CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20763

STATISTICAL REVIEW(S)

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Statistical Review and Evaluation SEP 18 1997

NDA #: 20-763

Applicant: Glaxo Wellcome Inc.

Name of the Drug: Naraptriptan Tablets

Indication: Acute Treatment of Migraine

Documents Reviewed: Volumes 1.1, 1.97, 1.124 to 1.199, and amendments dated 6-3-97, 6-24-97, 7-9-97, 7-29-97, 8-6-97, and 8-7-97

Clinical Reviewer: Randy Levin, M.D. (HFD-120)

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The issues in this review have been discussed with the reviewing medical officer, Dr. Randy Levin, M.D. (HFD-120).

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Various Sections of this review are:

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I. Background/Introduction

Eight (including one Pharmacokinetic/Pharmacodynamic Study)

clinical studies were carried out in which 4,207 adult and adolescent patients treated 15,583 migraine attacks with Naratriptan Tablets in doses ranging from 0.1mg to 10mg. Summary information of these studies is attached as Tables 0.1.1 to 0.1.4[1].

Dose-ranging studies: Three dose-ranging, placebo-controlled studies in adult migraineurs evaluated doses of Naratriptan Tablets between 0.1mg and 10mg: protocols S2WB2004 and S2WB2003 (single attack, single dose, in-clinic studies), and S2WA3001 (single attack, multiple dose, home based study).

Multiple-attack studies: Two phase-III, randomized, double-blind, placebo-controlled, multiple-attack, multiple-dose, outpatient studies were conducted in adult patients with migraine: protocols S2WB3002 (3-attack, parallel design) and S2WA3003 (up to 4 attacks, crossover design).

Oral active-controlled clinical study: Protocol S2WB3011 was a randomized, double-blind, two-attack, multiple-dose, out-patient study of crossover design, in which headache recurrence was evaluated in adult migraineurs with a history of high rates of headache recurrence (recurrence in ≥50% of successfully treated attacks over the 6 months prior to enrollment).

Adolescent study: One phase-III, US, randomized, double-blind, placebo-controlled, parallel-group, single-attack, multiple-dose study (protocol S2WA3012) was conducted in adolescent migraineurs 12 to 17 years of age.

The sponsor did not claim any statistically significant result in the adolescent Study S2WA3012. The placebo and .25mg naratriptan Relief Rates were unusually high in this study (65% and 72%, respectively, compared with 67% and 64%, respectively, for 1.0 and 2.5 mg naratriptan, at 4 hours). The average number of patients per treatment group was 75. This study has not been reviewed (individually) by this reviewer.

II. **Clinical Studies**

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer. The sponsor did not make multiple comparison

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[1] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

adjustments, although many pairwise comparisons were to be looked at.

This reviewer reviewed the protocol for one (S2WA3012 for adolescent patients producing non-significant results) of the 7 studies. This reviewer's comments on multiple comparison adjustments and on some others were not incorporated into the protocol.

Making strict multiple comparison adjustments may be too conservative because in some cases 21 pairwise comparisons (7 treatment groups) were possible. In some cases, the comparisons to be made were mentioned in the protocol.

Also, multiple comparison adjustments are essential only when statistically significant p-values are in-frequent. When majority of the p-values are significant, non-adjustment for multiplicity would not affect the Type I Error appreciably, when we look for consistency of results. Wherever provided, the linear trend test should be useful.

The efficacy variables considered in this review are based on consultation with Dr. Levin (HFD-120). Unless mentioned otherwise, all the results presented in this review are for the Intent-to-Treat patients set (but patients with initial headache severity grade 0 or 1 had to be excluded where needed according to the definitions of efficacy variables).

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

In an answer to the request for analysis of Severity of recurrent headaches, the sponsor answered (Amendment of June 3, 1997), "No assessment was made of the severity of headache recurrence in all studies except S2WB2004." Even in Study S2WB2004, the results are in the format "Shifts in Headache Severity Grade ... Minutes After Treatment Administration," and are not exactly the severity of recurrent headaches. These results are on pages 118 to 169 of Vol.1.165, in a 4x4 contingency table format with pre-treatment severity on one side and severity after ... minutes on the other side.

The sponsor provided, later, some results on Severity of Recurrence (for those patients in studies 2003 and 2004, who recorded a grade for recurrence and only those patients in Study 3002, who took a second dose for recurrence(attached Table 0.3.10)). General conclusion from these may be biased

(missingness and non-randomness).

With respect to the analyses of second dose results, the sponsor stated (June 3, 1997 submission), "We would like to be exempted from performing any formal analyses for the use of the second dose for the following: The use of the second dose to treat a recurrence was not randomized in any of the naratriptan studies. ... In addition, a large number of patients took the second dose as rescue in violation of the protocol."

With respect to imbalances in demographics and covariates, the sponsor stated (June 3, 1997 submission), "Analyses including some of these parameters as covariates have been performed and reported in each study report and the ISE and therefore any possible imbalance is adjusted for." This reviewer's checks on important efficacy results were done without covariate adjustments.

1. **Study S2WA3001 (Efficacy, Dose-Ranging, US)**

Some Design and Enrollment Aspects of this study are in the attached Table 0.1.2.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the Summary Report provided by the sponsor on pages 20 to 24 of the statistical vol. 1.124. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

1A. Objective

The primary objective of this study was to evaluate the efficacy of 0.1mg, 0.25mg, 1.0mg and 2.5mg oral naraptriptan compared to placebo in the treatment of a single migraine attack as measured by headache relief.

Secondary

• To evaluate the efficacy of 0.1mg, 0.25mg, 1.0mg and 2.5mg oral naraptriptan compared to placebo in the treatment of a migraine attack as measured by

- associated symptoms (nausea, vomiting, photophobia and phonophobia)
- clinical disability scores
- time to meaningful relief
- the recurrence of pain in subjects responding to naratriptan and placebo
- the use of rescue medication

• To evaluate the safety of 0.1mg, 0.25mg, 1.0mg and 2.5mg oral naraptriptan compared to placebo in the treatment of one migraine attack measured by the occurrence and severity of adverse events and changes in physical exams, vital signs, electrocardiograms, or clinical laboratories.

• To profile the lower end of the dose response curve for oral naratriptan.

1B. Disposition of Patients

Of the 694 randomized patients, 613 received treatment with study medication. Of those 613 patients, 122 received placebo, and a similar number received each of the test drug doses. Patients were balanced between treatment groups within sites. The total number of patients treated at each site varied between 5 and 32.

Of the 12% patients withdrawing from the study prior to the post-randomization visit, 10% withdrew because of never treating a migraine.

1C. Demography

Patients were generally Caucasian (93%), between 19 and 65 years, with a mean age of 40.2 years (lowest mean of 38.2 years in 1.0mg and the highest mean of 42.6 years in 0.25mg). There were more females (87%) than males (13%). Most patients (71%) suffered from migraine without aura, while 22% had both migraine with and without aura.

1D. Efficacy Results (Sponsor's Analyses)

(Single attack study, a second dose for recurrence)

Primary Efficacy Variable

Headache Relief Rates at 240 Minutes Post First Dose:

Placebo	Naratriptan (mg/dose) 0.1	0.25	1.0	2.5
42/122 (34%)	41/128 (32%)	42/119 (35%)	59/117 (50%)	76/127 (60%)

P-Values:	Pl.Vs 1.0	Pl.Vs 2.5	.1 Vs 1.0	.1 Vs 2.5	.25 Vs 2.5
	.022	<.001	.004	<.001	<.001

Above results are by the sponsor's analyses for a 4-period crossover design. This reviewer's checks by simple analyses support these significant results. The sponsor did not present p-values for other pairwise comparisons (provided later on request, another significant p-value of .025 for 1.0mg vs .25mg comparison. The p-value for 2.5mg vs 1.0mg comparison was .162).

By Linear Trend Test p-values (attached Table 1.3.1) and these results, there is statistical evidence of a dose response. Only the 1.0mg and 2.5mg doses were statistically superior to the placebo. They were statistically superior also to the lower doses.

Secondary Efficacy Variables

Headache Relief Rates at 30, 60, 90, 120, 180, and 240 (given above) minutes are attached as Table 1.3.1. Until at 180 minutes, none of the doses were statistically superior to the placebo. However, by the Linear Trend Test, the efficacy of the active drug as a whole was shown all along starting at 30 minutes.

The percentages of patients requiring rescue medication are in the attached Table 1.4.1. When the patients taking a second dose within 24 hours are included, these percentages (i.e., **of Retreatment**) are 70%, 66%, 67%, 62%, and 47%, respectively, for placebo, .1mg, .25mg, 1.0mg, and 2.5mg of naratriptan. Only the highest dose 2.5mg was statistically significantly superior to placebo; this dose was also statistically superior to the remaining doses in the study (attached Table 0.3.8). The linear trend test also provided significant results.

The estimated percentages of patients using a second dose/rescue (retreatment) for migraines over the 24 hours following the first dose of study treatment are in the attached Figure 1.5.1. In this Figure, 1.0mg dose of naratriptan also is well-separated

from the placebo. –

Attached Table 1.6.1 shows the **Headache Recurrence** Rates, where headache recurrence is defined as headache relief (score 0/1) at 4 hours, used no rescue medication prior to 4 hours, and then had significant worsening of migraine pain (score 2/3) between 4 and 24 hours after dosing. Of the patients with Headache Relief at 4 hours, 38%, 39%, 38%, 39%, and 28% had headache recurrence, respectively, from the placebo, .1mg, .25mg, 1.0mg, and 2.5mg of naratriptan groups. No statistically significant superiority to placebo was achieved by any dose, by the reviewer's analyses by Fisher's exact test (p-values were provided by the sponsor later, which were non-significant).

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

1E. Reviewer's Comments and Conclusions on Study S2WA3001

With respect to the Headache Relief Rate (first dose), there was overall statistical evidence in favor of the efficacy of naratriptan for 1.0mg and 2.5mg doses (although there was no statistical evidence with respect to Headache Recurrence). These doses were statistically superior also to the lower doses.

With respect to Retreatment (Rescue/Second dose) within 24 hours of first dose, only the highest dose 2.5mg was statistically significantly superior to placebo; this dose was also statistically superior to the remaining doses in the study.

The second dose results are not quite interpretable. The sponsor stated (June 3 amendment), "The use of the second dose to treat a recurrence was not randomized in any of the naratriptan studies." Also, due to the smaller number of patients involved, no statistical evidence is expected.

2. Study S2Wa3003 (Efficacy, US, Crossover)

Some Design and Enrollment Aspects of this study are in the attached Table 0.1.3.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the Summary Report provided by the sponsor in the

pages 3 to 7 of the statistical vol. 1.131. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

2A. Objective

The primary objective of this study was to evaluate the efficacy of 0.25mg, 1.0mg and 2.5mg oral naraptriptan compared to placebo in the treatment of four migraine attacks as measured by headache relief.

