migraine. Originally, the range was 5mg to ——, but after 32 patients had been dosed, the protocol was amended to include the 2.5mg dose and the —— dose was deleted. In this study, dosing was titrated up or down according to the 2 hour headache response of the preceding patient. The first patient received 20mg. After 55 patients had been dosed, additional patients were enrolled and treated, disregarding the previous patient's response. These latter patients were randomized 1:1 to receive either 2.5mg or 20mg. A total of 62 patients were dosed. No one received 40mg. Patients with significant cardiovascular or cerebrovascular disease were excluded.

The primary efficacy response was the 2-hour headache response rate. These were:

- Frovatriptan 2.5mg – 25% (2/8)
- Frovatriptan 5mg – 57% (13/23)
- Frovatriptan 10mg – 61% (11/18)
- Frovatriptan 20mg – 83% (10/12)

The non-randomized, uncontrolled nature of the design did not allow formulation of any definite conclusions.

7.11.4 Study 04

Study 04 was an open-label, crossover study of the effect of a migraine attack on the PK of frovatriptan 2.5mg in male and female patients. In this study, the PK of frovatriptan were measured during and outside a migraine attack. Each of the 12 patients in this study took a single oral dose of frovatriptan 2.5mg on 2 occasions. No primary efficacy measure was defined. Eleven out of 12 patients had a response between 0.58 and 3.5 hours after a single administration of frovatriptan 2.5mg during a migraine attack. Only 1 patient reported a recurrence within 24 hours (at 12.75 hours) but this was mild in severity and therefore did not satisfy the definition of a recurrence.

7.12 Sponsor's Efficacy Conclusions

I paraphrase the sponsor's efficacy conclusions from section 8.7.2.1.9 of the ISE, page 140-144.

- The three phase 3 studies (06, 07, 09) each demonstrated that frovatriptan 2.5mg was significantly more effective than placebo with respect to the 2-hour headache response.
- The two phase 2 studies (02, 14) are supportive of this conclusion.
- Headache response at 2 hours across the 5 studies was very consistent for both frovatriptan 2.5mg (37-46%) and for placebo (21-27%).
- The 4-hour headache response rates were significantly higher for frovatriptan compared to placebo in all 5 studies.
- Frovatriptan 2.5mg was also significantly superior to placebo in completely abolishing headache at 2 and 4 hours.
- The median time to first response was consistently shorter with frovatriptan 2.5mg compared to placebo.
- A similar pattern of response was obtained for the remaining secondary efficacy parameters. In particular, frovatriptan 2.5mg was significantly more effective than

placebo in relieving the migraine associated symptoms of nausea, photophobia, and phonophobia.

- Recurrence was a primary efficacy variable in studies 07 and 09, and a secondary variable in the remaining 3 studies. Recurrence was consistently lower with frovatriptan 2.5mg compared to placebo in all 5 studies and with frovatriptan 2.5mg compared to sumatriptan 100mg in study 09. [1] Recurrence rates were higher in the two studies that permitted a second dose, compared with the three that did not. The ability to take a second dose may have influenced the patient's reporting of recurrence in both treatment groups— a finding that has been seen in other migraine studies.
- In both studies 07 and 09, the median time to remedication was statistically significantly longer for frovatriptan 2.5mg than for placebo. In all 5 studies, use of rescue medication was notably less with frovatriptan 2.5mg compared to placebo.
- In all 5 studies, time to meaningful relief was significantly shorter for frovatriptan 2.5mg compared to placebo.
- Frovatriptan 2.5mg was consistently rated higher than placebo for all 5 studies and patients rated effectiveness similarly for frovatriptan 2.5mg and sumatriptan 100mg in study 09.
- Despite highly variable placebo response rates across studies involving other compounds, the placebo response at 2 and 4 hours in the frovatriptan clinical development program were consistent and were at the lower end of the range reported in other migraine studies.
- Study 09 was designed, but failed, to show equivalence between frovatriptan 2.5mg and sumatriptan 100mg. The 2 hour headache response rate for sumatriptan was significantly higher than frovatriptan 2.5mg and equivalence was rejected.
- For all 5 studies, individual interaction analyses conducted did not suggest a differential treatment effect between pre-specified subgroups. In particular, there was no evidence of a treatment by center interaction, and the conclusions can be regarded as robust.

In summary, the sponsor concludes that frovatriptan 2.5mg was consistently more effective than placebo in treating acute migraine headache and the accompanying symptoms of migraine. Although frovatriptan 2.5mg appeared less effective than sumatriptan 100mg for response and complete relief at 2 and 4 hours, for other efficacy parameters the 2 treatments were broadly similar.

7.13 Reviewer's Efficacy Analyses

7.13.1 Methods

As part of my efficacy review, I chose to perform the following analyses of the data:

- 2-hr headache response rate (worst case analysis)
- Time to response
- Time to Remedication

[1] Reviewer's note: although there was a numerical advantage in recurrence rates noted, none of the analyses reached statistical or nominal significance.

- Sustained response

The sponsor's analyses of response rate presented in this review (section 7.6.1, page 22) was performed on the ITT-observed population. This population was defined in section 7.3, page 17. The ITT-observed population excluded patients who were asleep or otherwise had a missing assessment. I chose to perform an analysis on the entire ITT population using a "worst case" scenario whereby I replaced missing headache severity values at 2 hours with "no pain" for placebo and sumatriptan patients and "severe pain" for frovatriptan patients.

The sponsor analyzed time to response and time to remedication (either a 2nd dose or rescue) but provided no Kaplan-Meier graphs. Furthermore, the data on time to remedication were taken from studies 07 and 09 only (the only studies that permitted a second dose). I chose to generate these graphs from the available data from all 5 efficacy studies.

They also analyzed recurrence rates within 24 hours. The problem with this analysis is that the recurrence population a non-randomized subset of the original study population. Inclusion into the recurrence population is contingent upon first having a response at 4 hours. I chose instead to analyze sustained response rates, which uses the entire ITT population. I define a sustained response as a response at 2 hours, no recurrence, no rescue, and no 2nd dose (if one was allowed) within 24 hours.

The sponsor provided efficacy data for the 5 major efficacy studies: 02, 14, 06, 07, and 09. This was provided as a single pooled SAS transport dataset called efficaf.xpt. I performed all of my analyses using JMP version 3.2.5.

One problem I quickly encountered is that the sponsor did not provide a define.pdf file to describe the variables fully. They did provide several documents (contents.doc, issise_f.doc, study08_.doc) which attempted to do this, but I found these files incomplete and generally not very helpful.

For example, efficaf.xpt contained the treatment group variable TRTGRP. This variable contained integer values between 0 and 13, as well as the integer 202. I could not find what these integers represented. In the file issise.f.doc (which was over 70 pages long), I searched for TRTGRP and found no instance where all 13 integers were defined. I was able to find definitions for some of the values, but not all. I then resorted to counting how many patients in the 5 efficacy studies were assigned to these treatment groups, and compared the numbers with the sponsor's numbers shown in Table 5: Efficacy Studies – Intent to Treat Population, on page 18. Using this approach, I constructed the following table of treatment assignment codes, which I used in my analyses (Table 41). I could still not find values for TRTGRP integers 7, 8, or 9, but I was able to determine that they all represented doses above 40mg, and since these doses were not used in the 5 efficacy studies, it did not effect my analyses. Throughout this review, (RA) in any caption denotes a reviewer analysis derived table or figure.

Table 41: (RA) – Table of Treatment Assignment Codes

TRTGRP	Treatment Assignment (trt)
0	Placebo (PBO)
1	2.5mg
2	5mg
3	10mg
4	20mg
5	40mg
6	1mg
10	0.4mg
11	0.8mg
12	1.2mg
13	0.5mg
202	Sumatriptan 100mg

The important treatment assignments were 0=PBO, 1=frovatriptan 2.5mg, and 202=sumatriptan 100mg.

7.13.2 Two-Hour Headache Response Rates – Worst Case Analysis

The sponsor's analyses of response rate presented in this review (section 7.6.1, page 22) was performed on the ITT-observed population. ITT-observed excluded patients who were asleep or otherwise had missing assessment. I chose to perform an analysis on the entire ITT population using a worst case scenario whereby I replaced missing headache severity values at 2 hours with "no pain" for placebo patients and "severe pain" for frovatriptan patients. I used data for attack one only in those studies that treated multiple attacks (06, 07, 09).

In previous triptan NDA's, the sponsors collected efficacy data prior to 2 hours, so that I could use a "last observation carried forward" approach to impute missing 2 hour data. Since post-treatment efficacy data was not collected in these studies, I was unable to use such an approach.

I identified 4052 patients across all 5 studies that reported a grade 2 or 3 headache at baseline. Of these, 58 lacked 2-hour headache severity data. These were distributed as follows (Table 42). There were 15 patients on frovatriptan 2.5mg with missing 2-hour headache severity scores, along with 11 on placebo and 4 on sumatriptan 100mg. In order to do a worst case analysis of response rates, I assigned a score of "3" to patients on frovatriptan 2.5mg and a score of "0" to patients on placebo or sumatriptan 100mg.

Table 42: (RA) – Missing Two-Hour Headache Assessments

Study	0.5mg	1mg	2.5mg	5mg	10mg	20mg	40mg	PBO	Suma 100mg	Total
02	0	0	3	1	3	6	9	1	0	23
14	2	2	5	5	0	0	0	3	0	17
06	0	0	2	0	0	0	0	1	0	3
07	0	0	3	0	0	0	0	5	0	8
09	0	0	2	0	0	0	0	1	4	7
Total	2	2	15	6	3	6	9	11	4	58

There were an additional 166 patients who did not provide a 2 hour headache severity score because they were asleep. The sponsor did not code these as missing, but rather assigned a score of "9" to signify asleep. I again assigned a headache score of "0" if the patient was on placebo or sumatriptan, and "3" if they were on frovatriptan. The distribution of asleep scores is shown in Table 43. There were no patients in studies 02 and 14 who were coded as "asleep" at 2 hours.

Table 43: (RA) – Patients Who Were Asleep At The Two Hour Assessment

Study	0.5mg	1mg	2.5mg	5mg	10mg	20mg	40mg	PBO	Suma 100mg	Total
06	0	0	12	0	0	0	0	3	0	**15**
07	0	0	49	0	0	0	0	24	0	**73**
09	0	0	32	0	0	0	0	15	31	**78**
Total	**0**	**0**	**93**	**0**	**0**	**0**	**0**	**42**	**31**	**166**

Having made these imputations on the 2-hour headache severity score, I then calculated 2 hour response rates. I used the definition of a responder as a patient with a baseline headache severity of 2 or 3 and a 2 hour headache severity of 0 or 1. The results for studies 06, 07, and 09 are shown in Table 44. The top table is my analysis and the bottom table is the sponsor's analysis on the ITT-observed population (copy of Table 12: Studies 06, 07, 09 – Two-Hour Headache Response Rates (ITT-observed), page 23).

My analysis shows that frovatriptan 2.5mg was numerically superior to placebo in all three phase 3 studies, and this comparison achieved statistical significance for studies 06 and 07, but not study 09. Sumatriptan 100mg was statistically better than frovatriptan 2.5mg in study 09. These results are similar to the sponsor's analysis except that statistical significance for the frovatriptan vs. placebo comparison was lost in my worst case analysis of study 09.

Table 44: (RA)Studies 06, 07, 09 – Two-Hour Response Rates (Worst Case Analysis)

Study	2.5mg	PBO	Sumatriptan 100mg	p-value*
06	73/201 (36%)	25/103 (24%)		0.029
07	308/726 (42%)	121/376 (32%)		<0.001
09	160/479 (33%)	67/244 (27%)	243/482 (50%)	<0.0001# <0.10

* Cochran-Mantel-Haenszel, stratified by baseline headache severity for 06, 07 and chi-square for study 09; p-value is frovatriptan vs. placebo unless otherwise noted

\# frovatriptan vs. sumatriptan

sponsor's analysis: ITT-observed population

Study	2.5mg	PBO	Sumatriptan 100mg	p-value*
06	73/187 (39%)	21/99 (21%)	n/a	0.001
07	308/672 (46%)	92/347 (27%)	n/a	<0.001
09	160/438 (37%)	51/225 (23%)	206/441 (47%)	<0.001# <0.001

* p-value is frovatriptan vs. placebo unless otherwise noted
# frovatriptan vs. sumatriptan

The results for studies 02 and 14 are shown in Table 45 The first table is my analysis and the second table is the sponsor's analysis on the ITT-observed population (copy of Table 13: Studies 02, 14 – Two-Hour Headache Response Rates (ITT-observed), page 23).

Numerically, frovatriptan 2.5mg was superior to placebo in both studies, but in my worst case analysis, the comparison did not reach nominal significance in study 14 (whereas it did in the sponsor's ITT-observed analysis of 2.5mg). Neither the 0.5mg nor the 1.0mg doses in study 14 was superior to placebo. In study 02, doses of 2.5mg and above were all nominally significantly better than placebo, but there was no dose response, as was seen in the sponsor's analysis.

Table 45: (RA) Studies 02, 14 – Two-Hour Response Rates (Worst Case Analysis)

Dose	Study 02	p-value*	Study 14	p-value*
PBO	21/92 (23%)		32/118 (27%)	
0.5mg			36/121 (30%)	0.65
1.0mg			28/111 (25%)	0.74
2.5mg	38/93 (41%)	0.013	46/126 (37%)	0.12
5mg	36/92 (39%)	0.019	42/120 (35%)	0.18
10mg	73/180 (41%)	0.007		
20mg	85/184 (46%)	<0.001		
40mg	80/201 (40%)	0.005		

* Cochran-Mantel-Haenszel test

sponsor's analysis: ITT-observed population

Dose	Study 02	p-value*	Study 14	p-value*
PBO	20/91 (22%)		29/115 (25%)	
0.5mg			36/119 (30%)	0.46
1.0mg			28/109 (26%)	0.97
2.5mg	38/90 (42%)	0.004	46/121 (38%)	0.047
5mg	36/91 (40%)	0.020	42/115 (37%)	0.097

Dose	Study 02	p-value*	Study 14	p-value*
10mg	73/177 (41%)	0.002		
20mg	85/178 (48%)	<0.001		
40mg	80/192 (42%)	0.001		

* Cochran-Mantel-Haenszel test

Although the worst case analysis resulted in loss of statistical significance for the 2.5mg dose in studies 09 and 14, the response rates were numerically in favor of drug and can be considered supportive of the results seen in studies 06, 07, and 02.

7.13.3 Time To Response

The time to response is defined as the first time, following the initial dose of study medication, when a headache response is achieved. For this analysis, I began with the entire efficacy dataset for all 5 major efficacy studies. There were efficacy data for attack 1 recorded for 4236 patients. I deleted patients who had no baseline headache data recorded (most of whom didn't treat a headache) or if they recorded mild or no headache at baseline (BASEHEAD=0 or 1), or if they were asleep at baseline (BASEHEAD=9). This resulted in 4052 patients with a recorded baseline headache of moderate or severe.

I created a new column (resp) that coded whether a patient had a response (HEADSEV=0 or 1). I next created a column which coded the time at which a patient went from no response to a response (resp=0 to resp=1). I summarized the table by PTID and selected the earliest time that such a conversion occurred for each patient. This I called "time to response (tresp).

