CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-006

MEDICAL REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Miguard**
Generic Name:	**frovatriptan**
Sponsor:	**Vanguard**
Indication:	**migraine**
NDA Number:	**21-006**
Original Receipt Date:	**1/29/99**
Clinical Reviewers:	**Armando Oliva, M.D.**
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1. Review Sources

The sponsor submitted the NDA in part paper and part electronic formats. The electronic documents consisted of case report forms and case report tabulations as PDF files. The remaining archival components of the NDA were in paper. The clinical section of the NDA included volumes 97-222, which included the NDA summary, the ISE, ISS, and individual study reports of the phase 2/3 clinical trials.

In addition, the sponsor submitted, as review aids on CD-ROM, PDF files for the clinical section (section 8), as well as electronic datasets as SAS transport files. I obtained the latter from the review biostatistician, Dr. Koti. I used the electronic copies of section 8, as well as the datasets, for my review.

2. Background

2.1 Indication

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

2.2 Important Information from pharmacologically related agents

Frovatriptan is pharmacologically similar to sumatriptan and other -triptans. Because of the potential for this class of compounds (5-$HT_{1D/1B}$ agonists) to cause coronary vasospasm, they should not be used in patients with coronary artery disease (CAD).

2.3 Administrative History

[redacted] submitted the IND on 9/30/95 on behalf of Vanguard. The sponsorship was transferred to [redacted] 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. [redacted] The protocol for the long term safety study (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.

A proposed study design to indicate there would be no cardiac safety concern associated with frovatriptan treatment was presented. The Division commented that the study would probably not demonstrate any effect and the "class" labeling for the 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 cardiovascular safety) but this would be a matter of review.

We agreed on the general format for the integrated summary of efficacy (ISE). Agreement was reached on the intent to treat population and a worst case analysis approach was acceptable for missing data.

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

The NDA was submitted on 1/29/99.

2.4 Proposed Labeling

2.5 Foreign Marketing

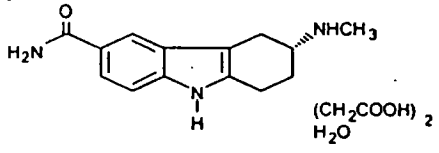
Frovatriptan is currently not marketed anywhere in the world.

3. Chemistry, Manufacturing and Controls

Frovatriptan succinate monohydrate is a white to off-white powder. It is manufactured as a 2.5mg oral tablet.

Generic Name:	**frovatriptan succinate monohydrate**
Trade Name:	**Miguard**
Chemical Name:	**(+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole monosuccinate monohydrate**
Alternative Name:	**VML 251**
Molecular Formula:	**$C_{14}H_{17}N_3O \bullet C_4H_6O_4 \bullet H_2O$**
Molecular Weight:	**379.4**

Figure 1: Frovatriptan—Chemical Structure



The proposed expiration date is 24 months.

4. Animal Pharmacology & Toxicology

I obtain the information in this section from the sponsor's NDA summary.

4.1 Pharmacology

Frovatriptan is the (R) enantiomer of a tetrahydrocarbazole derivative that has been characterized *in vitro* as a selective 5HT receptor agonist that binds with high affinity to both $5HT_{1B}$ and $5HT_{1D}$ receptors. At clinically relevant concentrations, it has no significant affinity for $5HT_2$, $5HT_3$, $5HT_4$, $5HT_6$, $5HT_7$, α-adrenergic, or histaminergic receptors. Relative to its potency at $5HT_{1D}$, frovatriptan exhibits a 25-fold selectivity over the $5HT_{1F}$ receptor, a >10 fold selectivity over $5HT_{1A}$, a 600-fold selectivity over $5HT_{1E}$, and a >1000-fold selectivity over the other 5HT, adrenergic, histamine, and dopamine

receptors studies. Frovatriptan has no significant effect on $GABA_A$ channel activity and has no benzodiazepine properties.

The sponsor states that frovatriptan displays a functional selectivity for human isolated cerebral arteries over coronary arteries, which should be therapeutically advantageous in terms of a superior side effect profile. At clinically relevant concentrations, frovatriptan produced constriction of human isolated cerebral arteries with little or no effect on human isolated coronary arteries. At high concentrations frovatriptan also displayed coronary artery relaxant properties.

In anesthetized dogs and cats, intravenous administration of frovatriptan produced selective constriction of the carotid vascular bed with no effect on blood pressure. A modest transient decrease was seen in the cat, whereas a slight increase was seen in 1 study in the dog. At the highest dose, heart rate was slightly increased in the cat but was unaltered in the dog. I.V. doses up to 2 mg/kg had no effect on ECG parameters in the dog. A transient hyperpnea was noted during and immediately after in 1 experiment in the dog.

In anesthetized dogs, intravenous frovatriptan did not increase coronary vascular resistance and had no effect on left ventricular pressure, left systolic pressure, cardiac contractility, aortic blood flow and systemic resistance. In a model of myocardial infarction in anesthetized dogs, frovatriptan had no adverse effect on coronary blood flow reperfusion following myocardial infarct and had no effect on myocardial infarct size.

Frovatriptan attenuates thermal-induced hyperalgesia, but was not found to have anti-nociceptive activity in the mouse.

4.2 Toxicology

Single dose toxicity studies in rats and mice indicate that frovatriptan has low acute oral toxicity with lethal dose in excess of 2000 mg/kg. Toxicity studies with frovatriptan using the maximum tolerated dose (MTD) in several species give no indication of adverse events likely to be relevant to the proposed clinical use of frovatriptan.

In rodents, repeat oral dose studies in mice demonstrated a no observed effect level (NOEL) of 40 mg/kg/d for 84 weeks, giving a 140 to 400 fold safety margin based upon a human exposure (AUC) to frovatriptan in blood at the proposed dose of 2.5mg (0.04 mg/kg). Repeat oral dose studies in rats demonstrated a NOEL of 10 mg/kg/d for 26 weeks, giving a 30-50 fold safety margin. Observed effects included peripheral vasodilatation, as well as renal, adrenal, and thyroid histopathological lesions. These effects occurred only at the high doses. Frovatriptan did not alter the overall tumor profile, or increase the incidence or multiplicity of any malignant tumor. After continuous administration for 84 weeks to mice and 104 weeks to rats, frovatriptan gave no indication of any potential to induce malignancy.

In dogs, repeat oral doses demonstrated no histopathologic changes attributable to frovatriptan administration at blood exposures up to 130-fold higher than ~~those~~

anticipated in man. Dose levels were limited by the pharmacological effects of frovatriptan on the central nervous and cardiovascular systems. No evidence of any ocular toxicity has been noted in long term oral studies at blood exposures 50- to 130 fold higher than those anticipated in man. Tachycardia, a compensatory response to peripheral vasodilatation and a consequence of frovatriptan administration, was observed in dogs.

In rats and rabbits, frovatriptan levels of 1000 and 540 fold (respectively) higher than man have no teratogenic effects and no effects on the fertility or fecundity of male and female rats. The slight increase in fetal loss in rabbits, minor alterations in a few reproductive parameters and a slight delay in fetal development seen following high doses of frovatriptan are attributable to maternal toxicity. Also noted was a minor prolongation of the duration of the estrus cycle in rats (by 1 day).

Frovatriptan was not found to possess genotoxic risk in a battery of *in vivo* and *in vitro* genotoxicity studies.

5. Clinical Data Sources

5.1 Phase 1 Program

Nineteen (19) phase 1 studies were conducted. Most were done in the U.K. in healthy subjects who were generally 18-45 years of age. Early studies included only males. Frovatriptan was administered either orally (1 to 100mg) or intravenously (3 studies, 0.4 to 1.2mg). I describe the studies below. The sponsor describes the phase 1 studies in the clinical section, but did not provide me any results. For complete details and results, I refer the reader to the biopharmaceutics review.

5.1.1 Pharmacokinetic Studies

The early phase 1 program consisted of 5 single dose PK studies (1165/24, 11/65/42, 11656/34, 251/96/04, and 251/96/12) and 2 multiple dose studies (251/96/01 and 251/96/03). They were designed to evaluate the safety, tolerability, and pharmacokinetics of frovatriptan in healthy subjects. Based on toxicological studies, the initial doses in humans were 1mg orally and 0.4mg intravenously.

Study 24 was the first phase 1 study. It was single-blind, placebo-controlled, ascending dose study in 18 male subjects. Doses used were 1, 2.5, 5, 10, 20, and 40mg orally, and 0.4 and 0.8mg intravenously.

Study 42 was then conducted to investigate higher doses. This study had a similar design to study 24 and it was conducted in 8 healthy male subjects. Oral doses were 40, 60, 80, or 100mg.

Study 34 was an open labeled, randomized 3-period crossover study in 9 healthy male subjects. It was designed to compare the absorption of frovatriptan when given orally as a capsule and when given as a solution. Subjects received either 40mg orally, either capsule or solution, or as a single 1.2mg i.v. dose.

Study 04 was open-label, 2 period crossover study to determine the extent of intra-individual variability of plasma and whole blood levels for frovatriptan following 2 single oral dose administrations. During each treatment period, 12 males and 12 females took 40mg.

Study 12 was conducted to investigate potential reasons for gender differences in the PK of frovatriptan. This open label, 3 way crossover study assessed the PK of frovatriptan in male and female subjects following i.v. infusion of frovatriptan 0.8mg and oral doses of 2.5mg and 40mg. Additionally, absolute bioavailability of single oral doses of frovatriptan 2.5 and 40mg was assessed.

In both multiple dose studies (01 and 03), frovatriptan was administered at 0, 2, and 12 hours in one day. This schedule was used to mimic the real-life possibility of taking a second dose for persistent pain, and a third dose for recurrence. Study 01 treated 24 male and female subjects with 40mg or placebo. Study 03 treated 20 male and female subjects with 20mg or placebo.

5.1.2 ADME Studies

Two studies were conducted to assess the metabolic profile of frovatriptan (1165/48 and 1165/135). Study 48 used a single 40mg dose of ^{14}C-frovatriptan as a solution in 4 male subjects. Study 135 was conducted with the clinical dose of 2.5mg of ^{14}C-frovatriptan in both males and females (due to the gender difference seen previously).

5.1.3 Bioavailability and Bioequivalence Studies

Bioequivalence of different formulations was demonstrated in 3 studies (1165/43, 1165/62, and 251/97/05). They were designed to show bioequivalence between each formulation and strength of formulation used in the clinical development of frovatriptan.

Study 43 compared the PK of 3 different capsule strengths of frovatriptan (2.5, 10, and 20mg) at a dose level of 20mg.

Study 62 compared the PK of 3 different tablet strengths of frovatriptan (2.5, 10, and 40mg) given as a total dose of 40mg, and 1 frovatriptan capsule formulation (10mg) also given as a total dose of 40mg.

Study 05 compared the PK of frovatriptan 2.5mg of the later clinical trial formulations (caplet and tablet) and the commercial tablet formulation.

A fourth study (VAD5-01) was conducted to compare the PK of frovatriptan 40mg during fed and fasting states. It was a randomized, balanced, open label, single dose, 2 way crossover study in 12 healthy subjects.

5.1.4 Special Population Studies

Study 251/97/01 was an open label study to compare the PK in elderly (>65) male and female subjects vs. the young.

Study 251/97/02 studied patients with renal impairment and study 251/97/06 studied patients with hepatic impairment.

5.1.5 Drug-Drug Interaction Studies

The sponsor conducted 3 drug-drug interaction studies: ergotamine (251/98/02), propranolol (251/98/06) and moclobemide (251/98/07).

5.2 Phase 2/3 Program

The completed phase 2/3 clinical trials are shown in Table 1 (sponsor table 8.2.2.1.1 page 12).

Table 1: Frovatriptan Clinical Trials

	N	<2.5mg	2.5mg	>2.5mg	PBO	Suma 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

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

There were four phase 2 trials (01, 02, 03, 14). An additional study (04) was conducted to evaluate the effect of migraine on the PK of frovatriptan.

