Drug product	Zomig®	**SYNOPSIS**	
Drug substance(s)	Zolmitriptan		
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A Multicenter, 2-phase, Double-blind, Randomized, Placebo-controlled, Parallel Trial to Evaluate the Efficacy of a Single Dose of Zolmitriptan (ZOMIG®) as Acute Treatment in Phase I and Repeated Doses as Preemptive Treatment in Phase II for Menstrual Migraine Headache

International Coordinating investigator

Not applicable.

Study center(s)

This study was conducted in the US (30 investigator sites enrolled patients in Phase I and 27 investigator sites enrolled patients in Phase II).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	16 August 2000	IIIB
Last patient completed	19 August 2002	

Objectives

The primary objective was to evaluate the response to a single oral dose of zolmitriptan 2.5 mg as acute treatment for menstrual migraine headaches.

The secondary objectives were to assess the efficacy and safety of repeated oral doses of zolmitriptan 2.5 mg twice daily (bid) or 2.5 mg 3 times daily (tid) as preemptive treatment for migraine headaches.

Study design

This was a multicenter, 2-phase, double-blind, randomized, placebo-controlled, parallel-group outpatient study. In Phase I, patients were randomly assigned to the acute treatment of a

maximum of 2 menstrual migraine headaches each menstrual period for 3 consecutive menstrual cycles with either oral zolmitriptan or placebo. In Phase II, patients who completed Phase I were randomly assigned, in parallel groups, to treatment with one of the following preemptive treatments: zolmitriptan 2.5 mg twice daily (bid), zolmitriptan 2.5 mg 3 times daily (tid), or placebo tid for 7 days per menstrual period over 3 consecutive menstrual cycles. In Phase II, patients began treatment with study drug 2 days before the expected onset of menses and continued treatment for a total of 7 days in each menstrual cycle. In Phases I and II, data related to menstrual migraine headaches and menses were collected, in addition to efficacy and safety data.

Target patient population and sample size

Women aged at least 18 years who had a history of regular menstrual periods and predictable menstrual migraine headaches.

A total of 366 patients were randomized in Phase I and 253 patients were randomized in Phase II of the study. Assuming that approximately 20% of patients would be unevaluable or withdrawn from the study, a sample size of 350 patients in Phase I of the study was required for a 90% chance of detecting a 20% clinically relevant difference in the primary efficacy endpoint, at the 5% level of significance. Phase II was adequately powered (81%) with 216 patients to detect a ≥50% reduction in the frequency of menstrual migraine headaches in 60% and 35% of patients in the zolmitriptan and placebo groups, respectively.

Study drug and comparator(s): dosage, mode of administration and batch numbers

Drug	Dosage	Mode of Administration	Batch Number
Zolmitriptan	2.5 mg tablets	oral	F12092
Placebo tablets for zolmitriptan	2.5 mg tablets	oral	F12134

Duration of treatment

The duration of study participation was approximately 6 months. In Phase I (Months 1, 2, and 3), patients acutely treated a maximum of 2 menstrual migraine headaches each month with 1 dose of study drug per headache. During Phase II (Months 4, 5, and 6), patients took study drug for 7 days during each of 3 consecutive menstrual cycles for preemptive treatment.

Criteria for evaluation (main variables)

Efficacy

Primary variable: Menstrual migraine headache response rate at 2 hours, using a 4-point scale, after initial treatment with study drug in Phase I.

Secondary variables for Phase I included:

- 1- and 4-hour migraine headache response rate based on a 4-point scale
- 1-, 2-, and 4-hour migraine headache response rate based on a Visual Analog Scale (VAS) (30-mm reduction and 50% reduction)
- change in migraine headache severity from baseline (pretreatment) to 1, 2, and 4 hours based on VAS
- pain-free migraine relief at 1, 2, and 4 hours
- frequency of menstrual migraine headache per menstrual period. The frequency of menstrual migraine headaches was calculated from 2 days before the expected onset of menses through the 5th day after the expected onset of menses.
- time to recurrence of menstrual migraine headache
- time to use of escape medication
- proportion of patients with menstrual migraine recurrence within 24 hours of initial treatment
- incidence of headache-associated symptoms of migraine (ie, nausea, photophobia, phonophobia).

