Study	Description	N	Dose	Assessment	Results
					during the study and there were no clinically important or statistically significant dose level or time-related relationships.
1165/34	Open-label; 3-way crossover; tolerability & PK	9	Single oral doses: frovatriptan 40 mg (capsule), 40 mg(solution) Single iv dose: 1.2 mg	Supine blood pressure Supine heart rate Oral temperature	For oral doses, there were no clinically important changes in SBP and DBP for any subject during the study. For the iv dose, there was a transient increase in both supine SBP and DBP for most subjects during the 30-minute infusion. 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 during the study.
1165/42	Single-blind; parallel, ascending single dose; tolerability & PK	8	Single oral doses: frovatriptan 40 mg, 60 mg, 80 mg, 100 mg; placebo	Supine blood pressure Supine heart rate Oral temperature	There were small, transient, statistically significant increases in supine SBP and DBP at 4 hours postdose for 80 mg and 100 mg frovatriptan. Mean increase in SBP was 13 mmHg for frovatriptan 80 mg and 12 mmHg for frovatriptan 100 mg. Mean increases in DBP were 8 mmHg and 9 mmHg for frovatriptan 80 mg and frovatriptan 100 mg, respectively. No clinically important events recorded by continuous cardiac monitoring or lead II rhythm strips. No clinically important changes in pulse rate were recorded for any subject during the study. No clinically important or statistically Significant changes or dose level or time-Related relationships in oral temperature were recorded during the study.
1165/43	Open-label; 3-way crossover; tolerability & bioequivalence	24	Single oral doses: frovatriptan 20 mg (3 different capsule strengths; 8 X 2.5 mg, 2 x 10 mg, or 1 x 20 mg)	Supine blood pressure Supine pulse rate	No clinically significant changes in supine SBP and DBP and supine pulse rate between pre-dose and 48 hours postdose for each of the 3 formulations were recorded.
1165/48	Open-label; single radiolabelled dose; absorption, metabolism, excretion	4	Single oral dose of frovatriptan 40 mg (14C-labelled)	Blood pressure (screening only) Pulse rate (screening only)	Not applicable (only screening blood pressure and pulse rate performed)
VAD5-01	Open-label; 2-way crossover; food interaction	12	Single oral doses: frovatriptan 20 mg	Sitting blood pressure Sitting pulse rate	No clinically significant changes in vital sign measurements were recorded during the study.
1165/62	Open-label; 4-way crossover; tolerability & bioequivalence	32	Single oral doses: frovatriptan 40 mg (3 different tablet strengths & 1 capsule strengths; 16 x 2.5 mg, 4 x 10 mg, or 1 x 40 mg)	Supine blood pressure Supine pulse rate	No clinically significant changes from predose in supine SBP and DBP and supine pulse rate at 48 hours postdose for all of the tablet and capsule formulations were recorded.

Study	Description	N	Dose	Assessment	Results
251/96/01	Double-blind; repeat dose; tolerability & PK	24	2 groups of subjects: frovatriptan 40 mg or placebo every 12 hours on days 1 to 5 inclusive frovatriptan 40 mg or placebo as 3 single doses at 0, 2, and 12 hours on Day 1	Supine blood pressure Supine heart rate	There was a general trend for mean SBP and DBP and heart rate to increase in the active (frovatriptan 40 mg) treatment groups; however these changes were not considered to be clinically significant. One subject in group 2 (frovatriptan 40 mg) experienced large decreases in DBP during the treatment period and was withdrawn pre-third dose due to AEs (nausea, somnolence)
251/96/03	Double blind; 2-way crossover; repeat dose; tolerability & PK	20	3 single oral doses at 0, 2, & 12 hours: frovatriptan 10 mg, 20 mg, placebo	Supine blood pressure Supine heart rate	No clinically important changes in supine SBP or DBP and pulse rate for any subject throughout the study were recorded, and there were no clinically important gender, drug or dose-related trends in these data. Small increases in supine heart rate were observed at some times postdose 1 for both males and females. These changes were thought to be due to the subjects being more active at these times during the study.
251/96/04	Open-label; male vs female PK	24	2 single oral doses of frovatriptan 40 mg at least 7 days apart	Supine blood pressure Supine pulse rate Oral temperature (screening only)	For the oral frovatriptan 2.5 mg and 40 mg groups, there were no clinically significant changes between predose and 48 hours postdose SBP and DBP and pulse rate measurements. For frovatriptan 0.8 mg iv, there were slight increases in SBP and DBP in both males and females within 2 hours from the start of the infusion. These changes were not considered to be clinically significant.
251/96/12	Open-label; 3-way crossover; male vs female PK	12	Single oral doses: frovatriptan 2.5 mg, 40 mg Single iv doses: frovatriptan 0.8 mg	Semi-recumbent blood pressure Semi-recumbent pulse rate	No clinically important changes in SBP and DBP or pulse rate, were measured for any subject during the study. There were no clinically important gender or treatment period-related trends in these data. Small increases in pulse rate were observed at some times, which were thought to be due to subjects being more active at these times, rather than any drug-related effect. Statistical analysis showed no significant interactions among gender, time, and period for blood pressure or pulse rate.
251/97/05	Open-label; 3-way crossover; bioequivalence	21	Single oral doses: frovatriptan 2.5 mg (2 tablets and 1 caplet)	Supine blood pressure Supine pulse rate Oral temperature	For all subjects, there were no clinically significant changes in SBP and DBP, supine pulse rate, or oral temperature during the study. There were no apparent differences in vital signs between the 3 treatments.
1165/46	Open-label	4	Single frovatriptan 40 mg dose; 14C-labelled	Blood pressure (screening only) Pulse rate (screening only)	Not applicable (only screening blood pressure and pulse rate performed)
251/98/01	Open-label	4	Single frovatriptan 2.5 mg dose; 14C-labelled	Supine blood pressure Supine pulse rate Oral temperature	No clinically significant changes in the SBP and DBP and supine pulse rate measurements were recorded for the male or female subjects.

8.8 ECG

This section discusses ECG and Holter-monitor data. I concentrate my review on the findings from controlled trials, and from the uncontrolled long term safety study, as well as any data from any study which was obtained shortly after drug administration.

8.8.1 Controlled Studies

In the five main controlled studies 06, 07, 09, 02, and 14, ECG's were performed at up to either 5 working days or 12 weeks after the last treated attack; therefore, transient acute changes were unlikely to be detected.

Because ECG's for studies 06 and 07 were obtained at approximately the same time (screening/baseline, and endpoint) and were recorded the same way, the data are pooled. For these studies, ECG's were classified as either normal, abnormal-not clinically significant (NCS), or abnormal-clinically significant (CS) as determined by the investigators at the individual sites. No other data regarding these ECG's (*e.g.*, heart rate, axis, intervals, durations) were recorded.

Studies 09, 02, and 14 were analyzed separately. In study 09, ECG findings were classified in the same way as 06 and 07 (normal, abnormal-NCS, abnormal-CS). In this study, 19 patients in center 2413 were excluded due to irregularities at that site. In studies 02 and 14, ECG's were characterized as either normal or abnormal.

In studies 06 and 07 combined, the number of patients with ECG findings that shifted from normal or abnormal-NCS at screening/baseline to abnormal-CS at endpoint was low (4/1349, ≤1%) and was similar in the frovatriptan 2.5mg group (3/898) and placebo (1/451) group. A change from normal to abnormal-CS was seen in only one frovatriptan 2.5mg patient (0.1%) and no placebo patients. This patient, 96/07_716_087, a 48 year old female, was randomized to frovatriptan 2.5mg in study 07. She had a normal ECG at baseline and sinus bradycardia with non-specific ST-T wave changes at endpoint. This was not reported as an AE.

A change from abnormal-NCS to abnormal-CS was observed in 1 placebo patient (0.2%) and 2 frovatriptan 2.5mg patients (0.2%). Patient 96/07_743_0198, a 53 year old male was randomized to placebo in study 07. He had a right bundle branch block at baseline that was not clinically significant. At endpoint, in addition to the right bundle branch block, he had premature ventricular contractions that were clinical significant but were not reported as an AE. The frovatriptan patient was 96/06_610_080, a 56 year old male who was randomized to frovatriptan 2.5mg in study 06. He had sinus bradycardia at baseline. At endpoint, he was found to have Q waves in leads V_1 and V_2 which were not present at baseline and were possibly indicative of an old anterior myocardial infarction. This was categorized as clinically significant but was not reported as an AE. He had no other history, symptoms, or signs of myocardial infarction. Patient 96/07_704_0280, a 44 year old female, was randomized to the frovatriptan 2.5mg group in study 07. She had poor R-wave progression at baseline which was attributed to precordial lead positioning by the investigator. At endpoint, she had first degree AV block and right atrial enlargement that were clinically significant but were not reported as AE's.

There was 1 patient in the frovatriptan group (0.1%) that went from abnormal-CS at baseline (poor R-wave progression, prominent P waves, ECG consistent with chronic pulmonary disease) at baseline, but was normal at endpoint. No placebo patients went from abnormal-CS at baseline to normal at endpoint.

Reviewer's note: The one frovatriptan patient with new Q waves at endpoint raises the possibility that he suffered a silent MI during the study period. Whether this is true, and whether it is related to study medication is not known, but this remains a possibility.

ECG's in study 02 were categorized as either normal or abnormal. The most frequent abnormality recorded was sinus bradycardia. It should be noted that in all treatment groups, there were higher shifts from abnormal to normal than the other way around. JA change from normal to abnormal was observed in 4/89 (4.5%) placebo patients, 4/93 (4.3%) in the frovatriptan 2.5mg group, 2/90 (2.2%) in the 5mg group, 6/178 (3.4%) in the 10mg group, and 16/383 (4.2%) in the >10mg group. No dose-response relationship was evident. The proportion going from abnormal to normal ranged from 6.7% to 10.8%. The majority of abnormal ECG results were classified as clinically insignificant by the investigator.

ECG's in study 09 were categorized as either normal, abnormal-NCS, or abnormal-CS. A change from normal to abnormal-CS was seen in 1/468 (0.2%) in the frovatriptan 2.5mg group, and in no patients in either the placebo or sumatriptan 100mg groups. Patient 96/09_1208_1159, a 59 year old female in the frovatriptan 2.5mg group, had a normal ECG at baseline and at endpoint had abnormal T-waves in the anterolateral leads, a right axis deviation, and occasional ventricular premature complexes. None of these was reported as AE's. She had no history, signs, or symptoms of cardiac disease. No clinically significant ECG's were reported in center 2413, which was excluded from the analysis.

ECG's in study 14 were categorized as either normal or abnormal. A change from normal to abnormal was seen in 8/118 (6.8%) in the placebo group, 12/234 (5.1%) in the frovatriptan <2.5mg groups, 5/127 (3.9%) in the frovatriptan 2.5mg group, and 9/118 (7.6%) in the frovatriptan 5mg group. No clear dose response relationship was evident. The most frequently reported ECG abnormality was again sinus bradycardia (≤50 bpm), as well as non-specific ST-T segment changes, and non-specific T wave changes. It should be noted that a similar percentage (5.9-10.2%) shifted from abnormal at baseline to normal at endpoint.

The best ECG data come from study 03, which was the inpatient study in patients with or at high risk of CAD. Patients took up to two doses of frovatriptan 2.5mg for the treatment of a single migraine attack. Cardiac safety variables included not only ECG intervals and morphology, but also ischemic and arrhythmic episodes on Holter ECG. ECG's were performed at regular intervals up to 24 hours post-dose and patients were monitored for 24 hours by Holter ECG.

ECG intervals (PR, QT, QTc, and QRS) by treatment group are shown in Table 74 (ISS table 11.1.4, page 1568). Only 3 of the 75 patients had known CAD, and only one of these took frovatriptan 2.5mg. There were no difference in ECG intervals detected between treatment groups at any time point.

Table 74: Study 03 – ECG Results

		Frovatriptan 2.5mg					PBO				
		HR bpm	PR ms	QRS ms	QT ms	QTc ms	HR bpm	PR ms	QRS ms	QT ms	QTc ms
Screening/Baseline	N	37	37	37	37	37	38	38	38	37	38
	Mean	70.6	160.5	90.9	397.7	420.2	71.0	158.5	87.6	398.3	424.4
	Median	70.0	160.0	90.0	400.0	416.0	70.0	152.0	88.0	398.0	425.0
	Minimum	[									]
	Maximum										
	SD	12.6	19.8	11.1	25.8	20.3	13.6	29.2	10.7	29.5	22.2
Pre-dose	N	36	36	36	36	36	38	38	38	38	38
	Mean	71.2	159.2	89.2	394.6	419.1	71.5	162.1	86.7	395.1	419.3
	Median	68.0	158.0	88.0	389.0	418.0	69.5	160.0	87.0	402.0	417.0
	Minimum	[									]
	Maximum										
	SD	13.6	19.2	10.4	29.3	23.8	12.9	25.5	12.0	31.2	21.4
1 hour post-dose	N	36	36	36	36	36	38	38	38	38	38
	Mean	65.6	165.1	90.8	405.3	416.9	68.8	162.1	86.8	403.5	421.9
	Median	64.0	163.5	89.0	407.0	416.5	69.0	161.0	87.0	396.0	419.0
	Minimum	[									]
	Maximum										
	SD	9.8	18.9	10.0	32.7	21.6	12.2	26.3	11.5	34.4	22.0
2 hour post-dose	N	35	35	35	35	35	38	38	38	38	38
	Mean	65.8	163.2	91.4	406.6	418.1	68.7	167.1	87.3	404.5	422.9
	Median	66.0	160.0	90.0	405.0	414.0	68.0	163.0	87.0	400.0	423.5
	Minimum	[									]
	Maximum										
	SD	9.2	18.3	9.7	30.8	18.1	12.1	26.8	11.3	36.9	24.9
4 hour post-dose	N	36	36	36	36	36	38	38	38	38	38
	Mean	65.7	165.6	90.3	407.9	419.7	68.4	164.2	88.0	405.8	423.4
	Median	62.5	168.0	88.0	407.0	413.0	68.0	163.0	88.0	406.0	424.0
	Minimum	[									]
	Maximum										
	SD	10.6	19.3	10.4	29.5	22.8	12.2	24.9	11.2	37.6	27.4
End of Study	N	36	36	36	36	36	38	38	38	38	38
	Mean	74.4	159.4	87.7	386.0	418.2	74.7	157.4	86.1	389.0	418.7
	Median	75.0	161.0	88.0	388.0	411.0	75.0	155.0	86.0	387.0	414.5
	Minimum	[									]
	Maximum										
	SD	11.5	20.5	9.9	30.0	24.3	13.2	26.2	11.0	33.9	22.6

The incidence of clinically significant ECG findings are summarized in Table 75 (ISS panel 8.8.11.1.2:1, page 351). At each time point, the placebo group had a higher

incidence of clinically significant ECG changes from baseline. Only one of the three CAD patients experienced a clinically significant ECG change. This was 97/03_060_089, a 58 year old male in the placebo treatment group. He had 1st degree AV block at 2 hours post dose. He had a normal ECG at other time points.

