SYNOPSIS

Name of Sponsor/Company: Ortho-McNeil Pharmaceutical, Inc.	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Product: Almotriptan malate	**Volume:**	
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Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study of Oral Almotriptan 6.25 mg, 12.5 mg, and 25 mg in the Acute Treatment of Migraine in Adolescents.

Protocol No: 638-CNS-0059-015

Investigators and Study Centers: A total of 93 investigators randomized patients; a complete list of participating investigators is provided in Appendix 16.1.4.

Publication (reference): Not applicable

Study period: 22 July 2003 to 29 April 2005	Phase of development: III

Study Objectives: Oral doses of Almotriptan 6.25 mg, 12.5 mg, and 25 mg and placebo were given to treat a migraine attack in patients aged 12 to 17 years to assess the following objectives.

Primary Objective: Efficacy of Almotriptan versus placebo at 2 hours post-dose.

Secondary Objectives:

- Efficacy of Almotriptan versus placebo at 0.25, 0.5, 1, 1.5, and 24 hours post-dose.
- Occurrence of associated symptoms at 0.25, 0.5, 1, 1.5, and 2 hours post-dose for vomiting and at 0.25, 0.5, 1, and 1.5 hours post-dose for nausea, photophobia, and phonophobia.
- Incidence of headache recurrence and the use of rescue medication within 2 to 24 hours after administration of Almotriptan versus placebo.
- Safety of Almotriptan versus placebo.

Methodology: This was a randomized, double-blind, parallel group, placebo-controlled acute treatment trial in patients who were 12 to 17 years of age. The trial included a 30-day run-in period beginning at Screening (Visit 1). Patients did not receive study medication during the run-in period but were permitted to treat their migraine(s) with their usual migraine treatment medications. The run-in period was used to assess and document the frequency and severity of migraine attacks. Patients who did not have at least 1 headache or who had >6 moderate or severe migraine attack(s) during the run-in period did not receive study medication and were not randomized into the study. At the end of the run-in period (Visit 2), patients were randomized (1:1:1:1) within 2 age strata (12 to 14 years old and 15 to 17 years old) using block sizes of 8 for each age group. One dose of Almotriptan 6.25 mg, Almotriptan 12.5 mg, Almotriptan 25 mg, or placebo was dispensed to each patient. At any time during the next 42 days (treatment period), patients took their dose of study medication as soon as possible and no more than 4 hours after their first attack of moderate or severe migraine pain. Patients returned to the clinic for a Final Visit within 2 to 14 days after their migraine attack. Patients who did not experience a migraine attack within 42 days after Visit 2 returned to the clinic for a final visit and returned their study medication.

Number of patients (planned and analyzed): Approximately 924 patients were planned to be enrolled, 866 patients were enrolled, 714 patients were analyzed for efficacy, and 720 patients were analyzed for safety.

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Diagnosis and main criteria for inclusion: Male or female patients, 12 to 17 years of age who would not reach their 18th birthday during the study, with a history consistent with the diagnosis of migraine with or without aura as defined by the International Headache Society Criteria for >1 year and have a ≥6 month history of moderate or severe migraine attacks that occurred at a monthly frequency of at least 1 to 6 moderate attacks during the 2 months preceding study enrollment; these attacks had to persist for a duration of >4 hours when untreated and occur at intervals >24 hours between attacks. Patients also had to verbalize the ability to distinguish migraine attacks from other types of headaches.

Test product, dose and mode of administration, batch number: Almotriptan was provided as 2 tablets that were taken orally. Patients in the Almotriptan 6.25 mg dose group were dispensed 1 tablet containing placebo and 1 tablet containing Almotriptan malate equivalent to 6.25 mg of Almotriptan. Patients in the Almotriptan 12.5 mg dose group were dispensed 1 tablet containing placebo and 1 tablet containing Almotriptan malate equivalent to 12.5 mg of Almotriptan. Patients in the Almotriptan 25 mg dose group were dispensed 2 tablets, each containing Almotriptan malate equivalent to 12.5 mg of Almotriptan.

