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## Rapid Responders to Frovatriptan in Acute Migraine Treatment: Results from a Long-Term, Open-Label Study

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### ABSTRACT

**Background.** The chronic nature of migraine and the reliance on acute treatment constitute the basis of the present long-term, open-label study.

**Objectives.** First, assessment of the tolerability and safety of frovatriptan, 2.5–7.5 mg taken orally over 24 hours, for the acute treatment of migraine, repeatedly over a 12-month period. Second, assessment of the efficacy and tolerability of a second, double-blind dose of 2.5-mg frovatriptan, compared with placebo, for nonresponse at 2 hours after treatment of moderate or severe headache with 2.5-mg frovatriptan.

**Results.** With regard to the first attack treated, 173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse. At 2 hours and 4 hours, these “rapid responders” experienced a decrease in headache intensity from moderate or severe to mild or no pain in 84% and 98%, respectively (“headache response”). Six percent of them experienced recurrence of moderate or severe headache within 24 hours following a response at 4 hours and 12% took rescue medication. The response, measured in terms of median time to “complete migraine relief,” was maintained over 30 subsequent migraine attacks, treated from attack 2 onwards over the course of 12 months.

**Conclusion.** Frovatriptan provides a remarkably fast and high headache response in a subgroup of more than one-third of migraineurs, with a very low 24-hour headache recurrence and low rescue medication intake.

**Key Words.** Frovatriptan; Migraine Treatment; Rapid Responders; Headache Response; Headache Freedom; Headache Recurrence; Complete Migraine Relief

### Introduction

Frovatriptan is a medication in the class of selective serotonin 1B/D agonists or triptans, a tetrahydrocarbazole derivative with high affinity for the serotonin-1B and serotonin-1D receptors and moderate affinity for the serotonin-1A, serotonin-1E, and serotonin-7 receptors [1]. Among the triptans, it is the most potent functional agonist of the serotonin-1B receptor [2],

the vascular serotonin receptor that mediates the cranial vasoconstriction induced by the triptans [3]. It also has the longest plasma elimination half-life (26 hours) [4] and, in addition, has demonstrated selectivity for the (human isolated) basilar *vs* coronary artery [5].

In five placebo-controlled, short-term studies involving more than 3,000 patients, frovatriptan, given in an oral dose of 2.5 mg, showed consistent efficacy in acute treatment of moderate or severe migraine headache, with, at 4 hours, an approximate twofold benefit in “headache response” (mild/no pain) compared with placebo [6]. In this article, it will also be demonstrated that frovatriptan, 2.5 mg taken orally for treatment of moderate or severe headache, conveys a remarkably fast

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\*Listed in the Appendix with number of subjects enrolled.

and high headache response with a very low 24-hour headache recurrence in a subgroup of migraineurs of more than one-third of the total group studied.

## Patients and Methods

### Study Population

The study, long-term and open-label in design, was conducted in 31 centers throughout the United States and involved men and women between the ages of 18 years and 65 years. They suffered from migraine without or with aura, as defined by the International Headache Society (IHS) under codes 1.1 and 1.2, respectively [7], and were otherwise healthy. The subjects had to be able and willing to give signed informed consent and to comply with study procedures, including the completion of diary cards. Further, they had to have had migraine for at least 1 year, with onset before age 50 years, and two to eight moderate or severe migraine headaches per month for at least 2 months prior to study entry. They could not suffer from hemiplegic (IHS code 1.2.3) or basilar migraine (IHS code 1.2.4) but could have other kinds of headaches, however, less than 15 days per month in total, and had to be able to distinguish between them and their migraine headaches. Women could not be pregnant or nursing and were required to prevent pregnancy for the duration of the study, if not postmenopausal, by using adequate contraception. In addition, the women of reproductive potential had to have a negative urine pregnancy test at the screening visit. Also, at the screening visit, the subjects were required to have a clinically acceptable physical exam, biochemistry, hematology, urinalysis, and 12-lead electrocardiogram (ECG).