Secondary variables for Phase II included:

- 50% reduction in frequency of menstrual migraine headache per menstrual period. The frequency of menstrual migraine headaches will be calculated from 2 days before the expected onset of menses through the 5th day after the expected onset of menses
- frequency of menstrual migraine headache per menstrual period
- average peak pain intensity of menstrual migraine headaches per menstrual period
- average number of menstrual migraine headaches treated with escape medication per menstrual period
- incidence of headache-associated symptoms of migraine (ie, nausea, photophobia, phonophobia)

Safety

Incidence, nature, and severity of treatment-emergent adverse events (AEs), clinical laboratory assessments, electrocardiogram (ECG) evaluations, physical examination, and vital signs.

Statistical methods

For the primary efficacy analysis (headache response rates at 2 hours), treatment comparison over multiple attacks was performed using the Generalized Estimating Equations (GEE) approach. The logistic link for the binomial error structure was used to model the probability of success. Results were presented in terms of odds ratios for the treatment effects together with the corresponding p-values and 95% confidence intervals (CI). The odds ratio and CI were obtained by taking the anti-logarithm of the estimate and 95% CI of the treatment. Secondary efficacy endpoints including 4-point scale migraine headache response at other time points, 30-mm VAS headache response, 50% VAS migraine headache response, pain-free rates, proportion of patients with non-headache symptoms of migraine, ≥50% reduction in menstrual migraine frequency, and frequency of menstrual migraine headache were also analyzed using GEE model, for multiple attacks/periods data. The GEE model for frequency of menstrual migraine headache was done with Poisson regression, whereas the GEE model for the other endpoints was done with logistic regression. In Phase II, simple logistic regression model and Poisson regression model were used to analyze single attack/period data for ≥50% reduction in menstrual migraine frequency and frequency of menstrual migraine headache, respectively. Results from logistic regression were presented in terms of odds ratios for the treatment effects together with the corresponding p-values and 95% confidence intervals (CI). The odds ratio and CI were obtained by taking the anti-logarithm of the estimate and 95% CI of the treatment. Analysis results for frequency count data were presented in terms of ratio of the 2 treatment means (zolmitriptan over placebo) together with the corresponding p-values and 95% CI. The estimated mean ratio and 95% CI were obtained by taking the anti-logarithm of the estimate and 95% CI of the treatment effect. The change from baseline in VAS score were analyzed using a linear mixed effect model for multiple attacks. The time-to-event variables (ie, time to migraine recurrence and time to escape medication) were graphically summarized using Kaplan-Meier estimation for each treated attack. The time to escape medication was compared between treatment groups using the Cox Proportional Hazards model for each treated attack. Covariates for the Cox Proportional Hazards Model included treatment, region, and baseline pain intensity.

Patient population

The first patient entered Phase I of the study on 16 August 2000 and the last patient completed Phase II of the study on 19 August 2002. Of 366 patients randomized to treatment in Phase I, 334 and 320 patients were included in the intent-to-treat (ITT) and per-protocol (PP) populations, respectively. Of 253 patients randomized to treatment in Phase II, 244 patients were included in the ITT population overall, and 218, 210, and 237 patients were included in the analyses for Periods 1, 2, and 3, respectively. A total of 284 and 217 patients completed Phases I and II of the study, respectively. The most common reasons for discontinuation of the study were lost to follow-up, AE, or protocol noncompliance. The patient population at entry to Phase I of the study comprised predominantly white women with a mean age of 38.46 years, a mean age at onset of menstrual migraine headaches of 24.4 years, and who experienced a mean of approximately 1.8 migraine headaches per menstrual period. The treatment groups for both study phases were well-balanced regarding demographic and baseline disease characteristics.