Almotriptan 6.25 mg Batch number: 4CG2324

Almotriptan 12.5 mg Batch number: 4GG3268

Duration of Treatment: The trial included a 30-day run-in period beginning at Screening. At the end of the run-in period (Visit 2), the patients were randomized to treatment groups. Patients could take their study medication anytime during the next 42 days that coincided with an attack of moderate or severe migraine pain. Patients who experienced a migraine attack returned to the clinic for a Final Visit within 2 to 14 days after their migraine attack. Patients, who did not experience a migraine attack within 42 days after Visit 2, also completed a final visit.

Reference therapy, dose and mode of administration, batch number: Placebo was provided as 2 tablets that were taken orally. Batch number: 012F0022

Criteria for evaluation :

Efficacy: All efficacy analyses were based on the Intent-to-treat (ITT) Population and included evaluations of the following endpoints:

Primary Endpoint: Headache pain relief 2 hours post-dose defined as a decrease in headache pain intensity (none, mild, moderate, or severe) from either moderate or severe intensity to mild or no pain. Patients who experienced headache pain relief were considered responders.

Co-primary Endpoints: Presence or absence of nausea, photophobia, and phonophobia at 2 hours post-dose.

Secondary Endpoints:

- Headache pain relief at 0.25, 0.5, 1.0, and 1.5 hours post-dose
- Nausea, photophobia, and phonophobia at 0.25, 0.5, 1.0, and 1.5 hours post-dose and vomiting at 0.25, 0.5, 1.0, 1.5, and 2.0 hours post-dose
- Headache pain free (decrease in headache pain intensity from moderate or severe to none) at 0.25, 0.5, 1.0, 1.5, and 2.0 hours post-dose

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Secondary Endpoints (continued):

- Headache recurrence (significant worsening of headache pain intensity from none or mild to moderate or severe) within 2 to 24 hours post-dose in responders
- Time to recurrence
- Use of rescue medication 2 to 24 hours post-dose
- Sustained pain relief defined as headache pain relief at 2 hours post-dose, no recurrence, and no use of rescue medication
- Sustained pain free defined as headache pain free at 2 hours post-dose, no recurrence, and no use of rescue medication

Safety: All safety analyses were based on the Safety Population. Safety assessments included adverse events (AEs), clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), physical examinations, concomitant medications, and pregnancy testing.

Statistical methods: Demographic and Baseline characteristics (sex, age, race, weight, and height) and safety endpoints were summarized by treatment group using descriptive statistics for the Safety and the ITT Populations. All safety analyses were based on the Safety Population and there were no formal comparisons of the safety parameters between treatment groups. Efficacy analyses were based on the ITT Population.

Homogeneity across treatment groups was assessed using hypothesis tests at the 2-sided alpha level of 0.05. Overall treatment group differences for continuous variables were assessed using an analysis of variance model. Treatment group differences for categorical variables were assessed using the uncorrected Chi-Squared test. For the primary efficacy analysis, comparison between treatment groups were done using either the Cochran-Mantel-Haenszel (CMH) test adjusted for Baseline pain intensity (moderate or severe) or a Likelihood Ratio Chi-Square test when not adjusted for Baseline pain intensity, and following a step-down procedure.

Results:

Efficacy**:**

Headache pain relief at 2 hours post-dose adjusted for Baseline pain intensity (primary endpoint) was statistically significantly better in the Almotriptan 25 mg group (66.7%) compared with the placebo group (55.3%), but the occurrence of nausea, photophobia, and phonophobia (co-primary endpoints) at 2 hours post-dose by Baseline pain intensity in the Almotriptan 25 mg group (20.7%, 34.6%, and 30.7%, respectively) compared with the placebo group (15.8%, 40.6%, and 34.5%, respectively) were not statistically significantly different.