Table 75: Study 03 – Clinically Significant ECG Changes

Hours Postdose	Frovatriptan 2.5 mg (n=37)	PBO (n=38)	p-value
1	6 (16%)	11 (29%)	0.214
2	8 (22%)	14 (37%)	0.182
4	7 (19%)	15 (39%)	0.026
24	6 (16%)	11 (29%)	0.118

The incidence of ischemic/arrhythmic episodes recorded during Holter monitoring is shown in Table 76 (ISS panel 8.8.11.1.2:3, page 352). The incidence was comparable or greater in the placebo group. However, the frovatriptan group experienced more ischemic episodes per patient (6.8 vs. 2.8). Two frovatriptan 2.5mg patients (both at high risk for CAD) had nine episodes, and a third had 8 episodes. The majority of episodes lasted less than 10 minutes. However, separate episodes of 22, 30, 51 minutes, and 2 hours 22 minutes were recorded for one frovatriptan patient. A placebo patient had 2 episodes lasting 1 hour 24 minutes and 1 hour 27 minutes, respectively.

Table 76: Study 03 – Ischemic/Arrhythmic Episodes on Holter ECG

	Ischemic		Arrhythmic	
	2.5mg	PBO	2.5mg	PBO
Patients with episodes	4 (11%)	5 (13%)	1 (3%)	4 (11%)
Mean number of episodes per patient	6.8	2.8	5	1.8
Range	—	—	—	—
Mean duration of episodes	12.2 min	14.1 min	2.8 sec	7.1 sec
Range	—	—	—	—

Reviewer's note: although I cannot tell if these ischemic episodes were symptomatic, there were no reported cases of chest pain in the frovatriptan treated group. Two patients in the placebo group reported chest pain in the study.

Arrhythmias reported were ventricular tachycardia, supraventricular tachycardia, sinus tachycardia (all placebo patients) and sinus arrest (frovatriptan 2.5mg).

8.8.2 Uncontrolled Study 08

In the year long open label safety study, ECG's were obtained at each visit (screening/baseline, 1, 3, 6, 9, 12 months). ECG's were rated as normal, abnormal not clinically significant NCS), or abnormal clinically significant (CS).

At each visit, shifts from normal or abnormal-NCS to abnormal-CS were low (<1%). Shifts in ECG from abnormal-CS to normal were also low (<1%).

At visit 3 (13 weeks), no patient shifted from normal at baseline to abnormal-CS, and 1/359 (<1%) shifted from abnormal-NCS at baseline to abnormal-CS (sinus bradycardia at baseline to T-wave inversion and possible ischemic changes at 3 months, but at 12 months, the ECG only showed sinus bradycardia again – patient 96/08_501_520).

At visits 4 and 5 (26 and 39 weeks), no patient shifted from normal or abnormal-NCS at baseline to abnormal-CS, but 1 patient shifted from abnormal-CS at baseline to normal.

At visit 6 (52 weeks), 1/209 (0.5%) shifted from normal at baseline to abnormal-CS. This was patient 251/96/08_830_350, who had a normal ECG at baseline but then showed sinus bradycardia, anterior T wave inversions, and possible ischemia at one year.

At endpoint, 1/462 (0.2%) shifted from normal at baseline to abnormal-CS. This is the same individual described at visit 6 above. In addition, 1 (0.2%) shifted from abnormal-NCS at baseline to abnormal-CS. She was patient 251/96/08_830_184, a 37 year old female who had an unspecified abnormal ECG finding at baseline characterized and not significant. She withdrew from the study due to lack of efficacy. At endpoint, her ECG showed bradycardia and signs of an inferior MI. However, the investigator commented that the new reading might have been due to poor lead placement with evidence of artifactual Q waves in the inferior leads.

8.8.3 Non-Migraine Studies

In general, the non-migraine studies (drug-disease, drug-drug interaction studies excluded) failed to disclose any ECG safety signals. Notable points are described below:

1. Study 1165/34 – one subject on 40mg solution had normal ECG at baseline and 1st degree AV block at 4 hours, considered normal physiological finding due to increased vagal tone
2. Study 251/96/01 – recorded 24 hour Holters and ECG's. There were no clinically significant changes in ECG intervals, and no significant events were recorded on Holter (n=24).
3. Study 251/97/05 – three abnormal findings were recorded (sinus arrhythmia, physiological atrial rhythm, left axis deviation). All were judged to be not clinically significant.

8.9 Special Populations

8.9.1 Methods

I limit discussion of specific populations to the four controlled trials 06, 07, 09, and 02. I don't include 14 since a considerable number of patients in that study also participated in study 02. For each sub-population, common treatment-emergent AE's within 48 hours are presented. Only the planned marketed dose of frovatriptan 2.5mg is shown. The sponsor calculated p-values based on logistic regression analyses. Interaction p-values <0.05 were considered nominally significant.

8.9.2 Drug-Demographic Interactions

The three demographic subpopulations included gender, race (white, black, other), and age (18-40, 41-64, and >65).

8.9.2.1 Gender

Table 77 (ISS panel 8.8.12.1.1:1, page 364) lists the most common AE's by gender. The overall incidence of common adverse events in frovatriptan patients was higher for females than for males (41.7% vs. 27.8%); however, this was also true for the placebo group (30.0% vs. 23.1%).

Table 77: Studies 06, 07, 09, 02 – Most Common Adverse Events, by Gender

	Frovatriptan 2.5mg		PBO		
	Male	Female	Male	Female	p-value
N	187	1367	117	721	
≥ 1 common AE	52 (27.8%)	570 (41.7%)	27 (23.1%)	216 (30.0%)	
AE preferred term					
Dizziness	10 (5.3%)	113 (8.3%)	4 (3.4%)	40 (5.5%)	0.95
Nausea	8 (4.3%)	92 (6.7%)	5 (4.3%)	47 (6.5%)	0.96
Fatigue	5 (2.7%)	77 (5.6%)	1 (0.9%)	18 (2.5%)	0.78
Headache	5 (2.7%)	58 (4.2%)	5 (4.3%)	17 (2.4%)	0.12
Somnolence	7 (3.7%)	56 (4.1%)	3 (2.6%)	31 (4.3%)	0.54
Abdominal pain	3 (1.6%)	24 (1.8%)	3 (2.6%)	7 (1.0%)	0.25
Paresthesia	8 (4.3%)	55 (4.0%)	2 (1.7%)	18 (2.5%)	0.58
Flushing	3 (1.6%)	52 (3.8%)	1 (0.9%)	16 (2.2%)	0.95
Temp. changed sensation	4 (2.1%)	47 (3.4%)	2 (1.7%)	17 (2.4%)	0.86
Skeletal pain	2 (1.1%)	47 (3.4%)	0	20 (2.8%)	1.000
Mouth dry	5 (2.7%)	43 (3.1%)	2 (1.7%)	10 (1.4%)	0.69
Chest pain	1 (0.5%)	36 (2.6%)	1 (0.9%)	10 (1.4%)	0.45
Dyspepsia	1 (0.5%)	32 (2.3%)	2 (1.7%)	9 (1.2%)	0.14
Vomiting	3 (1.6%)	27 (2.0%)	3 (2.6%)	18 (2.5%)	0.79

The most commonly reported AE's generally occurred more frequently in frovatriptan patients compared to placebo. The incidence of these events was generally higher in females, both for drug and placebo, and no nominally significant interactions were seen. In PK studies, females generally had a higher exposure to males (based on C_{max} and AUC data), especially those females taking oral contraceptives.

8.9.2.2 Race

Table 78 (ISS panel 8.8.12.1.2:1, page 365) shows the most common adverse events by race. For calculation of p-values, the black and other groups were combined since they were so small.

Table 78: Studies 06, 07, 09, 02 – Most Common Adverse Events, by Race

	Frovatriptan 2.5mg			PBO			
	White	Black	Other	White	Black	Other	p-value
N	1460	46	47	782	31	25	
≥ 1 common AE	582 (39.9%)	18 (39.1%)	22 (46.8%)	222 (28.4%)	9 (29.0%)	12 (48.0%)	
AE preferred term							
Dizziness	113 (7.7%)	5 (10.9%)	5 (10.6%)	39 (5.0%)	2 (6.5%)	3 (12.0%)	0.67
Flushing	51 (3.5%)	3 (6.5%)	1 (2.1%)	17 (2.2%)	0	0	0.56
Nausea	94 (6.4%)	3 (6.5%)	3 (6.4%)	45 (5.8%)	3 (9.7%)	4 (16.0%)	0.17
Fatigue	80 (5.5%)	0	2 (4.3%)	17 (2.2%)	0	2 (8.0%)	0.17
Somnolence	59 (4.0%)	1 (2.2%)	3 (6.4%)	31 (4.0%)	2 (6.5%)	1 (4.0%)	0.76
Paresthesia	58 (4.0%)	3 (6.5%)	2 (4.3%)	20 (2.6%)	0	0	0.31

	Frovatriptan 2.5mg			PBO			
	White	Black	Other	White	Black	Other	p-value
N	1460	46	47	782	31	25	
Headache	58 (4.0%)	1 (2.2%)	4 (8.5%)	21 (2.7%)	0	1 (4.0%)	0.49
Temp changed sens.	46 (3.2%)	1 (2.2%)	4 (8.5%)	16 (2.0%)	1 (3.2%)	2 (8.0%)	0.59
Mouth dry	45 (3.1%)	1 (2.2%)	2 (4.3%)	9 (1.2%)	2 (6.5%)	1 (4.0%)	0.10
Skeletal pain	43 (2.9%)	3 (6.5%)	3 (6.4%)	20 (2.6%)	0	0	0.16
Dyspepsia	32 (2.2%)	1 (2.2%)	0	10 (1.3%)	0	1 (4.0%)	0.48
Chest pain	31 (2.1%)	4 (8.7%)	2 (4.3%)	11 (1.4%)	0	0	0.31
Vomiting	27 (1.8%)	1 (2.2%)	2 (4.3%)	20 (2.6%)	0	1 (4.0%)	0.41
Abdominal pain	23 (1.6%)	2 (4.3%)	2 (4.3%)	8 (1.0%)	1 (3.2%)	1 (4.0%)	0.08

The overall incidence of common AE's were similar for the white and black populations. Definitive conclusions are impossible because the black and other populations were so small. None of the interaction p-values reached nominal significance.

8.9.2.3 Age

The sponsor split the continuous variable age into three strata: 18-40, 41-64, and >65. The most common AE's by age strata are shown in Table 79 (ISS panel 8.8.12.1.3:1, page 368). Again, because the numbers >65 were so small, they were pooled with the 41-64 age group to calculate the interaction p-values.

Table 79: Studies 06, 07, 09, 02 – Most Common Adverse Events, by Age

	Frovatriptan 2.5mg			PBO			
	18-40 yrs	41-64 yrs	>65 yrs	18-40 yrs	41-64 yrs	>65 yrs	p-value
N	705	841	6	392	442	4	
≥ 1 common AE	292 (41.4%)	326 (38.8%)	4 (66.7%)	112 (28.6%)	129 (29.2%)	2 (50.0%)	
AE preferred term							
Dizziness	61 (8.7%)	61 (7.3%)	1 (16.7%)	19 (4.8%)	25 (5.7%)	0	0.36
Nausea	44 (6.2%)	56 (6.7%)	0	18 (4.6%)	33 (7.5%)	1 (25.0%)	0.19
Fatigue	37 (5.2%)	45 (5.4%)	0	8 (2.0%)	10 (2.3%)	1 (25.0%)	0.73
Paresthesia	33 (4.7%)	30 (3.6%)	0	12 (3.1%)	7 (1.6%)	1 (25.0%)	0.63
Flushing	29 (4.1%)	25 (3.0%)	1 (16.7%)	6 (1.5%)	11 (2.5%)	0	0.17
Skeletal pain	28 (4.0%)	21 (2.5%)	0	6 (1.5%)	14 (3.2%)	0	0.028
Headache	27 (3.8%)	36 (4.3%)	0	7 (1.8%)	15 (3.4%)	0	0.30
Somnolence	26 (3.7%)	37 (4.4%)	0	22 (5.6%)	12 (2.7%)	0	0.033
Temp changed sens.	22 (3.1%)	29 (3.4%)	0	11 (2.8%)	8 (1.8%)	0	0.31
Vomiting	19 (2.7%)	11 (1.3%)	0	7 (1.8%)	14 (3.2%)	0	0.003
Mouth dry	18 (2.6%)	30 (3.6%)	0	6 (1.5%)	6 (1.4%)	0	0.48
Chest pain	20 (2.8%)	17 (2.0%)	0	7 (1.8%)	4 (0.9%)	0	0.63
Dyspepsia	17 (2.4%)	16 (1.9%)	0	5 (1.3%)	6 (1.4%)	0	0.67
Abdominal pain	16 (2.3%)	11 (1.3%)	0	4 (1.0%)	6 (1.4%)	0	0.26

The incidence of common AE's were generally similar in the 18-40 and 41-64 age groups. No conclusions can be drawn about AE incidence in the elderly because the numbers in the >65 year old age group were so small. Although there were nominally positive p-values for skeletal pain, somnolence and vomiting, the differences seen are not clinically meaningful.