Secondary

• To evaluate the efficacy of 0.25mg, 1.0mg and 2.5mg oral naraptriptan compared to placebo in the treatment of four migraine attacks as measured by the effect on the following parameters:

- associated symptoms (nausea, vomiting, photophobia and phonophobia)
- clinical disability scores
- time to meaningful relief
- the recurrence of pain in subjects responding to naratriptan and placebo
- the use of rescue medication

• To evaluate the safety of 0.25mg, 1.0mg and 2.5mg oral naraptriptan compared to placebo in the treatment of four migraine attacks measured by the occurrence of adverse events and changes in physical exams, vital signs, electrocardiograms, or clinical laboratories.

• To profile the intra-subject dose response curve for oral naratriptan measured by each subject's response to each study treatment.

2B. Disposition of Patients

Of the 740 randomized patients, 682 patients treated at least one migraine with study medication, and 514 treated all four attacks. Of those 682 patients, 602 treated one attack with placebo, 593 treated one attack with Naratriptan Tablets 0.25mg, 600 treated one attack with 1.0mg, and 590 treated one attack with 2.5mg.

Some other details about patients disposition can be seen in the attached Table 2.2.1.

The total number of patients treated at each site varied between 6 and 28.

2C. Demography

Patients were generally Caucasian (93%), females (90%),between 19 and 65 years, with a mean age of 41.2 years. Most patients (71%) had a history of migraine without aura, while 20% had both migraine with and without aura.

2D. Efficacy Results (Sponsor's Analyses)

(Four-attack, cross-over study, 2nd dose allowed for recurrence)

Primary Efficacy Variable

Headache Relief Rates at 240 Minutes Post First Dose - All Attacks:

	Naratriptan (mg/dose)		
Placebo	0.25	1.0	2.5
33%(197/602)	39%(233/591)	57%(338/595)	68%(396/586)

P-Values:	Pl.Vs 1.0	Pl.Vs 2.5	.25 Vs 1.0	.25 Vs 2.5
	< .001	<.001	<.001	<.001

This reviewer's analyses applying Fisher's exact test, support these significant results (and also showed statistically significant efficacy of .25mg). Each dose is statistically superior to the lower dose(s).

Also, by Linear Trend Test p-values (attached Table 2.3.1), there was statistical evidence of a dose response.

These results are stronger than those of the previous study.

Headache Relief Rates at 240 minutes post first dose, by attack is attached as Figure 2.3.2 (everything else in the report were for all attacks of this crossover study). The results were reasonably consistent across attacks (negligibly better responses, for all treatment groups except .25mg, in the latter

attacks than in the earlier attacks).

Secondary Efficacy Variables

Headache Relief Rates at 30, 60, 90, 120, 180, and 240 (given above) minutes are attached as Table 2.3.1. Starting at 60 minutes, at least, the higher doses were statistically superior to the placebo. There was statistical evidence of dose response too.

The percentages of patients taking post-dose rescue medication are in the attached Table 2.4.1. When the patients taking a second dose within 24 hours are included, these percentages (i.e., of **Retreatment)** are 66%, 63%, 53%, and 45%, respectively, for placebo, .25mg, 1.0mg, and 2.5mg of naratriptan. The higher doses were statistically significantly superior to placebo and the lower dose(s) (attached Table 0.3.8).

The estimated percentages of patients using a second dose/rescue (retreatment) for migraines over the 24 hours following the first dose of study treatment are in the attached Figure 2.5.1. In this Figure, all the treatment groups are somewhat evenly separated from each other, with the placebo doing the worst and 2.5 naratriptan doing the best.

Attached Table 2.6.1 shows the **Headache Recurrence** Rates, where headache recurrence is defined as headache relief (score 0/1) at 4 hours, used no rescue medication prior to 4 hours, and then had significant worsening of migraine pain (score2/3) between 4 and 24 hours after dosing. Of the patients with Headache Relief at 4 hours, 36%, 34%, 33%, and 27% had headache recurrence, respectively, from the placebo, .25mg, 1.0mg, and 2.5mg of naratriptan groups. By the p-values provided by the sponsor later (attached Table 0.3.9), 2.5mg naratriptan was statistically superior to the lower doses but not to the placebo (inspite of the highest recurrence rate 36%; probably, because the number of patients in the placebo group was 197 (smaller) compared with 233 and 338 in the .1 and .25 mg groups).

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

2E. Reviewer's Comments and Conclusions on Study S2WA3003

There was overall strong (for 2.5 and 1.0 mg) statistical evidence with respect to Headache Relief Rate and Retreatment in favor of the efficacy (first dose) of naratriptan. Each dose was statistically superior to the lower dose(s).

The second dose results are not quite interpretable. The sponsor stated (June 3 amendment), "The use of the second dose to treat a recurrence was not randomized in any of the naratriptan studies."

With respect to the Headache Relief Rate, the results were reasonably consistent across attacks (negligibly better responses, for all treatment groups except .25mg, in the latter attacks than in the earlier attacks). This is from the only "by attack" result (attached Figure 2.3.2) provided by the sponsor in this crossover study.

3. **Study S2Wa3002 (Efficacy, Non-US)**

Some Design and Enrollment Aspects of this study are in the attached Table 0.1.2.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the Summary Report provided by the sponsor in the pages 4 to 10 of the statistical vol. 1.148. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

3A. Objective

The primary objective of this study was to determine the proportion of patients with a headache relief at four hours for 0.1mg, 0.25mg, 1.0mg and 2.5mg doses of oral naraptriptan in the acute treatment of migraine headache.

Again, under "Calculation of Patient Numbers," on page 27 of the protocol, the sponsor stated, "The primary objective of this study is to compare improvement responses between 0.25mg and 2.5mg naratriptan 4 hours after treatment administration."

Secondary Objectives

• To determine the overall efficacy of oral naratriptan 0.1mg, 0.25mg, 1.0mg and 2.5mg in the acute treatment of acute migraine headache.

• To determine the safety and tolerability of 0.1mg, 0.25mg, 1.0mg and 2.5mg oral naraptriptan in the acute treatment of migraine headache.

• To determine the incidence and timing of headache recurrence following treatment with oral naratriptan 0.1mg, 0.25mg, 1.0mg and 2.5mg in the acute treatment of migraine headache.

• To determine the efficacy of 0.1mg, 0.25mg, 1.0mg and 2.5mg oral naraptriptan in the treatment of recurrence.

• To determine the consistency of response of oral naratriptan 0.1mg, 0.25mg, 1.0mg and 2.5mg in the acute treatment of migraine headache.

• To compare all primary and secondary endpoints to oral sumatriptan 100mg and placebo.

3B. Disposition of Patients

Of the 1400 randomized patients, 1222 patients treated at least one migraine with study medication. Details about treatment assignments and patient disposition can be seen in the attached Tables 3.2.1 and 3.2.2.

The total number of patients treated at each site varied between 1 and 31.

3C. Demography

Patients were generally Caucasian (99%), females (overall 84% with the lowest 81% in 1.0mg and the highest 90% in placebo), between 18 and 65 years, with a mean age of 40.4 years. Most patients (66% overall, with the lowest 61% in placebo and the highest 72% in 2.5mg naratriptan) had a history of migraine without aura, while 23% (with the lowest 17% in 2.5mg naratriptan and the highest 26% in 100mg sumatriptan) had both migraine with and without aura.

3D. Efficacy Results (Sponsor's Analyses)

(Three-attack study, second dose for recurrence allowed)

Primary Efficacy Variable

Headache Relief Rates at 240 Minutes (4 hours) Post First Dose - First Attack:

	Naratriptan (mg/dose)			
Placebo	0.1	0.25	1.0	2.5
28/104 (27%)	75/207 (36%)	78/214 (36%)	109/208 (52%)	132/199(66%)

P-Values:	Pl.Vs 1.0	Pl.Vs 2.5	Suma.Vs 2.5	.25 Vs 2.5	1.0 vs 2.5
	<.001	<.001	.039	<.001	<.006

The corresponding rate for sumatriptan 100mg was 173/229 (76%) and was statistically significantly better than each of the four naratriptan doses.

The sponsor's Table is attached as Tables 3.3.1 (Rates) and 3.3.2 (p-values).

Headache Relief results at 240 minutes post first dose, for attacks 2 and 3, also showed the efficacy of naratriptan and the superiority of 100mg sumatriptan to all four doses of naratriptan considered.

The two higher doses of naratriptan showed efficacy consistently across all attacks. The 2.5mg dose (of naratriptan) was statistically superior to the 1.0mg dose and the 1.0mg dose was statistically superior to 0.1mg (also to .25mg, in 1st and 3rd attacks, Table 0.3.7 (we are talking about results at 240 minutes here)).

Secondary Efficacy Variables

Headache Relief Rates at 60 and 120 minutes post first dose, first attack, are attached as Tables 3.3.3 to 3.3.6. Sumatriptan 100mg was consistently superior to each of the four naratriptan doses considered. None of the naratriptan doses showed statistically significant efficacy at 1 hour. Only the two higher doses 1mg and 2.5 mg of naratriptan showed statistically significant efficacy at 2 hours. At 2 hours, 2.5mg was statistically superior to 1.0mg.

Second and third attack results are similar with respect to statistical significance, except that for third attack, 2.5mg did not achieve statistical superiority over 1.0mg at 2 hours.

The percentages of patients who had **retreatment (rescue or second dose**, mislabeled as Rescue, as stated in the July 29, 1997 submission) 0-24 hours post first dose (1st attack) were 70%, 68%, 66%, 57%, 42%, and 44%, respectively, for the placebo, .1, .25, 1.0, 2.5 mg naratriptan groups, and the sumatriptan 100mg group. With respect to the need for retreatment, sumatriptan 100mg was statistically significantly better than the three lower doses of naratriptan, the two higher doses of naratriptan were statistically significantly better than the placebo, and 2.5mg naratriptan was statistically significantly better than even the 1.0mg and 0.25mg naratriptan doses. These results are in the attached Tables 3.4.1 and 3.4.2 (p-values).

The corresponding second attack results were about the same with respect to the statistical significance. The third attack results were more favorable for the active drugs; even the two lower doses of naratriptan were statistically significantly better than the placebo (Tables 56 and 83 of NDA Vol.1.148).

The estimated percentages of patients using a second dose/rescue for migraines over the 24 hours following the first dose of study treatment are in the attached Figure 3.5.1. In this Figure, placebo and .1 and .25 mg doses of naratriptan form one extreme group, sumatriptan 100mg and naratriptan 2.5mg form another extereme group, and 1.0mg dose of naratriptan is about the middle of these two groups.

