CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20763

MEDICAL REVIEW(S)

Review And Evaluation Of Clinical Data

NDA:	**20-763**
Sponsor:	**GlaxoWellcome**
Drug:	**Naratriptan Tablets**
Indication:	**Migraine**
Material Submitted:	**NDA application**
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Background:

Glaxo submitted NDA 20-763 for naratriptan, a 5-HT receptor agonist, for the indication of acute treatment of migraine headaches. In this document, I have reviewed the evidence presented to support the efficacy of the drug in the acute treatment of migraine headaches. Dr. Choudhury provided a statistical consult. Dr. Sevka has reviewed the evidence supporting the safety of the drug in patients with migraine headache.

This review is divided into four parts. The first part includes an overview of the efficacy portion of the NDA. The second and third part include a summary of the sponsor's conclusions and my comments, respectively. In the final part, I have provided specific details and analyses for each of the efficacy studies.

Part One: Overview of the efficacy studies:

Overview:

The sponsor has conducted 11 studies in patients with migraines. One study was an early PK/PD study (1007) and two were studies evaluating the subcutaneous formulation. Of the remaining 8 studies, one was an open label, multiple dose safety study (3004) and one was an active control study (3011) comparing naratriptan and sumatriptan. The final 6 studies were placebo controlled studies evaluating the efficacy of the drug for the acute treatment of migraines. 5 evaluated adults (2003, 2004, 3001, 3002 and 3003) and one evaluated adolescents (3012).

The 5 adult studies were presented by the sponsor as adequate and well controlled investigations providing evidence for the efficacy of oral naratriptan in the acute treatment of migraine headaches. Doses of 0.1 and 0.25 mg did not demonstrate evidence for efficacy. Doses of 1, 2.5, 5, 7.5 and 10 mg were found to be significantly better than placebo for the percentage of patients with headache response defined as no or mild pain 4 hours post dose. The effectiveness was not affected by sex, weight, presence or absence of an aura, use of migraine prophylaxis, use of tobacco or oral contraceptives or time to onset to first dose. Since most of the patients were white, it is difficult to determine the effect of race on efficacy. In the single study in adolescents (age 12 to 17), doses of 0.25, 1.0, and 2.5 mg did not lead to a significant difference in headache response rates at 4 hours post dose when compared to placebo.

Summary of the pivotal and supportive trials:

Study 2003: This was an 80 patient, in clinic, single attack, double blind, placebo controlled, randomized, parallel study evaluating 5 and 10 mg of naratriptan conducted in 6 European countries from 12/21/93 to 10/31/94. The formulation used in this study was different than the proposed marketed formulation. The study was designed as a safety study with efficacy as a secondary outcome measure. Both doses had significantly higher response rates compared to placebo. While there was no difference between groups, though numerically, the 5 mg dose group had the highest scores.

Percentage of patients experiencing headache relief (grade 2/3 to 0/1)

Time post study treatment	Placebo (n=18)	Naratriptan 5mg (n=29)	Naratriptan 10mg (n=33)
60 minutes	6%	39%	31%
120 minutes	28%	71%	47%
240 minutes	33%	89%	72%

Study 2004: This study was conducted in 1993 and, as in study 2003, the proposed marketed formulation was not used. The study was a 600 patient, in clinic, randomized (equal between groups), double blind, placebo controlled, dose ranging trial evaluating 0, 1.0, 2.5, 5, 7.5 and 10 mg as well as 100 mg of sumatriptan. The sponsor concluded all doses tested has significantly higher response rates when compared to patients on placebo. There were no statistically significant differences between any of the active treatments. Numerically, the response rates for patients on 7.5 and 10 mg were essentially the same, about 80%, and the rates for 1, 2.5 and 5 mg were essentially the same, about 64%. The incidence of adverse events was highest in patients on 7.5 and 10 mg. Because the 5 and 2.5 mg dose groups had similar response rates and the 7.5 and 10 mg dose groups had an unsatisfactory risk:benefit rate, the sponsor decided not to evaluate doses of > 2.5 mg.

Study 2004: Headache relief rates (*comparison with placebo p value < 0.05)							
Time post dose	0 mg N=91	1 mg N=85	2.5 mg N=87	5 mg N=93	7.5 mg N=93	10 mg N=96	Sumatriptan N=98
30 minutes	11%	8%	10%	13%	15%	11%	15%
60 minutes	20%	27%	31%	34%	43%*	40%*	36%
120 minutes	31%	59%*	53%*	54%*	68%*	68%*	60%*
180 minutes	38%	62%*	60%*	61%*	76%*	75%*	78%*
240 minutes	37%	64%*	63%*	63%*	80%*	79%*	80%*

Study 3001: This was one of three pivotal clinical trials. In this 694 patient, double blind, randomized, placebo controlled, parallel study, doses of 0.1, 0.25, 1.0 and 2.5 mg were evaluated. Patients on 1.0 and 2.5 mg had significantly higher response rates, defined as a headache with moderate or severe pain going to mild or no pain, at 3 and 4 hours compared to patients on placebo. Doses of 0.1 and 0.25 mg were not significantly different from placebo. The results for the placebo, 1 and 2.5 mg group are summarized in the following table.

Study 3001: Headache relief rates (*comparison with placebo p value < 0.05)					
Time post dose	Placebo (N=122)	0.1 mg (N=128)	0.25 mg (N=119)	1.0 mg (N=117)	2.5 mg (N=127)
30 minutes	4%	3%	3%	8%	8%
60 minutes	16%	10%	8%	15%	20%
90 minutes	25%	19%	13%	26%	31%
120 minutes	30%	25%	20%	42%	40%
180 minutes	35%	32%	32%	50%*	52%*
240 minutes	34%	32%	35%	50%*	60%*

Study 3002: This study had a similar design to study 3001 except patients were to treat 3 headaches. Doses of 0, 0.1, 0.25, 1.0 and 2.5 mg of the drug and 100 mg of sumatriptan were evaluated. The results for treatment of the first headache are summarized in the following table. Headache response and recurrence were similar for all headaches treated.

Study 3002: Headache response rates (no or mild pain)						
Time post dose	Placebo (N=104)	0.1 mg (N=207)	0.25 mg (N=214)	1.0 mg (N=208)	2.5 mg (N=199)	Sumatriptan (N=229)
30 minutes	8	7	4	10	10	11
60 minutes	17	14	15	18	22	33*
90 minutes	22	20	21	27	38*	47*
120 minutes	22	30	29	38*	50*	59*
180 minutes	26	35	34	46*	61*#	69*
240 minutes	27	36	36	52*	66*#	76*

*P value < 0.05 comparison with placebo
#p value < 0.05 comparison of 1 and 2.5 mg doses

Study 3003: This was a randomized, double blind, placebo controlled, four period cross over study evaluating doses of 0, 0.25, 1 and 2.5 mg. The result for the first period is summarized in the following table:

Study 3003: Headache response rates (no or mild pain) (*comparison with placebo p value < 0.05, #comparison with 0.25 mg <0.05)				
Time post dose	Placebo (N=169)	0.25 mg (N=172)	1.0 mg (N=166)	2.5 mg (N=167)
30 minutes	7%	4%	8%	6%
60 minutes	14%	19%	21%	21%
90 minutes	22%	25%	33%	34%
120 minutes	24%	29%	40%*	47%*#
180 minutes	30%	33%	48%*#	59%*#
240 minutes	32%	38%	54%*#	65%*#

Study 3012: This was a randomized, double blind, placebo controlled, parallel study evaluating 0, 0.25, 1.0 and 2.5 mg in patients between the ages of 12 and 17. Aside from age, the selection criteria and study design was similar to study 3001.

Study 3012: Headache relief rates (*comparison with 2.5 mg p value < 0.05)				
Time post dose	0 mg N=74	0.25 mg N=78	1.0 mg N=78	2.5 mg N=70
30 minutes	15	8	6	10
60 minutes	36*	27	40	21
120 minutes	62	47	55	47
180 minutes	66	58	62	59
240 minutes	65	72	67	64

Part Two: Sponsor's conclusions:

Based on the results of study 3001, 3002 and 3003, the sponsor has concluded that 2.5 mg of the drug is effective for the acute treatment of migraine headaches. Patients treated with 2.5 mg had significantly higher response rates at 4 hours compared to patients treated with placebo. The drug was also associated with relief of photophobia, phonophobia and nausea associated with migraine attacks. In study 3002, three headaches were treated and 72% of patients receiving 2.5 mg had headache relief in at least 2 of 3 headaches compared to 22% of patients receiving placebo. The sponsor also noted that the adverse event profile of patients on placebo and those on 2.5 mg were similar. The results are summarized by the sponsor in Chart 7. The efficacy of the drug was unaffected by the presence of an aura, duration of attack before dosing, sex, age or weight of the patient, use of tobacco, common migraine prophylactic drugs. There was insufficient information to assess the race of the patient on efficacy.

The sponsor recommends a single dose of 2.5 mg with a second dose at 4 hours if the headache returns or persists. They chose the 2.5 mg dose over the 1 mg dose because of the greater and more consistent response observed with similar safety profiles. Because of prolongation of the half life in patients with renal or hepatic impairment, the maximum dose in a 24 hours period should be 2.5 mg.

In comparison with sumatriptan, naratriptan had lower headache response rates at 4 hours and lower incidence of headache recurrence.