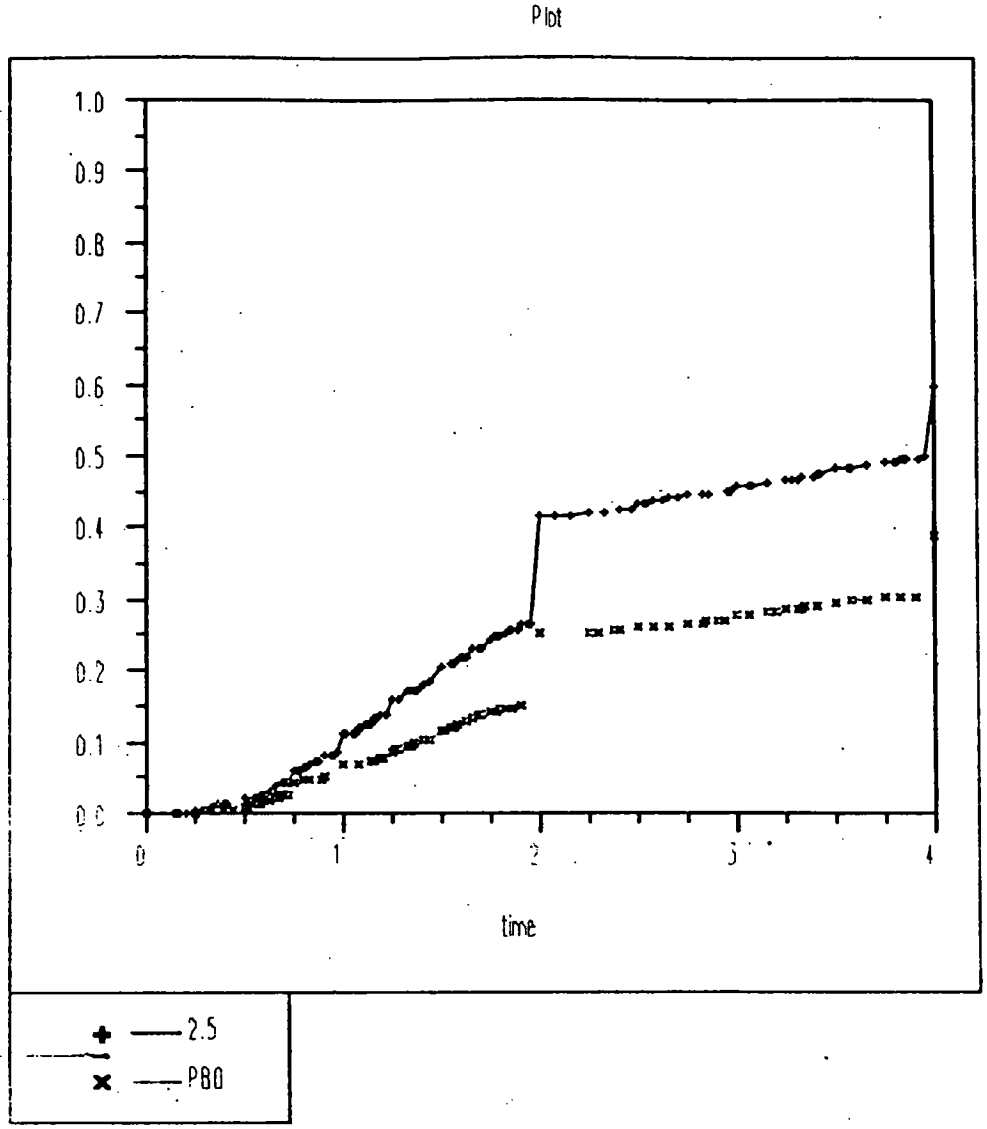
The sponsor provided two variables that allowed refinement of this outcome measure. The efficacy dataset contained the variables IMPD1TIM and IMPROVE1. The first variable, IMPD1TIM, was a continuous variable that coded the time (in hours) after the initial dose when the patient first experienced an improvement in headache severity. IMPROVE1 was a binary variable that coded whether the headache severity at the time of the improvement was mild or none. This information was recorded for studies 06, 07, and 09 only. The fields for these two variables in studies 02 and 14 were all blank.

Using these variables, I was able to refine "tresp" a bit further by comparing the time to response that I had generated with the recorded "time to improvement." If the recorded "time to improvement" resulted in a headache of 0 or 1 severity and if this time to improvement was earlier than the time to response that I had generated, then I replaced the time to response with this earlier time. I decided to use the data from all 5 studies, including study 14 (even though there were many duplicate patients from study 02).

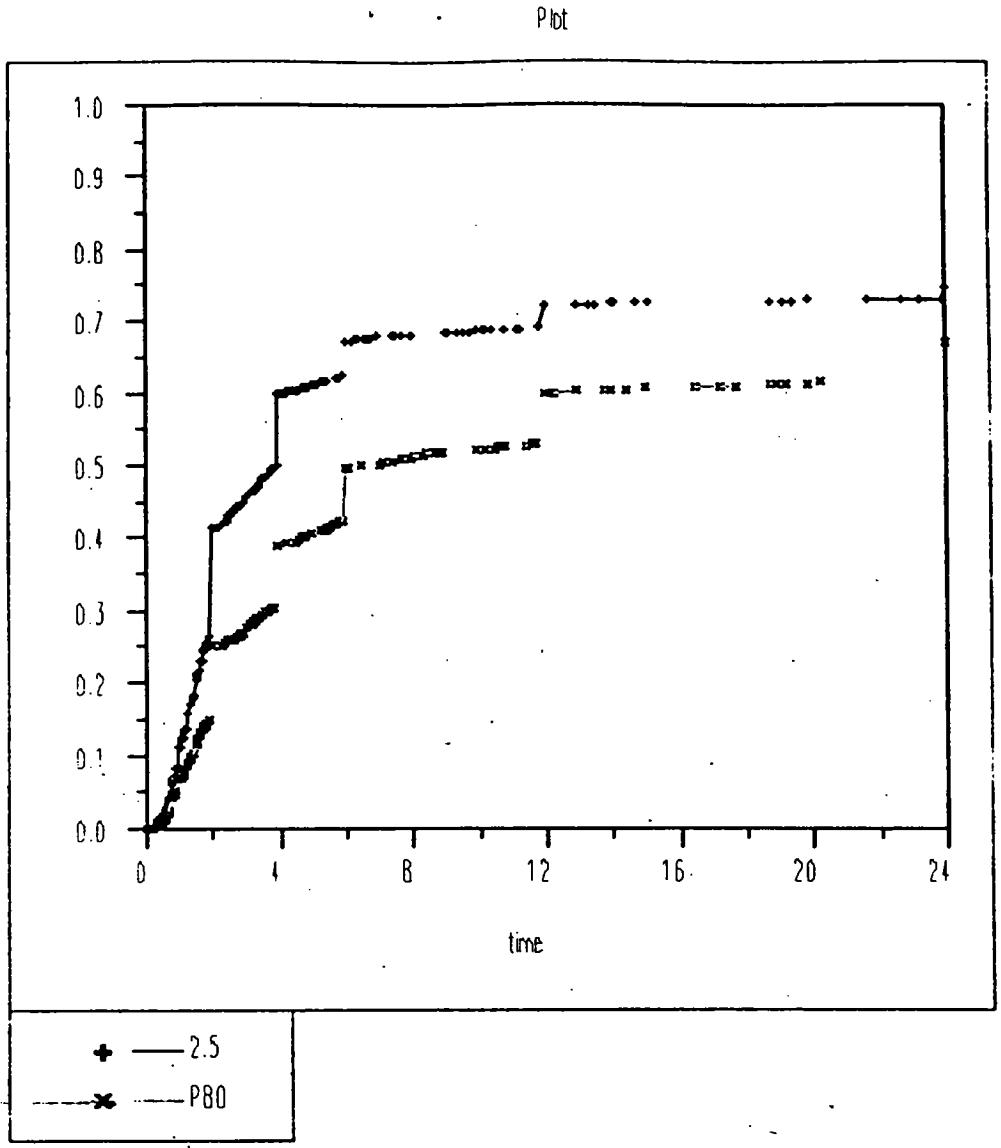
The time to response, for the pooled 5 efficacy studies, is shown in Figure 3. Those not recording a response within 4 hours were censored to 4 hours for the first figure, and those not recording a response within 24 hours were censored to 24 hours. The graphs show that the probability of achieving of a response was greater for frovatriptan 2.5mg compared to placebo.

Figure 3: (RA) Studies 02, 14, 06, 07, 09 – Time to Response (Kaplan-Meier Method)

0-4 hours



0-24 hours



7.13.4 Time To Remedication (Rescue or 2nd Dose)

The sponsor analyzed the time to remedication, which could either have been a second dose or rescue medication, for studies 07 and 09 only. These were the only two studies that permitted the use of a second dose. However, the efficacy dataset provided did record the time to rescue for all 5 studies. Therefore, I was able to generate "time to remedication" for all five studies using the following algorithm:

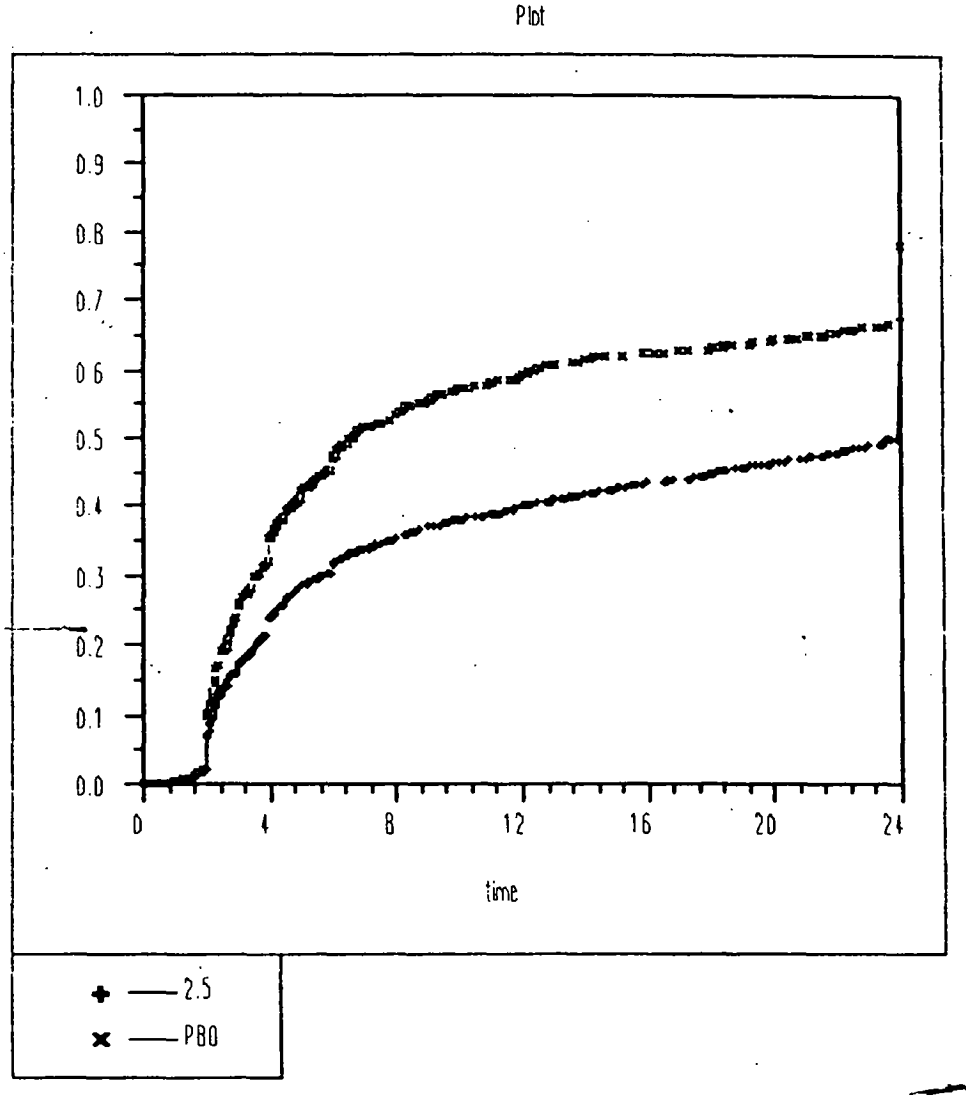
- If a 2nd dose was not permitted, then I used the time to rescue
- If a 2nd dose was permitted, but not taken, then I used the time to rescue
- If a 2nd dose was permitted and taken, then I used the smaller of the two times (time to rescue vs. time to 2nd dose)

- If neither a 2nd dose or rescue was taken, I left "time to remedication" blank and censored these patients to 24 hours

The population for analysis consisted of patients from the 5 major efficacy studies that reported a baseline headache intensity of moderate or severe. This included 4,052 patients.

Figure 4 shows the probability of requiring remedication over 24 hours for frovatriptan 2.5mg and placebo. I include data from all 5 studies in the graph. Patients not requiring remedication are censored to 24 hours. The graph shows that patients treated with frovatriptan 2.5mg have a lower probability of remedicating within 24 hours.

Figure 4: (RA) Studies 02, 14, 06, 07, 09 – Time to Remedication (Kaplan-Meier Method)



7.13.5 Sustained Response

I define a sustained response as a response at 2 hours, absence of recurrence, and no remedication within 24 hours. This has the benefit over recurrence rate in that one can compare sustained response rates in the original randomized population. I used the efficacy dataset for the 5 major efficacy studies. I started with the 4,052 patients that reported a baseline headache severity of moderate or severe. Of these, 4,046 had 2 hour efficacy data recorded. Of these, 223 did not have 2 hour headache severity data recorded, either because the information was missing (n=58) or because the patient was asleep (n=165). I removed them from the analysis. This resulted in 3,823 patients for my sustained response analysis. I then identified all patients who had a response at 2 hours, did not experience a recurrence within 24 hours and did not remedicate. The results of that analysis are shown in Table 46 and Table 47.

In all three phase 3 studies, frovatriptan 2.5mg was associated with a numerically higher sustained response rate compared with placebo. In study 06, the p value was borderline significant but the comparison reached nominal significance in studies 07 and 09. In study 09, sustained response rate was nominally significantly higher in sumatriptan 100mg treated patients compared with those treated with frovatriptan 2.5mg.

Table 46: (RA) Studies 06, 07, 09 – Sustained Response Rates

Study	2.5mg	PBO	Sumatriptan 100mg	p-value*
06	28/187 (15%)	7/99 (7%)		0.053
07	93/673 (14%)	15/347 (4%)		<0.0001
09	58/444 (13%)	15/228 (7%)	83/447 (19%)	0.018# 0.01

* Cochran-Mantel-Haenszel, stratified by baseline headache severity; p-value is frovatriptan vs. placebo unless otherwise noted
\# frovatriptan vs. sumatriptan

Table 47: (RA) Studies 02, 14 – Sustained Response Rates

Dose	Study 02	p-value*	Study 14	p-value*
PBO	9/91 (10%)		16/115 (14%)	
0.5mg			28/119 (24%)	
1.0mg			14/109 (13%)	
2.5mg	21/90 (23%)	0.027	25/121 (21%)	0.095
5mg	19/91 (21%)		27/115 (23%)	
10mg	34/177 (19%)			
20mg	49/178 (28%)			
40mg	47/192 (25%)			

* chi-square for the overall comparison

In the phase 2 studies, all doses except frovatriptan 1mg were associated with numerically higher sustained response rates compared with placebo. It's curious that the sustained response rate for the 0.5mg dose was so high, since the traditional 2-hr headache response rate in this study (30%, Table 45, page 50) was comparable to the placebo response rate in that study. Since this is not seen with the 1mg dose, it may simply represent a chance occurrence.

