Study Number: VML 251-3MRM02

Title of Study: A double-blind, placebo-controlled, parallel group study, with an open-label extension phase, to assess the efficacy, tolerability and safety of oral frovatriptan in the prevention of menstrually-related migraine (MRM) headaches in a 'difficult to treat' population.

Note: This report contains the results of the double-blind phase only.

Study Drug: Frovatriptan 2.5 mg tablet

EudraCT Number: 2004-001969-17

Investigators and Study Centres:

The study was conducted at 55 sites in the US, Canada, Finland, France, Sweden, Norway, Germany, Italy and the UK

Publications (reference): None to date

Date of first subject enrolment: 26 October 2004 **Date of last subject completed:** 14 March 2006	**Clinical Phase:** Phase IIIb

Objectives:

Primary:

To determine the efficacy of frovatriptan, taken for 6 days starting 2 days prior to the expected onset of a menstrual migraine (MM) headache, in the prevention of MM headaches, in a 'difficult to treat' population, compared to placebo.

Secondary:

To determine the effect of frovatriptan in reducing the incidence, and severity of MM headaches and associated symptoms over consecutive treated peri-menstrual periods (PMPs).

To determine the effect of frovatriptan on the incidence of non-MM headaches outside of the peri-menstrual period.

To evaluate the safety and tolerability of frovatriptan used as short-term prevention for MM headache.

To determine the effect of frovatriptan on health-related quality of life.

To evaluate and compare frovatriptan taken as a prophylaxis for the prevention of MM headache compared to 'no prophylaxis' regarding pharmacoeconomics (US only).

Methodology:

This double-blind, placebo-controlled, parallel group, multi-center study, with an open-label extension phase, was divided into three phases. After a screening visit at which the patient's status as difficult to treat was confirmed, patients initially entered a single-blind run-in phase, during which they were treated with placebo. Failure to experience an MM headache within 2 months excluded patients from further participation in the study. Patients who continued then entered the double-blind phase of the study, in which they were randomized to treat 3 PMPs with frovatriptan 2.5 mg once daily (od), 2.5 mg twice daily (bd) or placebo (in a ratio of 3:2:3). Efficacy data were captured in study-specific diary cards. For each PMP, patients were treated with 6 days of study medication starting from 2 days prior to the anticipated onset of an MM headache. Patients could treat any MM headache that occurred during this time with rescue medication. Additional frovatriptan that could be used as rescue medication was provided, but treatment with another triptan or an ergotamine-containing compound was not permitted. If 3 PMPs were treated in the double-blind phase and study medication was adequately tolerated, patients could enter an open-label extension phase, which is discussed in a separate report. Patients attended the clinic on eight occasions for safety assessments, including biochemistry, hematology and urine pregnancy tests, 12-lead electrocardiogram (ECG), and recording of vital signs, adverse events (AEs) and concomitant medication.

Diary cards were reviewed, collected and dispensed during patient visits. Patient quality of life (QoL) was assessed using the Short-Form Health Survey (12 items; SF-12) at Visits 2 and 6 and the final visit. This report presents the results of the single-blind run-in and double-blind phases of the study only.

Number of subjects:

Planned: 600 patients screened to obtain 500 randomized patients, with 400 treating 3 PMPs.

Analyzed: 587 patients screened, 427 patients randomized, 362 patients treating 3 PMPs.

Diagnosis and main criteria for inclusion:

- Females aged 15 years and over (18 years and over in Canada, Norway, Germany, Italy and the UK).
- At least a 12-month documented history of MM headache, according to International Headache Society classification.
- Patient classified as 'difficult to treat'.
- Adequate diary data provided during the run-in phase to confirm diagnosis of MM headache.
- At least 2 MM headaches experienced in the previous 3 months.
- Experienced regular predictable menstrual periods and MM headaches occurring between Day -2 and Day +3 of menses.
- Able and willing to sign informed consent and to comply with study procedures, including collection and reporting of diary data.