Study 01 was a single-center, single blind (patient), comparative, primarily non-randomized, dose-titration study to assess the safety, tolerability, PK and clinical efficacy of a single oral dose of frovatriptan, in the range 2.5mg to 40mg, in the acute treatment of migraine. Originally, the range was 5mg to — but after 32 patients had been dosed, the protocol was amended to include the 2.5mg dose and the — , dose was deleted. In this study, dosing was titrated up or down according to the 2 hour headache response of the preceding patient. The first patient received 20mg. After 55 patients had been dosed, additional patients were enrolled and treated, disregarding the previous patient's response. These latter patients were randomized 1:1 to receive either 2.5mg or 20mg. Patients with significant cardiovascular or cerebrovascular disease were excluded.

Studies 02 and 14 were virtually identical in design. Each was multicenter, randomized, placebo-controlled, parallel group, outpatient, dose range finding efficacy studies. In study 02, patients each took a single dose of placebo or frovatriptan 2.5mg, 5mg, 10mg, 20mg, or 40mg (1:1:1:2:2:2) for the acute treatment of a single migraine attaek. In study

14, each took a single dose of placebo or frovatriptan 0.5mg, 1mg, 2.5mg or 5mg (1:1:1:1:1).

Study 03 was conducted in a special population of patients with or at high risk for coronary artery disease. This was a multicenter, randomized, double blind, parallel group, placebo-controlled study. The efficacy and cardiovascular safety of frovatriptan was evaluated in the clinic. Patients received a first dose of double blind frovatriptan 2.5mg or placebo (1:1) and were offered a second dose of the same medication 2 hours after the first dose (independent of headache severity). Each patient treated one migraine attack only. For enrollment, patients had to be migraine sufferers who also had a Framingham Heart Study Coronary Artery Disease Risk Prediction score of ≥14, or documented CAD defined as a definite history of myocardial infarction, a positive coronary angiogram, or stable angina with a positive cardiac stress test within 6 months of study entry.

Study 04 was an open-label, crossover study of the effect of migraine on the PK of frovatriptan 2.5mg in male and female patients. In this study, the PK of frovatriptan were measured during and outside a migraine attack. Each of the 12 patients in this study took a single oral dose of frovatriptan 2.5mg on 2 occasions.

The three phase two studies 01, 02, and 14 were used to determine the dose-response relationship for frovatriptan. In study 01, the median effective dose for the per-protocol population was 4.65mg (95% CI, 0.83-7.18mg). However, there was no placebo group, and the dose was not randomized for most patients, and the numbers were small. No definite conclusion could be drawn from this study. In study 02, all doses (2.5, 5, 10, 20, and 40mg) were superior to placebo, but no dose-response relationship was shown. The 2-hour headache responses were approximately 2-fold that seen in the placebo group for all doses. A clear dose-response was seen for safety, with an obviously higher incidence of AE's at doses of 10mg and above. The third study, 14, was conducted to explore the lower end of the dose-response curves (placebo, 0.5, 1, 2.5, 5mg). Both 2.5mg and 5mg were superior to placebo but neither the 0.5mg or 1mg dose was better than placebo at 2hours. All doses, however, were better than placebo at 4 hours. There was a higher incidence of AE's in the 5mg compared to 2.5mg. The incidence of AE's were similar among 0.5mg, 1mg, and 2.5mg. Therefore, the 2.5mg dose was chosen for further study in phase 3.

Four phase 3 studies have been completed at the time of NDA filing. These are studies 06, 07, 09, and 08. An additional study (251/98/08, as opposed to 251/96/08, which I refer as study 08 throughout my review), was ongoing at the time of submission. With the exception of study 09, all studies were conducted in North America. Study 09 was conducted in Europe, South Africa, and Australia.

Study 06 was a multicenter, randomized, double blind, parallel group, placebo-controlled, unbalanced (frovatriptan 2.5mg:placebo was 2:1) study that compared 2.5mg and placebo in the acute treatment of up to 3 migraine attacks over a 12 week period. A single dose for each attack was used. Patients treated their attacks as outpatients and recorded data in diaries. A total of 352 patients were to be randomized to provide 246 evaluable patients.

Patients had to be 18-65 years old, have a least a 12 month history of migraines, with or without aura, according to IHS criteria; and have a frequency of migraine attacks between 1-8 per month over at least the previous 2 months, and be <50 years of age at initial migraine diagnosis.

The design for study 07 was the same as for study 06, with the exception that a second dose of (non-randomized) study medication for headache recurrence could be taken. A total of 1250 patients were to be randomized into the 12 week study to provide approximately 870 evaluable patients (580 frovatriptan, 290 placebo).

The design for study 09 was different from the other two. This was a multicenter, randomized, double blind, placebo-controlled, active comparator, parallel group, unbalanced (frovatriptan 2.5mg, sumatriptan 100mg, placebo, 2:2:1) study. Treatment was randomized for the first attack only. During the second and third attacks, all patients received up to two doses of frovatriptan 2.5mg. For the first attack, the efficacy of frovatriptan 2.5mg (up to 2 doses) was compared to that of up to 2 doses of sumatriptan 100mg and up to 2 doses of placebo. A total of 1240 patients were to be randomized into the study provide approximately 950 evaluable patients (380 frovatriptan, 380 sumatriptan, 190 placebo.

The completed 12-month study (251/96/08, referred here as "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 (and all subsequent attacks, for that matter). 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).

The ongoing study is 251/98/08. It is a 6 month open label study. Its objective is to collect additional safety data in patients treating at least 2 migraines a month over the six month period. As in the completed 12 month long term study (251/96/08), patients could take up to 3 doses of 2.5mg for each attack, within 24 hours. Interim results for the first three months of treatment are included in the four month safety update.

6. Human Pharmacokinetics

The sponsor conducted 21 studies to characterize the human pharmacokinetics of frovatriptan. These studies included: absorption, metabolism, excretion, absolute bioavailability, dose proportionality, multiple dose pharmacokinetics, pharmacokinetics during a migraine attack, pharmacokinetics in patients with renal or hepatic impairment, the effect of food on absorption, bioequivalence between dosage forms used in the clinical trials and that to be marketed, the effects of age and gender, and potential interactions with oral contraceptives, propranolol, moclobemide, and ergotamine.

The protein binding and blood uptake of frovatriptan have been examined *in vitro*, as have interactions of frovatriptan with cytochrome P450 isozymes and monoamine oxidase.

Frovatriptan is bound by blood cells. Consequently, whole blood concentrations have been measures and the PK parameters based on whole blood were estimated in all of the PK studies, although plasma concentrations and associated PK parameters were determined in some studies.

Mean maximum blood concentrations (C_{max}) in patients are achieved approximately 2 - 4 hours (T_{max}) after administration of a single oral dose of frovatriptan 2.5 mg. There is no difference between the pharmacokinetics of frovatriptan in the same patients during and outside a migraine attack. The pharmacokinetics of frovatriptan are similar in migraine patients and healthy subjects. The mean terminal elimination half-life of frovatriptan in both males and females is approximately 26 hours. The absolute bioavailability of an oral dose of frovatriptan 2.5 mg in healthy subjects is about 22% in males and 30% in females. Food has no significant effect on the bioavailability of frovatriptan, but delays t_{max} slightly.

The mean steady state volume of distribution of frovatriptan following intravenous administration of 0.8 mg is 4.2 L/kg in males and 3.0 L/kg in females. Mean systemic clearance of frovatriptan was 216 and 132 mL/min in males and females, respectively. Renal clearance accounted for 38% (82 mL/min) and 49% (55 mL/min) of total clearance in males and females, respectively.

Binding of frovatriptan to serum proteins is low (approximately 15%). Reversible binding to blood cells at equilibrium is approximately 60%, resulting in a blood:plasma ratio of about 2:1 in both males and females.

Following administration of a single oral dose of radiolabelled frovatriptan 2.5 mg to healthy male and female subjects, 32% of the dose was recovered in urine and 62% in feces. Radiolabelled compounds excreted in urine were unchanged frovatriptan (33% of urinary radioactivity), hydroxylated frovatriptan (16%) N-acetyl desmethyl frovatriptan (13%), hydroxylated N-acetyl desmethyl frovatriptan (9%), and desmethyl frovatriptan (8%), together with several other minor metabolites. Desmethyl frovatriptan is about 3-fold less active as an agonist at 5-HT receptors than the parent compound. The N-acetyl desmethyl metabolite is inactive at 5-HT receptors. The activity of the other metabolites is unknown.

In vitro, cytochrome P450 1A2 appears to be the principal enzyme involved in the metabolism of frovatriptan.

Age: Mean blood concentrations of frovatriptan were 1.5- to 2-fold higher in healthy elderly subjects (age 65 - 77 years) compared to those in healthy younger subjects (age 21 - 37 years). There was no difference in t_{max} between the two populations.

Gender: There was no difference in the mean terminal elimination half-life of frovatriptan in males and females. Bioavailability was higher, and systemic exposure to frovatriptan was approximately 2-fold greater, in females compared to males, irrespective of age. This difference is due in part to differences in absorption and in part to differences in disposition.

Renal Impairment: In both males and females systemic exposure to frovatriptan following a single oral dose of 2.5 mg was not significantly different in subjects with renal impairment (creatinine clearance 16-73 mL/min), compared to that in healthy subjects.

Hepatic Impairment: Following oral administration of a single 2.5 mg dose of frovatriptan to male and female subjects with mild or moderate hepatic impairment (Child-Pugh grades A and B), mean blood concentrations of frovatriptan were within the range observed in healthy elderly subjects.

Race: The effect of race on the pharmacokinetics of frovatriptan has not been examined.

7. Integrated Review of Efficacy

7.1 Description of the Clinical Studies

There are 5 adequate and well controlled phase 2/3 studies that support the efficacy of frovatriptan in the acute treatment of migraine: studies 02, 14, 06, 07, and 09 (Table 2). Studies 02 and 14 were phase 2 dose-range finding studies that evaluated single doses between 0.5mg and 40mg. The three phase 3 studies (06, 07, 09) all evaluated the 2.5mg dose. Both 06 and 07 were placebo controlled, and study 09 was placebo and active controlled (sumatriptan 100mg). All five studies were outpatient studies and all were conducted in North America, with the exception of study 09 which was conducted in Europe, South Africa, and Australia. Studies 02 and 14 were single attack studies, and studies 06, 07, and 09 permitted the treatment of 3 attacks. Studies 02, 14, and 06 were single dose studies, and studies 07 and 09 permitted a second non-randomized dose within 24 hours for the treatment of recurrence. Rescue was permitted after 2 hours.

Table 2: Major Efficacy Studies

Study	Location	Design	Dose Groups	Number of Doses	Number of Attacks
02	US	Placebo-controlled	2.5mg, 5mg, 10mg, 20mg, 40mg	1	1
14	US	Placebo-controlled	0.5mg, 1mg 2.5mg, 5mg	1	1
06	US	Placebo-controlled	2.5mg	1	3
07	US	Placebo-controlled	2.5mg	2*	3
09	Non-US	Placebo and active-controlled	2.5mg sumatriptan 100mg	2*	3

* optional non-randomized 2nd dose for recurrence within 24 hours

Patients enrolled in these studies were male and non-pregnant/nursing female patients aged 18-65 years, with at least a 12-month history of migraine, with or without aura, according to IHS criteria. They had a frequency of 1-8 migraines per month over at least the two previous months, and were less that 50 years of age at the time of their migraine diagnosis. They were generally healthy, and patients at risk for coronary artery disease were excluded. I summarize important details about each study individually below.

7.1.1 Study 02

Study 02 was a randomized, double blind, placebo-controlled, parallel group, unbalanced, dose range finding study. A single dose of frovatriptan 2.5, 5, 10, 20, or 40mg, or placebo was taken for the acute treatment of a single migraine attack. The efficacy of each dose was compared to placebo. The study was conducted in 38 centers in the U.S. A total of 1013 patients were randomized (113 to 2.5mg, 112 to 5mg, 224 to 10mg 223 to 20mg, 229 to 40mg and 112 to placebo). Of these, 844 were included in the ITT population. A second dose was not permitted.