7.14 Reviewer's Efficacy Conclusions

From the data presented in this NDA, I conclude that:

- A single dose of frovatriptan 2.5mg is effective for the acute treatment of migraine, as measured by the two hour headache response rate and by its effects at 2 hours on the secondary migraine symptoms of nausea, photophobia, and phonophobia.

However, the data:

- Fail to show that recurrence rates within 24 hours are lower with frovatriptan compared with placebo
- Fail to show that a second dose is effective for the treatment of either persistent or recurrent pain
- Fail to show that frovatriptan is superior to sumatriptan with regards to efficacy.

8. Integrated Review of Safety

8.1 Background and Methodology

Data from 28 completed studies contribute to the safety database. There were 9 studies conducted exclusively in migraine patients, and the remaining 19 were clinical pharmacology studies in subjects without migraine.

8.1.1 Safety Population in Migraine Studies

The numbers of patients in the safety population of the 9 migraine studies are shown in Table 48 (ISS panel 8.8.1.3.1:1, page 38).

Table 48: Safety Population in Migraine Studies

Study	Total	Frovatriptan Dose <2.5mg	2.5mg	5mg	10mg	>10mg	PBO	Suma 100mg	Comments
Controlled short-term studies									
06	322	0	214	0	0	0	108	0	Double-blind; parallel
07	1,148	0	760	0	0	0	388	0	Double-blind; parallel
09	1,206	0	480	0	0	0	244	482	Double-blind; parallel
02	899	0	100	99	192	410	98	0	Double-blind; parallel
14	635	255	131	126	0	0	123	0	Double-blind; parallel
03	75	0	37	0	0	0	38	0	Double-blind; parallel
Uncontrolled short-term studies									
01	62	0	8	24	18	12	0	0	Single-blind; dose-titration
04	12	0	12	0	0	0	0	0	Open-label; 2-way crossover
Uncontrolled long-term study									
08	496	0	496	0		0	172	0	First dose double-blind; open-label thereafter

Studies 02, 14, 06, 07, and 09 were the 5 major efficacy studies and have been described in the efficacy portion of this review (section 7.1, page 14). The other four studies, 08, 03, 01, and 04, were described in section 7.11, page 43.

Of the 4855 patients in the safety population of the 9 migraine studies, 4654 were unique, *i.e.*, approximately 4% of the overall migraine safety population is composed of duplicate patients. Of the 4654 unique patients, 3843 took at least 1 dose of frovatriptan and 2772 took at least one dose of the intended marketed dose of 2.5mg.

In many cases were duplicates occurred, the protocol did not specifically request frovatriptan naïve patients only. For example, patients from the phase 3 US studies 06 and 07 could enroll in the uncontrolled long term safety study 08 upon completion. Patients in either of the two phase 2 studies, 02 and 14, could not enroll in a short term phase 3 study (06, 07, 09), but could enroll in the long term safety study 08.

8.1.2 Safety Population in Non-Migraine Studies

Of the 19 clinical pharmacology studies in patients without migraine, 297 are included in the safety population, of which 284 received at least one dose of frovatriptan (Table 49, ISE panel 8.8.1.3.1:2, page 43).

Table 49: Safety Population in Non-Migraine Studies

Study	Total	Frovatriptan Dose					PBO	Comments
		<2.5mg	2.5 mg	5 mg	10 mg	>10mg		
1165/24 (Single Rising Dose)	18	18	5	6	6	11	17	Single-blind; parallel, ascending
1165/34 (Pharmacokinetics)	9	9	0	0	0	9	0	Open-label; 3-way crossover
1165/42 (Tolerance and PK)	8	0	0	0	0	8	8	Single-blind; parallel; ascending
1165/43 (Bioequivalence)	24	0	0	0	0	24	0	Open-label; 3-way crossover
1165/48 (Radiolabelled Study)	4	0	0	0	0	4	0	Open-label; single 40 mg dose
VAD5-01 (Food Interaction)	12	0	0	0	0	12	0	Open-label; 2-way crossover
1165/62 (Bioequivalence)	32	0	0	0	0	32	0	Open-label; 4-way crossover
251/96/01 (Repeat Dose Safety & PK)	24	0	0	0	0	16	8	Double-blind; multiple doses
251/96/03 (Repeat Dose Safety & PK	20	0	0	0	15	16	4	Double-blind; 2-way

Study	Total	Frovatriptan Dose <2.5mg	2.5 mg	5 mg	10 mg	>10mg	PBO	Comments
								crossover;
251/96/04 (Male vs. Female PK)	24	0	0	0	0	24	0	Open-label
251/96/12 (Male vs. Female PK)	14	13	12	0	0	13	0	Open-label; 3-way crossover
251/97/01 (PK in Elderly)	12	0	12	0	0	0	0	Open-label; single dose
251/97/02 (PK in Renal Impairment)	18	0	18	0	0	0	0	Open-label; single dose
251/97/05 (Bioequivalence)	21	0	21	0	0	0	0	Open-label; 3-way crossover
251/97/06 (PK in Hepatic Impairment)	8	0	8	0	0	0	0	Open-label; single dose
251/98/01 (Radiolabelled Study)	4	0	4	0	0	0	0	Open-label; single 2.5 mg dose
251/98/02 (Ergotamine Interaction Study)	12	0	0	12	0	0	0	Open-label; single dose; 3-way crossover
251/98/06 (Propranolol Interaction Study	14	0	14	0	0	0	0	Open-label; single dose; 2-way crossover
251/98/07 (Moclobemide Interaction Study)	19	0	18	0	0	0	0	Open-label; single dose; 2-way crossover
Total	**297**	**40**	**112**	**18**	**21**	**169**	**37**	

A brief description of the non-migraine clinical pharmacology studies is provided in section 5.1, page 8.

8.1.3 Rationale for ISS Study Groupings

As previously described, a total of 28 clinical studies (9 migraine, 19 non-migraine) are included in the ISS. Clinical studies were grouped by specific factors to permit analyses of safety parameters. These factors included: subject population, study duration (short-term vs. long-term), and study design (controlled vs. uncontrolled, parallel vs. crossover).

The 9 migraine studies are grouped as follows:

- controlled short-term studies (02, 14, 06, 07, 09-attack 1, 08-attack 1)
- uncontrolled short-term studies (01, 04, 09-attacks 2,3)
- uncontrolled long-term study (08-attacks >1)

Two of these 9 studies were designed such that some data are presented in a secondary category. Specifically, data for attack 1 in study 9 was controlled, but data for attacks 2 and 3 for the same study were uncontrolled. In study 08, the first attack contained controlled data and are presented in that category. Even though identical in design to study 02, data from study 14 is presented separately in the ISS because 94 patients who participated in study 02 were also enrolled in study 14 (81 of which were in the safety population).

The 19 non-migraine studies are grouped according to route of administration, and type of study (*i.e.*, drug-drug, drug-disease, radiolabelled).

8.1.4 Content of the Safety Review

In order to maintain clarity and avoid redundancy in my safety review, I chose the following strategy in presenting the safety data from this application. For deaths and serious adverse events, and adverse dropouts, I include information from the entire safety database. For other safety sections (adverse events, laboratory data, vitals signs, ECG), I only include in my review the results of the short-term controlled trials (which provide the best placebo-controlled data: studies 06, 07, 09, 02, and 14) as well as the results from the long term open label study 08. I mention any pertinent safety results from the other studies whenever they deviate in a clinically meaningful way from the results of these important studies, or when the information adds clinically meaningful insight into the safety of the drug that is not provided by these studies.

8.2 Deaths

There was one death during the clinical development program. This is described below.

97/07_734_0574 - This was a 42 year old Caucasian male with a history of migraine with and without aura for 4.25 years, insulin dependent diabetes mellitus, diabetic foot ulcers, right renal lithectomy, hypertension, chronic hepatitis since age 17, and an allergy to penicillin. He was enrolled in study 07 on 7/2/97 and was randomized to the frovatriptan 2.5mg group. At the time of enrollment, he was taking enalapril 25mg once daily since 1994 for hypertension, and isophane insulin suspension, 30 units once daily since 1994 for diabetes.

In July 1997, after enrollment but prior to taking study medication, he developed numerous necrotic ulcers on his right foot. On 8/4/97, he took one dose of frovatriptan 2.5mg to treat his first migraine attack. The attack started on 8/4/97 09:30 AM and the first dose was taken at 10:00 AM. Meaningful relief was noted at 08:00 PM that same day. No additional attacks were treated with study medication.

One week later, on 8/11/97, the patient was seen in the local emergency room with complaints of left knee pain (duration unknown). He stated that he had been walking when his left knee "gave out" and that there had been no twisting or unusual trauma when this occurred. He indicated that this had been occurring since he was 12 years old following a motor vehicle accident. This episode was more painful than previous events and involved some swelling.

In the emergency room on 8/11/97, blood pressure decreased to 95/49 from 140/90 at enrollment. Heart rate was 103, respirations were 18 per minute. Temperature was 96.9F. Blood sugar by finger stick was 128 mg/dl. On examination, his left knee was swollen and painful upon movement and walking. No bruising was observed. No numbness or paresthesias were observed. An x-ray showed no joint effusion. No laboratory tests were performed. He was diagnosed with a possible left knee sprain and probable internal derangement. He was treated with anti-inflammatory and analgesic agents: naprosyn 500mg bid x 4 days, and vicodin 5/500 qid x 4 days. He was given a knee immobilizer and crutches. He was discharged from

the emergency room and was scheduled to see an orthopedist later the same day. The patient did not keep the orthopedics appointment.

On 8/13/97, he returned to the emergency room complaining of increasing weakness, shortness of breath, and left rib pain (duration unknown). In the ER, he was hypotensive with a blood pressure of 91/41. Heart rate was 105, respirations were 30, temperature was 96.3F, and he had a reduced O_2 saturation of 95% on room air. Physical examination revealed multiple necrotic ulcers on the right foot, some of which were putrid smelling. There was no documentation that the right foot had been examined two days previously on 8/11/97. He also had edema of the right leg, ischemia of the right and left feet, and cellulitis of the right foot. Laboratory test results on that day, compared with screening on 7/2/97, are shown below:

Table 50: Patient 97/07_734_0574 – Laboratory Data

He was diagnosed with sepsis secondary to an infected foot, rhabdomyolysis, acute renal failure, metabolic acidosis, elevated liver function tests secondary to sepsis, hypoglycemia, coagulopathy, and thrombocytopenia and was admitted to the intensive care unit. Blood cultures were negative. Foot ulcer cultures were negative for gram negatives and staphylococcus. He was treated with ceftriaxone, vancomycin, and clindamycin (doses unknown) for the sepsis, and sliding scale insulin for diabetes, and normal saline with bicarbonate for the renal failure. A below knee amputation of the right foot was recommended and hemodialysis was ordered if the patient did not respond to fluids.

His condition deteriorated overnight. He became dusky, respirations increased, hypotension persisted with a systolic blood pressure in the 90's, and there was no urine output overnight. Laboratory tests showed worsening of most parameters on 8/14/97. He was dialyzed and given dopamine for acute renal failure (dose unknown). During dialysis, he developed acute respiratory distress syndrome and was intubated. He developed ventricular tachycardia, followed by bradycardia, and asystole and died.

The cause of death was reported as sepsis secondary to infected foot ulcers. All the events that the patient experienced were reported as unrelated to study medication. An autopsy was not performed.

Reviewer's note: Although it is theoretically possible that frovatriptan may have caused peripheral vasoconstriction and may have exacerbated the foot ischemia, the fact that he already had evidence of peripheral ischemia and foot ulcers prior to treatment, and that the acute illness leading to death occurred one week following a single dose of frovatriptan makes the death unlikely related to study medication, in my opinion.

8.3 Serious Adverse Events

A serious adverse event was defined as any experience that was fatal or life-threatening, was permanently disabling, cause patient hospitalization or prolonged hospitalization, or was a congenital anomaly, cancer, or overdose. Across all clinical trials, treatment-emergent SAE's were reported for 29 of 4655 patients treated with frovatriptan, all of which were judged by the investigator to be unrelated to study medication. Three patients who took sumatriptan 100mg experienced SAE's. In the clinical pharmacology studies, one subject experienced a constellation of SAE's thought to be related to study medication.

8.3.1 Short Term Studies

The number of patients and percentages of patients with treatment-emergent SAE's in the short term controlled trials are presented by preferred term in Table 51 (ISS panel 8.8.7.1:1, page 234). A treatment emergent AE was an AE that started or increased in severity after the first dose for the first migraine attack through the end of the study for 02, 06, 07, or until the first dose for attack 2 in study 09. No SAE's were reported at center 2413 in study 09, which is excluded from the safety population due to irregularities at that center. The incidence of SAE's was low (well below 1%) in all groups.

Table 51: Studies 02, 06, 07, 09 (attack 1) – Treatment Emergent SAE's

	Frovatriptan Dose					
	2.5 mg	5mg	10mg	>10mg	PBO	Suma 100mg
Number of patients	**1554**	**99**	**192**	**410**	**838**	**482**
Number of patients with ≥ 1 SAE	7 (0.5%)	0	0	0	2 (0.2%)	3 (0.6%)
AE Preferred Term						
Depression(1)	1 (0.1%)	0	0	0	1 (0.1%)	0
Migraine aggravated	1 (0.1%)	0	0	0	0	0
Cardiac arrest(2)	1 (0.1%)	0	0	0	0	0
Sepsis(2)	1 (0.1%)	0	0	0	0	0
Cholelithiasis	1 (0.1%)	0	0	0	0	0
Fracture pathological	1 (0.1%)	0	0	0	0	0
Infection	1 (0.1%)	0	0	0	0	0
Sinusitis	1 (0.1%)	0	0	0	0	0
Neurosis(1)	0	0	0	0	1 (0.1%)	0
Urinary tract infection	0	0	0	0	1 (0.1%)	0
Dyspepsia	0	0	0	0	0	1 (0.2%)
Ovarian cyst	0	0	0	0	0	1 (0.2%)
Glomerulonephritis	0	0	0	0	0	1 (0.2%)

(1) multiple SAE's (depression and neurosis) were reported for 96/07_745_1237
(2) multiple SAE's (sepsis and cardiac arrest) were reported for 96/07_734-0574 (detail discussion in previous section on deaths)

In study 14 (not included in the table above), there was one patient that reported an SAE. This was 96/14_002_0222. She was randomized to frovatriptan 5mg but prior to taking study medication, she develop an ovarian cyst. She had not received frovatriptan in any other study.

In study 03, there were no patients with treatment emergent SAE's. Three patients recorded pre-treatment SAE's: myocardial infarction resulting in withdrawal prior to treatment, chest pain (again prior to treatment), and a kidney stone.

In studies 01 and 04, there were no treatment emergent SAE's.

In study 09, there were six patients who reported SAE's during the uncontrolled treatment of attacks 2 and 3: abdominal pain, vomiting, dyspnea, pulmonary embolism, pleurisy, hydronephrosis, infection, ovarian cyst, maculopapular rash. None were felt to be related to study medication.

