

Clinical Trial Results Summary
Study VML 251-3MAM03

Study Number: VML 251-3MAM03	
Title of Study: An open label study to assess the safety, tolerability and efficacy of frovatriptan in the prevention of menstrually-associated migraine (MAM) headaches.	
Study Drug: Frovatriptan 2.5 mg tablet, Product code: HT056, Batch number: 006.	
Investigators and Study Centres: The study was conducted at a total of 40 sites in South Africa and Europe (Hungary, Poland, Germany and the United Kingdom).	
Publication (reference): 1. MacGregor EA, Tobin J, Hutchison J. An interim analysis of the safety and tolerability of frovatriptan for the prevention of menstrually-related migraine headaches. American Headache Society 47th Annual Scientific Meeting, 2005 Jun 23-26, Philadelphia (US). 2. Tobin J, Hutchison J, MacGregor EA. Interim safety and tolerability of frovatriptan during long-term intermittent treatment for prevention of menstrually-related migraine headaches. American Neurological Association 130th Annual Meeting, 2005 Sep 25-28, San Diego (US).	
Date of first subject enrolment: 9 September 2003 Date of last subject completed: 30 June 2005	Clinical Phase: Phase IIIb
Objectives: Primary: To evaluate the safety and tolerability of frovatriptan given for up to 12 peri-menstrual periods (PMPs) for the short-term prevention of MAM. Secondary: To determine whether frovatriptan is effective in reducing the incidence, severity and duration of MAM headaches and associated symptoms. To determine the effect of frovatriptan on the incidence and severity of non-MAM headaches. To determine the effect of frovatriptan on health-related quality of life.	
Methodology: In this open label, multi-centre study, patients were treated with frovatriptan for a maximum of 12 PMPs. For each PMP, dosing commenced 2 days before the anticipated onset of the menstrual migraine (MM) headache and continued for a total of 6 days. Patients were to take a loading dose of frovatriptan 5 mg (2 tablets) twice daily (bd) on Day 1, followed by frovatriptan 2.5 mg bd on Days 2-6. During the study, patients were to visit the study site a total of 6 times: screening, Visit 2 (third PMP or 5 months), Visit 3 (sixth PMP or 9 months), Visit 4 (ninth PMP or 12 months), Visit 4E (Day 5 of 12th PMP) and termination/completion (12th PMP or 15 months), at which times efficacy and/or safety assessments were performed.	
Number of subjects: Planned: 550 enrolled, with 100 treating 12 PMPs. Final analysis: 549 enrolled, with 308 who treated 12 PMPs.	
Diagnosis and main criteria for inclusion/exclusion: <ul style="list-style-type: none"> • Females aged ≥ 15 years (≥ 18 years in the UK and South Africa). • At least a 12-month documented history of migraine according to International Headache Society (IHS) criteria, including a 3-month diary-based documented history of MAM. 	

Clinical Trial Results Summary
Study VML 251-3MAM03

- All patients who had given written informed consent (and who had \geq Grade 7 level of education [South Africa only]).
- Average frequency of MAM headache in at least 2 out of 3 menstrual cycles, within the previous 12 months.
- Regular predictable menstrual periods.
- MAM headaches occurring between Day -2 and Day +4 of menses.

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

Frovatriptan, 2.5 mg tablets, oral administration. Loading dose of 5 mg (2 tablets) bd on Day 1, followed by 2.5 mg bd on Days 2-6. Product code: HT056. Batch number: 006.

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

None.

Duration of treatment: Patients were expected to treat 6 PMPs in a maximum of 9 months and 12 PMPs in a maximum of 15 months following screening.

Criteria for evaluation:

Safety:

- Incidence of all treatment-emergent adverse events (AEs).
- Standard haematology and biochemistry (assessed at screening, Visit 3 and the final visit).
- 12-lead electrocardiogram (ECG) and vital signs (conducted at every study visit except Visit 3), physical examination (conducted at the screening and final visits).

Efficacy:

- Incidence of MAM headache.
- Maximum headache severity.
- Number of headache-free days during a treated PMP.
- Occurrence and severity of MAM headache-associated symptoms (eg photophobia, phonophobia, nausea and vomiting).
- Maximum functional impairment during MAM headache.
- Incidence and severity of intercurrent migraine.
- Total migraine burden (days with menstrual migraine + days with intercurrent migraine).

Quality of life:

- Short-Form Health Survey (12 items; SF-12) health-related quality of life (QoL) survey.

Statistical methods:

All the analysis took the form of descriptive statistics. No statistical hypothesis testing was performed because the study was non-comparative. All statistical programming was performed using SASTM (version 8.2). Continuous variables were summarised using N, mean, median, standard deviation, minimum and maximum values. Categorical data were summarised using N and proportion. Life-tables were prepared for Kaplan-Meier survival estimates, and plots for time to onset of headache to Day 11. The safety population was used for the safety analyses, and for demographic and baseline characteristics. The intention-to-treat (ITT) population was used for the efficacy analyses and QoL analysis. One interim analysis was planned and conducted after 300 patients had treated 6 PMPs. Safety tables and listings were produced for both the interim and final analyses. Efficacy analyses were performed only for the final analysis.

