Clinical Review of Supplemental NDA Response to Approvable Letter

NDA:	**20-626 (SE5-004-BZ)**
Sponsor:	**GlaxoSmithKline**
Drug:	**Imitrex Nasal Spray (sumatriptan)**
Proposed Indication:	**Adolescent Migraine**
Correspondence Date:	**November 20, 2003**
Date Review Completed:	**March 8, 2004**
PDUFA Date	**May 21, 2004**
Division:	**Division of Neuropharmacological Drug Products (HFD-120)**
Reviewer:	**Kevin Prohaska, D.O.**

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Clinical Review for NDA 20626

Executive Summary

1. Recommendations

1.1 Recommendation on Approvability

Due to the lack of demonstrated efficacy the indication for adolescent migraine should not be granted at this time in my clinical opinion. My review of the adolescent safety database does not find any significant unique adverse events that require changes to labeling at this time.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

None.

2. Summary of Clinical Findings

2.1 Introduction

GlaxoSmithKline is developing Imitrex Nasal Spray for use in adolescent migraineurs. At this time there are no drugs approved in the United States for the treatment of migraine in adolescents although there is widespread off label use of triptans and other products in this population. On March 1, 2000 the sponsor submitted an original Pediatric Supplement containing the results of 11 clinical studies which were reviewed by Dr. Armando Oliva (medical reviewer), Dr. Yuan-Li Shen (statistical reviewer) and Dr. Hong Zhao (biopharmaceutical reviewer). The two key original clinical studies were trial SUMA3005 (controlled, single attack efficacy) and trial SUMA3006 (long term safety). As described below trial SUMA3005 failed to demonstrate statistical significance for the prestated primary endpoint (2 hour headache response) as well as efficacy for nausea. Similarly, the first long term trial did not obtain the minimum required amount of exposure expected for migraine NDAs. In response to the original supplement the sponsor was sent an Approvable letter (December 22, 2000) which outlined the following deficiencies and recommendations:

- We did not agree trial SUMA3005 (acute adolescent efficacy study) demonstrated efficacy.
- We provided draft labeling recommendations that needed to be agreed to prior to approval of the supplement.
- We expressed concern that an insufficient number of subjects were exposed for 1 year in trial SUMA3006 (long term trial).
- We requested additional information on the nasal mucosa examinations performed in trial SUMA3006.
- We requested the sponsor provide a safety update for the NDA.

In response to the Approvable Letter the sponsor conducted a new adolescent, single attack efficacy study (SUM30045, protocol submitted December 4, 2001) and a new long term safety study (SUM40276). SUM 30045 is a traditional randomized controlled study designed to evaluate the safety and efficacy of sumatriptan nasal spray 5 mg and 20 mg in the acute treatment of migraine in adolescents. Study SUM40276 is a standard open label, long-term (1

year) study to evaluate the safety and tolerability of sumatriptan nasal spray in adolescents. In addition to these new studies conducted under the IND the sponsor submits two non-US, non-IND, investigator initiated studies (SUM30009 and SUM40019) to support their claim of efficacy. Study SUM3009 is a single center, double blind, placebo controlled, crossover, single attack efficacy study in children 8 to 12 years. Study SUM40019 is a multicenter, double blind, placebo controlled, crossover, single attack efficacy study in children and adolescents between the age of 8 to 17 years. Additionally the sponsor submits a safety update (cut off date 30 June 2003) and labeling revisions for our review.

2.2 Brief Overview of Clinical Program

To date the sponsor's adolescent clinical development program for sumatriptan includes 3 completed clinical pharmacology studies (SUMB1006, SUMB40254 and SUMB2001), 2 completed single attack controlled efficacy studies (SUMA3005 and SUM30045) and 2 completed long term safety studies (SUM3006 and SUM40276). Additionally the sponsor reports they have an ongoing adolescent acute migraine efficacy study (trial SUM30042) being conducted in the Netherlands. All completed sponsor trials except trial SUM30045 and SUM40276 were previously submitted to the Agency and reviewed (see Dr. Oliva's review dated November 30, 2000). In addition the sponsor provides in this submission the results of 2 investigator initiated studies which enrolled subjects between 7 to 17 years of age (SUM30009 and SUM40019).

In the 4 adolescent clinical trials initiated by the sponsor all subjects were 12 to 17 years of age and had a migraine history meeting the IHS definition of migraine with or without an aura (1.1 and 1.2). Headache frequency for the 4 studies were from 1 or 2 to 6 or 8 attacks per month. All subjects had no contraindications to triptans and were expected to be in good health. Migraine prophylactics (excluding ergots) were permitted but had to be stable. MAOIs were prohibited in all studies. Ergots and triptans were not permitted within 24 hours of study medication. SSRI were not permitted in study SUMA3005 and SUMA3006. Subjects in study SUMA3005 were permitted to use rescue medication at 2 hours and subjects in study SUMA30045 were permitted to use rescue medication starting at 1 hour.

In both long term trials subjects were instructed to treat an unlimited number of migraines of any intensity over a 12 month period. In trial SUMA3006 all patients were initiated on sumatriptan 10 mg and were titrated up or down (5 mg or 20 mg) as needed. In trial SUM40276 all patients were initiated on sumatriptan 20 mg and reduced to 5 mg as required. Collectively 1248 subjects participated in 2 controlled, single attack studies and 921 subjects participated in 2 long term safety studies. However the sponsor reports 336 subjects participating in trial SUMA3005 (single attack efficacy study) also participated in trial SUM3006 (1 year safety study). The following table summarizes the number of participants in each study.

Table 1 Adolescent Clinical Development Plan Sumatriptan Nasal Spray

Trial #	Description	# of Subjects	
Controlled Acute Efficacy Trials			
SUMA3005	DB, PC, Parallel group, single attack study	Placebo	131
		SUMA 5 mg	128
		SUMA 10 mg	133
		SUMA 20 mg	118
SUMA30045	DB, PC, Parallel group, single attack study	Placebo	245
		SUMA 5 mg	255
		SUMA 20 mg	238
Uncontrolled Long Term (1 year) Trials			
SUMA3006	OL, long term safety study	SUMA 5 mg	7
		SUMA 10 mg	433
		SUMA 20 mg	197
SUMA40276	OL, long term safety study	SUMA 5 mg	10
		SUMA 20 mg	484
Investigator initiated studies			
SUM30009	DB, PC, Crossover, single center, single attack study in children 8 to 12 years old	SUM 10 mg	59
		Placebo	58
SUM40019	DB, PC, Crossover, multicenter, single attack study in children 7 to 17 years old	SUM 10 mg	29
		SUM 20 mg	61
		Placebo	87
Ongoing Acute Efficacy Trial			
SUM30042	MC, DB, PC, randomized, crossover, single attack (each crossover) study.	Placebo	Still blinded, to date 85 subjects have been enrolled.
		SUM 10 mg	
		SUM 20 mg	

Adapted from sponsor tables 4, and 5, final safety update report

Of the 1248 subjects participating in the single attack efficacy studies, 356 subject were administered sumatriptan nasal spray 20 mg, 133 subjects administered sumatriptan nasal spray 10 mg and 383 subjects administered sumatriptan nasal spray 5 mg. Overall 87% of all attacks were treated with a single dose of study medication (range per cohort 9 to 15%).

The sponsor calculates 6890 doses of sumatriptan 20 mg, 2208 doses of sumatriptan 10 mg and 80 doses of sumatriptan 5 mg were taken during the 2 long term studies. Overall 921 subjects treated 7990 attacks with the majority (75%) being treated with a single dose of study medication. For the purposes of assessing adequacy of long term exposure I chose to focus on the number of subjects taking the highest proposed dose over 6 months (180 days) and 12 months (360 days). The following table summarizes my analysis of the amount of long term exposure to sumatriptan nasal spray 20 mg seen during trials SUMA3006 and SUMA40276. As demonstrated there was sufficient long term exposure at the highest planned dose. As discussed in my Exclusivity review we did not require subjects participating in the long term studies to treat on average at least 2 attacks per month.

Table 2 Combined Long Term Exposure to Sumatriptan 20 mg

	Study 30006	Study 40276	Total
180 days			
Number of subject	170	391	561
Number of attack	906	2884	
Average attacks/month	0.9	1.2	
Subjects treating ≥2 attacks/month	15	57	
360 days			
Number of subject	115	124	239
Number of attack	1190	1947	
Average attacks/month	0.9	1.3	
Subjects treating ≥2 attacks/month	11	15	

Source: Agency table, derived from original dataset

All cohorts in all studies were fairly well balanced for baseline demographics such as gender, age, race and migraine type (IHS 1.1 or 1.2). Unlike adult migraine studies where the majority of participants are female, these adolescent studies tended to have an even mix of male and female subjects. However like most adult studies I have reviewed the majority of subjects were Caucasian. In the uncontrolled long term studies the mean age of participants was 14.1 years.

2.3 Efficacy

The following table briefly summarizes the essential results from trials SUMA 3005 and SUM30045 (controlled single attack studies).

Table 3 Efficacy Summary of Controlled Trials

Endpoint	**SUM 5mg**	**SUM 10 mg**	**SUM 20 mg**	**Placebo**
Study SUMA 3005 (old study reviewed by Dr Oliva)				
	N=127	N=133	N=117	N=130
2 Hour Response n(%)*	84 (66%)	85 (64%)	74 (63%)	69 (53%)
p-value (Sponsor)	p=0.044	p=0.107	p=0.059	
p-value (Agency)	p=0.043	p=0.074	p=0.169	
Nausea at 2 hours	26 (20%)	23 (17%)	24 (21%)	33 (25%)
p-value	NS	NS	NS	
Photophobia at 2 hours	48 (38%)	57 (43%)	42 (36%)	62 (48%)
p-value	NS	NS	p=0.025	
Phonophobia at 2 hours	36 (28%)	44 (33%)	29 (25%)	57 (44%)
p-value	p=0.016	p=0.096	p=0.001	
Study SUM30045 (new study, see text of this review for additional details)				
	SUM 5 mg N=247		**SUM 20 mg N=236**	**Placebo N=242**
1 Hour Response n(%)*	132 (53%)		143 (61%)	127 (52%)
p-value (sponsor)	p=0.719		p=0.087	
Sustained Relief n(%)*	92 (37%)		96 (41%)	78 (32%)
p-value (sponsor)	p=0.173		0.061	
Nausea at 1 hours	59 (24%)		50 (21%)	57 (23%)
p-value	p=0.918		p=0.521	
Photophobia at 1 hours	119 (48%)		102 (43%)	126 (52%)
p-value	p=0.423		p=0.072	
Phonophobia at 1 hours	95 (38%)		85 (36%)	107 (44%)
p-value	p=0.128		p=0.088	

*Primary endpoint(s), p-values in comparison to placebo

Source: Sponsor tables 12, 18, 20 and 21 study report sum3005.pdf, table 8 Dr Oliva's review; Figure 1 and 2 and tables 13.3, 13.4, 13.1, 13.213.9, 13, 14, 13.9, 15, 13.10, 16, 13.11, 17, and 13.12 study report 30045.pdf

Executive Summary Section

Study SUM3005 is a randomized, placebo controlled, double blind, parallel group, single attack study that evaluated the safety and efficacy of three dose levels of sumatriptan nasal spray (5 mg, 10 mg, and 20 mg) in the acute treatment of migraine in approximately 500 adolescent migraineurs. The primary endpoint for the pivotal trial was the traditional 2 hour headache response. The sponsor's analysis of the 2 headache response for subjects taking sumatriptan nasal spray 20 mg compared to subjects taking placebo did not reach the threshold for statistical significance (p=0.059) and the decision was made within the division to consider this a failed study. A further analysis done by Dr Oliva demonstrated a p-value of 0.169 for the comparison of sumatriptan nasal spray 20 mg compared to placebo. Additionally sumatriptan nasal spray did not demonstrate benefit for the proportion of subjects reporting nausea at 2 hours. A full discussion of this trial can be found in the review done by Dr. Oliva.

Study SUM30045 is a randomized, placebo controlled, double blind, parallel group, single attack study that evaluated the safety and efficacy of 2 dose levels of sumatriptan nasal spray (5 mg and 20 mg) in the acute treatment of migraine in approximately 700 adolescent migraineurs. The co-primary endpoints for this pivotal trial was 1 hour headache response and sustained headache response between 1 to 24 hours. Like the first study trial SUM30045 failed to demonstrate significant efficacy for the prestated primary endpoints. Overall 52% of all subjects taking placebo reported headache response at 1 hour compared to 61% of subjects taking sumatriptan 20 mg (p=0.087). Likewise 32% of all subjects taking placebo reported sustained headache relief compared to 41% of all subjects taking sumatriptan 20 mg (p=0.061). Additionally this study failed to demonstrate a significant difference between active treatment and placebo for the incidence of each associated symptom (nausea, photophobia and phonophobia) at 1 hour ($p \geq 0.072$).

In addition to these controlled studies the sponsor also submits the results of two non-IND studies (trials SUM3009 and SUM40019) to support their assertion of efficacy. Trial SUM3009 is a randomized, placebo controlled, single center, double blind, two-period, crossover, single attack (each crossover) study to evaluate the safety and efficacy of sumatriptan nasal spray 10 mg for the acute treatment of migraine in children 8 to 12 years of age suffering from refractory migraine with and without aura. Since this study did not include adolescent migraineurs I do not believe it is relevant to this supplement. A description of the trial results can be found later in this review. Trial SUM40019 is a randomized, placebo controlled, double blind, multicenter, two-period (single attack each), crossover, outpatient, efficacy study of sumatriptan nasal spray (10 mg or 20 mg). The primary objective of the study is to evaluate the safety and efficacy of sumatriptan nasal spray (10 or 20 mg) compared to placebo in the treatment of migraine in children between 8 to 17 years of age. Although a subset analysis of adolescents demonstrated statistically significant results for the primary endpoint (2 hour headache response, p=0.001) the trial has several design and methodology problems which prohibits its use as a pivotal adolescent efficacy trial. For example the design of the 24 hour migraine diary does not permit us to assess whether in fact a migraine was treated. Secondly the study fails to evaluate the efficacy of sumatriptan to treat the associated symptoms associated with migraine and finally all analysis presented by the sponsor are post hoc analysis.

In conclusion I do not believe the sponsor has provided sufficient evidence that sumatriptan nasal spray 5 and 20 mg is effective in the treatment of migraine syndrome in adolescents. The adolescent indication should not be granted in my clinical opinion.

2.4 Safety

The sponsor has presented a considerable amount of safety experience in adolescents. A complete description of the exposure was discussed earlier and will not be repeated here however the sponsor has greatly exceeded the minimal amount of long term exposure expected for adolescent migraine studies. Overall the safety experience from approximately 7 clinical trials, involving over 2000 subjects, demonstrates that sumatriptan in doses up to 20 mg is well tolerated in adolescents. The nature and character of adverse events experienced during these trials were similar to those seen in adult migraine studies using sumatriptan.

The following table summarizes the common adverse events seen in the two controlled clinical trials. For consistency only adverse events that occurred within 24 hours of taking study medication are included. For the combined data the proportion of subjects reporting at least 1 adverse event (AE) was higher in sumatriptan cohorts than in placebo (31 to 40% vs. 17%). As expected the most common adverse event was taste disturbance seen in 19 to 30% of all subjects using sumatriptan. Other common adverse events included nausea, vomiting, local burning/stinging sensation and parasthesias. The vast majority of adverse events were rated as mild or moderate (92 to 97%), were transient and generally required no treatment. No subject withdrew from the acute studies due to an adverse event.

Table 4 Combined Common (≥2%) Adverse Events in Controlled Trials

	Placebo N=376	SUMA 5 mg N=383	SUMA 10 mg N=133	SUMA 20 mg N=356
Any AE	65 (17%)	119 (31%)	62 (47%)	142 (40%)
AE, Severe Intensity	14 (4%)	11 (3%)	5 (4%)	30 (8%)
SAEs	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Taste Disturbance	6 (2%)	72 (19%)	40 (30%)	91 (26%)
Nausea	27 (7%)	21 (5%)	9 (7%)	36 (10%)
Vomiting	12 (3%)	11 (3%)	15 (11%)	21 (6%)
Burning/stinging sensation	1 (<1%)	5 (1%)	0 (0%)	9 (3%)
Migraines	11 (3%)	2 (<1%)	2 (2%)	23 (<1%)
Paresthesia	4 (1%)	4 (1%)	2 (2%)	8 (2%)
Dizziness	2 (<1%)	5 (1%)	2 (2%)	2 (<1%)
Phonophobia	1 (<1%)	2 (<1%)	2 (2%)	2 (<1%)
Photophobia	3 (<1%)	3 (<1%)	3 (2%)	3 (<1%)
GI discomfort/pain	0 (0%)	3 (<1%)	3 (2%)	3 (<1%)
Temperature disturbance	2 (<1%)	1 (<1%)	2 (2%)	0 (0%)

Source: sponsor tables 10, and 11 final safety update study report

The following table summarizes the common adverse events (≥2%) reported by patients during the long term study. In the integrated safety report the sponsor does not provide a summary of adverse events during long term studies at the attack level however this information can be found in the review of each individual study. As demonstrated in the table 74% of all subjects at some time during the long term studies complained of taste disturbance although this rarely led to withdrawal. Other frequent adverse events included ENT infections, headaches, and local nasal

signs and symptoms (generally rhinorrhea). The incidence rates for each of these adverse events (except for taste disturbance) was generally ≤3% at the attack level. The incidence of taste disturbance in both long term studies at the attack level was between 16% to 29% of all attacks treated. The majority of adverse events in both long term studies were rated as mild or moderate, were transient and required no treatment.

Table 5 Common AEs (≥2%) in Subjects Participating in Long Term Studies

	All 5mg N=17 n (%)	All 10mg N=433 n (%)	All 20mg N=681 n (%)
Any Adverse Event	9 (53)	286 (66)	501 (74)
Disturbances of sense of taste	3 (18)	190 (44)	199 (29)
Ear nose & throat infections	1 (6)	24 (6)	100 (15)
Headaches	0	13 (3)	61 (9)
Nasal signs & symptoms	2 (12)	19 (4)	56 (8)
Viral ear nose & throat infections	2 (12)	7 (2)	44 (6)
Nausea	0	21 (5)	41 (6)
Viral respiratory infections	0	6 (1)	41 (6)
Vomiting	1 (6)	24 (6)	31 (5)
Throat & tonsil discomfort & pain	0	16 (4)	24 (4)
Dizziness	0	12 (3)	28 (4)
Other pain	0	6 (1)	27 (4)
Viral infections	0	5 (1)	23 (3)
Bronchitis	0	4 (<1)	22 (3)
Muscle injuries	0	6 (1)	21 (3)
Bacterial ear nose & throat infections	0	4 (<1)	21 (3)
Gastrointestinal discomfort & pain	0	7 (2)	19 (3)
Menstruation symptoms	0	0	18 (3)
Migraines	0	13 (3)	17 (2)
Paresthesia	0	6 (1)	17 (2)
Cough	0	5 (1)	17 (2)
Ear nose & throat hemorrhage	1 (6)	4 (<1)	17 (2)
Acne & folliculitis	1 (6)	2 (<1)	16 (2)
Sinusitis	0	7 (2)	15 (2)
Joint Disorders	0	2 (<1)	15 (2)
Fractures	0	3 (<1)	13 (2)
Temperature regulation disturbances	0	5 (1)	12 (2)
Burning/stinging sensation	0	14 (3)	11 (2)
Viral gastrointestinal infections	1 (6)	3 (<1)	11 (2)
Chest symptoms	0	6 (1)	11 (2)
Depressive disorders	0	1 (<1)	11 (2)
Muscle cramps & spasms	1 (6)	0	7 (1)
Drowsiness	1 (6)	3 (<1)	4 (<1)
Throat & tonsil signs & symptoms	1 (6)	1 (<1)	3 (<1)
Asthma	1 (6)	1 (<1)	3 (<1)

Source: Sponsor table 16, final safety update report.pdf

In both controlled efficacy studies and both long term safety studies the incidence of cardiovascular events and "triptan" effects (ex. tightness, pain/pressure sensation, local parasthesias etc.) were generally uncommon (<1%) at the attack level and rarely resulted in withdrawal. A discussion of these adverse events is included in my review of each study.

In the controlled studies 4% of all subjects receiving any dose of sumatriptan nasal spray and 1% of all subject receiving placebo reported an AE possibly related to nose/throat irritation. No single complaint exceeded 1% incidence at the attack level. The only event reported as severe was local burning/stinging sensation reported in <1% of subjects receiving sumatriptan. The 6 month and end of treatment nasal examinations performed in trial SUM40276 did not find any significant findings.

There was a single death in the entire adolescent clinical development program. An 18 year old male, participating in trial SUM40276, was fatally injured in a motor vehicle accident. The event was not related to study medication. In addition to the single death during the clinical studies the sponsor reports in the safety update there were 2 spontaneous reports of deaths in patients <18 years of age during the period of January 2000 to June 2003. The first case, derived from the literature, was of a 16 year old male (A0383145A) who intentionally overdosed with sumatriptan. Details regarding the dose and route are sketchy but it appears he took at least 350 mg of sumatriptan tablets and an unknown amount of Sudafed. Over the next 2 to 3 days he became progressively lethargic and was found by the paramedics apneic and in asystole. He was initially resuscitated and placed on a ventilator however he was determined to be brain dead and all life support was stopped. Details about this case suggest a potential causal relationship in my opinion however Sudafed and other unknown factors may be contributive. The second death described occurred in a 13 year old female (B0274941). Details are few however the patient's pharmacist reports the young female collapsed and became unconscious after a "lengthy period of medication". Apparently she was hospitalized and died after a 7 month stay. Details about this case are too sketchy to consider a causal relationship. I discuss a few additional deaths reported in conjunction with sumatriptan use found during an DDRE AERS database search in section 6.6 of this review.

No serious adverse events were reported in subjects taking active drug during the 2 controlled efficacy studies. In trial SUMA3006 8 subjects reported 9 SAEs and in trial SUMA40276 10 subjects reported 14 SAEs. A discussion of each SAE can be found in the review of each trial however in general all except 2 adverse events were considered not related to study medication. In trial SUMA3006 a 15 year old male developed a facial nerve palsy soon after using sumatriptan and in study SUM40276 a 17 year old female developed a complicated migraine requiring hospitalization soon after taking sumatriptan. A further description of each case can be found in the reviews of each study.

There were no withdrawal due to adverse events in the 2 controlled efficacy studies. During trial SUMA3006 and trial SUM40276 44 subjects withdrew due to an adverse event. A description of these events can be found in the review of each study however in general the most common adverse event leading to withdrawal was taste disturbance.

A review of all serious adverse events reported during the trials as well as those in the AERS database and those provided by the sponsor in the safety update did not demonstrate any unique problems in adolescents that need to be described in labeling. As with adults, sumatriptan is on rare occasions associated with serious adverse events, including death. The use of sumatriptan in

adolescents in my opinion should only be considered when the diagnosis of migraine is clear, the attacks are generally disabling, and the risks have been adequately described to the patient and their guardians. In my clinical opinion all adolescents should be monitored by a responsible adult especially during the first few times sumatriptan is administered.

2.5 Dosing

Although not specifically a dose finding study, trial SUMA3005 evaluated the safety and efficacy of sumatriptan nasal spray 5 mg, 10 mg and 20 mg. Lower and higher doses in adolescents have not been evaluated for efficacy. As described in the review done by Dr. Oliva this trial failed to demonstrate efficacy for the prestated primary endpoint (2 hour headache response) for the 2 higher dose however oddly the 5 mg cohort did demonstrate statistical significance compared to placebo (p=0.044) for headache response at 2 hours. Ultimately the sponsor hopes to obtain approval for the use of sumatriptan nasal spray in adolescents using the same regimen approved in adults (5 and 20 mg at onset, repeat at 2 hours if required).

2.6 Special Populations

Other then pediatrics this supplement does not include any studies in special populations.

Clinical Review

1. Introduction and Background

GlaxoSmithKline is developing Imitrex Nasal Spray for use in adolescent migraineurs. At this time there are no drugs approved in the United States for the treatment of migraine in adolescents although there is widespread off label use of triptans and other products in this population. On March 1, 2000 the sponsor submitted an original Pediatric Supplement containing the results of 11 clinical studies which were reviewed by Dr. Armando Oliva (medical reviewer), Dr. Yuan-Li Shen (statistical reviewer) and Dr. Hong Zhao (biopharmaceutical reviewer). The two key original clinical studies were trial SUMA3005 (controlled, single attack efficacy) and trial SUMA3006 (long term safety). Trial SUMA3005 failed to demonstrate statistical significance for the prestated primary endpoint (2 hour headache response) as well as efficacy for nausea. Similarly, the long term trial did not obtain the minimum required amount of exposure expected for migraine NDAs. Due to these failures the sponsor has repeated the studies for this submission. All trials reviewed by Dr. Oliva failed to demonstrate any new significant safety concerns unique to adolescents. All reviews can be found in DFS.

In response to the original Pediatric Supplement an Approvable Letter was issued on December 22, 2000. The following issues where listed in the letter for the sponsor's action:

- We did not agree trial SUMA3005 (acute adolescent efficacy study) demonstrated efficacy.
- We provided draft labeling recommendations that needed to be agreed to prior to approval of the supplement. Additionally we requested the sponsor modify the "**Precautions: Pediatric Use"** section of the Imitrex Injection and Tablet label to be consistent with the changes recommended for the Imitrex Nasal Spray label.
- We expressed concern that an insufficient number of subjects were exposed for 1 year in trial SUMA3006 (long term trial) and requested clarification of the exposure dataset. Specifically we requested the sponsor provide a dataset with one row per Imitrex dose taken plus the following variables; patient ID, migraine attack number, study day, dose, first/second dose flag, actual date/time dose taken, study onset date, and study end date. We reminded the sponsor we expect a minimum of 300-600 patients should be exposed for 6 months, and 100 patients should be exposed for one year. It is important to note after some internal debate we agreed long term safety database did not need to demonstrate an average of 2 treated attacks per month.
- We requested additional information on the nasal mucosa examinations performed in trial SUMA3006.
- We requested the sponsor provide a safety update for the NDA that includes all non-clinical and clinical studies using Imitrex regardless of indication, dosage form or dose level. Specifically we requested they organize the safety update in the following manner:
    1. Describe in detail any significant changes or finding in the safety profile.
    2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows: (1) present new safety data using the same format as the original NDA, (2) present tabulations of the new safety data combined with the original NDA data, (3) include tables that compare frequencies of adverse events in the original NDA with the

retabulated frequencies described in item 2, and (4) for indications other than adolescent migraine provide a separate table for the frequency of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop outs for the newly completed studies and describe any trends or patterns identified.
4. Provide case report forms and narratives summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. Provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA.
6. Provide a summary of worldwide experience on the safety of Imitrex. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In this submission the sponsor supplies a complete response to our Approvable Letter dated December 22, 2000 and a request for Pediatric Exclusivity Determination. My review of the Pediatric Exclusivity Determination request is done in a separate document and will not be repeated in this review. The Pediatric Exclusivity Board met on February 18, 2004 and exclusivity was granted. In this review I will evaluate the sponsor's response to our requests contained in the Approvable Letter.

