vital signs, or ECGs. Overall, the safety profile of rizatriptan in the SUR was consistent with the safety findings of the PWR population that was submitted in the sNDA.

4 Conclusions

Review of the final results for the efficacy study (P082) and long term safety study (P086) submitted in the 120-day SUR were consistent with the findings of the sponsor's sNDA submission. No new or unexpected AEs were detected in the course of the development program of rizatriptan in the pediatric population. I therefore recommend approval of Maxalt for the acute treatment of migraine in pediatric patients, 6 to 17 years of age.

Nushin Todd, M.D., Ph.D.
Medical Reviewer – DNDP, ODE I

cc:
HFD-120

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

/s/

NUSHIN F TODD
12/15/2011

ERIC P BASTINGS
12/15/2011