In terms of exclusion criteria, the subjects could not have a diastolic blood pressure above 95 mm Hg or clinically significant cardiovascular, cerebrovascular, hepatic, or renal disease. They could not be taking symptomatic headache medications more than 2 days per week on average, could not be habitually abusing headache medications, including ergotamine-containing compounds, and could not have (a history of) alcohol and/or substance abuse. Preventive migraine treatment, with the exception of monoamine-oxidase inhibitors, was allowed, provided that the medication dose(s) had been stable for 30 days, and the treatment was expected to continue for the duration of the study. Subjects who had an allergy to

sumatriptan or had used an investigational medication, with the exception of frovatriptan, within 30 days of the screening visit were also excluded from study participation.

A total of 500 subjects were to be recruited for the study in order to achieve 300 subjects completing 6 months of treatment and 100 subjects completing 12 months of treatment, to satisfy International Conference on Harmonization requirements.

### Study Design

The subjects completed a screening visit, which included a headache and medical history, physical examination, blood and urine tests, and 12-lead ECG. They were enrolled when meeting the eligibility and exclusion criteria, pending the laboratory results. They were allocated to receive a second, optional, double-blind dose of 2.5-mg frovatriptan or identically looking placebo, randomly allocated in a 1:1 ratio. They treated the first attack, with the headache being moderate or severe in intensity, and completed the diary card immediately before and at  $2 \pm 0.5$ ,  $4 \pm 1$ ,  $6 \pm 1$ ,  $12 \pm 2$ , and  $24 \pm 2$  hours after taking the medication. At these time points, they rated the intensity of the headache, the level of their functional impairment, and the presence or absence of nausea, vomiting, photophobia, and phonophobia. Headache intensity was rated as mild (allowing normal activity), moderate (disturbing but not prohibiting normal activity and bed rest not necessary), or severe (normal activity had to be discontinued and bed rest may be necessary). In addition to rating headache intensity at the fixed time points, the subjects also documented the exact time when they first noticed the intensity of the headache to be mild or none, using a wristwatch ("stopwatch technique"). Hence, continuous data were collected on the onset of action of frovatriptan in the acute treatment of migraine headache. With no response to the first dose of frovatriptan, 2.5 mg taken orally, a second, optional, double-blind dose of the study medication, frovatriptan or placebo, was taken at 2 hours. The subjects were requested not to take rescue medication until 4 hours after the first dose of study medication. They returned to the center for visit 2 within five working days after the first attack was treated or 6 weeks after the screening visit, whichever came first.

At visit 2, subjects who had not treated a migraine attack within 6 weeks of the screening

visit were terminated from the study. The others were provided with sufficient open-label frovatriptan and diary cards to complete the next 13 weeks of the study and were asked to return to the center every  $13 \pm 2$  weeks, for a maximum of 52 weeks. At visit 2 and at each of the 13-week visits, the subjects underwent tolerability and safety assessments, the latter consisting of vital signs, laboratory tests, and a 12-lead ECG; at the termination visit, they also underwent another physical examination. For subsequent attacks, they were instructed to take study medication as soon as they felt it necessary to do so, regardless of headache intensity. They were instructed to take further doses of frovatriptan at 2 hours for nonresponse and/or recurrence of headache. Therefore, from the second treated attack onwards, a maximum of three doses of frovatriptan, that is, 7.5 mg in total, could be taken over 24 hours. Diary cards were completed at the time of each dosing of study medication, recording the presence or absence of aura, headache intensity, and the exact time to “complete migraine relief,” as measured by the stopwatch technique. Complete migraine relief was a subjective assessment made by the subjects, which encompassed relief of headache and associated symptoms as well as the ability to return to normal function.

Rescue medications for headache and nausea, with the exclusion of ergots and triptans within 24 hours of study medication, were taken as required, but preferably not within 2 hours of the first dose of frovatriptan, and recorded.

### Statistical Analysis

The first primary objective of the study was to assess the tolerability and safety of frovatriptan, 2.5 mg taken orally for the acute treatment of migraine up to three times in a 24-hour period, repeatedly and without other restrictions for a period of 12 months. The second primary objective, for the first attack only, was to assess the efficacy of a second, double-blind dose of frovatriptan, 2.5 mg taken orally, compared with placebo, at 2 hours after the first dose for nonresponse. From attack 2 onwards, efficacy was determined solely by having the subjects measure the exact time to complete migraine relief with the stopwatch technique. Statistical analysis was performed on the intent-to-treat (ITT) population using two-sided logistic regression analysis at 5% significance level.