8.3.2 Long Term Study 08

This was the one year long term safety study. The number and percentages of patients with treatment emergent SAE's are shown in Table 52 (ISS panel 8.8.7.2:1, page 238). The incidence of SAE's was low but fluctuated slightly over time. No SAE's in this study were reported as related to study medication. The only SAE's that occurred in 2 or more patients were migraine aggravated, abdominal pain, and inflicted injury. All others were reported by a single patient.

Table 52: Study 08 – SAE's by Duration of Treatment

	0-13 wks	>13-26 wks	>26-39 wks	>39-52 wks	Overall
Pts at beginning of interval	**496**	**438**	**356**	**281**	**496**
Patients with at least 1 SAE	3 (0.6%)	8 (1.8%)	4 (1.1%)	2 (0.7%)	15 (3.0%)
AE Preferred Term					
Migraine aggravated	1 (0.2%)	0	1 (0.3%)	0	2 (0.4%)
Abdominal pain	0	1 (0.2%)	0	1 (0.4%)	2 (0.4%)
Vertigo(1)	0	1 (0.2%)	0	0	1 (0.2%)
Chest pain(1)	0	1 (0.2%)	0	0	1 (0.2%)
Depression(2)	0	1 (0.2%)	0	0	1 (0.2%)
Anxiety(2)	0	1 (0.2%)	0	0	1 (0.2%)
Agitation(2)	0	1 (0.2%)	0	0	1 (0.2%)
Tremor(2)	0	0	1 (0.3%)	0	1 (0.2%)
Delusion(2)	0	0	1 (0.3%)	0	1 (0.2%)
Suicide attempt	0	1 (0.2%)	0	0	1 (0.2%)
Ovarian cyst	0	0	0	1 (0.4%)	1 (0.2%)
Lumbar disc lesion	0	0	1 (0.3%)	0	1 (0.2%)
Inflicted injury	0	1 (0.2%)	1 (0.3%)	0	2 (0.4%)
Fracture pathological	0	1 (0.2%)	0	0	1 (0.2%)
Convulsions	0	1 (0.2%)	0	0	1 (0.2%)
Cholecystitis	0	1 (0.2%)	0	0	1 (0.2%)
Cervical uterine polyp	1 (0.2%)	0	0	0	1 (0.2%)
Arthralgia	0	0	1 (0.3%)	0	1 (0.2%)
Appendicitis	1 (0.2%)	0	0	0	1 (0.2%)
Abdominal adhesions	0	1 (0.2%)	0	0	1 (0.2%)

8.3.3 Non-Migraine Studies

Only 1 subject experienced a treatment-emergent SAE in the 19 non-migraine studies. Subject 13 in study 251/96/03 received 2 doses of frovatriptan 2.5mg separated by 2 hours in the morning. In the afternoon, she experienced involuntary muscle contractions, dizziness, and conjunctivitis. All events resolved spontaneously on the same day. Because of this constellation of neurological symptoms, the third dose of study drug was withheld and the subject was kept in the investigational unit for an extra night of observation. These AE's were considered possibly related to treatment.

8.4 Adverse Dropouts

All treatment emergent AE's that resulted in dropouts were summarized only for clinical studies that permitted treatment of more than 1 migraine attack, since these were the only clinical studies from which patients could withdraw due to a treatment emergent AE. Patients from Dr. Fourie's center (2413) in study 09 are excluded because of irregularities at the center. The overall incidence of withdrawals due to AE's was low, suggesting that frovatriptan was well tolerated in both short and long-term studies (~1% for short-term and ~5% for study 08).

8.4.1 Short Term Studies

The number and percentages of adverse dropouts from studies 06, 07, and 09 (attack 1) are summarized by AE in Table 53 (ISS panel 8.8.6.1:1, page 223). The percentages of ADO's are quite small and comparable across all treatment groups.

Table 53: Studies 06, 07, 09 (attack 1) – Adverse Dropouts

Preferred Term	2.5 mg (n=1454)	PBO (n=740)	Suma 100mg (n=482)
Total	10 (0.7%)	8 (1.1%)	5 (1.0%)
Chest pain	2 (0.1%)	0	1 (0.2%)
Abdominal pain	2 (0.1%)	0	0
Nausea	1 (0.1%)	5 (0.7%)	1 (0.2%)
Palpitation	1 (0.1%)	2 (0.3%)	0
Dizziness	1 (0.1%)	1 (0.1%)	1(0.2%)
Change in bowel habits	1 (0.1%)	1 (0.1%)	0
Migraine aggravated	1 (0.1%)	1 (0.1%)	0
Flushing	1 (0.1%)	1 (0.1%)	0
Confusion	1 (0.1%)	0	1 (0.2%)
Fatigue	1 (0.1%)	0	1 (0.2%)
Pain	1 (0.1%)	0	0
Sinusitis	1 (0.1%)	0	0
Throat tightness	1 (0.1%)	0	0
Pregnancy unintended	1 (0.1%)	0	0
Abscess	1 (0.1%)	0	0
Photopsia	0	1 (0.1%)	0
Edema	0	1 (0.1%)	0
Rigors	0	1 (0.1%)	0
Eye abnormality	0	1 (0.1%)	0
Depression	0	1 (0.1%)	0

Preferred Term	2.5 mg (n=1454)	PBO (n=740)	Suma 100mg (n=482)
Neurosis	0	1 (0.1%)	0
Skin discoloration	0	1 (0.1%)	0
Paresthesia	0	1 (0.1%)	0
Asthenia	0	0	1 (0.2%)
Diarrhea	0	0	1 (0.2%)
Vomiting	0	0	1 (0.2%)
Depersonalization	0	0	1 (0.2%)
Rash	0	0	1 (0.2%)
Sweating increased	0	0	1 (0.2%)
Glomerulonephritis	0	0	1 (0.2%)

In the frovatriptan group, there were 15 treatment emergent AE's that resulted in discontinuation in 10 patients. Two withdrew due to chest pain and abdominal pain. No other AE was reported by more than 1 patient. Patient 96/07_733_1572 in study 07 had dizziness, fatigue, flushing, nausea, pain, and palpitation leading to withdrawal. Some of these events may have resulted from or have been part of the same syndrome.

In the placebo group, 19 AE's led to withdrawal in 8 patients. Patient 96/07_703_0330 in study 07 had flushing, nausea, edema, palpitations, paresthesia, photopsia, and 2 episodes of skin discoloration leading to withdrawal. Some of these events may have resulted from of have been part of the same syndrome. Five patients withdrew due to nausea and 2 patients withdrew due to palpitations and 1 patient withdrew due to each of the remaining AE's listed above.

In the sumatriptan 100mg treatment group, 12 AE's led to withdrawal of 5 patients. Patients 96/07_1806_1244 in study 07 had asthenia, depersonalization, diarrhea, dizziness, nausea, and increased sweating leading to withdrawal. Some of these events may have resulted from of have been part of the same syndrome.

8.4.2 Long Term Study 08

The number and percentages of ADO's in the long term study 08 are presented by body system and 13 week intervals in Table 54 (ISS panel 8.8.6.2:1, page 227). The percentage of ADO's was rather small, considering the long period (up to one year) during which withdrawals were possible. At the end of the study, only 5.2% (26/496) withdrew due to a treatment emergent adverse event. The most common AE leading to withdrawal was chest pain (5), followed by headache (4) , and hypoesthesia (3). The percentage of ADO's were similar during the first 9 months of treatment, and was somewhat lower during the last 3 quarter, possibly because most who were going to drop out would have done so by then.

Table 54: Study 08 – Adverse Dropouts by Body System and Treatment Interval

	2.5mg Time of Withdrawal (Wks)				Overall
	0-13	>13-26	>26-39	>39	
N at beginning of interval	496	438	356	281	496
Number of ADO's	9 (1.8%)	7 (1.6%)	8 (2.2%)	2 (0.7%)	26 (5.2%)
Chest pain	2 (0.4%)	3 (0.7%)	0	0	5 (1.0%)
Headache	3 (0.6%)	0	1 (0.3%)	0	4 (0.8%)
Hypoesthesia	0	1 (0.2%)	2 (0.6%)	0	3 (0.6%)
Nausea	1 (0.2%)	1 (0.2%)	0	0	2 (0.4%)
Migraine aggravated	1 (0.2%)	0	1 (0.3%)	0	2 (0.4%)
Paresthesia	1 (0.2%)	0	0	1 (0.4%)	2 (0.4%)
Skeletal pain	1 (0.2%)	0	0	1 (0.4%)	2 (0.4%)
Fatigue	0	2 (0.5%)	0	0	2 (0.4%)
Somnolence	0	2 (0.5%)	0	0	2 (0.4%)
Abdominal pain	0	0	1 (0.3%)	0	1 (0.2%)
Vision abnormal	0	0	1 (0.3%)	0	1 (0.2%)
Face Edema	1 (0.2%)	0	0	0	1 (0.2%)
Pain	1 (0.2%)	0	0	0	1 (0.2%)
Hypertension	1 (0.2%)	0	0	0	1 (0.2%)
Tachycardia	1 (0.2%)	0	0	0	1 (0.2%)
Pregnancy unintended	1 (0.2%)	0	0	0	1 (0.2%)
Rash	1 (0.2%)	0	0	0	1 (0.2%)
Micturition frequency	1 (0.2%)	0	0	0	1 (0.2%)
Coma	0	1 (0.2%)	0	0	1 (0.2%)
Dizziness	0	1 (0.2%)	0	0	1 (0.2%)
Suicide attempt	0	1 (0.2%)	0	0	1 (0.2%)
Dyspnea	0	1 (0.2%)	0	0	1 (0.2%)
Throat tightness	0	1 (0.2%)	0	0	1 (0.2%)
Anemia	0	1 (0.2%)	0	0	1 (0.2%)
Appendicitis	0	0	1 (0.3%)	0	1 (0.2%)
Aneurysm	0	0	0	1 (0.4%)	1 (0.2%)
Hyperglycemia	0	0	1 (0.3%)	0	1 (0.2%)

Five patients had more than one treatment emergent AE leading to withdrawal:

- 96/08_510_201: loss of consciousness, chest pain, throat tightness
- 96/08_510_203: chest pain, throat tightness
- 96/08_820_585: headache, skeletal pain, tachycardia, increased micturition frequency, paresthesia
- 96/08_822_252: chst pain, general pain, rash, face edema
- 96/08_830_012: paresthesia, skeletal pain

All of these resolved except for face edema and rash in patient 96/08_822_252 but neither required treatment.

8.4.3 Non-Migraine Studies

In the 297 subjects who received study medication in the 19 non-migraine studies, there were a total of 9 subjects, including 8 who received frovatriptan, who withdrew from four studies due to AE's. All but the herpes simplex rash in a placebo patient and a dental abscess in a frovatriptan 40mg patient were felt to be treatment related (Table 55).

Table 55: Non-Migraine Studies – Adverse Dropouts

Study	Patient ID	Treatment Group	AE Preferred Term
251/96/01	5	Frovatriptan 40 mg, bid postdose 5	Elevated liver enzymes
	14	Frovatriptan 40 mg, tid postdose 2	Speech impairment, ataxia, somnolence
	24	Frovatriptan 40 mg, tid postdose 2	Nausea, somnolence
251/96/03	2	Placebo	Mild rash (herpes simplex)
	13	Frovatriptan 20 mg, tid postdose 2	Involuntary muscle contractions, dizziness, conjunctivitis
251/96/04	14	Frovatriptan 40 mg, postdose 1	Dental abscess
	16	Frovatriptan 40 mg, postdose 1	Lower jaw cramp, nausea, vomiting, pallor
251/96/12	9	Frovatriptan 40 mg, oral	Fractured left forearm
	10	Frovatriptan 2.5 mg, oral Frovatriptan 40 mg oral Frovatriptan 0.8 mg IV	Flushing, temperature changed sensation, headache, dyspnea

8.5 Adverse Events

8.5.1 Methods

All AE's were coded using the World Health Organization Adverse Reaction Terms Dictionary (WHOART) coding system. Treatment emergent adverse events were coded as to whether they occurred within 48 hours of treatment (and before treatment of the next attack) or not. They were also coded as to severity using mild, moderate, or severe, and to drug relationship (not related, unlikely, possibly, or probably). AE's were considered treatment related if the investigator indicated the AE to be "possibly" or "probably" related to study medication.

AE's with a ≥ 1% incidence in the frovatriptan 2.5mg group compared to placebo group were considered to be of relevance to frovatriptan.

8.5.2 Controlled Studies

There were 6 controlled short term studies: 06, 07, 09, 02, 14, and 03. Of these, study 03 included patients with known or at increased risk of coronary artery. Of the other 5 studies, study 14 is excluded from the pooled analysis due to the high number of patients who also participated in study 02. As in previous analyses, Dr. Fourie's center in study 09 (center 213) was excluded.

Table 56 (ISS panel 8.8.5.1.1:2, page 150) shows the incidence of treatment emergent adverse events that occurred within 48 hours of treatment for frovatriptan, placebo, and sumatriptan groups in studies 02, 06, 07, and 09 (attack 1). Only those AE's that occurred with an incidence ≥2% in any group are included. The sponsor provided a second table of "treatment-related" AE's (ISS panel 8.8.5.1:4, page 155, not shown here). This naturally resulted in lower incidences across the board. Since the term "treatment-related" is subject to interpretation, I chose to show the former table in this review.