8.9.3 Drug-Drug Interactions

The sponsor performed a drug-drug interaction analysis on 4 controlled frovatriptan studies: 06, 07, 09 (first attack) and 02. Exposure to a concomitant medication is defined as any single usage during the interval from 1 day prior to the first dose to 2 days after the last dose for the first attack only. Concomitant medications included in these analyses are:

- Alimertary tract propulsives (ATP's, *e.g.* metoclopramide, cisapride, domperidone)
- Beta blockers
- Estrogen-containing compounds
- Ergot alkaloids
- Selective 5-HT_1 receptor agonists
- Non-selective monoamine reuptake inhibitors (*e.g.*, amitriptyline, imipramine, etc.)
- Selective serotonin reuptake inhibitors

The sponsor chose the seven categories of medication based upon theoretical PK/PD interactions which could have an impact on the safety of frovatriptan. These included commonly used migraine prophylactic agents, and other medications often prescribed in a migraine population.

Table 80 (ISS panel 8.8.13:1, page 378) shows the incidence of exposures to these various medication groups in the studies. The most commonly used concomitant medication was estrogen containing compounds (approximately 33%).

Table 80: Studies 06, 07, 09, 02 – Incidence of Exposures to Concomitant Medications

	2.5mg	PBO
Patients in safety population	1554	838
Patients exposed to:		
Estrogen containing products	459 (33.6%)	237 (32.9%)
Non-selective monoamine reuptake inhibitors	173 (11.1%)	91 (10.9%)
Selective 5-HT_1 receptor agonists	170 (10.9%)	144 (17.2%)
Beta blocking agents	168 (10.8%)	95 (11.3%)
Selective serotonin reuptake inhibitors	122 (7.9%)	70 (8.4%)
Ergot alkaloid containing product	42 (2.7%)	36 (4.3%)
Alimentary tract propulsives	41 (2.6%)	34 (4.1%)

The incidence of commonly occurring treatment emergent adverse events (≥2%) are shown in Table 81 (derived from ISS panels 8.8.13.1.1:1-7:1, pages 379-388).

Table 81: Studies 06, 07, 09, 02 – Incidence of At Least One Commonly Occurring Treatment Emergent AE, grouped by Concomitant Medication Use

Concomitant Medication	Frovatriptan 2.5mg		PBO	
	Exposed	Unexposed	Exposed	Unexposed
Alimentary tract propulsives	11/41 (26.8%)	412/1513 (27.2%)	8/34 23.5%)	144/804 (17.9%)
Beta blockers	50/168 (29.8%)	373/1386 (26.9%)	15/95 (15.8%)	137/743 (18.4%)

Concomitant Medication	Frovatriptan 2.5mg		PBO	
	Exposed	Unexposed	Exposed	Unexposed
Estrogens	137/459 (29.8%)	246/908 (27.1%)	37/237 (15.6%)	97/484 (20%)
Ergot Alkaloids	4/42 (9.5%)	419/1512 (27.7%)	4/36 (11.1%)	148/802 (18.5%)
5-HT_1 Agonists	42/170 (24.7%)	381/1384 (27.5%)	27/144 (18.8%)	125/694 (18%)
Non-selective monoamine reuptake inhibitors	51/173 (29.5%)	372/1381 (26.9%)	14/91 (15.4%)	138/747 (18.5%)
Selective serotonin reuptake inhibitors	41/122 (33.6%)	382/1432 (26.7%)	13/70 (18.6%)	139/768 (18.1%)

In general, the proportion of frovatriptan patients experiencing at least one common treatment emergent adverse event (≥2%) was similar for the exposed and unexposed groups. One exception was in the group taking "ergot alkaloids". In those exposed to ergot alkaloids, 9.5% (4/42) experienced at least one AE, compared to 27.7% (381/1384) of those not exposed to ergot alkaloids, but he numbers exposed to ergots were small. Also, frovatriptan patients exposed to SSRI's had a somewhat higher incidence of AE's (33.6%) compared to those who did not take an SSRI (26.7%). The incidence of AE's in the placebo-SSRI exposed and placebo-SSRI unexposed groups were similar (approximately 18%).

8.9.4 Drug-Drug Interaction Studies

There were three clinical pharmacology drug interactions studies: ergotamine (251/98/02), propranolol (251/98/06), and moclobemide (251/98/07). I refer the reader to the biopharmaceutical review for a more detailed review of these studies.

8.9.4.1 Ergotamine

Study 251/98/02 was an open label, randomized, balanced, three-way crossover study that compared a single oral dose of frovatriptan 5mg with a single sublingual dose of ergotamine tartrate 2mg, or the two in combination. During the study, AE's, vital signs, ECG's, clinical laboratory evaluations, and physical examinations were assessed at specific times up to 96 hours post-dose. Twelve females entered and completed the study.

There were no serious adverse events, and no adverse dropouts. The number of AE's reported were numerically higher when the combination frovatriptan + ergotamine was taken compared to either agent taken alone (16 AE's in all 12 patients for the combination treatment, compared to 10 AE's in 5 frovatriptan-alone patients and 10 AE's in 7 ergotamine-alone patients). All the AE's were mild except moderate headache in one patient taking frovatriptan alone, and moderate vomiting in 1 patient following frovatriptan + ergotamine.

Mean systolic and diastolic blood pressures were similar for all three treatment groups. However, the baseline mean BP's for the combination treatment group was lower, resulting in post-dose systolic BP of 3-12 mm above baseline for that group. All three treatment groups showed a drop in mean supine pulse rates between 0.5 and 4 hours post dose by about 8-10 bpm, followed by a rise in all treatment groups 6-20 hours post dose

by about 3-5 bpm. These findings were considered to be of no clinical significance. There were no clinically significant changes in post study assessment for laboratory or ECG.

Mean $AUC_{0\rightarrow\infty}$ and C_{max} were approximately 25% lower for frovatriptan when coadministered with ergotamine. T_{max} and $T_{1/2}$ were unaffected.

8.9.4.2 Propranolol

Study 251/98/06 was an open label, two way crossover study in healthy males and females. It compared a single oral dose frovatriptan 2.5mg given with or without co-administration of propranol 80mg twice daily for the preceding 7 days. There was a 10 day washout period before each treatment sequence. During the study, AE's, vital signs, ECG's, clinical laboratory evaluations, and physical examinations were assessed at specific times up to 96 hours post-dose. Fourteen (14) subjects (6 males and 8 females) entered the study and 12 subjects (6 males and 6 females) completed the study. Two subjects withdrew after the first period (frovatriptan 2.5mg alone) due to personal reasons unrelated to the study.

There were no serious adverse events and no adverse dropouts. Seven of 14 subjects who took frovatriptan alone reported 26 AE's, compared with 8/12 subjects who took frovatriptan and propranolol together who reported 10AE's. One frovatriptan-alone patient reported eight episodes of diarrhea. All AE's were considered mild except one moderate headache and one moderate nausea.

Mean systolic and diastolic BP and pulse rates remained in the normal range for both treatment groups. Pulse rates for patients on frovatriptan + propranolol were slightly lower at most time points, which is not unexpected for a beta blocker. There were no clinically significant changes in post study assessments of ECG or laboratory results for any of the subjects.

Mean $AUC_{0\rightarrow\infty}$ and C_{max} determinations in this study indicated that exposure to frovatriptan was higher for females than for males and was higher for both groups following co-administration of propranolol. $AUC_{0\rightarrow\infty}$ was increased approximately 25-35% and C_{max} was increased approximately 16-24% (from ISS panel 8.8.13.2.2:2, page 397, not shown here).

8.9.4.3 Moclobemide

Study 251/98/07 was an open label, two way crossover study that compared a singled oral dose of frovatriptan 2.5mg with or without co-administration of moclobemide 150mg twice daily for the preceding 7 days (plus a final dose of moclobemide 150mg 12 hours later). There was a 10 day washout period between each treatment sequence. During the study, AE's, vital signs, ECG's, clinical laboratory evaluations, and physical examinations were assessed at specific times up to 96 hours post-dose. Originally, males and females were enrolled. After 9 subjects were treated, the sponsor discovered that plasma samples had been collected rather than whole blood. They subsequently amended the study to increase the sample size and include only females. Nineteen subjects (6 males and 13 females) entered the study and were treated. Seven subjects (6 males, and 1

female) were discontinued because of the laboratory error and change in study population. Three female subjects withdrew from the amended study: 1 for personal reasons, one for a protocol violation, and one for an adverse event (adverse dropout).

There were 5 serious adverse events reported by one patient, who discontinued prior to frovatriptan treatment. Seven of 13 frovatriptan-alone treated patients reported AE's, compared with 4/14 frovatriptan + moclobemide treated patients.

Six subjects had BP and pulse measurements outside of the normal range during the course of the study. No drug-related trends were noticed. Two subjects had AE's of dizziness associated with low blood pressure.

Two subjects had abnormal ECG's during the study. One had ST/T wave changes in the inferolateral leads 96 hours after treatment with moclobemide. The investigator felt this might be related to hyperventilation and the ECG was normal when repeated.. Another subject had inverted T waves in the inferior leads 6 hours post-treatment with moclobemide. The abnormality was considered not clinically significant and all other ECG's were normal for this subject. There were no clinically significant hematology parameters during the study. One subject had an elevated ALT 72 hours after treatment with moclobemide. A repeat ALT was normal.

Mean $AUC_{0\rightarrow\infty}$ increased by 20%, but C_{max}, T_{max}, and $T_{1/2}$ were all unaffected by moclobemide co-administration.

8.9.5 Drug-Disease Interactions

The sponsor analyzed drug-disease interactions in these three settings:

- Adverse events in patients with risk factors for coronary artery disease, in studies 06, 07, 09 (first attack) and 02
- Adverse events for patients with or at high risk for coronary artery disease in study 03
- Safety data from the renal impairment study 251/97/02 and the hepatic impairment study 251/97/06.

8.9.5.1 Adverse Events in Patients with Risk Factors for CAD

For each disease sub-population, common treatment-emergent AE's within 48 hours of exposure to study medication are presented. Common AE's are those which occurred ≥1% of patients in the frovatriptan 2.5mg or placebo treatment group in the safety population in studies 06, 07, 09 (first attack), and 02.

The most common risk factors present in patients in these four controlled studies were obesity, postmenopausal status, hypertension, males over 40 years of age, and hypercholesterolemia. Individual risk factors were present in similar percentages of patients in both treatment groups (see Table 38, page 42). The incidence of hyperglycemia/diabetes mellitus, previous CAD, or peripheral vascular disease was low (≤1%) for both treatment groups. The majority of patients in both treatment groups had no risk factors (66.5% and 62.8% for frovatriptan 2.5mg and placebo, respectively).

Those with 1 risk factor comprised 26.2% of the frovatriptan 2.5mg population and 30% of the placebo group, whereas approximately 5-6% in both groups had 2 risk factors.

Table 82 (ISS panel 8.8.14.1.1:3) summarizes the incidences of the most common treatment emergent adverse events in each treatment group, according to the number of risk factors for CAD for each patient.

The overall incidence of common AE's appeared to be higher for patients with ≥2 risk factors for frovatriptan 2.5mg and placebo treatment groups. In general, the incidence of individual AE's was generally higher in any sub-population of number of risk factors in the frovatriptan 2.5mg group that in the placebo group.

Although certain AE's were more common with those frovatriptan 2.5mg patients with ≥2 risk factors, the differences were generally small and none reached nominal significance. Chest pain, if anything, was less common in the ≥2 risk factor group compared with those with only one or no risk factors.

Table 82: Studies 06, 07, 09 (attack 1) – Treatment Emergent AE's within 48 Hours, by Number of Risk Factors for CAD

	Frovatriptan 2.5mg			PBO			
No. of Risk Factors	**0**	**1**	**≥2**	**0**	**1**	**≥2**	**p-value**
N	**1034**	**407**	**113**	**526**	**251**	**61**	
≥1 common AE	421 (40.7%)	147 (36.1%)	54 (47.8%)	152 (28.9%)	68 (27.1%)	23 (37.7%)	
AE preferred term							
Mouth dry	24 (2.3%)	15 (3.7%)	9 (8.0%)	7 (1.3%)	4 (1.6%)	1 (1.6%)	0.59
Nausea	72 (7.0%)	20 (4.9%)	8 (7.1%)	31 (5.9%)	18 (7.2%)	3 (4.9%)	0.31
Fatigue	55 (5.3%)	20 (4.9%)	7 (6.2%)	13 (2.5%)	4 (1.6%)	2 (3.3%)	0.82
Somnolence	39 (3.8%)	17 (4.2%)	7 (6.2%)	21 (4.0%)	11 (4.4%)	2 (3.3%)	0.67
Headache	40 (3.9%)	16 (3.9%)	7 (6.2%)	13 (2.5%)	7 (2.8%)	2 (3.3%)	0.94
Paresthesia	39 (3.8%)	20 (4.9%)	4 (3.5%)	15 (2.9%)	4 (1.6%)	1 (1.6%)	0.35
Temperature changed sensation	32 (3.1%)	16 (3.9%)	3 (2.7%)	12 (2.3%)	5 (2.0%)	2 (3.3%)	0.66
Dyspepsia	25 (2.4%)	6 (1.5%)	2 (1.8%)	8 (1.5%)	2 (0.8%)	1 (1.6%)	0.94
Flushing	41 (4.0%)	12 (2.9%)	2 (1.8%)	9 (1.7%)	4 (1.6%)	4 (6.6%)	0.055
Chest pain	24 (2.3%)	11 (2.7%)	2 (1.8%)	8 (1.5%)	2 (0.8%)	1 (1.6%)	0.57
Dizziness	87 (8.4%)	25 (6.1%)	11 (9.7%)	28 (5.3%)	13 (5.2%)	3 (4.9%)	0.68
Skeletal pain	34 (3.3%)	14 (3.4%)	1 (0.9%)	16 (3.0%)	2 (0.8%)	2 (3.3%)	0.061
Vomiting	24 (2.3%)	6 (1.5%)	0	13 (2.5%)	8 (3.2%)	0	
Abdominal pain	18 (1.7%)	6 (1.5%)	3 (2.7%)	4 (0.8%)	3 (1.2%)	3 (4.9%)	0.33

8.9.5.2 Adverse Events in Study 03

Study 03 was the inpatient study in patients with or at high risk of coronary artery disease. The safety results from study 03 have already been presented in earlier sections of this review. The adverse events for that study are summarized in Table 59, page 70. There were no treatment emergent serious or severe adverse events in either treatment group. For the frovatriptan 2.5mg treatment group, 4 AE's were graded as moderate:

abdominal pain and dyspepsia, each in 1 patient, and hypertension in two patients (144/94 at baseline and 192/120 at 4 hours for one patient, and 157/105 at baseline and 192/120 at 2 hours in another patient). In general, the total incidence of treatment emergent AE's was similar for both groups (14% for frovatriptan 2.5mg and 11% for placebo). I remind the reader that only 3 patients in this study actually had coronary artery disease, and of these, only one patient was randomized to frovatriptan 2.5mg therapy.