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 MAM and should be taken to include migraines occurring between Day -2 and Day +4 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 549 patients enrolled in the study, 533 were treated with at least one dose of study medication. Of these patients, 525 were included in the safety population and 513 in the ITT population. Patients were predominantly Caucasian (98.5%), with a mean age of 37.8 years. Most patients had a long history of MM attacks, with a mean duration of 10.9 years. Non-MM attacks were suffered by 79.2% of patients. Overall, many more patients than expected (308 of 525; 58.7%) completed the 12-PMP study. The most frequent reason for withdrawal was at the patient’s request (95 of 549 enrolled; 17.3%), in most cases for reasons unrelated to the efficacy or safety of study medication. The proportion of patients discontinuing per cycle declined from cycle 7 onward, and the AE rate decreased over time (from 59.1% in cycle 1 to 28.6% in cycle 11, in the 308 patients who completed the entire study), suggesting no deleterious effect on long-term tolerability. The high degree of exposure to frovatriptan (mean total dose, 384.28 mg) and good treatment compliance provided a good basis for the safety evaluation.

Safety results:

An overall summary of treatment-emergent AEs is outlined below:

	Total (N=525) n (%)
Patients with ≥1 treatment-emergent AE	444 (84.6%)
Patients with ≥1 treatment-emergent cardiovascular AE	75 (14.3%)
Patients with ≥1 treatment-emergent AE within 48 hours of the last dose	385 (73.3%)
Patients with ≥ 1 SAE	13 (2.5%)
Patients with ≥1 severe treatment-emergent AE	219 (41.7%)
Patients with ≥1 related treatment-emergent AE ¹	315 (60%)
Patients withdrawn due to ≥1 treatment-emergent AE	59 (11.2%)
Deaths	0

SAE, serious adverse event

¹ Considered to be possibly or probably related to the study drug, or the relationship was missing.

A total of 3608 treatment-emergent AEs were recorded in 444 patients, reflecting the long study period and a low overall event prevalence rate of 0.8 per patient-month of exposure. The most common treatment-emergent AEs were migraine not otherwise specified (NOS), dizziness, nausea and headache, events typically associated with migraines or the use of triptans. The relatively low prevalence rate for migraine NOS (0.2409 per patient-month of exposure) represents approximately 1 event of migraine every 4 months per patient. The withdrawal of 6.5% of the patients due to migraine NOS was not unexpected and may reflect a lack of efficacy in these patients.

Most AEs of migraine and headache occurred during treatment and up to 48 hours after the last dose, which is consistent with a lack of rebound or delayed headache. When severe treatment-emergent AEs of migraine and headache were excluded, the most common related, severe AEs were those typically associated with migraines or the use of triptans: gastrointestinal disorders in 4.2% of patients (including nausea in 2.3%) and nervous system disorders in 4.8% (including dizziness in 2.1% and somnolence in

1.1%). There was no evidence that the symptoms of chest pain, discomfort or tightness experienced by a small proportion (5.5%) of patients were cardiac in origin, and they were similar in quality to those experienced by some patients who have taken frovatriptan and other triptans for the acute treatment of migraine.

There were no deaths or trends of specific types of SAEs. A total of 13 patients experienced 14 SAEs, the majority of which were not related to study drug. Of the 8 pregnancies, the occurrence of 3 spontaneous abortions was consistent with the rate of spontaneous abortion in the general population. None of the 43 clinically significant laboratory values were considered to be related to the study drug, and no patients were withdrawn due to laboratory abnormalities. Other than 2 episodes of sinus tachycardia, no clinically significant changes in ECG, vital signs or physical examination findings were noted during the study.

Efficacy results:

Although this was an open label, uncontrolled study and an evaluation of efficacy was not the primary objective, data obtained were consistent with previous studies in patients with MM. Frovatriptan was effective in reducing the incidence, severity and duration of MM headaches and associated symptoms over an approximate 12-month period. There was no evidence of drug tolerance, as efficacy was maintained over the entire study period, or of an increase in migraine headache frequency in the period immediately after the treated PMP. A trend suggesting an improvement in quality of life was observed in patients who completed all 12 PMPs.

During treated PMPs the incidence of MM headaches decreased (from 63.8% in PMP 1 to 45.0% in PMP 12, for patients who completed all 12 PMPs) and headaches tended to be less severe during the later PMPs. The proportion of patients who were migraine-free since the start of dosing improved throughout the study from approximately 33.2% and 17.3% on Days 6 and 11 following the start of dosing, respectively, of PMP 1, to approximately 55.1% and 47.8% on Days 6 and 11 of PMP 12. This improvement in efficacy between PMPs 1 and 12 may be explained by the fact that patients who remained in the study were those who responded to the drug, rather than a reflection of increasing benefit during long-term treatment.

The absence of any marked change in the number of patients who developed their first headache after Day 6 (ie post-dosing period) is evidence that there was no increase in frequency of migraine headache post treated PMP. While it is likely that a few patients did experience headache in the immediate post-dosing period, the evidence indicates that delayed or rebound migraine did not occur commonly or systematically in the populations studied in this trial. The overall incidence of MM-associated vomiting was low (9.8%). Although MM-associated nausea, photophobia and phonophobia occurred in approximately a third of all treated PMPs, the incidence and maximum severity of nausea and phonophobia decreased over the course of the study.

The incidence of patients experiencing functional impairment decreased from approximately 53% during PMP 1 to 37% during PMP 12. Similarly, the percentage of these episodes graded as severe also decreased over time. There was no clear evidence to suggest an impact on intercurrent migraines, although the total migraine burden appeared to decrease slightly.

Quality of life results:

For patients who completed all 12 PMPs, QoL changes suggested a trend of improvement from Visit 1 that continued throughout the 12-PMP study, for both the physical and mental components of the SF-12 questionnaire.