Table 56: Studies 02, 06, 07, 09 (attack 1) – Treatment Emergent Adverse Events within 48 hours (≥2%)

Body System Preferred Term	Frovatriptan 2.5 mg (n=1554)	Frovatriptan 5 mg (n=99)	Frovatriptan 10 mg (n=192)	Frovatriptan >10 mg (n=410)	PBO (n=838)	Suma 100 mg (n=482)
≥ 1 AE within 48 hrs	723 (46.5%)	34 (34.3%)	104 (54.2%)	270 (65.9%)	282 (33.7%)	181 (37.6%)
CNS and PNS	*285 (18.3%)*	*15 (15.2%)*	*52 (27.1%)*	*135 (32.9%)*	*97 (11.6%)*	*79 (16.4%)*
Dizziness	123 (7.9%)	6 (6.1%)	22 (11.5%)	73 (17.8%)	44 (5.3%)	24 (5.0%)
Paresthesia	63 (4.1%)	3 (3.0%)	12 (6.3%)	25 (6.1%)	20 (2.4%)	26 (5.4%)
Headache	63 (4.1%)	3 (3.0%)	11 (5.7%)	26 (6.3%)	22 (2.6%)	20 (4.1%)
Hypoesthesia	18 (1.2%)	1 (1.0%)	4 (2.1%)	7 (1.7%)	5 (0.6%)	6 (1.2%)
Hyperesthesia	9 (0.6%)	1 (1.0%)	5 (2.6%)	10 (2.4%)	1 (0.1%)	2 (0.4%)
Hypertonia	1 (0.1%)	4 (4.0%)	9 (4.7%)	13 (3.2%)	0	0
Gastro-intestinal	*235 (15.1%)*	*10 (10.1%)*	*38 (19.8%)*	*124 (30.2%)*	*105 (12.5%)*	*62 (12.9%)*
Nausea	100 (6.4%)	5 (5.1%)	12 (6.3%)	63 (15.4%)	52 (6.2%)	31 (6.4%)
Mouth dry	48 (3.1%)	1 (1.0%)	8 (4.2%)	16 (3.9%)	12 (1.4%)	11 (2.3%)
Dyspepsia	33 (2.1%)	3 (3.0%)	3 (1.6%)	23 (5.6%)	11 (1.3%)	3 (0.6%)
Vomiting	30 (1.9%)	2 (2.0%)	5 (2.6%)	23 (5.6%)	21 (2.5%)	10 (2.1%)
Abdominal pain	27 (1.7%)	1 (1.0%)	6 (3.1%)	11 (2.7%)	10 (1.2%)	16 (3.3%)
Diarrhea	18 (1.2%)	1 (1.0%)	3 (1.6%)	12 (2.9%)	6 (0.7%)	3 (0.6%)
Body as a whole	*191 (12.3%)*	*11 (11.1%)*	*24 (12.5%)*	*112 (27.3%)*	*74 (8.8%)*	*60 (12.4%)*
Fatigue	82 (5.3%)	4 (4.0%)	8 (4.2%)	36 (8.8%)	19 (2.3%)	25 (5.2%)
Temp change sens.	51 (3.3%)	0	0	1 (0.2%)	19 (2.3%)	13 (2.7%)
Chest pain	37 (2.4%)	3 (3.0%)	10 (5.2%)	37 (9.0%)	11 (1.3%)	14 (2.9%)
Pain	18 (1.2%)	0	2 (1.0%)	9 (2.2%)	5 (0.6%)	5 (1.0%)
Asthenia	11 (0.7%)	4 (4.0%)	1 (0.5%)	13 (3.2%)	4 (0.5%)	11 (2.3%)
Rigors	9 (0.6%)	2 (2.0%)	0	9 (2.2%)	6 (0.7%)	0
Hot flushes	2 (0.1%)	0	6 (3.1%)	25 (6.1%)	1 (0.1%)	0
Psychiatric	*154 (9.9%)*	*7 (7.1%)*	*23 (12.0%)*	*69 (16.8%)*	*60 (7.2%)*	*24 (5.0%)*
Somnolence	63 (4.1%)	4 (4.0%)	13 (6.8%)	37 (9.0%)	34 (4.1%)	13 (2.7%)
Anxiety	16 (1.0%)	0	0	8 (2.0%)	2 (0.2%)	2 (0.4%)
Confusion	13 (0.8%)	1 (1.0%)	1 (0.5%)	9 (2.2%)	4 (0.5%)	4 (0.8%)
Euphoria	8 (0.5%)	2 (2.0%)	0	3 (0.7%)	1 (0.1%)	0
Musculo-skeletal	*90 (5.8%)*	*3 (3.0%)*	*8 (4.2%)*	*45 (11.0%)*	*29 (3.5%)*	*27 (5.6%)*
Skeletal pain	49 (3.2%)	0	0	12 (2.9%)	20 (2.4%)	14 (2.9%)
Myalgia	13 (0.8%)	0	6 (3.1%)	26 (6.3%)	3 (0.4%)	8 (1.7%)
Respiratory	*86 (5.5%)*	*5 (5.1%)*	*19 (9.9%)*	*62 (15.1%)*	*23 (2.7%)*	*20 (4.1%)*
Throat tightness	25 (1.6%)	1 (1.0%)	9 (4.7%)	30 (7.3%)	1 (0.1%)	6 (1.2%)
Rhinitis	18 (1.2%)	3 (3.0%)	2 (1.0%)	10 (2.4%)	5 (0.6%)	0
Pharyngitis	10 (0.6%)	1 (1.0%)	3 (1.6%)	16 (3.9%)	2 (0.2%)	5 (1.0%)

Body System Preferred Term	Frovatriptan 2.5 mg (n=1554)	Frovatriptan 5 mg (n=99)	Frovatriptan 10 mg (n=192)	Frovatriptan >10 mg (n=410)	PBO (n=838)	Suma 100 mg (n=482)
Skin and Appendages	*34 (2.2%)*	*2 (2.0%)*	*8 (4.2%)*	*18 (4.4%)*	*17 (2.0%)*	*11 (2.3%)*
Sweating increased	21 (1.4%)	2 (2.0%)	2 (1.0%)	9 (2.2%)	10 (1.2%)	8 (1.7%)
Vascular, extracardiac	*55 (3.5%)*	*2 (2.0%)*	*3 (1.6%)*	*12 (2.9%)*	*18 (2.1%)*	*5 (1.0%)*
Flushing	55 (3.5%)	2 (2.0%)	3 (1.6%)	12 (2.9%)	17 (2.0%)	5 (1.0%)
Heart rate and rhythm	*29 (1.9%)*	*1 (1.0%)*	*2 (1.0%)*	*13 (3.2%)*		*9 (1.9%)*
Tachycardia	9 (0.6%)	1 (1.0%)	1 (0.5%)	8 (2.0%)	2 (0.2%)	2 (0.4%)
Special senses, other	*13 (0.8%)*	*0*	*5 (2.6%)*	*5 (1.2%)*	*7 (0.8%)*	*0*
Taste perversion	13 (08.%)	0	4 (2.1%)	4 (1.0%)	6 (0.7%)	0

Overall, patients treated with frovatriptan 2.5mg reported a higher incidence of AE's compared with placebo (46.5% vs. 33.7%). There was a dose related increase in AE incidence from 2.5mg to 10mg and >10mg (46.5%, 54.2%, and 65.9%, respectively); however, the incidence of AE's for 5mg was actually less than that seen at 2.5mg (34.3% vs. 46.5%, respectively). The large discrepancy in the numbers exposed between the two groups may account for this observation (1554 vs. 99).

Chest pain occurred at an incidence of 2.4% in frovatriptan 2.5mg treated patients. This was approximately twice as high as the incidence in placebo patients (1.3%) but comparable to that seen in the sumatriptan 100mg group (2.9%). There was a frovatriptan dose-related increase in chest pain seen (2.4%, 3%, 5.2%, 9% for 2.5mg, 5mg, 10mg, and >10mg, respectively).

In general, the types of AE's reported were similar to those seen with other triptan medications. For the most commonly reported AE's, a higher incidence was generally reported in the frovatriptan 2.5mg group compared to placebo. Within the placebo group, the 5 AE's reported with the highest incidences were nausea (6.2%), dizziness (5.3%), somnolence (4.1%), headache (2.6%), and vomiting (2.5%). Within the frovatriptan 2.5mg group, the most commonly reported AE's were dizziness (7.9%), nausea (6.4%), fatigue (5.3%), headache (4.1%), paresthesia (4.1%), somnolence (4.1%). Therefore, dizziness, nausea, headache, and somnolence were common to both placebo and frovatriptan 2.5mg patients.

Table 57 (adapted from ISS, page 152) shows the most commonly reported AE's for frovatriptan 2.5mg that occurred with an incidence ≥1% greater than placebo.

Table 57: Studies 02, 06, 07, 09 (attack 1) – Most Commonly Reported AE's for Frovatriptan 2.5mg (≥1% compared to placebo)

AE	Frovatriptan 2.5mg Incidence	PBO Incidence
Dizziness	7.9%	5.3%
Fatigue	5.3%	2.3%
Paresthesia	4.1%	2.4%
Headache	4.1%	2.6%
Flushing	3.5%	2.0%
Temp change sens.	3.3%	2.3%
Dry mouth	3.1%	1.4%
Chest Pain	2.4%	1.3%
Throat Tightness	1.6%	0.1%

No clinically meaningful differences in the incidences of any mild, moderate, or severe AE's were detected between the frovatriptan 2.5mg and placebo treatment groups. With the exception of the fatigue, there were no clinical meaningful difference in the incidences of severe AE's in the frovatriptan 2.5mg and placebo treatment groups. Severe fatigue was reported by 1% of frovatriptan patients and by 0% of placebo patients.

Study 14 was analyzed separately because of the number of patients in that study that also participated in study 02. Patients received either placebo, 0.5mg, 1mg, 2.5mg or 5mg. For purposes of analysis, the sponsor combined the 0.5mg and 1mg dose groups. Table 58 (ISS panel 8.8.5.1.1:12, page 174) contains an overall summary of the treatment-emergent AE's in this study. It again shows a dose-related increase in AE's for the frovatriptan treatment groups compared to placebo. I don't show the list of the AE's reported since they are similar to those seen in the other controlled trials.

Table 58: Study 14 – Treatment-Emergent Adverse Events – Summary Table

	Frovatriptan Dose			PBO
	< 2.5mg	2.5mg	5mg	
Number of patients in safety population	255	131	126	123
Number of patients with at least 1 treatment-emergent AE	90 (35.3%)	51 (38.9%)	62 (49.2%)	35 (28.5%)
Number of patients with at least 1 treatment-emergent AE within 48 hours	83 (32.5%)	47 (35.9%)	60 (47.6%)	34 (27.6%)
Number of deaths	0	0	0	0
Number of patients with at least 1 serious AE	0	0	0	0

Studies 01 and 04 were small short-term uncontrolled studies. Study 01 was non-randomized. There were no new or unusually severe AE's reported that were not seen in

the controlled studies. Because of their small size and study design, they contribute little to our understanding of the AE profile of the drug and I don't discuss them here.

Study 03 enrolled patients with or at high risk for coronary artery disease. Treatment-emergent adverse events for that study is shown in Table 59 (Study 03 report, Table 6.2-2, page 53). Chest pain, arrhythmias, and palpitations were reported for 2, 1, and 2. patients in the placebo group, respectively, and in no patients in the frovatriptan group.

Table 59: Study 03 – Treatment Emergent Adverse Events

	Patients with CAD		High Risk of CAD		Total	
	2.5mg n=1	PBO n=2	2.5mg n=36	PBO n=35	2.5mg n=37	PBO n=36
All events	*1 (100%)*	*1 (50%)*	*8 (22%)*	*9 (26%)*	*9 (24%)*	*10 (26%)*
Gastrointestinal disorders	*1 (100%)*	*1 (50%)*	*3 (8%)*	*3 (9%)*	*4 (11%)*	*4 (11%)*
Abdominal pain	-	-	1 (3%)	1 (3%)	1 (3%)	1 (3%)
Diarrhea	-	-	1 (3%)	1 (3%)	1 (3%)	1 (3%)
Dyspepsia	1 (100%)	-	-	1 (3%)	1 (3%)	1 (3%)
Mouth dry	-	1 (50%)	2 (6%)	1 (3%)	2 (5%)	2 (5%)
Nausea	-	-	1 (3%)	-	1 (3%)	-
Cardiovascular disorders, general	-	-	*3 (8%)*	*1 (3%)*	*3 (8%)*	*1 (3%)*
Hypertension	-	-	3 (8%)	1 (3%)	3 (8%)	1 (3%)
Body as a whole, general	-	*1 (50%)*	*2 (6%)*	*2 (6%)*	*2 (5%)*	*3 (8%)*
Chest pain	-	-	-	2 (6%)	-	2 (5%)
Leg pain	-	1 (50%)	-	-	-	1 (3%)
Pain	-	-	1 (3%)	-	1 (3%)	-
Temp changed sensation	-	-	1 (3%)	-	1 (3%)	-
CNS & PNS disorders	-	-	*1 (3%)*	*3 (9%)*	*1 (3%)*	*3 (8%)*
Dizziness	-	-	1 (3%)	2 (6%)	1 (3%)	2 (5%)
Headache	-	-	-	1 (3%)	-	1 (3%)
Psychiatric disorders	*1 (100%)*	-	-	*2 (6%)*	*1 (3%)*	*2 (5%)*
Agitation	-	-	-	1 (3%)	-	1 (3%)
Somnolence	1 (100%)	-	-	2 (6%)	1 (3%)	2 (5%)
Respiratory system disorders	-	*1 (50%)*	*1 (3%)*	*1 (3%)*	*1 (3%)*	*2 (5%)*
Coughing	-	1 (50%)	-	-	-	1 (3%)
Dyspnea	-	-	1 (3%)	1 (3%)	1 (3%)	1 (3%)
Heart rate and rhythm disorders	-	-	-	*2 (6%)*	-	*2 (5%)*
Arrhythmia	-	-	-	1 (3%)	-	1 (3%)
Palpitation	-	-	-	2 (6%)	-	2 (5%)
Application site disorders	-	1 (50%)	-	-	-	1 (3%)
Application site reaction	-	1 (50%)	-	-	-	1 (3%)
Musculoskeletal disorders	-	-	-	*1 (3%)*	-	*1 (3%)*
Myalgia	-	-	-	1 (3%)	-	1 (3%)
Skin and appendages disorders	-	-	-	1 (3%)	-	1 (3%)
Acne	-	-	-	1 (3%)	-	1 (3%)
Special senses other, disorders	-	-	-	*1 (3%)*	-	*1 (3%)*
Taste perversion	-	-	-	1 (3%)	-	1 (3%)
Urinary system disorders	-	-	-	*1 (3%)*	-	*1 (3%)*
Micturition frequency	-	-	-	1 (3%)	-	1 (3%)

8.5.3 Long-Term Study 08

Throughout the entire course of this year long study, 81% (401/496) reported at least one treatment emergent AE. Of these, 377 patients (76%) reported AE's within 48 hours of treatment. There were no deaths. Twenty-six (5.2%) discontinued due to an adverse event.

The incidence of treatment-emergent AE's are presented by treatment exposure intervals from the date of the first dose of study medication for attack 1 in Table 60 (ISS panel 8.8.5.3.1:2, page 189). The most commonly reported AE's were similar to those seen in the short term trials. Most commonly reported during the first 13 week interval were nausea (17.9%), dizziness (13.3%), fatigue (12.1%), and somnolence (9.5%). The incidence of treatment-emergent AE's generally dropped over time, which is not unexpected as only those who tolerated the drug would be expected to continue treatment out to one year. Prolonged exposure did not result in the emergence of AE's that were not seen in the first treatment exposure interval or in the controlled short-term studies.

Table 60: Study 08 – Treatment-Emergent AE's within 48 Hours in ≥2% of Patients During Any Treatment Interval.