8.9.5.3 Drug Disease Interaction Studies

The sponsor conducted two studies in special populations: renal (251/97/02) and hepatic impairment (251/97/06).

Study 251/97/02 was an open label comparative study that used a single oral dose frovatriptan 2.5mg in subjects with varying degrees of renal impairment, and in healthy male and female subjects. Safety was assessed by AE's, vital signs, ECG's, laboratory assessments, and physical examinations at specific time points ranging from baseline up to 168 hours (7 days) post dose. Eighteen subjects completed the study. This included 5 males and 6 females with renal impairment, and 4 healthy males and 3 healthy females as control. Renal impairment ranged from severe (creatinine clearance (ml/min) in 3 subjects, moderate (ml/min) in 6 subjects, and mild (ml/min) in 2.

There were no serious adverse events and no adverse dropouts. Eighteen AE's were reported by 8 subjects with renal impairment (73%) compared with 8 AE's in 5 of the healthy subjects (71%). All AE's resolved within 3 days of onset. The most common AE's reported were headache (in 3 and 2 patients in the renal impairment group and control, respectively). No severe AE's were reported. No episodes of chest pain were reported.

Eight subjects, (5 with renal impairment, and 3 without) had changes in blood pressure and/or pulse. None was considered clinically significant by the investigator. Abnormal, non-clinically significant, ECG changes were seen in 6 subjects (4 with renal impairment, 2 without). Nine had clinically significant laboratory abnormalities, but none was treatment emergent.

There were no apparent trends in whole blood frovatriptan pharmacokinetic parameters for severe, moderate, or mild renally-impaired subjects or for renally-impaired versus healthy subjects.

Study 251/97/06 was an open label study that used a single oral dose of frovatriptan 2.5mg in subjects with moderate hepatic impairment (Child-Pugh score of 5-9) with historical controls. Comparison with healthy subjects used PK data from studies 251/97/12, 01, and 05. Safety was assessed by AE's, vital signs, ECG's, laboratory assessments, and physical examinations at specific time points ranging from baseline up to 168 hours (7 days) post dose. Eight subjects, 2 of each gender with mild disease, and 2 of each gender with moderate disease, were studied. All had hepatic cirrhosis.

There were no serious adverse events and no adverse dropouts. There was only one treatment emergent AE recorded in the study—a female with mild hepatic impairment who had one episode of dizziness at approximately 5 minutes post dose. The episode resolved after 5 minutes.

There were no clinically significant abnormalities noted in supine systolic or diastolic BP, pulse rate, and oral temperature. There were no clinically significant changes in ECG, including PR, QTc, QRS intervals, or heart rate. All subjects had chemistry values (*i.e.*, liver function tests) outside the normal range, as would be expected in this population, but none of the values were considered likely related to treatment. All eight patients had low platelet counts, the lowest of which was ——— Low serum albumin was seen in one patient.

Mean $AUC_{0\rightarrow\infty}$ for men were higher than historical controls, but comparable to $AUC_{0\rightarrow\infty}$ seen in elderly historical controls (69.33 vs. 42.90, vs. 73.00 ng.h/ml for hepatically impaired men, historical young controls, and historical elderly controls, respectively). The same trend existed in females with the addition that $AUC_{0\rightarrow\infty}$ in hepatically impaired females were comparable to young normal females taking oral contraceptives. Mean C_{max} was generally unaffected by liver impairment, with the exception of hepatically impaired females had C_{max} higher than young females (either with or without oral contraceptives) but similar to that seen with normal elderly females (8.77, 4.39, 6.55, 8.61 ng.h/ml for hepatically impaired females, young females without and with oral contraceptives, and elderly females, respectively). In short, exposures in hepatically impaired patients were similar to those seen historically in young females taking oral contraceptives and in elderly healthy subjects. However, the numbers are small, with wide variability, and they use historical controls.

8.10 Long-Term Safety

Study 08 was the one year long safety study. Following attack one (which randomized the second dose for the treatment of persistent pain), all subsequent attacks were treated with open label frovatriptan 2.5mg. A maximum of 3 doses within 24 hours was permitted. Patients could treat all migraine attacks with frovatriptan for up to one year.

In this study, 496 patients took 25,280 doses of frovatriptan 2.5mg to treat 13,878 migraine attacks. The average number of frovatriptan doses per attack was 1.8. A total of 365 patients completed 6 months of treatment, of which 258 patients (52%) treated an average of 2 or more attacks per month during a 6-month period (≥24 weeks). This was measured from the date of first dose for attack 1. A total of 178 patients completed one year of treatment, of which 150 patients (30%) treated an average of 2 or more attacks per month for a 12 month study duration (Table 83). Since the protocol allowed a window of ± 2 weeks for the 26 week and 52 week visits, 6 months was defined as "at least 24 weeks" and 12 months was defined as "at least 50 weeks."

Table 83: Study 08 – Long Term Exposures

Duration of Treatment	All Patients (n=496)	Patients treating an average of ≥ 2 headaches/month
6 months	365	258
12 months	178	150

Table 84 (from sponsor table 6.1-3, Study Report 08, page 89) shows the total number of attacks treated, and the number of doses used to treat each attack. It shows that the most common regimen used was 1 dose per attack (42%). Thirty-four percent (34%) of attacks were treated with 2 doses, and 24% of attacks were treated with 3 doses.

Table 84: Study 08 – Number of Doses Used To Treat Migraine Attacks

Total no. doses taken	25,280
Total no. attacks treated	13,878
No. doses per attack	
1 dose	5,793 (42%)
2 doses	4,768 (34%)
3 doses	3,317 (24%)
3+ doses	0
Mean no. doses per attack [SD]	1.82 [0.79]

The safety of long-term therapy has been discussed separately in each previous section. In general, no new or unexpected safety concerns were raised during long term treatment. I refer the reader to each section of the safety review that discusses the results of the long-term safety study:

- Serious Adverse Events: section 8.3.2, page 62
- Adverse Dropouts: section 8.4.2, page 64
- Adverse Events: section 8.5.3, page 71
- Laboratory Findings: section 8.6.3, page 80
- Vital Signs: section 8.7.3, page 86
- ECG: section 8.8.2, page 93

8.11 Four Month Safety Update

The four month safety update was submitted on 6/11/99. Although the study report for the long term study 08 in the original NDA is described as a "complete study report," the safety update contains an addendum to that report which describes additional data for 50 patients who treated an additional 495 migraines in study 08. These are not new patients, but rather they are patients already identified in the original report who were still being treated at the time.

It also contains 3-month interim safety data on a new 6-month open label safety study, called 251/98/08 (not to be confused with study 08 in this review, which is actually called

study 251/96/08—I use the complete study names in this section in order to avoid confusion).

Study 251/98/08 is almost identical in design to the previously submitted year long safety study with the exception that it is only 6 months in duration, and it does not contain a randomized second dose for the first attack. Although the sponsor does not mention why this study was initiated, my guess is that it is intended to add additional six-month safety experience since the original long-term study did not meet ICH guidelines for six month exposures (see section 8.4.2, page 64). It was the sponsor's desire to study patients with higher headache frequencies in the this second study. It was designed such that patients who treated < 4 migraines/month would be withdrawn. As a result, 13 patients (5%) were withdrawn at the time of this report for this reason. At the time of the 3-month interim analysis, 196 patients were ongoing.

The disposition of patients for the two long term studies are shown in Table 85 (Safety Update panel 9.2.3:1, page 28).

Table 85: Studies 251/96/08, 251/98/08 – Patient Disposition

Population	Complete 96/08	Interim 98/08	Combined data
Patients enrolled	547	262	809
Patients who failed to treat an attack	51 (9%)	5 (2%)	56 (7%)
Patients in safety population	496	257	753
Patients who completed study	256 (52%)	-	256 (34%)
Patients ongoing at time of cutoff	-	196 (76%)	196 (26%)
Patients who withdrew due to an AE	27 (5%)	13 (5%)	40 (5%)
Patients who withdrew for other reasons	213 (43%)	48 (19%)	261 (35%)

In the original study report for 251/98/06, the sponsor reported that 258 patients treated an average of 2 or more headaches per month for six months, and 150 for one year (Table 83, page 104). With the updated information, the 6-month exposure stays the same at 258, but the one year number is now 184.

For the ongoing study 251/98/08, a total of 161 patients had treated an average of 2 or more attacks during the first 3 months. It appears quite likely that they will meet ICH guidelines at 6 months when those data are available and pooled with the earlier study.

There were no new deaths reported.

The percentage of adverse dropouts remains the same at about 5%. The adverse events leading to withdrawal were not appreciably different to those seen in the complete NDA.

There were no new serious adverse events reported in 251/96/08. There have been four patients who have reported a total of 6 serious adverse events in the new study 251/98/08. None was considered treatment-related. The six SAE's , grouped by patient, are:

- Coma
- Convulsion grand mal

- Depression and Aggravated depression
- Headache and Spinal Cord Compression

A brief narrative of each case follows. I agree that the events are not likely related to treatment.

Coma - 98/08_716_2038 – This 35 y/o female took 3 doses of frovatriptan 2.5mg on 12/20/98 to treat her sixth migraine attack. On 1/13/99, she experienced a "severe seizure" manifested by loss of consciousness, falling, and "muscle contractions." She was admitted on 1/13 and recovered. She continued in the study.

(Reviewer note: although important details of this case are lacking, the event occurred 3 weeks after her last dose of frovatriptan and for that reason appears unrelated to treatment).

Convulsion grand mal – 98/08_754_2084 – This 50 y/o female took 2 doses of frovatriptan on 12/28/98 to treated her 17th attack. The next day, on 12/29/98, she underwent a D&C for postmenopausal bleeding. The patient had no relevant medical history and CT/EEG were normal. The investigator recorded that the seizure could have been related to concomitant medication administration during the D&C with anesthetics and barbiturates. The patient continued in the study.

(Reviewer's note: seizures have been rarely reported with other triptans. Certainly events associated with the D&C may have played a more likely role in the development of this SAE, but a contributing factor of the frovatriptan cannot be excluded.)

Depression and Aggravated Depression – 98/08_808_2210 – This 43 y/o female took 2 doses of frovatriptan 10/29/98 to treat her second attack. She had a pre-existing history of depression and anxiety and was taking multiple medications to include fluoxetine and lorazepam. The following day, on 10/30/99, she was admitted to the hospital due to worsening depression. She withdrew from the study on 10/2/98 due to this event.

(Reviewer's note: she had a pre-existing history of depression and anxiety. It appears doubtful that the frovatriptan played a significant role in the exacerbation of her mood disorder.)

Headache and Spinal Cord Compression – 98/08_727_2204 – This 36 y/o female took 2 doses of frovatriptan on 10/16/98 to treat her first attack. On 10/28/98, 12 days later, she underwent a myelogram for reasons that are unclear in the documentation and she developed a severe post-LP headache. She continued in the study and took two additional doses of frovatriptan on 11/16/98. On the same day, she underwent a (scheduled?) surgery for cervical nerve root decompression at C6-7. She withdrew from the study on 3/1/99 due to lack of efficacy.

(Reviewer's note: although, again, clinical information is lacking, it appears she did not have spinal cord compression, but rather a cervical radiculopathy unrelated to treatment. The headache was likely due to the myelogram.)

There were no new safety concerns with regards to laboratory data, vital signs or ECG's.

8.12 Withdrawal Phenomenon and Abuse Potential

No information was submitted to address this issue. In general, other triptans have not demonstrated, to date, withdrawal phenomenon or abuse potential. According to the draft

labeling, the abuse potential of frovatriptan has not been specifically assessed in clinical trials; however, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received frovatriptan.

8.13 Human Reproduction Data

There were 7 pregnancies reported during the clinical studies. Five of these were reported in patients randomized to the frovatriptan 2.5mg group and 2 occurred in placebo-randomized patients. These are listed in Table 86 (ISS panel 8.8.5.5:1, page 219).

Table 86: Pregnancies During the Clinical Trials

Patient Number	Treatment Group	Date of Last Menstrual Period	Date of Last Study Drug	Pregnancy Outcome
	Frovatriptan 2.5mg	16 June 1997	19 July 1997	Voluntary termination
	Frovatriptan 2.5mg	Unknown	22 July 1997	Unknown
	Frovatriptan 2.5mg	1 Sep 1997	29 Sep 1997	Voluntary termination
	Placebo	13 July 1997	26 June 1997	Unknown
	Placebo	Unknown	14 Aug 1997	Unknown
	Frovatriptan 2.5mg/ Frovatriptan 2.5mg	Unknown	1 June 1997	Spontaneous termination
	Frovatriptan 2.5mg/ Frovatriptan 2.5mg	15 May 1997	21 July 1997	Term birth/ healthy infant

Of the 5 frovatriptan pregnancies, two resulted in voluntary termination, one aborted spontaneously on ——— (almost 5 months after last dose of study drug), one resulted in a term birth of a healthy infant, and two outcomes were unknown at the time of the reports. The two placebo pregnancy outcomes were also unknown.