7.1.2 Study 14

Study 14 was a randomized, double blind, placebo-controlled, parallel group, balanced, dose range finding study. A single dose of frovatriptan 0.5, 1, 2.5, or 5mg or placebo was taken for the acute treatment of a single migraine attack. The efficacy of each dose was compared to placebo. The study was conducted in 25 centers in the U.S. A total of 695 patients were randomized (141 to 0.5mg, 139 to 1mg, 140 to 2.5mg, 138 to 5mg, and 137 to placebo). Of these, 598 were included in the ITT population. A second dose was not permitted.

7.1.3 Study 06

Study 06 was a randomized, double blind, placebo-controlled, parallel group, unbalanced study (frovatriptan:placebo, 2:1) that compared the efficacy of a single oral dose of frovatriptan 2.5mg to placebo in the acute treatment of up to 3 migraine attacks. It was conducted at 16 centers in the U.S. A total of 374 patients were randomized (251 to frovatriptan and 123 to placebo) of whom 308 were in the intent to treat population (204 in the frovatriptan group, and 104 in the placebo group). Treatment of subsequent attacks was ~~not r~~randomized and was identical to the treatment used for the initial attack.

7.1.4 Study 07

Study 07 was a randomized, double blind, placebo-controlled, parallel group, unbalanced study (frovatriptan:placebo, 2:1) that compared the efficacy of up to 2 doses of oral frovatriptan 2.5mg to placebo in the acute treatment of up to 3 migraine attacks. It was conducted in 48 centers in North America. A total of 1274 patients were randomized (850 to frovatriptan 2.5mg and 424 to placebo), of whom 1111 patients were included in the ITT population (733 in the frovatriptan group and 378 in the placebo group). The second dose and treatment for subsequent attacks were not randomized and were identical to the first dose taken for the initial attack. Taking of the second dose was contingent upon the patient having a headache recurrence.

7.1.5 Study 09

Study 09 was a randomized, double blind, placebo-controlled and active controlled, parallel group, unbalanced study (frovatriptan 2mg:sumatriptan 100mg:placebo, 2:2:1) that compared the efficacy of up to two doses of frovatriptan 2.5mg to sumatriptan 100mg (up to two doses) and placebo in the acute treatment of up to 3 migraine attacks. Treatment was randomized in the first attack only. For the second and third attacks, all patients were treated with open label frovatriptan 2.5mg. The study was conducted in 128 centers in Europe, South Africa, and Australia. A total of 1316 patients were randomized for attack 1 (531 to frovatriptan, 521 to sumatriptan, and 264 to placebo). Of these 1196 were included in the ITT population (475 in the frovatriptan group, 479 in the sumatriptan group, and 242 in the placebo group). The second dose was not randomized and was identical to the first dose. As in study 07, the taking of the second dose was contingent upon having a headache recurrence. Therefore, patients could take either a total of 2.5mg or 5mg of frovatriptan, or a total 100mg or 200mg of sumatriptan for the first attack. All patients received up to 2 doses of frovatriptan 2.5mg to treat the second and third attacks.

The objective for the first attack was to compare the efficacy of up to 2 doses of frovatriptan 2.5mg with that of up to 2 doses of sumatriptan 100mg and up to 2 doses of placebo in the acute treatment of a migraine attack. Also, the safety and tolerability of the treatments were described for the first attack.

The study did not exclude patients with prior use of sumatriptan. It did exclude patients that were known to be allergic to sumatriptan.

7.2 Endpoints

All studies used the 2-hour headache response rate as the primary endpoint. Studies 07 and 09 also used the 24-hour recurrence rate as a primary endpoint:

- Response at 2 hours – was defined as the proportion of patients obtaining complete pain relief (grade 0) or mild pain (grade 1) at 2 hours after taking the first dose of study medication for the first attack, given an baseline headache severity of moderate (grade 2) or severe (grade 3)
- Recurrence – recurrence within 24 hours was defined in patients who responded at 4 hours post first dose and experienced a worsening of their headache from mild (grade 1) or none (grade 0) to moderate (grade 2) or severe (grade 3) within 24 hours of the first dose

A complete list of all efficacy outcome measures is shown in Table 3 (adapted from ISE panel 8.7.2.1.1:1, page 45). The primary measures are outlined in gray.

Table 3: Efficacy Evaluations Performed

Evaluation	02	14	06	07	09
2-Hr Response	1	1	1	1	1
4-Hr Response	2	2	2	2	2
Time to Response	n/d	n/d	2	2	2
6-Hr Response	2	2	2	2	2
Complete Headache Relief at 2, 4, 6 hours	2	2	2	2	2
Recurrence	2	2	2	1	1
Time to recurrence	2	2	2	2	2
Presence of nausea, vomiting, photophobia, phonophobia	2	2	2	2	2
No/mild functional impairment	2	2	2	2	2
Time to meaningful relief	2	2	2	2	2
% taking 2nd dose	n/a	n/a	n/a	2	2
% taking rescue	2	2	2	2	2
Time to remedication (2^{nd} dose or rescue)	n/a	n/a	n/a	2	2
Response at 4, 6, 12, 24 hrs in patients taking only 1 dose	n/a	n/a	n/a	2	2
Time to response following 2nd dose	n/a	n/a	n/a	2	2
Overall rating of effectiveness	2	2	2	2	2

1 = primary; 2 = secondary; n/a = not applicable; n/d = not done

Most endpoints were recorded in the headache diaries at 0, 2, 4, 6, 12, and 24 hours. Headache severity was rated on a 4 point scale (0=none, 1=mild, 2=moderate, 3=severe). Complete headache relief is defined as a headache grade=0. Time to recurrence was recorded for those who responded at 4 hours and recurred within 24 hours post first dose for the first attack. The associated migraine symptoms of nausea, vomiting, photophobia, and phonophobia were recorded as either present or absent at the aforementioned time points. Functional impairment was rated on a 4 point scale (0=none, 1=mild, 2=moderate, 3=severe) at each time point. Meaningful relief was patient defined.

7.3 Analysis Methods

The All Patients Randomized (APR) population is used in the ISE for some demographic summaries and contains all patients who were randomized to study treatment. The Intent To Treat (ITT) population was defined as all patients who received any study medication and who have any evaluable post-baseline efficacy data. The ITT-observed and ITT-worst case populations are modifications of the ITT population.

The ITT-observed population excluded patients who were asleep or otherwise had a missing assessment. The ITT-worst case population is applied to analyses of response at 2 and 4 hours only. If the 2 hour assessment was missing, a non-response was assigned. If the assessment at 4 hours was missing and the 2-hour assessment was present, this score was carried forward. If both assessments were missing, a non-response was assigned at 4 hours. If a patient took rescue prior to the 2 or 4 hour assessment, a non-response was assigned for that time point, regardless of the assessment recorded. The sponsor

performed a per-protocol (PP) analysis for each primary endpoint for each study, but I only include the ITT analyses in this review.

Categorical variables (*e.g.*, race, headache severity) are summarized by presenting the number and percentage of patients in each category. Continuous variables (*e.g.*, age, weight) are summarized through sample size (n), mean, median, minimum, maximum, and standard deviation.

Ninety-four (94) patients in study 02 were also enrolled in study 14 (81 of which were in the safety database). In order to avoid bias by including these patients twice in analyses, data from study 14 were not included in combined analyses of efficacy or safety data.

The sponsor used logistic regression analyses, using SAS GENMOD procedure to analyze the categorical data from the phase 3 studies. They used the Cochran-Mantel-Haenszel test, using the SAS FREQ procedure, to analyze the phase 2 studies.

7.4 Disposition

In terms of the number of randomized patients, study 09 was the largest study. It randomized 1316 patients, of which 1196 comprised the ITT population. These numbers exclude 19 patients randomized by Dr. Fourie (site number 2413) who have been omitted due to apparent irregularities at the site. All efficacy tables exclude patients enrolled at this center. The sponsor doesn't describe exactly what irregularities were noted. Two other studies randomized over 1000 patients (02, and 07). Table 4 summarizes the all patients randomized population.

Table 4: Efficacy Studies – All Patients Randomized

Study	<2.5mg	2.5mg	>2.5mg	Total Frovatriptan	PBO	Suma 100mg	Total
02		113	788	901	112		1013
14	280	140	138	558	137		695
06		251		251	123		374
07		850		850	424		1274
09		531		531	264	521	1316
Total	280	1885	926	3091	1060	521	4672

The number of patients comprising the intent to treat (ITT) population is shown in Table 5 (generated from ISE, pages 39-42).

Table 5: Efficacy Studies – Intent to Treat Population

Study	0.5mg	1.0mg	2.5mg	5mg	10mg	20mg	40mg	Total Frovatriptan	PBO	Suma 100mg	Total
02			93	93	180	185	201	752	92		844
14	123	111	126	120				480	118		598
06			204					204	104		308
07			733					733	378		1111
09			475					475	242	479	1196
Total	123	111	1631	213	180	185	201	2644	934	479	4057

The percentage of randomized patients who made up the ITT population ranged 80-92%of the APR population, depending on the study and treatment group. Randomized patients were excluded from the ITT population because they failed to treat a headache during the 8 or 12 week study period or treated a headache but had no post-baseline efficacy data (Table 6, adapted from ISE panel 8.7.2.1.3:3, page 64).

Table 6: Efficacy Studies – Randomized and ITT Populations, by Study

	02	14	06	07	09
Randomized	1013	695	374	1274	1316
Failed to treat an attack	114 (11%)	60 (9%)	52 (14%)	126 (10%)	111 (8%)
No post-baseline efficacy data	55 (5%)	37 (5%)	14 (4%)	37 (3%)	9 (<1%)
ITT	844 (83%)	598 (86%)	308 (82%)	1111 (87%)	1196 (91%)

Across the 5 studies, the percentages of randomized patients that met criteria for inclusion in the per protocol (PP) population ranged from 71% in study 06 to 89% in study 09. The reasons why patients in the ITT population were not included in the PP population ranged from adverse events, consent withdrawn, major protocol violation, lost to follow-up, and "other."

7.5 Baseline Characteristics

The sponsor summarized baseline characteristics from the 5 major short-term efficacy studies. Results from the 4 major studies are combined (minus study 14, for reasons described previously) and are presented for the frovatriptan 2.5mg and placebo groups only. The sponsor presents data for both the all patients randomized (APR) and ITT populations. I include data for the ITT population for the frovatriptan 2.5mg and placebo patients for the 4 pool-able studies only (02, 06, 07, 09).

7.5.1 Demography

Baseline Demographic Information is summarized in Table 7 (adapted from ISE panel 8.7.2.1.4:1, page 69). As is typical of migraine studies of this type, the vast majority were women (87-88%) and Caucasian (93-94%). The mean age was 41 years, and other demographic parameters were comparable between the 2.5mg and placebo groups, with the exception of body mass index. A higher percentage of placebo patients were in the overweight (BMI 25-29.9) or obese (BMI ≥ 30.0) categories, compared to frovatriptan 2.5mg patients. This analysis reached nominal significance (p=0.02).

Table 7: Studies 02, 06, 07, 09 – Baseline Demographics (ITT Population)

	2.5mg N=1505	PBO N=816	p-value
Gender			
Male	181 (12%)	110 (13%)	0.31
Female	1324 (88%)	706 (87%)	

	2.5mg N=1505	PBO N=816	p-value
Race			
Caucasian	1414 (94%)	761 (93%)	0.54
Black	45 (3%)	30 (4%)	
Other	45 (3%)	25 (3%)	
Age (years)			
Mean (SD)	41.5 (9.9)	40.8 (10.4)	0.16
Range	18-69	18-69	
Height (cm)			
Mean (SD)	165.9 (8.2)	165.5 (8.2)	0.38
Range	137-202	137-198	
Weight (kg)			
Mean (SD)	70.4 (16.2)	71.4 (17.1)	0.13
Range	41-200	42-156	
Body Mass Index (kg/m^3)			
<25.0	839 (56%)	418 (51%)	0.02
25.0-29.9	403 (27%)	237 (29%)	
≥30.0	252 (17%)	159 (20%)	

7.5.2 Migraine History

The frovatriptan 2.5mg and placebo ITT populations were well balanced with regard to duration of migraine history, number of attacks per month over the previous year, migraine type and previous use of sumatriptan (Table 8).