	Adverse Event Start Date (weeks)				
Body System Preferred Term	**0-13 (n=496)**	**>13-26 (n=438)**	**>26-39 (n=356)**	**>39-52 (n=281)**	**>52 (n=104)**
≥ 1 treatment-emergent AE starting during interval	335 (67.5%)	170 (38.8%)	130 (36.5%)	87 (31.0%)	10 (9.6%)
Gastro-intestinal	*165 (33.3%)*	*67 (15.3%)*	*49 (13.8%)*	*30 (10.7%)*	*4 (3.8%)*
Nausea	89 (17.9%)	32 (7.3%)	23 (6.5%)	16 (5.7%)	0
Dyspepsia	35 (7.1%)	14 (3.2%)	12 (3.4%)	6 (2.1%)	0
Vomiting	21 (4.2%)	7 (1.6%)	12 (3.4%)	5 (1.8%)	0
Diarrhea	20 (4.0%)	9 (2.1%)	6 (1.7%)	3 (1.1%)	1 (1.0%)
Abdominal pain	18 (3.6%)	7 (1.6%)	3 (0.8%)	1 (0.4%)	1 (1.0%)
Mouth dry	21 (4.2%)	8 (1.8%)	4 (1.1%)	2 (0.7%)	2 (1.9%)
Central and peripheral nervous	*137 (27.6%)*	*53 (12.1%)*	*48 (13.5%)*	*30 (10.7%)*	*2 (1.9%)*
Dizziness	66 (13.3%)	13 (3.0%)	16 (4.5%)	13 (4.6%)	1 (1.0%)
Headache	37 (7.5%)	22 (5.0%)	15 (4.2%)	7 (2.5%)	1 (1.0%)
Paresthesia	27 (5.4%)	12 (2.7%)	10 (2.8%)	5 (1.8%)	0
Migraine aggravated	10 (2.0%)	3 (0.7%)	1 (0.3%)	0	0
Body as a whole	*121 (24.4%)*	*42 (9.6%)*	*31 (8.7%)*	*17 (6.0%)*	*1 (1.0%)*
Fatigue	60 (12.1%)	20 (4.6%)	17 (4.8%)	10 (3.6%)	1 (1.0%)
Chest pain	23 (4.6%)	6 (1.4%)	5 (1.4%)	2 (0.7%)	0
Temperature changed sensation	22 (4.4%)	6 (1.4%)	3 (0.8%)	2 (0.7%)	0
Respiratory	*61 (12.3%)*	*45 (10.3%)*	*36 (10.1%)*	*18 (6.4%)*	*0*
Sinusitis	15 (3.0%)	16 (3.7%)	5 (1.4%)	7 (2.5%)	0
Upper respiratory tract infection	8 (1.6%)	13 (3.0%)	12 (3.4%)	3 (1.1%)	0
Rhinitis	16 (3.2%)	9 (2.1%)	9 (2.5%)	6 (2.1%)	0
Throat tightness	12 (2.4%)	4 (0.9%)	3 (0.8%)	2 (0.7%)	0

Body System Preferred Term	Adverse Event Start Date (weeks) 0-13 (n=496)	>13-26 (n=438)	>26-39 (n=356)	>39-52 (n=281)	>52 (n=104)
Psychiatric	*84 (16.9%)*	*27 (6.2%)*	*16 (4.5%)*	*8 (2.8%)*	*1 (1.0%)*
Somnolence	47 (9.5%)	9 (2.1%)	7 (2.0%)	3 (1.1%)	1 (1.0%)
Insomnia	13 (2.6%)	5 (1.1%)	0	0	0
Agitation	11 (2.2%)	5 (1.1%)	1 (0.3%)	1 (0.4%)	0
Musculo-skeletal	*70 (14.1%)*	*27 (6.2%)*	*20 (5.6%)*	*12 (4.3%)*	*2 (1.9%)*
Skeletal pain	32 (6.5%)	14 (3.2%)	9 (2.5%)	3 (1.1%)	1 (1.0%)
Myalgia	21 (4.2%)	6 (1.4%)	5 (1.4%)	5 (1.8%)	1 (1.0%)
Back pain	10 (2.0%)	5 (1.1%)	3 (0.8%)	3 (1.1%)	0
Vascular (extracardiac)	*31 (6.3%)*	*7 (1.6%)*	*2 (0.6%)*	*0*	*0*
Flushing	31 (6.3%)	6 (1.4%)	2 (0.6%)	0	0
Skin and appendages	*24 (4.8%)*	*5 (1.1%)*	*3 (0.8%)*	*5 (1.8%)*	*0*
Sweating increased	14 (2.8%)	2 (0.5%)	0	3 (1.1%)	0
Hearing and vestibular	*21 (4.2%)*	*10 (2.3%)*	*2 (0.6%)*	*1 (0.4%)*	*0*
Tinnitus	12 (2.4%)	6 (1.4%)	2 (0.6%)	0	0

Patients in study 08 could take up to 3 doses of study medication within 24 hours for the treatment of a migraine attack. Table 61 (ISS panel 8.8.5.3.1:4, page 194) shows the incidence of treatment emergent adverse events (all causalities) according to the number of doses taken per attack.

Table 61: Study 08 – Treatment-Emergent AE's by Number of Doses (≥2% Incidence)

Body System Preferred Term Number of attacks	Number of Doses per Attack 1 (n=466) 5968	2 (n=432) 4598	3 (n=362) 3316
Number of patients with at least 1 AE	281 (60.3%)	254 (58.8%)	184 (50.8%)
Gastro-intestinal	*118 (25.3%)*	*107 (24.8%)*	*98 (27.1%)*
Nausea	61 (13.1%)	51 (11.8%)	51 (14.1%)
Dyspepsia	27 (5.8%)	23 (5.3%)	21 (5.8%)
Vomiting	12 (2.6%)	17 (3.9%)	16 (4.4%)
Diarrhea	16 (3.4%)	12 (2.8%)	10 (2.8%)
Abdominal pain	13 (2.8%)	12 (2.8%)	8 (2.2%)
Mouth dry	12 (2.6%)	18 (4.2%)	12 (3.3%)
Central and peripheral nervous	104 (22.3%)	94 (21.8%)	63 (17.4%)
Dizziness	51 (10.9%)	37 (8.6%)	22 (6.1%)
Headache	30 (6.4%)	32 (7.4%)	22 (6.1%)
Paresthesia	23 (4.9%)	17 (3.9%)	11 (3.0%)
Body as a whole	*90 (19.3%)*	*69 (16.0%)*	*54 (14.9%)*
Fatigue	46 (9.9%)	31 (7.2%)	28 (7.7%)
Chest pain	16 (3.4%)	15 (3.5%)	7 (1.9%)
Temperature changed sensation	15 (3.2%)	10 (2.3%)	8 (2.2%)
Pain	10 (2.1%)	3 (0.7%)	4 (1.1%)

Body System Preferred Term Number of attacks	Number of Doses per Attack 1 (n=466) 5968	 2 (n=432) 4598	 3 (n=362) 3316
Respiratory	*62 (13.3%)*	*50 (11.6%)*	*38 (10.5%)*
Sinusitis	22 (4.7%)	13 (3.0%)	8 (2.2%)
Upper respiratory tract infection	11 (2.4%)	14 (3.2%)	9 (2.5%)
Rhinitis	17 (3.6%)	9 (2.1%)	10 (2.8%)
Psychiatric	*64 (13.7%)*	*46 (10.6%)*	*35 (9.7%)*
Somnolence	33 (7.1%)	24 (5.6%)	16 (4.4%)
Musculo-skeletal	*54 (11.6%)*	*51 (11.8%)*	*32 (8.8%)*
Skeletal pain	22 (4.7%)	22 (5.1%)	17 (4.7%)
Myalgia	15 (3.2%)	15 (3.5%)	6 (1.7%)
Back pain	10 (2.1%)	6 (1.4%)	5 (1.4%)
Vascular (extracardiac)	24 (5.2%)	13 (3.0%)	9 (2.5%)
Flushing	23 (4.9%)	13 (3.0%)	9 (2.5%)
Skin and appendages	*13 (2.8%)*	*19 (4.4%)*	*10 (2.8%)*
Sweating increased	5 (1.1%)	13 (3.0%)	5 (1.4%)
Hearing and vestibular	*11 (2.4%)*	*12 (2.8%)*	*12 (3.3%)*
Tinnitus	5 (1.1%)	9 (2.1%)	7 (1.9%)

In general, the incidence of AE's was similar regardless of the number of doses used per attack. This finding must be interpreted with caution because these are non-randomized subgroups. In general, patients were unlikely to take a 2nd or 3rd dose if the previous dose was not tolerated. Only vomiting showed a dose dependent increase in incidence.

Most AE's reported were mild or moderate in intensity. The most frequently reported severe AE's (≥2% incidence) during 0-13 weeks were nausea (5.2%), vomiting (3%), fatigue (2.8%), and headache (2.4) (ISS page 204).

8.6 Laboratory Findings

8.6.1 Methods

Laboratory measurements were obtained on blood and urine samples obtained at screening and at other protocol defined visits approximately 1 to 5 days after treatment of the last migraine attack for which study medication was taken or a maximum of 8 weeks (phase 2) or 12 weeks (phase 3) after the screening visit. In study 08, samples were drawn at screening/baseline, and at weeks 13, 26, 39 and 52. Blood samples were drawn from non-fasting patients, and samples were analyzed for hematology and chemistry results. Urine samples were collected and qualitative urinalysis was performed. In some studies, microscopic examinations were performed if indicated. The tests performed were standard clinical laboratory measurements. In addition, troponin T enzyme was measured in study 03, which assessed the potential safety of frovatriptan in patients with known or at high risk for CAD since this assessment is a specific marker of myocardial cell necrosis.

Samples were analyzed by [redacted] (study 06, 07, and 08). In study 09, 3 different commercial labs were used in the UK, South Africa, and Australia. Samples from studies 02, 03, 14, and 01 were analyzed by [redacted] Individual, site specific laboratories were used for the clinical pharmacology studies. Lab values were reported according to laboratory specific units, with their corresponding patient-specific reference ranges by the lab that performed the analysis. Lab results were converted to standard international units, if necessary, for this summary.

The sponsor used predefined criteria to determine clinically noteworthy values. These are shown in Table 62 (ISS panels 8.8.9:5/6, page 253/4),

Table 62: Clinically Noteworthy Criteria for Laboratory Tests

Laboratory Test	Gender	Clinically Noteworthy Criteria
Glucose		< 0.75x LLN > 1.30x ULN
Sodium		< 0.93x LLN > 1.07x ULN
Potassium		< 0.90x LLN > 1.10x ULN
Calcium		< 0.85x LLN > 1.08x ULN
Protein, Total		< 0.80x LLN
Albumin		< 0.90x LLN
Alkaline Phosphatase		> 1.25x ULN
ALT (SGPT)	Male	> 2.0x ULN
	Female	> 2.0x ULN
AST (SGOT)	Male	> 2.0x ULN
	Female	> 2.0x ULN
Bilirubin, Total		> 1.5x ULN
GGT	Male	> 2.0x ULN
	Female	> 2.0x ULN
BUN		> 1.25x ULN
Creatinine	Male	> 1.3x ULN
	Female	> 1.3x ULN
Uric Acid	Male	> 1.2 x ULN
	Female	> 1.2 x ULN
CPK	Male	> 2.0 x ULN
	Female	> 2.0x ULN

Laboratory Test	Gender	Clinically Noteworthy Criteria
Hemoglobin	Male	< 0.85x LLN > 1.15x ULN
	Female	< 0.83x LLN > 1.15x ULN
Hematocrit	Male	< 0.93x LLN > 1.15x ULN

Laboratory Test	Gender	Clinically Noteworthy Criteria
	Female	< 0.91x LLN > 1.15x ULN
RBC Count	Male	< 0.75 x LLN > 1.30x ULN
	Female	< 0.80x LLN > 1.30x ULN
MCV	Male	< 76 or > 100 fL
	Female	< 76 or > 100 fL
Platelet Count		< 0.50x LLN > 1.60x ULN
WBC Count		< 0.7x LLN > 1.3x ULN
Neutrophils		< 0.8x LLN > 1.3x ULN
Lymphocytes		< 0.8x LLN > 2.0x ULN
Eosinophils		> 1.7x ULN
Basophils		> 5.0x ULN
Monocytes		< 0.25x LLN > 2.0 x ULN

Summary tables display the numbers and percentages of patients with clinically noteworthy post baseline abnormalities and also list individual abnormalities, by study groupings. Adverse events were recorded by the investigators. From the list of AE's, the sponsor identified AE's that were clinical laboratory abnormalities. Clinical laboratory values or changes reported as AE's are summarized for study groups.

8.6.2 Controlled Studies

Clinical laboratory data for the five major controlled studies, 06, 07, 09 (attack 1), 02, 14 are shown in this section. As before, study 14 is shown separately. Also shown separately are the results for the first attack of study 09. Study 09 is discussed separately because attacks 2 and 3 of study 09 were open label, after which the laboratory assessment occurred. The hematology results for studies 06, 07, and 02 are shown in Table 63 (ISS panel 8.8.9.1.1:1, page 257).

Table 63: Studies 06, 07, 02 – Hematology Results

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
Hemoglobin (115-181 g/L)							
Frovatriptan 2.5 mg	1027	135.2	974	-0.9	12 (1.2%)	1 (0.1%)	4 (0.4%)
Placebo	570	134.6	531	-0.9	12 (2.3%)	2 (0.4%)	2 (0.3%)
Hematocrit (PCV) (0.34-0.54 v/v)							
Frovatriptan 2.5 mg	1027	0.41	973	-0.01	26 (2.7%)	2 (0.2%)	8 (0.7%)
Placebo	569	0.41	530	-0.01	19 (3.6%)	5 (0.9%)	6 (1.0%)

Lab Parameter / Treatment Group	Baseline n	Baseline Mean	Δ from Baseline n	Δ from Baseline Mean	Shifts (Baseline to Endpoint) N→Low	Shifts (Baseline to Endpoint) N→High	N with CNV*
RBC (3.8-6.4 x 1012/L)							
Frovatriptan 2.5 mg	1027	4.40	974	-0.05	33 (3.4%)	0	0
Placebo	570	4.42	531	-0.04	15 (2.8%)	1 (0.2%)	0
MCV (79-98 fL)							
Frovatriptan 2.5 mg	1027	93.0	973	-0.5	0	30 (3.1%)	53 (4.9%)
Placebo	569	92.3	530	-0.5	1 (0.2%)	13 (2.5%)	28 (4.7%)
MCH (26-34 pg/cell)							
Frovatriptan 2.5 mg	1027	30.9	974	0.1	3 (0.3%)	6 (0.6%)	0
Placebo	570	30.6	531	0.2	2 (0.4%)	4 (0.8%)	0
MCHC (310-380 gHb/L)							
Frovatriptan 2.5 mg	1027	331.9	973	3.6	1 (0.1%)	0	0
Placebo	569	331.3	530	4.0	3 (0.6%)	0	0
Platelets (140-450 x 109/L)							
Frovatriptan 2.5 mg	1016	252.4	959	-1.7	2 (0.2%)	3 (0.3%)	0
Placebo	567	256.0	526	0.2	3 (0.6%)	2 (0.4%)	1 (0.2%)
WBC (3.8-12.3 x 109/L)							
Frovatriptan 2.5 mg	1027	6.65	974	0.02	26 (2.7%)	8 (0.8%)	2 (0.2%)
Placebo	570	6.62	531	-0.06	15 (2.8%)	4 (0.8%)	1 (0.2%)
Neutrophils-segs (2.03-8.36 x 109/L)							
Frovatriptan 2.5 mg	1027	3.98	974	0.00	36 (3.7%)	16 (1.6%)	26 (2.4%)
Placebo	570	4.00	531	-0.07	22 (4.1%)	10 (1.9%)	19 (3.2%)
Lymphocytes (1.02-3.52 x 109/L)							
Frovatriptan 2.5 mg	1027	2.01	974	0.03	16 (1.6%)	17 (1.7%)	3 (0.3%)
Placebo	570	1.98	531	0.00	7 (1.3%)	10 (1.9%)	4 (0.7%)
Eosinophils (0.00-0.56 x 109/L)							
Frovatriptan 2.5 mg	1027	0.19	974	-0.01	0	6 (0.6%)	0
Placebo	570	0.18	531	-0.01	0	6 (1.1%)	0
Basophils (0.00-0.17 x 109/L)							
Frovatriptan 2.5 mg	1027	0.04	974	0.00	0	1 (0.1%)	0
Placebo	570	0.04	531	0.00	0	0	0
Monocytes (0.16-0.91 x 109/L)							
Frovatriptan 2.5 mg	1027	0.44	974	0.00	10 (1.0%)	6 (0.6%)	3 (0.3%)
Placebo	570	0.42	531	0.01	2 (0.4%)	7 (1.3%)	1 (0.2%)

*CNV = clinically noteworthy values, as defined in Table 62, page 74

Mean changes from baseline, shifts from normal to either low or high endpoint values, and number of patients with clinically noteworthy values were small and comparable for all parameters for frovatriptan 2.5mg and placebo groups.