8.14 Overdose

No information regarding frovatriptan overdoses is provided. The draft labeling states that there is no direct experience of any patient taking an overdose of frovatriptan. The maximum single dose of frovatriptan given to male and female patients with migraine was 40 mg (16 times the clinical dose) and the maximum single dose given to healthy male subjects was 100 mg (40 times the clinical dose). No serious outcomes resulted.

As with other 5-HT_1 receptor agonists, there is no specific antidote for frovatriptan. The elimination half-life of frovatriptan is 26 hours, therefore if overdose occurs, the patient should be monitored closely for at least 48 hours and be given any necessary symptomatic treatment. The effects of hemo- or peritoneal dialysis on blood concentrations of frovatriptan are unknown.

8.15 Sponsor's Safety Conclusions

From the safety data presented, the sponsor concludes (ISS page 429-30):

- 4655 patients and 297 healthy subjects were included in the clinical program. Of these, 2722 patients and 1206 healthy subjects have taken the intended oral therapeutic dose of frovatriptan 2.5 mg

- Frovatriptan was well tolerated in migraine patients at oral doses between 0.5 mg and 40 mg a day. Total daily oral doses of frovatriptan 1 mg to 120 mg and intravenous doses of 0.4 mg to 1.2 mg were generally well tolerated in healthy subjects.
- The incidence of AEs associated with frovatriptan 2.5 mg is slightly higher than with placebo and the types of AEs observed are similar to those observed with placebo.
- There are no safety concerns arising from prolonged intermittent use of up to 3 oral doses of frovatriptan 2.5 mg in a 24 hour period.
- Frovatriptan has a broad therapeutic index therefore the risk of significant side effects resulting from overdose is reduced.
- Frovatriptan 2.5 mg is generally well tolerated regardless of age, gender, race, mild-to moderate hepatic impairment, renal impairment, cardiovascular risk factors or commonly used concomitant drug therapy.
- Frovatriptan 2.5 mg appears to be suitable for the acute treatment of migraine in a wide variety of migraine patients.

8.16 Reviewer's Safety Conclusions

Based on my review of the safety data, I conclude that:

- Frovatriptan 2.5mg is generally well tolerated
- The most common AE's were dizziness, fatigue, paresthesia, headache, flushing, subjective changes in temperature, dry mouth, chest pain, and throat tightness. These are similar to AE's seen with other $5HT_{1B/1D}$ agonists.
- Frovatriptan does not exhibit systematic ECG or laboratory abnormalities.
- Elevations in blood pressures can be seen, particularly in patients with elevated blood pressures at baseline, or with higher doses.
- There are no clinically meaningful differences in the safety profile with regard to age, race or gender. Women generally have more AE's compared to men, but this was also present in placebo patients.
- The safety profile of frovatriptan is not generally affected by medications concomitantly used for migraine prophylaxis
- The long term safety study failed to disclose any new safety concerns that were not seen in the short term studies; however, the exposures in the long term study failed to meet ICH guidelines. Specifically, only 258 patients treated an average of 2 headaches per month for six months. The numbers at one year did reach ICH guidelines (n=150)
- The safety database do not suggest that frovatriptan possesses any safety advantage over currently approved triptans; therefore, current triptan class labeling should apply.

9. Labeling Review

Due to pre-clinical review issues regarding the adequacy of the carcinogenicity studies, it is not likely that frovatriptan will be approved in this review cycle. Therefore, I defer a detailed labeling review at this time. Ultimately, triptan class labeling will likely be appropriate for this product.

10. Discussion

From the efficacy data presented, the sponsor has demonstrated that a single dose of frovatriptan 2.5mg is effective for the treatment of acute migraine, as shown by the effects at two hours on the headache response rate, and associated symptoms of nausea, photophobia, and phonophobia. The application failed to demonstrate that frovatriptan 2.5mg was effective in preventing headache recurrence, or that it is superior, or even equivalent to sumatriptan 100mg.

Although the long-term safety database is somewhat deficient due to insufficient exposures at six months (which are below ICH guidelines), it does not raise any major safety concerns with the 2.5mg dose when used intermittently. Since exposures at one year easily exceed ICH guidelines, this is probably not an approvability issue.

The sponsor proposes that a maximum of 3 doses be permitted within a 24 hour period. In this regard, the rationale and safety of this regimen remains questionable. From an efficacy standpoint, the use of 3 doses within 24 hours was never employed in any of the efficacy trials so the efficacy of this regimen is not established.

Several studies did, however, employ the use of a second dose. What efficacy information about the second dose is gained from such studies? Studies 07 and 09 used a second dose to treat headache recurrence. However, this dose was not randomized such that patients received the same dose to treat a recurrence that had been used for the original attack. Therefore, the efficacy of a second dose is not established. The sponsor did analyze the time to response to a second dose. Numerically, patients who took a second dose of frovatriptan in these studies had a shorter time to achieve a second response compared to those who took placebo. However, it is not clear that this wasn't due to the fact that they also still had frovatriptan on board from treatment of the initial attack.

Study 08 was the only study that used a randomized second dose. This dose was taken at 2 hours to treat persistent pain during treatment of the first attack only. This analysis was negative—a second dose of frovatriptan 2.5mg was not shown to be effective to treat persistent pain. As the sponsor points out, the flat dose-response relationship, with regard to headache response, seen in the two phase 2 studies with doses above 2.5mg make it not-surprising that an additional dose for persistent pain is not effective.

As it stands, there seems to be little reason, from an efficacy standpoint, to take a second dose of frovatriptan.

One can argue that, in clinical practice, there may be isolated individuals that may benefit from a second (and maybe a third) dose. Additional doses may be included in labeling as long as they are shown to be reasonably safe. Certainly, in the case of rizatriptan, we approved three doses within 24 hours largely because the sponsor had an adequate long term safety database to suggest that three doses taken during 24 hours were reasonably safe. I also point out there they also had some evidence to suggest that the second dose, at least, was effective in treating recurrence. In the case of frovatriptan, the long-term safety

database is weak for the reason already described above, and no persuasive efficacy data for the second dose exist. Furthermore, the sponsor did not submit detailed patient exposure information for study 08 so I cannot verify the extent of exposures to either two or three doses. Therefore, I cannot recommend the use of additional frovatriptan doses within 24 hours at this time.

11. Conclusions

From a clinical standpoint, a single dose of frovatriptan 2.5mg is both safe and effective for the acute treatment of migraine attacks. There is insufficient efficacy and safety information to justify the use of additional doses within 24 hours.

12. Recommendations

Assuming that outstanding issues in other disciplines are resolved (namely pre-clinical), I recommend approval of frovatriptan 2.5mg as a single dose for the acute treatment of migraine attacks.

The use of additional doses during 24 hours may be approvable, subject to submission and review of the following additional information:

- Additional 6 month safety data to achieve 300-600 patients treating at least 2 migraines per month for six months. This is currently being collected in an ongoing 6 month safety study 251/98/08 (which differs from the completed long term safety study referred in this review as "08" but is actually study 251/96/08)
- Detailed exposure history on the long term safety patients. This should be submitted as dataset(s) in SAS transport format in accordance with the guidance. Each row should contain information about a single dose taken. Important variables include patient id, date of study entry, date/time of first dose, and date/time of current dose, attack number, and dose number for the attack.
- Efficacy data supporting the use of a second dose within 24 hours for the treatment of either recurrent or persistent pain.

/S/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. /S/
(See my memo)

ao 10/14/99
cc:
HFD-120
NDA 21-006
electronic copy-Levin

Review and Evaluation of Clinical Data

NDA (Serial Number)	21-006 (LRC)
Sponsor:	**Vanguard (now Vernalis)**
Drug:	**Frovatriptan**
Proposed Indication:	**Migraine**
Material Submitted:	**Response to approvable letter**
Correspondence Date:	**8/21/00**
Date Received / Agency:	**8/23/00**
Date Review Completed	**9/13/01**
Reviewer:	**Eric P. Bastings, MD**

Table of Contents

1. Review Sources

The sponsor submitted safety data from 300-600 patients treated for 6 months and the safety update to the NDA (in paper and electronic formats). The sponsor submitted 17 paper volumes plus .pdf files and SAS data sets. The sponsor also submitted a revised proposed draft labeling text.

2. Background

2.1 Indication

Frovatriptan is indicated for the acute treatment of migraine attacks with or without aura in adults.

2.2 Administrative History

—— submitted the IND on 9/30/95 on behalf of Vanguard. The sponsorship was transferred to —— on 6/16/97.

The end of phase 2 meeting took place on 2/5/97. Vanguard presented data to suggest that 2.5mg was the optimal dose. The Division suggested that doses below 2.5mg should be

further explored. The protocol for the long-term safety study (251/96/08) was discussed. The protocol employed a randomized second dose for persistent pain in the first attack. It included a 12-month safety assessment as well. After discussion of statistical considerations, the Division concurred with the design.

[ ]. The Division commented that the study would probably not demonstrate any effect and that the "class" labeling for triptans would apply.

The pre-NDA meeting took place on 7/1/98. The Division commented that the labeling should follow the same style and format as for other triptans. Vanguard could ask for additional claims (such as ———), but this would be a matter of review.

The Division agreed on the general format for the integrated summary of efficacy (ISE). The Division and the sponsor reached agreement on the intent to treat population and on a worst case analysis approach for missing data.

The Division accepted the overall organization, grouping of studies, and general methods of analysis for the integrated summary of safety (ISS). The Division clarified how the safety data should be presented in the safety update.

The NDA was submitted on 1/29/99. The sponsor submitted a (first) safety update on 06/11/99. This contained an addendum to the report of the long-term open-label safety study 251/96/08, concerning data on the 50 patients who were ongoing at the time of the original NDA submission, and data from the first 3 months of study 251/98/08 (6-month open-label).

The Division issued an approvable letter on 4/28/00. The Division informed the sponsor that the carcinogenic potential of frovatriptan had not yet been adequately characterized and that if the results of the mouse study yielded a clear signal of carcinogenicity, product approval would be in jeopardy. The Division also required the sponsor to provide safety data from 300 to 600 patients who have used the recommended dose to treat, on average, 2 or more migraines a month for 6 months. The Division requested detailed exposure history on the long-term safety patients. The Division informed the sponsor that the tradename ——— is unacceptable due to potential confusion with currently existing products (e.g., Midrin, Maduramycin). The Division also raised several chemistry issues, and requested to update the NDA by submitting all safety information the sponsor has regarding frovatriptan. In addition, The Division requested an assessment of the safety and effectiveness of the product in the pediatric population, and specifically requested a pediatric drug development plan within 120 days.

The sponsor proposed the new name ——— ' on 7/18/00, and this was accepted by OPDRA. The sponsor submitted a second clinical update with safety data in over 300 patients treated for 6 months on 8/21/00, and submitted updated SAS data sets on 11/16/00. The sponsor submitted a revised proposed draft labeling on 10/3/00, but withdrew it on 2/20/01 to stop the PDFUFA clock. The sponsor submitted a revised proposed draft labeling on 5/7/01. The sponsor requested on 7/5/00 a (partial) pediatric waiver to conduct pediatric studies in children < 12 years of age.

2.3 Foreign Marketing

Frovatriptan is currently marketed in France.

3. Clinical Data Sources

3.1 Phase 2/3 Program

The completed phase 2/3 clinical trials are shown in Table 1.

Table 1: Frovatriptan Phase 2/3 Clinical Trials

Study	Total	Frovatriptan dose <2.5mg	2.5mg	>2.5mg	PBO	Sumatriptan 100mg
Major controlled efficacy studies						
251/96/06	374	0	251	0	123	
251/96/07	1274	0	850	0	424	0
251/96/09	1335	0	539	0	267	479
251/95/02	1013	0	113	788	112	
251/96/14	695	280	140	138	137	0
Other controlled studies						
251/97/03	75	0	37	0	38	0
Short-term uncontrolled studies						
251/95/01	62	0	8	54	0	0
251/97/04	12	0	12	0	0	0
Long-term uncontrolled study						
251/96/08	547	0	272	0	275	0
251/98/08	262	0	262	0	0	0

The numbers shown represent those randomized. Ten patients in study 02 also enrolled in study 07. Ninety-four patients in study 02 also enrolled in study 14. For study 251/96/08, patients were randomized only for the second dose. 272 patients were randomized to frovatriptan 2.5mg and 275 to placebo. All patients were allocated to frovatriptan 2.5mg in the open-label phase of the study.

Study 251/96/08 (also referred here as "96/08") was a 12 month, multicenter, open-label study in 31 centers in the U.S. A secondary objective, for the first attack only, was to assess the efficacy of a second, double blind dose of 2.5mg or placebo taken 2 hours after the first dose for a non-response. All patients received frovatriptan 2.5mg as initial treatment for the first attack. For subsequent attacks, a second dose was permitted after 2 hours for non-response, and a third dose was permitted within 24 hours for recurrence. Thus, the maximum daily dose used in this study was 7.5mg (2.5mg x 3).

After the first (120-day) safety update, the sponsor completed study 251/98/08 (also referred as study "98/08"), which is the main object of the second safety update. It is a 6-month open label study, intended to collect additional safety data in patients treating at least 2 migraines a month over a six month period. As in the 12-month long-term study (251/96/08), patients could take up to 3 doses of 2.5mg for each attack, within 24 hours.

4. Clinical update

4.1 Background and Methodology

In the NDA original submission and the two safety updates, data from 29 studies contribute to the safety database. There were 10 studies conducted exclusively in migraine patients, and 19 clinical pharmacology studies in subjects without migraine. In the first and second safety updates, the sponsor has provided additional data on long-term studies 251/96/08 and 251/98/08. No new data were provided on short-term studies.