Table 8: Studies 02, 06, 07, 09 – Migraine History (ITT Population)

		2.5mg N=1505	PBO N=816
Time suffered from migraines (years)	N	1505	816
	Mean (SD)	19.2 (11.5)	19.1 (11.9)
Frequency (attacks/mo.) over the past year	N	1505	816
	Mean (SD)	3.3 (2.0)	3.2 (1.8)
Migraine Type	N	1505	816
	With aura	346 (23%)	175 (21%)
	Without aura	895 (59%)	514 (63%)
	Both	264 (18%)	127 (16%)
Previous sumatriptan use*	N	1412	724
	Yes	954 (68%)	489 (68%)
	No	458 (32%)	235 (32%)

* study 02 data are not included because a different "triptan use" question was asked and thus the data could not be pooled.

7.5.3 Baseline Headache Characteristics

The sponsor summarized the baseline headache severity, symptoms, and duration at the time of the first dose for the ITT population. The frovatriptan 2.5mg and placebo groups were well balanced with respect to these baseline variables (Table 9, ISE panel 8.7.2.1.4:4, page 77). As is typical of migraine studies of this type, approximately 2/3 of

the headaches treated were moderate in intensity at baseline. Nausea was present in approximately 60% of the headaches. Photophobia was the most commonly reported associated symptom (approximately 80%) and phonophobia was present in approximately 2/3 of the headaches treated.

Table 9: Studies 02, 06, 07, 09 – Baseline Headache Characteristics (ITT Population)

		2.5mg n=1505	PBO N=816
Headache Severity	N	1496	812
	None	1 (<1%)	0
	Mild	3 (<1%)	0
	Moderate	1023 (68%)	571 (70%)
	Severe	466 (31%)	241 (30%)
	Asleep	3 (<1%)	0
Headache Duration at time of 1st dose	N	1406	723
	0-2 Hrs	560 (40%)	297 (41%)
	>2-4 Hrs	327 (23%)	174 (24%)
	>4 Hrs	519 (37%)	252 (35%)
Assoc Symptoms at time of 1st dose	N	1505	816
	Nausea	902 (60%)	469 (57%)
	Vomiting	89 (6%)	39 (5%)
	Photophobia	1168 (78%)	644 (79%)
	Phonophobia	984 (65%)	550 (67%)

7.5.4 Drug Exposure

In studies 02, 14, and 06, patients took a single dose of study medication for a migraine attack. Although studies 06, 07, and 09 treated up to 3 attacks, only efficacy data from attack 1 are used, as is typical for other migraine studies of this type. In studies 07 and 09, patients could take a second (non-randomized) dose for headache recurrence. Table 10 (ISE panel 8.7.2.1.6:1, page 89) shows that the majority of patients treating attack 1 used only 1 dose (~70%). Since patients in studies 02 and 06 could only take one dose, this number should be interpreted with caution.

Table 10: Studies 02, 06, 07, 09 – Overall Summary of Exposure (ITT Population)

	Number of Doses to Treat attack	2.5mg	PBO
Number of Patients		1505	816
Number with dosing info		1505	816 (>99%)
Total # of doses taken		3959	1990
Total # of attacks treated		3057	1530
Number of patients treating attack 1	1 dose	1057 (70%)	564 (69%)
	2 doses	445	251

For attack 1, the next table (Table 11, adapted from ISE panel 8.7.2.1.6:2, page 90) shows the exposure for each of the 5 efficacy studies separately. Only the frovatriptan 2.5mg,

sumatriptan, and placebo groups are shown. In the studies that allowed 2 doses, approximately 60-65% used 1 dose, regardless of treatment.

Table 11: Efficacy Studies – Exposures for the First Attack

	Number of Doses to Treat Attack	2.5mg	PBO	Sumatriptan 100mg
Study 02: N		93	92	n/a
Attack 1		93 (100%)	92 (100%)	n/a
Study 14: N		126	118	
Attack 1		126 (100%)	118 (100%)	
Study 06: N		204	104	n/a
Attack 1		204 (100%)	104 (100%)	n/a
Study 07: N		733	378	n/a
Attack 1	1 dose	470 (64%)	221 (58%)	n/a
	2 doses	260 (35%)	157 (42%)	n/a
Study 09: N		475	242	479
Attack 1	1 dose	290 (61%)	147 (61%)	306 (64%)
	2 doses	185 (39%)	94 (39%)	173 (36%)

7.6 Primary Efficacy Results

All 5 efficacy studies used the 2-hr headache response rate as the primary efficacy measure. Studies 07 and 09 also used the 24 hour recurrence rate as a primary outcome measure. Only patients with moderate or severe headaches at baseline were included in the analyses. Initial headache severity was included in all logistic regression models for primary and secondary efficacy parameters for studies 06, 07, and 09.

For study 09, the comparison of frovatriptan 2.5mg vs. sumatriptan 100mg was defined in the protocol as the only primary pairwise comparison and so no adjustment for multiple comparisons is necessary. The sponsor had not originally planned to present a p-value for the comparison with placebo. However, at the request of the Agency in the pre-NDA meeting, p-values are presented for this comparison as well. This comparison is viewed as secondary and no adjustments are made for multiple comparisons. All analyses for study 09 exclude Dr. Fourie's center (center 2413) due to "apparent irregularities." An analysis which includes that center was presented as an appendix to the study report for study 09. It was included to demonstrate that the inclusion of this center had no effect on the overall conclusions for the primary efficacy parameters.

7.6.1 Two-Hour Headache Response

For the three phase 3 studies (06, 07, 09), the sponsor used a logistic regression model to analyze the 2-hr headache response rates. For the two phase 2 studies (02, 14), a Cochran-Mantel-Haenszel test, stratified by center, was used.

The 2-hr headache response rates for the three phase 3 studies are shown in Table 12 (adapted from ISE panel 8.7.2.1.7:1, page 98). It shows that frovatriptan 2.5mg was numerically and statistically superior to placebo in all 3 studies. This was the primary analysis for studies 06 and 07, and a secondary analysis for study 09. The primary

analysis for study 09 was a test for equivalence between frovatriptan and sumatriptan. This showed that sumatriptan 100mg was statistically superior to frovatriptan 2.5mg (47% vs. 37%) and the test for equivalence to sumatriptan failed.

Table 12: Studies 06, 07, 09 – Two-Hour Headache Response Rates (ITT-observed)

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

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

The sponsor performed additional analyses of the following variables to investigate any main interaction effects: center, gender, baseline severity, history of aura, previous sumatriptan use. None of the analyses was significant with the exception of history of aura in study 09 (p=0.046) but this was not felt to be of clinical significance.

The 2-hr headache response rates for the two phase 2 studies are shown in Table 13 (adapted from ISE panel 8.7.2.4:1, page 204). These are shown separately from the three phase 3 studies since multiple frovatriptan dose groups were involved in these two studies. The 2.5mg dose was nominally superior to placebo in both studies. It shows that doses lower than 2.5 (1.0 and 0.5mg) were not effective, and it also shows a fairly flat dose-response relationship between 2.5mg and 40mg.

Table 13: Studies 02, 14 – Two-Hour Headache Response Rates (ITT-observed)

Dose	Study 02	p-value*	Study 14	p-value*
PBO	20/91 (22%)		29/115 (25%)	
0.5mg			36/119 (30%)	0.46
1.0mg			28/109 (26%)	0.97
2.5mg	38/90 (42%)	0.004	46/121 (38%)	0.047
5mg	36/91 (40%)	0.020	42/115 (37%)	0.097
10mg	73/177 (41%)	0.002		
20mg	85/178 (48%)	<0.001		
40mg	80/192 (42%)	0.001		

* Cochran-Mantel-Haenszel test

7.6.2 Recurrence Within 24 Hours (Studies 07, 09)

For studies 07 and 09, recurrence within 24 hours was a second primary efficacy parameter. Recurrence was defined as the return of a grade 2 or 3 headache within 24 hours of the first dose, after having achieved a response at 4 hours. The proportion of

patients experiencing a recurrence was compared using a logistic regression model with terms for center, treatment group, and initial headache severity.

In both studies, there was no statistically significant difference between frovatriptan 2.5mg and placebo with respect to recurrence rates (Table 14, adapted from ISE panel 8.7.2.1.7:6, page 106).

Table 14: Studies 07, 09 – Recurrence Rates

Study	2.5mg	PBO	Sumatriptan 100mg	p-value*
07	89/378 (24%)	32/115 (28%)		0.33
09	60/242 (25%)	20/65 (31%)	87/275 (32%)	0.096# 0.32

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

7.7 Secondary Efficacy Results

This section provides the secondary efficacy results for the 5 efficacy studies. Only results for the frovatriptan 2.5mg , sumatriptan 100mg, and placebo groups are shown. As in the previous section, study 09 excludes Dr. Fourie's center (2413). The secondary endpoints are listed below. Results are presented for each study separately based on the ITT population. Those marked with an asterisk (*) are not included in this review since they add little to the overall efficacy conclusions.

- Response at 4 hours
- Time to response (after the first dose)
- Time to response (after the first dose) for attacks 2 and 3*
- Response at 6 hours
- Complete relief at 2, 4, 6 hours
- Response at 4 hours and recurrence within 24 hours (studies 02, 06, and 14 only)
- Time to recurrence following a 4 hour response
- Presence of nausea, vomiting, photophobia, and phonophobia
- No/mild functional impairment
- Time to meaningful relief
- Proportion taking a second dose (studies 07 and 09 only)
- Use of rescue within 24 hours
- Time to remedication (2nd dose or rescue, studies 07 and 09 only)
- Response at 4, 6, 12, and 24 hours separately, by number of doses (studies 07 and 09 only)*
- Time to response from 2nd dose (studies 07 and 09 only)
- Patient's overall rating of effectiveness of treatment

7.7.1 Response at 4 Hours

This analysis was performed on each of the 5 efficacy studies on patients with baseline pain intensity of 2 or 3. A logistic regression model was used with terms for center,

treatment group and initial headache severity. For the phase 2 studies, a Cochran-Mantel-Haenszel test, stratified by center, was used.

For the phase 3 studies, between 16-22% of patients in a treatment group, who had a moderate or severe baseline headache, had no assessment of headache severity at 4 hours. For the majority of cases, the reason being that they were asleep at the time of the scheduled assessment. Within each study, the treatment groups were well balanced with respect to "missing" and "asleep" categories. For the phase 2 studies, no patients were "asleep" at the time of the 4 hour assessment. The 4-hour response was confounded by the use of rescue, which was permitted after 2 hours. The results of this analysis is shown in Table 15 (adapted from ISE panels 8.7.2.1.8:1 and 8.7.2.1.8:2, pages 114 and 116). Frovatriptan was nominally significantly superior to placebo in all studies. Sumatriptan was numerically superior to frovatriptan in study 09, but this did not reach nominal significance.