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Chart 7: Summary of Efficacy, as Proposed for Labeling

	Study 1		Study 2		Study 3	
	Placebo (n = 612)	2.5 mg (n = 586)	Placebo (n = 107)	2.5 mg (n = 209)	Placebo (n = 122)	2.5 mg (n = 12
Results at 2 Hours						
Patients with headache relief (grade 0/1)‡	27%	49%***	22%	50%***	30%	40%
Patients with no pain‡	7%	24%***	5%	21%***	11%	18%
Patients without nausea	49%	60%***	51%	66%*	56%	55%
Patients without photophobia	26%	42%***	36%¶	53%**¶	29%	37%
Patients without phonophobia	31%	47%***	—	—	34%	45%
Patients with little or no clinical disability‖	49%	68%***	52%	63%*	46%	60%*
Results at 4 Hours						
Patients with headache relief (grade 0/1)‡	33%	68%***	27%	66%***	34%	60%**
Patients with no pain‡	15%	45%***	12%	43%***	20%	33%*
Patients with meaningful relief within 4 hours¶	34%	67%***	24%	60%***	36%	59%**
Patients without nausea	54%	75%***	56%	77%***	59%	71%*
Patients without photophobia	33%	61%***	34%¶	67%***¶	38%	57%**
Patients without phonophobia	36%	65%***	—	—	41%	59%**
Patients with little or no clinical disability‖	50%	76%***	49%	72%***	48%	70%**
24-Hour Overall Efficacy#	19%	48%***	21%	52%***	22%	43%**
Tolerability						
Overall incidence of adverse events	32%	31%	29%	32%	34%	34%

* $p<0.05$, ** $p<0.01$, *** $p\leq0.001$ vs. placebo.
† Efficacy data presented for attack 1, safety data presented across three attacks.
‡ Once patients received rescue medication, they were considered treatment failures from that point onward.
§ In Study 2, a combination of photophobia/phonophobia was assessed.
‖ A successful outcome is defined as ability to work mildly impaired or ability to work and function normally.
¶ Meaningful relief is a patient assessment of if he/she felt relief of migraine.
# Patients with headache relief at 4 through 24 hours postdose who did not take rescue medication or a second dose of study medication.

Part three: Reviewer's comments:

Background:

In my discussion of the efficacy findings, I am going to concentrate on the aspects that relate to the clinical trials section of labeling. Naratriptan is one in a series of 5 HT1 agonists that are being evaluated for the treatment of migraines. With the recent approval of Imitrex Nasal Spray, the division has worked on certain aspects of labeling, both safety and efficacy that can be consistent between drugs in this class and I will refer to these areas in my discussion.

Pivotal studies:

Of the 11 patient studies provided in the NDA, I considered three studies, 3001, 3002, 3003 and 3012 as studies adequate by design to provide evidence for efficacy. I have not included study 1007, a PK study. or two studies utilizing the subcutaneous formulation. I have not included studies 2003 and 2004 because they used a nonmarketed formulation. Study 3004 and 3011 were not included because of the lack of a placebo control group. Study 3004 was an open label study and study 3011 was an active control study using sumatriptan as an active control.

Studies 3001, 3002 and 3003 were conducted in adult patients and study 3012 evaluated adolescents.

Efficacy: The sponsor has demonstrated in more than one adequate and well controlled study that naratriptan is effective for the treatment of migraine headaches in adults. A single study in adolescents failed to demonstrate a statistically significant difference between any dose of naratriptan and placebo. The sponsor's prospectively defined measure of efficacy was the response rates 4 hours following treatment with response defined as a reduction in headache pain severity from moderate or severe to mild or no pain. This outcome measure is the same used in most recent migraine studies. In each adult study, there was a statistically significant increase in headache response rates in patients treated with the drug compared to those patients treated with placebo. The finding were consistent across all of the adult studies.

Dose effect: In the adult clinical studies, doses of 0.1 and 0.25 mg were not distinguishable from placebo whereas doses from 1 mg to 10 mg were effective. Because of the increase in adverse events, see safety review for additional details, the 7.5 and 10 mg doses were not studied further. Because there was no

difference in efficacy between the 2.5 and 5 mg dose, the sponsor did not evaluate the 5 mg dose in all studies.

Both the 1 mg and 2.5 mg doses were effective doses in the adult studies. The response rates for both the 1 and 2.5 mg dose was significantly better than placebo. Numerically, the 2.5 mg dose group had higher response rates at 4 hours, lower recurrence rates and longer time to recurrence than the 1 mg dose group. These differences were not statistically significant except in the largest study, 3002, were the difference in response rate between the 1 and 2.5 mg dose groups at 4 hours was associated with a p value of < 0.05. The choice of dose is based on the determination of the risk to benefit ratio for the individual patient.

Onset of effect: The response rates were evaluated as early as 30 minutes following treatment. The time to effect was not evaluated in the studies. In study 3002, a statistically significant difference in response rates between groups was noted as early as 90 minutes following dosing. To illustrate the time to response, we have used a Kaplan Meier plot of the estimated probability of achieving a headache response over the 4 hours following treatment.

Duration of effect: From experience with sumatriptan, an acute treatment for a migraine headache may not lead to complete resolution of the headache. Patients who have mild or no pain at 4 hours may have recurrent pain and/or require additional treatments. We have used a Kaplan Meier plot of the estimated probability of the using additional treatments for migraine over the 24 hour period following treatment to illustrate the duration of effect.

Efficacy of a second dose: When a second dose was used in the studies, the assignment was not randomized. This compromises the validity of any efficacy results obtained since it does not utilize a placebo group for comparisons. Effects from the initial dose and "placebo" effects cannot be separated from potential effects of the second dose.

Associated migraine symptoms: Though not a primary outcome measure, the studies show a consistent reduction in the incidence in the secondary outcome measures of nausea, photophobia and phonophobia in patients treated with the active treatment compared to those treated with placebo.

Effect of age: The sponsor evaluated the use of the drug in two age groups: age 12 to 17 (adolescents) and age 18 to 65 (adults). In both age groups, response rates to doses of 2.5 mg at 4 hours were similar, ranging from 60 to 65%. In the studies enrolling adults, placebo responses ranged from 27 to 34%. In the study

enrolling adolescents, the placebo response rate was 65%. The reason for the high placebo rate in the adolescent study is not known. It may be related to differences in the migraines in these age groups or differences in response to drug. In any case, labeling should reflect that the drug has not been shown to be effective in adolescent patients. Labeling for use in pediatric patients should also address if the drug may be harmful in this age group. This is mostly related to adverse events, which will be covered in the safety review. It can also be related to efficacy issues, specifically, does the drug worsen migraines in adolescents. The studies do not suggest that there is worsening, in terms of efficacy, in the adolescent population.

Long term benefit: The ability of naratriptan to effectively treat migraine headaches repeatedly over time was evaluated for three headaches in study 3002. In this study, the sponsor reported that about 3/4 of patients responded to 2 of 3 headaches treated. I calculated that for those patients treating three headaches about 50% of the patients on active drug had headache response at 4 hours for all three headaches without a change in the recurrence rate. The efficacy over longer periods of time was not evaluated in a controlled clinical trial. Because of the variability of response and potential for placebo effect, conclusions drawn from uncontrolled clinical trials may not be valid. In study 3004, the sponsor evaluated the long term safety of the drug in an open label study. Headache response was determined after each headache treatment. While the findings in this study suggest that the benefit of the drug does not dissipates over time, it has limited use in describing efficacy of the drug.

Comparison to sumatriptan: In study 3011, the sponsor compared naratriptan to sumatriptan 100 mg. This study was flawed in that it did not use a placebo group and it enrolled patients who had high recurrence rates on sumatriptan. The recurrence rates and use of second dose was higher in the sumatriptan group compared to the naratriptan group (p value < 0.05). The response rates were higher in the sumatriptan group.

In study 3002, a 100 mg sumatriptan arm was included in the study. Again, there was no statistically significant difference between the groups. Numerically, both the response rate and recurrence rate was higher in the sumatriptan group compared to naratriptan. While both groups had statistically higher response rates than placebo, the sumatriptan group had significant differences as early as 1 hour following treatment while the earliest the naratriptan group was significantly different was 2 hours.

Subgroup analyses: There were insufficient numbers of patients in each group

to determine the effect of race on the efficacy results. Dr. Choudhury, in his review, noted that in the 1 mg group the response rate was higher in the patients who took the dose > 4 hours following onset than those who took the drug ≤ 4 hours (p=0.038). Also in the 1 mg group, the age by treatment interaction was associated with a p value of 0.059. This appeared to be related to the higher response rate for placebo patients in the younger age group (39% for ages 18 to 30) compared to the older patients (25% response rate for patients age 51 to 65 on placebo). Similar analyses for the 2.5 mg group were associated with a p value of > 0.1. In regards to the effect of baseline severity, in the 2.5 mg group, the response rate was higher for patients with moderate headaches while for the 1 mg group, the response rates were similar to patients with moderate or severe headaches at baseline. Other interaction analyses for both groups were associated with p values > 0.1. Overall, the efficacy in adults did not appear to be affected by the presence or absence of aura or by age (18 to 65), gender, weight, menstrual cycle, or the duration of migraine attack.

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Part Four: Review of individual studies:

General comments for the pivotal studies:

Selection criteria:

In general, patients enrolled were 18 to 55, except in study 3012, patients were age 12 to 17. Patients were to have between one and 6 headaches with moderate to severe pain per month. Patients with confirmed or suspected cardiovascular or cerebrovascular disease were excluded. Patients with basilar or hemiplegic migraines were excluded. Investigation drugs were not allowed within 4 weeks of the study. Patients were instructed not to take any analgesics, antiemetic or other treatment for migraine within 6 hours of treatment.

Sponsor's Outcome definitions:

Headache severity was rated by the patient on a 4 point scale with 0= no pain, 1=mild pain, 2=moderate pain and 3= severe pain.

Headache relief (or response) was defined as a reduction in pain from moderate or severe at baseline to no or mild pain.

Migraine symptoms included nausea, vomiting, photophobia, phonophobia and were noted by the patient to be present or absent.

Clinical disability was rated by the patient on a 4 point scale with 0=able to work normally, 1=working ability mildly impaired, 2= working ability severely impaired and 3= requiring bed rest.

