1. SYNOPSIS

<table>
<tr><td>Name of Sponsor / Company:
Almirall Prodesfarma, S.A
(Laboratorios Almirall, S.A., since 01DEC06)

Name of Finished Product:
Almotriptan

Name of Active Ingredients:
Almotriptan, 5-HT Agonist</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: Treatment of Acute Migraine when Pain is Mild versus when Pain is Moderate to Severe: an Almotriptan Parallel, Placebo Controlled Clinical Trial. “Act when mild?”</td></tr>
<tr><td colspan="3">Investigators:
This study was conducted by 41 Investigators (see Appendix 16.1.4).
The Principal Investigator was [redacted] (site not initiated).</td></tr>
<tr><td colspan="3">Study centre (s):
This study was conducted in a total of 41 sites (only those sites that were initiated and recruited subjects are included here), 10 in France, 5 in Portugal, 8 in Germany, 6 in Belgium, 12 in Italy, (see Appendix 16.1.4).</td></tr>
<tr><td colspan="3">Publication (reference):
Poster Abstract, International Migraine Trust, 2006.Cephalalgia 26 (11), 1393-1394</td></tr>
<tr><td colspan="2">Studied period (years):
Date study initiated (first screening): 11 July 2005
Date study finalized (last subject last visit): 09 May 2006</td><td>Phase of development: Phase IV</td></tr>
<tr><td colspan="3">Objectives:
To evaluate the efficacy of Almotriptan in subjects with a history of migraine pain, reaching at least a moderate intensity when treatment is administered and whilst migraine pain is still mild (and during the first hour of pain onset), versus when treatment is administered while migraine pain has become moderate or severe.</td></tr>
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Methodology:
This was a multi-centre, randomized, four-arm parallel, placebo controlled trial. The trial was double-blind between placebo and active treatment. The four-treatment/regimen arms corresponded to placebo or Almotriptan 12.5-mg self-administered at two different stages of the migraine attack (either early, in the first hour since pain onset and while migraine pain was still mild or when it was moderate to severe).

Subjects attended the clinic for three study visits (Visit 1 and 2 could occur on the same day). Visit 1 was a screening assessment and eligible subjects who gave informed consent and medical history details underwent a physical examination, vital signs measurements, pregnancy test (if appropriate), and were asked about their current treatment satisfaction (Visual Analogue Scale [VAS]) and about their quality of life with migraine (the Migraine Specific Quality of Life [MSQ] was validated in the appropriate language [all participating countries except Portugal]).

Eligible subjects could attend Visit 2 up to 14 days following Screening. If Visit 2 was on a different day to Visit 1, concomitant medication, vital signs and potential adverse events (AEs) were reviewed. Subjects were then randomized to one of the four treatment arms in a 1:1:1:1 ratio to treat one migraine attack over a maximum period of 60 days. Administration occurred at the first symptom of migraine pain when pain was of mild intensity and no later than one hour after pain onset (two arms: one receiving placebo and one receiving 12.5 mg Almotriptan); or when pain had reached a moderate to severe intensity (two arms: one receiving placebo and one receiving 12.5 mg Almotriptan).

On occurrence of a migraine attack, subjects were to take the investigational medicinal product (IMP) as instructed by the Investigator at Visit 2. Subjects recorded baseline status, efficacy, AEs and concomitant medication on their diary card.

Two to six (+2) days after treatment of the migraine attack, subjects returned to the clinic for Visit 3. Physical examination, vital signs and treatment satisfaction scale completion were performed. Adverse events and concomitant medications were recorded throughout the trial.

Subjects who did not experience or missed a qualifying migraine attack by Day 60 (Visit 2 being Day 1) were to be withdrawn from the trial.

Name of Sponsor / Company: Almirall Prodesfarma, S.A. (Laboratorios Almirall, S.A. since 01DEC06) **Name of Finished Product:** Almotriptan **Name of Active Ingredients:** Almotriptan, 5-HT Agonist	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Number of subjects (planned and analyzed):
Planned: 388 evaluable
Screened: 491
Randomized: 491
Completed study: 404
Evaluated for safety: 404
Evaluated for efficacy (Intent to treat [ITT]): 403
Evaluated for efficacy (Per Protocol [PP]): 337

Diagnosis and main criteria for inclusion:
Male or female, 18 to 65 years old with a minimum one year of migraine history (International Headache Society criteria) of moderate or severe intensity and with a frequency of two to six attacks per month, for the past three months.