## Results

### Attack 1

Thirty-one investigators (see Appendix) enrolled a total of 547 subjects in the study, of whom 496 (58 men and 438 women) treated a first attack within 6 weeks of screening and were included in the safety population (Figure 1). Six of the subjects, however, were not included in the ITT population (ITT1) because of lack of information on dosing (N = 4) or efficacy (N = 1) or due to lack of available medication (empty blister pack; N = 1). Two hundred and one subjects treated at least 30 attacks from attack 2 onwards and constituted the ITT2 population.

Of the 490 subjects in the ITT1 population, 486 had moderate (N = 322) or severe headache (N = 164) at the time of treatment *and* assessed headache intensity at 2 hours after taking study medication. The response at 2 hours in these 486 subjects was 37%, defined as a decrease in headache intensity from moderate or severe to mild or no pain.

Of the 486 subjects, 173 (36%) did *not* take a second dose of study medication at 2 hours for nonresponse. The 2–24-hour headache response in these “rapid responders” is presented in Figure 2, showing a 2-hour headache response of 84%. The median time to headache response (mild/no headache) was 1.5 hours, compared with 3.3 hours for the whole ITT1 population, with the first quartile achieving this response

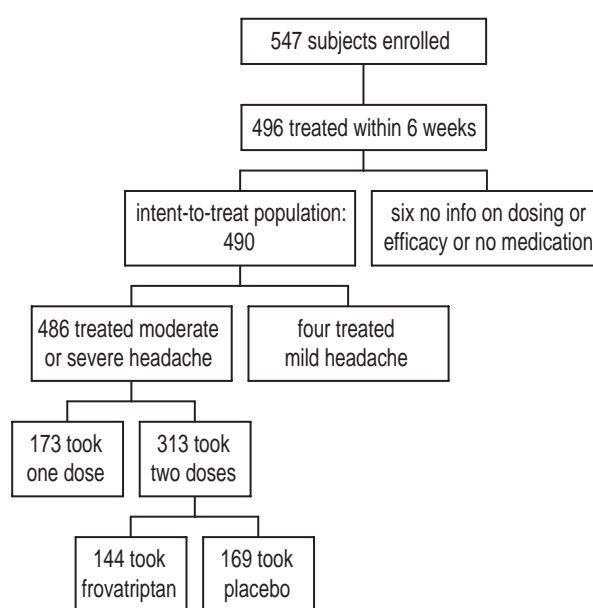
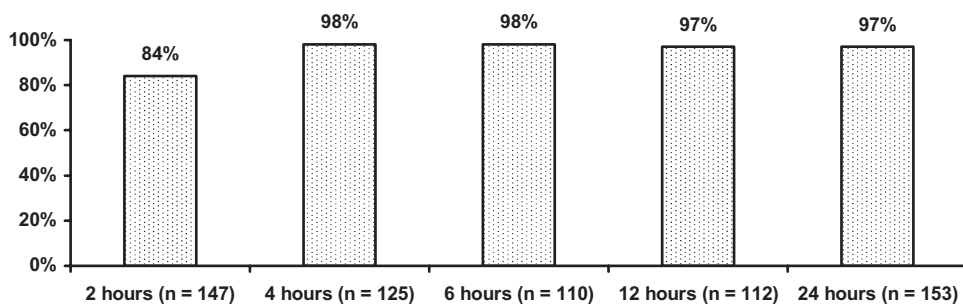


Figure 1 Flow diagram of the VML 251/96/08 study.

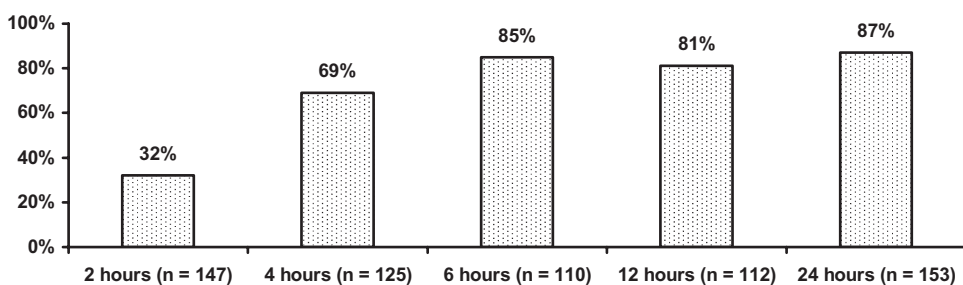


**Figure 2** Percentage of “rapid responders” with headache response, defined as a decrease in headache intensity to mild or no pain, after one dose of 2.5-mg frovatriptan, taken orally for moderate or severe migraine headache, 2–24 hours after treatment (N = 173; missing data due to sleep).