In response to the Approvable Letter the sponsor conducted a new adolescent controlled, single attack efficacy study (SUM30045, protocol submitted December 4, 2001) and a new long term study (SUM40276). SUM 30045 was a double blind, placebo controlled, parallel group study designed to evaluate the safety and efficacy of sumatriptan nasal spray 5 mg and 20 mg in the acute treatment of migraine in adolescents. Study SUM40276 was an open label, long-term (1 year) study to evaluate the safety and tolerability of sumatriptan nasal spray in adolescents. In addition to the acute study conducted under the IND the sponsor submits two non-US, non-IND, investigator initiated studies (SUM30009 and SUM40019) to support their claim of efficacy. Study SUM3009 was a single center, double blind, placebo controlled, crossover, single attack efficacy study in children 8 to 12 years. Study SUM40019 was a multicenter, double blind, placebo controlled, crossover, single attack efficacy study in children and adolescents between the age of 8 to 17 years.

To facilitate review of this submission I will organize my review in a similar manner as the review of the original supplement done by Dr. Oliva with some modifications. I will start by reviewing each new trial (controlled efficacy, long term safety and 2 non-IND studies) separately. This will be followed by a brief integrated summary of efficacy and integrated summary of safety. The integrated safety review will also include the sponsor's response to each of the safety items requested in the Approvable letter (i.e., updated safety from worldwide experience, review of foreign labels etc.). In order to facilitate team input my labeling recommendations will be done in a separate document. Elements of a complete NDA review

such a "State of Armamentarium" will not be included in this review since this submission is a response to an Approvable Letter.

1.1 Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Imitrex (sumatriptan) Nasal Spray is a 5-hydroxytryptamine$_{1B/1D}$ ($5HT_{1B/1D}$) receptor agonist often referred to as a "triptan". The Sponsor seeks Agency approval for the use of sumatriptan nasal spray 5.0 mg and 20 mg in adolescent patients (12 to 17 years of age) (b) (4) . The drug substance in the nasal spray is the same active moiety approved for use in adults in Imitrex Tablets (NDA 020132, approved June 1, 1995), Imitrex Injection (NDA 020080, approved December 28, 1992) and Imitrex Nasal Spray (NDA 02626, approved August 26, 1997).

1.2 Important Milestones in Product Development

- August 26, 1997 — Imitrex Nasal Spray approved (in adults)
- June 7, 1999 — Original Pediatric Written Request issued
- October 11, 1999 — Sponsor request changes to Written Request
- February 28, 2000 — Sponsor request changes to Written Request
- February 29, 2000 — Original Pediatric Supplement submitted
- May 16, 2002 — Sponsor requests changes to Written Request (time only)
- June 3, 2002 — Written Request Revised (timing only)
- June 21, 2000 — Written Request revised (design issues)
- December 22, 2000 — Approvable Letter issued
- November 20, 2003 — Response to Approvable Letter and Pediatric Exclusivity Determination request submitted.
- February 18, 2004 — Exclusivity Board met and exclusivity granted.

On October 11, 1999 and February 28, 2000 the sponsor requested multiple changes to the Pediatric Written request. In my review Pediatric Exclusivity Determination review I outline the changes however significant for this review is our agreement that subjects enrolled in the long term safety trials did not need to treat an average of at least 2 migraine attacks per month. Otherwise the sponsor was expected to meet the standard long term exposure of at least 300 subjects for 6 months and 100 subjects for 12 months. The rationale for this decision is outlined in the review of serial 140 done by Dr. Oliva.

1.3 Other Relevant Information

Background information on the original Pediatric Supplement can be found in the reviews done by Dr. Oliva (medical reviewer), Dr. Yuan-Li Shen (statistical reviewer) and Dr. Hong Zhao (biopharmaceutical reviewer).

2. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No new Chemistry, or Biopharmaceutical information is provided in this submission. A statistical consult has been requested to evaluate the analysis of the new efficacy studies. A

pharmacotoxicology consult has been requested to review any new preclinical data that may have been submitted in response to the Approvable letter.

3. Human Pharmacokinetics and Pharmacodynamics

No new pharmacokinetic or pharmacodynamic information is provided in this submission.

4. Description of Clinical Data and Sources

All new data reviewed in this submission can be found in the electronic data room at \\Cdsesub1\n20626\S_004\2003-11-20. In addition to this data I reviewed the following items from the original action package:

- Armando Oliva M.D. — Medical Officer's review of clinical data.
- Russell Katz, M.D. — Division Director Memorandum
- Yuan-Li Shen Ph.D. — Statistical Review
- Hong Zhao, Ph.D. — Biopharmacology Review
- Carol Pamer R. Ph — Office of Drug Safety Postmarketing Safety Review
- Approvable letter (12/22/00)

Additionally I requested the following consults to help in the review of the new materials submitted; statistical (review trial SUM30045), pharmacotoxicology (preclinical review) and DDMAC (labeling review).

4.1 New Data Overview

This submission contains the results from four human pediatric studies:

1. Trial SUM30045 is a double blind, placebo controlled, parallel group study designed to evaluate the safety and efficacy of sumatriptan nasal spray 5 mg and 20 mg in the acute treatment of migraine in adolescents. The final protocol for this study was submitted to the IND on March 21, 2002 (serial 163). My review of the original protocol can be found in DFS.
2. Trial Study SUM40276 is an open label, long-term study to evaluate the safety and tolerability of sumatriptan nasal spray in adolescents.
3. Trial SUM3009 was an investigator initiated, non-IND, randomized, placebo controlled, single center, double blind, two-period, crossover, single attack (each crossover), outpatient study to evaluate the safety and efficacy of sumatriptan nasal spray 10 mg for the acute treatment of migraine in children (8 to 12 years) suffering from refractory migraine with and without aura.
4. Trial SUM40019 was an investigator initiated, non-IND, randomized, placebo controlled, double blind, multicenter, two-period (single attack each), crossover, outpatient safety and efficacy study of sumatriptan nasal spray (10 mg or 20 mg).

The following table outlines the number of subjects in the new trials submitted in this supplement.

Table 6 Number of Participants in Clinical Trials

Study	Design	PB	SUM 5 mg	SUM 10 mg	SUM 20 mg	Comment
SUM30045	DB, PC, Parallel design, acute efficacy	245	255	O	238	IND study in adolescents
SUM30009	DB, PC, Crossover, acute efficacy	58	0	59	0	Non-IND study in children 2 to 12 years
SUM40019	DB, PC, Crossover acute efficacy	87	0	29	61	Non-IND study in pediatrics 8 to 17 years
SUM40276	OL, uncontrolled, long term safety	NA	10	0	484	IND study in adolescents

4.2 Clinical Review Methods

As discussed earlier the sponsor submits four new clinical trials in this submission (SUM30045, SUM30009, SUM40019, and SUM40276). Trial SUM30045 is a controlled efficacy study in adolescents, trial SUM40276 is a long term safety study in adolescents, trial SUM30009 is a controlled efficacy study in children 8 to 12 years of age and trial SUM40019 is a controlled efficacy study in children 8 to 17 years of age. Since trials SUM40019 and SUM30009 did not include adolescents exclusively, and were non-IND studies, I will focus my review primarily on trial SUM30045 for acute efficacy and safety and trial SUM40276 for long term safety.

Following my review of each new trial I will present a brief integrated efficacy discussion that incorporates the pivotal efficacy study (trial SUMA3005) submitted in the original supplement and reviewed by Dr. Oliva. This will be followed by an integrated safety review that describe the safety experience from all studies conducted in adolescents as well as describe the sponsor's response to each of the safety items requested in the Approvable Letter.

4.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor asserts all studies were conducted in accordance to accepted ethical standards.

4.4 Evaluation of Financial Disclosure

The sponsor submits FDA Form 3454 for all clinical investigators participating in studies covered by 63 FR 71171 included in this supplement (studies SUM30045, SUM30009 and SUM40019).

The sponsor asserts they have not compensated any clinical investigator in such a way as the total amount could vary with the outcome of the study. No investigator reports any significant proprietary interest in the tested product. No investigator reports having a significant equity interest (defined as >$50,000) in the sponsor. Four investigators (b) (6) report receiving greater than $25,000.00 for their participation in trial (b) (4). Collectively these investigators received $289,250 and enrolled 29 (3.9%) of the 738 subjects enrolled in the study. Although the total amount of compensation appears high to this reviewer I do not believe it had any significant impact on the results of the trial given that the study failed to show efficacy for its prestated primary endpoint (details described below).

5. Review of New Clinical Studies

5.1 Detailed Review of Trial SUM30045 (Controlled efficacy 12 to 18 years)

5.1.1 Protocol

The original protocol was submitted to IND 43272 on March 22, 2002. My review of the original submission can be found in DFS.

Trial SUM30045 was a randomized, double blind, placebo-controlled, parallel-group, multicenter, single migraine attack study in adolescents. The primary objective was to compare the efficacy and safety of sumatriptan nasal spray (5 and 20 mg) to placebo in the acute treatment of a single migraine attack in adolescents.

Eligible patients were male or non-pregnant female migraineurs, ages 12 to 17, with a history of migraine with or without aura (IHS criteria 1.1 and/or 1.2). Subjects were required to have a history of 1 to 8 migraines per month on average. As in most migraine studies patients with basilar or hemiplegic migraine as well as any contraindication to triptans were excluded from the study. Subjects were expected to be in good health and have no significant findings in their baseline safety visit. The following table briefly summarizes the schedule of events for each study visit. As demonstrated the screening and exit visit did not include a CBC, Chemistry Profile or a 12 lead ECG. At the time of my review of the protocol I noted this but agreed with the sponsor there was sufficient safety information on sumatriptan in adults and adolescents to preclude the need for additional CBC, chemistry panels or ECGs.

Table 7 Schedule of Events Trial 30045

Study Procedure	Screening Visit	Exit Visit*
Informed Consent	●	
Inclusion/exclusion criteria	●	
Medical/Migraine History	●	
Medication History	●	
Modified HIT-6 Questionnaire	●	
Vital Signs (sitting)	●	●
Complete Physical Examination	●	●
Demographics	●	
Pregnancy Test (urine or serum)	●	●
Randomization	●	
Review Study Design	●	
Instruct on use of nasal spray device	●	
Review Efficacy Assessments		●
Questionnaire to assess patient functioning		●
Adverse Event Query		●
Collect Diary Cards		●

* Exit visit to occur no less than 24 hours and no greater than 10 days after treatment

Patient on migraine prophylaxis were expected to be on a stable dose for a period of at least 2 months prior to the use of study medication. Prohibited medications included the following:

- any acute medication for migraine (rescue medication), including opiates, simple analgesics, and anti-emetic medications were prohibited within 6 hours before or 1 hour after treatment with investigational product.

- Ergot containing drugs and derivatives or any triptan product were excluded within 24 hours before or after treatment with study medication.
- MAOI were excluded for at least 2 weeks before screening.

The study report is inconsistent as to when rescue medication was permitted. In the list of prohibited medications it states acute medications for migraine could be used 1 hour after taking study medication however elsewhere in the protocol it states rescue medication was prohibited until hour 2. Likewise the final safety update report clearly states rescue medication was permitted in this study 1 hour after taking study medication. This issue is important relative the variable headache response at various timepoints. For the purposes of this review I will consider all findings after 1 hour as possibly confounded by the use of rescue medication after 1 hour.

After the screening visit, eligible patients were randomized equally to placebo, sumatriptan nasal spray 5 mg or sumatriptan nasal spray 20 mg. Subjects were instructed to treat their next migraine of moderate to severe intensity with randomized medication in the outpatient setting. Subjects who were triptan naive were required to treat their migraine in the presence of an adult. Subjects were encouraged to treat within 30 minutes of headache pain becoming moderate to severe.

Migraine response was monitored using a typical 24 hour migraine diary. Headache intensity was assessed at pre-specified time points using the traditional 4 point scale (0=none, 1=mild, 2=moderate, 3=severe). Migraine associated symptoms (nausea, photophobia and phonophobia) were assessed as present or absent. Sufficient baseline information was collected to determine whether the treated attack was a migraine.

The co-primary endpoints for this study were headache relief at 1 hour following the use of sumatriptan nasal spray 20 mg AND sustained relief between 1 and 24 hours following the use of sumatriptan nasal spray (20 mg). HA relief is defined as a reduction in baseline headache severity from moderate/severe to none/mild pain. Sustained relief is defined as headache relief at 1 hour with no use of rescue medications and no recurrence of moderate to severe pain within 1-24 hours of treatment with test product. The sponsor chose an earlier timepoint than the traditional 2 hours due to the results of trial SUMA3005 and the belief that migraine attacks in adolescents tend to be of shorter duration than in adults.

The co-primary endpoints were analyzed using CMH test, adjusted for center effects and for multiple comparisons (via Hochberg testing procedure). The comparison rule is as follows:

> *"If both comparisons results in p-values ≤0.05, then both are considered statistically significant. If either results in a p value >0.05, then comparison is considered not statistically significant and the other comparison must have a p-value ≤0.025 to be considered statistically significant."*

Secondary endpoints included the following:

- HA relief at 30, 60, and 120 minutes following treatment (comparison between 5 mg versus placebo, and 20 mg versus 5 mg).

- Sustained relief following treatment (comparison between 5 mg versus placebo, and 20 mg versus 5 mg).
- Pain free at 30, 60, and 120 minutes following treatment (pairwise comparison between 5 mg, 20 mg, and placebo).
- Presence/absence of the associated symptoms of nausea, vomiting, photophobia, and phonophobia at 30, 60 and 120 minutes after treatment (pairwise comparison between 5 mg, 20 mg, and placebo).
- Use of rescue medication for pain relief, or for return of moderate or severe pain taken within 2-24 hours after initial treatment.
- HA relief at 60 minutes following treatment summarized by subgroup factors (demographics, migraine history, and baseline characteristics).
- Sustained relief following treatment summarized by subgroup factors (demographics, migraine history, and baseline characteristics).
- HA recurrence defined as return of moderate or severe pain 1-24 hours after headache relief at 1 hour.
- Impact of migraine on school and work productivity, leisure activities, interactions with others and emotional state will be measured using questionnaire to assess patient functioning at 24 hours after treatment.

I briefly describe the analysis plan for each secondary endpoint later in this review. All statistical tests used an alpha of 0.05. No interim analysis was done. Missing data was handled using a last observation carried forward algorithm (LOCF). Subjects using rescue medication prior to 1 hour were treated as treatment failures. The sponsor intended to combine centers with less than 10 subjects if there were a small number of centers otherwise all centers were to be combined into regional groupings according to geographic proximity.

The primary efficacy population was the Intent to Treat population (ITT). The ITT Population was composed of all subjects that took study medication and who provided a post treatment evaluation of their randomized treatment. If the subject provided any post-treatment pain or associated symptom assessment, the subject was considered to have evaluated randomized treatment. If the subject had some but not all of the migraine symptoms with post-baseline assessments, then the subject was excluded from both the numerator and denominator for those symptoms for which no post-baseline assessments existed. The denominators therefore varied among the symptom summaries.

Safety monitoring is summarized in the table above. As noted this study did not include a screening or follow up CBC, chemistry profile or ECG however the safety of intermittent sumatriptan in adolescents and certainly in adults has been demonstrated in earlier studies. All safety data were to be described using descriptive statistics.

The study intended to screen 930 subjects and randomize 840 subjects in order to attain 696 treated subjects (232 per cohort). The sponsor calculated 232 subjects per treatment arm would provide 90% power to determine a 15% difference in headache relief between placebo and sumatriptan nasal spray 20 mg. Likewise 232 subjects per treatment arm would provide 95%

power to determine a 16% difference in sustained headache relief between placebo and sumatriptan nasal spray 20 mg.

The protocol had only a single relatively minor amendment (May 24, 2002) in order to exclude subjects who may have used Imitrex Nasal Spray or had participated in a study using sumatriptan nasal spray in the past. This change was conducted after 26 subjects had been enrolled and was done to improve blinding (sumatriptan nasal has a recognizable taste). The sponsor also states the data analysis plan was amended once (May 12, 2003) prior to unblinding. The original protocol stated (b) (4) This was changed in DAP so subjects whose baseline pain was not moderate or severe were not included in the per protocol analysis of post-dose headache relief. The sponsor asserts this was done to reduce the possibility of over-estimating the relief rate. I reviewed the migraine diary dataset and this change affected 7 subjects (3 placebo, 3 sumatriptan 5 mg and 1 sumatriptan 20 mg). A single subject (PID 100513) did not provide any baseline or post treatment pain intensity ratings. The other 6 subjects used study medication when their baseline pain intensity was mild (1). All except subject 101390, randomized to sumatriptan 5 mg, would have been considered treatment responders since their 1 hour pain intensity ratings were 0 or 1.

A post hoc analysis was performed to evaluate time to pain free within 30 minutes, 1 hour and 2 hours. Time to pain free was defined as the first post dose assessment at which a subject was pain free (headache severity reduced from any pain to no pain).

In addition, a minor change was made to the analysis of time to headache relief. In the analysis plan, time to headache relief was defined as the first timepoint at which the subject reported headache relief that persisted through the 2-hour timepoint. In the analysis that was actually performed, time to headache relief was defined as the time of the first post-dose assessment at which a subject reported headache relief.

The conduct of the study was uneventful except for a single investigator (site 11008) who did not follow proper consent procedures. This action resulted in the IRB revoking their site approval. Subjects from this site were included in the ITT population if they met the definition but were not included in the Per Protocol Population. This site enrolled 4 subjects of which 3 completed the study (1 each cohort).

5.1.2 Study Population

The following table briefly summarizes patient disposition during trial 30045. A total of 888 subjects from 65 sites were enrolled into the study of which 738 treated with trial medication (safety population). The ITT population consists of 731 subjects (placebo 244, sumatriptan 5 mg 250, sumatriptan 20 mg 237) since several subjects did not return the diary or were lost to follow up. No subject withdrew from the study due to an adverse event. Of the ITT population 37 subjects had major protocol violations and were excluded from the Per Protocol Population (PPP). Violations included early use of rescue medication (11 subjects), use of prohibited medications (23 subjects), migraine intensity not moderate to severe (6 subject), and improper

consent procedure followed (3 subjects). Overall there was no significant difference between cohorts for the proportion of subjects with a major protocol violation.

Table 8 Patient Disposition, Safety Population Trial 30045

	Placebo	Sumatriptan 5 mg	Sumatriptan 20 mg	Total
Randomized	299	295	294	888
Safety Population	245	255	238	738
ITT Population	244	250	237	731
Per Protocol Population	233	239	222	694
Primary Reason for Premature Discontinuation				
AE	0	0	0	0
Lost to Follow up	0	3	2	5
Other	0	1	0	1
Did not return diary	1	0	0	1
Major Protocol Violations	11 (5%)	11 (4%)	15 (6%)	37 (5%)

Source: Adapted from sponsor table 7 and 8, study report 30045

5.1.3 Demographics and Baseline Characteristics

As demonstrated in the following table all ITT cohorts were well balanced for baseline characteristics of age, gender, race and body mass index. As is typical of migraine studies I have reviewed the majority of subjects were female and Caucasian (55% and 80% respectively). In the ITT population the majority of subjects reported a history of migraine without aura (range 77 to 80%). Additionally cohorts were well balanced for pain intensity and the presence of associated symptoms at the time of treatment. Although not summarized here, subjects in each cohort were well balanced for concurrent medical conditions (ex allergies etc.) and previous use of triptans or other migraine medications.

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Table 9 Baseline Demographic and Migraine History Characteristics, ITT population

	Placebo N=244	Sumatriptan 5 mg N=250	Sumatriptan 20 mg N=237
Age, mean (SD)	14.2 (1.7)	14.3 (1.6)	14.3 (1.8)
Age category, %			
≤14 year	55%	54%	56%
>15 years	45%	46%	44%
Gender, %			
Female	141 (58%)	131 (52%)	128 (54%)
Male	103 (42%)	119 (48%)	109 (46%)
Race, n (%)			
White	196 (80%)	197 (79%)	191 (81%)
Black	36 (15%)	39 (16%)	34 (14%)
Hispanic	9 (4%)	10 (4%)	11 (5%)
Other	3 (1%)	4 (1%)	1 (<1%)
Body Mass Index, mean (SD)	22.9 (5.4)	23.1 (5.6)	22.4 (4.9)
Migraine without Aura, %	80%	77%	77%
Migraine with Aura	11%	10%	12%
Mixed	9%	13%	11%
Monthly Frequency, mean (SD)	3.9 (2.0)	3.9 (2.0)	4.1 (2.1)
Nausea at dosing, n(%)	109 (45%)	106 (43%)	98 (41%)
Photophobia at dosing, n(%)	197 (81%)	206 (83%)	184 (78%)
Phonophobia at dosing, n(%)	178 (73%)	175 (70%)	161 (68%)
Time to treatment, median (min)	30	30	30
Pain intensity at dosing, n(%)			
Severe	95 (38.8%)	96 (38.4%)	85 (35.9%)
Moderate	147 (60.0%)	151 (60.4%)	151 (63.7%)
Mild	2 (<1%)	3 (1.2%)	1 (<1%)

Source: Adapted from sponsor table 12.9, 12.11, 12.15 and 12.12

5.1.4 Efficacy Results

All efficacy results presented are for the ITT population unless otherwise stated.

5.1.4.1 Primary Endpoint

As previously stated the two co-primary endpoints for trial SUM30045 was headache relief at 1 hour AND sustained headache relief between 1 to 24 hours post-dose for sumatriptan nasal spray 20 mg compared to placebo. HA relief is defined as a reduction in baseline headache severity from moderate/severe to none/mild pain. Sustained relief is defined as headache relief at 1 hour with no use of rescue medications and no recurrence of moderate to severe pain within 1-24 hours of treatment with test product.

At the time of dosing the majority of subjects in each treatment group treated a migraine of moderate pain intensity (range 60 to 64%). The mean time to treatment from the onset of migraine for each cohort was less than 2 hours in all cohorts (range 1.5 to 1.8 hours). Hence the cohorts were fairly well balanced for pain intensity at baseline and time to treatment from the onset of the attack.

The following table summarizes the incidence of headache relief at 1 hour and sustained headache relief between 1 to 24 hours for each cohort. As demonstrated in the table the sponsor analysis of the co-primaries using the ITT population failed to demonstrate a significant difference between placebo and sumatriptan nasal spray 20 mg for headache relief at 1 hour (61% vs. 52%, p=0.087) and sustained headache relief between hour 1 and 24 (41% vs. 32%,

p=0.061). These comparisons were also not significant for sumatriptan nasal spray 5 mg compared to placebo using the ITT population (p≥0.157). Similar results were obtained using the per protocol population.

Table 10 Proportion of subjects reporting HA relief at 1 and sustained Headache Relief (1-24 hours)

ITT Population			
	Placebo N=242	**SUM 5 mg N=247**	**SUM 20 mg N=236**
Headache Relief at 1 hour, n(%)	127 (52%)	132 (53%)	143 (61%)
p-value[1]		0.719	0.087
Sustained Relief	78 (32%)	92 (37%)	96 (41%)
p-value[1]		0.173	0.061
PP Population			
	Placebo N=233	**SUM 5 mg N=239**	**SUM 20 mg N=222**
Headache Relief at 1 hour, n(%)	123 (53%)	131 (55%)	138 (62%)
p-value[1]		0.603	0.055
Sustained Relief	76 (33%)	91 (38%)	91 (41%)
p-value[1]		0.157	0.080

1 p-value compared to placebo, analyzed using CMH test controlling for investigator.
Source: Sponsor figure 1 and 2 and tables 13.3, 13.4, 13.1, and 13.2

In summary trial SUM30045 failed to demonstrate a significant difference between sumatriptan nasal spray 20 mg and placebo for the two co-primary endpoints of headache relief at 1 hour and sustained headache relief between 1 and 24 hours in either the ITT or the PP populations. For subjects taking sumatriptan nasal spray 20 mg there was a strong trend favoring active treatment for both endpoints. For the subjects taking sumatriptan nasal spray 5 mg there was a slight numerical benefit favoring active treatment for both endpoints however it is unlikely the treatment effects are clinically meaningful (generally < 5 points).

5.1.4.1 Secondary Endpoints

Due to the failure of the study to demonstrate efficacy for the prestated co-primary endpoints I will limit my review of secondary endpoints to pain response at various timepoints and the proportion of subjects reporting an associated symptom at various timepoints.

5.1.4.1 Associated Symptoms

The following table demonstrates the incidence of each associated symptoms at various timepoints. Each cohort was fairly well balanced for each associated symptom at the time of treatment. As demonstrated in the table the proportion of patients reporting either nausea, photophobia, phonophobia or vomiting at 30 minutes was not statistically different between placebo and active treatment (sumatriptan nasal spray 5 and 20 mg). Similarly, at 1 hour (timepoint for primary endpoint) the proportion of patients reporting either nausea, photophobia, phonophobia or vomiting was not statistically different between placebo and active treatment (p≥0.138). At 2 hours there was no consistent evidence of efficacy for active treatment compared to placebo. At 2 hours the comparison of sumatriptan nasal spray 20 mg versus placebo demonstrated a statistically significant benefit for the proportion of patients reporting photophobia (p=0.019) and the comparison of sumatriptan nasal spray 5 mg versus placebo demonstrated a statistically significant benefit for the proportion of subjects reporting

phonophobia (p=0.044). Otherwise all other 2 hour comparisons failed to demonstrate benefit. Findings at 2 hours could possibly be confounded by the use of rescue medication. The number of subjects reporting vomiting at various timepoints was too low to make a meaningful comparison between cohorts.