Table 15: Efficacy Studies – Four-Hour Headache Response Rates (ITT-observed)

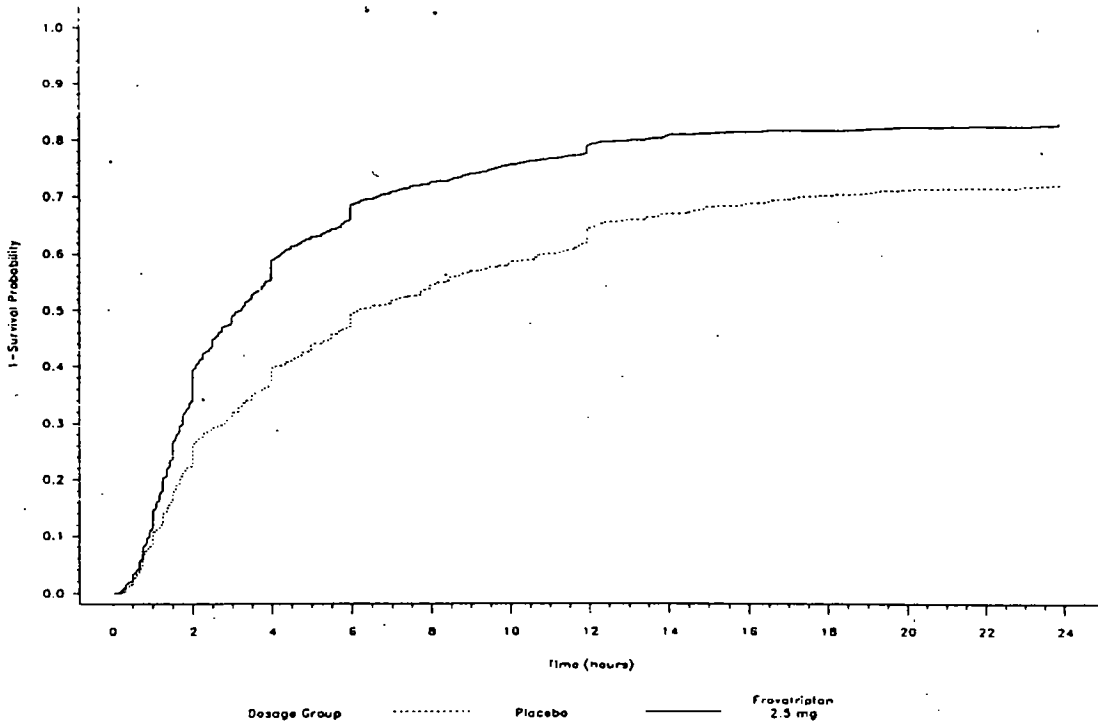
Study	2.5mg	PBO	Sumatriptan 100mg	p-value*
02	54/85 (64%)	31/81 (38%)		<0.001
14	79/117 (68%)	35/106 (33%)		<0.001
06	88/156 (56%)	25/81 (31%)		<0.001
07	378/586 (65%)	115/305 (38%)		<0.001
09	242/388 (62%)	65/202 (32%)	275/391 (70%)	0.667# <0.001

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

7.7.2 Time to Response

The time to first response after the first dose was analyzed for the three phase 3 studies 06, 07, and 09 for the ITT population of patients who had a baseline headache severity of 2 or 3. Figure 2 was constructed using a Kaplan-Meier approach (ISE figure 8.7.2.1.8:1, page 120). The figure shows that the probability of achieving a response was greater for frovatriptan 2.5mg compared to placebo, starting at about 30 minutes.

Figure 2: Studies 06, 07, 09 – Time to First Response, Attack 1 (0-24 Hours)



7.7.3 Response at 6 Hours

The response at 6 hours was analyzed in a similar fashion as was the 4-hour response. In all 5 studies, the response at 6 hours for frovatriptan was higher than placebo. They were:

- Study 02 – 75% vs. 49%
- Study 14 – 77% vs. 46%
- Study 06 – 75% vs. 48%
- Study 07 – 73% vs. 47%
- Study 09 – 75% vs. 45%

For comparison, the 6-hr sumatriptan headache response rate in study 09 was 75%.

7.7.4 Complete Relief at 2, 4, and 6 Hours

Complete relief is defined as no headache (grade 0). The proportions of patients achieving complete relief are shown in Table 16 (adapted from ISE panels 8.7.2.1.8:6-7 , pages 123-124). Complete relief rates were numerically higher for frovatriptan at all three time points, compared to placebo. P-values were calculated for the 2 and 4 hour time points only, and these were nominally significant. Sumatriptan was numerically better than frovatriptan in study 09 at all three time point, and it reached nominal significance at 4 hours.

Table 16: Efficacy Studies – Complete Relief at 2, 4, 6 Hours (ITT-observed)

Study	2.5mg	PBO	Sumatriptan 100mg	p-value*
2 Hours				
02	10/90 (11%)	1/91 (1%)		0.007
14	18/121 (15%)	6/115 (5%)		0.013
06	26/187 (14%)	2/99 (2%)		<0.001
07	88/672 (13%)	9/347 (3%)		<0.001
09	40/438 (9%)	7/225 (3%)	80/441 (18%)	0.421# 0.002
4 Hours				
02	25/85 (29%)	9/81 (11%)		0.001
14	36/117 (31%)	14/106 (13%)		0.002
06	42/146 (27%)	8/81 (10%)		0.001
07	190/586 (32%)	43/305 (14%)		<0.001
09	122/388 (31%)	19/202 (9%)	164/391 (42%)	0.001# <0.001
6 Hours				
02	37/79 (47%)	13/71 (18%)		
14	62/113 (55%)	24/97 (25%)		
06	52/139 (37%)	18/80 (23%)		
07	241/523 (46%)	56/265 (21%)		
09	157/338 (46%)	29/178 (16%)	188/341 (55%)	

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

7.7.5 Recurrence Within 24 Hours (Studies 02, 14, 06)

Recurrence rates for studies 07 and 09 were already discussed in section 7.6.2, page 23 since they were primary endpoints for those studies. This section describes the recurrence rates in the three other studies.

In study 06, 10% of frovatriptan patients (9/88) had a recurrence within 24 hours, compared to 24% (6/25) for placebo. Although numerically in favor of frovatriptan, it failed to reach nominal significance (p=0.082).

In study 02, the recurrence rates were 7% for frovatriptan (4/54) and 29% (9/31) for placebo (p=0.06), and for study 14, the rates were 19% for frovatriptan (15/79) and 20% (7/35) for placebo (p=0.96).

7.7.6 Time to Recurrence

The time to recurrence following a response at 4 hours was analyzed for all 5 studies. No formal statistical tests were planned or performed on these data. The time to recurrence were numerically longer for frovatriptan treated patients:

- Study 02 – frovatriptan 21.4 hours vs. placebo 12.5 hours
- Study 14 – frovatriptan 18.5 hours vs. placebo 13 hours
- Study 06 – frovatriptan 11 hours vs. placebo 7.9 hours
- Study 07 – frovatriptan 13.3 hours vs. placebo 6.5 hours
- Study 09 – frovatriptan 13.8 hours vs. placebo 6.2 hours

For sumatriptan 100mg in study 09, the time to recurrence was 14 hours.

7.7.7 Nausea, Vomiting, Photophobia, Phonophobia

In each of the five efficacy studies, the proportion of patients with nausea, photophobia, phonophobia was consistently lower for frovatriptan 2.5mg treated patients than placebo patients. The results of these secondary analyses are shown in Table 17 (ISE panel 8.7.2.1.8:10, page 129, and tables 2.19.1 – 2.19.5, pages 294-298). The nominally significant results are highlighted in gray.

Table 17: Efficacy Studies – Relief of Migraine Associated Symptoms

		Study 02	14	06	07	09
2 hours						
Nausea	2.5mg	32/90 (36%)	53/121 (44%)	80/188 (43%)	294/677 (43%)	203/441 (51%)
	PBO	46/91 (51%)	57/115 (50%)	52/100 (52%)	158/348 (45%)	131/226 (58%)
		p=0.039*	p=0.12	p=0.092	p=0.116	p=0.007*
Vomiting	2.5mg	1/90 (1%)	9/121 (7%)	14/188 (7%)	40/677 (6%)	35/441 (8%)
	PBO	6/91 (7%)	10/115 (9%)	8/100 (8%)	22/348 (6%)	20/226 (9%)
		p=0.044*	p=0.72	p=0.87	p=0.79	p=0.69
Photophobia	2.5mg	62/90 (69%)	79/121 (65%)	116/188 (62%)	383/677 (57%)	225/441 (51%)
	PBO	78/91 (86%)	88/115 (77%)	76/100 (76%)	238/348 (68%)	135/226 (60%)
		p=0.007*	p=0.006*	p=0.001*	p<0.001**	p=0.010*
Phonophobia	2.5mg	54/90 (60%)	66/121 (55%)	97/188 (52%)	325/677 (48%)	203/441 (46%)
	PBO	68/91 (75%)	71/115 (62%)	64/100 (64%)	189/348 (54%)	118/226 (52%)
		p=0.044*	p=0.16	p=0.018*	p=0.012*	p=0.16
4 hours						
Nausea	2.5mg	23/85 (27%)	29/117 (25%)	44/157 (28%)	161/590 (27%)	111/390 (28%)
	PBO	34/81 (42%)	46/106 (43%)	41/82 (50%)	120/305 (39%)	92/202 (46%)
		p=0.049*	p<0.001**	p<0.001**	p<0.001**	p<0.001**
Vomiting	2.5mg	3/85 (4%)	9/121 (7%)	7/157 (4%)	23/590 (4%)	23/390 (6%)
	PBO	3/81 (4%)	10/115 (9%)	6/82 (7%)	20/305 (7%)	17/202 (8%)
		p=0.95	p=0.86	p=0.37	p=0.084	p=0.25
Photophobia	2.5mg	43/85 (51%)	53/117 (45%)	72/157 (46%)	240/590 (41%)	118/390 (30%)
	PBO	55/81 (68%)	67/106 (63%)	54/82 (66%)	194/305 (64%)	100/202 (50%)
		p=0.030*	p<0.001**	p=0.001*	p<0.001**	p<0.001**
Phonophobia	2.5mg	34/85 (40%)	48/117 (41%)	52/157 (33%)	188/590 (32%)	115/390 (29%)
	PBO	43/81 (53%)	52/106 (49%)	45/82 (55%)	149/305 (49%)	84/202 (42%)
		p=0.070	p=0.17	p<0.001**	p<0.001**	p=0.002

* $0.001 < p < 0.05$; ** $p < 0.001$

The incidence of nausea at 2 and 4 hours was numerically lower for frovatriptan in all 5 studies, when compared to placebo. The comparisons achieved nominal significance in 2 studies at 2 hours (02, 09), and in all 5 studies at 4 hours.

The incidence of vomiting was generally low (1-9%) in all studies, and there is little evidence that frovatriptan relieves the vomiting associated with migraine.

The incidence of photophobia at 2 and 4 hours was numerically lower for frovatriptan in all 5 studies, when compared to placebo. The comparisons achieved nominal significance in all 5 studies at 2 hours and in 3 studies at 4 hours (06, 07, 09).

The incidence of phonophobia at 2 and 4 hours was numerically lower for frovatriptan in all 5 studies, when compared to placebo. The comparisons achieved nominal significance in 3 studies at 2 hours (02, 06, 07) and in 3 studies at 4 hours (06, 07, 09).

7.7.8 Functional Impairment

Functional impairment was assessed at 0 (baseline), 2, and 4 hours for all 5 efficacy studies. The sponsor included in the analysis only those patients who recorded information at each representative time point. No formal statistical tests were performed. Those achieving no or mild functional impairment at 2 or 4 hours are shown below (Table 18, adapted from ISE panels 8.7.2.1.8:11-12, pages 130-131). The proportion who had functional impairment of mild or none was numerically higher for frovatriptan in all 5 studies at both the 2 and 4 hour time points.

Table 18: Efficacy Studies – Mild or No Functional Impairment

Study		% Mild or No Functional Impairment	
		2.5mg	PBO
02	2 hours	59%	49%
	4 hours	75%	57%
14	2 hours	63%	57%
	4 hours	80%	58%
06	2 hours	45%	28%
	4 hours	59%	39%
07	2 hours	50%	36%
	4 hours	64%	43%
09	2 hours	39%	26%
	4 hours	57%	36%

7.7.9 Time to Meaningful Relief

The time to meaningful relief was analyzed for all 5 efficacy studies using a Kaplan-Meier approach. Patients who did not obtain meaningful relief within 24 hours were censored to 24 hours. Between treatment comparisons were carried out using the logrank test (not stratified by center). In all 5 studies, there were nominally significant differences between the frovatriptan 2.5mg group and placebo (Table 19, adapted from ISE Panel 8.7.2.1.8:13, page 132). Out of interest, the median time to meaningful relief for sumatriptan 100mg in study 09 was 10.71 hours.

Table 19: Efficacy Studies – Time to Meaningful Relief

Study	Median Time to Meaningful Relief (hours) 2.5mg	PBO	p-value
02	3.75	8.63	<0.001
14	4.00	9.25	<0.001
06	6.00	13.83	<0.001
07	12.00	15.00	0.004
09	10.48	16.50	<0.001

7.7.10 Proportion of Patients Taking a Second Dose

Studies 07 and 09 permitted a second dose for the treatment of recurrence within 24 hours. In study 07, 30% (217/723) of frovatriptan-treated patients took a second dose, compared with 38% (141/376) of placebo patients. In study 09, similar percentages in all three treatment groups took a second dose: frovatriptan 2.5mg – 34% (162/474), placebo – 35% (85/241), and sumatriptan 100mg – 31% (148/474). No statistical analyses were performed.