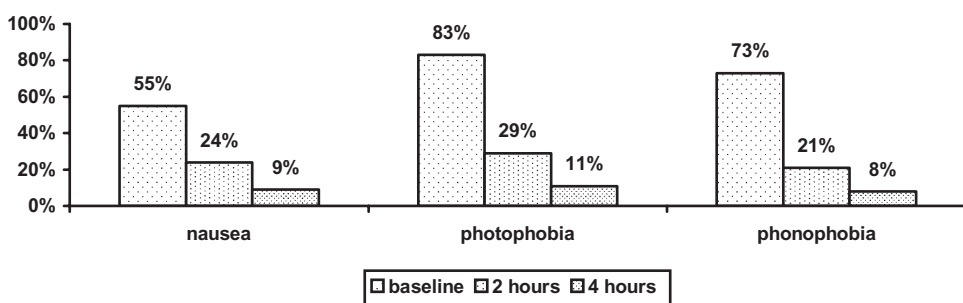
within 45 minutes. The percentage of rapid responders who were headache-free at 2–24 hours is shown in Figure 3. The headaches treated by them were moderate in 70% and severe in 30%; they treated the headaches within 2 hours of onset in 48%, from 2 hours to 4 hours of onset in 20%, and after more than 4 hours in 32%. The percentage of rapid responders whose headaches recurred within 24 hours at moderate or severe intensity following a response at 4 hours was 6%; the percentage taking rescue medication from 4 hours to 24 hours was 8%. Figure 4 presents the effect of frovatriptan in the

rapid responders on the migraine-associated symptoms, nausea, photophobia, and phonophobia. The time to complete migraine relief in these subjects was 2.0 hours, compared with 4.0 hours for the whole ITT1 population.

Thirty-seven percent of the 173 rapid responders reported adverse events; the more common adverse events reported by these subjects are shown in Table 1. The rapid responders did not differ from the others in terms of demographics or medical history characteristics, that is, age, gender, migraine diagnosis, concomitant medication intake, and prior use of sumatriptan.



**Figure 3** Percentage of “rapid responders” who were headache-free after one dose of 2.5-mg frovatriptan, taken orally for moderate or severe migraine headache, 2–24 hours after treatment (N = 173; missing data due to sleep).



**Figure 4** Percentage of “rapid responders” with nausea, photophobia, and phonophobia at baseline and at 2 hours and 4 hours after treatment with one dose of 2.5-mg frovatriptan, taken orally for moderate or severe migraine headache (N = 173).

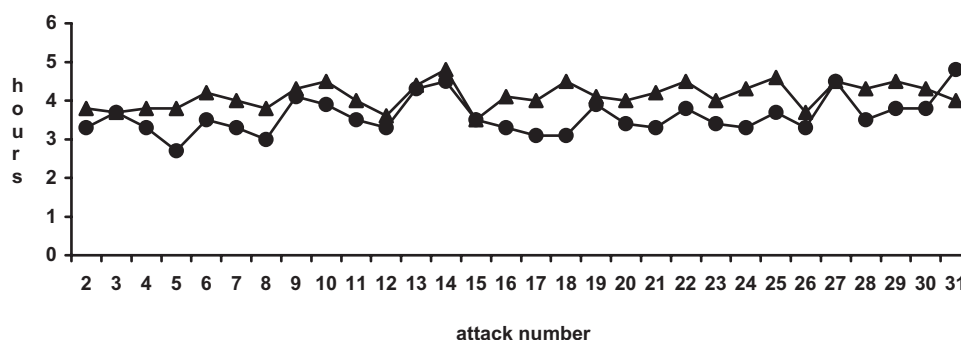


**Table 1** Adverse events reported by the 173 “rapid responders” in the study

Adverse Events	%
Dizziness	8.7
Nausea	5.2
Somnolence	4.6
Fatigue	4.0
Paresthesias	4.0
Headache	2.9
Myalgia	2.9
Chest pain	2.3
Flushing	2.3
Skeletal pain	1.2
Throat tightness	0.6