Time to meaningful relief was defined as achievement of a worthwhile degree of relief from any combination of headache, nausea, vomiting, photophobia and/or phonophobia. Patients started a stopwatch after taking the first and second dose and they were asked to stop the watch at the time of meaningful relief or at 240 minutes whichever came first.

Use of rescue medication , defined as use of any medication other than the study treatment for any of the migraine symptoms, was recorded by the patient. Rescue medication was not allowed within 240 minutes of administration of any study treatment.

Headache recurrence was recorded if the patient obtained headache relief 4 hours after taking the initial dose and then had a return of moderate to severe pain (significant worsening) between 4 and 24 hours post the initial dose.

Second dose outcome included assessment of headache severity and meaningful relief.

Headache relief maintenance rates was defined as headache relief without need for additional treatments.

Headache free rates was defined as a headache severity score of 0.

Other measures included time and date of onset of migraine, presence or absence of aura and data of last menstrual period.

Data sets:

Intent to treat: included patients who took study treatment and had any post treatment efficacy data. (In the non US studies, patients who had mild headaches at baseline were not included in the analyses).

Per protocol: this data set took all patients in the intent to treat data set and excluded those who had: taken study medication within 24 hours of taking ergotamine or dihydroergotamine containing medications, or sumatriptan; taken study medication within 6 hours of taking analgesics and/or antiemetic; taken rescue medications less than 4 hours post first dose; taken the second dose of study medication less than 4 hours post first dose; made their 240 minute efficacy assessments earlier than 210 minutes or later than 270 minutes post first dose; and a baseline headache severity score that was missing or 0/1 (no or mild pain).

Methods used for analyses: For the analyses, I used the following definitions:

Efficacy data set includes all patients in the study who received at least one dose of study treatment and had a baseline headache severity of moderate or severe pain.

Rescue is medication, other than the study treatment, taken for a treated migraine. Rescue includes analgesics, anti emetics, sedatives, etc.

Headache response, for the initial dose, is a change in the baseline headache severity from moderate or severe pain to mild or no pain at a given time point without intervening use of rescue or a second dose of study treatment. If there is no data available for the time of assessment, then data from the last observation is used.

A **responder** is a patient who has a change in the baseline headache severity from moderate or severe pain to mild or no pain at a given time point without intervening use of rescue or a second dose of study treatment.

A **non responder** is a patient who does not experience headache response at a given time point. In these patients, headache severity is moderate or severe at a given time point following the initial dose of study treatment from a baseline of severe or moderate pain. If there is no data available for the time of assessment, then data from the last observation is used. If a patient takes rescue or a second dose of study treatment prior to the determination of the headache severity at the given time point, the patient is also considered a non responder for the initial dose of study treatment.

Headache response rates are calculated by dividing the number of responders at a given time point by the total number of patients in the efficacy data set x 100.

Recurrence is when a responder has a return of moderate or severe headache pain or receives rescue or a second dose of study treatment within 24 hours of receiving the initial dose of study treatment.

Time to recurrence is the time of the return of moderate to severe headache pain, use of rescue or a second dose of study treatment which ever is comes first.

Maintenance of headache response is headache response obtained at a specified time point without headache recurrence, need for rescue or a second dose within 24 hours of the initial study treatment.

From the sponsor's analyses, the outcome of the patients treated with 0.1 and 0.25 mg were indistinguishable from those patients treated with placebo. After reviewing the results of the primary outcome measure, and defining the no effective dose, I focused on the comparisons of the placebo, 1 and 2.5 mg groups.

For all measures, unless otherwise specified, I have used the efficacy data set for my analyses. I have not analyzed the "per protocol" data sets.

To evaluate the efficacy of the drug in the treatment of migraine, I relied on the comparison of headache response rates at 4 hours, the primary outcome measure, for the active treatment groups and placebo. In order to illustrate the time course of headache release, I have calculated the headache relief rates at 1, 2 and 4 hours. If a patient took escape treatment prior to the time of assessment, I included them in the non responders group.

To gain information on the duration of the effect of the drug, I included five comparisons: (1) the recurrence rate for patients who responded to treatment at 4 hours. If patient's took a second dose of study treatment or used rescue, I included them in the recurrence group. (2) The mean time to recurrence, including patients taking a second dose or rescue. (3) The frequency of maintenance of headache response t. (4) Frequency of the use of a second dose or rescue treatment. (5) Time to use of a second dose or rescue.

Since use of rescue and use of second dose was not randomized, comparisons between groups for outcome measures obtained after using a second dose or using rescue may not be valid and I did not analyze them.

To evaluate the possibility of a rebound headache. I compared the frequency and severity of the recurrent headaches.

Since the efficacy of the drug for the treatment of migraines was determined by the primary efficacy measure, headache pain, I did not rely on related symptoms of migraines such as the absence of nausea, the absence of vomiting, absence of disability measures, time to meaningful relief, percentage of patients with no pain, etc. Since the sponsor has included some of these measures in the labeling, I will assess them.

My analyses were performed on JMP v3.1. I used one way ANOVA with Dunnet's to determine statistical significance at a two tailed p value of < 0.05 for comparisons with placebo. For comparison of all groups, I used Tukey Kramer HSD.

Pivotal studies:

Study 3001: –

Protocol:

Design: This was a randomized (equal between groups), double blind, placebo controlled, dose ranging trial evaluating 0.1, 0.25, 1.0 and 2.5 mg. Patients were allowed to take a second dose of the initial treatment 4 hours after the initial dose though they were supposed to take it for a recurrence of pain.

Sample: Approximately 600 to 700 patients were to be enrolled to have 80% power to detect a difference in headache relief for the two highest doses and placebo, the two highest doses and the lowest dose and between 0.25 and 2.5 mg.

Primary: The primary endpoint in all of the placebo controlled studies was the percentage of patients with headache relief at 4 hours after the first dose of study treatment for the first attack treated.

Secondary: Headache relief rates at 30, 60, 90, 120 and 180 minutes and at 8, 12 and 24 hours post the first dose, Headache relief maintenance rates was defined as headache relief without need for additional treatments at 8, 12, and 24 hours, Headache free rates (severity score 0) at 4 hours post dose, Meaningful relief, Migraine symptoms at 30, 60, 90, 120, 180, and 240 minutes as well as at 8, 12, and 24 hours post first dose, Clinical disability at 0 at 30, 60, 90, 120, 180, and 4 hours post first dose, Use of rescue medication within 24 hours post first dose, Recurrence of headache between 4 and 24 hours post first dose in patients with headache relief at 4 hours.

Analysis: Mantel Haenszel analysis will be used to compare the active groups with placebo. A linear trend analysis will also be performed.

Results:

Disposition: 694 patients were randomized at 54 centers with 613 receiving treatment. The range of patients enrolled in the individual centers was 5 to 32 with a mean of 11 patients. 10% of the patients withdrew because they did not treat a single headache during the study time. 7 patients either failed to return for

the final visit or did not return their diaries. All 613 patients were included in the intent to treat efficacy analysis. 111 patients had protocol violations and were not included in the per protocol analysis. The distribution of patients and protocol violations are summarized in the following table:

Study 3001: Disposition and protocol violations					
	0 N=122	0.1 N=128	0.25 N=119	1.0 N=117	2.5 N=127
Took drugs prior to treatment	5%	4%	9%	2%	3%
Took rescue < 4 hours after dose	6%	0%	4%	3%	0%
Took second dose < 4 hours after dose	2%	2%	3%	3%	2%
No efficacy data at 3.5 to 4.5 hours	12%	12%	11%	14%	9%
Total	22%	16%	21%	19%	13%

Demographics and baseline characteristics: The demographics were similar between groups. 93% of the patients were white. Patients were age 19 to 65 with a mean age of 40.2. 87% were female and 71% had migraines without an aura. The groups were similar in reference to medical conditions, baseline headaches and other characteristics. Patients waited on average 2.9 to 3.6 hours to treat their migraines. About 32% took medication to prevent migraines.

Primary outcome measure: For the headache relief rate, there was a statistically significant increase in headache relief rates at 180 and 240 minutes following the initial dose of treatment for patients on either 1 or 2.5 mg when compared to placebo. The 0.1 and 0.25 mg groups were indistinguishable from placebo. I have summarized the results in the following table.

Study 3001: Headache relief rates (*comparison with placebo p value < 0.05)					
Time post dose	Placebo (N=122)	0.1 mg (N=128)	0.25 mg (N=119)	1.0 mg (N=117)	2.5 mg (N=127)
30 minutes	4%	3%	3%	8%	8%
60 minutes	16%	10%	8%	15%	20%
90 minutes	25%	19%	13%	26%	31%
120 minutes	30%	25%	20%	42%	40%
180 minutes	35%	32%	32%	50%*	52%*
240 minutes	34%	32%	35%	50%*	60%*

Subgroup analyses: The majority of patients were white females between the ages of 30 and 50. The subgroup analyses for race, sex and age were limited to a small number of patients. For the primary outcome measure, the patients on 1 and 2.5 mg scored higher than patients on placebo for each of the subgroups except for non white patient where the placebo group was 60% and the 1 mg group was 55%. The results are summarized in the following table.

Study 3001: Subgroup analyses for the primary outcome measure			
Parameter	Placebo (N=128)	1.0 mg (N=127)	2.5 mg (N=122)
Race-non White (N)	9% (12)	6% (8)	4% (5)
headache relief at 4 hours	60%	75%	56%
Race-White (N)	91% (117)	94% (108)	96% (119)
headache relief at 4 hours	33%	50%	59%
Sex-male (N)	13% (15)	16% (19)	12% (15)
headache relief at 4 hours	20%	58%	77%
Sex-female	88% (107)	84% (98)	88% (114)
headache relief at 4 hours	36%	49%	58%
Age ≤ 30	18% (22)	25% (29)	19% (24)
headache relief at 4 hours	27%	55%	54%
Age > 50	10% (12)	13% (15)	20% (26)
headache relief at 4 hours	8%	53%	77%
Age 30 to 50	72% (88)	62% (73)	61% (77)
headache relief at 4 hours	40%	48%	56%

Other subgroups analyzed by the sponsor included weight, time from onset of migraine to first dose, migraine history, use of preventative medication, tobacco use, current migraine type and contraceptive method. Again, many of these subgroups, for example, history of migraine with aura, use of tobacco, had small numbers of patients.