Table 11 Incidence of Associated symptoms at Various Timepoints, ITT

	0 min	30 min	1 hour	2 hours
Nausea				
Placebo	109 (45%)	77 (32%)	57 (23%)	48 (20%)
Sumatriptan 5 mg p-value	106 (43%)	83 (33%) 0.558	59 (24%) 0.918	45 (18%) 0.769
Sumatriptan 20 mg p-value	98 (41%)	69 (29%) 0.579	50 (21%) 0.521	42 (18%) 0.583
Photophobia				
Placebo	197 (81%)	155 (64%)	126 (52%)	102 (42%)
Sumatriptan 5 mg p-value	206 (83%)	149 (60%) 0.425	119 (48%) 0.423	94 (38%) 0.314
Sumatriptan 20 mg p-value	184 (78%)	133 (56%) 0.138	102 (43%) 0.072	74 (31%) 0.019
Phonophobia				
Placebo	178 (73%)	134 (55%)	107 (44%)	88 (36%)
Sumatriptan 5 mg p-value	175 (70%)	132 (53%) 0.614	95 (38%) 0.128	70 (28%) 0.044
Sumatriptan 20 mg p-value	161 (68%)	117 (49%) 0.228	85 (36%) 0.088	66 (28%) 0.060
Vomiting				
Placebo	12 (5%)	11 (5%)	8 (3%)	8 (3%)
Sumatriptan 5 mg p-value	8 (3%)	5 (2%) 0.144	3 (1%) 0.125	3 (1%) 0.130
Sumatriptan 20 mg p-value	19 (8%)	12 (5%) 0.708	9 (4%) 0.685	4 (2%) 0.252

Source: Adapted from sponsor tables 13.9, 13, 14, 13.9, 15, 13.10, 16, 13.11, 17, and 13.12
Analyzed using Cochran-Mantel-Haenszel test controlling for investigator.

In summary trial SUM30045 failed to demonstrate any benefit of sumatriptan nasal spray (5 and 20 mg for the proportion of subjects reporting associated symptoms at 1 hour.

5.1.4.1 Headache relief at various timepoints.

The following table summarizes the proportion of subjects reporting headache relief at various timepoints. As demonstrated in the table the proportion of subjects taking sumatriptan nasal spray 20 mg reporting headache relief at 30 minutes and 2 hours was significantly greater than the proportion of subjects taking placebo reporting headache relief ($p \leq 0.046$) however this comparison did not reach statistical significance at 1 hour (p=0.087). Although these comparisons were significant at these timepoints it is debatable whether the treatment effects are clinically relevant (9 to 10%). Additionally, findings at 2 hours could possibly be confounded by the use of rescue medication.

As demonstrated in the table there was no statistically significant difference between subjects taking sumatriptan nasal spray 5 mg and subjects taking placebo for headache relief at any timepoint.

Table 12 Headache Relief at Various Timepoints, ITT

ITT Population			
Headache Relief at:	**Placebo N=244**	**SUM 5 mg N=250**	**SUM 20 mg N=237**
30 minutes, n(%)	79 (33%)	85 (34%)	99 (42%)
p-value[1]		0.610	0.046
1 hour, n(%)	127 (52%)	132 (53%)	143 (61%)
p-value[1]		0.719	0.087
2 hours	141 (58%)	155 (63%)	161 (68%)
p-value[1]		0.278	0.025

Source: Adapted from sponsor tables 11, 13.1 and 13.2
1 p-values compared to placebo
Analyzed using CMH test controlling for investigator

5.1.4.1 Conclusion

The sponsor provides the following efficacy conclusion statements:

- *Analyses of the dual primary efficacy endpoints demonstrate that sumatriptan nasal spray 20mg is effective in the treatment of acute migraine in an adolescent patient population (12-17 years of age).*
- *Sumatriptan nasal spray 20mg provided greater headache relief at 30 minutes, 1 hour, and 2 hours post-dose than placebo. The difference between treatment groups was statistically significant at both 30 minutes (p=0.046) and 2 hours (p=0.025) post-dose and approached significance for the primary efficacy endpoint of headache relief at 1 hour post-dose (p=0.087). Further, the probability of achieving headache relief was significantly greater with sumatriptan nasal spray 20mg than with placebo within 30 minutes (p=0.036), 1 hour (p=0.027), and 2 hours post-dose (p=0.007, log-rank test based on Kaplan-Meier methods).*
- *Sumatriptan nasal spray 20mg provided greater sustained relief from 1 to 24 hours post-dose than placebo; the difference between treatment groups for this primary efficacy endpoint neared significance (p=0.061).*

I do not concur with the sponsor's conclusions. Using the analysis presented by the sponsor it appears to me that trial SUM30045 failed to demonstrate efficacy for the prestated primary endpoints using the prestated analysis method. Specifically trial SUM30045 failed to demonstrate a significant difference between sumatriptan nasal spray 20 mg and placebo for the two co-primary endpoints of headache relief at 1 hour and sustained headache relief between 1 and 24 hours in the ITT population (p= 0.087 and 0.061 respectively). For subjects taking sumatriptan nasal spray 20 mg there was a strong trend favoring active treatment for both endpoints however the comparison to placebo did not reach the 0.05 threshold for statistical significance. Likewise there was no statistically significant difference between actively treated subjects and subject taking placebo for the proportion of subjects reporting nausea, photophobia or phonophobia at 1 hour ($p \geq 0.138$).

Although sumatriptan nasal spray 20 mg appears to provide significant efficacy for headache relief at 30 minutes and 120 minutes I do not feel the 9 to10% treatment effect (see Table 12) is clinically meaningful. Likewise the results of the analysis of associated symptoms at 1 and 2 hours fails to demonstrate consistent efficacy for sumatriptan nasal spray 20 gm compared to placebo especially for nausea ($p \geq 0.583$).

5.1.5 Safety Findings

5.1.5.1 Exposure

The safety population for trial SUM30045 consists of 738 subjects of which 245 administered placebo, 255 administered sumatriptan nasal spray 5 mg and 238 subjects administered sumatriptan nasal spray 20 mg. A second dose of study medication, used as rescue medication after hour 2, was taken by 45 (18%) subjects in the placebo cohort, 41 (16%) subjects in the sumatriptan 10 mg cohort and 25 (11%) subjects in the sumatriptan 20 mg cohort. The mean number of exposures per patient were comparable between cohorts: 1.18 for placebo, 1.16 for sumatriptan 5 mg, and 1.10 for sumatriptan 20 mg. Exposure in the safety population was defined as anyone who took study medication. The sponsor states the AE data were analyzed for all subjects who received investigational product regardless of whether the subject took 1 or 2 doses of medication (i.e. denominator is the size of the safety cohorts not number of exposures).

5.1.5.1 Adverse Events

The following table summarizes the overall safety experience from this study. As demonstrated in the table there were no serious adverse events or withdrawals due to an adverse events during this trial. Additionally there was a clear dose effect for the proportion of subjects reported at least one AEs with subjects receiving the highest dose of sumatriptan reporting more AEs then subjects receiving the low dose of sumatriptan or placebo (33% vs. 26% vs. 8% respectively).

Table 13 Overall Summary of AEs, safety population

Category	Placebo N=245 n (%)	Sum 5mg N=255 n (%)	Sum 20mg N=238 n (%)
Subjects With at Least One AE (Any AE)	20 (8)	66 (26)	79 (33)
Subjects With at Least One Drug-Related AE (Drug-Related AEs)	15 (6)	59 (23)	76 (32)
Subjects With at Least One Moderate or Severe AE (Moderate or Severe AEs)	11 (4)	25 (10)	48 (20)
Subjects With at Least One Severe AE (Severe AEs)	3 (1)	3 (1)	15 (6)
Subjects With an SAE (SAEs)	0 (0)	0 (0)	0 (0)
Subjects Discontinuing due to an AE (AEs Leading to Withdrawal)	0 (0)	0 (0)	0 (0)

Source: Sponsor table 19

The following table summarizes the most common adverse events (≥2%) reported. Across all treatment groups 589 AEs were reported. As demonstrated the most common AE reported in subjects taking active compound were taste disturbance, nausea, vomiting, and local burning sensation. These are common adverse events seen in adults receiving sumatriptan nasal spray. For the safety data base I reviewed the translation of verbatim terms to preferred terms and agree with the sponsor categorization. Additionally I reviewed the listing of less common adverse events and did not see any unusual signals for a safety concern. Of note, no subject taking active treatment reported a cardiovascular event. Additionally few subjects complained about the characteristic triptan complaint of burning/stinging sensation (see table below), paresthesia (see table below), tightness (<1%), pressure sensation (<1%), or similar type complaints.

Table 14 Most Common AEs (≥2%), Safety Population

Adverse Event	Placebo N=245 n (%)	Sum 5mg N=255 n (%)	Sum 20mg N=238 n (%)
Subjects With at Least One AE	20 (8)	66 (26)	79 (33)
Taste disturbance	4 (2)	48 (19)	60 (25)
Nausea	5 (2)	5 (2)	11 (5)
Vomiting	1 (<1)	1 (<1)	9 (4)
Burning/stinging sensation	1 (<1)	2 (<1)	7 (3)
Paresthesia	2 (<1)	4 (2)	5 (2)
Dizziness	1 (<1)	5 (2)	4 (2)
Nasal signs and symptoms	1 (<1)	5 (2)	4 (2)

Source: Sponsor table 20

The majority of all adverse events were transient and mild to moderate in intensity. Overall 6% of subjects in the high dose sumatriptan group rated their adverse events as severe compared to 1% for the other two treatment cohorts. The vast majority of reports in the high dose group receiving a severe rating were taste disturbances. None of these events resulted in patient withdrawal. A subgroup analysis of adverse events by gender, age, race and BMI did not reveal any specific trends.

5.1.5.1 Deaths, SAE and Withdrawals due to an AE

There were no deaths, serious adverse events or withdrawal due to an adverse event during this trial.

5.1.5.1 Pregnancies

A single pregnancy was reported during this study. A 15 year old female (PID 115495), randomized to sumatriptan nasal spray 5 mg, reported taking 2 doses of test product in the first trimester of the pregnancy. The study reports states the pregnancy went to term with the delivery of a male infant however the report does not describe the newborn's health condition.

5.1.5.1 Clinical laboratories/ECGs

No clinical laboratories or ECGs were performed during this study.

5.1.5.1 Vital Signs

Vital signs (blood pressure and pulse) were assessed at the screening and exit visits for all subjects. A review of the mean changes in each vital sign did not reveal any significant trends however as should be expected in any study there were a few subjects who had significant changes from their baseline assessments as demonstrated in the following table. As demonstrated in the table 5 subjects taking sumatriptan nasal spray 5 mg and 6 subjects taking sumatriptan nasal spray 20 mg reported a clinically significant drop in their systolic blood pressure. Otherwise no noteworthy number of subjects taking active treatment experienced a clinically significant change in their vital signs. Since most of these readings were collected several days after taking sumatriptan the findings are probably normal variations in daily blood pressure and pulse.

Table 15 Clinically significant changes in vital signs

		Systolic/Diastolic BP (mmHg)			Pulse (bpm)		
Cohort	**PID**	**Baseline**	**Exit**	**Change**	**Baseline**	**Exit**	**Change**
Low Systolic Changes							
Placebo	100139	118/78	88/58	-30/-20	80	78	-2
SUMA 5 mg	115481	115/70	90/51	-25/-19	70	80	+10
	100160	110/68	90/60	-20/-8	64	78	+14
	100526	122/68	86/54	-36/-14	58	68	+10
	100945	110/65	80/60	-30/-5	80	72	-8
	100950	114/78	85/65	-29/-13	72	72	0
SUMA 20 mg	100280	110/70	90/68	-20/-2	62	90	+28
	100142	112/68	90/64	-22/-4	52	60	+8
	100733	125/65	84/66	-41/+1	56	68	+12
	101220	112/61	90/60	-22/-1	69	75	+6
	100330	118/80	90/70	-28/-10	72	80	+8
	100560	112/66	88/60	-24/-6	60	64	+4
High Systolic Changes							
SUMA 5 mg	102396	102/75	136/60	+34/-15	68	78	+10
Low Diastolic Changes							
SUMA 5 mg	100971	90/60	90/40	0/-20	100	84	-16
	100729	98/64	112/48	+14/-16	72	60	-12
	100553	88/64	84/40	-4/-24	80	84	+4
High Diastolic Changes							
Placebo	100492	110/64	121/92	+11/+28	72	85	+13
	100524	128/66	113/89	-15/+23	66	80	+14
Increased Heart Rate							
Placebo	100497	110/72	108/74	-2/+2	100	120	+20

Source: Adapted from sponsor table 22.

5.1.5.1 Safety Conclusions

The sponsor provides the following safety conclusions:

- Both doses of sumatriptan nasal spray were well tolerated.
- No subject reported an SAE or withdrew due to an AE.
- The overall incidence of AEs was lower in the placebo group (8%) than in the sumatriptan nasal spray 5 mg (26%) and sumatriptan nasal spray 20 mg (33%) groups.
- The overall incidence of severe AEs was 1% in the placebo and sumatriptan nasal spray 5 mg groups versus 6% in the sumatriptan nasal spray 20 mg group.
- A dose-dependent effect was observed for overall AE incidence with lower incidences observed in the sumatriptan nasal spray 5 mg group than in the 20 mg group.
- The most common AE was taste disturbance (2%, placebo; 19%, sumatriptan nasal spray 5 mg; 25%, sumatriptan nasal spray 20 mg).
- Incidences of AEs other than taste disturbance were generally low (≤5%) in each treatment group. In the sumatriptan nasal spray 20 mg group, the most common AEs other than taste disturbance were nausea (5%), vomiting (4%), and burning/stinging sensation (3%).
- None of the vital signs results were indicative of a safety concern for sumatriptan nasal spray in adolescent subjects.
- No clear treatment effect was observed in the AE or vital signs analyses by subgroup factor (i.e., sex, age, race, weight, and BMI)

I agree with the sponsor's conclusion. Based on the evidence presented, Imitrex Nasal Spray 5 and 20 mg was generally well tolerated in the population tested. The adverse events reported are similar to those reported in previous adults studies. A similar conclusion was provided by Dr. Oliva from his safety review of trial SUM3005 (1st acute adolescent efficacy trial). Trial SUM3005 had closer safety monitoring with baseline and post treatment laboratories and 12 lead ECGs.

5.2 Detailed Review of Trial SUM3009 (Controlled efficacy 8 to 12 years)

Trial SUM3009 was an investigator initiated, non-IND study, done in the Germany and was first submitted to the Agency with this present submission. The sponsor states the results of this study are being submitted as supportive of clinical efficacy. The study report asserts that the study protocol, any amendments and the informed consent were all reviewed by national, regional, or investigational ethic committees or institutional review boards. The final study report was completed by GlaxoSmithKline and represents a "*reanalysis of selected efficacy and safety data"* from the original data provided by the investigator. The sponsor states this was done to confirm the efficacy and safety results reported by the investigator in May 2001 and they cite several problems with the analysis plan employed by the investigator. Presumably this reanalysis was done after unblinding. The original study report completed by Dr. Michael Ueberall is contained in the modular appendix of the supplement and is entitled "Investigator's Statistical & Clinical Report".

5.2.1 Protocol

This was a randomized, placebo controlled, single center, double blind, two-period, crossover, single attack (each crossover) study to evaluate the safety and efficacy of sumatriptan nasal spray 10 mg for the acute treatment of migraine in children suffering from refractory migraine with and without aura. The primary objective was to compare the efficacy and safety of sumatriptan nasal spray 10 mg to placebo in the acute treatment of a single migraine attack of moderate to severe pain intensity. A single 10 mg dose of sumatriptan nasal spray is not available in the United States however the present U.S. label states a 10 mg dose can be achieved by administering 2 doses of sumatriptan nasal spray 5 mg. The proposed maximum adolescent dose for the US market is 20 mg hence this study does not evaluate the safety and efficacy of doses proposed for the US market.

To be eligible for enrollment patients had to be between 8 to 12 years of age and have a history of migraine (IHS 1.1 and 1.2) for at least 6 months. Migraine frequency had to be at least 2 but no more than 8 attacks per month and the typical duration had to be greater than 4 hours. Additionally enrolled subjects had to have a history of failed or inadequate response to commonly used anti-migraine drugs, be otherwise healthy, have no contraindications for triptans, and not be on any migraine prophylaxis therapy. Since subjects were between 8 and 12 years of age the applicability of this study to adolescents is questionable in my opinion.

Subjects were screened at visit 1 and given randomized treatment if they were eligible. Randomized treatment included either sumatriptan nasal spray 10 mg or matching placebo in order to treat a single attack in the outpatient setting. A second dose of identical treatment was

provided for recurrence if required. Safety evaluations in visit 1 included a 12-lead ECG and vital signs assessment (blood pressure, pulse and temperature). No blood tests were done. After treating an attack with study medication subjects returned to the clinic to receive the alternate treatment for their next attack. Visit 2 did not include any safety evaluations other than a vital sign assessment (and presumably adverse events assessment). Subjects were encouraged to not use rescue medication for at least 2 hours after treatment with study medication. At visit 3 subjects were asked to express a preference for one of the two study drugs. Additionally subjects were asked to rate the effectiveness of the medication (very good, good, satisfactory, sufficient, poor or fail) and its tolerability (very good, good, satisfactory, and poor). The reliability and validity of these scales are not described by the sponsor. Although vital signs and a screening ECG were done they are not described in this study report.

Migraine recurrence or incomplete response could be treated with the second dose of study medication or other approved migraine treatments if required. Prohibited medications included any continuous oral drug treatment (not specified), ergot-alkaloids, triptans, *or any other analgesic or anti-emetic 24 hours before and after study medication*. The last italicized statement appears to indicate that no analgesics or anti-emetics were permitted as rescue medication for incomplete response or recurrence within 24 hours however this appears to be contraindicated by the statement that other approved migraine therapies can be used between 2 to 24 hours.

All data was recorded in a case report form and 24 hour migraine diary. The migraine diary included typical details such as date/time of pain onset, date/time of study drug administration, specific characteristics of migraine pain before and after treatment, presence of aura, pain severity, the presence of associated symptoms, and rescue medication use. The sponsor states that their review of the original datasets showed that 21 out of 60 subjects (35%) had some form of error between the CRF/Diary cards and the Excel spreadsheet provided by the investigator. The sponsor states all discrepancies were corrected prior to their statistical analysis. A description of the discrepancies is not provided.

The primary endpoint of trial SUM3009 is the incidence of subjects achieving headache relief 2 hours after dosing. Headache relief is defined as a reduction of at least 2 points in headache pain intensity from a baseline severity of moderate (2) or severe (3). This is a higher threshold for 2 hour headache response than we usually see in migraine trials which tend to define headache response as a reduction of pain intensity from moderate (2) or severe (3) at baseline going to none (0) or mild (1) at 2 hours (i.e., a reduction from 2 to 1 would be a responder). Secondary endpoints included headache pain relief at various timepoints (15, 30, 60, 90, 180 and 240 minutes), pain freedom, incidence of associated symptoms, use of rescue medication, and subject satisfaction. The Generalized Estimating Equations (GEE) approach was used by the sponsor to compare cohorts with respect to each efficacy parameter in this two-period crossover study. The sponsor states a sample size of 50 subjects per treatment sequence will provide 80% power to detect a 30% difference in efficacy between sumatriptan nasal spray 10 mg and placebo.

The primary efficacy population in the sponsor's report is the Intent to treat population (ITT) defined as all subjects that took study medication and provide some post treatment efficacy data. The per protocol population included all subjects who treated with both study treatments and

provided an evaluation of both treatments. The safety population included all subjects that took any amount of study medication.

The sponsor does not describe whether a LOCF algorithm was used for missing data however they report no missing pain scores or associated symptoms scores were observed for any patient during both periods (an unusual occurrence in migraine studies I have reviewed). However in the report the sponsor states subjects who fell asleep within 120 minutes after taking study drug and woke up symptom free were considered a treatment success. I am fairly confident this division would not have agreed to this plan since this would give medications with sedative qualities an unfair advantage in the treatment of migraine. In my opinion subjects not providing a 2 hour assessment should have had their last observation carried forward. The sponsor does not provide the datasets in SAS transport file so a quick manipulation of the datasets is not possible however I reviewed the data listing for each patient diary and could not find any missing pain intensity data elements. I am uncertain whether this means the sponsor imputed values consistent with treatment success for children who feel asleep prior to 2 hours or whether no child fell asleep and all data fields were completed by the subject (or parent). Obviously I have some concerns about data quality and would prefer a full review by DSI before accepting the data however since this study is not pivotal and its relevance to adolescent minimal I do not see the need to request an investigation.

5.2.2 Study Population

The following table provides a summary of the various populations in trial SUM30009. A total of 60 subjects (28 males, 32 females) were enrolled into the study and only a few subjects failed to take study medication or not participate in both periods. Three subjects did not treat with study medication during both treatment period and are not included in the per protocol analysis. Additionally 8 subjects (13%) were below the age of 8 years (range 7.24 to 7.95) however they are included in the per protocol population since this was considered a minor protocol violation. A 13% protocol violation for something a simple as checking the age of subjects suggest a lack of attention to details in patient selection and further adds to my concern about the quality of this study.

Table 16 Summary of Populations

Population	Placebo	Sumatriptan	Total
Safety	58	59	60
ITT	58	59	60
Did not treat both attacks	1	2	3
Per Protocol	57	57	57

Source: Sponsor table 2 and 12.2

5.2.3 Demographics and Baseline Characteristics

The following table summarizes the demographic characteristics of the safety population. All subjects were Caucasian and the average age across all groups was 9.7±1.3 years (range 7.2 to 11.7 years). A total of 17 subjects (28%) reported a history of migraine with aura. Overall the treatment sequences were similar with regards to age, weight and race. Data on current medical conditions and previous medication use was not collected.

Table 17 Demographics: Safety Population

Characteristic	Suma/Placebo N=30	Placebo/Suma N=30	All patients N=60
Age (Years) mean Median (range)	9.7 10.0 (7.4-11.7)	9.6 9.9 (7.2-11.5)	9.7 10.0 (7.2-11.7)
Weight (kg) mean Median (range)	32.0 31.6 (22.0-48.2)	32.0 32.2 (21.5-44.0)	32.0 31.8 (21.5-48.2)

Source: Sponsor table 3 and 12.3

The following table summarizes the baseline characteristics of the treated migraine attacks. The percentages of subjects experiencing moderate or severe pain, nausea, vomiting, photophobia and phonophobia at baseline were similar between attacks treated with placebo and sumatriptan nasal spray. As demonstrated in the table the majority of subjects reported multiple associated symptoms with their treated attack. Of particular interest is the high incidence of nausea (75 to 81%) and vomiting (68 to 74%) seen in these young children. Studies with adolescents generally have a much lower incidence of nausea and vomiting suggesting a significant difference in the migraine syndrome in these two populations. Likewise many authorities believe the prevalence of migraine in prepubescent children is higher in males than females suggesting yet another difference between migraineurs less than 12 years of age and adolescents.

Table 18 Baseline migraine symptoms

	Placebo N=58 n (%)	Sumatriptan N=59 n (%)
Moderate pain Severe pain	7 (12%) 51 (88%)	6 (10%) 53 (90%)
Nausea	47 (81%)	44 (75%)
Vomiting	43 (74%)	40 (68%)
Photophobia	47 (81%)	49 (83%)
Phonophobia	45 (78%)	48 (81%)

Source: Sponsor table 4 and 12.4

5.2.4 Efficacy Results

As previously discussed the sponsor performed a reanalysis of the investigator's results after correcting a fairly large number of mistakes in the original dataset. The investigator's original study report and protocol (in English) can be found in the appendices of the sponsor's study report.

The Generalized Estimating Equations (GEE) approach was used by the sponsor to compare cohorts with respect to each efficacy parameter in this two-period crossover study. The analysis

plan described in the investigator's report states efficacy would be evaluated using chi square test according to Pearson, and, if the expected frequency was <5, using the exact test according to Fisher. However the original protocol states "*the comparison of the direct treatment effect on the basis of the above-mentioned ordinal-scaled data between active substance and placebo will be made with the parameter-free McNemar test, and interval-scaled data will be tested for significance with the non-parametric Wilcoxon test for pair differences. Further test methods can additionally be used according to the data situation. There will be a test for whether there is an influence of the treatment periods on efficacy.*" Since there were no protocol amendments it appears the investigator report also uses a post hoc analysis. The situation is confusing to this reviewer and would require further investigation if this were a pivotal trial or had significant relevance to adolescent migraineurs. Although the sponsor did not use the prestated statistical plan it appears the results are very similar to the results obtained by the investigator. Since the sponsor analysis using the ITT population is clearly stated and errors in the data listings have been corrected I have chosen to present the sponsor's analysis in this review. When appropriate I will supplement the discussion with results from the investigator's analysis. Since I believe the relevance of this study to adolescents is limited I will limit my discussion of the results the primary endpoint and a few selected secondary endpoints.

5.2.4.1 Primary Endpoint

The primary efficacy endpoint was the percentage of patients who achieved headache relief, defined as at least a 2 point decrease in headache intensity two hours post dose from a baseline grade of 3 or 2, using a 4 point scale, where 0=none, 1=mild, 2=moderate and 3=severe. As described above the primary endpoint was analyzed by the sponsor using GEE. Term used included subject, period and treatment. Since treatment by period was found not to be significant (p>0.70) for the primary endpoint it was dropped from the final model.

The following table summarizes the sponsor's analysis of the proportion of patients reporting a pain reduction of at least 2 points from baseline at 2 hours. As demonstrated in the table subjects from each period using sumatriptan nasal spray 10 mg to treat their attack reported significantly more improvement in headache pain then when they treated an attack with placebo (64% vs. 41%). These results are particularly good when you consider headache response was defined as a reduction in pain severity of 2 points rather then the usual manner in which it is defined. As demonstrated in the table the results from each period were comparable and the period effect was found to be not significant (p=0.963).