Attached Table 3.6.1 shows the **Headache Recurrence** Rates (Yes or No), where headache recurrence is defined as headache relief (score 0/1) at 4 hours, used no rescue medication prior to 4 hours, and then had significant worsening of migraine pain (score2/3) between 4 and 24 hours after dosing. Of the patients with Headache Relief at 4 hours, 10%, 36%, 39%, 43%, 42%, and 19% had headache recurrence, respectively, from the placebo, 100mg sumtriptan, 0.1mg, 0.25mg, 1.0mg, and 2.5mg of naratriptan groups. The corresponding number of patients who improved at 4 hours but for whom nothing (Yes or No) about recurrence was recorded were 8, 24, 14, 8, 16, and 16. With so many unrecorded observations, these rates are somewhat unreliable. As it is, the headache recurrence was the least among the placebo and then among the 2.5mg patients, who had relief at 4 hours, and statistically significantly different from other groups (Table 0.3.9). Placebo and naratriptan 2.5mg rates were not

statistically significantly different from each other.

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful (apparently so in this study).

The sponsor provided some results on Severity of Recurrence (attached Table 0.3.10) and stated, "Data are available, however, on baseline severity if a patient took a second dose of study medication for recurrence. These are not the same as recurrence headache severity since there could be a large time gap between experiencing and treating a recurrence, and only exist for the subset of patients who took the second dose." There was only one patient in the placebo group (unable to detect any difference statistically). General conclusion from these may be biased (small and non-random samples). As it is, the 1.0mg group was statistically (nominally, i.e., without multiple comparison adjustments) significantly better than the .1mg and .25mg groups.

3E. Reviewer's Comments and Conclusions on Study S2WA3002

There was overall strong statistical evidence in favor of the efficacy of naratriptan 2.5 and 1.0 mg doses, with respect to Headache Relief Rate (and Retreatment Rate). Sumatriptan 100mg was, generally, statistically superior to the naratriptan doses (not to 2.5mg with respect to Retreatment).

With respect to Headache Relief Rate, the 2.5mg dose (of naratriptan) was statistically superior to the 1.0mg dose and the 1.0mg dose was statistically superior to 0.1mg (at 240 minutes, also to .25mg, in 1st and 3rd attacks).

With respect to the Retreatment Rate, 2.5mg naratriptan was statistically significantly better than the 1.0mg and 0.25mg naratriptan doses. The third attack results were more favorable for the active drugs; even the two lower doses of naratriptan were statistically significantly better than the placebo.

The results were reasonably consistent across attacks, except what have been pointed out specifically.

4. **Study S2WB2003** (Dose-Ranging, Non-US)

Some Design and Enrollment Aspects of this study (single attack, single dose) are in the attached Table 0.1.1.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the Summary Report provided by the sponsor in the pages 3 to 7 of the statistical vol. 1.161. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

4A. Objective

The primary objective of this study was to assess blood pressure changes during the four, eight and 24 hour periods following treatment of a migraine attack with oral naratriptan (5 and 10 mg) compared with placebo.

The secondary objectives were to compare the efficacy, safety and tolerability of two doses of oral naratriptan (5 and 10 mg) with placebo in the acute treatment of migraine.

4B. Disposition of Patients

Supplies for 90 patients who were randomized were allocated to the study centers. The intent-to-treat population consisted of the 80 patients who were randomized to one of three treatment groups (Placebo 18, Naratriptan 5mg 29, Naratriptan 10mg 33) and treated a single migraine attack with study medication in the clinic. Safety analysis has been performed for all 80 patients.

4C. Demography

All except 3 patients were Caucasian. The population included five males and 75 females, in the age range 19-55 years (mean age around 32.5). Most patients (80%) suffered from migraine without aura, while 15% had both migraine with and without aura.

4D. Sponsor's Efficacy Results (Secondary Objectives)

(Single attack, single dose study)

The primary objective of this study was to evaluate the effect of oral naratriptan on ambulatory blood pressure.

Efficacy Variables—(All efficacy data in this study were treated as secondary)

Headache Relief Rates at 240 Minutes Post-Treatment:

	Naratriptan (mg/dose)	
Placebo	5mg	10mg
6/18 (33%)	25/28 (89%)	23/33 (72%)
P-Values (vs Placebo)	<.001	.009

This study has shown the efficacy of 5mg and 10mg doses of naratriptan.

Headache Relief Rates at 60, and 120 minutes are attached as Tables 4.3.1 and 4.3.2. Ten mg dose was not statistically superior to the placebo; however, 5mg was.

The numbers of patients requiring rescue medication (i.e. **re-treatment** for this one-dose study) within 24 hours, are in the attached Table 4.5.1. There were only 3 out of 29 patients in the 5mg naratriptan group who needed rescue medication (statistically marginally superior to 10mg). Both doses were statistically superior to the placebo (attached Table 0.3.8).

Of the patients with Headache Relief at 4 hours, 4 out of 6, 9 out of 25, and 6 out of 23 had **headache recurrence**, respectively, from the placebo, 5mg, and 10mg naratriptan groups (Table 40 of the NDA report). The corresponding number of patients who improved at 4 hours but for whom nothing about recurrence was recorded were 0, 3, and 2. With so few patients, these rates are not quite capable of showing statistical evidence. As it is, the headache recurrence was the least among the 10mg patients who had relief at 4 hours.

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

The sponsor provided some results on Severity of Recurrence for those patients who recorded a grade for recurrence (attached Table 0.3.10). General conclusion from these may be biased (problem of sample size and missingness). As it is, the 5mg dose was statistically significantly better than the 10mg dose.

Number of patients whose headache severity grade became 0 whilst in clinic, and the median time to this event are in the attached Table 4.7.1. Here also 5mg was numerically superior to 10mg.

4E. Reviewer's Comments and Conclusions on Study S2WA2003

There was overall statistical evidence in favor of the efficacy of naratriptan 5mg (10mg also at 4 hours post-dose). Inferiority of 10mg to 5mg may not be concluded from this one study with only 80 patients (10mg is statistically significantly superior to 5mg in Study 2004 - reviewed next).

A comment on a statistical issue related to the sponsor's claim on the Blood Pressure Changes: Even in the cases (0-24 hours for naratriptan 5mg (systolic) and 10mg (systolic and diastolic)) where statistically significantly different mean results with the placebo were observed, the sponsor claims that the differences were not clinically significant. In any case, the statistical reviewer would like to remind that, for claiming equivalence, a proper statistical method (not relevant if even the statistically significant differences are not clinically significant) has not been followed.

5. **Study S2WB2004** (Dose-Ranging, Non-US)

Some Design and Enrollment Aspects of this study (single attack, single dose) are in the attached Table 0.1.1.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the Summary Report provided by the sponsor in the pages 3 to 7 of the statistical vol. 1.165. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

5A. Objectives

Primary Objectives

• To compare the efficacy of five doses of oral naratriptan (1mg, 2.5mg, 5mg, 7.5mg and 10.0mg) with placebo in the acute treatment of migraine headache.

• To compare the safety and tolerability of five doses of oral naraptriptan with placebo in the treatment of acute migraine headache.

• To assess patient perception of the study medication compared to their normal migraine medication and/or sumatriptan (previous use)

Secondary Objectives

• To compare the efficacy, safety and tolerability of five doses of oral naratriptan with that of oral sumatriptan 100mg in the acute treatment of migraine headache.

• To evaluate the pharmacokinetics of oral naratriptan in migraine patients.

5B. Disposition of Patients

The safety and the intent-to-treat population were the same in this study which consisted of 643 patients who were randomized to receive study treatment and who treated an attack. The numbers of patients were 91, 98, 85, 87, 93, 93, and 96, respectively, in the placebo, 100mg sumatriptan, 1mg naratriptan, 2.5mg naratriptan, 5mg naratriptan, 7.5mg naratriptan, and 10mg naratriptan groups.

5C. Demography

All (643) except 9 patients were Caucasian. Around 88% patients were females. The mean age of the patients was about 39 years. Seven of the patients entered were in violation of the upper age limit (55 years) set for the study. The oldest patient in the study was 62 years. Most patients (75%) suffered from migraine without aura, while 16% had both migraine with and without aura.

5D. Sponsor's Efficacy Results
(Single attack, single dose study)

Primary Efficacy Variables

Headache Relief Rates at 240 Minutes Post-Treatment:

Placebo	Suma.100mg	Naratriptan 1.0mg	Naratriptan 2.5mg
35/91 (39%)	78/97 (80%)	53/83 (64%)	54/86(63%)

P-Values:	Pl.vs 1.0	Pl.vs 2.5	1.0 vs 2.5	Pl.vs 5	1.0 vs. 5
	.001	.002	.886	.001	.927

	Naratriptan 5mg	Naratriptan 7.5mg	Naratriptan 10mg
	60/93 (65%)	74/93 (80%)	76/96 (80%)

P-values:	Pl.vs. 7.5	5 vs. 7.5	Pl.vs. 10	5 vs. 10	7.5 vs. 10
	.001	.016	.001	.018	.941

The sponsor's Tables are attached as Tables 5.3.4 (Rates), 5.3.5 (confidence intervals), and 0.3.7 (p-values). All the active treatments were statistically significantly better than the placebo treatment. The sumatriptan 100mg was statistically significantly better than the 1.0, 2.5, and 5 mg naratriptan doses.

The Relief Rates at 60 minutes and at 120 minutes were also to be among the primary efficacy variables. These results are attached as Tables 5.3.1 to 5.3.3. Except at 60 minutes for 1.0 and 2.5 mg naratriptan, all the active treatments were statistically significantly better than placebo at 60 and 120 minutes too but sumatriptan was not statistically better than any of the studied naratriptan doses at these time points.

The percentages of patients who had **retreatment (i.e. rescue for this one-dose study)** 0-24 hours post dose were 66%, 26%, 47%, 35%, 39%, 25%, and 22%, respectively, for the placebo, 100mg

sumatriptan, 1.0, 2.5, 5.0, 7.5, and 10.0 mg naratriptan groups. With respect to the need for retreatment, sumatriptan 100mg was statistically significantly better than 1.0mg and marginally better than 5mg of naratriptan. All the active treatments (of naratriptan and sumatriptan) were statistically significantly better than the placebo. These results are in the attached Tables 5.4.1 and 5.4.2 (some also in 0.3.8).

P-values for between naratriptan doses comparisons were not provided by the sponsor. By the reviewer-performed Fisher's exact test 2.5mg was not (some higher doses may be) statistically significantly better than 1.0mg. [P-values provided by the sponsor later does not contradict the former statement. Naratriptan 7.5 and 10 mg doses were statistically significantly better than 1.0mg.]

The estimated percentages of patients needing retreatment for migraines over the 24 hours following the only dose of study treatment are in the attached Figure 5.5.1. In this Figure, placebo is clearly an outlier (inferior) and 1.0mg naratriptan is at the middle of placebo and 10mg naratriptan.