Test product, dose and mode of administration, lot number:

Frovatriptan, 2.5 mg tablets, oral administration.

Once-daily regimen: 2 × 2.5 mg (loading dose) in the morning and 2 × matching placebo tablets in the evening on Day 1, followed by 2.5 mg (morning) and matching placebo (evening) on Days 2-6.

Twice-daily regimen: 2 × 2.5 mg bd (loading dose) on Day 1, followed by 2.5 mg bd on Days 2-6.

Product code: HT067. Batch number: 011.

Reference therapy, dose and mode of administration, lot number:

Matching placebo, oral administration, 2 × bd on Day 1, followed by 1 × bd on Days 2-6.

Two (2) batches were used:

Product code: HT064. Batch number: 002.

Product code: HT135. Batch number: 001.

Duration of treatment: Patients entered into a single-blind run-in phase of 2 months' maximum duration to confirm the diagnosis of MM headache. Once randomized into the double-blind phase of the study, a maximum of 3 PMPs were treated within 4 months. On completion of the 3 treated PMPs, patients were offered entry into an open-label extension phase. During this phase, a further 3 PMPs were treated with frovatriptan 2.5 mg bd over a maximum period of 4 months. Over the 3 phases of the study, a total of 8 PMPs could be treated.

Criteria for evaluation:

Efficacy:

- Number of MM headache-free PMPs out of a potential of 3 treated PMPs
- Number of treated PMPs with one or less days of mild migraine headache
- Number of MM headache-free days during treated PMPs
- Incidence of MM headache
- Maximum headache intensity

- Incidence of moderate or severe MM headaches
- Incidence and severity of MM headache-associated symptoms (eg photophobia, phonophobia, nausea, vomiting and aura)
- Functional impairment during treatment phase
- Incidence of intercurrent migraine
- Total burden of migraine (any migraine experienced during a 28-day period)
- Use of rescue medication (includes all triptan medications taken during the PMP)
- Time to onset (days) of MM headache (during the treated PMP and until 5 days post-treatment)
- Time to onset of first post-treatment migraine
- Time to first use of rescue medication.

Safety:

- Incidence and severity of all treatment-emergent AEs
- Vital signs (systolic and diastolic blood pressure, heart rate)
- 12-lead ECGs
- Routine laboratory safety tests
- Pregnancy tests.

Quality of life:

- SF-12 health-related QoL survey.

Pharmacoeconomics:

- These criteria are described in a separate report.

Statistical methods:

The principal efficacy analyses were conducted on the modified intention-to-treat (mITT) population, with supportive analyses conducted on the completed patients population (CPP). The primary endpoint was analyzed using a Cochran-Mantel-Haenszel (CMH) test with table scores.

Secondary endpoints were also analyzed using a CMH test. A supportive analysis using ordinal logistic regression analysis with a statistical model appropriate to the endpoint, but primarily repeated-measures analysis, was performed across all 3 treated PMPs, with a secondary univariate analysis of individual treated PMPs. Time to onset of MM headache, first post-treatment migraine and to first use of rescue medication were analyzed using the multiple- failures time model. QoL data were analyzed for change from pre-treatment using a non- parametric analysis-of-variance model. The incidence of treatment-emergent AEs was tabulated by the treated PMP of emergence, both for AEs up to 48 hours after the last dose in that period, and for all treatment-emergent AEs. All other safety parameters were summarized over time.

Continuous variables were summarized using N, mean, median, standard deviation, minimum and maximum values. Categorical data were summarized using N and proportion.

Terminology: The sponsor decided that, for consistency both within and across trials, the term "menstrual migraine" (MM) will be used in all current and future documentation. Thus, in this document, the term MM is used in place of MRM and should be taken to include migraines occurring between Day -2 and Day +3 of menstruation, with or without aura, in patients who either do or do not experience migraine headaches at other times in the menstrual cycle.