Efficacy results

Key efficacy findings for Phases I and II of the study are summarized in Table S1.

Table S1 Main efficacy findings (Phase I and Phase II)

Phase I		Zolmitriptan 2.5 mg			Placebo			4-point scale	
Time point	Analysis population	4-point (%)	30-mm (%)	50% (%)	4-point (%)	30-mm (%)	50% (%)	Odds ratio[a]	p-value
		Menstrual migraine headache response							
2 hr	ITT	66	49	54	33	20	22	4.6 (3.2, 6.6)	<0.0001
	PP	68	51	57	37	22	25	4.3 (2.9, 6.3)	<0.0001
1 hr	ITT	41	27	28	22	11	13	2.7 (1.9, 3.8)	<0.0001
4 hr	ITT	82	68	73	58	40	45	3.6 (2.5, 5.1)	<0.0001

Phase II (ITT population)

Overall results (all periods)	Zolmitriptan 2.5 mg tid		Zolmitriptan 2.5 mg bid		Placebo			
	NAS[b]	n (%)[b]	NAS	n (%)	NAS	n (%)	Odds ratio[a]	p-value
≥50% reduction in menstrual migraine frequency , n (%)	222	130 (58.6)	225	123 (54.7)	217	82 (37.8)	2.3 (1.43, 3.81)[c] 2.0 (1.30, 3.20)[d]	0.0007 0.002
	NAS[b]	n (mean)[b]	NAS	n (mean)	NAS	n (mean)	Mean ratio[e]	p-value
Frequency of menstrual migraine , n (mean)	222	125 (0.56)	225	168 (0.75)	217	207 (0.95)	0.6 (0.46, 0.79)[c] 0.8 (0.62, 1.03)[d]	0.0002 0.08 (NS)

[a] Odds (95% CI) for patients treated with zolmitriptan to odds for patients treated with placebo.
[b] NAS is the number of patients assessed and n is the number of patients with a ≥50% reduction in frequency of menstrual migraine headache or the number of patients with menstrual migraine.
[c] Zolmitriptan 2.5 mg tid vs. placebo.
[d] Zolmitriptan 2.5 mg bid vs. placebo.
[e] Mean ratio (CI) is the mean for zolmitriptan divided by the mean for placebo.
NS Not significant

Phase I efficacy findings:

- Acute treatment with a single oral dose of zolmitriptan 2.5 mg resulted in a significantly higher 2-hour menstrual migraine headache response rate, as measured on the 4-point scale (the primary efficacy outcome), than did placebo treatment, in both the ITT and PP populations. The 2-hour menstrual migraine headache response rate was 66% and 68% in the zolmitriptan ITT and PP populations versus 33% and 37% in the placebo ITT and PP populations, respectively ($p<0.0001$ for all zolmitriptan versus placebo comparisons).

- Acute treatment with zolmitriptan 2.5 mg resulted in a statistically significantly higher 1- and 4-hour menstrual migraine headache response rate using the 4-point scale than did placebo treatment ($p<0.0001$ for zolmitriptan versus placebo in the ITT population).

- Acute treatment with zolmitriptan 2.5 mg resulted in a significantly higher 1-, 2-, and 4-hour menstrual migraine headache response rate than did placebo as measured by a 30-mm or 50% reduction in VAS, irrespective of the analysis population.

- Acute treatment with zolmitriptan reduced the intensity of migraine headache measured by VAS, from a mean value of 60.6 mm at pre-dose to 44.7, 32.6, and 21.7 mm at 1, 2, and 4 hours after treatment, compared with 57.6 mm at pre-dose and 51.8, 48.8, and 36.8 mm for the placebo group, respectively.

- Acute treatment with zolmitriptan 2.5 mg produced a significantly higher 2-hour pain-free response rate than did placebo in both the ITT and PP populations. The 2-hour pain-free response rate was 28% and 29% for zolmitriptan in the ITT and PP population, respectively, versus 9% and 11% for placebo, respectively.