For this document, I have reviewed in detail the safety data from the 2 long-term uncontrolled studies. I have reviewed data from both safety updates, since the first safety

update contained detailed information about study 251/96/08, and the second safety update contained detailed information on study 251/98/08. In the original NDA submission, the safety analysis was separated for the controlled short-term studies, uncontrolled short-term studies and uncontrolled long-term studies. Since this submission contains only new data for the uncontrolled long-term studies, I have not performed an additional review of the controlled short-term studies and uncontrolled short-term studies, but I have compared the data of the short-term studies with the combined data of the uncontrolled long-term studies. I have also reviewed the case reports and data of all patients who withdrew since the original NDA, and compared these data to earlier withdrawals. For completeness of the information, I have included the description of the safety population in migraine studies (Table 2).

4.1.1 Safety Population in Migraine Studies

The numbers of patients in the safety population of the 10 migraine studies are shown in Table 2 (adapted from ISS panel 8.8.1.3.1:1, page 38, original NDA).

Table 2: Safety Population in Migraine Studies

Study	Total	Frovatriptan Dose					PBO	Sumatriptan 100mg	Comments
		<2.5mg	2.5mg	5mg	10mg	>10mg			
Controlled short-term									
251/96/06	322	0	214	0	0	0	108	0	Double-blind; parallel
251/96/07	1,148	0	760	0	0	0	388	0	Double-blind; parallel
251/96/09	1,206	0	480	0	0	0	244	482	Double-blind; parallel
251/95/02	899	0	100	99	192	410	98	0	Double-blind; parallel
251/96/14	635	255	131	126	0	0	123	0	Double-blind; parallel
251/97/03	75	0	37	0	0	0	38	0	Double-blind; parallel
Uncontrolled short-term									
251/95/01	62	0	8	24	18	12	0	0	Single-blind; dose-titration
251/97/04	12	0	12	0	0	0	0	0	Open-label; 2-way crossover
Uncontrolled long-term									
251/96//08	496	0	496	0	0	0	172	0	First dose double-blind; open-label thereafter
251/98/08	257	0	257	0	0	0	0	0	Open-Label

At least 201 duplicates occurred in the clinical studies. In many cases where duplicates occurred, the protocol did not specifically request frovatriptan naïve patients only. For example, patients from the phase 3 studies 06 and 07 could enroll in the uncontrolled long-term safety study 96/08 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 96/08. Patients in study 96/08 could not enroll in study 98/08. The patient did not identify any duplicate between these 2 studies. The sponsor did not specify duplicates between long term and short-term studies. In the worst case scenario (all long term patients being duplicates of short-term studies), of the 5112 patients in the safety population, 4654 were unique. Since long term and short term data were analyzed separately, and the total number of patients studied is large enough, this does not constitute a real issue.

4.1.2 Rationale for ISS Study Groupings

Clinical studies were grouped by specific factors to permit analyses of safety parameters. These factors include subject population, study duration (short-term vs. long-term), and study design (controlled vs. uncontrolled, parallel vs. crossover).

The 10 migraine studies are grouped as follows:

- controlled short-term studies (02, 14, 06, 07, 09-attack 1, 96/08-attack 1)
- uncontrolled short-term studies (01, 04, 09-attacks 2,3)
- uncontrolled long-term study (96/08-attacks >1, 98/08)

This document contains a detailed review of the long-term uncontrolled studies (96/08 and 98/08). A review of the other migraine studies and of the non-migraine studies is available in the original NDA review of 10/14/1999, by Dr. Armando Oliva.

4.1.3 Content of the Safety Review

I used a similar strategy as in the original NDA safety review in presenting the safety data from this application. For deaths, serious adverse events, adverse dropouts, and adverse events, I include information from long term and short-term studies. For other safety sections (adverse events, laboratory data, vitals signs, ECG), I only include the results from the long-term open label studies 96/08 and 98/08.

4.2 Clinical studies completed since original NDA submission

Table 3 includes a list of clinical studies completed since the original NDA.

Table 3: New clinical studies completed since the NDA

Study Number Designation	Title	Status
251/99/01	A Phase 1 single center, open label randomized, cross-over, pharmacokinetic trial to evaluate the potential interaction between frovatriptan and fluvoxamine in healthy male and female subjects	Draft synopsis filed August 21, 2000
251/98/08 (interim); 251/96/08 (complete)	120 day (first) safety update	Filed June 11, 1999
251/98/08 (complete); and combined with 251/96/08	Second safety update	Filed August 21, 2000

Detailed results of study 251/99/01 were not part of this submission and are not reviewed here. Study 251/98/08 is the 6-month safety study requested in the approvable letter.

4.3 Sponsor's response to specific points in the approvable letter.

This section contains the sponsor's response to the comments transmitted in the approvable letter.

4.3.1 Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

"At the time of the original NDA submission, two safety studies were ongoing, studies 251/98/08 and 251/96/08. These have now been completed. Complete data from Study 251/96/08 and partial data from Study 251/98/08 were presented in the first safety update. A second safety update .../... has now been completed. This contains complete data from both studies, with the data from the recently completed study, study 251/98/08 presented individually and combined with the data from study 251/96/08. .../...

In the ISS in the original NDA, there were two populations discussed, the short-term and the long-term. In the first and second safety update, the only new data were those added to the long-term population. As a result, the new safety data provided in the second safety update are presented cumulatively to account for the longer-term exposure of the patients already identified. A discussion of the combined long-term data set is provided in this introductory text and throughout the text in the second safety update."

4.3.2 Retabulation of dropouts with new dropouts identified.

"The incidence of withdrawals due to adverse events was described in the original NDA (ISS Volume 1.101). Updated tables of withdrawals from studies completed since the NDA (study 251/96/08 and 251/98/08) are included in the second safety report.

Since the submission of the NDA an additional 15 patients withdrew from studies due to adverse events. The original NDA included 85 patients who withdrew from studies due to adverse events. The CRFs for these patients were provided in electronic format in the NDA on CDs, which also contained a complete list of the CRFs provided, consistent with FDA guidance on provision of electronic CRFs.

The first safety update (filed to the NDA on June 11th 1999) included data and CRFs for a further 14 patients (Table 16.1 of first safety update), one patient from study 251/96/08 and 13 patients from 251/98/08. The second safety update includes data for all patients who withdrew from the long-terms studies (Tables 16.1 and 16.2) and the CRFs for the one additional patient, not included in the first safety update, who withdrew from Study 251/98/08 due to an adverse event.

Overall, these additional 15 patients who, post-NDA, have withdrawn from clinical trials for adverse event related reasons. It should be noted that the NDA database was essentially comprised of patients with short-term exposures to frovatriptan, unlike these more recent patients who have been in long-term tolerability studies.

However, the nature of the adverse events leading to withdrawal in these 15 patients does not differ from those identified in the original application and first safety update.

It should be noted that although overall, approximately 5% of patients in both studies 251/96/08 and 251/98/06 withdrew due to adverse events as opposed to approximately 1% in the short-term database, (as reported in the original ISS), when analyzed as proportion of treated migraine attacks, these withdrawals occurred at a lower frequency of frovatriptan exposures. In summary, no new clinical hazard associated with frovatriptan is identified by these cases."

4.3.3 Details of any significant changes or findings.

"There are no new or significant changes or findings in the recent data (see additional data below)."

4.3.4 Summary of worldwide experience on the safety of this drug.

"Frovatriptan is not marketed in any country in the world nor has a marketing application been denied or withdrawn due to safety reasons. Frovatriptan has recently been recommended for approval in France (July 2000)."

Reviewer's note: Frovatriptan was marketed in France since submission of the 2nd safety update.

4.3.5 Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

"CRFs for 85 patients were supplied to the FDA as part of the original NDA. Since the NDA was filed, no patients have died during a clinical study. A further 15 patients have been withdrawn due to adverse events since the NDA and the patient numbers are listed below in Table 4 (adapted from table D, Vol. 1, page 5, second safety update). Fourteen of these cases were presented in the first safety update report. One additional patient who withdrew from study 251/98/08 is included in the second safety update.

A listing of all patients in the long-term safety database who dropped out due to adverse events are presented in Tables 16.1 and 16.2 of the second safety report (Appendix 1). CRFs for all but one of these patients were also included in the first safety report. The CRF for the additional patient that had not previously been provided is presented in Volume 4 page 242.

Table 4: Additional patients withdrawn due to adverse events

First safety update			Second safety update		
Study #	**Patient #**	**Adverse Event**	**Study #**	**Patient #**	**Adverse Event**
98/08	**510-2243**	Diarrhea, vomiting	98/08	**607-2009**	Brain Neoplasm
98/08	**603-2117**	Nausea, vomiting			
98/08	**603-2118**	Nausea			
98/08	**607-2003**	Pruritus, urticaria			
98/08	**712-2068**	Nausea			
98/08	**753-2223**	Inflicted Injury			
98/08	**805-2041**	Dizziness			
98/08	**808-2210**	Depression aggravated			
98/08	**808-2215**	Nausea			
98/08	**821-2166**	Hypertension			
98/08	**821-2168**	Chest Pain			
98/08	**821-2174**	Vision Abnormal			
96/08	**509-546**	CPK increased			
98/08	**510-2242**	SGOT/SGPT increased			

4.3.6 English translations of any approved foreign labeling not previously submitted.

"Frovatriptan has recently been recommended for approval in France, but the final label has not been approved. The approved label text will be submitted as soon as it is available."

4.3.7 Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

"The most commonly reported treatment emergent non-serious AEs (> 5%) for patients treated for at least 6 months, (n=533) were nausea, vomiting, dyspepsia, diarrhea, headache, dizziness, fatigue, paresthesia, skeletal pain, myalgia, sinusitis, somnolence, abdominal pain, upper respiratory tract infection, rhinitus, chest pain, back pain and flushing. These were all reported with a similar incidence in the original NDA. Further, many of these symptoms are those which occur typically during a migraine attack and are not unexpected.

Therefore, there is no substantial difference in the nature and frequency of common, less serious adverse events in the combined long-term safety dataset provided in the second safety update in comparison to the original NDA and first safety update."

4.3.8 Safety data from 300 to 600 patients who had the dose of 2.5mg to treat 2 or more migraines for 6 months.

"Of the 809 patients who were included in the 2 long-term studies frovatriptan 2.5mg/96/08 and frovatriptan 2.5mg/98/08, 533 treated migraine attacks for at least six months from the date of the first dose for the first attack. A total of 400 patients treated 2 or more migraine attacks per month for six months. Data from these 400 patients and the population as a whole are presented in the second safety update. Additional analyses to those included in the second safety report have been performed to evaluate the adverse event profile specifically from the group of patients who had 2 or more migraines for 6 months in comparison with the overall population.

The data show that the adverse event incidence in 400 patients treating 2 migraine attacks per month does not markedly differ from the population as a whole or the 133 patients who treated <2 attacks per month. In the six-month period from date of first dose, patients treating 2 or more migraine attacks per month formed the majority of the safety population (400/533; 75%). The total incidence of all causality adverse events both within 48 hours (75.0%) and all treatment emergent AEs (83.3%) for the 400 patients treating 2 attacks per month was very similar to that of the overall population (75.4% and 82.9% respectively). It was also very similar to that reported for the 133 patients who treated <2 attacks per month (76.7% and 82.0% respectively).

In each body system, the total incidence of adverse events was also very similar for the <2 attacks per month patients and the overall population. In the majority of body systems, the incidences of AEs were only marginally higher than the incidences reported in the 133 patients who treated <2 attacks per month.

The severity of adverse events was not affected by the frequency of attack treatment. There was a tendency for severe nausea, vomiting, headache, and dizziness to be reported more frequently in the ≥2 attacks per month group compared to the <2 attacks per month group. As these symptoms occur commonly during a migraine attack, it is likely that they would be reported more often by patients treating more frequent attacks. There was no evidence that more frequent treatment with frovatriptan exacerbated these symptoms.

The incidence of adverse events of special interest within the triptan class in the 400 patients who treated ≥2 attacks per month was very similar to the overall population and

that in the 133 patients who treated <2 attacks per month, for both AEs occurring within 48 hours and all treatment emergent AEs. Approximately 50% of patients experienced one or more special interest adverse events. Nausea, dizziness, fatigue, flushing and chest pain were reported more commonly by patients treating ≥2 attacks per month compared to patients treating <2 attacks per month, but the incidence of somnolence, paresthesia and throat tightness was higher in the <2 attacks per month group than the ≥2 attacks per month group.

The incidence of serious adverse events was not affected by the frequency of migraine attack treatment. However it should be noted that in calculating the incidences for patients who treated attacks for at least 6 months any patients who had SAEs that led to withdrawal were excluded from the analysis. The number of these patients however was small and does not affect the result."

Reviewer's comment: The sponsor has provided tables comparing by attack frequency all treatment emergent serious adverse events (table 1, page 8-9, vol.1, 8/21/00 clinical update), all treatment emergent adverse events (table 2, page 10-23 vol. 1, 8/21/00 clinical update), and all treatment emergent adverse events (table 3, page 24-82, vol. 1, 8/21/00 clinical update). I did not identify clinically significant differences in incidence of adverse events between patients who treated less than 2 attacks or at least 2 attacks per month for 6 months. I believe that it is reasonable to analyze the entire dataset (like the sponsor did in the second safety update) versus only the data of patients who treated at least 2 attacks per month.

4.3.9 Please provide detailed exposure history on the long-term safety patients. This should be submitted as dataset(s) in SAS transport format in accordance with guidance documents.

"Appendix 2 of this clinical update contains supporting documentation for the datasets. This is a description of the content and format of derived data sets including direct and derived variables. This documentation is also included on the CD."