Attached Table 5.6.1 shows the **Headache Recurrence** Rates, where headache recurrence is defined as headache relief (score 0/1) at 4 hours, used no rescue medication prior to 4 hours, and then had significant worsening of migraine pain (score2/3) between 4 and 24 hours after dosing. Of the patients with Headache Relief at 4 hours, 36%, 44%, 31%, 17%, 32%, 30%, and 29% had headache recurrence, respectively, from the placebo, 100mg sumtriptan, 1.0mg, 2.5mg, 5.0mg, 7.5mg, and 10.0mg of naratriptan groups. The corresponding number of patients who improved at 4 hours but for whom nothing about recurrence was recorded were 7, 7, 8, 6, 13, 10, and 7. With so many unrecorded observations, these rates are somewhat unreliable. As it is, the headache recurrence was the least among the 2.5mg naratriptan and highest among the sumatriptan 100mg patients (who had relief at 4 hours).

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

The sponsor provided some results on Severity of Recurrence <u>for those patients who recorded a grade for recurrence</u> (attached Table 0.3.10). General conclusion from these may be biased (missingness may be non-random). As it is, none of the groups (in Table 0.3.10) was statistically significantly different from any other group.

5E. Reviewer's Comments and Conclusions on Study S2WA2004

All the 6 active treatments, 1.0 (not at 60 minutes), 2.5 (not at 60 minutes), 5.0, 7.5, and 10 mg naratriptan, and sumatriptan 100mg showed efficacy with respect to the Relief Rate at 60, 120, and 240 minutes. Sumatriptan 100mg was statistically significantly better than 1.0, 2.5, and 5.0 mg naratriptan only at 240 minutes.

With respect to Retreatment Rate, all the active treatments (of naratriptan and sumatriptan) were statistically significantly better than the placebo. Naratriptan 7.5 and 10 mg doses were statistically significantly better than 1.0mg dose.

Sumatriptan 100mg had the highest recurrence rate (however, data were not recorded for a lot of patients).

Based on an amendment to the protocol, an interim analysis was performed. The sponsor reports to that effect, "... to assist in the selection of a dose or doses for further clinical development. Details of the analysis were restricted to a small group within the Glaxo Wellcome international development team who were not directly involved in the study. The outcome of this analysis did not affect the conduct of this study. ... adjusted accordingly using the O'Brien-Fleming method." These are according to the protocol amendment provided in the NDA (this reviewer did not take an investigation to confirm the prospectiveness of the amendment)..

6. **Study S2WB3011** (Efficacy, Non-US, Crossover, Active Controlled)

Some Design and Enrollment Aspects of this study (two-attack, active controlled crossover, two-dose) are in the attached Table 0.1.4.

Essential features of the study, including details of the Design and study conduct, (Patient) Population, Results, and Conclusions may be seen in the Summary Report provided by the sponsor in the pages 3 to 6 of the statistical vol. 1.183. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

6A. Objectives

Primary Objectives

To determine the 24 hour overall efficacy of oral naratriptan (2.5mg).

To determine the incidence of headache recurrence following treatment with oral naratriptan (2.5mg) in the acute treatment of migraine.

To compare the above with oral sumatriptan (100mg)

Secondary Objectives

To determine the safety and tolerability of oral naratriptan (2.5mg) in the acute treatment of migraine.

To determine the timing of headache recurrence following treatment with oral naratriptan (2.5mg) in the acute treatment of migraine.

To determine the number of doses of oral naratriptan (2.5mg) used in the acute treatment of migraine.

To determine the efficacy of oral naratriptan (2.5mg) in the acute treatment of migraine.

To determine the relative preference for oral naratriptan (2.5mg) in the acute treatment of migraine when compared with oral sumatriptan (100mg).

To compare the above with oral sumatriptan (100mg).

6B. Disposition of Patients

Of the 264 randomized patients, 253 patients (safety population) treated at least one migraine with study medication, and 225 (intent-to-treat population) treated both attacks.

The total number of patients treated at each center varied between 3 and 20 (39 centers in 6 countries).

6C. Demography —

All except 3 patients were Caucasian. The population included 23 males(9%) and 230 females (91%), in the age range 18-65 years (mean age around 44.5). Most patients (65%) suffered from migraine without aura, while 21% had both migraine with and without aura.

6D. Sponsor's Efficacy Results

(Two-attack, crossover study, optional second dose for recurrence)

The sponsor stated, "The results from the two treatment sequence groups have been pooled, since no evidence of a sequence group effect was observed. Efficacy data are presented in tables according to whether the required parameters were evaluable on at least one attack or on both attacks."

Primary Efficacy Variables

Twenty-four hour overall efficacy

These results are presented as Tables 6.3.1 to 6.3.3. Naratriptan 2.5mg (about 40%) was numerically (not statistically significantly) better than sumatriptan 100mg (about 35%). Proper statistical methods have not been employed to conclude equivalence statistically.

No significant sequence effect was observed. For both treatments, 24-hour overall efficacy was higher for the second attack (naratriptan: 47% for attack 2 compared to 33% for attack 1; sumatriptan: 37% for attack 2 compared to 33% for attack 1), leading to a significant period effect (p=0.043). The sponsor concluded, "Since the odds-ratios of response for treatment comparisons are adjusted for these differences, the conclusions remain valid."

Headache recurrence 4-24 hours post-first dose

These results are presented as Tables 6.4.1 to 6.4.4. The p-value .005 (Table 6.4.4) for naratriptan 2.5mg (41%) vs sumatriptan 100mg (57%) is based only on patients who obtained relief on both attacks rather than the intent-to-treat population. However, even in patients who obtained relief in at least one attack, there was less recurrence from the 2.5mg naratriptan group (45%) than from the 100mg sumatriptan group

(57%).

Neither a statistically significant sequence effect nor a statistically significant period effect was found. However, the incidence of recurrence on oral naratriptan 2.5mg reduced from 46% on attack 1 to 36% on attack 2.

Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

Secondary Efficacy Variables

Headache Relief Rates at 240 Minutes Post-First Dose:

Naratriptan 2.5mg	Sumatriptan 100mg
160/207 (77%)	173/207 (84%)

The p-Value for naratriptan 2.5mg vs sumatriptan 100mg was .093, which is not significant. However, the numerical superiority of sumatriptan 100mg to naratriptan 2.5mg was shown (statistical superiority also was shown in studies 3002 and 2004).

No significant sequence effect was observed. For both treatments, Headache Relief Rate at 4 hours was higher for the second attack (naratriptan: 81% for attack 2 compared to 72% for attack 1; sumatriptan: 87% for attack 2 compared to 79% for attack 1), leading to a significant period effect (p=0.016). The sponsor concluded, "Since the odds-ratios of response for treatment comparisons are adjusted for these differences, the conclusions remain valid."

The estimated percentages of patients needing **retreatment** for migraines over the 24 hours following the first dose of study treatment are in the attached Figure 6.5.1. During the period slightly less than 4 hours to 16 hours, relatively fewer (compared with naratriptan 2.5mg) sumatriptan 100mg patients needed retreatment. However, overall, relatively more sumatriptan 100mg patients needed retreatment.

6E. Reviewer's Comments and Conclusions on Study S2WA3011

Naratriptan 2.5mg was numerically better than sumatriptan 100mg

with respect to Twenty-Four Hour Overall Efficacy and need for Retreatment (this relation with respect to Retreatment Rate was opposite in this study and Study 3002 to that in Study 2004) but the opposite was true with respect to Headache Relief Rate at 240 Minutes Post First Dose. With respect to the Headache Recurrence Rate (no treatment group should be declared superior based on this, in isolation of the Headache Relief Rate), naratriptan 2.5mg was better than sumatriptan 100mg.

For the same treatment (whether naratriptan 2.5mg or sumatriptan 100mg), the patients who received it for the second attack showed a better response rate than that of the patients receiving that treatment for the first attack.

Eighteen patients treated an attack when baseline headache severity was 0, 1, or missing. (P.46, Vol. 1.183)

III. Overall Reviewer's Comments

Overall, the submitted studies provided statistical evidence for the efficacy (first dose) of naratriptan, 1.0mg and above, in adults.

Statistical evidence for the efficacy of 0.25mg naratriptan (with respect to **Headache Relief Rate**) was shown only sporadically (nowhere statistically better than 0.1mg dose). Study S2WA3012 among adolescent migraine population did not show the efficacy of any of the naratriptan doses studied: 0.25, 1.0, or 2.5 mg.

A comprehensive Table for all studies, on one page, for Headache Relief Rates at 60, 120, and 240 minutes, with numbers of patients involved and percentages (starred ones are significantly different from placebo, all pairwise-cmparison p-values are provided in Table 0.3.7) is attached as Table 0.3.6.

Ninety-five percent confidence intervals for Odds Ratios relative to placebo for the main studies side-by-side, for each naratriptan dose, are presented in Figures 0.3.3 to 0.3.5. These graphs provide an acceptable picture about the efficacy of naratriptan doses, 1.0mg and above, starting from 120 minutes post-dose, although Study S2WA3012 in adolescents did not provide any statistical evidence about the efficacy of naratriptan. Also, these graphs provide some idea about the probable margins of errors involved in the studies.

The pairwise-comparison p-values for naratriptan doses, including "vs. placebo" p-values, are in Table 0.3.7. At 240 minutes, the trend of the superiority to the next lower dose may be considered stronger for 1.0mg than for 2.5mg (excluding no-evidence adolescent Study 3012) because in Study 2004, the 2.5mg vs 1.0mg p-value was .886 (one more small non-significant p-value is there for each dose).

The estimated probability of achieving initial headache response within 4 hours of treatment, from the four studies S2WA3001, S2WA3003, S2WB2004, and S2WB3002 combined, is attached as Figure 0.3.11. The sponsor stated, "The four studies are the major, placebo-controlled, double-blind, pivotal efficacy studies that were included in the Naratriptan Tablets NDA that included the 1mg and 2.5mg doses ..."

In Figure 0.3.11, the differences between treatment groups became wider over time, although less pronounced for 2.5mg vs 1mg than for 2.5 or 1.0 mg naratriptan vs placebo. The overall Rates of Headache Relief at 240 minutes for different treatment groups are mentioned under "Dose Response" below.

The percentages (also ratios) of patients needing **Retreatment** are in Table 0.3.8a. The placebo rate varied from 52% in Study 3003 to 70% in Studies 3001 and 3002 (32% in the no-evidence adolescent Study 3012). The 1.0mg rate varied from 47% in Study 2004 to 62% in Study 3001 (28% in the no-evidence adolescent Study 3012). The 2.5mg rate varied from 35% in Study 2004 to 55% in Study 3011 (3011 was a special population study with patients susceptible to recurrence, 2.5mg was the only naratriptan dose) (31% in the no-evidence adolescent Study 3012).