The results are summarized by the sponsor in the following table:

Table 15
Headache Relief Rates at 240 Minutes Post First Dose by Subgroup Factors

		NARATRIPTAN (mg/dose)			
	Placebo	0.1	0.25	1.0	2.5
Intent-to-Treat Population					
No. of Patients	122	128	119	117	127
Gender					
Female	39 (36%)	38 (34%)	33 (32%)	48 (49%)	66 (58%)
Male	2 (20%)	3 (12%)	9 (56%)	11 (58%)	10 (77%)
Ethnic Origin					
Black	2 (67%)	5 (63%)	1 (100%)	2 (67%)	4 (67%)
Hispanic	1 (50%)	3 (75%)	1 (25%)	2 (50%)	2 (100%)
Oriental	0	0	1 (100%)	1 (50%)	0
Caucasian	39 (33%)	33 (28%)	39 (35%)	64 (50%)	70 (59%)
Age (years)					
< 18 yrs	0	0	0	0	0
18-30 yrs	6 (27%)	5 (25%)	4 (21%)	16 (58%)	13 (54%)
31-40 yrs	15 (44%)	18 (33%)	13 (41%)	17 (45%)	27 (60%)
41-50 yrs	20 (37%)	11 (22%)	14 (30%)	18 (81%)	16 (80%)
51-65 yrs	1 (8%)	7 (37%)	11 (41%)	8 (53%)	20 (77%)
> 65 yrs	0	0	0	0	0
Weight (kg)					
<75	30 (33%)	27 (32%)	24 (30%)	41 (51%)	46 (55%)
>=75	12 (29%)	14 (33%)	18 (45%)	18 (49%)	29 (69%)
Time from Onset to First Dose					
<= 4 hrs	33 (37%)	34 (36%)	33 (37%)	45 (51%)	58 (59%)
> 4 hrs	9 (27%)	7 (21%)	9 (30%)	13 (42%)	18 (62%)
Migraine History					
Without Aura Only	24 (29%)	25 (29%)	24 (28%)	43 (51%)	59 (60%)
With Aura Only	4 (44%)	2 (18%)	2 (40%)	4 (50%)	3 (50%)
Both	14 (48%)	14 (44%)	16 (62%)	12 (42%)	14 (61%)
Prophylactic Med: Used					
No	30 (28%)	29 (33%)	25 (32%)	42 (48%)	49 (60%)
Yes	12 (29%)	12 (30%)	17 (41%)	17 (57%)	27 (59%)
Tobacco Use					
Current User	9 (53%)	8 (33%)	7 (32%)	11 (61%)	8 (32%)
Former User	6 (20%)	8 (25%)	14 (38%)	12 (43%)	23 (62%)
Never Used	27 (36%)	25 (35%)	21 (35%)	36 (51%)	45 (63%)
Current Migraine Type					
Without Aura	35 (35%)	30 (30%)	32 (32%)	47 (50%)	66 (60%)
With Aura	7 (33%)	11 (38%)	10 (45%)	11 (50%)	10 (59%)
Contraceptive Method					
IUD	1 (50%)	0	0	2 (100%)	0
Implant/Injectible	0	1 (100%)	0	3 (60%)	0
Oral Contraceptive	7 (32%)	6 (33%)	3 (25%)	7 (50%)	9 (53%)
Other	12 (33%)	12 (32%)	11 (32%)	13 (36%)	23 (61%)

Secondary outcome measures: The sponsor described over 50 analyses on secondary outcome measures. This included analyses at each time point in the study and for each variable. I have reviewed these outcome measures and have summarized a number of them in the following table.

Summary of secondary outcome measures (*P value < 0.05 when compared to placebo)			
–	Placebo (N=122)	1.0 mg (N=117)	2.5 mg (N=127)
Headache free rate at 4 hours	20%	27%	33%*
% of patients with meaningful relief within 4 hours	36%	56%	59%
Mean time to meaningful relief (minutes) without censoring	120	131	135
Mean time to meaningful relief (minutes) with censoring (Patients without relief by 240 minutes are to censored to 240 minutes)	197	176	178
% of patients with nausea at 240 minutes (p value)	41%	32%	29%* (0.021)
% of patients with vomiting at 240 minutes	9%	3%	7%
% of patients with photophobia at 240 minutes (p value)	62%	48%* (0.022)	43%* (0.022)
% of patients with phonophobia at 240 minutes (p value)	59%	46%* (0.029)	41%* (0.029)
% of patients able to resume normal activity at 240 minutes	29%	36%	46%*
% of patients requiring bed rest at 240 minutes	38%	16%	16%
% of patients using a rescue medication	56%	38%	31%*
% of patients using a second dose of study treatment	24%	33%	24%
% of patients using rescue medication and/or a second dose	71%	62%	47%
Time (minutes) to use of rescue medication and/or second dose	298	299	235
Number of patients with recurrent headache/ Number of patients with headache relief at 4 hours (%)	16/42 (38%)	23/59 (39%)	21/76 (28%)
Mean time (hours) to recurrence	10.2	12.6	11.4
Number of patients with recurrence (including second dose or escape)/ Number of patients with headache relief at 4 hours (%)	16/42 (38%)	25/59 (42%)	22/76 (29%)
Mean time (hours) to recurrence (including second dose or escape)	10.2	12.8	11.4
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (%)	5/16 (31%)	9/23 (39%)	6/21 (29%)
Second dose- headache relief rate within 240 minutes	67%	76%	81%
Second dose- meaningful relief within 240 minutes	73%	71%	71%
Second dose -mean time (minutes) to meaningful relief	103	109	144

Headache relief rates at 8, 12 and 24 hours post the first dose: In calculating the relief rates, I excluded all patients who took rescue and/or second dose by the time the relief rate was determined. For example, to determine the relief rate at 8 hours, I excluded all patients from the calculations who had taken rescue or second dose by 8 hours. The results are in the following table. I have plotted the percentage of patients with headache relief over time censoring patients who have taken rescue or a second dose of treatment in the following figure (this is not a Kaplan-Meier plot).

Patients with relief at 8, 12 and 24 hours without taking rescue or second dose of treatment				
		Placebo	1.0 mg	2.5 mg
8 hours	Percentage with relief	49%	78%	86%
	Total number of patients	58	69	87
12 hours	Percentage with relief	72%	85%	90%
	Total number of patients	46	59	81
24 hours	Percentage with relief	84%	89%	91%
	Total number of patients	37	45	68

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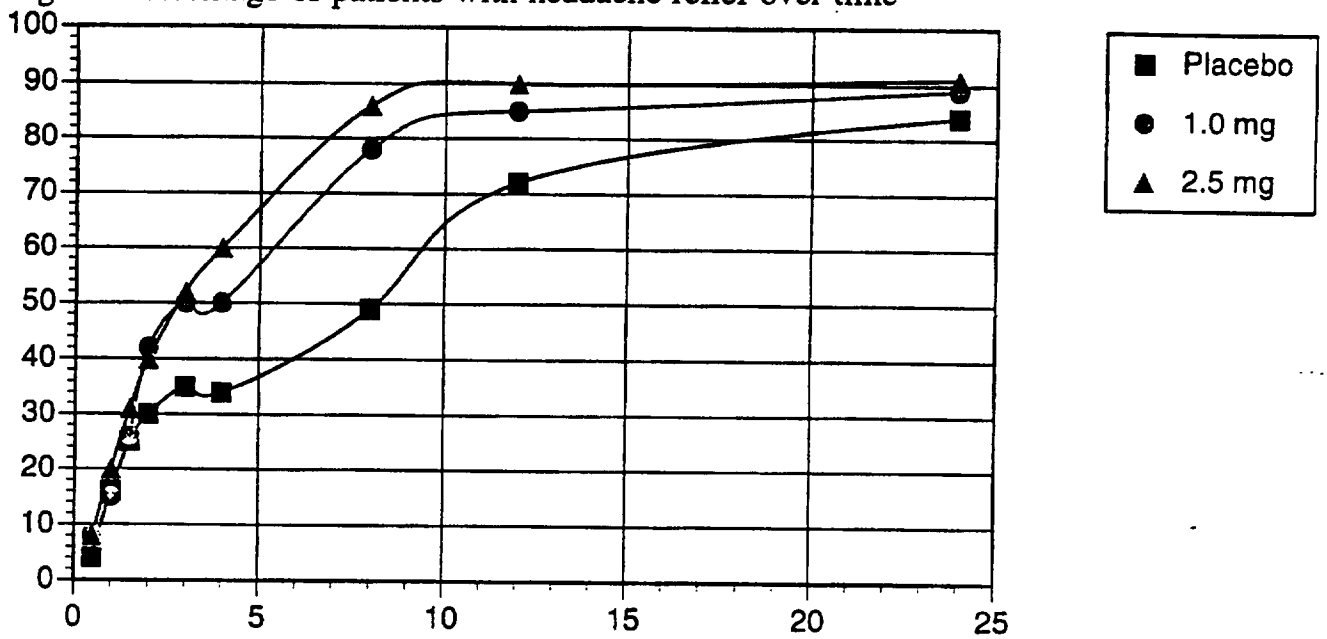
Figure: Percentage of patients with headache relief over time



Meaningful relief: This was recorded by the patients as the time to achievement of a worthwhile degree of relief from any combination of headache, nausea, vomiting, photophobia and/or phonophobia. Patients used a stopwatch and stop it at the time of meaningful relief or at 240 minutes whichever came first. The sponsor reported the median time for relief, censoring patients without relief to 240 minutes. The median time for relief was > 240 minutes for the placebo group and 219 and 214 minutes for the 1 and 2.5 mg group respectively. I have included the percentage of patients with meaningful relief by 240 minutes and the mean time to relief with and without censoring. See the secondary outcome table for the results.