Table 19 Headache response at 2 hours, ITT population

Combined periods			
	Placebo (N=58)	Sumatriptan 10 mg (N=59)	p-value
2 hour Response	24 (41%)	38 (64%)	0.022
Period 1			
	Placebo (n=30)	Sumatriptan 10 mg (n=30)	p-value
2 hour Response	13 (43%)	19 (63%)	Not provided
Period 2			
	Placebo (n=28)	Sumatriptan 10 mg (n=29)	p-value
2 hour Response	11 (39%)	19 (66%)	Not provided

Source: Sponsor graph 1, table 13.1 and 13.3.

The investigator report states headache relief was achieved in 38 (63.3%) attacks treated with sumatriptan nasal spray and 24 (40%) of those treated with placebo (p=0.013).

5.2.4.1 Secondary Endpoints

The secondary endpoints presented by the sponsor in their study report included the following:

- Percentage of subjects experiencing headache relief (defined earlier) at 15, 30, 60, 90, 180 and 240 minutes post dose.
- Percentage of subjects pain free, defined as a decrease in headache pain from grade 3 or 2 to grade 0 at 15, 30, 60, 90, 120, 180 and 240 minutes post dose.
- Percentage of subjects experiencing nausea, vomiting, phonophobia and photophobia at 15, 30, 60, 90, 120, 180 and 240 minutes after treatment with sumatriptan 10 mg nasal spray.
- Percentage of subjects using a second dose of study drug or other migraine medication within 24 hours after treatment with sumatriptan 10 mg nasal spray.
- Percentage of subjects stating a preference for study drug. (not discussed in this review)

The GEE method was used by the sponsor to analyze these endpoints. For the purposes of this review I only present the analysis done by the sponsor. The analysis done by the investigator resulted in similar findings and will not be repeated here unless relevant.

5.2.4.1 Associated symptoms

The following table summarizes the proportion of subjects reporting each associated symptom at various timepoints.

At 30, 60 and 90 minutes a statistically significant lower proportion of subjects using sumatriptan nasal spray 10 mg reported nausea compared to subjects using placebo ($p \leq 0.016$). At 120 minutes (timepoint for primary endpoint) the results were nearly statistically significant favoring sumatriptan nasal spray (p=0.075).

Starting at 30 minutes a statistically significant lower proportion of subjects using sumatriptan nasal spray reported vomiting compared to subjects using placebo ($p \leq 0.005$). This benefit continued through 240 minutes of observation. This result is particularly interesting since most migraine studies I have reviewed (adolescent and adults) generally have too few subjects reporting vomiting at baseline to make a meaningful comparison between cohorts.

Starting at 60 minutes a statistically significant lower proportion of subject using sumatriptan nasal spray reported photophobia compared to subjects using placebo ($p \leq 0.03$). This benefit continued through 240 minutes of observation.

At 60 minutes the proportion of subject using sumatriptan nasal spray reported significantly less phonophobia than subjects using placebo (p= 0.04). This comparison was nearly significant at 90 and 120 minutes (p = 0.059 and 0.086).

Table 20 Proportion of Subjects Reporting Associated Symptoms

	Placebo N=58	Sumatriptan 10 mg N=59	p-value
Nausea			
0 minutes	47 (81%)	44 (75%)	
15 minutes	45 (96%)	40 (91%)	0.208
30 minutes	44 (94%)	33 (75%)	0.016
60 minutes	41 (87%)	26 (59%)	<0.001
90 minutes	36 (77%)	22 (50%)	0.004
120 minutes	**29 (62%)**	**20 (46%)**	**0.075***
180 minutes	25 (53%)	18 (41%)	0.148
240 minutes	24 (51%)	16 (36%)	0.095
Photophobia			
0 minutes	47 (81%)	49 (83%)	
15 minutes	43 (92%)	41 (84%)	0.601
30 minutes	42 (89%)	35 (71%)	0.154
60 minutes	40 (85%)	27 (55%)	0.012
90 minutes	37 (79%)	21 (43%)	0.003
120 minutes	**34 (72%)**	**17 (35%)**	**0.002**
180 minutes	28 (60%)	14 (29%)	0.010
240 minutes	25 (53%)	13 (27%)	0.030
Phonophobia			
0 minutes	45 (78%)	48 (81%)	
15 minutes	43 (96%)	42 (88%)	0.737
30 minutes	42 (93%)	36 (75%)	0.186
60 minutes	39 (87%)	29 (60%)	0.040
90 minutes	35 (78%)	25 (52%)	0.059
120 minutes	**30 (67%)**	**22 (46%)**	**0.086**
180 minutes	23 (51%)	19 (40%)	0.409
240 minutes	21 (47%)	18 (38%)	0.521
Vomiting			
0 minutes	43 (74%)	40 (68%)	
15 minutes	40 (93%)	35 (88%)	0.271
30 minutes	38 (88%)	25 (63%)	0.004
60 minutes	35 (81%)	17 (43%)	<0.001
90 minutes	32 (74%)	13 (33%)	<0.001
120 minutes	**28 (65%)**	**11 (28%)**	**<0.001**
180 minutes	23 (54%)	9 (23%)	0.005
240 minutes	22 (51%)	7 (18%)	0.002

Source: Sponsor table 13.8, 13.9, 13.10 and 13.11

* The investigator had a p value of 0.12 for this comparison.

In summary attacks treated with active compound demonstrated numerically and in most cases statistically superior results at 2 hours compared to attacks treated with placebo for each of the associated symptoms listed above. The comparison of cohorts demonstrated superior benefit at times earlier than 2 hours for each associated symptom. The results for vomiting are particularly impressive.

5.2.4.1 Headache response at various timepoints

The following table summarizes the proportion of patients reporting headache relief at various timepoints. As demonstrated in the table when subjects used sumatriptan to treat an attack they reported significantly more headache pain relief than when they used placebo to treat an attack starting as early as 30 minutes.

Table 21 Headache relief at various timepoints

	Placebo N=58	Sumatriptan 10 mg N=59	p-value
15 minutes	3 (5%)	5 (9%)	0.500
30 minutes	4 (7%)	20 (34%)	0.001
60 minutes	9 (16%)	26 (44%)	0.001
90 minutes	16 (28%)	31 (53%)	0.011
120 minutes	24 (41%)	38 (64%)	0.022

Source: Sponsor table 13.1 and 13.4

5.2.4.1 Pain Free at various timepoints

The following table summarizes the proportion of patients reporting complete pain relief at various timepoints. As demonstrated in the table when subjects used sumatriptan to treat an attack they reported significantly more complete relief of headache pain than when they used placebo to treat an attack starting as early as 60 minutes. This benefit continued through 2 hours.

Table 22 Pain Free

	Placebo N=58	Sumatriptan 10 mg N=59	p-value
15 minutes	0 (0%)	1 (2%)	
30 minutes	2 (3%)	9 (15%)	0.051
60 minutes	5 (9%)	18 (31%)	0.004
90 minutes	10 (17%)	25 (42%)	0.005
120 minutes	15 (26%)	27 (46%)	0.027
180 minutes	20 (35%)	29 (49%)	0.141
240 minutes	22 (38%)	32 (54%)	0.082

Source: Sponsor table 13.5 and 13.6

5.2.4.1 Use of Rescue Medication

The following table summarizes the proportion of subjects using a second dose of study medication or some other approved migraine medication within 24 hours. As demonstrated in the table a statistically significant lower proportion of subjects using sumatriptan required additional migraine medication within 24 hours than subject using placebo (33% vs. 15%, p=0.049). However twice as many attacks treated with sumatriptan required a second dose of trial medication than attacks treated with placebo (3 versus 6, p=0.336) however the numbers may be too low to make a meaningful comparison for this endpoint. The sponsor does not provide a statistical comparison of subjects using either a second dose of study medication or some other migraine treatment to treat a recurrence or incomplete response. Assuming no subject took both a second dose of study medication and some other approved migraine product then the combined populations would be 22 (38%) placebo subjects compared to 15 (25%) sumatriptan subjects. Roughly this comparison does not appear to be statistically significantly different.

Table 23 Use of Rescue/2nd dose of trial medication

	Placebo N=58	Sumatriptan 10 mg N=59	p-value
Additional migraine medication	19 (33%)	9 (15%)	0.049*
Second dose of study medication	3 (5%)	6 (10%)	0.336

Source: sponsor table 5

* The investigator had a p-value of 0.027 for this comparison.

5.2.4.1 Efficacy Conclusion

The sponsor concludes sumatriptan nasal spray is significantly more effective in treating migraines in children (8 to 12 years) compared to placebo as measured by headache relief at 2 hours (primary endpoint), relief of associated symptoms, the proportion of subjects reporting complete pain freedom, and the use of additional migraine medication between 2 to 24 hours.

I agree the sponsor's analysis of the data supports these conclusions however I have several concerns about the study. First of all I have some concerns about the data quality and the conduct of the study. Although this was a single investigator study there was still a 13% error rate in enrolling children within the prestated age range. Although I agree this was probably a minor violation it calls into question the quality of the study conduct. Likewise the sponsor reports that data from 35% of all subjects had some sort of error (not described) between the CFR/Diary Card and the data listings. I also have concerns about maintaining the blind in a single center, single investigator, crossover study using a product with significant local effects. As I discuss in the safety section of this review 20% of the subjects reported local irritation from sumatriptan nasal spray compared to no subject taking placebo. Finally the analysis presented by the sponsor (and presumably by the investigator) is post hoc.

Despite these concerns the study may be supportive of efficacy in children between the ages of 7 to <12 (age range enrolled) however in my opinion it is not supportive of efficacy in adolescents. As I describe in my review and as discussed by the sponsor and investigator migraine presents in a different manner in children than it does in adolescents. For this reason it can not be stated with certainty that effectiveness in children (7 to <12 years) is the same as effectiveness in adolescents (12 to <18 years).

5.2.5 Safety Findings

Safety terms in trial SUM3009 were coded using the MIDAS coding dictionary to collapse similar investigator terms for the AEs prior to analysis. The following table summarizes the most common adverse events (≥2%) reported in trial SUM30009. A total of 60 subjects participated in the 2 period crossover trial. There were no deaths, adverse events leading to withdrawal, pregnancies, or serious adverse events during the trial. As demonstrated in the table reported adverse events in children (8 to 12 years) are similar in nature to those reported in older populations. Of particular note is the 20% of subjects reporting taste disturbance while using active treatment. This may have caused some unblinding particularly in a crossover study. The sponsor states the investigator's attribution of intensity and causality of adverse events are not available for review.

Table 24 Common Adverse Events, (≥2%)

Adverse Event	Placebo N=58	Sumatriptan N=59
Any event	7 (12%)	16 (27%)
Taste disturbance	0	12 (20%)
Nasal signs and symptoms	3(5%)	2(3%)
Throat/tonsil discomfort	1 (2%)	5 (8%)
Tinnitus	1(2%)	0
Abdominal pain/discomfort	2(3%)	0
Nausea	1(2%)	0
Vomiting	1(2%)	0
Eye irritation and itching	2(3%)	0
Chest symptoms	1(2%)	0

Source: Adapted from sponsor table 7

Interestingly the sponsor's tabulation of adverse events suggests 23 adverse events were reported (7 plus 16, table above) in an unstated number of subjects whereas the investigator's report clearly states 30 adverse events were reported by 19 patients (33.3%). The difference in these reporting rates are not obvious to this reviewer. The investigator refers the reader to table 3 in appendix A however no investigator tables are provided. The investigator does report all adverse events were of short duration and none were severe.

The sponsor does not present the results of the vital signs done at each visit in their study report. I reviewed the investigator's study report and could not find the results. In the original study report the author states there were no "pathological levels" for blood pressure, heart rate, body temperature, weight and size. The author refers the reader to table 1 for a comparison of vital signs however I could not find any tables in the report. The appendix for the investigator's report refers the reader to a "separate file" for all tables however I could not find this separate file.

The sponsor concludes sumatriptan nasal spray 10 mg was well tolerated in the treatment of "*adolescen*t" migraine. Since adolescents were not enrolled in this study I am not able to agree with the sponsor's conclusion. In summary this study supports the safe use of sumatriptan nasal spray in children between 7 and 12 years of age however the data is limited by the lack of information on symptom intensity and causality as well as missing investigator tables. Similarly the study is too small to provide adequate assurance of safety in this population. This study is also limited due to the lack of safety surveillance such as CBC and a comprehensive chemistry panel. Finally the sponsor does not provide the results of the vital signs collected at each visit. If the sponsor intends to further pursue the indication of migraine in children of 8 to 12 years of age I would recommend significantly more safety monitoring be conducted than what was done in this study. Likewise we would need to consult with the pharmacotoxicology reviewer to determine whether preclinical studies support the use of sumatriptan in children 8 to 12 years of age.

5.3 Detailed Review of Trial SUM40019 (Controlled efficacy 8 to 17 yrs)

Trial SUM40019 was an investigator initiated, non-IND study, done in Finland and was first submitted to this Agency with this present submission. The sponsor states the results are being submitted as supportive of clinical efficacy. The study report asserts that the study protocol, any amendments and the informed consent were all reviewed by national, regional, or investigational

ethic committees or institutional review boards. The final study report was completed by GlaxoSmithKline and represents a reanalysis of safety and efficacy data from the original data provided by the investigator. I am unable to locate the original study report completed by the investigator however the original protocol can be found in the appendices section of the sponsor's report. I requested the original investigator study report from the sponsor however in an e-mail dated January 29, 2004 they directed me to the report written by the sponsor. Data listings are available however they are not submitted in SAS transport files as generally requested.

5.3.1 Protocol

Trial SUM40019 is a randomized, placebo controlled, double blind, multicenter, two-period (single attack each), crossover, outpatient, efficacy study of sumatriptan nasal spray (10 mg or 20 mg). The primary objective of the study was to evaluate the safety and efficacy of sumatriptan nasal spray (10 or 20 mg) compared to placebo in the treatment of migraine in children between 8 to 17 years of age. A secondary objective of the study was to determine whether the stage of puberty has an effect on the response to sumatriptan. Potentially eligible subjects entered a one-month run-in phase whereby they underwent baseline investigations and observations to characterize their headache and to exclude any other causes of the headache. If a subject had already been followed at one of the 3 study centers and the appropriate migraine diagnosis had been determined, the run-in period was shortened or omitted, as appropriate. Subjects then entered the randomized treatment phase during which each subject received two identical packages containing one sumatriptan nasal spray (either 10 mg or 20 mg depending upon weight) and a matching placebo to treat, in a randomized order, two migraine attacks. Subjects weighing between < 40 kg received the 10 mg sumatriptan dose, and subjects weighing 40 kg or more received the 20 mg sumatriptan dose. Subjects were instructed to not use rescue medication for at least 2 hours if they had an incomplete response or recurrence. Each subject only received a single dose of active compound and placebo in order to treat 2 attacks. Permitted rescue medication included anti-emetics, NSAIDs or paracetamol. There was no specified time in which subjects had to treat their two migraine attacks. The protocol dose not describe a washout period between attacks however the sponsor states patients were instructed to have at least 24 hours between treatments. The target was to recruit approximately 130 patients. Prohibited medications included any ergot alkaloids, triptans, analgesics or anti-emetics within 24 hours of treatment. There were no protocol amendments.

To be eligible for enrollment patients had to be between 8 to 17 years of age and have shown a failure or inadequate response to at least one over the counter medication when treating their migraines. Additionally subjects had to have a diagnosis of migraine meeting the International Headache Society 1988 classification for migraine with or without an aura (1.1 or 1.2) typically lasting greater than 4 hours. Migraine frequency was expected to be at least 2 attacks per month. A maximum frequency is not described. Subjects were excluded if they had any significant chronic medical condition, used daily medications or had a family history of early coronary artery disease.

The primary endpoint was the proportion of subjects reporting headache relief at 2 hours post dosing (standard migraine endpoint). Relief was defined as obtaining at least a 2 point reduction

in pain intensity at 2 hours using a 5 point pain scale. The scale used was a facial scale diagramed below (grade 1 = happy face). Subjects were instructed to treat with study medication only if they had a grade 3 or higher on the scale. The protocol states the reliability and validity of the scale has been documented in children (age not specified). I find the scale a bit confusing and potentially misleading in that the third figure could easily be interpreted as mild pain which is generally not treated with study medication in most migraine studies.

Figure 1 5 grade facial scale

Secondary endpoints included pain relief at various times, pain freedom, sustained pain freedom, time to significant alleviation of pain, use of rescue medication, and patient preference. Data on associated symptoms were not collected.

All data was recorded in a case report form and a migraine diary card. The dairy card provided shows pain intensity, using the 5 point facial scale, being collected out to hour 7 however the protocol states pain intensity scale will be completed only out to 240 minutes. An additional question was asked about 24 hours response however the sample diary card is difficult to understand since it is poorly scanned and contains several possible translation errors. For example the 24 hour question is *"If headache disappeared within 2 hours, did it start 24 hours after drug intake?*". Presumably this is a translation error and I assume they are asking whether the migraine recurred within 24 hours of treatment. No assessment of pain intensity was collected for recurrence. The diary card also did not collect information on associated symptoms or other typical secondary endpoints we generally request. Additionally the diary card did not obtain sufficient baseline information to determine whether the treated attack was indeed a migraine. For example the diary did not ask for pain location, nature of pain (throbbing, stabbing etc), presence of aura or any other symptoms used to assessed whether the event treated was a migraine attack. The case report form was considerably better and appears to document sufficient historical information to determine whether a subject experienced migraines (1.1 and 1.2) however other than a neurologic assessment no other safety assessments are documented in the CRF.

Apparently the sponsor and the investigator performed separate analyses, although I am unable to locate the investigator's report. As written in the protocol the investigator planned to test the primary endpoint using McNemar's tests, which assumed no treatment effect, and included only subjects completing both treatment periods (investigator defined ITT population). This approach obviously eliminates subjects only treating a single attack and the assumption of no treatment effect may be invalid. The sponsor believes this is an invalid test and chose to analyze all efficacy endpoints using GEE, a statistical method that allows for a test of treatment by period interaction and a test of direct treatment effects adjusted for period effects. The sponsor's analysis includes all subjects who treat at least 1 attack and provided a post treatment assessment (ITT population). A per protocol analysis, including subjects who treat both attacks, was also done by the sponsor. The treatment comparison of interest were the combined sumatriptan populations (10 and 20 mg) versus placebo. Covariates were not considered in any analysis.

The sponsor does not describe whether a LOCF algorithm was used for missing data. As in trial SUM3009 subjects who were asleep during the 2 hour assessment and woke up symptom free were considered a treatment success. As previously stated I do not believe this division would have agreed to this procedure. In my opinion a last observation carried forward should have been employed for these subjects as well as for any other missing data. The data listings do not list patient facial/numeric response for each timepoint but rather list response as yes/no. I reviewed the data listing for each patient and it appears the sponsor may have imputed yes (under variable column "relief") for subjects who were asleep at 2 hours. According to the data listings it appears 13 subjects treating a migraine attack with placebo, 8 subjects treating with sumatriptan nasal spray 10 mg, and 5 subjects treating with sumatriptan nasal spray 20 mg were asleep at 2 hours and had their response imputed by the sponsor. These numbers may be incorrect since it is difficult to determine whether subjects labeled asleep at times earlier than 2 hours were awake or continued to be asleep at 2 hours. The data listings do not list patient assessment of pain intensity done at hour 5, 6 and 7 even though the diary suggests these timepoints were collected.

The investigator/sponsor calculates an enrollment sample size of 120 to 130 subjects will provide 80% power to detect a 20% difference between cohorts. They assumed a drop out rate of 20 to 30%. The sponsor reports their internal quality control of the database demonstrated a single discrepancy between the CRF and the dataset in the nine subjects randomly selected for 100% QC review.

All subject had a screening visit (visit 1) in which a complete physical and neurologic examination was performed. Blood samples for CBC and a chemistry panel and a urinalysis were collected at this visit although the results are not provided in the study report. This visit was followed by an observation period of variable duration in order to characterize subjects migraine (up to 1 month). At visit 2 eligible subjects underwent a complete physical and neurologic examination and were given randomized sequenced treatment (sumatriptan/placebo or placebo/sumatriptan) in order to treat their next 2 attacks. Other than the physical it does not appear any safety studies were conducted at this visit. Finally all patients had a final follow up visit (visit 3) in which the migraine diaries were collected and adverse events were assessed if required. No post treatment follow-up laboratories were done at this visit.

The design of study, in my opinion has several limitations especially as it may apply to this adolescent supplement. First of all the study did not exclusively enroll adolescents hence its applicability to this supplement is limited. Secondly the fact that both treatments (active and placebo) were provided at the first visit in order to treat the next two migraine attacks raises the possibility that subjects may incorrectly follow the sequence of treatment they were assigned. Similarly since subjects were permitted to treat their next two attacks it is possible there was minimal washout period between the two treatments thus permitting a carryover effect. Finally I have concerns about the maintenance of the blind in a crossover study that evaluates an active product with significant local adverse effects. Imitrex nasal spray has a distinctive taste and approximately 20 to 25% of subjects report taste disturbance with this product in previous studies.

5.3.2 Study Population

The following table provides a summary of the various populations in trial SUM40019. A total of 129 subjects were recruited of which 50 were eligible for sumatriptan nasal spray 10 mg and 79 were eligible for sumatriptan nasal spray 20 mg. Thirty five subjects discontinued from the study prior to receiving randomized treatment (i.e. during the observation period). Overall 94 subjects were randomized and 83 subjects completed the study (treated both attacks and followed up). All subjects took their first dose of randomized treatment whereas 11 subjects failed to take treat their second attack with study medication. The sponsor states the reasons reported by subjects for not treating the second event with study medication was due to a diminished frequency of attacks, the short shelf life of the drug and having their second attack in situations where the use of a nasal spray was not possible. No other protocol deviations were reported.

Table 25 Summary of Populations, Trial SUM40019

	SUMA/PBO	PBO/SUMA	Total
Enrolled			129
Randomized	46	48	94
Treatment A			
Entered	46	48	94
Did not treat	0	0	0
Treatment B			
Entered	46	48	94
Did not treat	7	4	11
Per protocol Population	39	44	83
Safety Population	46	48	94
ITT Population	46	48	94

Source: Adapted from sponsor table 2 and 12.1

5.3.3 Demographics and Baseline Characteristics

The following table summarizes the demographic characteristics of the safety population. The population was nearly evenly divided by gender (males 54% vs. females 46%) and age category (< 12 years 44%, 12 and older 56%). The majority of subjects reported a history of no aura with their attacks (69%) and the majority (67%) were over 40 kg thus receiving sumatriptan nasal spray 20 mg to treat their attack. All subjects were Caucasian. The 2 treatment sequences were well balanced for age, weight and history of aura however there was slightly more males receiving placebo (63% vs. 38%) in the first treatment period of the sequence. Data on current medical conditions and previous medication use were not collected.

Table 26 Demographics, Study SUM40019

Characteristic	SUMA/PBO N=46	PBO/SUMA N=48	All subjects N=94
Age, mean (years)	12.7	12.1	12.4 (range 8.1 to 17.5)
< 12 years	15 (33%)	26 (54%)	41 (44%)
12 to 17 years	31 (67%)	22 (46%)	53 (56%)
Weight, mean (kg)	46.8	46.5	46.7
< 40 kg	13 (28%)	18 (38%)	31 (33%)
≥ 40 kg	33 (72%)	30 (63%)	63 (67%)
Gender			
Male	21 (46%)	30 (63%)	51 (54%)
Female	25 (54%)	18 (38%)	43 (46%)
History of Aura			
Yes	13 (28%)	16 (33%)	29 (31%)
No	33 (72%)	32 (67%)	65 (69%)

Source: Adapted from sponsor table 12.3

The following table shows the distribution of subjects by dose group, weight and age.

Table 27 Subject distribution by dose, weight, and age

Category	Placebo 20mg (≥40kg)	Placebo 10mg (<40kg)	Sumatriptan 20mg (≥ 40kg)	Sumatriptan 10mg (<40kg)
Total subjects	57	30	61	29
< 12 years	15 (26%)	25 (83%)	15 (25%)	24 (83%)
12-17	42 (74%)	5 (17%)	46 (75%)	5 (17%)
<12 years	15	25	15	24
<40kg	0	25 (100%)	0	24 (100%)
≥40kg	15 (100%)	0	15 (100%)	0
12 –17 years	42	5	46	5
<40kg	0	5 (100%)	0	5 (100%)
≥40kg	42 (100%)	0	46 (100%)	0

Source: Sponsor table 4

The following table summarizes the baseline characteristics of treated migraine attacks by treatment (active vs. placebo) and by sequence/dose group. The percentage of subjects reporting grade 3 to 5 pain at baseline were similar between attacks. However for subjects receiving sumatriptan nasal spray 20 mg there was a slight increase in the proportion of patients reporting grade 5 pain compared to subjects receiving sumatriptan nasal spray 10 mg in both sequences (25% vs. 17% and 14%). The presence of associated symptoms was not collected.

Table 28 Baseline pain by treatment and sequence/dose, Trial SUM40019

	Placebo N=87		Sumatriptan N=90	
Pain Severity				
Grade ≤ 2	0		0	
Grade 3	24 (28%)		23 (26%)	
Grade 4	44 (51%)		48 (53%)	
Grade 5	19 (22%)		19 (21%)	
Baseline pain by sequence and dose group	Placebo		SUMA 10 mg	SUMA 20 mg
	SUMA 10 mg	SUMA 20 mg	Placebo	
Grade 3	11 (37%)	13 (20%)	10 (34%)	13 (21%)
Grade 4	14 (47%)	30 (53%)	15 (52%)	33 (54%)
Grade 5	5 (17%)	14 (25%)	4 (14%)	15 (25%)

Source: Adapted from sponsor table 12.4 and 12.7

5.3.4 Efficacy Results

As previously discussed the sponsor performed a reanalysis of the investigator's results. Presumably this was done after the study was unblinded. The original protocol (in English) can be found in the appendices of the sponsor's study report however I am unable to locate the original report from the investigator.

The Generalized Estimating Equations (GEE) approach was used by the sponsor to compare cohorts with respect to each efficacy parameter in this two-period crossover study. The ITT population for the sponsor's analysis is defined as all subjects who use test medication and provide a post treatment assessment (preferred definition). The analysis plan described in the original protocol states efficacy would be evaluated using McNemar test. Further the original investigator protocol states the ITT population will include all subjects who treat both attacks with study medication. Since the sponsor's analysis uses the preferred ITT definition and is clearly stated and since the investigator's report is not available I will present the sponsor's analysis in this review.