From Table 0.3.8, we see that, except for 1.0mg in Study 3001, doses of naratriptan 1.0mg and above were efficacious with respect to Retreatment (no-evidence adolescent Study 3012 is excluded from discussion). Except for 1.0mg in Study 3001 and 2.5mg in Study 2004, both these doses were statistically significantly better than the respective lower doses.

The estimated probability of patients taking a second dose or other medication for migraines over the 24 hours period following the initial dose of the study treatment, from the four studies S2WA3001, S2WA3003, S2WB2004, and S2WB3002 combined, is attached as Figure 0.3.12. The differences between the 1.0mg and the 2.5mg doses for Retreatment Rates over 4-24 hours is more pronounced than for "Probability of Initial Headache Response" discussed above. In Figure 0.3.12, the "Retreatment Rates" were approximately 43.3%, 55.3%, and 68.0%, respectively, for 2.5mg,

1.0mg, and placebo.

The percentages (also ratios) of patients with **Recurrence of Headache** are in Table 0.3.9a (p-values in Table 0.3.9). The placebo rate varied from 10% in Study 3002 to 67% in Study 2003 (19% in the no-evidence adolescent Study 3012). The 1.0mg rate varied from 31% in Study 2004 to 42% in Study 3002 (13% in the no-evidence adolescent Study 3012). The 2.5mg rate varied from 17% in Study 2004 to 28% in Study 3001 (45% in Study 3011 with patients susceptible to recurrence; 2.5mg was the only naratriptan dose in this study) (13% in the no-evidence adolescent Study 3012). Since only those patients who obtained headache relief at four hours could experience a recurrence, comparison of treatment groups based on recurrence (in isolation) may not be meaningful.

The **incidence of secondary symptoms of Migraine, Nausea, and Photophobia/Phonophobia** were statistically significantly less in the 2.5mg and 1.0mg naratriptan groups than in the placebo group. The Photophobia and Phonophobia categories were dealt separately in studies 3001 and 3003 and jointly in studies 3002 and 2004. The 2.5mg group was statistically superior to .25 and .1 mg groups. The 1.0mg group was statistically superior to .1mg group (except with respect to nausea in Study 3002). There were no .25 and .1 mg naratriptan doses in Study 2004.

Above paragraph is based on the p-values provided by the sponsor for studies 3001 and 3003, and the p-values obtained by the reviewer by employing Fisher's exact test to the frequencies provided by the sponsor for studies 3002 and 2004. These secondary symptoms are not considered in the remaining discussions.

Sumatriptan 100mg was more efficacious than naratriptan 2.5mg and lower doses with respect to Headache Relief Rate at 4 hours, in all studies containing sumatriptan 100mg: 3002, 2004, and 3011 (also, than 5mg naratriptan in the only study (2004) containing both this dose and sumatriptan 100mg). With respect to Headache Recurrence Rate 4-24 Hours Post First Dose (Relief Rate at 4 hours, should be considered along with this, since relief is needed before recurrence), Naratriptan 2.5mg was better than sumatriptan 100mg (in all these studies; placebo was even better than 2.5mg naratriptan in study 3002). Naratriptan 2.5mg was better than sumatriptan 100mg, at least numerically, with respect to Twenty-Four Hour Overall Efficacy (studies 2004 and 3011). With respect to Retreatment Rate within 24 hours of initial treatment, sumatriptan 100mg was, numerically, much better than 2.5mg in Study 2004 but marginally worse than 2.5mg naratriptan

in studies 3002 and 3011.

Following discussions are with respect the Headache Relief Rate unless mentioned otherwise.

Dose Response

The sponsor performed dose response tests in studies 2004, 3001, 3003, and 3002 (amendment of June 3, 1997, Section 5), all of which were highly significant. Because of the presence of inefficacious doses and efficacious doses, statistical significance only should not be taken as the proof of clear-cut (or unqualified) dose-response.

The sponsor stated, "As depicted in the Figure ..., patients receiving Naratriptan Tablets 10mg and 7.5mg had the highest combined rates of headache relief at 240 minutes post-dose (78% and 80%, respectively), followed by 70% for 5mg, 66% for 2.5mg, and 56% for 1mg. The two lowest doses (0.1mg and 0.25mg) were not different from placebo. ... Data from clinical pharmacology and/or phase-II clinical studies indicated that the 5mg dose of Naratriptan Tablets had comparable efficacy to 2.5mg, and that doses above 5mg were associated with increased rates of adverse effects, resulting in unsatisfactory risk:benefit profiles for 7.5mg and 10mg."

Consistency of Response Across Attacks

The sponsor stated, "Table 27 of the ISE provides percentages of patients with 0/3, 1/3, 2/3 and 3/3 headache relief for those treating three attacks (S2WB3002). ... In the remaining studies, patients did not receive the same dose more than once per attack (initial treatment) and therefore an analysis of consistency across attacks was not applicable."

For consistency across attacks (within each patient), this reviewer would expect very few patients to have 1 or 2 out of 3 attacks relieved. Instead, the percentage of patients under these two categories varied from 16% to 38% (both these limits belonged to 2.5mg, attached Table 3.3.7).

This does not imply that the drug was less effective in second and third attacks. There were patients who did not have successful relief in the first attack but had successful relief in another attack. For example (attached Table 3.3.8), in the 2.5mg naratriptan group, for the patients who treated 3 attacks,

11.72% patients did not have successful relief in the first attack but had successful relief in both other attacks.

The Relief Rates at 4 hours were similar across the 3 attacks.

(In Study 3011 (2 period crossover between naratriptan 2.5mg and sumatriptan 100mg), for the same treatment (whether naratriptan 2.5mg or sumatriptan 100mg), the patients who received it for the second attack showed a better response rate than that of the patients receiving that treatment for the first attack.)

Subgroup Analyses

The sponsor stated, "Data from four studies, protocols S2WB2004, S2WA3001, S2WB3002 (first attack data only) and S2WA3003 (first attack data only), were combined to generate the proportion of patients with headache relief at 240 minutes post first dose. The interaction of these variables with Naratriptan Tablets 2.5mg, 1mg or placebo on headache relief was investigated using the Breslow-Day statistics."

The variables referred to are: Gender, Ethnic Origin, Age, Weight, Time From Onset to First Dose, Migraine Prophylactic Use, Smoking/Tobacco Use, Current Migraine Type, and Oral Contraceptive Use.

These subgroup-rates and the p-values for interaction of these factors and treatments are in the attached Tables 0.4.1 and 0.4.2. Out of the 27 interaction p-values, there were only 4 p-values significant at .1 nominal level (not by multiple comparison adjustments): 2 for placebo vs 1.0mg, and one each for placebo vs 2.5 and 1.0mg vs 2.5mg comparisons. These interactions are noted and discussed below for archival purposes but should not be taken too seriously.

There was a significant (p-value= .038) treatment (1.0 mg naratriptan vs placebo) by Time From Onset to First Dose interaction. The 1.0mg treatment was more efficacious in the >4 hours group than in the ≤4 hours group. This could be a happenstance because there is no statistically significant interaction in the placebo vs 2.5mg treatment comparison, although there may be some truth in the differences in the placebo Relief Rates (35% for ≤4 hours and 28% for >4 hours).

The significant (p-value=.059) age by treatment (1.0mg vs placebo) interaction arose primarily due to the high placebo response (39%) and low drug response in the 18-30 years age

group, and low placebo response (25%) in the 51-65 years group.

With respect to Smoking/Tobacco, the placebo response is low (22%) in the former user group and high (52%) in the current user group. The interaction occurred when 2.5mg naratriptan was involved but not for 1.0mg because the 1.0mg followed a response pattern similar to the placebo group.

The 1.0mg response rate was low (51%) among lighter (<75kg) and high (62%) among heavier (≥75) patients, which is opposite to the placebo or the 2.5mg response pattern.

Baseline Headache Severity

A combined analysis of headache relief at 4-hours (first attack) by baseline headache score (frequencies and homogeneity of differences) in all placebo-controlled parallel group efficacy studies in adult patients has been provided in June 24, 1997 amendment (attached Table 0.4.3). For naratriptan 1.0mg, the Relief Rate was about the same whether the baseline severity of headache was moderate or severe. However, for 2.5mg naratriptan and placebo the relief rates were much higher for patients with baseline severity of headache "moderate". This led to treatment by baseline severity of headache interactions for the comparisons containing 1.0mg naratriptan (interaction p-values of .026 and .011).

Consistency Across Sites

The sponsor provided Breslow-Day Test (p-values) for homogeneity of headache relief 240 minutes after treatment among centers for placebo, 1mg, and 2.5mg naratriptan (Table 5 of June 24 amendment).

In Study S2WA3012, which did not provide any statistical evidence for efficacy, a statistically significant center by treatment interaction occurred for the 2.5mg naratriptan vs placebo comparison. There being 44 centers, 95% confidence intervals or descriptive statistics by center were not provided.

In the fourth attack of Study S2WA3003, there was some center by treatment interaction, in comparisons involving 2.5mg naratriptan, mostly caused by S_Cen region (one of the ten groupings by investigator, state, or region). Since this is a crossover study, the overall results should not be affected by this 4th attack results.

Second Dose Results

The second dose results are not quite interpretable. The sponsor stated (June 3 amendment), "The use of the second dose to treat a recurrence was not randomized in any of the naratriptan studies." In addition, a second dose was used for rescue in vioation of the protocol. Also, due to the smaller number of patients involved, no statistical evidence is expected.

IV. Overall Conclusion

Overall, the submitted studies provided statistical evidence for the efficacy (especially, with respect to Rates of Relief and Retreatment) of naratriptan, 1.0mg and above, in adults.

Sumatriptan 100mg was better than 2.5mg and lower naratriptan doses (and also better than 5.0mg naratriptan, in the only study containing both these treatments), with respect to the Headache Relief Rate. However, the opposite was true with respect to Headache Recurrence (not to be considered in isolation of the Headache Relief Rate) and, only numerically, 24-hour Overall Efficacy, where done.

Japo Choudhury 9-16-97

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot 9/16/97

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This review consists of 33 pages of text and 66 pages of Tables, Figures, etc.

