CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, LLC	
Name of Finished Product	Axert®	
Name of Active Ingredient(s)	almotriptan malate	

Protocol No.: CAPSS-368 (CR002827)

Title of Study: Long-Term, Open-Label Safety Study of Oral Almotriptan Malate 12.5 mg in the Treatment of Migraine in Adolescents

Investigator: This was a multicenter study at 55 investigative sites.

Publication (Reference): None to date

Study Period: 23 December 2005/ 19 December 2007 | **Phase of Development:** 3b

Objectives: The objective of this study was to evaluate the long-term safety of oral administration of almotriptan 12.5 mg in the treatment of multiple migraine episodes over a period of up to 12 months in adolescent subjects 12 to 17 years of age. Efficacy was assessed as a secondary objective of the study.

Methodology: This was an open-label, multicenter study of adolescent subjects with a diagnosis of migraine headache. Subjects were to treat all migraine headaches or attacks with almotriptan malate 12.5 mg. Allowable rescue medication (including anti-emetics and a second dose of study medication) was permitted at any time, but subjects were encouraged to wait a minimum of 2 hours after taking study medication. The study consisted of two phases: screening and open-label treatment. During the screening phase, subjects who had a history of migraine with or without aura as defined by the International Headache Society (IHS) classification criteria and who met entry criteria for the study were identified. The open-label phase began at Visit 2, which occurred within 14 days following the screening visit (Visit 1). Eligible subjects left the investigative center with study medication and headache records and were instructed to self-dose with study medication to treat sequential migraine attacks for up to 12 months. Study visits occurred at Months 1, 3, 6, 9 and 12. Following Visit 3 (Month 1), telephone contacts were initiated by site staff each month when there was no study visit scheduled (Months 2, 4, 5, 7, 8, 10, and 11) to address subject and/or parent/caregiver concerns and to inquire about adverse events.

Number of Subjects (planned and analyzed): Planned: 450 adolescent subjects; Analyzed for safety: 420 subjects; Analyzed for efficacy: 420 subjects.

Diagnosis and Main Criteria for Inclusion: Adolescent male and female subjects between the ages of 12 and 17 with a history of migraine headache with or without aura, according to IHS classification criteria.

Test Product, Dose and Mode of Administration, Batch No.:

Axert® (almotriptan malate) 12.5 mg Tablets: Batch numbers R13641 (expiration 03/07), 6MG520 (expiration 10/09), and R13934 (expiration 11/08).

One almotriptan (12.5 mg) tablet was self-administered orally soon after the onset of migraine headache pain, preferably within an hour of onset.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: Open-label treatment for multiple migraine episodes was self-administered for a period of up to 12 months.

Criteria for Evaluation:

Efficacy: Subjects used headache records to capture pain intensity, occurrence, intensity of migraine headache-associated symptoms (i.e., nausea, photophobia, and phonophobia), vomiting, and use of supplemental pain medication and/or anti-emetic medication.

Safety: Safety evaluations included adverse events, brief physical examinations, brief neurological examinations, clinical laboratory tests, electrocardiogram (ECG), vital signs, and a urine drug screen. Urine pregnancy tests were performed on female subjects of childbearing potential at each study visit.

Statistical Methods: Descriptive statistics were used for the analyses of safety and efficacy data. Safety analyses were conducted on all enrolled subjects who took at least one dose of study medication according to the Headache Record (Safety population). Adverse events were to be summarized using counts and percentages. Descriptive statistics for continuous parameters and the number and percentage of subjects in each category for categorical parameters were to be calculated for each study visit for clinical laboratory tests and vital signs data.

SYNOPSIS (CONTINUED)

For ECG assessments, changes from baseline to the Final Visit were to be summarized descriptively for heart rate, PR interval, QRS interval, QTc-Bazetts, and QTc-Frederica. Laboratory tests, vital signs, and adverse event analyses were to be performed for the following subgroups: age (12 to 14 years and 15 to 17 years), gender, and race.