5.3.4.1 Primary Endpoint

The following table summarizes the sponsor's analysis of the primary endpoint. The primary endpoint was headache response at 2 hours defined as at least a 2 point drop in pain intensity from baseline using a 5 point pain scale (previously defined). All subjects had a baseline pain score of 3 or higher at baseline. In my opinion 3 could easily be considered mild pain. The sponsor analyzed the results using GEE.

As demonstrated in the table subjects treating their attacks with sumatriptan (10 or 20 mg) reported significantly more relief at 2 hours then when they treated an attack with placebo (67%vs. 38% respectively, $p<0.001$). The per protocol population results were nearly identical ($p=0.003$). The sponsor reports there was no evidence of a significant treatment period effect in either population ($p>0.70$) although the treatment by period interaction was nearly significant ($p=0.069$) in the ITT population.

Table 29 2 Hour Pain Response, ITT Population, Trial SUM40019

Pain response	Placebo N=87	Sumatriptan N=90	p-value
2 hours	33 (38%)	60 (67%)	<0.001

Source: Adapted from sponsor table 13.1

These results may seem rather impressive however there are several problems I see with how the analysis was conducted. The sponsor did not use a last observation carried forward algorithm for missing data. The sponsor treated all subjects as 2 hour responders if they fell asleep before the 2 hour assessment window and woke up without pain. As previously discussed this would favor products with sedative qualities and in my opinion is not correct methodology for a migraine study. The protocol did not specifically state a washout period between treatments (although the sponsor asserts subjects were instructed to not treat 2 attacks within 24 hours of each other) so it is conceivable subjects treated attacks that occurred in a short period of time allowing for a carryover effect. The "sumatriptan" cohort is a heterogeneous group consisting of children and adolescents and 2 different doses of sumatriptan. The sponsor does not describe how they handled headache response in subjects who may have taken rescue medication prior to 2 hours. Since subjects were given both treatments at randomization there is no guarantee subjects did not confuse treatment sequences. The 3rd character in the 5 figure scale could easily be considered as mild pain which is generally not treated with study medications in migraine studies. Actual pain intensity levels at various timepoints is not provided in the data listings (see listing 2) but rather a yes/no response is inputted by the sponsor under the variable "Relief". Finally the analysis used by the sponsor is not the analysis stated in the protocol.

In order to attempt to salvage the study's usefulness for our needs I analyzed the dataset using only the first attack data in adolescent subjects (12 to <18 years) using sumatriptan nasal spray 20 mg compared to adolescents using placebo in the first attack. Subject falling asleep prior to the 2 hour window had their last awake observation carried forward. I assumed any subject asleep at times prior to 2 hours was still asleep at 2 hours. Subjects who used rescue medication prior to 2 hours were treated as treatment failures. The following table summarizes my results. As demonstrated in the table I was able to get very similar results as those derived by the sponsor however the sample size is rather small. It should be noted that the sponsor also presents a reanalysis of their results in which they reclassify subjects falling asleep prior to 2 hours as treatment failures. Their analysis demonstrated a response rate for sumatriptan treated subjects of 56% compared to 29% for placebo treated subjects (p<0.001). Additionally the sponsor performed an analysis of their results in adolescents however they did not make a distinction between treatment periods. In their analysis a significantly higher proportion of subjects reported headache relief at 2 hours when treated with sumatriptan nasal spray (20 mg only) compared to placebo (65% vs. 33%, p=0.001).

Table 30 Agency Analysis of HA Response in Adolescents, Trial SUM40019

Pain response	Placebo N=19	Sumatriptan N=28	p-value*
2 hours	3 (15.8%)	18 (64.3%)	0.001

*Analyzed using Pearson's test

Due to the possible treatment by period interaction the sponsor also compared headache response for each treatment separately. As demonstrated in the following table there was no statistical

difference between cohorts for subjects reporting headache relief in the second treated attack. The reason for this is not immediately clear to this reviewer however the sponsor attributes this difference in response to fewer attacks being treated in the second crossover period as well as the possibility of a crossover effect favoring placebo.

Table 31 Headache Response by Attack, ITT population, all ages, Trial SUM40019

		Placebo	Sumatriptan 10 and 20 mg	p-value
Attack 1		N=48	N=46	
	HA relief at 2 hours	16 (33%)	34 (74%)	<0.001
Attack 2		N=39	N=44	
	HA relief at 2 hours	17 (44%)	26 (59%)	0.161

Source: Sponsor table 13.3

In summary there appears to be robust evidence from the first attack treated that sumatriptan nasal spray 10 and 20 mg is effective for the treatment of pain associated with migraine in adolescents and children. Additionally sumatriptan nasal spray 20 mg appears to be effective in the treatment of pain associated with migraine in adolescents.

5.3.4.1 Secondary Endpoints

Headache relief at various timepoints

The following table summarizes the sponsor's analysis of headache relief at various times. As demonstrated in the table significantly more subjects taking sumatriptan compared to placebo reported headache relief as early as 30 minutes.

Table 32 Headache relief at various timepoints, ITT population

Relief at time (min)	Placebo N=87	Sumatriptan N=90	p-value
15	4 (5%)	6 (7%)	0.576
30	14 (16%)	28 (31%)	0.029
60	25 (29%)	48 (53%)	0.003
120	**33 (38%)**	**60 (67%)**	**<0.001**
180	40 (46%)	61 (68%)	0.007
240	41 (47%)	62 (69%)	0.009

Source: Sponsor tables 13.1 and 13.2

Pain Freedom at 60 and 120 minutes

The following table summarizes the sponsor's analysis of pain freedom at 60 and 120 minutes. The sponsor does not present data for other timepoints. As demonstrated in the table there was no significant difference between cohorts for the proportion of patients reporting complete pain freedom at 60 and 120 minutes although sumatriptan was numerically superior to placebo for both timepoints. The sponsor's analysis of adolescents reporting pain free at 2 hours also failed to demonstrate a significant difference between cohorts (28% sumatriptan vs. 17% placebo, p=0.209). It is interesting to note the sponsor's table containing these results defines pain freedom as no pain "on a four point scale" however a 5 point scale was used in this study. The protocol does not include pain free as an endpoint. Although this appears to be a post hoc endpoint I present the result here since pain freedom is the preferred endpoint suggested by the International Headache Society.

Table 33 Pain Freedom, ITT Population, Trial SUM40019

Pain freedom	Placebo N=87	Sumatriptan N=90	p-value
60 min	11 (13%)	16 (18%)	0.367
120 min	18 (21%)	29 (32%)	0.102

Source: Sponsor table 13.6

Use of Rescue medication

The following table summarizes the sponsor's analysis of the proportion of patients reporting the use of additional migraine medication within 24 hours of treatment with test medication. As demonstrated in the table significantly more subject randomized to placebo, compared to subjects taking sumatriptan, required the use of rescue medication within 24 hour of treatment.

Table 34 Rescue medication use, ITT population, Trial SUM40019

Use of Rescue	Placebo N=87	Sumatriptan N=90	p-value
	43 (49%)	29 (32%)	0.033

Source: Sponsor table 13.7

5.3.4.1 Efficacy Conclusion

In summary there appears to be robust evidence that sumatriptan nasal spray 10 and 20 mg is effective for the treatment of pain associated with migraine in children 8 to 17 years of age as demonstrated by headache response at 2 hours ($p<0.001$). Additionally a subset analysis suggests sumatriptan nasal spray 20 mg appears to be effective in the treatment of pain associated with migraine in adolescents. However the trial has several design problems which prohibits its use as a pivotal adolescent efficacy trial. Unfortunately the design of the 24 hour migraine diary does not permit us to assess whether a migraine was treated. Additionally the study fails to evaluate the efficacy of sumatriptan to treat the associated symptoms associated with migraine. Finally it must be remembered all analysis presented by the sponsor are post hoc analysis.

5.3.5 Safety Findings

Safety terms in trial SUM40019 were coded using the MIDAS coding dictionary to collapse similar investigator terms for AE prior to analysis. The study report is somewhat inconsistent on how they define an adverse event. Initially the report states an AE is defined as any untoward event, whether or not caused by the study drug, recorded from the time the subject first took study medication until discharged from the study. This is an acceptable definition although we would have probably consenting to limiting AEs to the first 24 hour after treatment. However the study report also states for this study only adverse events considered related to study medication and began after treatment were recorded as adverse events (except for serious adverse events). The sponsor clearly states only the drug related AEs have been analyzed in this study report. This is a significant limitation to the safety data provided since the issue of causality is subjective.

A total of 94 subjects participated in the 2 period crossover trial, 90 attacks were treated with sumatriptan and 87 attacks were treated with placebo. There were no deaths, adverse events

leading to withdrawal, pregnancies, or serious adverse events during the trial. The following table summarizes the most common adverse events (≥ 2%) reported in trial SUM40019. In total 90 subjects taking sumatriptan (10 and 20 mg) reported 35 (39%) adverse events and 87 subjects taking placebo reported 7 (8%) adverse events. The nature and character of adverse events reported in this study are similar to those in adults taking sumatriptan nasal spray. All adverse events were rated as mild or moderate in severity. Of particular note is the 33% of subjects reporting taste disturbance while using active treatment. This may have caused some unblinding particularly in a crossover study.

Table 35 Adverse Events, Trial SUM40019

Adverse Event	Placebo N=87	Sumatriptan 10 and 20 mg N=90
Any event	7 (8%)	35 (39%)
Taste disturbance	5 (6%)	30 (33%)
Dizziness	0	2 (2%)
Vomiting	2 (2%)	3 (3%)
Nausea	1 (1%)	3 (3%)

Source: Sponsor tables 6 and 14.1

A subgroup analysis of the incidence of adverse events by age (<12 years/12-17 years), gender and dose (10 mg/ 20 mg) demonstrates no significant difference between gender and age cohorts however a numerically more subjects taking sumatriptan nasal spray 20 reported an adverse events then subjects taking sumatriptan nasal spray 10 mg (28% vs. 44% respectively).

Table 36 Incidence of drug-related AE in various sub-groups, Trial SUM40019

	Placebo N=87 n (%)	Sumatriptan 10mg and 20mg N=90 n (%)	Sumatriptan 10mg N=29 n (%)	Sumatriptan 20mg N=61 n (%)
Any event	7 (8%)	35 (39%)	8 (28%)	27 (44%)
Male	4/47 (9%)	20/49 (41%)	5/17 (29%)	15/32 (47%)
Female	3/40(8%)	15/41 (37%)	3/12 (25%)	12/29 (41%)
<12 years	3/40 (8%)	11/39 (28%)	5/24 (21%)	6/15 (40%)
12-17 years	4/47 (9%)	24/51 (47%)	3/5 (60%)	21/46 (46%)

Source: Sponsor table 8

The laboratory studies conducted at the screening visit are not described in the study report. No post treatment laboratory or ECGs were performed.

The sponsor concludes sumatriptan nasal spray was well tolerated in the treatment of "*adolescents*" migraine compared to placebo. The sponsor does not provide a conclusion for the entire population studied (age 8 to 17 years) however sumatriptan appears to have been well tolerated in children and adolescents. The most common adverse events with sumatriptan use were taste disturbance, vomiting and nausea. As would be expected subjects taking the high dose of sumatriptan nasal spray reported more adverse events then subjects taking the low dose. There were no deaths, serious adverse events, withdrawals due to an adverse event or pregnancy during this study.

In summary this study supports the safe use of sumatriptan nasal spray in children and adolescents however the data is limited since only adverse events thought to be related to study medication are reported. Similarly the study is too small to provide adequate assurance of safety in this population. This study is also limited due to the lack of safety surveillance such as CBC, comprehensive chemistry panel or ECGs. If the sponsor intends to further pursue the indication of migraine in children of 8 to 12 years of age I would recommend significantly more safety monitoring be conducted than what was done in this study. Likewise we would need to consult with the pharmacotoxicology reviewer to determine whether preclinical studies support the use of sumatriptan in children 8 to 12 years of age.

5.4 Detailed Review of Trial SUM40276 (Long term Safety Study)

5.4.1 Protocol

Trial SUM40276 was an open label, single arm, multicenter, outpatient, U.S. study in approximately 500 adolescent migraineurs. The primary objective and endpoint was to evaluate the long term safety of sumatriptan nasal spray in adolescents over a 12 month period. This study was conducted in order to obtain additional long term exposure as requested in the Pediatric Written Request. The study also included multiple efficacy assessments as secondary endpoints.

To be eligible for entry subjects were expected to have a migraine history (IHS 1.1 and 1.2) of at least 6 months, a migraine frequency of at least 2 but no more than 8 attacks per months and a typical migraine duration of at least 2 hours. Other significant inclusion criteria included: age 12 to 17 years at screening, effective birth control, and stable doses of migraine prophylaxis (if required). Exclusion criteria included significant risk factors for cardiovascular/cerebrovascular disease, contraindications for triptans, any significant medical or psychiatric disease/condition, the use of ergotamines within 2 months of entry or the use of MAOI within 2 weeks of entry.

All subjects were seen at a screening visit and assessed for eligibility. Thereafter subjects were seen periodically (approximately every 3 months) and at the end of the study for an exit visit. Subjects were requested to return to the study center for at least 5 visits. Additionally subjects were contacted by telephone monthly while in the study. At the screening visit, and when required, subjects were given a supply of 12 sumatriptan nasal spray devices. Subjects were instructed to treat an unlimited number of migraines, of any pain intensity, with sumatriptan nasal spray over a 12 month period. For each attack treated with study medication subjects were instructed to complete a 24 hour migraine diary. The migraine diary collected the typical efficacy assessments such as pain intensity (4 point scale) and the presence of associated symptoms (absent/present) at 60 and 120 minutes as well as at the time of occurrence if applicable. All subjects were started on sumatriptan nasal spray 20 mg however a dose reduction to 5 mg was permitted if required for tolerance. A second dose of trial medication was permitted at 2 hours if required. Triptan naive subjects were instructed to treat their first migraine in the presence of a responsible adult. All subjects were instructed to contact the study center after treating their first attack in order to review procedures and assess any adverse events if required.

Safety assessments included the following:

- Adverse events were evaluated at each visit and as required.

- A complete physical examination was completed at the entry and exit visits.
- Vital signs (sitting, after 5 minute rest) were collected at each visit.
- A CBC, and Comprehensive Chemistry Panel was collected at the entry and exit visits.
- A 12-lead ECG will be performed at the entry and exit visits.
- A urine pregnancy test was done at each visit.
- Nasal Examination (added as an amendment) were completed at the mid-term and exit visits. (After the mid-term nasal examination subjects were instructed to administer all future doses of sumatriptan in the same designated nostril.)

Prohibited medications included ergotamine containing drugs or other triptans 24 hours before and after treatment with sumatriptan, as well as other acute medications for migraine 6 hours before or 2 hours after treatment with study medication. Additionally MAOIs are prohibited at study entry and at any time during the course of this study.

A sample size of 500 subjects was planned empirically in order to obtain at least 300 subjects with 6 month exposure experience and at least 100 subjects with 12 months of exposure experience. Descriptive statistics was used to describe safety findings. All subjects who take at least a single dose of study medication are included in the safety population. Descriptive statistics was used to analyze the secondary efficacy endpoints for sumatriptan nasal spray 20 mg and sumatriptan nasal spray 5 mg. Only attacks in which subjects entered a post treatment efficacy assessment were used in the calculations.

The original protocol was amended twice. The first amendment clarified the entry guidelines for subjects on migraine prophylaxes and the second amendment added nasal examinations to the study procedures.

5.4.2 Study Population

The sponsor reports the study coordinator at site #85638 admitted to falsifying ECG data. As a results of this information the sponsor presents all safety and efficacy data in a variety of manners. The sponsor presents all safety information with and without data from this site. Since efficacy was secondary the sponsor presents all efficacy data without data from site #85638. The sponsor presents data on patient disposition with and without the site. For simplicity I will present information on subject disposition using all subjects enrolled into the study. For my safety review I will present information on all subjects who take study medication including subjects from site #85638, although they will be excluded in my discussion of ECG findings. Since all efficacy endpoints were secondary and this was an open label, uncontrolled study I will not describe efficacy in this review. When appropriate I will discuss how the data differs from the alternate approach. Study center #85638 (Dr. Bean) had 22 subjects in their safety population.

The following table summarizes patient disposition during trial SUM40276. As demonstrated in the table 518 subjects were enrolled into the study. The sponsor calls this population "randomized" however all subjects were initially given sumatriptan nasal spray 20 mg to treat their attacks. A dose reduction to 5 mg was permitted if the higher dose was not tolerated however the vast majority of subjects remained on 20 mg (96.7 to 99.3%, see table below). Of

this group, 484 subjects took at least a single dose of study medication (safety population) and 452 subjects provided post treatment assessments (ITT population). From this group 319 subjects remained in the study for at least 165 days and provided usable data (6 month completers) and 142 subjects remained in the study for at least 345 days and provided usable data (12 month completers).

In my evaluation of exposure I chose to define 6 month and 12 months completers as subjects who remain in the study for 180 and 360 days respectively. Additionally I limited my calculations to only those subjects remaining on sumatriptan nasal spray 20 mg. Using this definition I calculated 391 subjects, using sumatriptan nasal spray 20 mg, remained in the study for at least 180 days and treated 2884 attacks in the first 180 days (average 1.2 attacks per month). Similarly I calculated 124 subjects, using sumatriptan nasal spray 20 mg, remained in the study for at least 360 days and treated 1947 attacks in the first 360 days (average 1.3 attacks per month). The amount of long term exposure is sufficient to meet the minimum requirements of at least 300 subjects for 6 months and 100 subjects for 1 year. I discuss exposure elsewhere.

Table 37 Patient disposition.

Population	Definition	Total
Randomized	Given medication	518
Safety Population	Took medication at least once	484 (93.4%)
ITT	Supplied efficacy data	452 (87.3%)
6 month completers **Remained on 20 mg** **Changed to 5 mg**	Completed 165 days	319 (61.6%) 309 (96.7%) 10 (3.1%)
12 month completers **Remained on 20 mg** **Changed to 5 mg**	Completed 345 days	142 (27.4%) 141 (99.3%) 1 (0.7%)
Reason for discontinuation		
Lost to follow up	44	
Consent withdrawn	19	
Adverse event	18	
Protocol Violation	6	
Other	112 74 Decreased or resolved attacks 16 Non-compliant 10 Lack of efficacy 3 No longer meet entry criteria 3 Pregnancy 2 Moved away 1 In error 1 Died (motor vehicle accident) 1 Inconvenience with treatment and protocol 1 Decrease headache frequency with prophylaxis	

Source: Adapted from Sponsor table 3.1 and text of study report

The sponsor reports 54 subjects had major protocol violations. Thirty-one subjects took 3 doses of study drug within 24 hours, 4 subjects had baseline blood pressures exceeding the upper limit of normal, 3 subjects became pregnant during the study, 2 subjects had a baseline headache frequency > 15/month, 2 subjects had missing baseline ECG data, 2 subjects had abnormal baseline laboratory results and several subjects had exclusion medical conditions or were taking prohibited medications. Of the 31 subjects taking 3 doses of sumatriptan within 24 hours all but

one exceeded the maximum daily dose of 40 mg. Of these overdoses only a single patient reported an adverse event (nausea and vomiting).

5.4.3 Demographics and Baseline Characteristics

The following table summarizes the baseline demographic of subjects in the safety population. As demonstrated in the table the majority of subjects were female (60%), Caucasian (85%) and had a history of migraine without aura (61%). This is typical of migraine studies I have reviewed. The mean age of all subjects combined was 14.2 years and all subjects combined were generally well distributed between the age groupings of 12 to 14 years and 15 to 17 years. However the distribution of age by gender was not equal for males (142 between 12 to 14 vs. 52 between 15 to 17 years). I don't believe this will have any implications for interpreting the study results.

Table 38 Baseline Demographics, Safety Population

Age	
mean (SD)	14.2 (1.64)
min-max	12-17
12-14 cohort	274 (female 132, male 142)
15-17 cohort	210 (female 158, male 52)
Gender	
Female	290 (60%)
Male	194 (40%)
Race	
White	409 (85%)
Black	44 (9%)
Asian	4 (<1%)
Hispanic	23 (5%)
Other	4 (<1%)
Migraine Type	
With aura	68 (14%)
Without aura	294 (61%)
Mixed	122 (25%)
Mean Migraine Duration	
< 4 hours	30 (6%)
4-8 hours	245 (51%)
> 8 hours	208 (43%)
Migraine Frequency/Month	
2	147 (30%)
3	117 (24%)
4-6	180 (37%)
>6	40 (8%)
Height, mean (SD)	162.1 (9.93) cm
Weight	
male, mean (SD)	60.2 (19.5) kg
female, mean (SD)	59.0 (14.27) kg

Adapted from sponsor tables 5.1, 8

Approximately 80% of all subjects reported some other medical condition at baseline. Overall the most common condition reported at baseline were allergies (39%), neurological conditions (26%), muscular conditions (21%), ENT conditions (19%) and respiratory conditions (17%). Approximately 48% of all subjects report having used Imitrex in the past and 27% report having used other triptans in the past. Since this is an open label safety study this should not be a

problem however it is possible patient self-selection favored subjects who know they have responded to sumatriptan or other triptans in the past thus potentially skewing efficacy results in favor of sumatriptan.

5.4.4 Efficacy Results

Since trial SUM40276 was an uncontrolled safety study, and all efficacy endpoints were secondary, I will limit my review of the study to the safety findings.

5.4.5 Safety Findings

As discussed earlier the study coordinator from site #85638 admitted to falsifying ECG data. As a result the sponsor presents all safety comparisons with and without the safety information from this site. A review of the data demonstrates no significant difference between the two methodologies therefore I will present safety data from the entire safety population in all cases except for my discussion of ECGs.

All subjects were initially provided sumatriptan nasal spray 20 mg to treat their migraine attacks. Although the protocol permitted a dose reduction to 5 mg only 10 subjects (2 %) required a dose reduction. Since the number of subjects taking sumatriptan 5 mg is small a meaningful comparison between high and low dose for safety and efficacy is not meaningful. Therefore for the purpose of this safety review I focus on the safety findings from subjects who took 20 mg.

In the study report the sponsor presents safety findings in several ways which at times becomes a little confusing to follow. The sponsor presents safety findings based on events per subject and further break down the population by the number of doses they may have taken to treat a particular attack (i.e. 5 mg, 5 mg X 2 doses, 5 mg X 3 doses, and "all 5 mg"; 20 mg, 20 mg X 2 doses, 20 mg X 3 doses, and "all 20 mg"). Additionally the sponsor presents safety findings based on attacks treated and in a similar manner as before breaks the population down by the number of doses taken for a particular attack. I find the presentation of adverse events based on per patient a bit misleading since it doesn't give a clear picture of the safety experience with sumatriptan in my opinion. For example a patient may have experienced a single minor adverse event after treating many migraines yet that individual would be counted the same way as an individual who experience the same adverse event each time they take sumatriptan. Therefore I will focus my attention on the per attack incidence rates. Likewise, since the vast majority (85%) of attacks were treated with a single dose of sumatriptan 20 mg I will focus my attention primarily on this cohort. Approximately 15% of all attacks were treated with 2 doses of sumatriptan nasal spray and < 1% were treated with 3 doses. When incidence rates for a particular adverse event differ considerable between cohorts (single, double, triple dose) I will elaborate. Further, since a triple dose of 20 mg constitutes an overdosage (maximum daily dose is 40 mg) I will discuss the safety experience in this subset in section 5.4.5.1 "Overdosage".

5.4.5.1 Exposure

In total 484 subjects (safety population) treated 4718 migraine attacks. Only 42 attacks in 10 subjects were treated with sumatriptan nasal spray 5 mg therefore the vast majority (99.1%) of attacks were treated with 20 mg. The sponsor reports 3632 attacks were treated in the first 6 months of the study and 1086 attacks were treated in the second six months of the study. For all

subjects using 20 mg, the mean number of doses used per attack overall was 1.2. For the 5 mg dose group the mean number of doses used per attack was 1.3.

The sponsor reports 389 subjects treated an average of 1.15 (0.84) migraine attacks per month (range 0.08 to 6.85) over a 6 month period with sumatriptan nasal spray 20 mg and 122 subjects treated an average of 1.37 (0.98) migraine attacks per month (0.08 to 6.95) for at least 12 months using sumatriptan nasal spray 20 mg. From my own calculations 391 subjects, using 20 mg, remained in the study for at least 180 days and treated 2884 attacks in the first 180 days (average of 1.2 attacks per month). Of this group, 57 subjects treated ≥ 2 attacks per month on average and 229 subjects treated ≥ 1 attack per month. Similarly, 124 subjects, using sumatriptan 20 mg, remained in the study for at least 360 days and treated 1947 attacks in the first 360 days (average of 1.3 attacks/month). Of this group, 15 subjects treated ≥ 2 attacks per month and 78 subjects treated ≥ 1 attack per month.

Although the monthly average number of attacks treated in the safety population did not exceed two, as we generally request, the extent of the exposure is significant. Despite the low monthly average the sponsor did exceed the ICH recommended minimum exposure of 300 to 600 subjects for 6 months and at least 100 subjects for 1 year. In a previous agreement with the sponsor we agreed the monthly treated attack average in the long term exposure did not need to exceed 2 attacks per month.

5.4.5.1 Adverse Events

The following table briefly summarizes the overall incidence of adverse events experienced during trial SUM40276 on a per patient and per attack basis. Since so few subjects used sumatriptan nasal spray 5 mg a comparison of incidences between high and low dose cohorts is not meaningful, therefore in most circumstances I will limit my discussion to the safety findings from the higher dose group.

In the 20 mg cohort the percentage of attacks in which at least a single adverse event was reported was 29%. Overall 97% of the adverse events in this group were rated as mild to moderate. Although the incidence of attacks with any AE was higher in the 5 mg group (40%) it must be remembered this group is a subset of the entire population and represents subjects who earlier could not tolerate 20 mg therefore a higher incidence rate does not surprise me. Additionally the cohort size is much smaller and is therefore more prone to random skewing. The proportion of attacks with any AE reported in the first 6 months of the study compared to the second 6 months does not demonstrate any significant difference in incidence rates (29% vs. 31%). The overall incidence of adverse events and serious adverse events are similar between attacks treated with a single, double or triple dose of sumatriptan nasal spray 20 mg. Attacks treated with three doses of sumatriptan nasal spray resulted in a higher incidence of subjects reporting severe adverse events (11% vs. 3%) however the numbers are very small and it doesn't surprise me since these subjects in general were probably experiencing a very severe migraine attack.