7.7.11 Use of Rescue Medication

Rescue medication was permitted after 2 hours. The sponsor analyzed the proportion of patients who took rescue medication within 24 hours of the first dose. No formal statistical analyses were planned or performed . The results for each study is summarized in Table 20 (ISE panel 8.7.2.1.8:14, page 134). The proportion of patients using rescue within 24 hours was numerically lower for frovatriptan, compared to placebo, in all 5 studies.

Table 20: Efficacy Studies – Use of Rescue Medication

Study	2.5mg	PBO	Sumatriptan 100mg
02	29/93 (31%)	46/92 (50%)	n/a
14	36/126 (29%)	57/118 (48%)	n/a
06	86/204 (42%)	69/104 (66%)	n/a
07	250/733 (34%)	211/378 (56%)	n/a
09	150/475 (32%)	135/242 (56%)	130/479 (27%)

7.7.12 Time to Remedication (Rescue or 2nd Dose)

The sponsor analyzed the time to remedication, which could either have been a second dose or rescue medication, for studies 07 and 09 only since these data were not captured in the other three studies (see Table 3: Efficacy Evaluations Performed, page 17). Those who did not take a second dose or rescue were censored to 24 hours. Between group comparisons were carried out using the logrank test. In both studies, there was a nominally significant difference between frovatriptan 2.5mg and placebo groups in favor of frovatriptan (Table 21, adapted from ISE panel 8.7.2.1.8:15, page 135). Fifty-seven percent (57%) of the frovatriptan-treated patients took either a 2nd dose or rescue, compared to 74% of placebo patients. The sponsor did not provide a graph of the data.

Table 21: Studies 07, 09 – Time to Remedication (Rescue or 2nd Dose)

	Median Time to Remedication (hours)		
Study	2.5mg	PBO	p-value
07	17.88	5.61	<0.001
09	18.50	4.96	<0.001

7.7.13 Time to Response after a Second Dose

The time to response after a second dose was analyzed for studies 07 and 09 (the only 2 studies which permitted a second dose for recurrence). I should point out that the second dose was not randomized, therefore no definitive efficacy conclusions about the second dose can be drawn. The time to response was analyzed using a Kaplan-Meier approach. Between group comparisons were carried out using the logrank test. In both studies, there were nominally significant differences between the frovatriptan 2.5mg and placebo treatment groups in favor of frovatriptan 2.5mg (Table 22, adapted from ISE panel 8:7.2.1.8:17, page 138). Out of interest, the median time to response after a second dose of sumatriptan 100mg in study 09 was 2.5 hours.

Table 22: Studies 07, 09 – Time to Response after a Second Dose

	Median Time to Response after a Second Dose (hours)		
Study	2.5mg	PBO	p-value
07	3.5	7.0	0.009
09	2.7	13.6	<0.001

7.7.14 Overall Rating of Effectiveness

All five studies collected patients' overall ratings of effectiveness. For studies 06 and 07, this was collected after the last attack, whereas for study 09 it was collected after the first attack. No formal statistical tests were performed. "Good" or "Excellent" ratings numerically were higher for frovatriptan patients compared to placebo patients in all 5 studies, and comparable to sumatriptan ratings in study 09.

Table 23: Efficacy Studies – Patients' Overall Rating of Effectiveness

Study	Rating	2.5mg	PBO	Sumatriptan 100mg
02	Poor	35/93 (38%)	55/92 (60%)	n/a
	Fair	17/93 (18%)	19/92 (21%)	n/a
	Good	25/93 (27%)	13/92 (14%)	n/a
	Excellent	16/93 (17%)	5/92 (5%)	n/a
14	Poor	40/126 (32%)	69/118 (58%)	n/a
	Fair	30/126 (24%)	22/118 (19%)	n/a
	Good	34/126 (27%)	16/118 (14%)	n/a
	Excellent	22/126 (17%)	11/118 (9%)	n/a

Study	Rating	2.5mg	PBO	Sumatriptan 100mg
06	Poor	55/194 (28%)	53/95 (56%)	n/a
	Fair	44/194 (23%)	13/95 (14%)	n/a
	Good	69/194 (36%)	26/95 (27%)	n/a
	Excellent	26/194 (13%)	3/95 (3%)	n/a
07	Poor	195/708 (28%)	202/358 (56%)	n/a
	Fair	153/708 (22%)	82/358 (23%)	n/a
	Good	229/708 (32%)	62/358 (17%)	n/a
	Excellent	131/708 (19%)	12/358 (3%)	n/a
09	Poor	162/466 (35%)	160/237 (68%)	155/464 (33%)
	Fair	101/466 (22%)	38/237 (16%)	85/464 (18%)
	Good	149/466 (32%)	33/237 (14%)	157/464 (34%)
	Excellent	54/466 (12%)	6/237 (3%)	67/464 (14%)

7.8 Drug-Demographic Interactions

This section compares the efficacy of frovatriptan 2.5mg to placebo with respect to the impact of demographic factors and baseline characteristics. The sponsor focused on a pooled analysis of studies 02, 06, 07, 09. Study 14 was not included because 94 patients who participated in study 02 also enrolled in study 14, 81 of whom are included in the safety populations of both studies. Only the frovatriptan 2.5mg and placebo groups are included in these analyses. The efficacy parameters that were evaluated are the 2-hr and 4-hr headache response rates, and recurrence rates within 24 hours. In the three multiple attack studies (06, 07, 09), only the data from attack 1 are used. The demographic and baseline headache characteristics considered were:

- Gender
- Race (Caucasian, black, vs. other)
- Age (18-40 vs. 41-64, vs. ≥65)
- Initial headache severity (moderate vs. severe)
- History of aura
- Duration of headache prior to 1st dose (0-2 hours vs. >2-4 hours, vs. >4 hours)

7.8.1 Gender

Females dominated the 5 efficacy trials (88% for frovatriptan and 87% for placebo groups). This is typical of migraine trials of this type. The efficacy of frovatriptan by gender is shown in Table 24 (sponsor Panel 8.7.4.1:1, ISE, page 231). There were no significant treatment by gender interaction for any of the three efficacy parameters tested. Response rates were higher and recurrence rates were lower for both males and females treated with frovatriptan compared to placebo.

Table 24: Studies 02, 06, 07, 09 – Treatment by Gender Effects

Efficacy parameter	Gender	2.5 mg	PBO	Interaction p-value
2-hr Response	Male	63/173 (36%)	28/105 (27%)	0.15
	Female	516/1214 (43%)	156/657 (24%)	
4-hr Response	Male	93/154 (60%)	33/96 (34%)	0.73
	Female	669/1061 (63%)	203/573 (35%)	
Recurrence within 24 hrs	Male	17/93 (18%)	10/33 (30%)	0.51
	Female	145/669 (22%)	57/203 (28%)	

7.8.2 Race

Caucasians comprised 94% of the frovatriptan and 93% of the placebo groups. Table 25 summarizes the pooled efficacy data by race. Blacks on frovatriptan had a lower 2-hr response rate compared to placebo; however, the numbers were small. There was a nominally positive treatment by race interaction with respect to the recurrence rate, but again the black and other subgroups were so small any definite conclusions are not possible.

Table 25: Studies 02, 06, 07, 09 – Treatment by Race Effects

Efficacy Parameter	Race	2.5mg	PBO	Interaction p-value
2-hr Response	Caucasian	554/1310 (42%)	169/715 (24%)	0.073
	Black	12/41 (29%)	10/26 (38%)	
	Other	13/35 (37%)	5/21 (24%)	
4-hr Response	Caucasian	726/1148 (63%)	224/630 (36%)	0.79
	Black	15/33 (45%)	6/20 (30%)	
	Other	21/34 (62%)	6/19 (32%)	
Recurrence within 24 hrs	Caucasian	156/726 (21%)	61/224 (27%)	0.032
	Black	4/15 (27%)	4/6 (67%)	
	Other	2/21 (10%)	2/6 (33%)	

7.8.3 Age

The mean age in the studies was approximately 41 years. There were few people in the ≥65 year age group (n=9) and this prevented drawing any conclusions about efficacy in the elderly. The effects of age on efficacy are shown in Table 26 (ISE panel 8.7.4.3:1, page 237). There were no significant treatment by age interactions. Response rates at 2 and 4 hours were higher for frovatriptan patients regardless of whether they were 18-40 or 41-64.

Table 26: Studies 02, 06, 07, 09 – Treatment by Age Effects

Efficacy Parameter	Age	2.5mg	PBO	Interaction p-value
2-hr Response	18-40	253/619 (41%)	90/351 (26%)	0.28
	41-64	326/761 (43%)	92/407 (23%)	
	≥ 65	0/5 (0%)	2/4 (50%)	
4-hr Response	18-40	339/541 (63%)	115/288 (40%)	0.10
	41-64	419/668 (63%)	119/377 (32%)	
	≥ 65	3/5 (60%)	2/4 (50%)	
Recurrence within 24 hrs	18-40	65/339 (19%)	26/115 (23%)	0.43
	41-64	96/419 (23%)	41/119 (34%)	
	≥ 65	1/3 (33%)	0/2 (0%)	

7.8.4 Baseline Headache Severity

Initial headache severity was characterized as either moderate (grade 2) or severe (grade 3). Approximately two-thirds of the patients had moderate pain at baseline (68% for frovatriptan treated patients and 70% for placebo treated patients). This is similar to other migraine studies of this type. Table 27 (from ISE panel 8.7.4.4:1, page 239) summarizes the efficacy of frovatriptan according to baseline headache severity.

Table 27: Studies 02, 06, 07, 09 – Treatment by Baseline Headache Severity Effects

Efficacy parameter	Baseline severity	2.5 mg	PBO	Interaction p-value
2-hr Response	Moderate	455/969 (47%)	151/541 (24%)	0.88
	Severe	124/418 (30%)	33/221 (15%)	
4-hr Response	Moderate	566/845 (67%)	185/478 (39%)	0.90
	Severe	196/370 (53%)	51/191 (27%)	
Recurrence within 24 hours	Moderate	109/566 (19%)	49/185 (26%)	0.97
	Severe	53/196 (27%)	18/51 (35%)	

As might be expected response rates were higher and recurrence rates were lower for patients who had moderate pain at baseline, compared to those with severe pain. This was true for both frovatriptan and placebo patients. However, no significant drug by severity interaction were found between treatment groups with respect to the 2- or 4-hour response or recurrence rates.

7.8.5 History of Aura

History of aura was classified into 3 subgroups: with aura, without aura, and both with and without aura. The percentages of patients without aura in the frovatriptan group was 59% and in the placebo group were 63%. Those with aura were 23% in frovatriptan and 21% in the placebo group. Table 28 (from ISE panel 8.7.4.5:1, page 242) summarizes the treatment by history of aura interaction. There were no significant interactions found for the three efficacy parameters analyzed.

Table 28: Studies 02, 06, 07, 09 – Treatment by History of Aura Effects

Efficacy Parameter	Aura	2.5mg	PBO	Interaction p-value
2-hr Response	With	136/310 (44%)	39/159 (25%)	0.96
	Without	351/825 (43%)	122/484 (25%)	
	Both	92/252 (37%)	23/119 (19%)	
4-hr Response	With	168/275 (61%)	49/143 (34%)	0.73
	Without	467/729 (64%)	156/419 (37%)	
	Both	127/211 (60%)	31/107 (29%)	
Recurrence within 24 hrs	With	40/168 (24%)	16/49 (33%)	0.99
	Without	94/467 (20%)	42/156 (27%)	
	Both	28/127 (22%)	9/31 (29%)	

7.8.6 Duration of Headache at the Time of First Dose

Duration of headache at the time of the first dose was not recorded in studies 02 or 14. As a result, these were excluded from the analysis of this baseline characteristic. For studies 06, 07, 09, duration of headache at time of first dose was categorized as 0-2 hours, >2-4 hours, and >4 hours.