4.4 Demography of long-term studies

Baseline demographic information is summarized in Table 5 (adapted from panel 9.4.3:1, second safety update). As is typical of migraine studies of this type, the vast majority of patients were women (88-91%) and Caucasian (88-96%). The mean age was 41.4-42.8 years, and other demographic parameters were comparable between both studies.

Table 5: Study 251/96/08 and 251/98/08 - Baseline Demographics

Characteristic	251/96/08 (n=496)	251/98/08 (n=257)	Combined (n=753)
Gender			
Female	438 (88%)	234 (91%)	672 (89%)
Male	58 (12%)	23 (9%)	81 (11%)
Race			
Caucasian	476 (96%)	226 (88%)	702 (93%)
Black	9 (2%)	14 (5%)	23 (3%)
Other	11 (2%)	17 (7%)	28 (4%)
Mean age (Years)	41.4	42.8	41.9
Age range	18-65	20-66	18-66

Characteristic	251/96/08 (n=496)	251/98/08 (n=257)	Combined (n=753)
Age Group:			
18 – 40	215 (43%)	100 (39%)	315 (42%)
41 – 64	280 (56%)	156 (61%)	436 (58%)
>65	1 (<1%)	1 (<1%)	2 (<1%)
Weight (kg)			
Mean	74.3	73.7	74.1
Range	39-174	45-154	39-174
Body Mass Index			
<25.0 kg/m	2 220 (45%)	113 (44%)	333 (45%)
25 – 29.9 kg/m2	142 (29%)	77 (30%)	219 (30%)
>30 kg/m2	124 (26%)	65 (25%)	189 (26%)

4.5 Migraine history of long-term studies

Patients in both long-term studies have a similar average duration of history of migraine headache, close to 20 years. The proportion of patients with migraine aura was slightly higher in study 251/96/08 (18% versus 8%), and previous sumatriptan use ranged from 70 to 78% (Table 6, adapted from panel 9.4.3:2, second safety update).

Table 6: Study 251/96/08 and 251/98/08- migraine history

Study	251/96/08 (n=496)	251/98/08 (n=257)	Combined (n=753)
Mean Time suffered from migraines (Y)	19.8	19.9	19.8
Mean attacks/month over past year	3.9	4.2	4
Migraine Type			
With aura	87 (18%)	21 (8%)	108 (14%)
Without aura	312 (63%)	163 (63%)	475 (63%)
Both	97 (20%)	73 (28%)	170 (23%)
Previous sumatriptan use*			
Yes	347 (70%)	201 (78%)	548 (73%)
No	148 (30%)	56 (22%)	204 (27%)

4.6 Drug exposure in long-term studies

4.6.1 Drug exposure in study 251/96/08

Study 96/08 was the one year long safety study. Following attack one (which randomized the second dose for the treatment of persistent pain), all subsequent attacks were treated with open label frovatriptan 2.5mg. A maximum of 3 doses within 24 hours was permitted. Patients could treat all migraine attacks with frovatriptan for up to one year.

The sponsor claims that 178 patients completed one year of treatment, of which 150 patients (30%) treated an average of 2 or more attacks per month for 12-month study duration. The sponsor also reports that 365 patients completed 6 months of treatment, of which 258 patients (52%) treated an average of 2 or more attacks per month during a 6-month period from the date of first dose for attack 1 (Table 7).

Table 7: Study 96/08 – Long-term exposure (as presented by the sponsor)

Duration of Treatment	All Patients (n=496)	Patients treating an average of ≥ 2 headaches/month
6 months	365	258
12 months	178	150

The sponsor claims that in study 96/08, 496 patients took 25,942 doses of frovatriptan 2.5mg to treat 14,373 migraine attacks. The average number of frovatriptan doses per attack was 1.8.

Table 8 (adapted from table 6.1A-5, first safety update, and table 6.1-5, second safety update) shows the number of doses used to treat each attack. The most common regimen used was 1 dose per attack (42%). Thirty-four percent (34%) of attacks were treated with 2 doses, and 24% of attacks were treated with 3 doses.

Table 8: Study 96/08 and 98/08 – Number of Doses Used To Treat Migraine Attacks

Study	96/08	98/08	96/08 and 98/08 combined
Total no. doses taken	25,942	8,318	34260
Total no. attacks treated	14373	4,534	18907
No. doses per attack			
1 dose	6053 (42%)	1980 (44%)	8033 (42%)
2 doses	4899 (34%)	1324 (29%)	6223 (33%)
3 doses	3421 (24%)	1230 (27%)	4651 (25%)
Mean no. doses / attack	1.8	1.8	1.8

Table 9 shows the exposure I calculated from the SAS database provided by the sponsor. I used the variables A1D1DTM of attack 1 (dose and time of first dose of first attack treated), COMPLTDT (date of completion of the study) and NOATTS (total number of attacks). I calculated the duration of exposure from the first dose of the first attack to the completion date. I compared these data to two exposure variables provided by the sponsor: ATT1DAYS, which is the number of days between the date of treatment of attack 1 and date of completion of study, and RANDDAYS, which is the number of days between randomization and completion of the study. For practical purpose, ATT1DAYS should be the same as A1D1DTM to COMPLTDT.

Table 9: Exposure in study 96/08 (calculated from SAS database)

Total exposure Treatment period	≥140	≥147	≥154	≥161	≥168	≥175	≥180	≥182	≥336	≥360
A1D1DTM to COMPLTDT	378	377	371	368	364	361	356	356	261	176
RANDDAYS	395	389	383	379	374	368	365	365	272	248
ATT1DAYS	380	378	372	370	365	363	358	356	261	184

The sponsor apparently used ATT1DAYS at 168 days to identify patient exposure at 6 months (n=365). For one year exposure, the number presented by the sponsor (n=178) does not correspond to ATT1DAYS at 336 days (n=261) or 360 days (n=184). N=178 falls between AAT1DAYS at day 360 (n=184) and 361 (n=176). I suspect that the sponsor used AAT1DAYS at day 360, and that the small number difference (n=6) is

related to the inclusion or exclusion of hour in addition to date in computations (*Table 9*). *Table 10* shows the exposure for patients in relation to different headache monthly frequency. Exposure in this table is calculated as the duration from A1D1DTM to COMPLTDT. The table shows that 245 patients treated at least 2 migraine attacks for 6 months (day 168, 180 or 182), and 143 patients for 1 year (at day 360).

Table 10: Exposure (A1D1DTM to COMPLTDT)/headache frequency in study 96/08

# attacks/month A1D1DTM to COMPLTDT	>0	≥ 2	≥ 3	≥ 4	≥ 5	≥ 6
≥168	364	245	169	104	63	42
≥180	356	245	167	104	63	42
≥182	356	245	167	104	63	42
≥336	261	202	144	88	53	33
≥360	176	143	96	54	32	21

Since the sponsor apparently used ATT1DAYS for his exposure data presentation in the ISS, I also calculated the exposure for different headache monthly frequencies based on ATT1DAYS (Table 11). The data reproduce the n=150 patients treating at least 2 migraine attacks per month for ≥ 360 ATT1DAYS, but shows a smaller number (n=248) of patients at ≥ 168 days than reported by the sponsor in the safety update (n=258). I can not explain that difference (typo?). The exposure data from ATT1DAYS are also slightly more optimistic than the exposure calculated from A1D1DTM to COMPLTDT, with 248 versus 245 patients at ≥168 days and 150 versus 143 patients at ≥ 360 days. These differences remain minimal.

Table 11: Exposure (ATT1DAYS) /headache frequency in study 96/08

# attacks/month ATT1DAYS	>0	≥ 2	≥ 4	≥ 6
≥168	365	248	105	43
≥180	358	246	105	43
≥336	261	202	88	33
≥360	184	150	56	23

4.6.2 Drug exposure in study 251/98/08

Study 98/08 was the 6-month open label safety study. All attacks were treated with frovatriptan 2.5mg. Patients could take a second and thrid dose from 2 hours after the initial dose if their migraine had not responded or recurred, to a maximum of 3 doses within 24 hours. Patients could treat all migraine attacks with frovatriptan for up to 6 months.

The sponsor reports that 257 patients took 8318 doses of frovatriptan 2.5mg to treat 4534 migraine attacks. The average number of frovatriptan doses per attack was 1.8, and the average number of frovatriptan 2.5mg doses per patient was 33. The sponsor claims that 168 patients completed 6 months of treatment, of which 142 patients (85%) treated an average of 2 or more attacks per month during a 6-month period (≥24 weeks) from the date of first dose for attack 1.

Table 8 shows that the most common regimen used was 1 dose per attack (44%). Twenty-nine % of attacks were treated with 2 doses, and 27% of attacks were treated with 3 doses.

I recalculated the exposure to medication using the SAS data sets provided by the sponsor. I used the variables A1D1DTM of attack 1 (dose and time of first dose of first attack treated), DOSEDT (dose and time of first dose of last attack treated), corresponding to the last attack treated (LASTMIG=1), as identified in the "efficaf.xpt" file, VISITDT (visit date) of the last visit (V3), as identified in the file "vitalaf.xpt", and NOATTS (total number of attacks). I calculated the duration of exposure from the first dose of the first attack to the last visit and from the first dose of the first attack treated to the first dose of the last attack treated. I compared these data to two exposure variables provided by the sponsor: ATT1DAYS, which is the number of days between the treatment of attack 1 and completion of study, and RANDDAYS, which is the number of days between randomization and completion of the study. For practical purpose, ATT1DAYS should be equal to the duration from the first dose of the first attack to the last visit. I identified 5 cases where the difference between these parameters was equal of greater than 2 days. In 3 cases, the patient withdrawal date, which was prior to the final visit date, was used by the sponsor for computing ATT1 days. In these cases, I replaced Visit 3 date by withdrawal date for my calculations of exposure. In one case, the difference was negative and exceeded two days (but was less than 6 days). In this case, I suspect that the difference came from an error in the sponsor database. The sponsor used the date of the first dose of attack 1 in several redundant variables, such as A1D1DTM and DOS1DTM. In the case mentioned here above (patient 2188), the difference I found was the same as the difference between A1D1DTM and DOS1DTM, which should normally be zero. I summarize the exposure data in Table 12.

Table 12: Exposure (A1D1DTM to COMPLTDT)/headache frequency in study 98/08

Total exposure Treatment period	≥140	≥147	≥154	≥161	≥168	≥175	≥180	≥182
Attack 1 to last attack	171	163	148	131	89	50	28	17
Attack 1 to last visit	194	192	187	184	163	115	73	49
RANDDAYS	196	195	194	194	194	194	192	188
ATT1DAYS	194	192	188	183	168	128	81	49

The exposure at 6 months reported by the sponsor in the safety update corresponds to ATT1DAYS at day 168 (n=168). This number is slightly larger that the exposure I calculated from "Attack 1 to the last visit" (n=163).

I also calculated the exposure in term of headache monthly frequency (*Table 13*), based on the duration from attack 1 to the last visit. The number calculated for a duration ≥168 days and ≥2 headache attacks per month (n=139) is again slightly smaller than the number provided by the sponsor in the safety update (n=142). *Table 14* shows that this number corresponds to ATT1DAYS at day ≥ 168 for ≥2 migraine attacks per month.

Table 13: Exposure (Attack 1 to last visit)/headache frequency in study 98/08

# attacks/month (30 days) Attack 1 to last visit	>0	≥ 2	≥ 3	≥ 4	≥ 5	≥ 6

≥168	163	139	93	55	34	19
≥180	73	59	40	24	13	8
≥182	49	40	30	17	11	7

Table 14: Exposure (ATT1DAYS)/headache frequency in study 98/08

# attacks/month (30 days) ATT1DAYS	>0	≥ 2
≥168	168	142
≥180	81	66
≥182	59	48

4.6.3 Six-month exposure in long-term studies combined

The sponsor claims that 400 patients treated at least 2 attacks per month for 6 months after treatment of the first attack in combined studies 96/08 and 98/08 (Table 15).

Table 15: Six-month exposure in long-term studies (≥2 attacks per month)

	Study 96/08	Study 98/08	Combined
Sponsor calculated (at day 168)	258	142	400
Based on my calculated duration from the first attack to study completion (SAS database), at day 168	245	139	384
Based on my calculated duration from the first attack to study completion (SAS database), at day 180	245	59	304

Based on my calculations, the total exposure for patients treating at least 2 attacks per month is 384 at day 168 and 304 at day 180 (table 18). Of note, the sponsor used day 168 as the 6 months mark. This corresponds to 24 weeks. Following the same logic, one year would be 48 weeks, or 336 days. However, the sponsor used day 360 for the one year exposure data, which is inconsistent with the "168 days" representing a 6-month study.

The sponsor exceeded ICH guidelines for both day 168 and day 180, so that the issue is mostly academic in this case. The sponsor also exceeded ICH guidelines for the one-year safety data, with 143 patients treating at least 2 migraine attacks per month for 360 days.

4.7 Deaths

There was no additional death to the one reported in the original NDA. The cause of the death reported in the original NDA was described 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. The death was thought to be unrelated to frovatriptan by Dr. Oliva in the original NDA review.

4.8 Serious Adverse Events

A serious adverse event (SAE) was defined as any experience that was fatal or life-threatening, was permanently disabling, caused patient hospitalization or prolonged hospitalization, or was a congenital anomaly, cancer, or overdose. Across both long-term studies, treatment-emergent SAE's were reported for 18 of 753 patients (2.4%) in the treatment interval 0-26 weeks. All of these SAEs were judged unrelated to study

medication by the investigator. An additional six patients had SAEs reported in the period >26-52 weeks in study 96/08.