Table 39 Overall incidence of AE, safety population

Incidence of AE on per patient basis	All 5 mg N=10	20 mg N=477	20 mg X 2 N=242	20 mg X 3 N=29	All 20 mg N=484
Subjects reporting any AE	6 (60%)	348 (73%)	108 (45%)	9 (31%)	374 (77%)
Subjects with AE graded as severe	1 (10%)	76 (16%)	21 (9%)	4 (14%)	89 (18%)
Subjects with serious AE	0	9 (2%)	2 (<1%)	0	10 (2%)
Incidence of AEs on a per attack basis	**All 5 mg N= 42**	**20 mg N=3940**	**20 mg X 2 N=699**	**20 mg X 3 N=37**	**All 20 mg N=4676**
Attack with any AE	17 (40%)	1155 (29%)	199 (28%)	9 (24%)	1363 (29%)
Attack with an AE graded as severe	1 (2%)	109 (3%)	24 (3%)	4 (11%)	137 (3%)
Attack with an AE graded as serious	0	9 (<1%)	2 (<1%)	0	11 (<1%)
Attacks with any AE 1st 6 months	17 (44%)	873 (29%)	159 (29%)	6 (19%)	1038 (29%)
Attacks with any AE 2nd 6 months	0	294 (32%)	43 (27%)	4 (67%)	341 (31%)

Source: sponsor tables 43.1, 44.1, 52.1, 54.1

The following table summarizes the common adverse events (≥2%) reported in trial SUM40276 based on the attack level. As demonstrated the most common adverse event was taste disturbance (17%) and headache (2%). Other than taste disturbance, few attacks treated with sumatriptan nasal spray 20 mg, 1 or 2 doses, resulted in a report of an adverse event. Similar findings were seen for the few subjects using 5 mg (1, 2, or 3 doses) and for subjects using 3 doses sumatriptan nasal spray 20 mg (described in detail elsewhere). I reviewed the sponsor's translation of verbatim terms (variable AEVTX) to preferred term (variable pref) and did not see any systematic errors or omissions. The preferred term "nasal signs and symptoms" includes verbatim terms from rhinorrhea to dry nose but in most cases referred to nasal congestion. A few verbatim terms translated to "nasal signs and symptoms" included local edema and inflammation which I will discuss in section 5.4.5.1 (Nasal Examination).

Table 40 Common AEs (≥2%), Attack Level

Adverse Event	20 mg N=3940	20 mg X 2 N=699
Taste Disturbance	664 (17%)	113 (16%)
Headaches	67 (2%)	10 (1%)
ENT Infection	86 (2%)	15 (2%)
Nasal Signs and Symptoms	74 (2%)	9 (1%)

Source: Adapted from sponsor table 55.1

The following table summarizes the common adverse events (≥2%) derived from my review of the safety database. The incidence rates I present here are crude since they are derived from all attacks treated and do not adjust for what dose of sumatriptan was used. As demonstrated my results are very similar to the results obtained by the sponsor.

Table 41 Agency AE Incidence, all treatments

Adverse Event	All doses N=4718
Taste Disturbance	884 (18.7%)
ENT Infection	115 (2.4%)
Nasal Signs and Symptoms	111 (2.6%)
Headaches	100 (2.1%)

The following table summarizes the common adverse events (≥5%) reported in trial SUM40276 based on the subject level. As demonstrated in the table approximately 25% of all subjects reported taste disturbance at some point in the study after using sumatriptan nasal spray 20 mg. This of course does not mean they experienced this adverse events after each treatment and as discussed elsewhere few subjects withdrew due to taste disturbance.

Table 42 Common Adverse Events (≥5%), Subject Level

Body System Preferred Term	20 mg N=477	20 mg + 20 mg N=242	20 mg + 20 mg + 20 mg N=29	All 20 mg N=484
	n (%)	n (%)	n (%)	n (%)
Ear, Nose, and Throat	180 (38%)	34 (14%)	3 (10%)	201 (42%)
Ear, Nose , and Throat Infections	71 (15%)	13 (5%)	1 (3%)	85 (18%)
Nasal Signs and Symptoms	44 (9%)	8 (3%)	1 (3%)	50 (10%)
Viral Ear, Nose, and Throat Infections	35 (7%)	2 (<1%)	0 (0%)	37 (8%)
Neurology	171 (36%)	63 (26%)	5 (17%)	189 (39%)
Disturbances of Sense of Taste	120 (25%)	45 (19%)	3 (10%)	125 (26%)
Headaches	46 (10%)	10 (4%)	0 (0%)	53 (11%)
Migraines	10 (2%)	5 (2%)	2 (7%)	15 (3%)
Lower Respiratory	74 (16%)	8 (3%)	0 (0%)	78 (16%)
Viral Respiratory Infections	35 (7%)	3 (1%)	0 (0%)	37 (8%)
Gastrointestinal	70 (15%)	21 (9%)	2 (7%)	86 (18%)
Nausea	27 (6%)	9 (4%)	2 (7%)	36 (7%)
Pain/Pressure Sensations	29 (6%)	5 (2%)	0 (0%)	32 (7%)
Other Pain	22 (5%)	3 (1%)	0 (0%)	24 (5%)

Source: Sponsor table on page 47 of report not enumerated.

Overall 180 (3.8%) adverse events were graded as severe in intensity by subjects (all attacks, all doses). As expected the most frequent adverse event reported as severe was taste disturbance (12%) followed by migraine (9%), ENT infection (6%), headache (4%), menstruation symptoms (4%), nausea (4%), and throat/tonsil pain/discomfort (4%). There is no difference between

attacks treated with a single sumatriptan nasal spray 20 mg or 2 sumatriptan nasal spray 20 mg. in the proportion of adverse events rated as severe

The sponsor analyzed adverse events by the subgroups sex, race, weight (50 kg, ≥50 kg) and age group (12-14 years, 15-17 years) using data from the subject level. Other subgroups were also examined (ex. typical migraine duration, migraine frequency and prior use of triptans), however since I do not see the clinical relevance of these subgroups I will not present them here. The sponsor reports the following:

- *Adverse rates were somewhat higher for females receiving 1 dose of sumatriptan nasal spray 20 mg compared to males (77% vs. 66%).*
- *Adverse events were also somewhat higher in the single, 20 mg group for subjects in the race category White (74%) compared to Black (61%).*
- *Subjects in both age categories who treated attacks with one dose of 20 mg reported adverse events at a higher rate (71% and 75% respectively) than did subjects in these same age groups who treated attacks with two doses of 20 mg (43% and 46% respectively).*
- *The analysis of the subgroup factor weight showed similar results to age.*

The sponsor does not provide a discussion of adverse events by the various subgroups using data from the attack level. Since nearly 85% of all participants are Caucasian and only 9% are African American a meaningful comparison between subgroups can not be made in my opinion. My comparison of adverse events reported by gender at the attack level did not demonstrate any significant difference between males and females. Likewise my review of adverse events reported by age group at the attack level did not demonstrate any clinically significant differences between adverse events reported in adolescents <15 years and adolescents ≥15 years of age.

A review of adverse events with very low incidence rates did not reveal any particular concerns or patterns. As with most drugs a few subjects reported dizziness, tiredness and grogginess. Three subjects (PID 14605, 15221, and 14599) reported complete loss of consciousness however none of the events were considered related to study medication. Two subjects reported seizures after taking sumatriptan (PID 14988 and 14852). Subject 14988 discontinued due to the event and subject 14852 continued in the study without recurrence. Both events were considered unrelated to study medication by the investigators.

5.4.5.1 Deaths, SAE and Withdrawals due to an AE

There was a single death during this long term study. An 18 year old male (PID #14957) was involved in a fatal motor vehicle accident almost 10 weeks after his last dose of study medication (sumatriptan 20 mg). I reviewed the narrative and agree with the investigator's assessment that the event was unrelated to study medication.

A total of 14 serious adverse events were reported in 10 subjects during this study. The following table provides a brief overview of each event (excludes subject #14957 described above). I reviewed the case narratives for each patient and agree with the investigator's assessment of relationship to medication. The only SAE considered possibly related to study medication occurred in a 17 year old female (PID #15220). The patient woke up with a migraine and within

10 minutes administered sumatriptan nasal spray 20 mg. Soon after treatment she developed pain on the left side of her head and neck and could not turn her head to the left or up and down. Additionally she was experiencing tingling sensation in her fingertips and the left side of her face. An MRI and CT scan did not support a diagnosis of a stroke however the medication was discontinued. All complaints resolved in 2 days of onset. All SAEs were resolved at the time of the study report except for the appendicitis. As demonstrated in the table few of these SAEs resulted in patient withdrawal from the study.

Table 43 Serious Adverse Events*

Subject Number	Age/Sex/Weight[a]	Dose	Event	Possibly related to study drug?	Subject withdrawn due to event?
14489	13Y/M/42.3 kg	20 mg	Thyroglossal cyst	No	No
14599	13Y/M/55.9 kg	20 mg	Diabetic ketoacidosis GI virus Loss of consciousness	No No No	Yes Temp. interr. Yes
14656	17Y/M/82.7 kg	20 mg	Suicidal ideation	No	Yes
14914	13Y/M/40.6 kg	20 mg	Viral meningitis Mesenteric lymphadenitis	No No	No No
14965	13Y/M/71.6 kg	20 mg	Aseptic meningitis	No	No
15220	17Y/F/66.8 kg	20 mg	Complicated migraine	Yes	Yes
15221	15Y/F/60.0 kg	20 mg	Status migrainosus	No	Temp. interr.
15031	13Y/F/54.5 kg	20 mg	Dehydration Acute migraine	No No	No No
15345	17Y/F/61.4 kg	20 mg	Appendicitis	No	No

Source: Sponsor table on page 54, not enumerated
*Excludes MVA/death experienced by subject 14957

The following table summarizes the adverse events resulting in subject withdrawal from the study. As demonstrated in the table only 20 subjects (4%) withdrew due to an adverse event. Of the events leading to withdrawal 4 subjects (<1%) withdrew due to taste disturbance and 3 subjects (<1%) withdrew due to local numbness/burning sensation. The CRF and narratives for these subjects are not provided however I reviewed each case in the original AE dataset. Of particular interest was subject 15016. She was a 14 year old female who reported hives on 2 occasions after using sumatriptan. Both events were considered treatment related by the investigator. The patient was withdrawn only after the second event. There is no evidence the patient experienced fever of any other event that would make me consider the event was Steven Johnson's Syndrome or something similar.

Table 44 AE resulting in withdrawal

Subject Number	Age/Sex/Weight [a]	Dose	Reason for discontinuation	Possibly related to study drug?
14689	14Y/F/49.6 kg	20 mg	Bad taste	Yes
14828	12Y/M/83.6 kg	20 mg	Status migrainosus	No
14765	15Y/F/70.0 kg	20 mg	Burning sensation face Increased nausea Increased migraine pain	Yes Yes Yes
14599[b]	13Y/M/55.9 kg	20 mg	Diabetic ketoacidosis Loss of consciousness	No No
14605	15Y/F/46.8	20 mg	Systemic lupus erythematosus	No
14778	12Y/M/55.0 kg	20 mg	Bad taste	Yes
14656[b]	17Y/M/82.7 kg	20 mg	Suicidal ideation	No
14664	16Y/F/55.0 kg	20 mg	Bad taste	Yes
15323	14Y/F/45.9 kg	20 mg	Numbness of face Tightness around jaw Dizziness	Yes Yes Yes
14894	16Y/F/90.0 kg	5 mg	Nose bleed	Yes
14933	14Y/F/54.5 kg	20 mg	Vomiting	Yes
14934	15Y/F/41.8 kg	5 mg	Gagging	Yes
14957[b]	17Y/M/72.7 kg	20 mg	Fatal car accident	No
14988	14Y/M/64.5 kg	20 mg	Complex partial seizure	No
15220[b]	17Y/F/66.8 kg	20 mg	Complicated migraine	Yes
15016	14Y/F/59.0 kg	20 mg	Pruritus Hives	Yes Yes
15031	13Y/F/54.5 kg	20 mg	Depression Anorexia nervosa Bulimia	No No No
15270	16Y/F/48.6 kg	20 mg	Numbness	Yes
15274	15Y/F/60.0 kg	20 mg	Bad taste Tired	Yes Yes
15336	15Y/F/45.5 kg	20 mg	Raynaud's syndrome	No

Source: Sponsor table page 55, not enumerated.
a: age in years at time of event
b: event reported as a SAE

5.4.5.1 Overdosage

Thirty subjects took 3 doses of sumatriptan nasal spray 20 mg within a 24 hour period despite being instructed to not exceed more than 2 doses in any 24 hour period (maximum daily dose is 40 mg). One subject took 3 doses of sumatriptan nasal spray 5 mg however this doesn't constitute an overdosage. Although 60 mg total is not a significant overdosage it does provide us an opportunity to evaluate the safety of 3 doses of 20 mg in a 24 hour period. Nine out of the 30

subjects reported an adverse event however only a single subject reported an adverse event after taking the 3rd dose. This subject reported severe nausea and vomiting. The investigator did not believe the event was related to study medication. The other 8 subjects reported adverse events of similar nature and severity to those reported in the general safety population. Again the event did not lead to withdrawal in any subject.

5.4.5.1 Events of Special interest: Triptan Effect

The sponsor describes subjects reporting the following "characteristic sensations" separately: paresthesia, burning/stinging sensation, temperature sensation, and feeling strange. Overall 16 subjects (3%) reported one or more of these adverse events. Ten subjects reported parasthesias of which 6 were considered related to study medication and one led to subject withdrawal. The parasthesias reported occurred in various location such as left arm, lips, fingers, throat, nostrils, and head.

Two subjects reported 5 episodes of temperature changes after taking sumatriptan nasal spray. One subject reported a single episode of a sensation of coldness in the extremities and fingers and a second subjects reported 4 episodes of a sensation of "hot and cold feeling" (location not specified). All events were graded as mild. None of the events resulted in subject withdrawal.

Two subjects reported 2 episodes of "feeling strange" after taking sumatriptan nasal spray. One subject described it as a fogginess and the other described the feeling as "funny feeling" in the stomach. Both events were graded as mild and neither led to withdrawal.

Overall there was a very low incidence of "characteristic sensations" however most authorities would include adverse events such as pain/pressure sensation, tightness and chest symptoms as characteristics sensations with the use of triptans. For this population the proportion of subjects reporting pain/pressure sensation was 7% (32 subjects), chest symptoms was 1% (7 subjects) and tightness was 1% (5 subjects). The vast majority of these adverse events were rated as mild and none resulted in patient withdrawal.

5.4.5.1 Pregnancies

The following table summarizes the 3 pregnancies reported during trial SUM40276. Subject 14684's pregnancy was noted (b) (6) days after taking her last dose of study medication. She was terminated from the study after taking 5 doses of sumatriptan 20 mg. The patient electively terminated the pregnancy at (b) (6) gestations. Subject 14481's pregnancy was detected approximately (b) (6) months after taking her last dose of sumatriptan 20 mg. The sponsor reports the patient delivered a normal healthy baby. Subject 14634's pregnancy was detected approximately (b) (6) weeks after her last dose of study medication. The patient had taken a total of 4 doses of sumatriptan nasal spray 20 mg. The subject delivered a healthy baby without complications.

Table 45 Pregnancies during trial SUM40276

Subject Number	Subject Age	Dates of Study Drug Exposure	Study Drug Dose	Outcome
14684	17 years	9 Aug 00 00 Sep 00 5 Sep 00 25 Sep 00 28 Sep 00	20 mg 20 mg 20 mg 20 mg	Pregnancy Electively Terminated
14481	16 years	28 Sep 00 29 Sep 00 (2nd dose)	20 mg 20 mg	Normal Birth/baby
14634	16 years	9 Aug 00 15 Sep 00 5 Nov 00 6 Nov 00 (2nd dose)	20 mg 20 mg 20 mg 20 mg	Normal Birth/baby

Source: Sponsor table on page 62, not enumerated

Overall the amount of exposure to sumatriptan nasal spray during pregnancy is very limited in this study. No new safety conclusions can be established from this limited experience.

5.4.5.1 Clinical Laboratories

All laboratory assessments were captured at baseline and exit visits. Presumably all exit visits were days to weeks after the last dose of study medication (not specified in protocol) hence the utility of these safety assessments to evaluate acute changes in laboratory parameters is very limited. Early inpatient safety studies of sumatriptan did not reveal any clinically significant changes in clinical chemistries or CBC. The label for sumatriptan nasal spray states no specific laboratory tests are required to follow subjects using the product.

The following table summarizes the sponsor's threshold for clinically significant changes in laboratory values.

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Table 46 Threshold for clinically significant laboratories

Test	LLN threshold criteria	ULN threshold criteria
Alk. Phosphatase	None	> 1.25 x ULN
Basophils	None	> 5.0 x ULN
Bilirubin (Total)	None	> 1.50 x ULN
Calcium	< 0.85 x LLN	> 1.08 x ULN
Chloride	< 0.90 x LLN	> 1.10 x ULN
Creatinine	None	> 1.30 x ULN
Eosinophils	None	> 1.70 x ULN
GGT	None	> 2.00 x ULN
Hemoglobin	< 0.83 x female LLN < 0.85 x male LLN	> 1.20 x ULN
Hematocrit	< 0.91 x female LLN < 0.93 x male LLN	> 1.20 x ULN
Lymphocytes	< 0.80 x LLN	> 2.00 x ULN
Monocytes	< 0.25 x LLN	> 2.00 x ULN
Bands	None	> 1.00 x ULN
Neutrophil, Segs	< 0.80 x LLN	> 1.60 x ULN
Phosphorus	< 0.50 x LLN	> 1.30 x ULN
Platelet	< 0.80 x LLN	> 1.50 x ULN
Potassium	< 0.90 x LLN	> 1.10 x ULN
RBC	< 0.80 x female LLN, < 0.75 x male LLN	> 1.30 x ULN
SGOT (AST)	none	> 2.00 x ULN
SGPT (ALT)	None	> 2.00 x ULN
Sodium	< 0.93 x LLN	> 1.07 x ULN
Urea Nitrogen	None	> 1.25 x ULN
WBC	< 0.70 x LLN	> 1.60 x ULN

The following table summarizes the mean laboratory values done at baseline and at the exit visits. As demonstrated in the table there were no significant changes between mean baseline and exit values for each of the laboratories tested although the exit visit mean alkaline phosphatase level was considerably lower then the baseline value. The reason for this change is not obvious to this reviewer however I do not believe it is clinically relevant.

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Table 47 Mean (SD) Laboratory Findings

	Baseline	Exit
CBC		
Basophils (%)	0.63 (0.36)	0.70 (0.38)
Eosinophils (%)	2.42 (1.77)	2.19 (1.63)
Hematocrit (%)	40.19 (3.12)	40.79 (3.12)
Hemoglobin (g/dl)	13.83 (1.10)	13.82 (1.11)
Lymphocytes (%)	35.15 (8.26)	34.43 (8.49)
Monocytes (%)	5.85 (1.64)	5.83 (1.60)
Neutrophils (%)	55.83 (8.99)	56.84 (9.36)
Platelet Counts ($x10^3$/ul)	280.10 (63.03)	276.67 (60.29)
RBC Count ($x10^6$/ul)	4.78 (0.39)	4.78 (0.38)
WBC Count ($x10^3$/ul)	7.19 (1.98)	6.71 (2.02)
Chemistry Panel		
Alkaline Phos. (U/L)	172.85 (99.68)	156.79 (97.83)
SGOT (U/L)	18.31 (15.58)	17.26 (11.77)
Calcium (mg/dl)	9.76 (0.34)	9.77 (0.34)
SGPT (U/L)	22.89 (8.13)	22.11 (8.57)
Chloride (mEq/L)	104.28 (2.43)	105.16 (2.23)
Creatinine (mg/dl)	0.65 (0.13)	0.68 (0.13)
Glucose (mg/dl)	88.12 (20.28)	90.61 (28.35)
Phosphorus (mg/dl)	4.60 (0.70)	4.49 (0.71)
Potassium (mEq/L)	4.27 (0.37)	4.22 (0.34)
Sodium (mEq/L)	141.04 (2.17)	141.87 (2.16)
Bilirubin Total (mg/dl)	0.43 (0.23)	0.46 (0.25)
Urea Nitrogen (mg/dl)	11.90 (3.17)	12.11 (3.17)

Source: Sponsor tables 63.1, 67.1

A review of individual patient shift in each of these laboratory parameters did not reveal any particular pattern for concern. No changes met the criteria for a serious adverse event. Overall changes in laboratory values resulted in 11 adverse events including 2 increases in WBCs, 2 increases in SGOT, 2 increases in total bilirubin, 1 increase each in glucose and SGPT, and 1 decrease each in glucose, hematocrit and hemoglobin. Of these events only 2 events (both bilirubin cases) were considered to be drug related by the investigator. Subject 15053 was a 13 year old female who was found to have an elevated total bilirubin (1.6 mg/dl, baseline 1.0 mg/dl) on her exit visit. She had taken a total of 10 doses of sumatriptan over a 6 month period. Follow up testing revealed normalized bilirubin values after leaving the study. Subject 15081 was a 16 year old female who was found to have an elevated total bilirubin (1.3 mg/dl, baseline 1.0 mg/dl) on her exit visit. She had taken a total of 6 doses of sumatriptan over a 6 month period. Follow up testing demonstrated a continued elevation in total bilirubin 2 weeks after leaving the study. Both events were rated as mild.

ECGs were done at baseline and exit visits. Presumably all exit visits were days to weeks after the last dose of study medication (not specified in protocol) hence the utility of this safety assessment to evaluate acute changes in ECG parameters is very limited. Early inpatient safety studies of sumatriptan did not reveal any clinically significant changes ECGs. As previously discussed the study coordinator at site 85638 admitted to falsifying ECG data in this study therefore I will not include the ECG data from this site in my review.

The following table briefly summarizes the abnormal post treatment ECGs. Overall only 4 subjects were found to have an abnormal ECGs post dosing. Subject #15149 was found to have an accessory pathway (Wolff Parkinson White Syndrome). Subject #15022 was found to have a left atrial abnormality/incomplete bundle branch block and possible borderline mitral valve prolapse. Patient #14634 was noted to have an incomplete bundle branch block. Patient 14560 was noted to have sinus bradycardia.

Table 48 Abnormal ECGs, Post Dosing

Subject Number	Post-Dose Interval Values (sec)	Visit	AE?	Significant Change from Baseline Abnormality
15149	PR=0.100 QT=0.390 QRS=0.090 QTc=0.430	Exit	No	Accessory pathway
15022	PR=0.150 QT=0.364 QRS=0.076 QTc=0.397	Exit Exit	Yes No	Left atrial abnormality Incomplete bundle branch block
14634	PR=0.124 QT=0.366 QRS=0.092 QTc=0.416	Exit	No	Incomplete bundle branch block
Subject Number	**Other Abnormalities**	**Visit**	**AE?**	**Significant Change from Baseline Abnormality**
14560	HR=49	Exit	No	Sinus bradycardia

Source: Sponsor table on page 67, not enumerated.

Overall there were few subjects with any abnormalities on their post treatment ECG.

5.4.5.1 Vital Signs

Vital signs were done at each visit. Since the protocol did not specify how soon after an attack a subject was to return to the clinic it can be assumed that most readings were collected days to weeks after use of sumatriptan nasal spray. Hence the vital sign data collected in this study is of limited clinical relevance in assessing the acute effects of sumatriptan on blood pressure and pulse. The label for sumatriptan nasal spray warns that significant elevations of blood pressure including hypertensive crises have been rarely reported with the use of sumatriptan. Sumatriptan is contraindicated in subjects with uncontrolled hypertension.

The following table summarizes the sponsor's threshold for clinically significant changes in vital signs.

Table 49 Criteria for clinically significant changes in vitals

Vital Sign	Age (yrs)	Criteria for Clinically Significant Change
Systolic BP	12	≤90mmHg and at least 20mmHg decrease from baseline
		≥133mmHg and at least 20mmHg increase from baseline
	13-15	≤90mmHg and at least 20mmHg decrease from baseline
		≥143mmHg and at least 20mmHg increase from baseline
	16-17	≤90mmHg and at least 20mmHg decrease from baseline
		≥149mmHg and at least 20mmHg increase from baseline
Diastolic BP	12	≤50mmHg and at least 15mmHg decrease from baseline
		≥89mmHg and at least 15mmHg increase from baseline
	13-15	≤50mmHg and at least 15mmHg decrease from baseline
		≥91mmHg and at least 15mmHg increase from baseline
	16-17	≤50mmHg and at least 15mmHg decrease from baseline
		≥97mmHg and at least 15mmHg increase from baseline
Heart Rate	12-17	≤50 bpm and at least 15 bpm decrease from baseline
		≥120 bpm and at least 15 bpm increase from baseline

A clinically significant increase in blood pressure was experienced by three subjects (see following table). Subject 14989, using sumatriptan nasal spray 20 mg, was noted to have blood pressure of 120-122/74-78 on all visits between baseline and 9 months however at the end of study visit the patient had a reading of 150/90. The increase was not considered related to study medication in my opinion since there were 15 days between the event and the last dose of study medication. Patient 14736, using sumatriptan nasal spray 20 mg, was noted to have an increased heart rate of 122 bpm at her 6 month visit. Baseline and exit values were normal. The event was not considered drug related and required no treatment. Subject 15010, using sumatriptan nasal spray 20 mg, was noted to have a low pulse rate of 46 at her exit visit. Since the event occurred more than 1 month after taking her last dose of study medication the sponsor did not feel the event was related to study medication.