- Acute treatment with zolmitriptan 2.5 mg had no apparent effect on the frequency of menstrual migraine headache.

- Acute treatment with zolmitriptan 2.5 mg significantly reduced the proportion of patients with headache-associated symptoms of migraine at 1, 2, and 4 hours after treatment (all p-values <0.009) as compared with placebo treatment.

- Acute treatment with zolmitriptan 2.5 mg significantly reduced the proportion of patients using escape medication ($p<0.0001$) and significantly increased the time to escape medication ($p\leq0.005$) as compared with placebo treatment.

Phase II efficacy findings:

- Preemptive treatment with zolmitriptan 2.5 mg tid or zolmitriptan 2.5 mg bid was significantly superior to placebo for producing a ≥50% reduction in migraine headache frequency in the ITT population. The proportions of patients who experienced a ≥50% reduction in headache frequency across 3 periods were 58.6%, 54.7%, and 37.8% for zolmitriptan 2.5 mg tid, zolmitriptan 2.5 mg bid, and placebo, respectively ($p=0.0007$ and 0.002 for zolmitriptan tid or zolmitriptan bid versus placebo, respectively). Similar results were obtained in the PP population.

- Preemptive treatment with either zolmitriptan 2.5 mg tid or bid reduced the absolute frequency of menstrual migraine headache; however, only the tid regimen produced a reduction that achieved statistical significance ($p=0.0002$ and 0.08 for zolmitriptan tid or zolmitriptan bid versus placebo, respectively).

- Average peak pain intensity (VAS score) was 50.98, 55.22, and 55.15 for patients treated with zolmitriptan tid, zolmitriptan bid, and placebo, respectively.

- There was no apparent effect of preemptive treatment with zolmitriptan 2.5 mg tid or bid on the incidence of headache-associated symptoms of migraine in those patients who experienced a migraine headache.

- Substantially fewer migraine headaches required the use of escape medication in patients treated preemptively with zolmitriptan 2.5 mg tid or bid compared with placebo. Moreover, a lower percentage of those headaches that occurred were treated with escape medication in the zolmitriptan tid or bid groups: 77/125 (61.6%), 102/168 (60.7%), and 154/207 (74.4%) menstrual migraine headaches were treated with escape medication in the zolmitriptan tid, zolmitriptan bid, and placebo groups, respectively.

Safety results

The numbers and percentages of patients in the safety population with AEs by category and treatment in Phases I and II of the study are summarized in Table S2.

Table S2 Number (%) of patients who had an adverse event in any category during Phases I and II of the study (safety population)

Category of adverse event	Zolmitriptan 2.5 mg (n=175)		Placebo (n=161)		Total (n=336)	
Phase I	**n**	**%**	**n**	**%**	**n**	**%**
Any adverse event	110	62.86	43	26.71	153	45.54
Drug-related adverse event	86	49.14	22	13.66	108	32.14
Serious adverse event	1	0.57	0		1	0.30
Withdrawals due to adverse event	3	1.71	0		3	0.89

	Zolmitriptan 2.5 mg tid (n=84)		Zolmitriptan 2.5 mg bid (n=80)		Placebo (n=82)		Total (n=246)	
Phase II	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any adverse event	64	76.19	74	92.50	49	59.76	187	76.02
Drug-related adverse event	42	50.00	49	61.25	28	34.15	119	48.37
Serious adverse event	2	2.38	2	2.50	1	1.22	5	2.03
Withdrawals due to adverse event	3	3.57	2	2.50	1	1.22	6	2.44