Efficacy analyses were to be conducted on all enrolled subjects who took at least one dose of study medication and for whom at least one post-dose efficacy assessment was available (Intent-to-Treat population). The number and percentage of headache events that achieved pain free status, relief from pain, absence of symptoms (photophobia, phonophobia, and nausea), and absence of vomiting at 2 hours and at 24 hours post-dosing and the percentage of headache events that achieved sustained pain free and sustained pain relief status were to be calculated. The percentage of headache events associated with the use of supplemental pain medication and/or anti-emetic medication was also to be summarized.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Efficacy was assessed descriptively. Efficacy data included assessments of headache pain intensity and symptom intensity at 2 hours and at 24 hours after the administration of almotriptan malate. At 2 hours after the oral administration of an almotriptan malate 12.5 mg tablet, 40.5% of all headaches were reported to have a pain free response and at 24 hours after treatment, 65.9% of all headaches had a pain free response. A sustained pain free response was reported for 38.4% of all treated headaches. Greater proportions of severe baseline intensity headaches in the 12 to 14 year age group were reported to achieve the pain free and sustained pain free responses compared with severe baseline intensity headaches in the 15 to 17 year age group.

At 2 hours after the oral administration of an almotriptan malate 12.5 mg tablet, a pain relief response was achieved for 61.7% of headaches with severe or moderate baseline pain intensity, and at 24 hours after treatment, 68.6% of severe or moderate headaches were reported to have a pain relief response. A sustained pain relief response was reported for 55.5% of severe or moderate baseline intensity headaches. Greater proportions of severe intensity headaches in the 12 to 14 year age group were reported to achieve the pain relief and sustained pain relief response; however, greater proportions of moderate intensity headaches in the 15 to 17 year age group were reported to achieve these responses.

Pain Free Headache and Pain Relief From Headache at 2 and 24 Hours Post Dose

	12-14 yr Age Group N=213		15-17 yr Age Group (N=207)		Overall N=420	
Total number of treated headaches	4097		3955		8052	
Number of treated headaches with severe, moderate or mild baseline pain intensity	4049		3892		7941	
Headaches achieving pain free in 2 hours	1671	41.3 %	1547	39.7%	3218	40.5%
Headaches achieving pain free in 24 hours	2640	65.2%	2596	66.7%	5236	65.9%
Headaches achieving sustained pain free	1561	38.6%	1487	38.2%	3048	38.4%
Number of treated headaches with severe or moderate baseline pain intensity	3051		3048		6099	
Headaches achieving pain relief in 2 hours	1885	61.8%	1880	61.7%	3765	61.7%
Headaches achieving pain relief in 24 hours	2051	67.2%	2131	69.9%	4182	68.6%
Headaches achieving sustained pain relief	1675	54.9%	1709	56.1%	3384	55.5%

Overall, when present at baseline, the presence of migraine associated symptoms (photophobia, phonophobia, and nausea) and vomiting at 2 hours and at 24 hours after treatment with almotriptan malate was also substantially reduced. Overall, treatment with almotriptan malate was more effective for migraine associated symptoms with less severity. There were some between age group differences in migraine-associated symptoms and their response to treatment; the 15 to 17 year age group had greater proportions of headaches with photophobia and phonophobia at baseline, and if these symptoms were severe, there were greater proportions of headaches with persistence of these symptoms at 2 hours and at 24 hours after almotriptan treatment. In addition, greater proportions of headaches with severe nausea at baseline in the 15 to 17 year age group had persistence of nausea at 2 hours and at 24 hours after treatment with almotriptan malate. Lastly, greater proportions of treated headaches were reported to have the presence of vomiting at baseline and at 2 hours and at 24 hours after treatment in the 12 to 14 year age group.

SYNOPSIS (CONTINUED)

Approximately 6% of all headaches were treated with a second dose of almotriptan malate within 2 hours of the first dose and 21% of all headaches were treated with a second dose within 24 hours of the first dose. Approximately 9% of all headaches were treated with rescue medication within 2 hours, and 25% of all headaches were treated with rescue medication within 24 hours of a first almotriptan dose. The most commonly used rescue medications were non-steroidal anti-inflammatory/anti-rheumatic products and other analgesics and antipyretics.

