Study Number: EN3266-401	
Title of Study: Effectiveness and Safety of Frovatriptan for the Management (Acute Treatment) of Menstrual Migraine	
Investigators: 27 investigators (21 investigators enrolled patients)	
Study Centers: 27 sites (21 sites with enrolled patients)	
Publication (reference): Not Applicable	
Study Period (years): 7 months	**Phase of Development:** IV
Objectives: The primary objective of this study was to evaluate the efficacy of frovatriptan when used at the early stage (International Headache Society [IHS] Grade 1) of menstrual migraine (MM) compared with patients' current treatment as measured by episodes of migraine headaches occurring during Day -2 to Day +3 of the onset of menstruation. The secondary objective of this study was to assess the safety and tolerability of frovatriptan.	
Methodology: This study employed a prospective, non-randomized, open-label single-sequence design. The study was conducted in two phases: 1. A Usual Care phase (approximately 1 month in duration) included one menstrual period during which female patients treated all episodes of migraine headaches using their current treatment (referred to as the Baseline phase in the protocol) 2. An Acute Treatment phase (approximately 1 month in duration), following the Usual Care phase, included one menstrual period during which female patients used frovatriptan 2.5 mg to treat all episodes of migraine headache when their headache reached IHS Grade 1. If needed, a second dose of frovatriptan 2.5 mg was administered; however, this second dose could not be administered within 2 hours of the initial dose (i.e., there must have been at least 2 hours between doses of frovatriptan). The total daily dose of frovatriptan was not to exceed 3 tablets over a 24-hour period. Patients recorded outcome data in an electronic diary for all episodes of migraine headaches during both study phases. Within 1 week after treating their MMs in each phase, patients returned to the study site for study evaluations. Following the end-of-study visit, site personnel contacted patients 15 days after the last dose of study medication to collect adverse event (AE) information.	
Number of Patients Planned and Analyzed: Planned: 168 Enrolled: 192 Analyzed: 179 (safety – Usual Care); 161 (safety – Acute Treatment); 153 (Intent-to-Treat – Usual Care); 145 (Intent-to-Treat – Acute Treatment); 152 (efficacy evaluable – Usual Care); 43 (efficacy evaluable – Acute Treatment)	
Diagnosis and Main Criteria for Inclusion: Females 18 years of age or older with at least one year history of MM headaches, MM headaches occurring between Day -2 and Day +3 of menses, at least 8 MM headaches in the previous 12 menstrual cycles (1 year); with regular predictable menstrual periods (28 ± 4 days); with no more than 15 headache days per month; and with current MM treatment that did not include intermittent prevention with an analgesic (e.g., naproxen for 5 days to prevent the onset of MM).	
Test Product, Dose and Mode of Administration, Batch Number(s): Frovatriptan 2.5 mg oral tablet, Lot #004	
Reference Therapy, Dose and Mode of Administration, Batch Number(s): Not applicable	

Duration of Treatment: Approximately 2 months

Criteria for Evaluation:

Efficacy was assessed by:

- Headache pain severity
- Occurrence and severity of MM symptoms associated with migraine headache pain (nausea, vomiting, photophobia, and phonophobia)
- Occurrence and severity of functional impairment during MM
- Use of rescue medication and additional frovatriptan dose
- Patient satisfaction with treatment
- Patient preference of current vs study treatment (end-of-study only)

Safety was assessed by occurrence of AEs.

Statistical Methods: Descriptive statistical summaries, unless otherwise noted, included the number of patients, mean, standard deviation, median, minimum, and maximum for the continuous endpoints, and the number and percent of patients for the categorical endpoints. For both continuous and categorical endpoints, the number and percent of missing values were presented where applicable. Mean and median were presented to one decimal place and standard deviation (SD) was presented to two decimal places beyond the precision with which the data were captured. Minimum and maximum were presented to the precision with which the data were captured. For counts of zero, percent was not presented. The denominator used in the calculation of percentages was the number of patients in the study phase within the population of interest.

All statistical tests were two-sided and were performed at a significance level of 0.05 unless otherwise specified. Unless otherwise noted, safety tables summarized patients separately by Usual Care phase, Acute Treatment phase, and total patients, or by total patients only, and efficacy tables summarized patients separately by Usual Care phase and Acute Treatment phase. All sites were pooled for all analyses.

SUMMARY:

Due to deviations from the protocol at the site level during study conduct, presented efficacy results were derived using the Intent-to-Treat population.

Efficacy Results: Analysis of the primary endpoint (the proportion of patients with no MM at 4 hours post-dose) indicated that patients were significantly more likely to be pain-free after treating an MM with frovatriptan than after treating an MM with Usual Care treatment in the Intent-to-Treat population (ITT). Twenty-one (13.7%) patients who still had MM pain 4 hours post-dose during the Usual Care phase were pain-free 4 hours post-dose during the Acute Treatment phase. Nine (5.9%) patients who had no MM pain 4 hours post-dose during the Usual Care phase experienced MM pain 4 hours post-dose during the Acute Treatment phase. Additionally, at each timepoint, the percentage of patients who were pain-free after treatment with frovatriptan was greater than the percentage of patients who were pain-free after Usual Care treatment.

Safety Results: Based on the study results, frovatriptan 2.5 mg was generally safe and well tolerated. There were no deaths, 2 patients experienced non-fatal serious adverse events (SAEs), and 1 patient discontinued due to an AE. Both SAEs (abdominal pain and ovarian neoplasm) occurred during the Acute Treatment phase and were assessed as not related to the study drug. During exposure to frovatriptan (during the Acute Treatment phase), 22 (13.7%) of the 161 patients experienced a Treatment-Emergent Adverse Event (TEAE), compared to 14 (7.8%) of the 179 patients during the Usual Care phase. The AEs observed were consistent with the known profile of frovatriptan. No new safety concerns were identified based on the results.