AE's related to clinical hematology were reported in 7 patients in the frovatriptan group compared to 2 patients in the placebo group. One patient randomized to frovatriptan 2.5mg experienced 11 episodes of 8 individual AE's related to hematology values. This is the same patient who died and is discussed in section 8.2, page 59. Other AE's related to hematology values for one to three patients were: abnormal platelets, anemia, eosinophilia, and abnormal WBC.

The chemistry results for the same studies are shown in Table 64 (ISS panel 8.8.9.1.1:2, page 262/3).

Table 64: Studies 06, 07, 02 – Clinical Chemistry Results

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
Glucose (3.8-6.5 mmol/L)							
Frovatriptan 2.5 mg	1029	5.21	992	0.04	33 (3.3%)	52 (5.2%)	18 (1.7%)
Placebo	571	5.22	539	0.05	18 (3.3%)	36 (6.7%)	8 (1.4%)
Sodium (132-147 mmol/L)							
Frovatriptan 2.5 mg	1030	138.2	992	-0.2	4 (0.4%)	0	0
Placebo	571	138.2	541	-0.2	1 (0.2%)	0	0
Potassium (3.3-5.5 mmol/L)							
Frovatriptan 2.5 mg	1030	4.19	992	-0.05	1 (0.1%)	2 (0.2%)	0
Placebo	571	4.20	541	-0.05	0	0	0
Phosphorous (0.71-1.65 mmol/L)							
Frovatriptan 2.5 mg	1030	1.17	992	-0.01	4 (0.4%)	3 (0.3%)	0
Placebo	571	1.17	541	-0.01	3 (0.6%)	0	0
Calcium (2.10-2.58 mmol/L)							
Frovatriptan 2.5 mg	1030	2.25	992	-0.03	80 (8.1%)	0	0
Placebo	571	2.25	541	-0.03	47 (8.7%)	1 (0.2%)	0
Total protein (60-84 g/L)							
Frovatriptan 2.5 mg	1030	71.7	992	-0.7	3 (0.3%)	1 (0.1%)	0
Placebo	571	71.3	541	-0.5	0	1 (0.2%)	0
Albumin (32-50g/L)							
Frovatriptan 2.5 mg	1030	43.4	992	-0.4	0	6 (0.6%)	0
Placebo	571	43.0	541	-0.3	0	4 (0.7%)	0
Alkaline phosphatase (31-121 U/L)							
Frovatriptan 2.5 mg	1030	74.5	992	0.1	1 (0.1%)	12 (1.2%)	11 (1.0%)
Placebo	571	73.2	541	0.0	1 (0.2%)	5 (0.9%)	4 (0.7%)
ALT (SGPT) (6-46 U/L)							
Frovatriptan 2.5 mg	1030	20.2	992	-0.3	1 (0.1%)	20 (2.0%)	4 (0.4%)
Placebo	571	19.8	541	0.1	0	13 (2.4%)	1 (0.2%)

Lab Parameter / Treatment Group	Baseline n	Baseline Mean	Δ from Baseline n	Δ from Baseline Mean	Shifts (Baseline to Endpoint) N→Low	Shifts (Baseline to Endpoint) N→High	N with CNV*
AST (SGOT) (5-37 U/L)							
Frovatriptan 2.5 mg	1030	20.7	992	-0.3	0	18 (1.8%)	2 (0.2%)
Placebo	571	20.4	541	-0.3	0	6 (1.1%)	1 (0.2%)
Total bilirubin (3-21 µmol/L)							
Frovatriptan 2.5 mg	1030	8.27	992	0.09	1 (0.1%)	6 (0.6%)	2 (0.2%)
Placebo	571	8.27	541	-0.14	1 (0.2%)	2 (0.4%)	0
GGT (4 – 64 U/L)							
Frovatriptan 2.5 mg	1030	27.6	992	-0.1	0	27 (2.7%)	23 (2.1%)
Placebo	571	27.9	541	0.3	0	16 (3.0%)	15 (2.5%)
BUN (1.43-8.57 mmol/L)							
Frovatriptan 2.5 mg	1030	4.44	992	-0.02	1 (0.1%)	1 (0.1%)	0
Placebo	571	4.52	541	0.00	1 (0.2%)	3 (0.6%)	1 (0.2%)
Creatinine (35-115 µmol/L)							
Frovatriptan 2.5 mg	1030	72.8	992	-0.4	0	7 (0.7%)	0
Placebo	571	72.5	541	-0.6	0	1 (0.2%)	1 (0.2%)
Uric acid (125-517 µmol/L)							
Frovatriptan 2.5 mg	937	265.1	899	-4.1	6 (0.7%)	8 (0.9%)	1 (0.1%)
Placebo	480	269.0	451	-5.4	2 (0.4%)	6 (1.3%)	1 (0.2%)
CPK (24-195 U/L)							
Frovatriptan 2.5 mg	937	91.8	899	5.8	2 (0.2%)	40 (4.4%)	25 (2.3%)
Placebo	480	94.8	451	2.3	1 (0.2%)	18 (4.0%)	5 (0.8%)

*CNV = clinically noteworthy values, as defined in Table 62, page 74

With the exception of CPK , mean changes from baseline, shifts from normal to either low or high endpoint values, and number of patients with clinically noteworthy values were small and comparable for all parameters for frovatriptan 2.5mg and placebo groups.

Mean increases CPK levels were higher post-treatment in the frovatriptan 2.5mg group compared to placebo (5.8 vs. 2.3). This by itself is not a clinically large increase in CPK levels, and the proportion of those who shifted from normal to high were comparable in the two groups (4.4% vs. 4.0%). However, the percentage who had clinically noteworthy elevations in CPK were 2.3% (n=25) in the frovatriptan 2.5mg group compared with 0.8% (n=5) for placebo. Closer inspection of these 25 frovatriptan cases reveal that 3 of the 25 had clinically noteworthy CPK abnormalities at baseline, and an additional 9 cases had elevated CPK's at baseline. In comparison, 2 of the 5 placebo patients had elevated CPK's at baseline. When these are removed from the analysis, then the percentages are 1.4% (13/937) for the frovatriptan group and 0.6% (3/480) for the placebo group. This, combined with the difference in mean changes in CPK values, continues to show a small signal.

The most common AE's related to clinical chemistry abnormalities in the frovatriptan group were increased GGT, reported for 12 patients, and elevated CPK, reported for 8

patients. Patient 97/07_734_0574, who was randomized to frovatriptan 2.5mg in study 07, had 22 clinical laboratory values reported as AE's. This patient died of sepsis secondary to an infected foot and is discussed in section 8.2, page 59. Another patient, 96/06_605_209, was randomized to frovatriptan 2.5mg in study 06 and had GGT, ALT, AST, and ALKP values or changes reported as AE's. Patient 95/02-027-0112, who was randomized to frovatriptan 10mg in study 02, patient 95/02_029_0027 (frovatriptan 20mg in study 02), and patient 95/02_031_1049 (frovatriptan 20mg in study 02) all had GGT, ALT, and AST values or changes reported as AE's. For patients in the placebo group, the most common AE related to clinical chemistry was increased CPK, reported for 4 patients. None of the AE's related to clinical chemistry were considered serious or resulted in withdrawal of a patient from any study. The majority of AE's related to clinical chemistry were reported by the investigator as mild or moderate.

Qualitative assessments were performed on the urinalysis for these three studies. Results for pH, protein, glucose, ketones, and bilirubin are grouped for discussion. Bilirubin was not measured for study 02. Review of shift tables (not shown here) showed there were no clear trends in change between the frovatriptan 2.5mg and placebo groups for any urinalysis assessment. The percentage of patients with shifts from normal to abnormal was generally low (≤ 1.5%). No clinically noteworthy abnormalities were associated with changes in urinalysis and no urinalysis assessments were reported as AE's.

Patients in study 09 treated three attacks. The first one was randomized to frovatriptan 2.5mg, sumatriptan 100mg, or placebo and the last two were treated with open-label frovatriptan 2.5mg. Laboratory assessments were performed at the end of the study. Although the data are presented in the ISS by randomized dose groups, all patients received frovatriptan. For hematological and chemistry assessments, mean values for all treatment groups were within the reference range limits at baseline and at endpoint. There were no clinically meaningful difference among the treatment group sat baseline or endpoint and no remarkable changes from baseline to endpoint. Review of shift tables showed no clear trends for change across treatment groups for any individual hematological assessment. The percentage of patients with shifts either from normal to low or normal to high was generally low (≤ 5.2%) and similar across treatment groups. The percentage with clinically noteworthy abnormalities was generally similar for the frovatriptan 2.5mg group (4.2%, 4.6%, for hematology and chemistry parameters, respectively), sumatriptan 100mg (5.2%, 6.0%), and placebo (5.7%, 7.4%). Out of interest, endpoint CPK levels rose by a mean of 6.1 and 5.8 units for the frovatriptan and placebo groups, and fell a mean of 8 U/L for the sumatriptan 100mg group (remembering that the sumatriptan group also received frovatriptan 2.5mg for attacks 2 and 3). The percentages with clinical noteworthy CPK abnormalities were low (0.6-1.2%). There were no clinically meaningful findings on urinalysis.

Patients in study 14 treated a single attack. It is discussed separately because of the high number of patients that also participated in study 02. Results were similar to those seen in the other controlled trials. No hematology of clinical chemistry safety signals were evident. The study did not measure CPK, however.

Study 03 was analyzed separately because it was the only short term controlled study that evaluated patients with or at high risk for CAD. This was a small study, with 37 and 38 patients in the frovatriptan 2.5mg and placebo groups, respectively. Although patients were treated in the clinic, laboratory assessments were not done at the day of treatment, but instead were done at the follow-up visit, which was at 24-36 hours after treatment (Study report for VML251-97-03, page 22). There were no clinically meaningful changes in clinical hematology, chemistry, or urinalysis results in this study. There was higher variability seen in the results which most likely reflect the small sample size. Two transient raised troponin T values (> 0.2 ng/mL) occurred. One occurred in one patient (17/069) at baseline, the other occurred at 24 hours post-dose in patient 05/159. There was no other evidence of myocardial infarction or ischemia in either patient nor were either considered to be clinically significant by the investigator.

8.6.3 Long Term Study 08

In this year long study, lab samples were drawn at baseline, and at three month intervals up to one year. Table 65 (ISS panel 8.8.9.3:1, page 303) shows the hematology results for this study. Visit 4 in the table occurred at the 6 month visit, and visit 6 occurred at 12 months. It is not clear to me when the "endpoint" observation occurred, since it is not described in the protocol. For all hematology assessments, mean values were within the reference range limits at baseline, at visits 3, 4, 5, and 6 (13, 26, 39, 52 weeks) and at endpoint. There were no clinically meaningful differences from baseline to endpoint. The percentage of patients with shift from normal to high or to low was generally low (≤3.8%). There were no clear trends in the percentage of patients with clinically noteworthy abnormalities for any hematological assessment.

Table 65: Study 08 – Hematology Results

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
Hemoglobin							
(116-175 g/L)	487	135.0					2 (0.4%) – baseline
Visit 4 (26 wks)			286	-0.9	-	-	1 (0.3%)
Visit 6 (52 wks)			247	-2.6	-	-	1 (0.4%)
Endpoint			453	-2.1	15 (3.3%)	1 (0.2%)	3 (0.7%)
Hematocrit (PCV)							
(0.35-0.52 v/v)	487	0.41					2 (0.4%)– baseline
Visit 4			286	-0.02	-	-	2 (0.7%)
Visit 6			247	-0.01	-	-	3 (1.2%)
Endpoint			453	-0.01	17 (3.8%)	3 (0.7%)	6 (1.3%)
RBC							
(3.8-5.9 x 1012/L)	487	4.43					0 – baseline
Visit 4			286	-0.08	-	-	1 (0.3%)
Visit 6			247	-0.08	-	-	0
Endpoint			453	-0.09	16 (3.5%)	0	1 (0.2%)
MCV							
(79-98 fL)	487	92.5					24 (4.9%) – baseline
Visit 4			286	-1.9	-	-	4 (1.4%)
Visit 6			247	-0.5	-	-	11 (4.4%)
Endpoint			453	-0.7	2 (0.4%)	12 (2.6%)	15 (3.3%)

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
MCH							
(26-34 pg/cell)	487	30.6					0 – baseline
Visit 4			286	0.4	-	-	0
Visit 6			247	0.0	-	-	0
Endpoint			453	0.1	2 (0.4%)	2 (0.4%)	0
MCHC							
(310-370 gHb/L)	487	330.9					0 – baseline
Visit 4			286	10.7	-	-	0
Visit 6			247	1.3	-	-	0
Endpoint			453	3.9	0	0	0
Platelets							
(140-450 x 109/L)	486	251.4					0 – baseline
Visit 4			286	2.1	-	-	0
Visit 6			246	2.7	-	-	0
Endpoint			451	2.2	3 (0.7%)	1 (0.2%)	0
WBC							
(4.1-12.3 x 109/L)	487	6.76					1 (0.2%) – baseline
Visit 4			286	-0.07			1 (0.3%)
Visit 6			247	-0.30	-	-	0
Endpoint			453	-0.11	12 (2.6%)	2 (0.4%)	0
Neutrophils-segs							
(2.03 –8.36 x 109/L)	487	4.03					3 (0.6%) – baseline
Visit 4			286	0.00	-	-	3 (1.0%)
Visit 6			247	-0.15	-	-	1 (0.4%)
Endpoint			453	0.01	6 (1.3%)	3 (0.7%)	3 (0.7%)
Lymphocytes							
(1.02-3.36 x 109/L)	487	2.04					0 – baseline
Visit 4			286	-0.03	-	-	2 (0.7%)
Visit 6			247	-0.07	-	-	2 (0.8%)
Endpoint			453	-0.05	9 (2.0%)	2 (0.4%)	3 (0.7%)
Eosinophils							
(0.00-0.56 x 109/L)	487	0.20					0 – baseline
Visit 4			286	-0.03	-	-	0
Visit 6			247	-0.02	-	-	1 (0.4%)
Endpoint			453	-0.02	0	4 (0.9%)	1 (0.2%)
Basophils							
(0.00-0.17 x 109/L)	487	0.046					0 – baseline
Visit 4			286	-0.01	-	-	0
Visit 6			247	-0.02	-	-	0
Endpoint			453	-0.01	0	0	0
Monocytes							
(0.16-0.91 x 109/L)	487	0.452					0 – baseline
Visit 4			286	0.01	-	-	0
Visit 6			247	-0.06	-	-	0
Endpoint			453	-0.02	1 (0.2%)	5 (1.1%)	0

*CNV = clinically noteworthy values, as defined in Table 62, page 74

The most commonly reported AE related to hematology was anemia, reported for 4 patients. Thrombocytopenia and megaloblastic anemia were each reported for 1 patients. None was considered serious. One patient (96/08_510_0201) was diagnosed with autoimmune hemolytic anemia, considered by the investigator to be related to study

medication, and withdrawn from the study. Hemoglobin and hematocrit at baseline for this patient was 143 g/L and 0.427, respectively, and 85 g/L and 0.239 at visit 4 (26 weeks).

Results for clinical chemistry are shown in Table 66 (ISS panel 8.8.9.3:2, page 308). For all clinical chemistry assessments, mean values were within the reference range limits at baseline and subsequent visits. There were no clinically meaningful differences or other remarkable changes from baseline to endpoint.