Phase I safety: Single doses of zolmitriptan 2.5 mg for the acute treatment of menstrual migraine headache were safe and well tolerated. A higher percentage of patients taking zolmitriptan versus placebo experienced AEs (62.86% and 26.71%, respectively) and potentially drug-related AEs (49.14% and 13.66%, respectively); however, most events were mild to moderate in intensity, and 4 patients were withdrawn from the study due to 3 non-serious and 1 serious AE (SAE), respectively. The SAE (attempted suicide) was not considered by the investigator to be drug-related. There were no deaths during Phase I of the study. The most commonly reported AEs were from the system organ classes of nervous system (dizziness, paresthesia, and somnolence), body as a whole (tightness, asthenia, pain,

abdominal pain, and aggravation reaction), digestive system (nausea, dry mouth, and vomiting), cardiovascular system (vasodilatation), and musculoskeletal system (myalgia). There were no apparent trends in mean hematology, clinical chemistry, urinalysis, vital signs or electrocardiogram (ECG) evaluations.

Phase II safety: Preemptive treatment for menstrual migraine headache with repeated doses of zolmitriptan 2.5 mg administered either tid or bid was safe and well tolerated. A higher percentage of patients taking zolmitriptan tid or zolmitriptan bid versus placebo experienced AEs (76.19%, 92.50%, and 59.76%, respectively) and potentially drug-related AEs (50.00%, 61.25%, and 34.15%, respectively); however, most events were mild or moderate in intensity, and 6 patients were withdrawn from study treatment due to AE. The most commonly reported AEs were from the system organ classes of body as a whole (asthenia, headache, tightness, and pain), digestive system (nausea, dry mouth, and diarrhea), nervous system (dizziness, somnolence, and paresthesia), cardiovascular system (vasodilatation, tachycardia, and palpitation), respiratory system (sinusitis and dyspnea), urogenital system (dysmenorrhea), metabolic/nutritional system (alanine aminotransferase [ALT] increased), and special senses (unusual taste). There were no deaths during Phase II. A total of 5 patients experienced SAEs during Phase II, none of which were considered to be related to study treatment, and 1 of these patients was withdrawn from the study. There were no clinically important changes in mean hematology, clinical chemistry, urinalysis, vital signs or ECG evaluations, nor were there any differences between the treatment groups with regard to the numbers of categorical shifts (normal to abnormal findings) for any of these parameters.

Conclusions

Phase I efficacy conclusions:

- The 1-, 2-, and 4-hour migraine headache response rate was significantly ($p<0.0001$ for all time points) higher following acute treatment with zolmitriptan 2.5 mg than with placebo.
- The 1-, 2-, and 4-hour pain-free response rate was significantly ($p<0.02$ for all time points) higher following acute treatment with zolmitriptan 2.5 mg than with placebo.
- The proportion of patients using escape medication and the time to escape medication were significantly ($p<0.005$ for both efficacy outcomes) reduced and increased, respectively, by zolmitriptan compared with placebo.
- These results demonstrate the efficacy of a single oral dose of zolmitriptan 2.5 mg for the acute treatment of menstrual migraine headache.
- The Phase I efficacy findings were consistent with findings from Zomig US0002.

Phase II efficacy conclusions:

- Preemptive treatment with zolmitriptan 2.5 mg tid and bid was significantly better than placebo (p=0.0007 and 0.002 for tid and bid treatment, respectively) with regard to ≥50% reduction in the frequency of menstrual migraine headaches.
- Preemptive treatment with zolmitriptan 2.5 mg tid significantly reduced (p=0.002) the frequency of menstrual migraine headaches compared with placebo.
- Preemptive treatment with zolmitriptan 2.5 mg tid and bid reduced the need to use escape medication for menstrual migraine headaches overall and in patients who experienced menstrual migraine headaches.
- These results demonstrate the efficacy of repeated oral doses of zolmitriptan 2.5 mg tid or bid for the preemptive treatment of menstrual migraine headache.

Safety conclusions:

- Both single doses of zolmitriptan for acute treatment and repeated oral doses of zolmitriptan for preemptive treatment of menstrual migraine headache were safe and well tolerated; most AEs were mild or moderate.
- There were no deaths during the study nor were there any SAEs considered by the investigator to be drug-related.
- No safety concerns arose with multiple dosing of zolmitriptan.

Date of the report

20 December 2005