Use of rescue medication: Medication used to treat any of the symptoms of migraines within 24 hours post first dose was recorded. The most common medications were Fiorinal (8%), ibuprofen (6%), Fioricet (4%), Midrin (3%), promethazine (3%) and sumatriptan (3%). The use of a second dose of study treatment and the use of either a second dose and/or rescue medication and the time to use is included in the table of secondary outcome measures.

Recurrence of headache: This was noted if a patient had mild or no pain (headache relief) at 4 hours followed by return of headache with moderate to severe pain between 4 and 24 hours post the first dose and did not use rescue medication or a second dose of study treatment. The number of patients with recurrence is summarized in the secondary outcome table.

Second dose: Efficacy was measured by the headache relief rate and meaningful relief within 240 minutes of the second dose. The relief rates for the second dose are summarized in the secondary outcome table.

Study 3002:

Protocol:

Design: This was a randomized, double blind, placebo controlled, dose ranging trial evaluating 0.1, 0.25, 1.0 and 2.5 mg of the drug and 100 mg of sumatriptan. Patients were randomized 1:2:2:2:2:2 placebo: 0.1 mg: 0.25 mg: 1.0 mg: 2.5 mg: sumatriptan. Patients were allowed to take a second dose of the initial treatment 4 hours after the initial dose though they were supposed to take it for a recurrence of pain. Patients on placebo were give sumatriptan. Patients were to treat three migraine attacks of moderate to severe pain.

Sample: Approximately 1400 patients were to be enrolled to have 80% power to detect a difference in headache relief for 0.25 and 2.5 mg. The sponsor estimated 30% drop out and a 45% improvement in the 0.25 mg group and 65% in the 2.5 mg group.

Primary: The primary endpoint in all of the placebo controlled studies was the percentage of patients with headache relief at 4 hours after the first dose of study treatment for the first attack treated.

Secondary: Partial listing includes: Headache relief rates at time points other than 240 minutes post dose, Meaningful relief, Migraine symptom, Clinical disability, Use of rescue medication within 24 hours post first dose, Recurrence of headache within 24 hours.

Analysis: Mantel Haenszel analysis will be used to compare the active groups with placebo. A linear trend analysis will also be performed. Patients who required rescue was assigned their last headache severity scores before rescue medication for the analysis of headache relief.

Results:

Methods: In this study, patients treated up to 4 headache. For determination of efficacy of the drug in the treatment of migraines, I have analyzed the results for the treatment of the first headache. Since this was the initial exposure to the drug, any concerns about unblinding would not apply. If a patient treated a mild headache, I did not include them in the analysis. I used the LOCF to fill in for missing values.

To evaluate the possibility of patients developing tolerance to the drug, I have assessed the 4 hour relief rates for all headaches treated to see if there is a trend for the development of tolerance.

Disposition: 1220 patients were randomized, treated at least one headache and had at least one post treatment assessment. 241 patients were treated with sumatriptan 100 mg. 1062 patients treated two attacks and 931 treated three attacks. 7 patients treated 4 attacks. There were 113 centers in 14 countries with a range of 1 to 31 patients per center.The distribution of patients and protocol violations are summarized in the following table:

Study 3002: Disposition and protocol violators (Number of patients)					
Number of patients who:	0	0.1	0.25	1.0	2.5
Took at least one dose and had at least one post treatment assessment	107	220	224	219	209
Baseline severity < 2 or missing	3	13	10	11	10
Total efficacy population	104	206	213	208	199
Took drugs prior to treatment	0	2	3	2	3
Took rescue < 4 hours after dose	11	23	12	12	4
Took second dose < 4 hours after dose	1	2	1	4	0
No efficacy data at 3.5 to 4.5 hours	22	37	33	24	38

Demographics and baseline characteristics: The demographics were similar between groups. 99% of the patients were white. Patients were age 18 to 65 with a mean age of 40.4. 84% were female and 61 to 68% had migraines without an aura. The groups were similar in reference to medical conditions, baseline headaches and other characteristics. 61 to 65% had taken sumatriptan in the past. Patients waited on average 2.9 to 3.6 hours to treat their migraines. About 32% took medication to prevent migraines.

Primary outcome measure: For the headache relief rate for the first attack, there was a statistically significant increase in headache relief rates at 240 minutes following the initial dose of treatment for patients on either 1 or 2.5 mg when compared to placebo. The 2.5 mg dose was statistically better than the 1 mg dose. The 0.1 and 0.25 mg groups were indistinguishable from placebo. I have summarized the results in the following table.

Study 3002: Headache relief rates (no or mild pain)						
Time post dose	Placebo (N=104)	0.1 mg (N=207)	0.25 mg (N=214)	1.0 mg (N=208)	2.5 mg (N=199)	Sumatriptan (N=229)
30 minutes	8	7	4	10	10	11
60 minutes	17	14	15	18	22	33*
90 minutes	22	20	21	27	38*	47*
120 minutes	22	30	29	38*	50*	59*
180 minutes	26	35	34	46*	61*#	69*
240 minutes	27	36	36	52*	66*#	76*

*P value < 0.05 comparison with placebo
#p value < 0.05 comparison of 1 and 2.5 mg doses

Subgroup analyses: The majority of patients were white females between the ages of 30 and 50. The subgroup analyses for race, sex and age were limited to a small number of patients. For the primary outcome measure, the patients on 1 and 2.5 mg scored higher than patients on placebo for each of the subgroups (race was not done). The results from subgroup analysis for sex, age, migraine type and duration from onset to treatment are summarized in the following table.

Study 3002: Subgroup analyses for the primary outcome measure			
Parameter	Placebo (N=104)	1.0 mg (N=208)	2.5 mg (N=199)
Race-non White (N)	0	3	0
Sex-male (N)	10	38	37
headache relief at 4 hours	30%	55%	62%
Sex-female	94	170	162
headache relief at 4 hours	27%	52%	67%
Age ≤ 30	16	31	32
headache relief at 4 hours	19%	39%	69%
Age > 50	14	32	51
headache relief at 4 hours	21%	41%	67%
Age 30 to 50	74	145	116
headache relief at 4 hours	30%	58%	66%
Migraine without Aura[1]	79	176	168
headache relief at 4 hours	25%	54%	65%
Migraine with Aura[1]	26	51	41
headache relief at 4 hours	36%	44%	73%
Duration of headache before dose ≤ 4 hrs[1]	91	174	164
headache relief at 4 hours	30%	52%	69%
Duration of headache before dose > 4 hrs[1]	15	44	43
headache relief at 4 hours	13%	53%	56%

[1]The data from these categories were obtained from the sponsor's study report (Tables 19 and 20) and differ slightly in total number of patients because of differences in patient selection criteria.

Secondary outcome measures: The sponsor described over 50 analyses on secondary outcome measures. This included analyses at each time point in the study and for each variable. I have reviewed these outcome measures and have summarized a number of them in the foliowing table.

Study 3002: Summary of secondary outcome measures			
–	Placebo (N=104)	1.0 mg (N=208)	2.5 mg (N=199)
Headache free rate at 4 hours	12	27	43
% of patients with meaningful relief within 4 hours			
% of patients with nausea at 240 minutes	45	30	23
% of patients with vomiting at 240 minutes	8	6	5
% of patients with photo/phono phobia at 240 minutes	68	44	33
% of patients able to resume normal activity at 240 minutes	17	29	44
% of patients requiring bed rest at 240 minutes	30	20	14
% of patients using a rescue medication	67	46	35
% of patients using a second dose of study treatment	13	28	16
% of patients using rescue medication and/or a second dose	70	58	42
Time (hours) to use of rescue medication and/or second dose	5.9	7.4	7.7
Number of patients with recurrence/ Number of patients with headache relief at 4 hours (%)	6/28 21%	40/109 37%	28/132 21%
Mean time (hours) to recurrence	8.4	10.4	11.7
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (%)	0/1 0%	5/34 15%	4/19 21%

Headache response for all headaches treated: Patients were allowed to treat up to three headaches. 883 patients treated three moderate to severe headaches.

Headache response at 4 hours and recurrence rates for all three headaches				
		Placebo	1 mg	2.5 mg
Response rate	1st headache	32%	55%	69%
	2nd headache	28%	52%	70%
	3rd headache	33%	54%	66%
Responded to treatment for all three headaches		9%	34%	53%
Recurrence rates	1st headache	18%	39%	21%
	2nd headache	30%	32%	28%
	3rd headache	33%	36%	25%

Study 3003:

Protocol: –

Design: This was a randomized, double blind, placebo controlled, four period crossover study. All patients will receive four different treatments, 0, 0.25, 1 and 2.5 mg, for each moderate to severe headache. Patients were allowed to take a second dose of the initial treatment 4 hours after the initial dose though they were supposed to take it for a recurrence of pain.

Sample: Approximately 600 to 700 patients were to be enrolled to have 80% power to detect a difference in headache relief for the 1 and 2.5 mg group and placebo and a difference between the 2.5 and 1 mg group and the 0.25 mg group.

Primary: The primary endpoint in all of the placebo controlled studies was the percentage of patients with headache relief at 4 hours after the first dose of study treatment for the first attack treated.