Adjustments for Baseline pain intensity did not affect whether or not any of the secondary efficacy endpoints were statistically significantly different in the 3 Almotriptan dose groups compared with placebo. Statistically significant improvements occurred in the following Almotriptan dose groups compared with placebo for: headache pain relief (unadjusted) at 1.5 hours in the Almotriptan 12.5 mg dose group (55.2% versus 44.1%) and at 2 hours in the Almotriptan 6.25, 12.5, and 25 mg dose groups (71.8%, 72.9%, and 66.7%, respectively, versus 55.3%); phonophobia (adjusted and unadjusted) at 1.5 hours post-dose in the Almotriptan 12.5 mg dose group (34.1% versus 45.8%); and sustained headache pain relief (adjusted and unadjusted) at 24 hours in responders in the Almotriptan 6.25, 12.5 and 25 mg dose groups (67.2%, 66.9%, and 64.5%, respectively versus 52.4%).

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Results:

Efficacy (continued)**:**

Exploratory analyses indicated that the Almotriptan 12.5 mg dose group had the best combined efficacy of improved headache pain relief and associated symptoms at 2 hours post-dose with and without adjustments for Baseline pain intensity combined with and without adjustments for the presence of Baseline nausea, photophobia, or phonophobia. Patients in the 15 to 17 years of age group were more responsive to treatment with Almotriptan compared with patients in the 12 to 14 years of age group. In the 12 to 14 year age group, there were statistically significant improvements in photophobia at 2 hours post-dose in the Almotriptan 12.5 mg dose group (21.5%) compared with placebo (37.2%) with and without adjustments for Baseline pain intensity. In the 15 to 17 year age group, there were statistically significant improvements in headache pain relief, photophobia, and phonophobia in all 3 Almotriptan dose groups compared with placebo with and without adjustments for Baseline pain intensity. Results for headache pain relief and associated symptoms for patients in the PP Population were very similar to those for the ITT Population; headache pain relief, photophobia, and phonophobia at 2 hours post-dose in the Almotriptan 12.5 mg were statistically significantly improved compared with placebo with and without adjustments for Baseline pain intensity.

Safety:

No deaths, SAEs, or discontinuations due to AEs occurred. The overall incidence of AEs and treatment-related AEs was higher in the Almotriptan 12.5 mg and 25 mg dose groups compared with the Almotriptan 6.25 mg and placebo groups. The overall incidence of treatment-related AEs in all 4 treatment groups was 9.3%. The incidence of patients 12 to 14 years of age and patients 15 to 17 years of age who reported treatment-related AEs was similar in both age groups (10.1% and 8.4%, respectively). The most common treatment-related AEs overall and in both age groups were dizziness and somnolence; the overall incidence of dizziness was 2.8% in the 12 to 14 year age group and 1.8% in the 15 to 17 year age group and the overall incidence of somnolence was 2.3% in the 12 to 14 year age group and 2.1% in the 15 to 17 year age group. The overall incidence of patients with moderate and severe treatment-related AEs was low (1.9% and 1.1%, respectively).

Mean values for hematology, clinical chemistry, and urinalysis parameters were within normal range and were similar across the 4 treatment groups at Screening and did not noticeably change at Final Visit. The incidence of N→L and N→H shifts were also similar across the 4 treatment groups. Mean values for vital signs and ECG results were similar across the 4 treatment groups at Screening and did not noticeably change at Final Visit; the incidence of patients who had increases or decreases of ≥15 mm Hg in their systolic or diastolic BP were also similar across the 4 treatment groups. Shifts in ECG interpretations of normal to abnormal significant or abnormal insignificant to abnormal significant occurred in 5 patients.

Conclusions: Headache pain relief at 2 hours post-dose adjusted for Baseline pain intensity (primary endpoint) was statistically significantly better in the Almotriptan 25 mg group compared with the placebo group but the occurrence of nausea, photophobia, and phonophobia (co-primary endpoints) at 2 hours post-dose by Baseline pain intensity in the Almotriptan 25 mg group compared with the placebo group were not statistically significantly different. Results of the analyses of secondary efficacy endpoints and exploratory analyses indicate that Almotriptan 12.5 mg improved both headache pain relief and reduced the incidence of photophobia and

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phonophobia compared with placebo at 2 hours post-dose. All 3 doses of Almotriptan were well tolerated.		
Date of the report: 31 October 2005		

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