Table 66: Study 08 – Clinical Chemistry Results

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
Glucose							
(3.8-6.5 mmol/L)	488	5.39					7 (1.4%) – baseline
Visit 4			295	-0.13			6 (2.0%)
Visit 6			252	0.08			5 (2.0%)
Endpoint			456	-0.03	8 (1.8%)	23 (5.0%)	8 (1.7%)
Sodium							
(132-147 mmol/L)	488	138.4					0 – baseline
Visit 4			295	-0.3			0
Visit 6			252	-0.5			0
Endpoint			456	-0.4	6 (1.3%)	0	0
Potassium							
(3.3-5.5 mmol/L)	488	4.21					0 – baseline
Visit 4			295	-0.09			0
Visit 6			252	-0.03			0
Endpoint			456	-0.04	0	0	0
Phosphorous							
(0.74-1.65 mmol/L)	488	1.20					0 – baseline
Visit 4			295	-0.07			0
Visit 6			252	-0.03			0
Endpoint			456	-0.04	1 (0.2%)	0	0
Calcium							
(2.10-2.58 mmol/L)	488	2.26					0 – baseline
Visit 4			295	-0.06			0
Visit 6			252	-0.04			0
Endpoint			456	-0.04	43 (9.4%)	1 (0.2%)	0
Total protein							
(60-84 g/L)	488	71.7					0 – baseline
Visit 4			295	-1.2			0
Visit 6			252	-0.9			0
Endpoint			456	-0.9	1 (0.2%)	0	0
Albumin							
(32-50 g/L)	488	43.8					0 – baseline
Visit 4			295	-0.6			0
Visit 6			252	-0.5			0
Endpoint			456	-0.5	0	3 (0.7%)	0
Alkaline phosphatase							
(31-121 U/L)	488	74.2					3 (0.6%) – baseline
Visit 4			295	1.2			0
Visit 6			252	4.4			1 (0.4%)
Endpoint			456	2.6	1 (0.2%)	9 (2.0%)	2 (0.4%)

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
ALT (SGPT)							
(6-46 U/L)	488	20.7					3 (0.6%) – baseline
Visit 4			295	0.7			2 (0.7%)
Visit 6			252	0.8			0
Endpoint			456	0.5	0	15 (3.3%)	2 (0.4%)
AST (SGOT)							
(5-37 U/L)	488	21.9					1 (0.2%)
Visit 4			295	-0.4			0
Visit 6			252	0.0			1 (0.4%)
Endpoint			456	-0.6	0	9 (2.0%)	1 (0.2%)
Total bilirubin							
(3-21 µmol/L)	488	7.92					2 (0.4%) – baseline
Visit 4			295	0.05			1 (0.3%)
Visit 6			252	0.28			0
Endpoint			456	0.17	1 (0.2%)	2 (0.4%)	0
GGT (5-64 U/L)	*488*	*29.3*					*11 (2.3%) – baseline*
Visit 4			295	-0.7			5 (1.7%)
Visit 6			252	-2.8			3 (1.2%)
Endpoint			456	-1.9	0	11 (2.4%)	8 (1.7%)
Blood urea nitrogen							
(1.43-8.57 mmol/L)	488	4.46					0 – baseline
Visit 4			295	-0.06			0
Visit 6			252	-0.05			0
Endpoint			456	-0.03	0	1 (0.2%)	0
Creatinine							
(35-115 µmol/L)	488	71.8					0 – baseline
Visit 4			295	-2.0			1 (0.3%)
Visit 6			252	-0.5			0
Endpoint			456	-0.5	0	1 (0.2%)	0
Uric acid							
(125-517 mol/L)	488	263.6					0 – baseline
Visit 4			295	-11.0			0
Visit 6			252	2.4			0
Endpoint			456	0.6	2 (0.4%)	10 (2.2%)	1 (0.2%)
CPK							
(24-195 U/L)	488	93.7					2 (0.4%)-baseline
Visit 4			295	-4.3			1 (0.3%)
Visit 6			252	5.9			4 (1.6%)
Endpoint			456	1.6	1 (0.2%)	13 (2.9%)	5 (1.1%)

*CNV = clinically noteworthy values, as defined in Table 62, page 74

Review of shifts from normal to low or high values showed no clear trends for change in any clinical chemistry assessment. The percentage of patients with a shift was generally low (≤2.9%), with the exception of glucose (normal → high, 5%) and calcium (normal → low, 9.4%). On the other hand, the percentage of patients with glucose values that shifted from high to normal was 4.8%, and the percentage of patients with calcium measurements that shifted from low to normal was 3.7%.

In a follow-up of the mild CPK signal seen in the controlled trials, the percentage of patients with CPK values that shifted from normal to high was 2.9% compared with 3.7% of patients with CPK values that shifted from high to normal.

The overall percentage of patients with clinically noteworthy abnormalities was 5.4% at visit 4 (26 weeks), 5.1% at visit 6 (52 weeks), and 5.4% at endpoint. There were no clear trends in the percentage of patients with clinically noteworthy abnormalities for any clinical chemistry value.

The most common AE's related to clinical chemistry values were increased GGT, reported for 5 patients, and increased SGPT, reported for 3 patients. None was considered serious or resulted in withdrawal.

8.7 Vital Signs

8.7.1 Methods

Vital signs, including supine blood pressure and pulse rate, were monitored during drug development as part of the safety monitoring. As most of the studies were outpatient, these measurements often occurred days after study medication was taken and don't document vital sign changes immediately after ingestion. For that information, one needs to turn to the inpatient studies, which I also describe below.

The sponsor used post-hoc criteria for identifying clinically significant vital signs. These are shown in Table 67 (ISS panel 8.8.10:1, page 320).

Table 67: Criteria Used to Define Clinically Significant Vital Sign Abnormalities

Parameter	Increase	Decrease
Systolic blood pressure (mmHg)	≥ 180 mmHg and 20 mmHg increase	≤ 90 mmHg and 20 mmHg decrease
Diastolic blood pressure (mmHg)	≥ 105 mmHg and 15 mmHg increase	≤ 50 mmHg and 15 mmHg decrease
Pulse rate (bpm)	≥ 120 bpm and 15 bpm increase	≤ 50 bpm and 15 bpm decrease

Studies 06, 07, and 02 are described together because vitals signs were measured at the same time in each study (screening/baseline, and endpoint). Again, these are outpatient studies, so vital signs measurements occurred at least a day after dosing. Study 14 was analyzed separately for the same reasons outlined previously. Study 09 included both controlled (attack 1) and uncontrolled (attacks 2,3) treatment periods. Since post-treatment vital signs were obtained after attack 3, this study was also analyzed separately. As before, center 2413 was excluded from that analysis due to irregularities at that site.

8.7.2 Controlled Studies

The mean changes for systolic and diastolic blood pressures and pulse rate from screening/baseline to endpoint are presented in Table 68 (ISS panel 8.8.10.1.1:1, page 323). Mean changes were small in all treatment groups and not clinically meaningful.

Table 68: Studies 06, 07, 02 – Vital Signs Results, Mean Change from Screening/Baseline to Endpoint

	Frovatriptan Dose				PBO
	2.5mg	5mg	10mg	>10mg	
Systolic blood pressure, mmHg	-0.5 (n=985)	-0.9 (n=90)	-1.6 (n=179)	-0.8 (n=383)	-0.6 (n=541)
Diastolic blood pressure, mmHg	-0.3 (n=984)	-0.1 (n=90)	-1.6 (n=179)	-0.1 (n=383)	-0.5 (n=541)
Pulse rate, bpm	1.6 (n=984)	0.6 (n=90)	0.3 (n=178)	0.8 (n=383)	1.4 (n=542)

A total of 23 patients in these 3 studies combined had vital sign value that met the criteria for clinical noteworthiness. These are shown in Table 69 (ISS Panel 8.8.10.1.1:2, page 323). The incidence of these changes was low and similar among treatment groups. Those who exhibited a clinically noteworthy vital sign change in one parameter did not exhibit changes in the other parameters. The majority of the changes were decreases in systolic or diastolic blood pressures. There was no apparent dose-response relationship. None of these changes was reported as an adverse event (either hypertension or hypotension).

Table 69: Studies 06, 07, 02 – Clinically Noteworthy Vital Signs Changes

	Frovatriptan Dose				PBO
	2.5mg	5mg	10mg	>10mg	
Number of patients with at least 1 clinically noteworthy vital sign	11 (1.0%) (n = 984)	0 (n = 90)	1 (< 1%) (n = 178)	4 (< 1%) (n = 383)	7 (1.2%) (n = 541)
Systolic blood pressure	7 (< 1%) (n = 985)	0 (n = 90)	0 (n = 179)	2 (< 1%) (n = 383)	4 (< 1%) (n = 541)
Diastolic blood pressure	3 (< 1%) (n = 984)	0 (n = 90)	1 (< 1%) (n = 179)	2 (< 1%) (n = 383)	2 (< 1%) (n = 541)
Pulse rate	1 (< 1%) (n = 984)	0 (n = 90)	0 (n = 178)	0 (n = 383)	1 (< 1%) (n = 542)

The changes seen in vital signs were low and similar for studies 09 and 14 (not shown here).

Study 03 was the controlled trial in patients with or at risk for coronary artery disease. This was an inpatient study and provides vital sign measurements shortly after treatment. Those results are shown in Table 70 (ISS panel 8.8.10.1.2:1, page 329). Blood pressure measurements were done at 1, 2, and 4 hours post-dose (T_{max} 2-4 hours). The end of

study measurement was done 24-36 hours after dosing. There were no clinically meaningful changes in either BP or pulse in either treatment group.

Table 70: Study 03 – Post-treatment Vital Signs Changes

	Screening	Predose	Postdose 1 hour	Postdose 2 hours	Postdose 4 hours	End of Study
Systolic blood pressure (mmHg)						
Frovatriptan 2.5 mg (n=37)	145.5	137.5	136.7	136.9	134.5	131.8
Placebo (n=38)	138.4	133.3	132.2	130.8	133.8	130.4
Diastolic blood pressure (mmHg)						
Frovatriptan 2.5 mg (n=37)	83.3	81.1	81.9	82.1	83.2	79.9
Placebo (n=38)	80.9	81.2	79.8	80.9	80.8	80.5
Pulse rate (bpm)						
Frovatriptan 2.5 mg (n=37)	73.5	73.9	71.0	70.2	70.4	74.0
Placebo (n=38)	74.1	72.0	70.3	70.9	72.5	75.7

One patient in this study met the criteria for a clinically noteworthy change. This was patient 97/03_12_138, a 54 y/o male with a history of hypertension who was randomized to frovatriptan 2.5mg. He had a BP of 157/105 at pre-dose, and 175/108 at 1 hour post-dose. Blood pressure increased to 192/120 at 2 hours. This was reported as an adverse event but was judged by the investigator not to be related to treatment (??). At four hours, the BP was 186/117. At the end of the study, the blood pressure was 163/112. No other AE's were reported for this patient.

8.7.3 Uncontrolled Study 08

Vital signs were measured at each visit during the year long uncontrolled, open-label safety study. Table 71 shows the mean changes from baseline to specified post-dose visits (ISS panel 8.8.10.3:1, page 335).

Table 71: Study 08 – Vital Signs Results, Mean Changes from Screening/Baseline

	Screening	Visit 3 (13 wks)	Visit 4 (26 wks)	Visit 5 (39 wks)	Visit 6 (52 wks)	Endpoint
Systolic blood pressure, mmHg	(n=495)	(n=361)	(n=293)	(n=252)	(n=211)	(n=467)
Mean value	118.3	118.2	118.2	118.6	118.9	118.7
Change from baseline	NA	-0.1	0.1	0.5	0.3	0.3
Diastolic blood pressure, mmHg	(n=495)	(n=361)	(n=293)	(n=252)	(n=211)	(n=467)
Mean value	74.5	75.9	76.1	72.6	75.7	75.5
Change from baseline	NA	1.3	1.5	1.5	1.0	1.1
Pulse rate, bpm	(n=495)	(n=361)	(n=292)	(n=252)	(n=211)	(n=467)
Mean value	71.9	72.1	72.9	73.0	72.6	72.7
Change from baseline	NA	-0.2	0.7	1.1	0.9	0.7

Vital signs measurements were similar at each visit with the mean systolic BP ranging 118-119 mm Hg, mean diastolic BP ranging 72-76 mm Hg, and mean pulse ranging 72-73 bpm. The most frequent clinically noteworthy vital sign across all visits was decreased diastolic blood pressure. The number and percentages of clinically noteworthy changes in

vital signs are shown in Table 72 (ISS panel 8.8.10.3:2, page 336). Clinically noteworthy changes were recorded in 6 of 495 patients (1.2%). No patient had a clinically noteworthy in more than one vital sign and none were reported as AE's. Only one patient (96/08_827_307), a 42 year old female, had more than one clinically noteworthy change (all were diastolic blood pressure decreases). She had a diastolic BP of 65mm Hg at baseline, and this decreased to 50mg Hg at visit 3, 46 mm Hg at visit 4, and 50 mmHg at visit 5. All of the these values were clinically noteworthy. At visit 6, her diastolic BP had risen to 73 mm Hg.

Table 72: Study 08 – Clinically Noteworthy Vital Signs Changes

Parameter	Visit 3 (13 wks)	Visit 4 (26 wks)	Visit 5 (39 wks)	Visit 6 (52 wks)
Number of patients with at least 1 CN* vital sign	1 (< 1%) (n = 361)	2 (< 1%) (n = 293)	2 (< 1%) (n = 252)	3 (< 1%) (n = 467)
Systolic blood pressure	0 (n = 361)	1 (< 1%) (n = 293)	0 (n = 252)	1 (< 1%) (n = 467)
Diastolic blood pressure	1 (< 1%) (n = 361)	1 (< 1%) (n = 293)	2 (< 1%) (n = 252)	2 (< 1%) (n = 467)
Pulse rate	0 (n = 361)	0 (n = 292)	0 (n = 252)	0 (n = 467)

*clinically noteworthy

8.7.4 Non-Migraine Studies

I discuss vital signs result explicitly in this section because many of these measurements occurred shortly after drug administration and, along with study 03 (described previously) provide the best data to evaluate treatment-associated changes in vital signs. The sponsor excluded drug-disease and drug-drug interaction studies from this analysis, as this is discussed separately (section 8.9.3, page 97 and section 8.9.5, page 100). The results of vital signs assessments are listed for each study individually in Table 73 (ISS panel 8.8.10.4:1, pages 337-341). In general, blood pressure elevations were seen with the highest doses (*e.g.* ≥20mg) and with the i.v. infusions.

Table 73: Non-Migraine Studies – Summary of Vital Signs Results (excluding drug-drug, drug-disease interaction studies)

Study	Description	N	Dose	Assessment	Results
1165/24	Single-blind; parallel, ascending single dose; tolerability & PK	17	Single oral doses: frovatriptan 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg; placebo Single iv doses: frovatriptan 0.4mg, 0.8 mg	Supine blood pressure Supine heart rate Oral temperature	For oral and iv doses, there were no clinically important changes in SBP and DBP for any subject, and there were no clinically important dose level or time-related trends. Increases in blood pressure were detected during the iv infusion, however, they were transient. For the oral and iv doses, there were no clinically important changes in supine heart rate for any subject throughout the study. For the oral and iv doses, there were no clinically important changes in the oral temperature for any subject