Secondary: Headache relief rates at 30, 60, 90, 120 and 180 minutes and at 8, 12 and 24 hours post the first dose, Headache relief maintenance rates , Headache free rates (severity score 0) at 4 hours post dose, Meaningful relief, Migraine symptoms at 30, 60, 90, 120, 180, and 240 minutes as well as at 8, 12, and 24 hours post first dose, Clinical disability at 0 at 30, 60, 90, 120, 180, and 4 hours post first dose, Use of rescue medication within 24 hours post first dose, Recurrence of headache between 4 and 24 hours post first dose in patients with headache relief at 4 hours.

Analysis: Active versus placebo comparisons will be made using a logistic crossover model for categorical data. Treatment, period, and carryover effects will be evaluated as appropriate. A linear trend analysis will also be performed as appropriate.

Results:

Disposition: 682 patients treated at least one headache. 514 treated all four attacks. 1220 patients were randomized, treated at least one headache and had at least one post treatment assessment. 241 patients were treated with sumatriptan

100 mg. 1062 patients treated two attacks and 931 treated three attacks. 7 patients treated 4 attacks. There were 113 centers in 14 countries with a range of 1 to 31 patients per center.The number of patients treating headaches and the distribution of patients and protocol violations for attack 1 are summarized in the following tables:

Study 3003: Number of patients in study				
	Placebo	0.25	1.0	2.5
All attacks	606	593	600	590
Attack 1	172	174	167	169
Attack 2	164	156	158	154
Attack 3	142	134	145	140
Attack 4	128	129	130	127

Disposition and protocol violators for attack 1 (Number of patients)				
Number of patients who:	0	0.25	1.0	2.5
Took at least one dose and had at least one post treatment assessment	169	172	166	167
Took drugs prior to treatment	6	7	3	4
Took rescue < 4 hours after dose	3	7	3	4
Took second dose < 4 hours after dose	4	4	4	4
No efficacy data at 3.5 to 4.5 hours	25	24	22	33
Baseline severity < 2 or missing	0	0	0	0

Demographics and baseline characteristics: The demographics were similar between groups. 93% of the patients were white. Patients were age 19 to 65 with a mean age of 41.2. 90% were female and 71% had migraines without an aura. The groups were similar in reference to medical conditions, baseline headaches and other characteristics. 61 to 65% had taken sumatriptan in the past. Patients waited on average 2.7 to 3.2 hours to treat their migraines. 29 to 31% took medication to prevent migraines.

Efficacy outcome measures:

Methods: In this study, patients treated up to 4 headache. For determination of efficacy of the drug in the treatment of migraines, I have analyzed the results for

the treatment of the first headache. Since this was the initial exposure to the drug, any concerns about unblinding would not apply.

If an assessment was missing at 4 hours, then the last available observation was used. Patients who took rescue or second dose prior to the assessment time were considered non responders.

Primary outcome measure: For the headache relief rate for the first attack, there was a statistically significant increase in headache relief rates at 240 minutes following the initial dose of treatment for patients on either 1 or 2.5 mg when compared to placebo or the 0.25 mg dose group. The 2.5 mg dose was not statistically better than the 1 mg dose. The 0.25 mg group was indistinguishable from placebo. I have summarized the results in the following table.

Study 3003: Headache relief rates (no or mild pain)
(*comparison with placebo p value < 0.05, #comparison with 0.25 mg <0.05)

Time post dose	Placebo (N=169)	0.25 mg (N=172)	1.0 mg (N=166)	2.5 mg (N=167)
30 minutes	7%	4%	8%	6%
60 minutes	14%	19%	21%	21%
90 minutes	22%	25%	33%	34%
120 minutes	24%	29%	40%*	47%*#
180 minutes	30%	33%	48%*#	59%*#
240 minutes	32%	38%	54%*#	65%*#

Subgroup analyses: The majority of patients were white females between the ages of 30 and 50. The subgroup analyses for race, sex and age were limited to a small number of patients. Race was not evaluated because of the small number of patients involved. For the primary outcome measure, the patients on 1 and 2.5 mg scored higher than patients on placebo for each of the subgroups except for patients 30 and younger where the placebo group scored higher than the 1 mg group. The results are summarized in the following table.

Study 3003: Subgroup analyses for the primary outcome measure			
Parameter	Placebo (N=)	1.0 mg (N=)	2.5 mg (N=)
Sex-male (N)	15	14	16
headache relief at 4 hours	33%	64%	62%
Sex-female	154	152	151
headache relief at 4 hours	32%	53%	66%
Age ≤ 30	20	25	33
headache relief at 4 hours	50%	36%	61%
Age > 50	35	29	28
headache relief at 4 hours	29%	62%	71%
Age 30 to 50	114	112	106
headache relief at 4 hours	30%	56%	65%

Other subgroups analyzed by the sponsor included weight, time from onset of migraine to first dose, migraine history, use of preventative medication, tobacco use, current migraine type and contraceptive method. Again, many of these subgroups, for example, history of migraine with aura, use of tobacco, had small numbers of patients. The results for all attacks are summarized by the sponsor in the following table:

Table 42
Headache Relief Rates at 240 Minutes Post First Dose by Subgroup Factors – All Attacks

		NARATRIPTAN (mg/dose)		
	Placebo	0.25	1.0	2.5
Intent-to-Treat Population				
No. of Patients	602	591	595	586
Gender				
Female	175 (32%)	207 (39%)	306 (57%)	364 (68%)
Male	22 (37%)	26 (46%)	32 (53%)	32 (60%)
Ethnic Origin				
Black	8 (50%)	10 (59%)	6 (38%)	12 (71%)
Hispanic	7 (37%)	8 (40%)	15 (71%)	13 (59%)
Oriental	1 (33%)	2 (67%)	1 (33%)	3 (100%)
Caucasian	180 (32%)	212 (39%)	315 (57%)	367 (62%)
Other	1 (50%)	1 (100%)	1 (100%)	1 (50%)
Age (years)				
< 18 yrs	0	0	0	0
18–30 yrs	39 (44%)	35 (38%)	48 (54%)	64 (68%)
31–40 yrs	58 (30%)	75 (40%)	107 (57%)	120 (64%)
41–50 yrs	67 (31%)	88 (42%)	124 (58%)	140 (69%)
51–65 yrs	33 (33%)	35 (34%)	59 (57%)	72 (71%)
> 65 yrs	0	0	0	0
Weight (kg)				
<75	127 (32%)	161 (40%)	230 (57%)	271 (69%)
>=75	70 (36%)	71 (38%)	102 (56%)	124 (64%)
Time from Onset to First Dose				
<= 4 hrs	164 (35%)	184 (40%)	260 (55%)	312 (66%)
> 4 hrs	33 (26%)	49 (38%)	78 (62%)	83 (72%)
Migraine History				
Without Aura Only	138 (32%)	160 (38%)	244 (58%)	288 (70%)
With Aura Only	22 (46%)	22 (43%)	24 (49%)	26 (53%)
Both	37 (31%)	51 (43%)	70 (57%)	82 (67%)
Prophylactic Med Used				
No	143 (34%)	168 (41%)	238 (57%)	272 (67%)
Yes	54 (30%)	65 (37%)	100 (56%)	124 (68%)
Tobacco Use				
Current User	33 (40%)	38 (48%)	45 (56%)	53 (65%)
Former User	55 (31%)	63 (35%)	106 (59%)	120 (67%)
Never Used	109 (32%)	132 (40%)	187 (56%)	221 (68%)
Current Migraine Type				
Without Aura	160 (32%)	190 (39%)	295 (59%)	336 (71%)
With Aura	37 (35%)	41 (41%)	43 (44%)	60 (54%)
Contraceptive Method				
IUD	0	1 (25%)	4 (80%)	3 (100%)
Implant/Injectible	3 (50%)	2 (33%)	3 (50%)	5 (83%)
Oral Contraceptive	30 (38%)	32 (42%)	46 (61%)	60 (75%)
Other	58 (33%)	71 (43%)	101 (59%)	119 (68%)

Secondary outcome measures: The sponsor described over 50 analyses on secondary outcome measures. This included analyses at each time point in the study and for each variable. I have reviewed these outcome measures and have summarized a number of them in the following table for the first attack.

Study 3003: Summary of secondary outcome measures for the first attack			
–	Placebo (N=169)	1.0 mg (N=166)	2.5 mg (N=167)
Headache free rate at 4 hours	12%	30%	38%
% of patients with meaningful relief within 4 hours	32%	52%	62%
Mean time to meaningful relief (minutes) without censoring	132	128	119
Mean time to meaningful relief (minutes) with censoring (Patients without relief by 240 minutes are to censored to 240 minutes)			
% of patients with nausea at 240 minutes (p value)	48%	33%	26%*
% of patients with vomiting at 240 minutes	8%	5%	5%
% of patients with photophobia at 240 minutes (p value)	69%	51%*	44%*
% of patients with phonophobia at 240 minutes (p value)	68%	49%*	36%*
% of patients able to resume normal activity at 240 minutes			
% of patients requiring bed rest at 240 minutes			
% of patients using a rescue medication	54%	35%	29%
% of patients using a second dose of study treatment	30%	28%	26%
% of patients using rescue medication and/or a second dose	67%	52%	46%
Time (minutes) to use of rescue medication and/or second dose	343	441	534
Number of patients with recurrence(including rescue or 2nd dose)/ Number of patients with headache relief at 4 hours (%)	27/54 (50%)	31/90 (34%)	30/109 (28%)
Mean time (hours) to recurrence	7.8	10.8	13.6*
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (not including rescue or second dose) (%)	9/22 (41%)	7/28 (25%)	8/28 (29%)

**P value < 0.05 when compared to placebo*

Study 3012:

Protocol:

Design: This was a randomized (equal between groups), double blind, placebo controlled, parallel study evaluating 0, 0.25, 1.0 and 2.5 mg in adolescents. Four hours after the dose the patients were allowed to take rescue treatment. Patients were allowed to take an identical second dose for headache recurrence only.