Summary results:

Of the 427 patients randomized (168 to placebo, 155 to frovatriptan od, 104 to frovatriptan bd), 416 had taken at least one dose of study medication and/or rescue frovatriptan (safety population), 410 were included in the mITT population, and 362 completed treatment in the 3 double-blind PMPs (CPP population). Patients were predominantly Caucasian (94%), with a mean age of 38.1 years. Most patients had a longstanding history of MM attacks, with a mean duration of 11.5 years. Non-MM attacks were suffered by 83% of patients. A total of 78 randomized patients were withdrawn prematurely from the study. There were slightly more withdrawals in the frovatriptan groups (20% in od and 23% in bd groups) compared to placebo (14%). However, this difference was due to a range of factors, most of which were not related to treatment.

Efficacy results: Results from the mITT population were used for the primary analysis and are presented here; the primary analysis was supported by results from the CPP population.

There was a highly statistically significant advantage provided by both frovatriptan dosing regimens compared to placebo, based on the mean number of MM headache-free PMPs per patient, which was 0.42, 0.69 and 0.92 for the placebo and frovatriptan 2.5 mg od and bd groups, respectively. Compared to the mean value of 0.42 MM headache-free PMPs per patient with placebo, the frovatriptan od and bd dosing regimens provided benefits of 64% and 119% increases in the mean number of MM headache-free PMPs, respectively. These values translate into 1 in 7.1 PMPs being MM headache-free with placebo, compared to 1 in 4.3 and 1 in 3.3 PMPs being MM headache-free with frovatriptan od and bd, respectively. Similarly, there was a statistically significant difference favoring both frovatriptan dosing groups over placebo in the mean number of PMPs with ≤1 day of mild MM headache per patient. Over the course of the 3 treated PMPs, the mean number of MM headache-free days per patient increased more in the frovatriptan groups than with placebo.

Over the course of the 3 treated PMPs, the percentage of patients who experienced MM headache decreased by 17% in the placebo group, compared to 34% and 43% in the frovatriptan od and bd groups, respectively. Similarly, the percentage of patients who experienced moderate or severe MM headache decreased substantially more in the frovatriptan groups compared to placebo over this period.

Nausea affected a progressively smaller proportion of patients over the course of the 3 treated PMPs, most markedly in the frovatriptan bd group. Vomiting did not significantly improve during the treated PMPs, although there was a trend towards improvement in the frovatriptan od group. Photophobia and phonophobia affected a smaller proportion of patients over the course of the 3 treated PMPs, most markedly in the frovatriptan od group. Over the course of the 3 treated PMPs, the proportion of patients who were functionally unimpaired improved significantly in the frovatriptan groups. There was a trend of improvement in QoL in the frovatriptan groups, but the differences compared to placebo were not statistically significant.

During treated PMPs, the onset of patients' first MM headache occurred later with frovatriptan than with placebo, and this treatment effect was most marked with bd dosing. A slightly higher number of frovatriptan-treated patients (compared to placebo patients) experienced migraine during the post-dosing period; however, there is no clear evidence that intercurrent migraine was more common following preventative treatment with frovatriptan, therefore rebound or delayed headache after frovatriptan dosing does not appear to be a significant issue. Over the course of the 3 treated PMPs, migraine burden improved significantly in the frovatriptan groups compared to placebo. This improvement was driven by a lower incidence of MM in the frovatriptan groups because there was little change in intercurrent migraine over all the 3 treated PMPs.

Over all 3 treated PMPs, a significantly smaller proportion of patients used rescue medication in the frovatriptan groups compared to placebo. Additionally, the use of rescue medication occurred later in frovatriptan-treated patients.

Safety results: Analysis was performed on the safety population. An overall summary of treatment-emergent AEs is outlined below.