Table 2 0.1.1
Description of All Controlled Efficacy Studies

Study Type	Study Design/ Protocol Number	Study Title	Treatments	No. of Treated Patients	No. of Pts. in Intent-to-Treat (ITT) Population[1]	No. (%) of ITT Population Evaluated for Assessment of Headache Relief[1]	Full Report (Data Listing) Vol./page
Placebo-Controlled Studies in Adult Patients							
Dose-Ranging Non-US	Parallel, Single Attack, Single-Dose, Clinic Based/ S2WB2003	A Double-Blind, Placebo-Controlled, Randomized, Parallel Group Study to Evaluate the Safety and Efficacy of Oral Naratriptan (5mg and 10mg) Following Dosing during a Migraine Attack	Placebo Naratriptan 5.0mg Naratriptan 10.0mg	18 29 33 n=80	18 29 33	18 (100%) 28 (97%) 33 (100%)	161/1 (163/1)
Dose-Ranging Non-US	Parallel, Single-Attack, Single-Dose, Clinic Based/ S2WB2004	A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study to Compare the Efficacy and Safety of Oral Naratriptan with that of Oral Sumatriptan and Placebo in the Acute Treatment of Migraine Headache	Placebo Naratriptan 1.0mg Naratriptan 2.5mg Naratriptan 5.0mg Naratriptan 7.5mg Naratriptan 10.0mg Sumatriptan 100mg	91 85 87 93 93 96 98 n=643	91 85 87 93 93 96 98	91 (100%) 83 (98%) 86 (99%) 93 (100%) 93 (100%) 96 (100%) 97 (99%)	165/1 (169/1)

[1] All randomized patients known to have taken study medication with follow-up efficacy data in all studies. In addition, for all non-US studies, the intent-to-treat population evaluated for assessment of headache relief included only those patients who presented with a moderate or severe headache at baseline.

[2] First attack data only.

Table 2 ~~continued~~ 0.1.2.
Description of All Controlled Efficacy Studies

Study Type	Study Design/ Protocol Number	Study Title	Treatments	No. of Treated Patients	No. of Pts. in Intent-to-Treat (ITT) Population[1]	No. (%) of ITT Population Evaluated for Assessment of Headache Relief[1]	Full Report (Data Listing) Vol./page
Placebo-Controlled Studies in Adult Patients (cont'd)							
Efficacy Dose-Ranging US	Parallel, Single Attack, Multiple-Dose, Home Based/ S2WA3001	A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Four Doses of Oral Naratriptan in the Acute Treatment of a Single Migraine Attack	Placebo Naratriptan 0.1mg Naratriptan 0.25mg Naratriptan 1.0mg Naratriptan 2.5mg	122 128 119 117 127 n=613	122 128 119 117 127	122 (100%) 128 (100%) 119 (100%) 117 (100%) 127 (100%)	124/18 (126/1)
Efficacy Non-US	Parallel, Multiple Attack, Multiple-Dose, Home Based/ S2WB3002[2]	A Randomized, Double-Blind, Placebo-Controlled, Oral Sumatriptan-Controlled (100mg), Three Attack, Parallel Group Study to Determine the Efficacy, Safety and Tolerability of Oral Naratriptan (0.1mg, 0.25mg, 1.0mg and 2.5mg) in the Acute Treatment of Migraine Headache	Placebo Naratriptan 0.1mg Naratriptan 0.25mg Naratriptan 1.0mg Naratriptan 2.5mg Sumatriptan 100mg	108 221 224 219 209 241 n=1,222	107 220 224 219 209 240	104 (97%) 207 (94%) 214 (96%) 208 (95%) 199 (95%) 229 (95%)	148/1 (153/1)

[1] All randomized patients known to have taken study medication with follow-up efficacy data in all studies. In addition, for all non-US studies, the intent-to-treat population evaluated for assessment of headache relief included only those patients who presented with a moderate or severe headache at baseline.

[2] First attack data only.

Table 2 ~~continued~~ 0.1.3
Description of All Controlled Efficacy Studies

Study Type	Study Design/ Protocol Number	Study Title	Treatments	No. of Treated Patients	No. of Pts. in Intent-to-Treat (ITT) Population[1]	No. (%) of ITT Population Evaluated for Assessment of Headache Relief[1]	Full Report (Data Listing) Vol./page
Placebo-Controlled Studies in Adult Patients (cont'd)							
Efficacy US	Crossover, Multiple Attack, Multiple-Dose, Home Based/ S2WA3003	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Safety and Efficacy of Oral Naratriptan in the Acute Treatment of Four Migraine Attacks	Placebo Naratriptan 0.25mg Naratriptan 1.0mg Naratriptan 2.5mg	606 593 600 590 n=682	602 591 595 586	602 (100%) 591 (100%) 595 (100%) 586 (100%)	131/1 (133/1)

[1] All randomized patients known to have taken study medication with follow-up efficacy data in all studies. In addition, for all non-US studies, the intent-to-treat population evaluated for assessment of headache relief included only those patients who presented with a moderate or severe headache at baseline.

[2] First attack data only.

Table 2 ~~continued~~ 0.1.4
Description of All Controlled Efficacy Studies

Study Type	Study Design/ Protocol Number	Study Title	Treatments	No. of Treated Patients	No. of Pts. in Intent-to-Treat (ITT) Population[1]	No. (%) of ITT Population Evaluated for Assessment of Headache Relief[1]	Full Report (Data Listing) Vol./page
Placebo-Controlled Study in Adolescent Patients							
Efficacy US	**Parallel, Single Attack, Multiple-Dose, Home Based/ S2WA3012**	A Randomized, Double-Blind, Placebo-Controlled, Parallel Study to Evaluate the Efficacy, Safety and Tolerability of Oral Naratriptan in an Adolescent Migraine Population	Placebo Naratriptan 0.25mg Naratriptan 1.0mg Naratriptan 2.5mg	74 78 78 70 n=300	74 78 78 70	74 (100%) 78 (100%) 78 (100%) 70 (100%)	144/1 (145/1)
Active-Controlled Studies in Adult Patients							
Efficacy Non-US	**Crossover, Multiple Attack, Multiple-Dose, Home Based/ S2WB3011**	A Randomized, Double-Blind, Two Attack, Crossover Study to Compare the Efficacy, Safety and Tolerability of Oral Naratriptan (2.5mg) with Oral Sumatriptan (100mg) in the Acute Treatment of Migraine in Patients Susceptible to Headache Recurrence	Naratriptan 2.5mg Sumatriptan 100mg	239 239 n=253	225 225	215 (96%) 216 (96%)	183/1 (185/1)

[1] All randomized patients known to have taken study medication with follow-up efficacy data in all studies. In addition, for all non-US studies, the intent-to-treat population evaluated for assessment of headache relief included only those patients who presented with a moderate or severe headache at baseline.

[2] First attack data only.

Figure 0.3.3

Figure 3: Odds Ratios and corresponding 95% CI for naratriptan 1.0mg relative to placebo

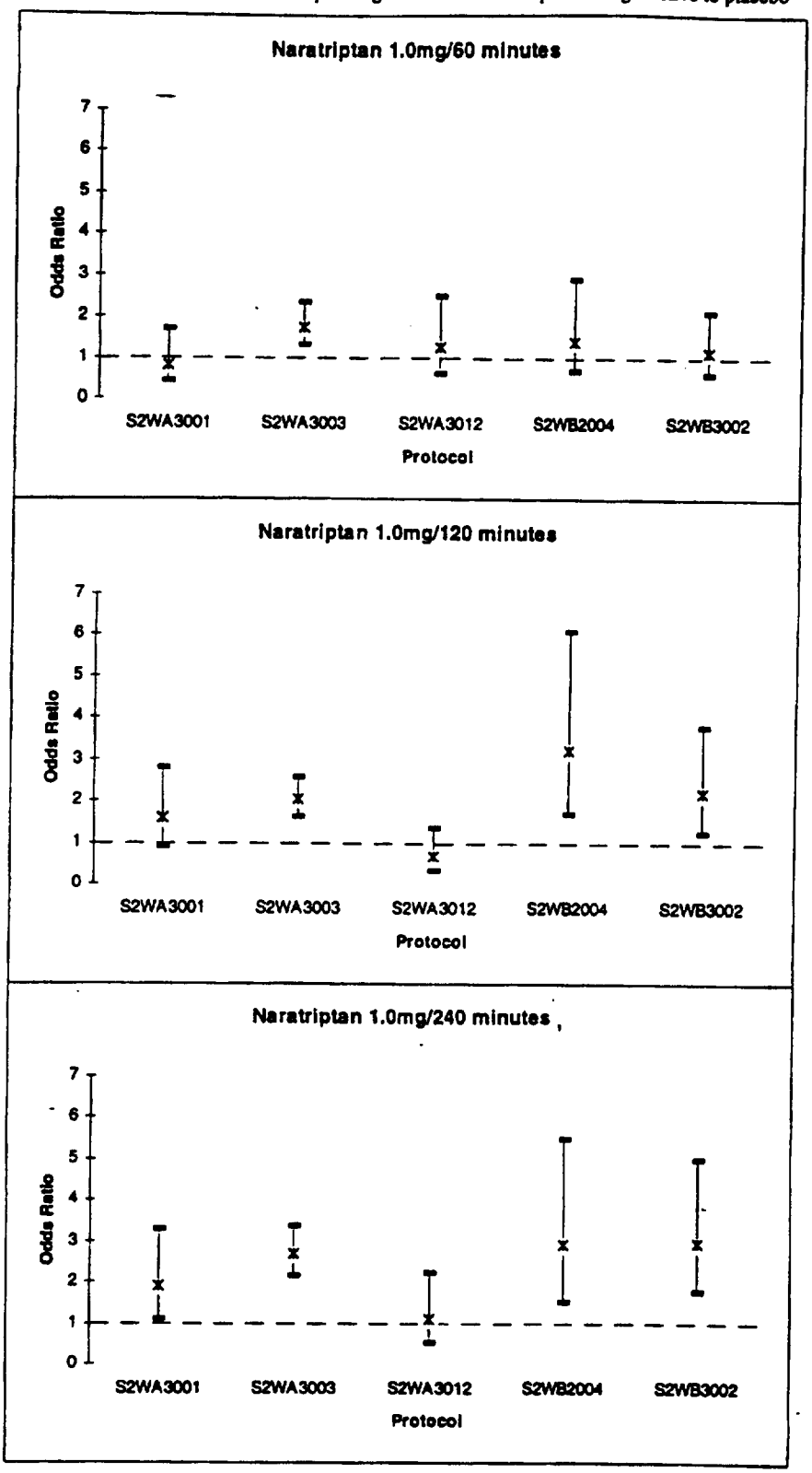

Figure 0.3.4

Figure 4: Odds Ratios and corresponding 95% CI for naratriptan 2.5mg relative to placebo