Sample: Approximately 300 patients were to be enrolled in order to have 50 patients per group for the study to have 80% power to detect a difference in headache relief between 1 and 2.5 mg and placebo.

Selection: Patients enrolled were 12 to 17. Patients were to have between one and 8 headaches with moderate to severe pain per month.

Primary: The primary endpoint was the percentage of patients with headache relief at 240 hours post dose.

Secondary: Headache relief maintenance rates, Headache free rates (severity score 0) at 4 hours post dose, Time to meaningful relief, Migraine symptoms, Clinical disability, Headache relief without recurrence within 24 hour, Use of rescue medication between 4 and 24 hours post first dose, Recurrence of headache between 4 and 24 hours post first dose in patients with headache relief at 4 hours.

Analysis: Not described

Results:

Disposition: 300 patients were randomized, received treatment and had post treatment data. 2 patients had only a mild headache at baseline. The distribution of patients and protocol violations are summarized in the following table:

Study 3012: Disposition and protocol violations				
–	0 mg N=74	0.25 mg N=78	1.0 mg N=78	2.5 mg N=70
Headache mild at baseline	1	1	0	0
Took drugs prior to treatment	0	0	0	1
Took rescue < 4 hours after dose	2	2	1	1
Took second dose < 4 hours after dose	0	0	4	2
No efficacy data 3.5 to 4.5 hours after dose	7	9	6	7

Demographics and baseline characteristics: 89% of patients were white. The mean age was 14.3 with a range of 12 to 17. 51 to 59% were age 12 to 14 and 41 to 49% were age 15 to 17. Approximately 54% of the patients were female. 80% of the patients had common migraines. Patients waited 2 to 2.9 hours prior to treating their headaches. 46 to 58% of patients had severe headaches at baseline. 20% of patients took migraine preventative medications. 48% of the patients had a severe headache at baseline. The demographic between groups are summarized by the sponsor in the following table:

Table 4
Screening Demographics and Migraine History

		NARATRIPTAN (mg/dose)			
	Placebo	0.25	1.0	2.5	Total
Total No. of Patients:	74	78	78	70	300
Age (Years)					
N	74	78	78	70	300
Mean	14.1	14.4	14.3	14.4	14.3
Std.Dev.	1.7	1.7	1.8	1.7	1.7
Median	14.0	14.0	14.0	14.0	14.0
Minimum	12.0	12.0	12.0	12.0	12.0
Maximum	17.0	17.0	17.0	17.0	17.0
Males					
Total	34 (46%)	34 (44%)	40 (51%)	30 (43%)	138 (46%)
< 12 yrs	0	0	0	0	0
12-14 yrs	25 (74%)	19 (56%)	27 (68%)	21 (70%)	92 (67%)
15-17 yrs	9 (26%)	15 (44%)	13 (33%)	9 (30%)	46 (33%)
> 17 yrs	0	0	0	0	0
Females					
Total	40 (54%)	44 (56%)	38 (49%)	40 (57%)	162 (54%)
< 12 yrs	0	0	0	0	0
12-14 yrs	19 (48%)	21 (48%)	17 (45%)	16 (40%)	73 (45%)
15-17 yrs	21 (53%)	23 (52%)	21 (55%)	24 (60%)	89 (55%)
> 17 yrs	0	0	0	0	0
Menarcheal Status					
Sterile	0	0	0	0	0
Pre-menarche	7 (12%)	8 (18%)	5 (13%)	3 (8%)	23 (14%)
Able to Bear Children	33 (82%)	36 (82%)	33 (87%)	37 (92%)	139 (86%)
Contraceptive Method					
IUD	0	0	0	0	0
Implant/Injectible	0	0	0	0	0
Oral Contraceptive	5 (13%)	3 (7%)	3 (9%)	1 (3%)	12 (8%)
Other	33 (87%)	39 (93%)	32 (91%)	37 (97%)	141 (92%)

Primary outcome measure:There was no statistically significant difference in the headache relief rate for any of the dose groups compared with placebo at any time point post dose. I have summarized the results in the following table.

Study 3012: Headache relief rates (*comparison with 2.5 mg p value < 0.05)				
Time post dose	0 mg N=74	0.25 mg N=78	1.0 mg N=78	2.5 mg N=70
30 minutes	15	8	6	10
60 minutes	36*	27	40	21
120 minutes	62	47	55	47
180 minutes	66	58	62	59
240 minutes	65	72	67	64

Subgroup analyses: The sponsor reported that subgroup analyses for headache relief at 240 minutes did not suggest any clear treatment effects from gender, weight, time from onset to treatment, migraine type, use of prophylactic medications, baseline headache severity, or body mass index. A possible age effect was noted with placebo where patients 12-14 years had relief rates of 80% while patients 15-17 years had relief rates of 43%. Due to the low numbers of non white patients, the effects of race were not studied. The results of the subgroup analysis for race, sex and age are summarized in the following table. Other subgroup analyses are summarized by the sponsor in Table 34.

Study 3012: Subgroup analyses (*p value when compared to placebo)				
Parameter	Placebo (N=74)	0.25 mg (N=78	1.0 mg (N=78)	2.5 mg (N=70)
Race-non White (N)	5	14	4	7
Sex-male (N)	34	34	40	30
headache relief at 4 hours	71%	59%	68%	63%
Sex-female	40	44	38	40
headache relief at 4 hours	60%	82%	66%	65%
Age ≤ 14 (N)	44	40	44	37
headache relief at 4 hours	79%	70%	61%	76%
Age > 14 (N)	30	38	34	33
headache relief at 4 hours	43%	74%*	74%*	52%

Table 14
Headache Relief Rates at 240 Minutes Post First Dose by Subgroup Factors

	Placebo	NARATRIPTAN (mg/dose) 0.25	1.0	2.5
Intent-to-Treat Population				
No. of Patients	74	78	78	70
Gender				
Female	24 (60%)	36 (82%)	25 (66%)	26 (65%)
Male	24 (71%)	20 (59%)	27 (82%)	19 (63%)
Ethnic Origin				
Black	3 (75%)	9 (82%)	1 (33%)	0
Hispanic	4 (100%)	3 (100%)	0	1 (100%)
Caucasian	40 (62%)	44 (69%)	51 (69%)	44 (70%)
Other	1 (100%)	0	0	0
Age (Years)				
< 12 yrs	0	0	0	0
12-14 yrs	35 (80%)	28 (70%)	27 (61%)	28 (76%)
15-17 yrs	13 (43%)	22 (74%)	25 (74%)	17 (52%)
> 17 yrs	0	0	0	0
Weight (kg)				
< 50	20 (74%)	13 (59%)	20 (71%)	21 (75%)
>=50	27 (59%)	41 (77%)	32 (64%)	24 (59%)
Time from Onset to First Dose				
<= 4 hrs	42 (67%)	49 (72%)	46 (68%)	39 (63%)
> 4 hrs	6 (55%)	7 (70%)	6 (60%)	6 (75%)
Migraine History				
Without Aura Only	35 (66%)	42 (75%)	47 (68%)	41 (67%)
With Aura Only	4 (44%)	3 (50%)	2 (50%)	1 (50%)
Both	9 (75%)	11 (69%)	3 (100%)	3 (43%)
Prophylactic Med Used				
No	40 (69%)	46 (74%)	43 (67%)	33 (61%)
Yes	8 (50%)	10 (63%)	9 (64%)	12 (75%)
Tobacco Use				
Current User	3 (75%)	3 (60%)	1 (20%)	0
Former User	0	2 (100%)	2 (67%)	0
Never Used	45 (66%)	51 (72%)	49 (70%)	45 (62%)
Baseline Headache Severity				
None	0	0	0	0
Mild	1 (100%)	0	0	0
Moderate	31 (74%)	23 (64%)	24 (62%)	20 (79%)
Severe	16 (52%)	33 (80%)	28 (72%)	15 (47%)
Current Migraine Type				
Without Aura	37 (64%)	44 (72%)	46 (69%)	32 (62%)
With Aura	11 (69%)	12 (71%)	6 (55%)	7 (70%)
Contraceptive Method				
IUD	0	0	0	0
Implant/Injectible	0	0	0	0
Oral Contraceptive	2 (40%)	2 (67%)	3 (100%)	0
Other	21 (64%)	32 (82%)	21 (66%)	24 (65%)
Body Mass Index				
Less than 4	21 (78%)	15 (63%)	22 (73%)	20 (74%)
4 to less than 6	19 (54%)	30 (78%)	21 (60%)	22 (67%)
6 to less than 8	5 (56%)	10 (83%)	6 (67%)	3 (43%)
8 or more	1 (100%)	1 (50%)	3 (75%)	0
Missing	2 (100%)	0	0	0

Secondary outcome measures: The sponsor described over 50 analyses on secondary outcome measures. This included analyses at each time point in the study and for each variable. I have reviewed these outcome measures and have summarized a number of them in the following table.