The treatment groups were well balanced with respect to the distribution of duration of headache at the time of first dose. The percentages of patients with a duration of 0-2 hours were 40% in the frovatriptan group and 41% in the placebo group. With regard to duration >2-4 hours, the percentages were 23% in the frovatriptan group and 24% in the placebo group. The remaining had duration of headache >4 hours.

Table 29 (ISE panel 8.7.4.6:1, page 244) shows the effects of the duration of headache at the time of first dose on efficacy. There were significant interactions noted in both the 2-hr and 4-hr response rates. In both cases, the treatment effect was greatest (in favor of frovatriptan) when the headache was >4 hours in duration at the time of the first dose.

Table 29: Studies 06, 07, 09 – Treatment by Duration of Headache Effects

Efficacy Parameter	Duration (hours)	2.5mg	PBO	Interaction p-value
2-hr Response	0-2 hours	206/528 (39%)	80/270 (30%)	<0.001
	>2-4 hours	115/299 (38%)	39/163 (24%)	
	>4 hours	220/469 (47%)	45/238 (19%)	
4-hr Response	0-2 hours	27/459 (59%)	97/248 (39%)	0.015
	>2-4 hours	151/255 (59%)	41/141 (29%)	
	>4 hours	285/415 (69%)	67/199 (34%)	
Recurrence within 24 hrs	0-2 hours	59/271 (22%)	22/97 (23%)	0.22
	>2-4 hours	29/151 (19%)	15/41 (37%)	
	>4 hours	70/285 (25%)	21/67 (31%)	

At the individual study level, statistically significant drug-duration interactions were also found for the 2-hr response and the 4-hr response for study 07 (p=0.015) and borderline difference for study 09 for the 2-hr response only (p=0.057).

One possible explanation is that headaches treated early may not be migraines and as such are less likely to respond to triptan type compounds. This could explain why the placebo response is highest for headaches treated between 0-2 hours of onset. In contrast, it might be expected that those patients who delay treatment are more likely to have a response at 2 and 4 hours simply due to the time limiting nature of a migraine attack. However, the lower placebo responses for the >4 hours subgroups do not support this explanation. From a clinical perspective, it doesn't make much sense that efficacy is enhanced by treating a headache of longer duration prior to dosing. Therefore this observation has no simple explanation.

No significant interaction was noted with respect to recurrence at 24 hours.

7.9 Drug-Drug Interactions

This section discusses frovatriptan drug-drug interactions in a clinical, rather than pharmacokinetic, context. As in the previous section, the main analysis is the pooled analysis of the four studies 02, 06, 07, 19. Study 14, as mentioned earlier, is not included in the pooled analysis due to the large number of patients who were also in study 02. The efficacy parameters that were evaluated were, as in the previous sections, the 2-hr and 4-hr headache response rates, and the recurrence rates within 24 hours.

Drugs were selected on the basis of medical review of the pooled databases and were chosen primarily from a safety perspective. Consideration was given to both commonly known drugs used chronically in this disease population, to drugs typically used as rescue medication, and possible PK interactions. The drug or drug groups chosen for analysis were the following:

- Gastrointestinal propulsives
- Beta blockers
- Estrogen, conjugated
- Ergot alkaloids
- Tricyclics
- Selective 5-HT_1 agonists
- Selective serotonin reuptake inhibitors

The following table shows the percentage of patients using each drug type during the concomitant treatment interval defined as 1 day prior to the first dose and 2 days after the last dose for attack 1 (Table 30, ISE panel 8.7.5:1, page 249).

Table 30: Studies 02, 06, 07, 09 – Incidence of Exposure to Concomitant Medications

Drug type	2.5 mg N=1505	PBO N=816
Estrogen containing products (females only)	449/1324 (33.9%)	232/706 (32.9%)
Non-selective monoamine reuptake inhibitors	167 (11.1%)	88 (10.8%)
Beta blocking agents	166 (11.0%)	94 (11.5%)
Selective 5HT1 receptor agonists	162 (10.8%)	143 (~~17.5%~~)

Drug type	2.5 mg N=1505	PBO N=816
Selective serotonin reuptake inhibitors	114 (7.6%)	68 (8.3%)
Alimentary tract propulsives	41 (2.7%)	34 (4.2%)
Ergot alkaloid containing products	40 (2.7%)	36 (4.4%)

Estrogen containing products (in females) was the most frequently used concomitant medication. The "non-selective monoamine reuptake inhibitors" included the tricyclic antidepressants.

7.9.1 Gastrointestinal Propulsives

The alimentary tract propulsives generally include metoclopramide and other anti-emetics that were usually used as rescue. Interpretation of these results requires caution since concurrent drug usage is unlikely to be independent of randomized treatment. A total of 75 patients in the combined ITT population took 1 or more gastrointestinal propulsive within the pre-defined concomitant treatment interval. The percentage exposed to the frovatriptan group (2.7%) was lower than the percentage exposed to placebo (4.2%).

Table 31 (ISE panel 8.7.5.1:1, page 252) shows the effects of gastrointestinal propulsive use on efficacy. There were positive interactions noted for the 2-hr and 4-hr response rates. Treatment effects in favor of frovatriptan were larger if gastrointestinal propulsives were not take. Clinically, this is probably due to the fact than non-responders were more likely to take these drugs, and not the other way around.

Table 31: Studies 02, 06, 07, 09 – Effect of Gastrointestinal Propulsives

Efficacy parameter	ATP exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Exposed	10/40 (25%)	7/31 (23%)	0.025
	Not exposed	569/1347 (42%)	177/731 (24%)	
Response at 4 hours	Exposed	15/32 (47%)	9/28 (32%)	0.005
	Not exposed	747/1183 (63%)	227/641 (35%)	
Recurrence within 24 hours	Exposed	5/15 (33%)	4/9 (44%)	0.61
	Not exposed	157/747 (21%)	63/227 (28%)	

ATP = alimentary tract propulsive

7.9.2 Beta-Blockers

A total of 260 patients in the combined ITT population for studies 02, 06, 07, and 09 took 1 or more beta blocker during the concomitant treatment interval. Approximately 11% of frovatriptan treated patients and placebo patients were exposed to beta blockers. Table 32 (ISE panel 8.7.5.2:1, page 255) shows the effect of beta blockers on efficacy.

A significant interaction was found at 4-hours but not at 2 hours. However, the percentages at 4 hours for each subgroup do not suggest a clinically relevant interaction. (62% - 37%, vs. 63% - 35%).

Table 32: Studies 02, 06, 07, 09 – Effect of Beta-Blockers

Efficacy parameter	BBA exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Exposed	68/156 (44%)	20/86 (23%)	0.54
	Not exposed	511/1231 (42%)	164/676 (24%)	
Response at 4 hours	Exposed	78/126 (62%)	26/70 (37%)	0.025
	Not exposed	684/1089 (63%)	210/599 (35%)	
Recurrence within 24 hours	Exposed	13/78 (17%)	9/26 (35%)	0.56
	Not exposed	149/684 (22%)	58/210 (28%)	

BBA = beta blocking agent

A specific frovatriptan-propranolol PK interaction study was performed during drug development. In this non-randomized study (study 251/98/06), 6 males and 6 females took propranolol for 8 days and then took a single dose of frovatriptan 2.5mg on day 8. Frovatriptan AUC and C_{max} were increased by 20-25% regardless of gender. These changes were well within the population range for frovatriptan.

7.9.3 Estrogen

A total of 681 female patients took 1 or more estrogen containing products within the concomitant treatment interval. The percentages of female patients in the frovatriptan 2.5mg and placebo groups were similar (33.9% vs. 32.9%, respectively).

No statistically significant treatment group by estrogen use interaction was found for either the 2-hour or 4-hour response rates or recurrence rates (Table 33, ISE panel 8.7.5.3:1, page 258). The data for males are presented for comparison, but were not included in the analyses.

Table 33: Studies 02, 06, 07, 09 – Effect of Estrogen

Efficacy parameter	ECP exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Females: Exposed	185/417 (44%)	56/214 (26%)	0.68
	Females: Not exposed	331/797 (42%)	100/443 (23%)	
	Males	63/173 (36%)	28/105 (27%)	
Response at 4 hours	Females: Exposed	233/355 (66%)	66/189 (35%)	0.88
	Females: Not exposed	436/706 (62%)	137/384 (36%)	
	Males	93/154 (60%)	33/96 (34%)	
Recurrence within 24 hours	Females: Exposed	49/233 (21%)	19/66 (29%)	0.97
	Females: Not exposed	96/436 (22%)	38/137 (28%)	
	Males	17/93 (18%)	10/33 (30%)	

Pharmacokinetic studies have demonstrated increased systemic exposure to frovatriptan in females taking oral contraceptives compared to females of a similar age not taking oral contraceptives. However, the above data suggest little effect on overall efficacy of frovatriptan 2.5mg at 2 and 4 hours.

7.9.4 Ergot Alkaloids

Ergot alkaloids taken during the predefined concomitant treatment period were most likely taken as rescue medication. In this respect, the same difficulties with interpretation of the interaction results can be said with those results generated with the gastrointestinal

propulsives section (section 7.9.1, page 37) since rescue use is unlikely to be independent of randomized treatment.

A total of 76 patients in the combined ITT population took 1 or more ergot alkaloid during the concomitant treatment period. The percentage of patients exposed in the frovatriptan 2.5mg group was lower than the percentage exposed in the placebo group (2.7% vs. 4.4%, respectively). There was a positive interaction noted in the 4-hr headache response rate. Response rates were higher for frovatriptan in the exposed and non-exposed subgroups, but the treatment effect was slightly greater in those not exposed. The absolute response rates were higher in patients not-exposed to ergot alkaloids, consistent with rescue use due to lack of efficacy.

Table 34 Studies 02, 06, 07, 09 – Effect of Ergot Alkaloids

Efficacy parameter	EA exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Exposed	12/34 (35%)	6/35 (17%)	0.10
	Not exposed	567/1353 (42%)	178/727 (24%)	
Response at 4 hours	Exposed	14/31 (45%)	8/31 (26%)	0.012
	Not exposed	748/1184 (63%)	228/638 (36%)	
Recurrence within 24 hours	Exposed	3/14 (21%)	3/8 (38%)	0.21
	Not exposed	159/748 (21%)	64/228 (28%)	

EA = ergot alkaloid

7.9.5 Selective 5-HT$_1$ Agonists

As in the previous section, use of selective 5-HT$_1$ agonists during the predefined concomitant treatment period was most likely due to rescue use. The protocols generally prohibited triptan use for the 24 hours prior and following study drug administration. Nonetheless, 305 patients in the combined ITT population took 1 or more selective 5-HT$_1$ agonists in the interval 2 days prior up to 1 day following study drug use for attack 1. Exposure in the frovatriptan 2.5mg group was lower than in the placebo group (10.8% vs. 17.5%).

A statistically significant drug-drug interaction was found for the 2-hr and the 4-hr headache response rates (Table 35, ISE panel 8.7.5.5:1, page 264). The response rates were lower for the exposed groups than for the non-exposed groups, consistent with use of rescue due to lack of efficacy.

Table 35: Study 02, 06, 07, 09 – Effect of 5-HT$_1$ Agonists

Efficacy parameter	5-HT$_1$ exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Exposed	55/149 (37%)	23/125 (18%)	0.019
	Not exposed	524/1238 (42%)	161/637 (25%)	
Response at 4 hours	Exposed	69/131 (53%)	27/114 (24%)	0.004
	Not exposed	693/1084 (64%)	209/555 (38%)	
Recurrence within 24 hours	Exposed	15/69 (22%)	12/27 (44%)	0.13
	Not exposed	147/693 (21%)	55/209 (26%)	

7.9.6 Non-Selective Monoamine Reuptake Inhibitors

A total of 255 patients in the combined ITT population for studies 02, 06, 07, 09 took one or more non-selective monoamine reuptake inhibitors (NSMRI, *e.g.* amitriptyline) during the concomitant treatment period. Exposure in the frovatriptan and placebo groups were similar (11.1% vs. 10.8%, respectively).