4.8.1 SAEs in Study 251/96/08

This was the one-year long-term safety study. Overall, 15/496 (3.0%) experienced treatment emergent SAE's (Table 16, adapted from ISS, panel 8.8.7.2:1, page 238, original NDA). No new SAEs were reported in either safety update. 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 16: Study 96/08 – SAE's by Duration of Treatment

	0-13 Weeks	>13-26 Weeks	>26-39 Weeks	>39-52 Weeks	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%)
Migraine aggravated	1	0	1	0	2 (0.4%)
Abdominal pain	0	1	0	1	2 (0.4%)
Inflicted injury	0	1	1	0	2 (0.4%)
Vertigo	0	1	0	0	1 (0.2%)
Chest pain	0	1	0	0	1 (0.2%)
Depression	0	1	0	0	1 (0.2%)
Anxiety	0	1	0	0	1 (0.2%)
Agitation	0	1	0	0	1 (0.2%)
Tremor	0	0	1	0	1 (0.2%)
Delusion	0	0	1	0	1 (0.2%)
Suicide attempt	0	1	0	0	1 (0.2%)
Ovarian cyst	0	0	0	1	1 (0.2%)
Lumbar disc lesion	0	0	1	0	1 (0.2%)
Fracture pathological	0	1	0	0	1 (0.2%)
Convulsions	0	1	0	0	1 (0.2%)
Cholecystitis	0	1	0	0	1 (0.2%)
Cervical uterine polyp	1	0	0	0	1 (0.2%)
Arthralgia	0	0	1	0	1 (0.2%)
Appendicitis	1	0	0	0	1 (0.2%)
Abdominal adhesions	0	1	0	0	1 (0.2%)

Patients with treatment-emergent serious adverse event are summarized in Table 17.

Table 17: Summary of patients with treatment-emergent SAEs in study 251/96/08

Patient	Age (y)/ Sex	Attack no./ Relative day no.	Event
Frovatriptan 2.5mg/frovatriptan 2.5mg sequence			
502108	37/F	4/51	Convulsions
		4/86	Fracture pathological [broken right leg]
812118	34/F	10/28	Chest pain
			Vertigo
814477	41/F	5/7	Abdominal pain
821161	26/F	1/102	Suicide attempt
827301	47/M	29/1	Migraine aggravated
827515	38/F	40/4	Abdominal pain
827594	50/F	2/2	Migraine aggravated,
828411	47/F	3/126	Abdominal adhesions
Frovatriptan 2.5mg/placebo sequence			

503014	52/F	5/4	Cervical uterine polyp
806573	43/F	10/5	Cholecystitis
		26/7	Ovarian cyst
814479	42/F	6/18	Depression [anxiety]
816378	41/F	20/60	Inflicted injury
816528	49/F	5/26	Appendicitis
820180	61/F	23/4	Lumbar disc lesion
830350	49/F	27/7, 33/4	Inflicted injury [knee surgery]

The following narratives are adapted from the original NDA for the first 13 cases, and the first safety update for the last 2 cases.

1. **Convulsions – 502108:** This 37 year-old female with a past history of seizures was hospitalized 50 days after treating her fourth migraine attack with two doses of frovatriptan 2.5mg, having suffered convulsions. Symptoms were moderate in severity and resolved within one day. The event was considered unrelated to study treatment and the investigator commented that convulsions were likely to be a manifestation of migraine (?). Later on, the patient was hospitalized a second time having broken her right leg 85 days after the last dose. The event was considered unrelated to study treatment.

2. **Chest pain and vertigo –812118:** This 34 year-old female experienced chest pain and vertigo, which were reported as two serious adverse events, 27 days after treating her 10th attack with one dose of frovatriptan 2.5mg. She was hospitalized for 24 hours. Both events were severe and neither was considered related to study medication. The patient subsequently completed the study.

3. **Abdominal pain –814477:** This 41 year-old female with a history of chronic right lower quadrant and pelvic pain. Seven days after treating her 5th migraine attack with two doses of frovatriptan 2.5mg, she experienced a further severe abdominal pain. She was admitted to hospital and underwent a bilateral salpingo-oopherectomy. The condition resolved and the patient was discharged the following day. The event was considered unrelated to study medication and the patient completed the study.

4. **Suicide attempt –821161:** This 26 year-old female, she was hospitalized 101 days after treating her first migraine attack with two doses of frovatriptan 2.5mg because she made a number of suicide threats. As a result, study drug was discontinued. The event was considered unrelated to study medication.

5. **Migraine aggravated –827301:** This 47 year-old male had a history of intractable migraine attacks lasting from three to four days and hypertension. The day of treating his 29th migraine attack with two doses of frovatriptan 2.5mg, the patient reported severe intractable migraine. He was discontinued from the study as a result of the event. The event was judged unrelated to study medication and at the time of discontinuation, symptoms continued despite treatment.

6. **Abdominal pain –827515:** This 38 year-old female with a history of endometriosis reported moderate pelvic pain in the lower right quadrant three days after treating her 40th attack with two doses of frovatriptan 2.5mg. She was hospitalized and a laparoscopy determined that symptoms were not due to endometriosis. Pelvic pain was considered unrelated to study medication and the patient completed the study.

7. **Migraine aggravated –827594:** This 50 year-old female with a history of severe migraines experienced severe, acute migraine pain for 8 days, with an onset one day after treating her second attack with two doses of study medication. She was hospitalized for 2 days. The patient was discontinued from the study. Symptoms resolved with treatment and the event was judged unrelated to study medication.

8. **Abdominal adhesions –828411:** This 47 year-old female, with prior history of previous abdominal surgery and multiple abdominal adhesions. Approximately four months after treating her third attack

with three doses of frovatriptan 2.5mg, she experienced further severe abdominal adhesions and was hospitalized for corrective surgery. The event was considered unrelated to study medication. She was withdrawn.

9. **Uterine polyps –503014:** This 52 year-old female had been receiving hormone replacement therapy since 1995. Three days after treatment of her fifth attack with two doses of frovatriptan 2.5mg, she was diagnosed with severe uterine polyps and hospitalized for their surgical removal. The patient was discharged from hospital two days later and made a complete recovery. The event was considered not related to study treatment.

10. **Cholecystitis –806573:** This 43 year-old female has a history of right oophorectomy in 1986, and hysterectomy in 1990. Four days after treating her 10th migraine attack with three doses of frovatriptan 2.5mg, she suffered severe cholecystitis and was hospitalized three days later. Study medication continued and symptoms resolved following a cholecystectomy. Seven days after treating her 26th migraine attack, the patient reported severe left abdominal pain. She was admitted to hospital on the same day and diagnosed with a left ovarian cyst. Symptoms initially resolved without treatment and the patient was discharged from hospital. However, she was readmitted 9 days later for left oophorectomy and recovered. Neither event was considered related to study medication and the patient completed the study.

11. **Depression (anxiety) –814479** - This 42 year-old female who had suffered previous panic attacks related to childhood trauma. She treated her sixth migraine attack with one dose of frovatriptan, and reported severe anxiety, panic attacks and depression 17 days later. She was hospitalized, but continued the study. Symptoms persisted and she continued to treat migraine attacks with study medication. She experienced severe delusions and was hospitalized for treatment. Three days later, she also experienced mild extrapyramidal symptoms. None of the events reported were considered related to study medication. Symptoms persisted, but the patient completed the study.

12. **Inflicted injury –816378:** This 41 year-old female presented with a C5 cervical radiculopathy with herniation following an accident at home 60 days after treating her 20th migraine attack with 3 doses. She was admitted to hospital and received various anti-inflammatory drugs. She underwent cervical resection and recovered to complete the study. The event was considered not related to study medication.

13. **Appendicitis –816528:** This 49 year-old female with a past history of "inflamed appendix" was hospitalized with severe appendicitis 25 days after treatment of her fifth attack with two doses of frovatriptan 2.5mg. She underwent appendectomy, with hernia repair and removal of a necrotic lymph node. Symptoms were considered unrelated to study medication and the patient recovered. However, she withdrew as a result of the serious adverse event.

14. **Lumbar disc lesion –820180** - This 61 year-old female who had treated 23 previous migraine attacks with study medication suffered a severe herniated disc 3 days after treating her last attack and was admitted to the hospital for laminectomy, followed by physiotherapy. Symptoms resolved and the event was judged unrelated to study medication. The patient completed the study.

15. **Inflicted injury –830350:** This 49 year-old female experienced severe knee pain following a fall 6 days after treating attack 27. The condition persisted and she was hospitalized for surgical treatment. The patient recovered with sequelae which required prolonged treatment. Both events were considered not related to study medication and the patient completed the study.

4.8.2 Study 251/98/08

Seven out of 257 patients (2.7%) reported 9 serious adverse events in study 251/98/08 (Table 18, adapted from table 17.1, second safety update). None was considered treatment-related.

Table 18: Study 98/08 - SAE's by Duration of Treatment

	0-13 Weeks	>13-26 Weeks	>26 Weeks	Overall
Patients at beginning of time interval	257	214	48	257
Patients with at least 1 SAE	5 (1.9%)	2 (0.9%)	0	7 (2.7%)
Convulsions	1	0	0	1
Convulsions grand mal	1	0	0	1
Headache	1	0	0	1
Intestinal obstruction	1	0	0	1
Brain neoplasm benign	0	1	0	1
Depression aggravated	1	0	0	1
Ovarian disorder	0	1	0	1
Pelvic inflammation	0	1	0	1
Spinal cord compression	1	0	0	1

Patients with treatment-emergent serious adverse event are summarized in Table 19 (adapted from table 6.2.1-1, second safety update). I verified SAE's data in the AEAF.crf file provided in the SAS database. I identified these nine patients with serious adverse events. I did not find any discrepancy between the database and the tables/data presented by the sponsor. Only two SAEs occurred within 48 hours of taking a dose of study medication (patients 7542084 and 8082210). All but one (patient 7272044, pelvic inflammation) SAE resolved. SAEs led to withdrawal in two patients (6072009 and 8082210).

Table 19: Summary of patients with treatment-emergent SAEs in study 251/98/08

Patient	Age (y)/ Sex	Attack no./ Relative day no.	Event
716-2038	35/F	6/25	Convulsions
754-2084	50/F	17/2	Convulsions grand mal
808-2210	43/F	4/1	Depression aggravated
727-2204	36/F	1/13	Headache
		1/32	Spinal Cord Compression
607-2009	54/F	12/4	Brain neoplasm benign
727-2057	37/F	6/4	Small bowel obstruction
805-2044	29/F	15/48	Pelvic inflammation
805-2044	29/F	15/58	Ovarian disorder

A brief narrative of each case follows. The 4 first cases were reported in the first safety update, and the last 3 cases in the second safety update. Dr. Oliva agreed that the first 4 cases are not likely related to treatment. In my opinion, the last 3 cases are not likely related to treatment either.

1. **Convulsion – 7162038** – This 35 y/o female experienced a "severe seizure", manifested by loss of consciousness, falling, and "muscle contractions" 24 days after taking 3 doses of frovatriptan 2.5mg to treat her sixth migraine attack. She was admitted to the hospital and recovered. She continued in the study.

2. **Convulsion grand mal – 7542084:** This 50-year-old female took 2 doses of frovatriptan to treat her 17th attack. The next day, she underwent a D&C for postmenopausal bleeding and experienced a severe grand mal seizure during recovery. The patient had no relevant medical history and CT/EEG were normal. The investigator recorded that the seizure could have been related to concomitant medication administration during the D&C with anesthetics and barbiturates. The patient continued in the study.

3. **Depression and Aggravated Depression – 8082210:** This 43 y/o female had a pre-existing history of depression and anxiety and was taking multiple medications including fluoxetine and lorazepam. On the day of treating her 4th attack with 2 doses of frovatriptan, she was admitted to the hospital due to worsening depression. She withdrew from the study due to this event.

4. **Headache and Spinal Cord Compression – 7272204:** This 36 y/o female took 2 doses of frovatriptan to treat her first attack. Twelve days later, she underwent a myelogram for reasons that are unclear in the documentation and she developed a severe post-LP headache. Thirty-one days later, she underwent a (scheduled?) surgery for cervical nerve root decompression at C6-7. She withdrew from the study due to lack of efficacy.

5. **Brain tumor – 6072009:** This 54 year-old female, Caucasian, treated 12 attacks with frovatriptan. Three days after treating her 12th attack with 3 doses of frovatriptan 2.5mg, she was hospitalized with a brain tumor, which was considered not related to frovatriptan. The patient underwent surgery and the adverse event resolved. She withdrew from the study due to this adverse event.

6. **Small bowel obstruction – 7272057** – This 37 year-old female, Caucasian, treated 12 attacks with VML251. Three days after treating her 6th attack with 2 doses of frovatriptan 2.5mg, she was hospitalized with small bowel obstruction, which was considered not related to study treatment. This adverse event resolved.

7. **Pelvic inflammation and ruptured ovarian endometrioma – 8052044** – This 29 year-old female, Caucasian, treated 15 attacks with frovatriptan 2.5mg. Forty-seven days after treating her 15th attack with 1 dose of frovatriptan 2.5mg, she was hospitalized with suspected pelvic inflammation and ruptured ovarian endometrioma, which were moderate and required hospitalization. The events were considered not related to frovatriptan 2.5mg and persisted, requiring treatment.

4.8.3 Combined long-term studies (first 6 months)

In the 0-26 week interval, treatment-emergent SAEs occurred in 2.4% (18/753) of patients who took frovatriptan 2.5 mg (Table 20, adapted from panel 9.7.3:1, second safety update). No SAEs were reported as related to study medication in either study. Please refer to sections 4.8.1 and 4.8.2 for more details.

Table 20: Combined long-term studies SAEs (first 6 months)

	First 6 months
Patients	753
Patients with at least 1 SAE	18 (2.4%)
Convulsions	2 (0.3%)
Abdominal adhesions	1 (0.1%)
Abdominal pain	1 (0.1%)
Agitation	1 (0.1%)
Anxiety	1 (0.1%)
Appendicitis	1 (0.1%)
Brain neoplasm benign	1 (0.1%)
Cervical uterine polyp	1 (0.1%)
Cholecystitis	1 (0.1%)
Chest pain	1 (0.1%)
Convulsions grand mal	1 (0.1%)
Depression	1 (0.1%)
Depression aggravated	1 (0.1%)
Fracture pathological	1 (0.1%)
Headache	1 (0.1%)
Inflicted injury	1 (0.1%)