Study 3012: Summary of secondary outcome measures				
	Placebo (N=74)	0.25 (N=78)	1.0 mg (N=78)	2.5 mg (N=70)
Headache free rate at 4 hours	43%	41%	51%	43%
% of patients with meaningful relief within 4 hours	65%	76%	71%	66%
% patients with headache relief at 4 hours without recurrence or need of rescue or second dose over 24 hours	50%	56%	58%	53%
Mean time to meaningful relief (minutes) with censoring (Patients without relief by 240 minutes are to censored to 240 minutes)	180	173	162	194
% of patients with nausea at 240 minutes	16%	19%	9%	20%
% of patients with vomiting at 240 minutes	0%	1%	3%	0%
% of patients with photophobia at 240 minutes	32%	38%	32%	36%
% of patients with phonophobia at 240 minutes	27%	27%	27%	29%
% of patients able to resume normal activity at 240 minutes	53%	55%	55%	57%
% of patients taking a second dose	9%	12%	8%	9%
% of patients using a rescue medication	22%	23%	14%	23%
Time (minutes) to use of rescue medication	757	617	587	770
% of patients taking a second dose and/or rescue medication	32%	36%	28%	31%
Number of patients with recurrence[1]/ Number of patients with headache relief at 4 hours (%)	11/48 (23%)	16/56 (29%)	12/52 (23%)	8/45 (18%)
Mean time (hours) to recurrence	726	638	543	722
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (%)	5/48 (10%)	6/56 (11%)	5/52 (10%)	3/45 (7%)

[1] Recurrence defined as recurrence of headache, use of second dose and/or use of rescue medication

Non pivotal clinical studies:

The sponsor conducted 7 studies that they did not include as pivotal studies. These studies included: a PK/PD evaluation study (1007), two studies evaluating the subcutaneous formulation (2001 and 2002), an active control trial (3011), an open label safety study (3004), a phase 2 safety study evaluating non recommended doses (study 2003), a phase 2 dose finding study using a non marketed oral formulation (2004) and a failed efficacy study in adolescents (3012). A summary of these studies are included in this review. Additional information will also be contained in the biopharm and safety reviews.

Study 1007: This study was designed as a PK/PD study to investigate the relationship between clinical findings and blood levels. The study was divided into 2 parts. Part 1 was an open label, two period cross over study in 15 adults female patients. The patients took the drug during a migraine and during a non migraine period. Part 2 was a randomized, placebo controlled, single attack, parallel study evaluating 0, 0.25, 1 and 2.5 mg. This study was not described in the efficacy summaries but the data was included in the safety summary. The sponsor reported that headache relief for both the 1 and 2.5 mg was better than placebo at 4 hours while there was no difference between the 0.25 mg dose and placebo. Additional information concerning this study is in the biopharm and safety reviews.

Study 2001 and 2001: These studies evaluated subcutaneous formulation of naratriptan. The results were not presented in the efficacy portion of the NDA but were discussed in the safety review.

Study 3004: This is an open label study assessing the safety of the drug and is discussed in the safety review.

Study 3011: This was a randomized, double blind, 2 period crossover study comparing the safety and efficacy of 100 mg of sumatriptan and 2.5 mg of naratriptan conducted in 39 centers in 5 European countries and Canada. A second, identical dose was allowed to treat headache recurrence. Rescue was allowed after 4 hours. Aside from the standard selection criteria, patients were required to have, on average, an incidence of migraine recurrence of $\geq$ 50% of successfully treated attacks.

Patients were randomized to treat their first migraine with either naratriptan or sumatriptan. Following a 24 hours pain free interval, the patient then received the other treatment. 253 patients treated at least one attack and 225 treated two

attacks. The primary endpoint was the 24 hours overall efficacy defined as a patient having headache relief (moderate to severe pain reduced to mild or no pain) at 4 hours following treatment without significant deterioration or use of rescue between 4 and 24 hours following treatment. Another primary endpoint was the proportion of patients with recurrence defined as significant worsening (defined by the patient) following relief at 4 hours. This analysis was based only on patients who had relief following both treatments.

The results are summarized in the following table provided by the sponsor:

Efficacy results for study 3011 presented by the sponsor

#complete resolution at 4 hours, *p = 0.005, **p<0.001, ns=not significant

	24h Overall Efficacy (%)	Recurrence incidence (%)	Relief at 4h (%)	0-24h use of rescue medication (%)	Use of second dose (%)	Relief of recurrence at 4h (%)
Naratriptan 2.5mg	39 ns	45 *	76 ns 43 #	21	40 **	66 46 #
Sumatriptan 100mg	34	57	84 56 #	16	57	84 57 #

Comments: In this study, the headache relief 4 hours after dosing was lower in the naratriptan group. The difference was associated with a nominal p value of > 0.05. The recurrence rate was higher in the patients treated with sumatriptan. The difference was associated with a nominal p value of < 0.05. The validity of these results are questionable for at least two reasons. One, the enrollment criteria of a history of a high recurrence rate with treatments. In the study, 86% of the patients were previous users of sumatriptan (mostly oral dosing) and 75% were current users. Only 5 patients had previous use of naratriptan in a study. Since the selection criteria included patients with a high recurrence rate, most likely while on sumatriptan, this could easily bias the study against sumatriptan and in favor of naratriptan. Two, there was no placebo arm to compare the efficacy rates.

Study 2003: This was an inpatient, single attack, double blind, placebo controlled, randomized, parallel study evaluating 5 and 10 mg of naratriptan conducted in 6 European countries from 12/21/93 to 10/31/94. Only a single dose was used and patients were able to use rescue treatments 4 hours after treatment. The primary objective of this study was to evaluate the BP changes associated with use of the drug. Efficacy was a secondary outcome measure.

80 patients received treatment. The headache relief rates are summarized in the following table provided by the sponsor. At 1, 2 and 3 hour, the differences between 5 mg and placebo were associated with p values < 0.05. At 4 hours, the differences between either the 5 and 10 mg groups and placebo were associated with a p value < 0.05.

Percentage of patients experiencing headache relief (grade 2/3 to 0/1)

Time post study treatment	Placebo (n=18)	Naratriptan 5mg (n=29)	Naratriptan 10mg (n=33)
60 minutes	6%	38%	31%
120 minutes	28%	71%	47%
240 minutes	33%	89%	72%

Comment: This study was designed as a safety study and while it was well controlled, it did not evaluate the recommended doses. In this study, the tablet used was not the same as the form to be marketed (white tablet). The study did not provide any negative information concerning the efficacy of the naratriptan.

Study 2004: This study was conducted in 1993 and did not use the marketed formulation so it was not included as a pivotal trial.

Protocol:

Design: This was a randomized (equal between groups), double blind, placebo controlled, dose ranging trial evaluating 0, 1.0, 2.5, 5, 7.5 and 10 mg as well as 100 mg of sumatriptan. Patients reported to the clinic following onset of a moderate to severe migraine for treatment. treated the migraine in the clinic. Four hours after the dose the patients were allowed to take rescue treatment.

Sample: Approximately 600 patients were to be enrolled with about 86 evaluable patients per group. With 22 patients per group, the study would have 80% power to detect a difference in headache relief between the 10 mg and placebo. 143 patients per group was needed to detect a difference of 55 and 70% relief rate for the 7.5 and 10 mg group.

Schedule: Efficacy assessments were at 0, 10, 20, 30, 60, 90, 120, 180 and 240 minutes following the dose. A final assessment took place 24 hours

after treatment.

Primary: The primary endpoint was the percentage of patients with headache relief at 60, 120 and 240 hours post dose.

Secondary: Headache relief maintenance rates , Headache free rates ,Time to meaningful relief, Migraine symptoms, Clinical disability, Headache relief without recurrence within 24 hours, Use of rescue medication between 4 and 24 hours post first dose, Recurrence of headache between 4 and 24 hours post first dose in patients with headache relief at 4 hours.

Interim: An interim analysis was to be performed once 420 patients were enrolled to assist in the development of further studies. The stopping rule was 0.001 by the O'Brien-Fleming rule.

Analysis: The primary analysis will be patients with mild or no pain at 60, 120 and 240 minutes.

Results:

Disposition: 643 patients were randomized, received treatment and had post treatment data at 74 centers in 12 countries. 4 patients treated a mild headache. There were a mean of 7 patients randomized at each site with a range of 1 patient randomized at 4 sites to 28 patients at 2 sites. 4 patients withdrew from the study. Three patients for lack of efficacy (one placebo, one 2.5 mg and one 5 mg) and one failed to return (placebo). 4 patients had only a mild headache at baseline. The distribution of patients and protocol violations are summarized in the following table:

Disposition and protocol violations							
	0 mg N=91	1 mg N=85	2.5 mg N=87	5 mg N=93	7.5 mg N=93	10 mg N=96	Sumatriptan N=98
Headache mild at baseline	0	2	1	0	0	0	1
Took drugs prior to treatment	3	0	2	4	3	3	2
Took rescue < 4 hours after dose	13	6	6	9	4	4	3

Demographics and baseline characteristics: The demographic between groups were similar. All but 9 patients were white. The mean age was 39, ranging from 18 to 61. Approximately 88% of the patients were female. 75% of the patients had common migraines. Patients waited 4 to 5 hours prior to treating their headaches. 46 to 58% of patients had severe headaches at baseline. 12.8% of patients took migraine preventative medications.

Efficacy outcome measures:

Primary outcome measure:There was a statistically significant increase in the headache relief rate for the high dose groups, 7.5 and 10 mg starting at 60 minutes. By two hours, all treatments were significantly better than placebo. There was no statistically significant difference between active group using paired analyses. I have summarized the results in the following table.

Headache relief rates (*comparison with placebo p value < 0.05)							
Time post dose	0 mg N=91	1 mg N=85	2.5 mg N=87	5 mg N=93	7.5 mg N=93	10 mg N=96	Sumatriptan N=98
30 minutes	11%	8%	10%	13%	15%	11%	15%
60 minutes	20%	27%	31%	34%	43%*	40%*	36%
120 minutes	31%	59%*	53%*	54%*	68%*	68%*	60%*
180 minutes	38%	62%*	60%*	61%*	76%*	75%*	78%*
240 minutes	37%	64%*	63%*	63%*	80%*	79%*	80%*

Subgroup analyses: The majority of patients were white females between the ages of 30 and 50. The subgroup analyses for race and sex and age were limited to a small number of patients. The sponsor reported that the results were similar for the subgroups including sex, patients with and without an aura, treating headaches before or after 4 hours. The sponsor did not perform analyses based on age. For age, I arbitrarily divided it into three groups. I found that in the younger group, age $\leq$ 30, the placebo group had an unusually high response rate and the 1 mg group did not do as well as the placebo group. The sponsor did not perform other subgroup analyses. The results are summarized in the following table.