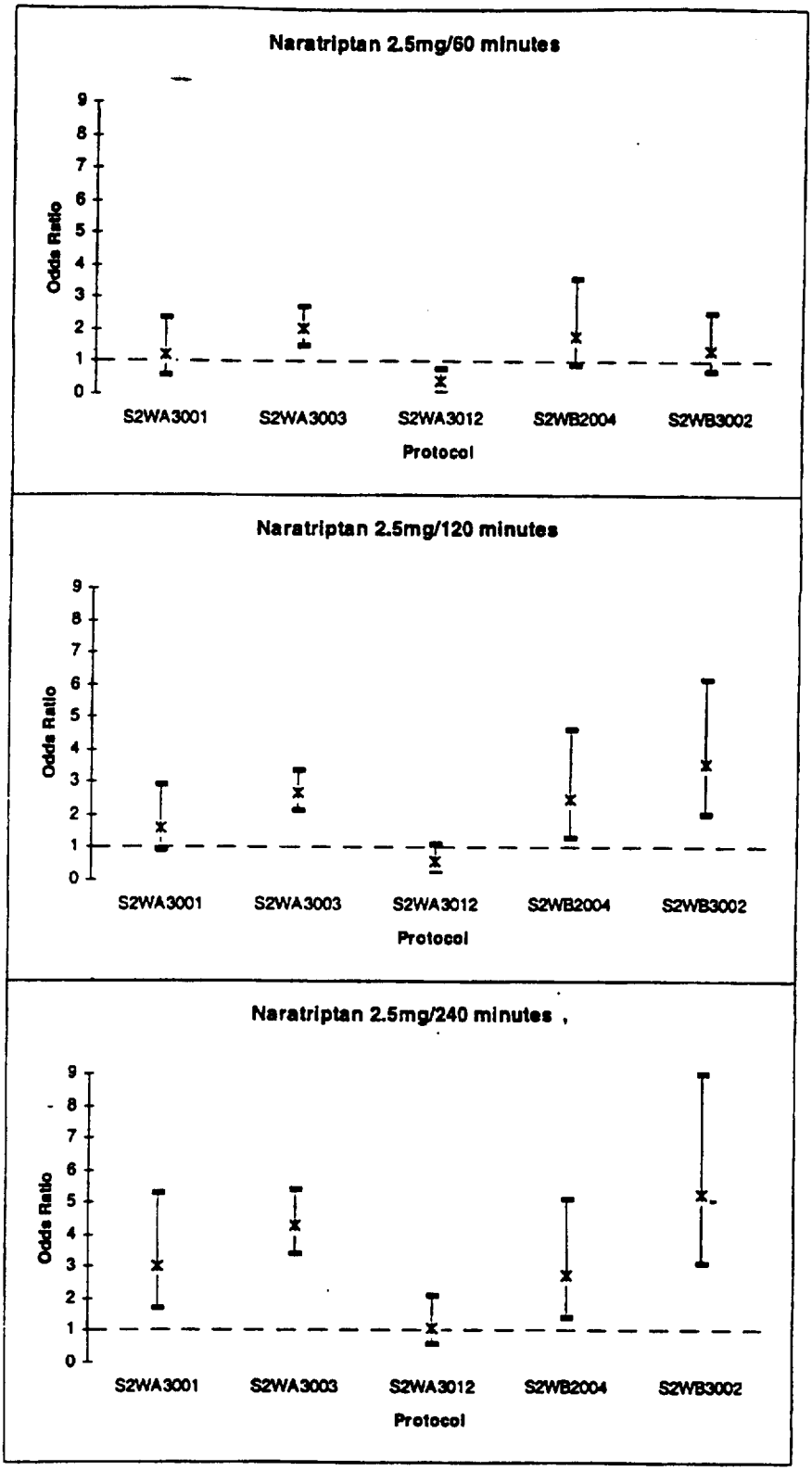

Figure C.3.5

Figure 5: Odds Ratios and corresponding 95% CI for naratriptan 5.0mg relative to placebo

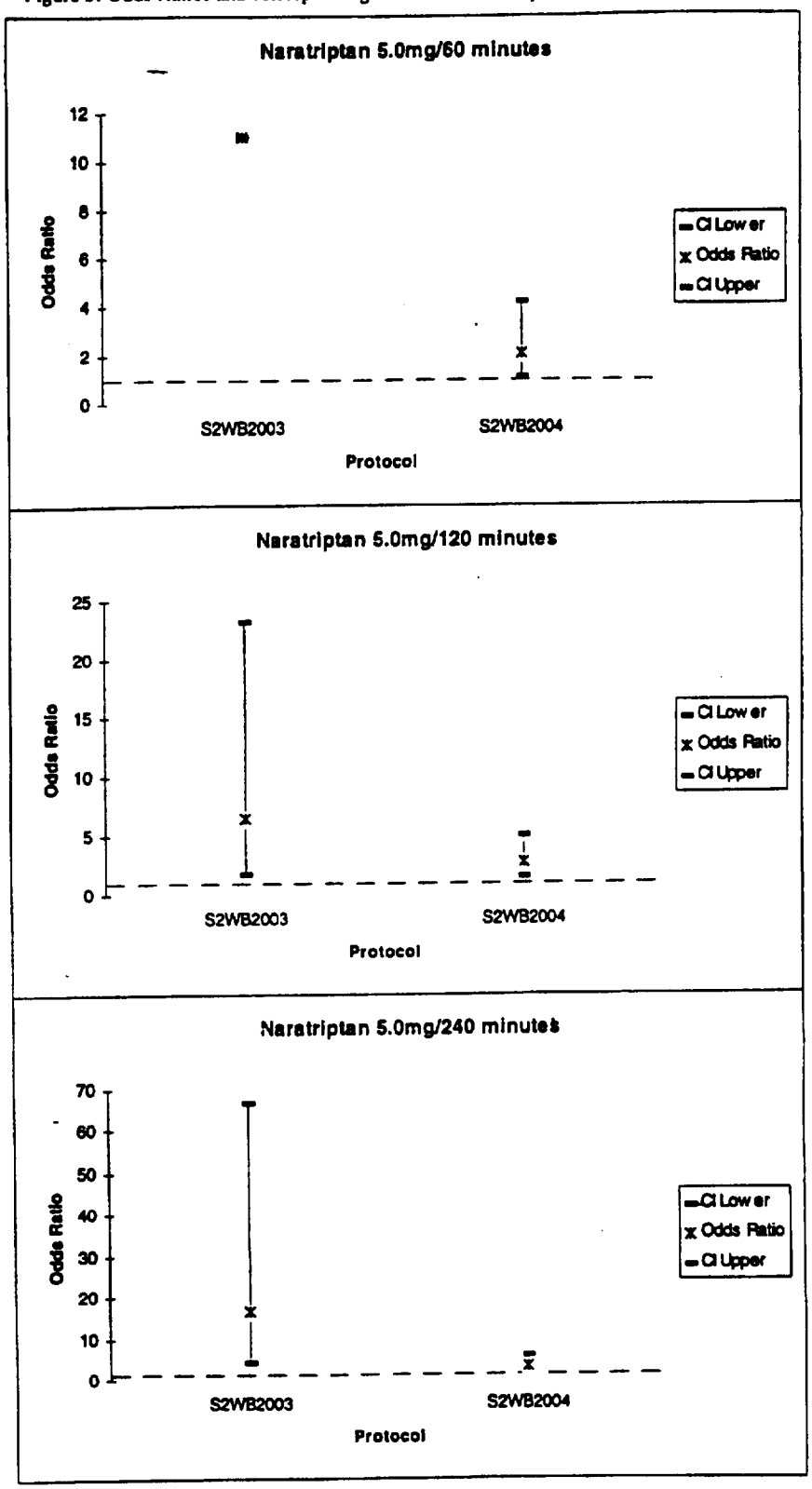

Table 0.3.6

~~Table 2.~~ **Headache relief 60,120 and 240 minutes post first dose**

	Minutes post first dose	Placebo		Naratriptan (mg/dose)													
				0.1		0.25		1.0		2.5		5.0		7.5		10	
Single attack studies																	
S2WB2003	60	1/18	(6%)									11/28*	(39%)			10/32	(31%)
	120	5/18	(28%)									20/28*	(71%)			15/32	(47%)
	240	6/18	(33%)									25/28*	(89%)			23/32*	(72%)
S2WB2004	60	18/91	(20%)					21/83	(25%)	26/86	(30%)	32/93*	(34%)	40/93*	(43%)	38/96*	(40%)
	120	28/91	(31%)					48/83*	(58%)	45/86*	(52%)	50/93*	(54%)	63/93*	(68%)	66/96*	(69%)
	240	35/91	(39%)					53/83*	(64%)	54/86*	(63%)	60/93*	(65%)	74/93*	(80%)	76/96*	(80%)
S2WA3001	60	19/122	(16%)	13/128	(10%)	10/119	(8%)	17/117	(15%)	25/127	(20%)						
	120	37/122	(30%)	32/128	(25%)	24/119	(20%)	49/117	(42%)	51/127	(40%)						
	240	42/122	(34%)	41/128	(32%)	42/119	(35%)	59/117*	(50%)	76/127*	(60%)						
Multiple attack studies																	
S2WB3002																	
Attack 1	60	18/104	(17%)	30/207	(14%)	33/214	(15%)	38/208	(18%)	44/199	(22%)						
	120	23/104	(22%)	62/207	(30%)	62/214	(29%)	79/208*	(38%)	100/199*	(50%)						
	240	28/104	(27%)	75/207	(36%)	78/214	(36%)	109/208*	(52%)	132/199*	(66%)						
Attack 2	60	7/91	(8%)	20/167	(12%)	26/178	(15%)	31/186*	(17%)	31/177*	(18%)						
	120	16/91	(18%)	41/167	(25%)	57/178*	(32%)	58/186*	(31%)	78/177*	(44%)						
	240	20/91	(22%)	59/177*	(35%)	76/178*	(43%)	94/186*	(51%)	120/177*	(68%)						
Attack 3	60	9/73	(12%)	18/154	(12%)	22/159	(14%)	21/156	(13%)	29/159	(18%)						
	120	20/73	(27%)	39/154	(25%)	53/159	(33%)	53/156	(34%)	68/159*	(43%)						
	240	24/73	(33%)	55/154	(36%)	64/159	(40%)	84/156*	(54%)	105/159*	(66%)						
S2WA3003	60	76/602	(13%)			101/591*	(17%)	120/595*	(20%)	133/586*	(23%)						
	120	160/602	(27%)			175/591	(30%)	253/595*	(43%)	289/586*	(49%)						
	240	197/602	(33%)			233/591*	(39%)	338/595*	(57%)	396/586*	(68%)						
Active comparator studies																	
S2WB3011	60																
	120																
	240																
Adolescent studies																	
S2WA3012	60	27/74	(36%)			21/78	(27%)	31/78	(40%)	15/70*	(21%)						
	120	46/74	(62%)			37/78	(47%)	43/78	(55%)	33/70	(47%)						
	240	48/74	(65%)			56/78	(72%)	52/78	(67%)	45/70	(64%)						

*: Significant at the 5% level of significance versus Placebo

Table 0.3.7

All pairwise comparisons for headache relief 60, 120 and 240 minutes post first dose

