Clinical Study Report Synopsis

Drug Substance ZOMIG (zolmitriptan)

Study Code D1220C00001

A Multicenter, Double-blind, Randomized, Placebo-controlled, 4-Armed Parallel Group Study to Evaluate the Efficacy of Zolmitriptan 0.5-, 2.5- and 5-mg Nasal Spray in the Treatment of Acute Migraine Headache in Adolescents

Study dates: First subject enrolled: 7 October 2010
Last subject last visit: 31 October 2013

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted at 153 study centers in the United States (US), Latin America, and Europe. A total of 1653 patients were enrolled (or screened) and 798 were randomized.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

See Table S1 below.

Table S1 Objectives and outcome variables

Objective			Variable	
Priority	**Description**	**Type**	**Description**	**Method of assessment and derivation**
Primary	To compare the efficacy of ZOMIG nasal spray 0.5, 2.5, and 5 mg with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17 years)	Efficacy	Pain-free status at 2 hours post-treatment	See CSP Section 11.1.1 in Appendix 12.1.1 and SAP in Appendix 12.1.9
Secondary	To evaluate the efficacy of ZOMIG nasal spray 0.5, 2.5, and 5 mg as compared with placebo in the acute treatment of migraine headache in adolescents (aged 12 to 17 years)	Efficacy	The secondary outcome variables are as follows:	
			• Pain-free status at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See CSP Section 11.1.1 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			• Headache response at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See CSP Section 11.1.2 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			• Sustained headache response at 2 hours	See SAP in Appendix 12.1.9
			• Presence of associated symptoms of photophobia, phonophobia, nausea, or vomiting at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See SAP in Appendix 12.1.9
			• Resolution of associated symptoms of photophobia, phonophobia, nausea, or vomiting at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See CSP Section 11.1.3 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			• Use of rescue medications up to 24 hours post-treatment	See CSP Section 11.1.4 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			• Time to use of rescue medications up to 24 hours post-treatment	See CSP Section 11.1.4 in Appendix 12.1.1 and SAP in Appendix 12.1.9

Objective			Variable	
Priority	**Description**	**Type**	**Description**	**Method of assessment and derivation**
			• Ability to perform normal activities at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See CSP Section 11.1.5 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			• Headache recurrence 2 to 24 hours post-treatment	See SAP in Appendix 12.1.9
			• Bilateral headache at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See SAP in Appendix 12.1.9
			• Intensity increased by movement (yes/no) at 15 minutes and at 1, 2, 3, 4, and 24 hours post-treatment	See CSP Section 11.1.6 in Appendix 12.1.1 and SAP in Appendix 12.1.9
Secondary	To assess safety and tolerability of ZOMIG when used for the acute treatment of migraine headache in adolescents	Safety	AEs (ie, incidence, nature, and intensity of AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, and AEs of special interest)	See CSP Sections 11.2.1 and 12.2.5 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			Changes in vital signs, and changes in physical examination	See CSP Sections 11.2.1 and 12.2.5 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			Changes in laboratory assessments (ie, chemistry, hematology, and urinalysis)	See CSP Sections 11.2.1 and 12.2.5 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			Changes in ECGs	See CSP Sections 11.2.1 and 12.2.5 in Appendix 12.1.1 and SAP in Appendix 12.1.9
			Occurrence of suicidal behavior/suicidal ideation throughout the study based on the C-SSRS	See CSP Sections 11.2.1 and 12.2.5 in Appendix 12.1.1 and SAP in Appendix 12.1.9

AE adverse event; CSP clinical study protocol; C-SSRS Columbia-Suicide Severity Rating Scale; ECG electrocardiogram; SAE serious adverse event; SAP statistical analysis plan.

Study design

This was a Phase III, global, multicenter, double-blind, randomized, parallel group, placebo-controlled study with a single-blind run-in period. The study included treatment of a single migraine headache attack during the run-in period with 1 dose of single-blind placebo. If the patient met all conditions for randomization, including a lack of response to placebo during run-in, another single migraine headache attack was treated with 1 blinded dose of ZOMIG nasal spray 0.5, 2.5, 5 mg, or matching placebo.

Target subject population and sample size

Adolescent patients, aged 12 to 17 years with an established diagnosis of migraine, as defined by the International Headache Society (IHS) or IHS-Revised (IHS-R) criteria were enrolled in the study. Patients were screened for eligibility during Visit 1 (screening visit) after the informed consent and assent were obtained.

A sufficient number of male and female adolescent patients, age 12 to 17 years with an established diagnosis of migraine, were screened to ensure that approximately 1000 patients (312 in the ZOMIG 5 mg and placebo arms, 188 in the ZOMIG 0.5 and 2.5 mg arms) were randomized into the study to obtain 800 evaluable patients (250, 150, 150, and 250 patients in the placebo, ZOMIG 0.5, 2.5, and 5 mg treatment groups, respectively).