### Attack 2 Onwards

Of the 173 rapid responders, 80 treated at least 30 subsequent migraine attacks from attack 2 onwards, with a median frequency of one per 6.9 days. The median time to complete migraine relief for all attacks treated by these subjects ( $N = 5,447$ ) was 3.5 hours. The comparable time for the attacks ( $N = 13,784$ ) treated by all subjects who treated at least 30 subsequent migraine attacks (ITT2;  $N = 201$ ) was 4.1 hours. When the headache was treated at mild intensity ( $N = 1,333$ ), complete migraine relief was accomplished by the rapid responders in a median time of 2.2 hours. Recurrence, defined here as a need to redose within 24 hours, occurred in 16% of the attacks treated. Of the rapid responders, 83% stayed in the study for 6 months and 57% for 12 months; only 6% withdrew from the study specifically because of lack of benefit. The median time to complete migraine relief remained remarkably similar over the 30 subsequent migraine attacks treated over the course of a year, as is shown in Figure 5.



**Figure 5** Median time to complete migraine relief for the 80 “rapid responders” to 2.5-mg frovatriptan taken orally for migraine who treated at least 30 subsequent attacks from attack 2 onwards (circles), in comparison to all subjects who treated at least 30 subsequent attacks from attack 2 onwards ( $N = 201$ ) (triangles).

### Discussion

Unintentionally, the study design identified a distinct group of subjects with a consistently rapid response to treatment of migraine headache with frovatriptan. The identification of this group arose as a result of the directive for the first treated attack only, to repeat dosing with study medication after 2 hours in case of nonresponse. More than one-third of the subjects in the study did *not* take the second dose of study medication after 2 hours, classifying themselves as “rapid responders.” These self-defined rapid responders did not show a headache response at 2 hours as is generally seen with the triptans, that is, between 42% and 77% (pivotal trials of the oral triptans [U.S. labeling]). They showed a response with 84% of the subjects reporting mild or no pain at 2 hours and 98% at 4 hours, which maintained itself at that level over the subsequent 20 hours. Compatible with this high maintenance of the headache response are the remarkably low 24-hour headache recurrence and rescue medication intake (6% and 12%, respectively). The results conveyed a high level of satisfaction with the treatment, deduced from the fact that more than 80% of the rapid responders stayed in the study for 6 months and almost 60% for 12 months.

It has been demonstrated in randomized, double-blind, placebo-controlled studies that frovatriptan in the oral dose of 2.5 mg has a similar adverse event profile to placebo and that it is well tolerated with long-term use [8]. This good tolerability in combination with the above reported, remarkably fast and high headache response in a subgroup of more than one-third of migraineurs, makes the medication an ideal, first-line triptan.

### Acknowledgments

We thank Vernalis, Winnersh, United Kingdom, for financially supporting the study, the investigators listed in the Appendix and their coordinators for conducting it, Martin Pue, PhD, Vernalis, for assistance in the preparation of the manuscript, and Maria K. B. Spierings, MA, for editorial assistance. The study could not have been realized without the willing participation of the migraineurs, to whom we express our gratitude.

### Disclosures

Dr. Spierings received honoraria (advisory board) and grants (clinical trials) from Vernalis, Winnersh, United Kingdom. He was the lead investigator of study VML 251/96/08, entitled: A 12-month study of VML 251 in the acute treatment of migraine. The study was conducted according to the guidelines of Good Clinical Practice and in compliance with the World Medical Assembly Declaration of Helsinki. Dr. Spierings had full access to the results and analysis of the study as presented in a report he signed off on for purposes of submission to the Federal Drug Administration. Dr. Keywood was employed by Vernalis at the time of the study. She functioned as the medical monitor for the study and coauthored the article.

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### Appendix

#### VML 251/96/08 Investigators with Number of Subjects Enrolled in Parentheses

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