	Minutes post first dose		Placebo	Naratriptan (mg/dose)						
				0.1	0.25	1.0	2.5	5.0	7.5	10
S2WB2003	60	5mg	0.015							0.519
		10mg	0.072							
	120	5mg	0.004							0.056
		10mg	0.190							
	240	5mg	<0.001							0.095
		10mg	0.009							
S2WB2004	60	1mg	0.384				0.476	0.190	0.014	0.043
		2.5mg	0.109					0.552	0.077	0.188
		5mg	0.026						0.230	0.463
		7.5mg	0.001							0.633
		10mg	0.003							
	120	1mg	<0.001				0.473	0.589	0.175	0.131
		2.5mg	0.004					0.848	0.038	0.024
		5mg	0.002						0.052	0.035
		7.5mg	<0.001							0.882
		10mg	<0.001							
	240	1mg	0.001				0.886	0.927	0.014	0.016
		2.5mg	0.002					0.811	0.009	0.010
		5mg	0.001						0.016	0.018
		7.5mg	<0.001							0.941
		10mg	<0.001							
S2WB3002										
Attack 1	60	0.1mg	0.541		0.773	0.277	0.055			
		0.25mg	0.882			0.391	0.073			
		1.0mg	0.878				0.523			
		2.5mg	0.335							
	120	0.1mg	0.130		0.698	0.102	<0.001			
		0.25mg	0.157			0.036	<0.001			
		1.0mg	0.004				0.020			
		2.5mg	<0.001							
	240	0.1mg	0.083		0.871	0.002	<0.001			
		0.25mg	0.078			<0.001	<0.001			
		1.0mg	<0.001				0.005			
		2.5mg	<0.001							
Attack 2	60	0.1mg	0.287		0.456	0.132	0.189			
		0.25mg	0.101			0.536	0.478			
		1.0mg	0.032				0.869			
		2.5mg	0.020							
	120	0.1mg	0.166		0.114	0.132	<0.001			
		0.25mg	0.008			0.865	0.018			
		1.0mg	0.016				0.017			
		2.5mg	<0.001							
	240	0.1mg	0.014		0.159	0.006	<0.001			
		0.25mg	<0.001			0.134	<0.001			
		1.0mg	<0.001				0.001			
		2.5mg	<0.001							
Attack 3	60	0.1mg	0.934		0.646	0.884	0.109			
		0.25mg	0.682			0.684	0.253			
		1.0mg	0.773				0.173			
		2.5mg	0.203							
	120	0.1mg	0.993		0.125	0.138	0.003			
		0.25mg	0.278			0.833	0.131			
		1.0mg	0.361				0.198			
		2.5mg	0.028							
	240	0.1mg	0.449		0.550	0.007	<0.001			
		0.25mg	0.137			0.032	<0.001			
		1.0mg	0.003				0.035			
		2.5mg	<0.001							

Table 0.3.7 (contd.) NOT POOLED

Table 3. All pairwise comparisons from headache relief 60, 120 and 240 minutes post first dose (continued)

	Minutes post first dose		Placebo	Naratriptan (mg/dose)						
				0.1	0.25	1.0	2.5	5.0	7.5	10
S2WA3001	60	0.1mg	0.208	-	0.699	0.219	0.058			
		0.25mg	0.087	-	-	0.221	0.015			
		1.0mg	0.570			-	0.221			
		2.5mg	0.575				-			
	120	0.1mg	0.342	-	0.435	0.001	0.013			
		0.25mg	0.104		-	<0.001	0.002			
		1.0mg	0.108			-	0.687			
		2.5mg	0.112				-			
	240	0.1mg	0.774	-	0.531	0.004	<0.001			
		0.25mg	0.702		-	0.025	<0.001			
		1.0mg	0.022			-	0.162			
		2.5mg	<0.001				-			
S2WA3003	60	0.25mg	0.012			0.146	0.012			
		1.0mg	<0.001			-	0.249			
		2.5mg	<0.001				-			
	120	0.25mg	0.205			<0.001	<0.001			
		1.0mg	<0.001			-	0.009			
		2.5mg	<0.001				-			
	240	0.25mg	0.008			<0.001	<0.001			
		1.0mg	<0.001			-	<0.001			
		2.5mg	<0.001				-			
S2WA3012	60	0.25mg	0.298		-	0.078	0.642			
		1.0mg	0.531			-	0.010			
		2.5mg	0.013				-			
	120	0.25mg	0.102		-	0.247	0.401			
		1.0mg	0.270			-	0.782			
		2.5mg	0.112				-			
	240	0.25mg	0.211		-	0.701	0.338			
		1.0mg	0.812			-	0.623			
		2.5mg	0.794				-			

Table 0.3.8

~~TABLE 6~~. P-values for all pairwise comparisons from retreatment (0-24 hours after treatment)

		Placebo	Naratriptan (mg/dose)						
			0.1	0.25	1.0	2.5	5.0	7.5	10
S2WB2003	5mg	<0.001							0.056
	10mg	0.013							
S2WB2004	1mg	0.012	-			0.111	0.269	0.002	<0.001
	2.5mg	<0.001					0.597	0.138	0.052
	5mg	<0.001						0.041	0.012
	7.5mg	<0.001							0.643
	10mg	<0.001							
S2WB3002	0.1mg	0.709	-	0.747	0.020	<0.001			
	0.25mg	0.493		-	0.039	<0.001			
	1.0mg	0.029			-	0.003			
	2.5mg	<0.001				-			
S2WA3001	0.1mg	0.530	-	0.936	0.551	0.006			
	0.25mg	0.672		-	0.554	0.005			
	1.0mg	0.690			-	0.007			
	2.5mg	0.005				-			
S2WA3003	0.25mg	0.328		-	0.001	<0.001			
	1.0mg	<0.001			-	0.002			
	2.5mg	<0.001				-			
S2WA3012	0.25mg	0.047		-	0.037	0.356			
	1.0mg	0.244			-	0.859			
	2.5mg	0.805				-			

Table 0.3.8a

~~TABLE 5.~~ Number (%) of patients who Retreated within 24 hours of initial treatment (rescue and/or second dose)

	Placebo	Naratriptan (mg/dose)						
		0.1	0.25	1.0	2.5	5.0	7.5	10
Single attack studies								
S2WB2003	12/18 (67%)					3/29 (10%)		10/33 (30%)
S2WB2004	60/91 (66%)			39/83 (47%)	30/86 (35%)	36/93 (39%)	23/93 (25%)	21/96 (22%)
S2WA3001	85/122 (70%)	84/128 (66%)	80/119 (67%)	72/117 (62%)	60/127 (47%)			
Multiple attack studies								
S2WB3002	75/107 (70%)	150/220 (68%)	148/224 (66%)	125/219 (57%)	88/209 (42%)			
S2WA3003	395/602 (52%)		374/591 (63%)	316/595 (53%)	264/586 (45%)			
Active comparator studies								
S2WB3011					118/215 (55%)			
Adolescent studies								
S2WA3012	24/74 (32%)		28/78 (36%)	22/78 (28%)	22/70 (31%)			

Table 0.3.9

TABLE 2. All pairwise comparisons from incidence of recurrence (4-24 hours after treatment)

		Placebo	Naratriptan (mg/dose)						
			0.1	0.25	1.0	2.5	5.0	7.5	10
S2WB2003	5mg	0.372							0.402
	10mg	0.153							
S2W2004	1mg	0.686	-			0.103	0.934	0.916	0.809
	2.5mg	0.061					0.064	0.102	0.126
	5mg	0.737						0.844	0.737
	7.5mg	0.602							0.883
	10mg	0.518							
S2WB3002	0.1mg	0.020	-	0.748	0.639	0.012			
	0.25mg	0.031		-	0.883	0.002			
	1.0mg	0.006			-	0.001			
	2.5mg	0.340				-			
S2WA3001	0.1mg	0.386	-	0.970	0.831	0.344			
	0.25mg	0.368		-	0.817	0.410			
	1.0mg	0.345			-	0.313			
	2.5mg	0.896				-			
S2WA3003	0.25mg	0.602		-	0.624	0.016			
	1.0mg	0.924			-	0.042			
	2.5mg	0.116				-			
S2WA3012	0.25mg	0.598		-	0.428	0.219			
	1.0mg	0.337			-	0.648			
	2.5mg	0.629				-			

Table 0.3.9a

TABLE: **Number and Proportion of patients who experienced a recurrence between 4-24 hours after initial study treatment**

	Placebo	Naratriptan (mg/dose)						
		0.1	0.25	1.0	2.5	5.0	7.5	10
Single attack studies								
S2WB2003	4/6 (67%)					9/22 (41%)		6/21 (29%)
S2WB2004	10/28 (36%)			14/45 (31%)	8/48 (17%)	15/47 (32%)	19/63 (30%)	20/69 (29%)
S2WA3001	16/42 (38%)	16/41 (39%)	16/42 (38%)	23/59 (39%)	21/76 (28%)			
Multiple attack studies								
S2WB3002	2/20 (10%)	24/61 (39%)	30/70 (43%)	39/93 (42%)	22/116 (19%)			
S2WA3003	70/197 (36%)		79/233 (34%)	111/338 (33%)	105/396 (27%)			
Active comparator studies								
S2WB3011					74/163 (45%)			
Adolescent studies								
S2WA3012	9/48 (19%)		11/56 (20%)	7/52 (13%)	6/45 (13%)			

Note: Recurrence is defined as obtaing headache relief 4 hours after treatment (2/3 ---> 0/1) and a significant worsening of headache between 4-24 hours as indicated by the patient.

Note: S2WB3011 was active (not placebo) controlled study is a special patient population which experienced high incidence of recurrence

Table 0.3.10

~~TABLE 3.~~ Number and proportion of patients according to severity of recurrence (or Baseline severity of recurrence)

	Placebo		Naratriptan (mg/dose)											
			0.1		0.25		1.0		2.5		5.0		7.5		10	
S2WB2003														
Mild	0										6	(67%)			1	(14%)
Moderate	2	(50%)									2	(22%)			6	(86%)
Severe	2	(50%)									1	(11%)			0	
S2WB2004																
Mild	3	(23%)					5	(31%)	5	(38%)	6	(40%)	8	(38%)	11	(50%)
Moderate	6	(46%)					7	(44%)	7	(54%)	5	(33%)	5	(24%)	8	(36%)
Severe	4	(31%)					4	(25%)	1	(8%)	4	(27%)	8	(38%)	3	(14%)
S2WB3002 (Attack 1)																
Mild	0		1	(5%)	1	(4%)	2	(5%)	3	(15%)						
Moderate	1	(100%)	10	(48%)	15	(54%)	29	(78%)	13	(65%)						
Severe	0		10	(48%)	12	(43%)	6	(16%)	4	(20%)						

Note: S2WB2004/2004 - The severity of recurrence headache is reported as recorded on the diary card irrespective of headache relief at 4 hours or the timing from the initial dose.

: S2WB3002 - Baseline headache severity grade before taking second dose for treating recurrence

Figure 0.3.11

Naratriptan Tablets

Protocols S2WB2004, S2WB3002 (1st Attack), S2WA3001 and S2WA3003 (1st Attack)

Estimated Probability of Achieving Initial Headache Response Within 240 Minutes