An interim analysis was performed based on the blinded data from approximately 267 evaluable patients to ensure that the total sample size provided sufficient power to detect a clinically relevant difference of 0.11 in the 2-hour pain-free response rate. The interim sample size re-estimation analysis was performed by an independent statistician who was not involved with this trial. The sample size re-estimation analysis was performed on 18 June 2012 and included 2-hour pain-free status data from 286 randomized patients. Based on the results of this blinded interim analysis, calculated sample size per group was less than 250 patients. Thus, the original sample size assumptions were determined reasonable with no increase to the sample size required.

After confirmation of the total sample size required from the sample size re-estimation interim analysis, an additional interim analysis was performed to identify and discontinue randomization to any doses unlikely to demonstrate statistically significant improvements over placebo at the conclusion of the study. This interim futility analysis was performed on unblinded 2-hour pain-free response data by an independent statistician who was not involved with this trial. The interim futility analysis was performed on 5 October 2012. As a result of this analysis, the ZOMIG 0.5 and 2.5 mg dose groups met the futility definition with patient allocation to these 2 doses discontinued. After protocol amendment and Institutional Review Board approval, all new patients were randomly assigned to either ZOMIG 5 mg or placebo in a 1:1 ratio with the total sample size adjusted to ensure 250 evaluable patients into the ZOMIG 5 mg and placebo groups.

Investigational product and comparator: dosage, mode of administration and batch numbers

The study comprised treatment of a single migraine headache or attack with 1 dose of ZOMIG nasal spray 0.5, 2.5, or 5 mg, or matching placebo, in a blinded manner.

Duration of treatment

Patients had approximately 14 weeks to complete the study, which consisted of a 30-day run-in period followed by 10 weeks to complete treatment.

Statistical methods

All statistical comparisons were conducted using 2-sided tests at the 5% level of significance. For the primary analysis of pain-free status at 2 hours, a step-down approach was used to control for multiple statistical comparisons across all ZOMIG doses. All comparisons of secondary endpoints were tested at the 5% significance level without any multiplicity correction.

Descriptive statistics and graphs were used to summarize efficacy and safety variables. For continuous variables, summaries included using number of patients [n], mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized by counts of patients and percentages.

Subject population

A total of 798 patients were randomized to the study: 288 to ZOMIG 5 mg, 99 to ZOMIG 2.5 mg, 115 to ZOMIG 0.5 mg, and 296 to placebo. Of the 798 patients, 82.3% (657/798 patients) received study drug, 90.4% (721/798 patients) completed the study and 9.5% (76/798 patients) discontinued from the study. For 1 randomized patient receiving placebo (E1230101), the primary investigator did not complete the TERM page or sign the casebook. Thus, this patient was not counted as either completed (721 patients) or discontinued (76 patients).

All patients received their assigned treatment. There were no deaths during the study.

Overall, the most common reason for study discontinuation was eligibility criteria not fulfilled (6.6%, 53/798 patients). No patients discontinued due to AEs.

Treatment groups were similar with regard to demographics and baseline characteristics. The patient population recruited to the study was adequately representative of the target population and was appropriate for this study.

Summary of efficacy results

For the primary objective, the rates for pain-free status at 2 hours (last observation carried forward) were numerically higher for all ZOMIG treatment groups compared to placebo. ZOMIG was significantly better than placebo for 5 mg ($p<0.001$), with about 30% of patients receiving ZOMIG 5 mg being pain-free at 2 hours vs. about 17% of those receiving placebo.

The odds of a patient in the 5 mg group being pain-free at 2 hours was 2.18 times that of a patient in the placebo group.

At the interim futility analysis, the ZOMIG 0.5 and 2.5 mg groups were declared futile. As expected, ZOMIG was not significantly better than placebo for 2.5 mg ($p<0.071$); therefore, the 0.5 mg dose was not compared to placebo.

Secondary objectives

- The results of the primary efficacy analysis showed that ZOMIG 5 mg was more effective than placebo in achieving pain-free status at 2 hours after treatment ($p<0.001$), with about 30% of patients receiving ZOMIG 5 mg being pain-free at 2 hours vs. about 17% of those receiving placebo. At the interim futility analysis, the ZOMIG 0.5 and 2.5 mg groups were declared futile; as expected, these ZOMIG groups were not significantly better than placebo at 2 hours after treatment.