Overall, when baseline pain or migraine associated symptom intensity were not considered, there were no clinically relevant between group differences in the efficacy responses at 2 hours and at 24 hours after treatment with almotriptan malate 12.5 mg comparing the 12 to 14 year age group with the 15 to 17 year age group. The intensity of pain and migraine associated symptoms at baseline did appear to have clinical relevance for between age group differences in the 2 hour and 24 hour efficacy responses for the pain free, sustained pain free, pain relief, and sustained pain relief responses, as well as the persistence of photophobia, phonophobia, and nausea at 2 hours and 24 hours after almotriptan malate treatment. These findings suggest a phenotypic change in migraine presentation over time related to either age-related changes in neurophysiologic processing or migraine-related changes in pathophysiologic mechanisms of the condition. Lastly, greater proportions of treated headaches were reported to have the presence of vomiting at baseline and at 2 hours and at 24 hours after treatment in the 12 to 14 year age group.

SAFETY RESULTS:

Overall, 67.1% of the subjects participating in this study had an adverse event (all causality). Approximately 44% of the subjects participating in this study had at least one adverse event (all causality) that was reported to be of moderate or marked intensity. None of the enrolled subjects died during the study. Eight (1.9%) subjects had a serious adverse event, none of which were considered related to treatment with almotriptan malate.

Thirty-two (7.6%) subjects had at least one adverse event that was judged to be related to treatment with almotriptan malate. The most common treatment-related events were nausea (1.4%) and somnolence (1.4%). All other treatment-related adverse events were reported by less than 1% of the subjects.

Ten (2.4%) subjects withdrew from the study because of an adverse event. Seven of the 10 subjects who withdrew had adverse events that were judged to be related to treatment with almotriptan malate. These adverse events were nausea, somnolence, vomiting, upper abdominal pain, muscle spasms, and migraine.

Subjects With Adverse Events/Reactions

	12-14 yr Age Group N=213		15-17 yr Age Group N=207		Overall N=420	
	n	%	n	%	n	%
Subject who had at least one adverse event	142	66.7	140	67.6	282	67.1
Subjects who had at least one treatment-related adverse event [a]	17	8.0	15	7.2	32	7.6
Subjects who had at least one moderate or marked adverse event	92	43.2	91	44.0	183	43.6
Subjects who died during the study	0	0	0	0	0	0
Subjects who had a serious adverse event	3	1.4	5	2.4	8	1.9
Subjects who discontinued due to an adverse event	7	3.3	3	1.4	10	2.4

[a] Treatment-related adverse events were those that the investigator regarded as possible, probable, or very likely related to treatment or missing.

Abnormal increases (pre-defined as a change of at least 15 mm Hg) in systolic blood pressure and diastolic blood pressure occurred in ≤ 12.2% and ≤ 6.6% of all subjects, respectively, across all study visits. Abnormal decreases (pre-defined as a change of at least 15 mm Hg) in systolic and diastolic blood pressure occurred in ≤ 7.0% and ≤ 4.7% of all subjects, respectively.

The majority of the ECG results were normal at both baseline and the Final assessment; however, for 14 subjects, there was a shift in the interpretation of their ECG results from normal at baseline to abnormal, possibly clinically significant at the final assessment. Only 2 subjects had ECG abnormalities (prolonged QRS complex and prolonged PR interval) that were reported as adverse events. Both of these events were judged to have a doubtful relationship to treatment with almotriptan malate.

Three subjects became pregnant during the study; all three subjects gave birth to normal, healthy babies.

SYNOPSIS (CONTINUED)

CONCLUSION: Oral administration of almotriptan malate 12.5 mg tablet for the treatment of multiple migraine episodes over a period of up to 12 months in adolescent subjects, 12 to 17 years of age, was generally well tolerated. No unexpected safety or tolerability concerns were revealed over the course of this study in the full study population or in the 12 to 14 year and 15 to 17 year age groups. Overall, oral tablet administration of almotriptan malate 12.5 mg demonstrated effectiveness for the acute treatment of pain and symptoms associated with migraine episodes in adolescent subjects, 12 to 17 years of age.
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