Test product, dose and mode of administration, batch number, expiry date:
Name: Almotriptan (LAS31416)
Administration route: Oral
Dosage form: Tablets
Dose and regimen: 12.5 mg, single dose treating one attack.
Batch number: 024F0042.
Expiry date: January 2008.

Duration of treatment:
One single dose of Almotriptan. Subjects participated in the study for a maximum of approximately 67 to 81 days.

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo
Administration route: Oral
Dosage form: Tablets
Dose and regimen: single dose treating one attack.
Batch number: 012F0041.

Criteria for evaluation:

Efficacy:

Primary endpoint
Number and percentage of subjects being pain free at 2 hours after IMP administration.

Secondary endpoints
- Number and percentage of subjects being pain free at 15 min, 30 min, 1 h, 1 h 30 min, and 24 h after IMP administration.
- Number and percentage of subjects with sustained pain free (from 2 h to 24 h and no rescue medication use).
- Number and percentage of subjects with pain relief at 15 min, 30 min, 1 h, 1 h 30 min, 2 h and 24 h after IMP administration (in regimen groups where treatment was when pain was moderate to severe).

- Number and percentage of subjects using rescue medication.
- Number and percentage of subjects with relapse within 24 h after IMP administration
- Number and percentage of subjects with relapse between 24 and 48 h after IMP administration
- Migraine attack duration in hours.
- Time between onset of migraine attack and IMP administration.
- Time between IMP administration and end of attack.
- Time loss in hours at 48 h.
- Number and percentage of subjects with nausea, vomiting, phonophobia, photophobia, osmophobia, each assessed before (baseline), and 30 min, 1 h, 1 h 30 min, 2 h, and 24 h after IMP administration
- Number and percentage of subjects presenting central sensitization and cutaneous allodynia sign(s) before (baseline), and 30 min, 1 h, and 2 h after IMP administration
- Subjects' treatment satisfaction measured by a Visual Analogue Scale

Safety endpoints:

- Occurrence of AEs
- Vital signs.
- Physical examination.
- Concomitant medications including rescue medications were also recorded

Statistical methods:

Efficacy variables: Were analyzed using the ITT population. The primary efficacy variable was also analyzed using the PP population. For all statistical tests, the significance level was set at 0.05 two-tailed. The primary variable was analyzed by means of a logistic regression model including centre and treatment as covariates.

Safety variables: Were analyzed through descriptive analyses (listings and tabulations) using the Safety Population.

Sample size: A sample size of 388 evaluable subjects (97 subjects per treatment/regimen group) was planned to provide an 80% power, to detect an estimated difference of 20% in the proportion of subjects with pain free at two hours between Almotriptan 12.5 mg treated when early/mild and Almotriptan 12.5 mg treated when moderate to severe (60% vs. 40% respectively). To account for approximately 19% of expected dropouts and non-evaluable subjects after randomization, a total of approximately 480 subjects, 120 subjects per treatment/regimen group, were randomized.

Demographic and other Baseline characteristics: Were summarized by means of the appropriate descriptive statistics using the Safety Population.

Continuous variables: Number of observations (N), number of missing values, mean, standard deviation (SD), standard error of the mean (SEM), 95% confidence intervals (CI) (except laboratory data), percentiles 25 and 75, median, minimum, and maximum.

Categorical and ordinal scale variables: Frequencies (n) and percentages (%) where specified.

SUMMARY – CONCLUSIONS

Efficacy Results:

With respect to the primary efficacy variable, the number and percentage of subjects in the ITT population (n=403) who were pain free at 2 h after drug administration were: 50 (48.5%) in the Almotriptan 12.5 mg mild group (n=103); 38 (40.0%) in the Almotriptan 12.5 mg moderate to severe group (n=95); 27 (25.2%) in the Placebo mild group (n=107); 15 (15.3%) in the Placebo moderate to severe group (n=98).

Primary treatment comparison: the Almotriptan 12.5 mg mild group was not significantly different from the Almotriptan 12.5 mg moderate to severe group for the ITT population (p=0.2154). Results were significantly impacted by the number of subjects in the ITT population who did not treat themselves according to the intensity of pain they were randomly assigned to treat. According to the review of data

before unblinding, 38 subjects assigned to treatment for mild pain, had missed the correct timing and were treated for moderate or severe pain, while 2 subjects assigned to treatment for moderate or severe pain were treated for mild pain (see below Conclusions paragraph for interpretation).