	Placebo (N=161)	Frovatriptan 2.5 mg od (N=152)	Frovatriptan 2.5 mg bd (N=103)
	n (%)	n (%)	n (%)
Patients with ≥1 treatment-emergent AE	112 (70)	106 (70)	61 (59)
Patients with ≥1 treatment-emergent cardiovascular AE	7 (4)	13 (9)	8 (8)
Patients with ≥1 treatment-emergent AE within 48 hours of the last dose	84 (52)	88 (58)	49 (48)
Patients with ≥1 SAE	2 (1)	0	0
Patients with ≥1 severe treatment-emergent AE	30 (19)	33 (22)	14 (14)
Patients with ≥1 related treatment-emergent AE[1]	30 (19)	48 (32)	25 (24)
Patients withdrawn due to ≥1 treatment-emergent AE	3 (2)	9 (6)	4 (4)
Deaths	0	0	0

SAE, serious adverse event.
[1] Considered to be possibly or probably related to study medication.

As expected in a study extending over several months, the majority of patients in each treatment group experienced 1 or more treatment-emergent AEs during the study (70%, 70% and 59% of patients in the placebo, frovatriptan od and frovatriptan bd groups, respectively). The incidence of treatment-emergent AEs did not differ markedly between treatment groups, and the proportion of patients experiencing treatment-emergent AEs decreased over time. The incidence of individual events was generally low in all treatment groups. The most commonly reported events were upper respiratory tract infection (37 patients), nausea (36 patients) and dizziness (31 patients).

A small number of patients withdrew from the study because of AEs: 19 treatment-emergent AEs led to the withdrawal of 16 patients. Only 3 patients withdrew due to migraine, all of whom were in the frovatriptan od group.

A slightly higher proportion of patients in the frovatriptan od group experienced AEs of migraine and headache, although the incidence of these and other central nervous system events was low in each treatment group. Overall, the majority of treatment-emergent AEs were reported as mild or moderate in severity.

The majority of events were reported within 48 hours of the treated PMP, probably reflecting the fact that data collection focused on the period in and around the treated PMP, as well as the occurrence of expected triptan-related adverse drug reactions (ADRs).

Rebound or delayed MM was not a significant problem in this study, with the majority of migraines reported as AEs in frovatriptan-treated patients occurring during and immediately after the PMP, when drug was probably still present in the body.

AEs that were judged to be related to study medication were single reports of a wide range of events. The occurrence of ADRs that are expected with frovatriptan use (dizziness, migraine, fatigue and chest pain/discomfort) largely accounted for the higher incidence of events related to study medication in the 2 frovatriptan groups compared to placebo (32% and 24% in the frovatriptan od and bd groups, respectively; 19% in the placebo group).

In general, the analyses of treatment-emergent AEs by frovatriptan use revealed no increase in the incidence or severity of AEs at higher cumulative doses. Similarly, the likelihood of AEs considered related to study medication did not increase with higher cumulative doses of frovatriptan.

In all treatment groups, most AEs did not increase in frequency following additional frovatriptan use as rescue medication. However, in the placebo group, AEs of chest discomfort increased from 1 to 7 events per 100 patient-months. Similarly, the rate of events of dizziness increased from 3 to 9 events per 100 patient-months in the frovatriptan bd group.

The incidence of cardiovascular events was very low in all treatment groups, and the majority of events were of mild or moderate severity. Only one cardiovascular AE was reported as serious: Patient 118-003 (placebo group) experienced an event of severe chest discomfort the day after taking rescue frovatriptan. Results of echocardiogram, ECG stress test and lipid tests did not show any significant changes, and no evidence of myocardial ischaemia was found during follow-up investigations. The investigator initially judged the event to be possibly related to study medication; however, chest pressure remained ongoing at least 8 days after onset, and the causality was revised (after database closure) to an unrelated relationship with study medication. A second treatment-emergent serious adverse event (SAE) was reported during the study (inguinal hernia), which was considered unrelated to study drug. Four patients became pregnant and were subsequently withdrawn from the study. There were no clinically relevant changes in laboratory parameters, vital signs, height, weight or physical examination findings post-treatment in the study. No deaths were reported during the study.

Pharmacoeconomic results: These results are reported separately.

Open-label extension results: These results are reported separately.