There were significant drug-drug interaction for both 2-hr and 4-hr response rates. At two hours, this was due to a lower placebo response rate in those not exposed to NSMRI. At four hours, it is due to a relatively lower response in the exposed frovatriptan group compared with the non-exposed frovatriptan group.

Table 36: Study 02, 06, 07, 09 – Effects of Non-Selective Monoamine Reuptake Inhibitors

Efficacy parameter	NSMRI exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Exposed	63/155 (41%)	29/83 (35%)	0.011
	Not exposed	516/1232 (42%)	155/679 (23%)	
Response at 4 hours	Exposed	71/134 (53%)	27/73 (37%)	0.005
	Not exposed	691/1081 (64%)	209/596 (35%)	
Recurrence within 24 hours	Exposed	18/71 (25%)	8/27 (30%)	0.42
	Not exposed	144/691 (21%)	59/209 (28%)	

NSMRI – non-selective monoamine reuptake inhibitors

The inconsistent findings between the 2-hr and 4-hr response rates makes them difficult to interpret. In the individual studies, study 07 contributed the largest number of patients exposed to NSMRI's. Study 14 (not included in the pooled analysis) contributed the smallest. At 2 hours, response rates were higher in the frovatriptan groups compared to placebo in both the exposed and non-exposed subgroups for studies 07, 02, and 14. In studies 06 and 09, while responses were higher for frovatriptan groups of non-exposed patients, response was lower for the subgroup of exposed patients. At 4 hours, the response was higher for frovatriptan groups compared to placebo in both subgroups for all 5 studies. However, the trend was for the difference between the treatments to be greater in the non exposed subgroups compared to the exposed subgroups.

No significant difference was found between the treatment groups with respect to recurrence.

The sponsor concludes there is no consistent effect of NSMRI's on efficacy of frovatriptan at 2 and 4 hours and it is unlikely that a true drug-drug interaction exists.

7.9.7 Selective Serotonin Reuptake Inhibitors

A total of 182 patients in the combined ITT populations for studies 02, 06, 07, and 09 took one or more selective serotonin reuptake inhibitor (SSRI) within the concomitant treatment period. Exposures in the frovatriptan and placebo groups were similar (7.7% vs. 8.3%).

Although no significant interaction was seen in the 2-hr response rate and in the recurrence rate, a significant interaction (p=0.001) was seen in the 4-hr headache response rate (Table 37, ISE panel 8.7.5.7:1, page 270). Both subgroups of frovatriptan patients (exposed and not exposed) had higher response rates compared to placebo, but the not-exposed group had an even higher response rate compared to the exposed group. This trend was not seen at 2 hours. Placebo responses in both groups were comparable.

Table 37: Study 02, 06, 07, 09 – Effects of Selective Serotonin Reuptake Inhibitors

Efficacy parameter	SSRI exposure	2.5 mg	PBO	Interaction p-value
Response at 2 hours	Exposed	46/107 (43%)	15/62 (24%)	0.23
	Not Exposed	533/1280 (42%)	169/700 (24%)	
Response at 4 hours	Exposed	50/89 (56%)	23/60 (38%)	0.001
	Not exposed	712/1126 (63%)	213/609 (35%)	
Recurrence within 24 hours	Exposed	14/50 (28%)	10/23 (43%)	0.20
	Not exposed	148/712 (21%)	57/213 (27%)	

7.10 Drug-Disease Interactions – Coronary Artery Disease

The sponsor examined the impact of risk from coronary artery disease on the efficacy of frovatriptan compared to placebo. This was done to confirm the efficacy in patients at risk of CAD to support the use of the drug in this population. This drug-disease interaction was evaluated for the 5 major efficacy studies (02, 14, 06, 07, 09). The inpatient efficacy study (study 03) in patients with or at risk for CAD is discussed separately (section 7.11.2, page 44).

As in previous pooled analyses, the sponsor excluded study 14. Only the frovatriptan 2.5mg and placebo groups are included in the combined analyses. The efficacy parameters evaluated were the 2-hr and 4-hr headache response rates and the recurrence rates within 24 hours. The efficacy parameters were examined for the first attack only.

Eight risk factors for CAD are considered in the analysis:

- Obesity
- Postmenopausal females
- Males > 40 years of age
- Hypertension
- Hypercholesterolemia
- Diabetes mellitus / hyperglycemia
- Previous CAD
- Peripheral vascular disease

As a patient could not be both postmenopausal female and male > 40, the maximum number of risk factors that each patients could have was seven. Five of the risk factors were identified from a clinical review of the medical history. Three risk factors (obesity; postmenopausal female, and male > 40) were selected directly from the pooled database.

Table 38 (ISE panel 8.7.6:1, page 275) shows the incidence of the individual risk factors in the combined database. Obesity was the most common risk factor, and it was more common in the placebo group. The placebo group also had a greater proportion of postmenopausal females and men > 40. The other risk factors were more common in the frovatriptan group.

Table 38: Studies 02, 06, 07, 09 – Incidence of Individual Risk Factors for CAD

Risk Factor for CAD	2.5mg N=1505	PBO N=816
Obesity (BMI ≥ 30)	252 (16.7%)	159 (19.5%)
Postmenopausal females	129 (8.6%)	77 (9.4%)
Percentages based on female patients	*129/1324 (9.7%)*	*77/706 (10.9%)*
Males > 40 years of age	95 (6.3%)	66 (8.1%)
Percentages based on male patients	*95/181 (52.5%)*	*66/110 (60.0%)*
Hypertension	93 (6.2%)	43 (5.3%)
Hypercholesterolemia	50 (3.3%)	26 (3.2%)
Diabetes mellitus / hyperglycemia	16 (1.1%)	6 (0.7%)
Previous CAD	6 (0.4%)	2 (0.2%)
Peripheral vascular disease	2 (0.1%)	0

Only 3 patients had more than 3 risk factors and none had more than 5. The frovatriptan 2.5mg group had the greater proportion with no risk factors (66.7% vs. 62.4%, taken from sponsor panel 8.7.6:2, ISE page 276, not shown here) but in general the groups were well balanced.

Due to the small number of patients with three or more risk factors, the numbers of risk factors for each patient were grouped into 3 categories. These were: no risk factors, 1 risk factors, 2 or more risk factors. The percentage having 1 risk factor was 25.8% and 30.1% for frovatriptan and placebo, respectively, and the percentage have 2 or more risk factors were 7.4% and 7.5%, respectively. Grouping of risk factors in this way assumes that all risk factors would have the same effect on efficacy.

For each study, the interaction between treatment group and risk factors for CAD was tested using a logistic regression model with terms for: initial headache severity, number of risk factors (none vs. 1 vs. 2 or more), treatment group, treatment group vs. number of CAD risk factors interaction. Interaction p values < 0.05 were considered significant.

The next table (Table 39, ISE panel 8.7.6:3, page 278) summarizes the results for the combined analysis. There were no significant interactions between treatment group and number of risk factors for CAD for any of the efficacy parameters.

Table 39: Studies 02, 06, 07, 09 – Efficacy by Number of Risk Factors for CAD

Efficacy parameter	Number of risk factors	2.5mg	PBO	Interaction p-value
Response at 2 hours	No risk factors	379/922 (41%)	120/481 (25%)	0.64
	1 risk factor	161/363 (44%)	54/224 (24%)	
	≥ 2 risk factors	39/102 (38%)	10/57 (18%)	
Response at 4 hours	No risk factors	500/801 (62%)	151/418 (36%)	0.66
	1 risk factor	205/321 (64%)	66/200 (33%)	
	≥ 2 risk factors	57/93 (61%)	19/51 (37%)	
Recurrence within 24 hours	No risk factors	111/500 (22%)	47/151 (31%)	0.57
	1 risk factor	31/205 (15%)	14/66 (21%)	
	≥ 2 risk factors	20/57 (35%)	6/19 (32%)	

In the individual studies, there was a significant drug-disease interaction in study 07 for response at 2 hours (p=0.048) with an apparent increase in efficacy of frovatriptan compared to placebo with increasing number of risk factors. However, this is of borderline significance was not seen at 4 hours or in the other studies.

7.11 Other Studies

There were two other studies that contain controlled efficacy data. These are studies 08 (1st attack) and study 03. Finally, there were two small open-label phase 2 studies, 01 and 04, which are included here for completeness.

7.11.1 Study 08 (First Attack Only)

Study 08 was the open label long-term safety study. For the treatment of the first attack only, migraine patients were randomized to two treatment sequences: either 2.5mg/2.5mg or 2.5/placebo. The second dose could be taken to treat a persistent headache (non-response) after 2 hours. A non-response was defined as a grade 2 or 3 headache 2 hours after the first dose of frovatriptan.

From the phase 2 dose-ranging studies, no dose relationship for efficacy was seen with frovatriptan doses above 2.5mg. That is, in studies 02 and 14, frovatriptan 5mg and 2.5mg had similar efficacy, and doses above 5mg (up to 40mg) in study 02 similarly ~~failed to~~ achieve greater efficacy. Therefore, it might be expected that a second 2.5mg dose for persistent pain would not be effective.

The primary efficacy parameter for attack 1 was the headache response at 4 and 6 hours in the subgroup of patients who took a 2nd dose at 2 hours for non-response (all patients took 2.5mg as the first dose).

The study was conducted in 31 centers in the U.S. A total of 547 patients were randomized for attack 1. The number of randomized patients who met the criteria for the ITT population was 490, and of these, 224 took a 2nd dose for non-response and thus met the criteria for the non-response population.

Table 40 (adapted from ISE panel 8.7.2.2.7:1, page 173) shows the primary efficacy results for the first attack of study 08. A logistic regression analysis with ~~terms for~~ center,

initial headache severity, and treatment sequence was performed. It showed that taking a 2nd dose for non-response at 2 hours had no effect on the 4 and 6 hour response rates. There was a borderline nominally significant treatment sequence-by-baseline headache severity interaction, showing that patients with severe headache taking placebo as a second dose did better than those who took 2.5mg as the second dose. This certainly doesn't make any clinical sense and is more likely due to small, non-randomized nature of the subgroups.

Table 40: Study 08: Four- and 6-Hour Headache Response (First Attack)

	2.5mg/2.5mg	2.5mg/PBO	p-value
4-hr headache response	37/96 (39%)	43/97 (44%)	0.63
6-hr headache response	52/86 (60%)	52/82 (63%)	0.96
Moderate at baseline	*36/48 (75%)*	*36/56 (64%)*	*0.053**
Severe at baseline	*16/38 (42%)*	*16/26 (62%)*	

* treatment by initial headache severity interaction

In summary, there is no evidence that the use of a 2nd dose for non-response is of any benefit.

7.11.2 Study 03 (Inpatient Study)

Study 03 was the randomized, double blind, placebo-controlled, parallel group, multicenter inpatient study to assess the efficacy and cardiovascular safety of frovatriptan in patients with known or at high risk of coronary artery disease treating an acute migraine attack. Patients reported to the clinic as soon as possible after the onset of a moderate of severe migraine attack. At the clinic, they received a first dose of frovatriptan 2.5mg or placebo and were offered a second (non-randomized) dose of the same medication 2 hours after the first dose (independent of headache severity). Each patient treated one migraine attack only.

The primary efficacy variable was the 4-hour headache response rate.

The study was conducted in 14 centers in the U.S. A total of 75 patients were randomized and all were included in the ITT population. Three patients had a history of coronary artery disease, 71 were at high risk of CAD, and 1 patient was incorrectly diagnosed as having a history of CAD.

The 4-hour headache response rate for the frovatriptan 2.5mg treated group was 84% (31/37) and for the placebo treated group was 79% (30/38). The difference was not statistically significant (p=0.42, Cochran-Mantel-Haenszel test). The high response rates, both for frovatriptan and placebo, may have been a result of the patients being treated in clinic.

7.11.3 Study 01

Study 01 was a single-center, single blind (patient), comparative, primarily non-randomized, dose-titration study to assess the safety, tolerability, PK and clinical efficacy of a single oral dose of frovatriptan, in the range 2.5mg to 40mg, in the acute treatment of