Table 50 Subjects with Clinically Significant Vital Signs Changes

Subject Number	Age/Sex Weight (kg)[b]	Dose/ # doses taken	Dose date / time of dose prior to significant value	Significant Values Visit(date)= bp(mmHg), hr(bpm)	BL values =bp(mmHg), hr(bpm) Exit values =bp(mmHg), hr(bpm)	Adverse Event?
14736[c]	12/F 51.4 kg	20 mg/18	29Jan01/ ~4 days	6 mo. (02Feb00= 100/80, 122$^{\Delta}$	BL (31Jul00)= 100/80, 80 Exit (25Jul01)= 100/80, 76	Yes
14989[c]	15/M 125.4 kg	20 mg/18	18Jul01/ ~15 days	Exit (02Aug01)= 150$^{\Delta}$/90, 76	BL (02Aug00)= 122/78, 66	Yes
15010	14/F 63.0 kg	20 mg/9	2Aug01/ ~48 days	Exit (19Sep01)= 94/51, 46$^{\Delta}$	BL (14Sep00)= 107/62, 61	No

Source: Sponsor table on page 65, not enumerated
b Age in years, weigh in kg; c narrative provided by sponsor; Δ clinically significant values

Population mean changes in vital signs between each visit were minimal and not clinically significant. Clinically 4 subjects reported tachycardia after taking sumatriptan. A review of their baseline and follow up heart rates is unremarkable. All cases of tachycardia were rated a mild to moderate by the subject. Three of the 4 cases of tachycardia were considered related to study medication by the investigator however no subject was withdrawn.

Overall there was no consistent evidence that intermittent dosing of sumatriptan nasal spray in adolescents results in clinically significant changes in vital signs.

5.4.5.1 Physical Examination/Nasal Examination

A physical examination was performed on all subjects at the baseline and exit visits. Amendment 2 required a detailed nasal examination be done at the mid-treatment point as well as the exit visit in all subjects. Nasal examinations included an evaluation for crusting, bleeding, turbinate swelling, and mucosal color. Overall there were few subjects with any significant changes in their physical and nasal examinations. A comparison of nasal findings between subjects using few doses of sumatriptan (defined as 4 or fewer doses) to those using sumatriptan frequently (defined as 16 or more doses) did not reveal any difference between cohorts.

5.4.5.1 Safety Conclusions

Intermittent dosing of sumatriptan nasal spray 20 mg was well tolerated in adolescent migraineurs during this 12 month study. The most common adverse event following dosing with 1 dose of sumatriptan nasal spray 20 mg was taste disturbance (26%) followed by ENT infections (18%) and headaches (11%) on the patient level and taste disturbance (16%) ENT infections (2%) and headache (1%) on the attack level. Similar findings were seen after 2 doses of sumatriptan nasal spray 20 mg. The majority (97%) of adverse events reported were rated as mild to moderate. Few required treatment.

Overall, 10 subjects experienced 14 serious adverse events, including 13 that were assessed as not reasonably attributable to study drug. Only 1 adverse event, complicated migraine, was

deemed reasonably attributable to study drug. Other SAEs included diabetic ketoacidosis, GI virus, and loss of consciousness (3 events, 1 subject); viral meningitis and mesenteric lymphadenitis (2 events, 1 subject); dehydration and acute migraine (2 events, 1 subject); thyroglossal cyst (1 subject); aseptic meningitis (1 subject); status migrainosus (1 subject); fatal car accident (1 subject); appendicitis (1 subject); and suicidal ideation (1 subject).

Thirty subjects violated the protocol by taking 3 doses of sumatriptan nasal spray 20 mg within any 24 hour period. In this small subset of patients sumatriptan was well tolerated with only a single subject reporting an adverse event (nausea) after their 3rd dose.

A review of less common adverse events did not reveal any particular signals for concern. Few subjects reported adverse events considered class effects for triptans such as parasthesias, and tightness. There were no clinically relevant changes in mean vital signs, mean clinical chemistries or mean hematology values although most tests were conducted days to weeks after the last dose of study medication. Few subjects (4) had abnormal post treatment ECGs. Finally there was no clinically significant changes in nasal examination from mid-treatment visit (generally month 6) to the exit visit (month 12).

In summary, sumatriptan nasal spray 20 mg was well tolerated in this study.

5.5 Statement of Overall Conclusions

5.5.1 Integrated Efficacy Conclusion

In the original submission the sponsor submitted the results of a single acute adolescent migraine study, trial SUMA3005. Other studies included in the original submission, but not relevant to this discussion of efficacy, included study SUMA3006 (1 year safety study), study SUMB 3005 (open label efficacy study of sumatriptan tablet 100 mg in adolescents), study SUM40254 (open label PK study in children 6 to 11 years of age), and the interim results of study SUM40019 (controlled efficacy study in children 8 to 17 years of age). The final study report for study SUM40019 is contained in this submission and reviewed earlier in this review.

Study SUM3005 is randomized, placebo controlled, double blind, parallel group, single attack study that evaluated the safety and efficacy of three dose levels of sumatriptan nasal spray (5 mg, 10 mg, and 20 mg) in the acute treatment of migraine in approximately 500 adolescent migraineurs. The primary endpoint for the pivotal trial was the traditional 2 hour headache response. Unfortunately the sponsor's analysis of the 2 headache response for subject taking sumatriptan nasal spray 20 mg compared to subjects taking placebo did not reach the threshold for statistical significance (p=0.059) and the decision was made within the division to consider this a failed study. The analysis done by Dr Oliva demonstrated a p-value of 0.169 for the comparison of sumatriptan nasal spray 20 mg compared to placebo. Additionally sumatriptan nasal spray did not demonstrate benefit for the proportion of subjects reporting nausea at 2 hours. There were no unusual safety concerns noted in study SUM3005 or any other study reviewed by Dr. Oliva. Please see Dr. Oliva's review for additional details.

As a result of the experienced gained from trial SUM3005 the sponsor developed a new adolescent efficacy study (SUM30045) using an earlier timepoint to assess efficacy. The results of this second trial are contained in this new submission and reviewed earlier in this review. Although the sponsor argues trial SUM30045 demonstrates efficacy, using the analysis presented by the sponsor it appears to me trial SUM30045 failed to demonstrate efficacy for the prestated primary endpoints using the prestated analysis method. Specifically trial SUM30045 failed to demonstrate a significant difference between sumatriptan nasal spray 20 mg and placebo for the two co-primary endpoints of headache relief at 1 hour and sustained headache relief between 1 and 24 hours in the ITT population (p= 0.087 and 0.061 respectively). For subjects taking sumatriptan nasal spray 20 mg there was a strong trend favoring active treatment for both endpoints however the comparison to placebo did not reach the 0.05 threshold for statistical significance expected by this Agency. Likewise there was no statistically significant difference between actively treated subjects and subject taking placebo for the proportion of subjects reporting nausea, photophobia or phonophobia at 1 hour.

In addition to trial SUM30045 the sponsor also submits the results of two non-IND studies (trials SUM3009 and SUM40019) to support their assertion of efficacy. Trial SUM3009 was a randomized, placebo controlled, single center, double blind, two-period, crossover, single attack (each crossover) study to evaluate the safety and efficacy of sumatriptan nasal spray 10 mg for the acute treatment of migraine in children 8 to 12 years of age suffering from refractory migraine with and without aura. Since this study did not include adolescent migraineurs I do not believe it is relevant to this supplement. Trial 40019 was a randomized, placebo controlled, double blind, multicenter, two-period (single attack each), crossover, outpatient, efficacy study of sumatriptan nasal spray (10 mg or 20 mg). The primary objective of the study was to evaluate the safety and efficacy of sumatriptan nasal spray (10 or 20 mg) compared to placebo in the treatment of migraine in children between 8 to 17 years of age. Although a subset analysis of adolescents demonstrated statistically significant results for the primary endpoint (2 hour headache response, p=0.001) the trial has several design and methodology problems which prohibits its use as a pivotal adolescent efficacy trial. First of all the design of the 24 hour migraine diary does not permit us to assess whether in fact a migraine was treated. Secondly the study fails to evaluate the efficacy of sumatriptan to treat the associated symptoms associated with migraine and finally it must be remembered all analysis presented by the sponsor are post hoc analysis.

In summary I do not believe the sponsor has provided sufficient evidence that sumatriptan nasal spray 5 and 20 mg is effective in the treatment of migraine syndrome in adolescents.

5.5.2 Integrated Safety Conclusions from New Studies

Overall the 4 new clinical trials provided by the sponsor in this submission did not demonstrate any new safety concerns relative to the use of sumatriptan in children between 8 to 17 years of age. The nature and character of adverse events experienced by these children are similar to those seen adult controlled studies.

6. Final Safety Update

In this section of my review I will focus on final safety update report provided by the sponsor. The safety update provided by the sponsor includes integrated safety information from all clinical studies conducted between 1 January 2000 through 30 June 2003. Additionally I will present the safety items requested in the Approvable letter. In the Approvable letter we requested the sponsor provide a final safety update that incorporates safety information from recently completed clinical and non-clinical studies (if any), post marketing reports of serious adverse events reported in adolescents, as well as a review of the worldwide literature. In the approvable letter we requested the sponsor organize their safety update in the following manner:

1. Describe any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows: (1) present new safety data using the same format as the original NDA, (2) present tabulations of the new safety data combined with the original NDA data, (3) include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in item 2, and (4) for indications other than adolescent migraine provide a separate table for the frequency of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop outs for the newly completed studies and describe any trends or patterns identified.
4. Provide case report forms and narratives summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. Provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA.
6. Provide a summary of worldwide experience on the safety of Imitrex. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Although the sponsor did not organize the update in the manner requested the report was complete enough to address the essential safety items requested. As requested in the Approvable letter the sponsor provides a final safety update report that incorporates safety information from recently completed clinical and non-clinical studies, post marketing reports of serious adverse events reported in adolescents, as well as a review of the worldwide literature. For the purpose of my review I chose to summarize the safety findings from the 4 new clinical studies individually. My safety review of these studies can be found earlier in this review. My review of all other clinical safety items requested in the Approvable letter is included in this section. A review of any new preclinical information is being conducted by the pharmacotoxicology reviewer.

Since the safety findings from each adolescent study has been reviewed and described earlier, either by myself or Dr. Oliva, I will limit my discussion here to the overall findings in order to get a clear picture of total exposure and safety experience with the use of sumatriptan in adolescents.

6.1 Integrated Safety Review of Sponsor Initiated Controlled and Uncontrolled Studies

6.1.1 Patients Demographics and Exposure

To date the sponsor's adolescent clinical development program for sumatriptan includes 3 completed clinical pharmacology studies (SUMB1006, SUMB40254 and SUMB2001), 2 completed single attack controlled efficacy studies (SUMA3005 and SUM30045) and 2 completed long term safety studies (SUM3006 and SUM40276). Additionally the sponsor reports they have an ongoing adolescent acute migraine efficacy study (trial SUM30042) being conducted in the Netherlands. All completed sponsor trials except trial SUM30045 and SUM40276 were previously submitted to the Agency and reviewed. In addition the sponsor provides the results of 2 investigator initiated studies which enrolled subjects between 7 to 17 years of age (SUM30009 and SUM40019). My review of the safety findings from each newly submitted study is described earlier in this review. Deaths, SAE and pregnancy for the ongoing study are included in this safety update up until the cutoff date of 30 June 2003.

In the 4 adolescent clinical trials initiated by the sponsor all subjects were 12 to 17 years of age and had a migraine history meeting the IHS definition of migraine with or without an aura. Headache frequency for the 4 studies were from 1 or 2 to 6 or 8 attacks per month. All subjects had no contraindications to triptans and were expected to be in good health. Migraine prophylactics (excluding ergots) were permitted but had to be stable. MAOIs were prohibited in all studies. Ergots and triptans were not permitted within 24 hours of study medication. SSRI were not permitted in study SUMA3005 and SUMA3006. Subjects in study SUMA3005 were permitted to use rescue medication at 2 hours and subjects in study SUMA30045 were permitted to use rescue medication starting at 1 hour.

In both long term trials subjects were instructed to treat an unlimited number of migraines of any intensity over a 12 month period. In trial SUMA3006 all patients were initiated on sumatriptan 10 mg and were titrated up or down as needed. In trial SUM40276 all patients were initiated on sumatriptan 20 mg and reduced to 5 mg as required. Collectively 1248 subjects participated in 2 controlled single attack studies and 921 subjects participated in 2 long term safety studies. However the sponsor reports 336 subjects participating in trial SUMA3005 (single attack efficacy study) also participated in trial SUM3006 (1 year safety study). The following table summarizes the number of participants in each study.

Table 51 Adolescent Clinical Development Plan Sumatriptan Nasal Spray

Trial #	Description	# of Subjects	
Controlled Acute Efficacy Trials			
SUMA3005	DB, PC, Parallel group, single attack study	Placebo	131
		SUMA 5 mg	128
		SUMA 10 mg	133
		SUMA 20 mg	118
SUMA30045	DB, PC, Parallel group, single attack study	Placebo	245
		SUMA 5 mg	255
		SUMA 20 mg	238
Uncontrolled Long Term (1 year) Trials			
SUMA3006	OL, long term safety study	SUMA 5 mg	7
		SUMA 10 mg	433
		SUMA 20 mg	197
SUMA40276	OL, long term safety study	SUMA 5 mg	10
		SUMA 20 mg	484
Investigator initiated studies			
SUM30009	DB, PC, Crossover, single center, single attack study in children 8 to 12 years old	SUM 10 mg	59
		Placebo	58
SUM40019	DB, PC, Crossover, multicenter, single attack study in children 7 to 17 years old	SUM 10 mg	29
		SUM 20 mg	61
		Placebo	87
Ongoing Acute Efficacy Trial			
SUM30042	MC, DB, PC, randomized, crossover, single attack (each crossover) study.	Placebo	Still blinded, to date 85 subjects have been enrolled.
		SUM 10 mg	
		SUM 20 mg	

Adapted from sponsor tables 4, and 5, final safety update report

Of the 1248 subjects participating in the single attack efficacy studies, 356 subject were administered sumatriptan nasal spray 20 mg, 133 administered 10 mg and 383 administered 5 mg. Overall 87% of all attacks were treated with a single dose of study medication (range per cohort 9 to 15%).

The sponsor calculates 6890 doses of sumatriptan 20 mg, 2208 doses of sumatriptan 10 mg and 80 doses of sumatriptan 5 mg were taken during the 2 long term studies. Overall 921 subjects treated 7990 attacks with the majority (75%) being treated with a single dose of study medication. For the purposes of assessing adequacy of long term exposure I chose to focus on the number of subjects taking the highest proposed dose over 6 months (180 days) and 12 months (360 days). The following table summarizes my analysis of the amount of long term exposure to sumatriptan nasal spray 20 mg seen during trials SUMA3006 and SUMA40276. As demonstrated there was sufficient long term exposure at the highest planned dose.

Table 52 Combined Long Term Exposure to Sumatriptan 20 mg

	Study 30006	Study 40276	Total
180 days			
Number of subject	170	391	561
Number of attack	906	2884	
Average attacks/month	0.9	1.2	
Subjects treating ≥2 attacks/month	15	57	
360 days			
Number of subject	115	124	239
Number of attack	1190	1947	
Average attacks/month	0.9	1.3	
Subjects treating ≥2 attacks/month	11	15	

Source: Agency table, derived from original dataset

The following table summarizes the baseline demographics of the entire adolescent safety database. The description of subject demographics is described in the reviews of each study individually however collectively in the controlled studies each cohort was well balanced for baseline demographics of age, race and gender. Unlike adult studies, these adolescent studies tended to have an even mix of male and female participant. However like most adult studies I have reviewed the majority of subjects were Caucasian. In the uncontrolled long term studies the mean age of participants was 14.1 years and the majority were Caucasian.

Table 53 Demographics, Controlled and Uncontrolled Studies

Controlled Studies					
	Placebo N=376	SUMA 5 mg N=383	SUMA 10 mg N=133	SUMA 20 mg N=356	Total N=1248
Mean Age	14.2	14.2	14.0	14.2	14.2
Age Group					
<15	56%	57%	64%	57%	57%
≥15	44%	43%	36%	43%	43%
Gender					
Female	55%	52%	55%	53%	53%
Male	45%	48%	45%	47%	47%
Race					
White	84%	83%	89%	84%	84%
Black	11%	11%	7%	11%	11%
Other	5%	6%	4%	5%	5%
Uncontrolled studies					
	SUMA 3006 N=437	SUMA40276 N=484	Total N=921		
Mean Age	14.1	14.2	14.1		
Age Group					
<15	61%	57%	59%		
≥15	39%	43%	41%		
Gender					
Female	53%	60%	57%		
Male	47%	40%	43%		
Race					
White	91%	85%	88%		
Black	4%	9%	7%		
Other	5%	6%	6%		

Source: Adapted from sponsor table 5 1 and 5.5, final safety update report

In the two controlled efficacy studies no subject withdrew due to an adverse event or lack of efficacy although this is not surprising since these were single attack studies. In the two long term studies 40 subjects withdrew due to an adverse event and 35 subjects withdrew due to lack of efficacy. A description of these withdrawals can be found in the review of each study however the most common reason cited was taste disturbance and local numbness/burning sensation.

6.1.2 Common Adverse Events, Integrated

The following table summarizes the common adverse events seen in the two controlled clinical trials. For consistency only adverse events that occurred within 24 hours of taking study medication are included. For the combined data the proportion of subjects reporting at least 1 adverse event (AE) was higher in sumatriptan cohorts than in placebo (31 to 40% vs. 17%). As expected the most common adverse event was taste disturbance seen in 19 to 30% of all subjects using sumatriptan. Other common adverse events included nausea, vomiting, local burning/stinging sensation and parasthesias. The vast majority of adverse events were rated as mild or moderate (92 to 97%), were transient and generally required no treatment. No subject withdrew from the acute studies due to an adverse event.

Table 54 Combined Common (≥2%) Adverse Events in Controlled Trials

	Placebo N=376	SUMA 5 mg N=383	SUMA 10 mg N=133	SUMA 20 mg N=356
Any AE	65 (17%)	119 (31%)	62 (47%)	142 (40%)
AE, Severe Intensity	14 (4%)	11 (3%)	5 (4%)	30 (8%)
SAEs	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Taste Disturbance	6 (2%)	72 (19%)	40 (30%)	91 (26%)
Nausea	27 (7%)	21 (5%)	9 (7%)	36 (10%)
Vomiting	12 (3%)	11 (3%)	15 (11%)	21 (6%)
Burning/stinging sensation	1 (<1%)	5 (1%)	0 (0%)	9 (3%)
Migraines	11 (3%)	2 (<1%)	2 (2%)	23 (<1%)
Paresthesia	4 (1%)	4 (1%)	2 (2%)	8 (2%)
Dizziness	2 (<1%)	5 (1%)	2 (2%)	2 (<1%)
Phonophobia	1 (<1%)	2 (<1%)	2 (2%)	2 (<1%)
Photophobia	3 (<1%)	3 (<1%)	3 (2%)	3 (<1%)
GI discomfort/pain	0 (0%)	3 (<1%)	3 (2%)	3 (<1%)
Temperature disturbance	2 (<1%)	1 (<1%)	2 (2%)	0 (0%)

Source: sponsor tables 10, and 11 final safety update study report

The following table summarizes the common adverse events (≥2%) reported by patients during the long term study. In the integrated safety report the sponsor does not provide a summary of adverse events during long term studies at the attack level however this information can be found in the review of each individual study. As demonstrated in the table 74% of all subjects at some time during the long term studies complained of taste disturbance although this rarely led to withdrawal. Other frequent adverse events included ENT infections, headaches, and local nasal signs and symptoms (generally rhinorrhea). The incidence levels for each of these adverse events (except for taste disturbance) was generally ≤3% at the attack level. The incidence of taste disturbance in both long term studies at the attack level was between 16% to 29% of all attacks treated. The majority of adverse events in both long term studies were rated as mild or moderate, were transient and required no treatment.

Table 55 Common AEs (≥2%) in Subjects Participating in Long Term Studies

	All 5mg N=17 n (%)	All 10mg N=433 n (%)	All 20mg N=681 n (%)
Any Adverse Event	9 (53)	286 (66)	501 (74)
Disturbances of sense of taste	3 (18)	190 (44)	199 (29)
Ear nose & throat infections	1 (6)	24 (6)	100 (15)
Headaches	0	13 (3)	61 (9)
Nasal signs & symptoms	2 (12)	19 (4)	56 (8)
Viral ear nose & throat infections	2 (12)	7 (2)	44 (6)
Nausea	0	21 (5)	41 (6)
Viral respiratory infections	0	6 (1)	41 (6)
Vomiting	1 (6)	24 (6)	31 (5)
Throat & tonsil discomfort & pain	0	16 (4)	24 (4)
Dizziness	0	12 (3)	28 (4)
Other pain	0	6 (1)	27 (4)
Viral infections	0	5 (1)	23 (3)
Bronchitis	0	4 (<1)	22 (3)
Muscle injuries	0	6 (1)	21 (3)
Bacterial ear nose & throat infections	0	4 (<1)	21 (3)
Gastrointestinal discomfort & pain	0	7 (2)	19 (3)
Menstruation symptoms	0	0	18 (3)
Migraines	0	13 (3)	17 (2)
Paresthesia	0	6 (1)	17 (2)
Cough	0	5 (1)	17 (2)
Ear nose & throat hemorrhage	1 (6)	4 (<1)	17 (2)
Acne & folliculitis	1 (6)	2 (<1)	16 (2)
Sinusitis	0	7 (2)	15 (2)
Joint Disorders	0	2 (<1)	15 (2)
Fractures	0	3 (<1)	13 (2)
Temperature regulation disturbances	0	5 (1)	12 (2)
Burning/stinging sensation	0	14 (3)	11 (2)
Viral gastrointestinal infections	1 (6)	3 (<1)	11 (2)
Chest symptoms	0	6 (1)	11 (2)
Depressive disorders	0	1 (<1)	11 (2)
Muscle cramps & spasms	1 (6)	0	7 (1)
Drowsiness	1 (6)	3 (<1)	4 (<1)
Throat & tonsil signs & symptoms	1 (6)	1 (<1)	3 (<1)
Asthma	1 (6)	1 (<1)	3 (<1)

Source: Sponsor table 16, final safety update report.pdf

In both controlled efficacy studies and both long term safety studies the incidence of cardiovascular events and "triptan" effects (ex. tightness, pain/pressure sensation, local parasthesias etc.) were generally uncommon (<1%) at the attack level and rarely resulted in withdrawal. A discussion of these adverse events is included in my review of each study.

In the controlled studies 4% of all subjects receiving any dose of sumatriptan nasal spray and 1% of all subject receiving placebo reported an AE possibly related to nose/throat irritation. No single complaint exceeded 1% incidence at the attack level. The only event reported as severe was local burning/stinging sensation reported in <1% of subjects receiving sumatriptan. The 6

month and end of treatment nasal examinations performed in trial SUM40276 did not find any significant findings.

6.1.3 Deaths, Serious Adverse Events and Withdrawals

There was a single death in the entire adolescent clinical development program. An 18 year old male, participating in trial SUM40276, was fatally injured in a motor vehicle accident. The event was not related to study medication.

In addition to the single death during the clinical studies the sponsor reports there were 2 spontaneous reports of deaths in patients <18 years of age during the period of January 2000 to June 2003. The first case, derived from the literature, was of a 16 year old male (A0383145A) who intentionally overdosed with sumatriptan. Details regarding the dose and route are sketchy but it appears he took at least 350 mg of sumatriptan tablets and an unknown amount of Sudafed. Over the next 2 to 3 days he became progressively lethargic and was found by the paramedics apneic and in asystole. He was initially resuscitated and placed on a ventilator however he was determined to be brain dead and all life support was stopped. Details about this case suggest a possible causal relationship in my opinion however Sudafed and other unknown factors may be contributive. The second death described occurred in a 13 year old female (B0274941). Details are few however the patient's pharmacist reports the young female collapsed and became unconscious after a "lengthy period of medication". Apparently she was hospitalized and died after a 7 month stay. Details about this case are too sketchy to consider a causal relationship. I discuss a few additional deaths reported in conjunction with sumatriptan use found during an DDRE AERS database search in section 6.6 of this review.

No serious adverse events were reported in subjects taking active drug during the 2 controlled efficacy studies. In trial SUMA3006 8 subjects reported 9 SAEs and in trial SUMA40276 10 subjects reported 14 SAEs. A discussion of each SAE can be found in the review of each trial however in general all except 2 adverse events were considered not related to study medication. In trial SUMA3006 a 15 year old male developed a facial nerve palsy soon after using sumatriptan and in study SUM40276 a 17 year old female developed a complicated migraine requiring hospitalization soon after taking sumatriptan. A further description of each case can be found in the reviews of each study.

There were no withdrawal due to adverse events in the 2 controlled efficacy studies. During trial SUMA3006 and trial SUM40276 44 subjects withdrew due to an adverse event. A description of these events can be found in the review of each study however in general the most common adverse event leading to withdrawal was taste disturbance.

To date there have been no death or serious adverse events in the ongoing trial SUM30042.

6.1.4 Pregnancies

A total of 6 pregnancies were reported during the entire adolescent clinical development program (3 from SUM40276, 2 from SUMA3006 and 1 from SUM30045) for sumatriptan nasal spray. Two pregnancies were terminated electively, 2 resulted in normal healthy newborns, and 2 have

unknown outcomes. A further description of each pregnancy can be found in the review of each trial. To date no pregnancies have been reported in the ongoing trial SUM30042. Overall there is insufficient new evidence to support a change in labeling for the use of sumatriptan during pregnancy.

6.1.5 Laboratory Findings

Laboratory evaluations (CBC and comprehensive chemistry panel) were not conducted in trial SUM30045. In trial SUMA3005 laboratory evaluations were conducted at screening and at the end of study. In study SUMA3006 laboratory safety evaluations were conducted at baseline, month 6 and at the end of the study. In study SUM40276 laboratory safety evaluations were conducted at baseline and the end of the study. In all cases laboratory evaluations were done days to weeks after the last dose of study medication hence their usefulness in assessing acute changes is limited.

A detailed discussion about laboratory findings during these controlled efficacy studies can be found in the review of each study however in general there were no clinically significant changes. In the long term studies a few subjects had shifts (high or low) in various hematology and/or chemistry parameters however in general there was no consistent pattern. No abnormal laboratory findings were considered serious by the investigator.

6.1.6 Vital signs/ECGs

Vital signs were collected in all studies at all visits. The protocol defined method for all studies was to take all vitals in the sitting position after the subject has rested for 5 minutes. In trials SUMA3005, SUMA3006 and SUM40276, 12 lead ECGs were collected for each subjects at baseline and exit visits. In most cases exit visits occurred days to weeks after the last dose of study medication hence the ability to assess acute changes is limited. A detailed discussion about vital signs and ECG findings from each study can be found in the reviews of each study.