For the PP population (n=337), in which the 40 (38+2) subjects already mentioned were removed, (representing 2/3 of the Protocol violations), the difference for the primary variable between primary comparison groups was not statistically significant, however it was increased: respectively 41/80 (51.3%) patients in the Almotriptan 12.5 mg mild group and 35/90 (38.9%) in the Almotriptan 12.5 mg moderate/severe group were pain free at 2 hours after almotriptan administration; p= 0.1130.

Secondary treatment comparisons for the primary variable: both Almotriptan groups were each significantly different from their corresponding placebo group whether considering the ITT (48.5% vs. 25.2% for Almotriptan and placebo mild migraine groups respectively, p=0.0004; 40.0% vs. 15.3%, p=0.0002 for moderate/severe migraine groups) or the PP population (51.3% vs. 28.6% for mild migraine groups, p=0.0031; 38.9% vs. 14.4%, p=0.0003 for moderate/severe migraine groups).

When considering the secondary efficacy variables (ITT population), treating a mild migraine attack rather than treating a moderate to severe attack was beneficial for the subjects in terms of: sustained pain free (respectively 45.6% vs. 30.5%, p=0.0240), migraine attack duration from pain onset (medians 2 h vs. 5 h, p=0.0005), time loss (medians 0 h vs 2 h, p=0.0015), relapse at 24 h (6% vs 23.7%, p=0.0124).

The use of rescue medication was significantly lower in Almotriptan treated subjects as compared to the corresponding placebo treated subjects. However the difference between percentages of subjects taking rescue medication in the group instructed to treat mild migraine pain (25.2%) and in the group instructed to treat moderate or severe migraine pain (33.7%) was not statistically significant.

When compared to Placebo, Almotriptan was consistently more successful at treating both mild and moderate to severe migraines.

Safety Results:
There were no deaths or serious adverse drug reactions reported during this study.

There was one serious non-related Individual Case Safety Report containing 3 SAEs for subject 627-0001, prior to taking any study medication; all 3 SAEs resolved.

Twenty-six treatment emergent AEs occurred in this study. The incidence of AEs was similar in the Almotriptan 12.5 mg and the Placebo groups. The number of subjects experiencing AEs during the treatment phase is presented in the table below:

Treatment	***Subjects***			***Number of AEs***
	with AEs	***total***	***%***	
Almotriptan mild	5	103	4.9	8
Almotriptan Moderate/Severe	4	95	4.2	4
Placebo Mild	5	107	4.7	9
Placebo Moderate/Severe	4	99	4.0	5

Source: Post-text Table 26.

Most of the AEs reported were of mild or moderate intensity and all AEs resolved. A small proportion of AEs were deemed 'probably' or 'possibly' related to study medication.

No significant changes were seen in vital signs (systolic and diastolic blood pressure and pulse rate).

CONCLUSIONS:

- This study supports, for the first time in a prospective and placebo controlled manner that treating a migraine attack with Almotriptan while the pain is still mild is beneficial to migraine patients. However, it does also show that a number of subjects (20%), although instructed to take their medication early during the course of the attack, are unable to do so. A post-hoc analysis, that can be found in the proceedings of the 2006 International Migraine Trust, published in the November issue of Cephalalgia, showed that when these subjects, who were incorrectly treated, were analyzed as per their actual treatment (not removing them as per Protocol population), statistical power was reached for a statistically significant difference on the primary comparison for the main variable, with about 15% more patients who treated a mild intensity migraine being pain free at 2h.
- Almotriptan 12.5 mg when treating a mild migraine attack resulted in significantly more subjects who sustained the pain free state, had a lower incidence of relapse at 24 h, had a shorter migraine duration and experienced less time loss when compared with Almotriptan treating a moderate to severe attack.
- Patients in the “Mild” group experienced less pain intensity, as they did not reach the “Moderate-Severe” pain level and suffered less associated symptoms before improving faster and reaching the mentioned higher sustained pain free status.
- As expected, in terms of subjects being free from migraine pain at 2 h after drug administration, Almotriptan at a dose of 12.5 mg was significantly more successful at treating both mild and moderate to severe attacks when compared with Placebo.
- Almotriptan at a dose of 12.5 mg was as safe and well tolerated in this study population, as placebo.

DATE OF REPORT:

Final Version Almirall (1 June 2007)