- ZOMIG 5 mg was nominally more effective than placebo in achieving pain-free status at 2, 3, and 4 hours after treatment (all $p<0.001$). Despite being declared futile at the interim analysis, ZOMIG 2.5 mg was nominally more effective than placebo in achieving pain-free status at 3 and 24 hours (both $p=0.032$). ZOMIG 0.5 mg was similar to placebo at all time points.

- ZOMIG 5 and 2.5 mg were nominally more effective than placebo in achieving headache response 2 hours after treatment ($p=0.010$ and $p=0.021$, respectively).

- ZOMIG 5 and 2.5 mg were nominally more effective than placebo in achieving headache response at 2, 3, and 4 hours after treatment (for 5 mg, all $p\leq0.011$; for 2.5 mg, all $p\leq0.026$).

- Sustained headache response was not statistically better than placebo for any ZOMIG dose. About 30% of all ZOMIG patients achieved sustained headache response 2 hours after treatment compared to 24% of placebo patients.

- For the symptoms of nausea and vomiting, no significant reductions in the presence of symptoms were seen for any ZOMIG dose at any time. For the symptom of sensitivity to light, nominally significant reductions were seen at 2, 3, and 4 hours for the ZOMIG 2.5 and 5 mg groups. For sensitivity to sound, nominally significant reductions were seen at 2 and 3 hours for ZOMIG 2.5 and 5 mg. ZOMIG 0.5 mg was not significantly better than placebo at any time point for either sensitivity to light or sound.

- For the symptom of nausea, no significant improvements in the resolution of symptoms were seen for any ZOMIG dose except for the 0.5 mg dose at 15 minutes post-treatment. For resolution of sensitivity to light, nominally significant improvements were seen at 2, 3, and 4 hours for the ZOMIG 2.5 mg group and at 3 hours for the 5 mg group. For sensitivity to sound, nominally significant

improvements in resolution of symptoms were only seen at 3 hours for ZOMIG 2.5 and 5 mg. For vomiting, improvements were observed for the 2.5 and 5 mg groups, but the resolution of symptoms only reached nominal statistical significance at 1 hour for the 2.5 mg dose.

- Fewer patients in the ZOMIG treatment groups used rescue medication during the first 24 hours compared to placebo, with significantly less rescue medication used for ZOMIG 5 mg (20.3%) vs. placebo (31.6%) (p=0.004).

- Patients in the ZOMIG treatment groups showed increased ability to perform normal activities with higher rates observed for the ZOMIG groups compared to placebo from 2 to 24 hours post-treatment. At the 2-hour time point, ability to perform normal activity rates were 54.4%, 67.5%, and 55.0% for ZOMIG 0.5, 2.5, and 5 mg groups, respectively, vs. 47.8% for placebo. Nominally significant improvements were observed for ZOMIG 2.5 mg from 2 to 24 hours and for ZOMIG 5 mg from 3 to 24 hours.

- Of those patients pain-free at 2 hours, less than 10% of patients across all treatment groups had a recurrence of their headache between 2 and 24 hours after treatment. Rates of headache recurrence were 10.5% (4 of 38), 0% (0 of 18), 11.8% (2 of 17), and 8.1% (5 of 62) for placebo, ZOMIG 0.5, 2.5, and 5 mg groups, respectively. With so few headache recurrences, no statistical comparisons of the ZOMIG dose groups and placebo were performed.

- The rates of bilateral headache post-treatment were generally similar across treatment groups at all time points with the only nominally significant difference versus placebo noted for ZOMIG 2.5 mg at 2 hours.

- Overall, rates of increase in intensity by movement reduced over time across all treatment groups. At 2 hours post-treatment, rates of increase in intensity were 47.4% and 51.6% for ZOMIG 2.5 and 5 mg groups with these rates being nominally significantly different from placebo (64.2%). Statistical significance continued for both ZOMIG doses through 24 hours. At no time point was the 0.5 mg dose significantly different from placebo.

Summary of safety results

In this study, ZOMIG was safe and well-tolerated at all doses. No deaths, SAEs or AEs leading to discontinuation were reported during the study.

- The overall incidence of AEs increased with ZOMIG dose with 9.9%, 15.2%, 11.1%, and 25.5% of patients reporting at least 1 AE in the placebo, 0.5 mg, 2.5 mg, and 5 mg groups, respectively. Most AEs were mild or moderate in severity.

- Dysgeusia was the most frequently reported AE, with greater frequencies being reported in the active treatment groups versus placebo (6.5%, 6.2%, and 12.6% for

the ZOMIG 0.5, 2.5, and 5 mg groups, respectively, vs. 1.2% of patients receiving placebo). This most likely represents a transient "medicinal taste" from nasal instillation rather than a more lasting alteration or dysfunction of taste.

- No clinically meaningful differences were observed for any vital signs, hematology, clinical chemistry, urinalysis, or ECG parameter.