No subject in the controlled efficacy studies had significant changes in their systolic blood pressure, diastolic blood pressure or pulse. One subject in trial SUMA3006 and 2 subjects in trial SUM40276 experienced a significant change in their vital signs and were reported as an adverse event. The subject in SUMA3006 reported elevated blood pressure and the 2 subjects in trial SUM40276 reported increased heart rate and elevated systolic blood pressure. None of the events were considered drug related by the investigator and did not lead to discontinuation.

In the controlled efficacy studies only a single post treatment ECG met the criteria for investigator-defined significant change from baseline. A review by the central cardiologist felt the change was not clinically significant. No finding on the ECGs were reported as adverse events in the acute studies. In trial SUMA3006 no subject experienced a clinically significant change in their ECG. In trial SUM40276 four subjects had a post treatment ECG changes rated as clinically significant. None of the events were considered drug related and only a single event (left atrial abnormality) was reported as an adverse event. The sponsor reports there were no dose dependent changes in ECG intervals (notably PR or QTc) however since most tracing were done days after dosing with study medication I would not expect to see changes.

6.1.7 Nasal Examinations

Six month and end of study nasal examinations were done in trial SUM40276. A detailed discussion of the findings can be found earlier in this review however in general there were no consistent significant changes noted.

6.1.8 Summary

In summary in both single-attack controlled efficacy studies and both long term safety studies sumatriptan nasal spray in doses up to 20 mg was well tolerated in adolescents. Additionally repeat dosing at 1 or 2 hours was also well tolerated. The most common adverse event in all studies was unpleasant taste. When this event is excluded in the controlled study all other adverse events had incidence rates similar to placebo. Safety laboratories, vital signs and ECGs demonstrated no significant changes although these studies were often done days to weeks after the last dose of study medication. Serial nasal examinations in trial SUM40276 failed to demonstrate any significant changes with repeated use of sumatriptan.

6.2 Integrated Safety Findings from Investigator Initiated Studies.

A safety review of the 2 investigator-initiated studies (SUM30009 and SUM40019) are described earlier in this review. In this section I will briefly summarize the essential safety findings.

Trial SUM30009 was a single center, placebo controlled, double blind, randomized, crossover singe attack efficacy study done in children 7 to 12 years of age. Migraines were treated with either sumatriptan nasal spray 10 mg or placebo in a crossover fashion in 60 subjects. Rescue medication was permitted at 2 hours if required. The average age of the participants was 9.7 years and there were 28 males and 32 females. Overall sumatriptan was well tolerated with 27% of all subjects reporting at least 1 AE compared to 12% of subjects on placebo. The most common adverse events on sumatriptan included taste disturbance (20%), throat/tonsil pain (8%) and nose signs and symptoms (3%). There were no deaths, serious adverse events or pregnancies during this trial.

Trial SUM40019 was a multicenter (all Finish), double blind, placebo controlled, crossover over, single attack study in children between 8 to 17 years of age. Subject less than 40 kg received sumatriptan nasal spray 10 mg and children weighing more received 20 mg. A second dose of study medication was permitted at 2 hours if required. Ninety subjects took sumatriptan in the study. Overall sumatriptan was well tolerated with 39% of all subjects reporting at least 1 adverse event compared to 8% of subject taking placebo. The most common adverse event while on sumatriptan was taste disturbance (33%), dizziness (2%), vomiting (3%) and nausea (3%). All adverse events were considered mild or moderate. There were no deaths, serious adverse events or pregnancies during this trial.

In summary, sumatriptan nasal spray 10 and 20 mg was well tolerated in these investigator initiated studies. However as I discussed earlier these studies did not include baseline and post treatment safety laboratories such as a CBC, chemistry profile and ECG.

6.3 Post Marketing Experience Update.

The sponsor estimates worldwide exposure to sumatriptan (all formulation, all ages) is 576 million migraine attacks treated with approximately 10% of these exposures occurring with the nasal spray formulation. The sponsor does not describe the amount of estimated exposure in adolescents however they state 19 cases of serious adverse events and 69 cases of non-serious adverse events have been reported in children less than 18 years between the period of January 1, 2000 to June 30, 2003. The following table summarizes the serious adverse events reported.

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Table 56 Summary of SAE, Adolescents January 1, 2000 through June 30, 2003

PID	Age Gender	Event	Comments
Tablet Formulation			
A0411839A USA	13 y/o female	Diplopia, Dizziness	Events occurred several days after starting sumatriptan. No other details available.
B0274941A UK	13 y/o female	Circulatory collapse, eye rolling, somnolence, loss of consciousness, death NOS	Events occurred after a lengthy period of sumatriptan use. The patient died after 7 month of hospitalization.
B0301148A Italy	14 y/o female	Hemiplegia, coordination abnormal NOS, Hypoaesthesia	Occurred soon after using 50 mg of sumatriptan. The event resolved with discontinuation.
A0174633A USA	14 y/o male	Anaphylactic reaction and shock, feeling cold, cold sweat, dyspnea, wheezing, throat tightness, increased sweating, oxygen saturation decreased, headache, upper abdominal pain	Event occurred soon after using 100 mg. Previous treatment with lower doses were tolerated. Event treated with epinephrine, diphenhydramine and steroids.
B0086570A UK	15 y/o female	Oropharyngeal swelling, Musculoskeletal stiffness	Event resolved with sumatriptan discontinuation.
A0383145A USA	16 y/o male	Completed suicide, non-accidental overdose, lethargy, vomiting, apnea, cardiac arrest, pupil fixed, brain death, brain edema, respiratory disorder NOS, idiosyncratic drug reaction	Case reported in literature. Intentional overdose with approximately 350 mg of sumatriptan and Sudafed. Death occurred after life support withdrawn.
Nasal Formulation			
B0117768A NL	4 y/o male	Mucous membrane disorder NOS, accidental exposure.	One hour after the child was seen chewing on the nasal spray device mucous drainage was seen coming from the mouth.
A0137684A USA	10 y/o male	Blindness	History of unilateral migraine with pain behind the right eye. No further information is known.
B0275952A AUS	11 y/o female	Anaphylactic reaction, stridor, dyspnea, mental disorder NOS	Episodes of dyspnea when sumatriptan not given.
B0078140A FR	13 y/o female	Migraine NOS, vision blurred, vertigo, vomiting NOS	Events resolved 2 days after sumatriptan withdrawn.
A0139352A USA	14 y/o male	Ileus, rectal hemorrhage, blood in stool, abdominal pain NOS, Hepatitis A positive, drug ineffective.	Lack of efficacy with tablets. After 1 year of treatment with nasal formulation patient developed paralytic ileus and rectal bleeding.
B0095006A FR	14 y/o male	Dyspnea, drug interaction with dihydroergotamine, medication error	Received co-suspect dihydroergotamine X2 and sumatriptan 7 hours apart.
B0287482A UK	14 y/o male	Dysphasia, confusional state	Events resolved same day. Patient concurrently on paracetamol every 6 hours, daily ibuprofen and feverfew.
A0364864A USA	16 y/o male	IIIrd nerve paralysis, diplopia	History of migraine of 5 days duration at the time of sumatriptan use. No prior use of triptans.
A0133922A USA	17 y/o male	Cerebrovascular accident	Physician report to sales rep, event reported to have resolved.
Injection			
A0174494A USA	8 y/o male	Cycloplegia, mydriasis	Patient received sumatriptan 3 mg. Event resolved in 1 week.
D0041267A GER	11 y/o female	Hypersensitivity NOS, cardiovascular disorder NOS, anaphylactic reaction.	Patient without any significant PMH. Event persisted for 30 days.
B0123975A JAP	15 y/o female	Increased blood pressure, headache, hypertensive encephalopathy, dyspnea, facial pain, Pharyngolaryngeal pain, chest discomfort, Hypoaesthesia, hyperventilation, anxiety	1st exposure to sumatriptan (3 mg). Facial/throat pain began 5 minutes after injection followed by dyspnea, HA and hypertension. Initially treated with good results but patient readmitted due to chest discomfort and hand and feet numbness. MRI normal. Attending physician felt hypertension due to intra-cerebral hemorrhage.
Unknown Formulation			
A0121876A ???*	14 y/o male	Cerebrovascular accident, hypertension, seizure, coma, hemiplegia, aphasia, cognitive and visual deficits	Physician reports subject developed a stroke within a few hours of taking 1 dose of sumatriptan. Patient developed hypertension, seizures and coma while in hospital. Discharged with hemiplegia, aphasia, cognitive and visual deficits.

Source: Adapted from sponsor table 28, 29, and 30, final safety update study report.
*Country not stated, report found in narratives and not included in sponsor's summary tables

Overall there have been 19 cases with a total of 84 adverse events including the two subjects (A0383145A, B0274941) I previously described under deaths (6.1.3). Nine subjects were using the nasal spray formulation, 3 used the injection formulation, 7 used tablets, and 1 is unknown (1

included both tablet and nasal). All except 3 cases occurred in adolescents. I reviewed the case narratives for each case and provide the following commentary:

- Three cases (A0121876, A0133922A and B0301148A) of possible cerebrovascular accidents are included in the updated safety summary. Patient A0121876 was a 14 year old male who developed a CVA several hours after taking an unknown form of sumatriptan. The patient was hospitalized and had several complications including hypertension, seizures and coma. The patient was discharged a month later with persistent hemiplegia, aphasia, cognitive and visual deficits. The attending physician felt the patient had a "unknown vascular abnormality, possibly vasculitis" prior to the use of sumatriptan. Patient A0133922A was a 17 year old male who developed a stroke after using sumatriptan nasal spray. Few details are provided. Patient B0301148A was a 14 year old female who developed partial right hemiplegia, lack of coordination and right side of body hypoaesthesia the same day as using sumatriptan tablets. The event resolved. Concomitant medications included indomethacin. CVAs and transient hemiplegia are labeled events with sumatriptan.
- Patient A0137684A was a 10 year old male who developed blindness in his right eye after using sumatriptan nasal spray. No other details are provided. Blindness is included in the list of rare AEs seen with sumatriptan use.
- Patient A0139352A was a 14 year old male who developed rectal bleeding, abdominal pain, ileus, and hepatitis A after using sumatriptan nasal spray for approximately 1 year. The events resolved with discontinuation of sumatriptan and was considered possibly related. Certainly I would not consider sumatriptan the cause of hepatitis A. Ileus is not included in the list of adverse events seen with sumatriptan however abdominal pain, intestinal obstruction (could include ileus) and GI hemorrhage are listed.
- Patient A0174494A was an 8 year old male who developed transient cycloplegia after using sumatriptan injection 3 mg. The event lasted 1 week. The patient was evaluated by an Ophthalmologist who reports "everything was fine". The label for sumatriptan does not include cycloplegia. It does however include mydriasis. Since this is the 1st report of cycloplegia and the event was transient and not well documented I do not see any critical reason to include this AE in the label at this time.
- There were 3 cases (A0174633A, B0275952and D0041267A) of anaphylaxis reported in children during this period. A0174633A was a 14 year old male who developed anaphylactic shock (sweating, feet cold, clammy, difficulty breathing, wheezing, throat closing and decrease O_2 level) 1 hour after using sumatriptan tablet 100 mg. Previous treatment with sumatriptan (generally lower doses) and rizatriptan was well tolerated. Patient B0275952A was an 11 year old female who developed anaphylactic reaction with stridor after using sumatriptan nasal spray 20 mg for abdominal migraine. The event resolved in 4 hours with treatment. The attending physician felt the event was due to a viral infection. The following day the patient had another event of difficulty breathing and was evaluated by an ENT doctor who diagnosed "psychogenic cause". It is not clear to this reviewer that true anaphylaxis occurred in this case. D0041267A was an 11 year old female who developed hypersensitivity reaction/anaphylaxis "later the same day" after using sumatriptan injection. The patient had no contributory past medical history or used any other medications. The event sounds like a possible delayed hypersensitivity however significant details are not available. Hypersensitivity and anaphylaxis are already included in the label for sumatriptan.

- Three cases (A0364864A, A0411839A and B0078140A) of changes in vision were reported during this period. Patient A0364864A was a 16 year old male who developed 3rd Nerve Palsy and double vision within 1 hour of taking sumatriptan nasal spray. Despite discontinuation of sumatriptan the event was unresolved months after onset. A second case of double vision was reported in a 13 year old female (A0411839A). She developed double vision several days after using sumatriptan tablets. Few details about the case are available. Subject B0078140A was a 13 year old female who developed blurred vision, vertigo, vomiting and exasperation of migraine after using sumatriptan nasal spray. All events resolved in 2 days. The label for sumatriptan does not include 3rd Nerve Palsy or double vision (diplopia) however it does include "vision alterations" and "external ocular muscle disorders". Vomiting, vertigo and headache are labeled adverse events for sumatriptan.
- Patient A0383145A and B0095006A were two deaths associated with the use of sumatriptan and are described in section 6.1.3 of this review.
- Patient B0086570A was a 15 year old female who developed throat and mouth swelling and stiff neck after using sumatriptan tablets. Upper respiratory inflammation and muscle stiffness are labeled adverse events seen with sumatriptan use.
- Patient B0117768A was a 4 year old male who developed excessive drooling described as "some additional mucus production" 1 hour after chewing on a sumatriptan nasal spray device. The patient was hospitalized for observation and released. Hypersalivation is a labeled adverse event seen with sumatriptan.
- Patient B0123975 was a 15 year old female who developed facial and throat pain 5 minutes after receiving sumatriptan injection. Five minutes later the patient developed dyspnea and hypertension (260/110). Treatment resulted in resolution of complaints 1 hour later however 6 hours later the patient complained of chest discomfort and numbness in her hands and feet. An MRI at the time was normal. The physician suggested the elevated blood pressure was due to an intra-cerebral bleed however I would expect an acute blled to be visible on the scan. The headache was attributed to hypertensive encephalopathy. Significant elevations in blood pressure and hypertensive crises are already included in the label for sumatriptan. Chest pain an peripheral parasthesias are well known adverse events associated with the use of sumatriptan.
- Patient B0287482A was a 14 year old male who developed expressive dysphasia and confusion after using sumatriptan nasal spray. Concomitant medications included paracetamol, ibuprofen, and feverfew. The event resolved within 1 day. Dysphasia and mental confusion are labeled adverse events seen with sumatriptan.
- Patient B0095006A developed dyspnea after receiving 2 injections of dihydroergotamine (5 hours apart) and sumatriptan nasal spray (7 hours later). Concurrent medications included amitriptyline. The event resolved with treatment. Dyspnea is a labeled event with sumatriptan. Sumatriptan is contraindicated in subjects using dihydroergotamines.

6.4 Foreign Label Review.

As of June 2003, Imitrex Nasal Spray is approved in 61 countries for the acute treatment of migraine in adults. Of these countries sumatriptan nasal spray is approved for use in adolescent migraineurs in 23 countries. There have been no withdrawals of sumatriptan for reasons related to safety in any country. The following table summarizes the 23 countries where sumatriptan is

approved for adolescent use. In addition there are 3 countries in which approval in adolescents is pending.

Table 57 Worldwide Approval History of Sumatriptan Nasal Spray

Country	Dose approved	Date of Approval
Argentina	10 mg	9/2001
Australia	10, 20 mg	1/2001
Belgium, Germany, Greece, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom	10 mg	4/2003
Columbia	10 mg	2/2002
Denmark	10 mg	6/2003
Dominican Republic, El Salvador, Nicaragua, France	10, 20 mg	6/2003
Finland	10. 20 mg	4/2003
Norway	10 mg	7/2003
Panama	10, 20 mg	3/2003
Switzerland	10, 20 mg	7/2003

The sponsor provides the approved labeling from each country in this submission. Most of the countries have mutual agreements for labeling hence many national labels are identical. I reviewed the safety sections of each label and did not find any significant new information that is not already outlined in the Imitrex Nasal Spray label approved in the United States. A few labels do include a general statement about the theoretical risk of using a nasal spray in asthmatics and the use of the device in subjects allergic to latex or rubber (device sealed with rubber stopper). The US label does not specifically make these recommendations however it does state "bronchospasms can occur in patients with and without a history of asthma" (post marketing experience) and "Imitrex Nasal Spray is contraindicated in patients with hypersensitivity to sumatriptan or any of its components" (contraindications).

6.5 New Safety Findings from Literature

The sponsor reports they performed a worldwide literature search for articles relative to the use of sumatriptan nasal spray in pediatrics using the EAGLE database. The EAGLE database is a GSK internal database which is sourced from Embase, Medline, Derwent Drug File, Biosis, SciSearch and abstracts from conferences not covered by commercial databases. A total of 49 citations are provided by the sponsor. A review of each article by the sponsor failed to find any new safety concerns. I reviewed the title and abstracts (when available) of each article and did not find any significant signals for new safety concerns. Additionally I performed my own search of PubMed and could not find any significant new safety concerns relative to the use of sumatriptan in pediatrics.

6.6 Safety Findings from AERS Database

Coincidentally, not in conjunction with this NDA submission, Carol Pamer, a reviewer from the Division of Drug Risk Evaluation, performed an AERS database search for all adverse events reported with the use of all formulations of sumatriptan in children up to 17 years of age up until the cut off date of April 2, 2003. The full report can be found in DFS (OPDRA PID D030145). The reviewer reports a total of 125 unduplicated reports were found for children 0 to 17 years of age. Only 13 reports involved the use of sumatriptan nasal spray. For the pediatric reports the 20

most frequently reported MedDRA PT terms were as follows: headache (17), vomiting NOS (13), chest pain (13), drug ineffective (11), dyspnea NOS (10), paresthesia (10), convulsions NOS (8), apnea (8), condition aggravated (8), vasodilatation (8), dizziness (7), hypertonia (7), asthenia (7), hypertension (7), hypoaesthesia (6), laryngospasm (6), nausea (6), pain NOS (6), confusional state (5), and dermatitis NOS (5). Overall the reviewer states 54 of these reports were consistent with serious outcomes (death, hospitalization, life-threatening, disabled, or required intervention). The reviewer states there were 5 deaths in adolescents exposed to sumatriptan. The 5 fatal cases consisted of the following: intentional overdose with multiple drugs (previously described); congenital cardiac anomaly in an infant exposed in utero; obstructive hydrocephalus found on autopsy in adolescent female with a history of meningococcal meningitis with hydrocephalus; foreign report of collapse leading to death 7 months later in a 13 year old female (previously described); and a report with minimal information regarding death of a 9 year old patient under the care of a different physician after using nasal Imitrex (see following table). I reviewed the consult in its entirety and did not see any significant new information. The author of the review concludes the most frequently reported adverse events in children were generally consistent with adverse events reported in the adult population.

Table 58 Pediatric Deaths from AERS Search, Imitrex All Formulations

Age/Gender	PID	All reactions	Route	Contributing factors	Comments
Neonate/ NS*	A0112413A	Hypoplastic left heart syndrome, complication of maternal exposure	In utero		Sent to pregnancy registry
9 years/ NS	A0080709	Death NOS	NS	NS	Minimal information provided
13 years/ female	B0274941A	Collapse, eye rolling, LOC, somnolence	Oral		Previously described
15 years/ female	A0044668	Headache NOS, Hydrocephalus NOS	SC	Hx of meningococcal meningitis with hydrocephalus	Considered unrelated
16 years. Male	A0383145A	Apnea, brain death, cardiac arrest, suicide, lethargy,	Oral	Also on Zomig and Sudafed	Previously described

NS = not stated

7. Conclusions and Recommendations

7.1 Conclusion

In this reviewer's opinion the sponsor has failed to adequately demonstrate the efficacy of sumatriptan nasal spray in the treatment of migraine in adolescent patients. Between this submission and the original Pediatric Supplement (March 1, 2000, reviewed by Dr. Oliva) the sponsor has conducted 2 controlled adolescent efficacy studies (trials SUMA3005 and SUM30045). The following table briefly summarizes the essential results from both studies.

Table 59 Efficacy Summary of Controlled Trials

Endpoint	SUM 5mg	SUM 10 mg	SUM 20 mg	Placebo
Study SUMA 3005				
	N=127	N=133	N=117	N=130
2 Hour Response n(%)* p-value (Sponsor) p-value (Agency)	84 (66%) p=0.044 p=0.043	85 (64%) p=0.107 p=0.074	74 (63%) p=0.059 p=0.169	69 (53%)
Nausea at 2 hours p-value	26 (20%) NS	23 (17%) NS	24 (21%) NS	33 (25%)
Photophobia at 2 hours p-value	48 (38%) NS	57 (43%) NS	42 (36%) p=0.025	62 (48%)
Phonophobia at 2 hours p-value	36 (28%) p=0.016	44 (33%) p=0.096	29 (25%) p=0.001	57 (44%)
Study SUM30045				
	SUM 5 mg N=247		SUM 20 mg N=236	Placebo N=242
1 Hour Response n(%)* p-value (sponsor)	132 (53%) p=0.719		143 (61%) p=0.087	127 (52%)
Sustained Relief n(%)* p-value (sponsor)	92 (37%) p=0.173		96 (41%) 0.061	78 (32%)
Nausea at 1 hours p-value	59 (24%) p=0.918		50 (21%) p=0.521	57 (23%)
Photophobia at 1 hours p-value	119 (48%) p=0.423		102 (43%) p=0.072	126 (52%)
Phonophobia at 1 hours p-value	95 (38%) p=0.128		85 (36%) p=0.088	107 (44%)

*Primary endpoint(s), p-values in comparison to placebo

Source: Sponsor tables 12, 18, 20 and 21 study report sum3005.pdf, table 8 Dr Oliva's review; Figure 1 and 2 and tables 13.3, 13.4, 13.1, 13.213.9, 13, 14, 13.9, 15, 13.10, 16, 13.11, 17, and 13.12 study report 30045.pdf

Study SUM3005 was a randomized, placebo controlled, double blind, parallel group, single attack study that evaluated the safety and efficacy of three dose levels of sumatriptan nasal spray (5 mg, 10 mg, and 20 mg) in the acute treatment of migraine in approximately 500 adolescent migraineurs. The primary endpoint for the pivotal trial was the traditional 2 hour headache response. Unfortunately the sponsor's analysis of the 2 headache response for subjects taking sumatriptan nasal spray 20 mg compared to subjects taking placebo did not reach the threshold for statistical significance (p=0.059) and the decision was made within the division to consider this a failed study. A further analysis done by Dr Oliva demonstrated a p-value of 0.169 for the comparison of sumatriptan nasal spray 20 mg compared to placebo. Additionally sumatriptan nasal spray did not demonstrate benefit for the proportion of subjects reporting nausea at 2 hours.

Study SUM30045 was a randomized, placebo controlled, double blind, parallel group, single attack study that evaluated the safety and efficacy of 2 dose levels of sumatriptan nasal spray (5 mg and 20 mg) in the acute treatment of migraine in approximately 700 adolescent migraineurs. The co-primary endpoints for this pivotal trial was 1 hour headache response and sustained headache response between 1 to 24 hours. Unlike the earlier controlled study this study did not demonstrate a significant difference between active treatment and placebo for headache response at 1 hour ($p \geq 0.087$). Additionally this study failed to demonstrate a significant difference between active treatment and placebo for sustained headache response ($p \geq 0.061$, co-primary) as well as the incidence of each associated symptom (nausea, photophobia and phonophobia) at 1 hour ($p \geq 0.072$).

In addition to these controlled studies the sponsor also submits the results of two non-IND studies (trials SUM3009 and SUM40019) to support their assertion of efficacy. Trial SUM3009 was a randomized, placebo controlled, single center, double blind, two-period, crossover, single attack (each crossover) study to evaluate the safety and efficacy of sumatriptan nasal spray 10 mg for the acute treatment of migraine in children 8 to 12 years of age suffering from refractory migraine with and without aura. Since this study did not include adolescent migraineurs I do not believe it is relevant to this supplement. Trial 40019 was a randomized, placebo controlled, double blind, multicenter, two-period (single attack each), crossover, outpatient, efficacy study of sumatriptan nasal spray (10 mg or 20 mg). The primary objective of the study was to evaluate the safety and efficacy of sumatriptan nasal spray (10 or 20 mg) compared to placebo in the treatment of migraine in children between 8 to 17 years of age. Although a subset analysis of adolescents demonstrated statistically significant results for the primary endpoint (2 hour headache response, p=0.001) the trial has several design and methodology problems which prohibits its use as a pivotal adolescent efficacy trial. First of all the design of the 24 hour migraine diary does not permit us to assess whether in fact a migraine was treated. Secondly the study fails to evaluate the efficacy of sumatriptan to treat the associated symptoms associated with migraine and finally all analysis presented by the sponsor are post hoc analysis.

In summary I do not believe the sponsor has provided sufficient evidence that sumatriptan nasal spray 5 and 20 mg is effective in the treatment of migraine syndrome in adolescents. The new indication should not be granted in my opinion.

Relative to safety the sponsor has presented a considerable amount of safety experience in adolescents. A complete description of the exposure and safety experience was discussed earlier in this review and will not be repeated here however the sponsor has greatly exceeded the minimal amount of long term exposure expected for adolescent migraine studies. Overall the safety experience from approximately 7 clinical trials, involving over 2000 subjects, demonstrates that sumatriptan in doses up to 20 mg is well tolerated in adolescents. The nature and character of adverse events experienced during these trials were similar to those seen in adult migraine studies using sumatriptan. A review of all serious adverse events reported during the trials as well as those in the AERS database and those provided by the sponsor did not demonstrate any unique problems in adolescents. As with adults, sumatriptan is on rare occasions associated with serious adverse events, including death. The use of sumatriptan in adolescents should only be considered only when the diagnosis of migraine is clear and the risks have been adequately described to the patient and their guardians. In my clinical opinion all adolescents should be monitored by a responsible adult during the first few times sumatriptan is administered.

7.2 Recommendations

In my clinical opinion the indication for adolescent migraine should not be granted at this time. My review of the adolescent safety database does not find any significant unique adverse events that require changes to labeling.

Appendices

1. Tables

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/s/

Kevin Prohaska
4/13/04 11:50:00 AM
MEDICAL OFFICER

Eric Bastings
4/13/04 01:27:21 PM
MEDICAL OFFICER
See my memo to the file for additional comments.