Study synopsis

Name of finished product: Almogran **Name of active ingredient:** Almotriptan

Title of study: A randomized, prospective, cross-over, double blind, placebo-controlled multicentre study to assess the efficacy and tolerability of Almotriptan 12.5 mg in the mild pain phase of Menstrual Migraine (MM) followed by an open follow-up evaluation to assess consistency

Investigators: [redacted]

Study center(s): 7 in Italy

1. **Centre 1**

[redacted]

Milan

2. **Centre 2**

[redacted]

Turin

3. **Centre 3**

[redacted]

Arcugnano (VI)

4. **Centre 4**

[redacted]

Parma

5. **Centre 7**

[redacted]

Merate (LC)

6. **Centre 8**

[redacted]

[redacted]

Monforte Irpino (AV)

7. Centre 9

[redacted]

[redacted]

Sestri Ponente (GE)

Publication(s): None

Study period: First patient enrolled:
31/05/2005 (Screened)
01/07/2008 (Enrolled)

Last patient completed:
05/09/2008 (V3 completed)
08/10/2008 (Dropped)

Development phase: IV

Objectives:

The primary objective of the study consisted in proving the effectiveness (superiority hypothesis) of Almotriptan in a placebo controlled trial by testing the percentages of patients pain free at 2 hours (primary study end-point).

The secondary objectives consisted in comparing the two treatments in terms of percentages of patients pain free at 0.25, 0.5, 1.0, 1.5, 24 hour after study drug administration, sustained pain free and in comparing the two treatments in terms of patients' percentage with rescue medication intake, of patients' percentage who experienced attack recurrence within 48 hour, of duration of migraine attack,
of evolution of migraine associated symptoms (each assessed at 0.25, 0.5, 1, 1.5, 2, and 24 hours after study drug intake), of tolerability (based on assessment and recording of adverse events (AEs), physical examinations and vital signs).

Assessment of Almotriptan consistency was the objective of the open follow-up phase.

Study status: completed as planned

Methodology:

Multicentre, double blind, placebo controlled, randomized, crossover study followed by an active treatment open follow-up evaluation to assess consistency, using a placebo control and Almogran tablets containing 12.5mg of Almotriptan malate.

Number of patients:

A total of 160 patients were planned (to have 130 evaluable subjects, about 160 patients were to be screened and randomized), 194 patients were screened and 147 randomized, 74 to Almotriptan-Placebo and 73 to Placebo-Almotriptan; 122 patients completed the double blind phase.

Indication and main criteria for inclusion:

Planned trial population: women 18-50 years of age, whatever ethnic group, outpatients, suffering from menstrually-related migraine without aura.

Main inclusion criteria.

1. Women 18-50 years of age who meet the IHS diagnostic criteria for menstrual migraine.

2. Subject with regular menstrual periods and an history of predictable migraine attack occurring from 2 days before to 3 days after onset of menses in at least two of the three preceding months.
3. Subjects must be Almotriptan's naive patients.
4. Subjects may take a single medication effective for migraine prophylaxis, for any reason. If taking a medication effective for migraine prophylaxis, subjects must have been taking a maintenance dose for at least 1 month prior to the Screening Visit (Visit "S"), and must remain on a stable dose for the duration of the study.
5. Subjects must be in generally good health as confirmed by medical and medication history, and baseline physical examination including vital signs.
6. Childbearing potential women must use an acceptable means of contraception or hormonal contraceptives for at least 30 days prior to study entry and throughout the study; or be practicing abstinence and agree to continue abstinence or to use an acceptable method of contraception should sexual activity commence.

Main exclusion criteria.

1. Subjects who routinely experience any other type of headache that would confound discrimination from a menstrual migraine headache or subjects who typically have headache which start without a mild phase.
2. Subjects who have had 15 or more headache days per month in the previous 6 months (chronic daily headache), or subjects having an average migraine headache frequency of more than 6 per month for the past 3 months
3. Subjects taking more than 1 medication for any reason which is effective for the prophylaxis of migraine headache.
4. Subjects taking any of the prohibited concomitant medications listed in the protocol or starting non-pharmacologic approaches for migraine treatment within 14 days of Visit "S".
5. Subjects who typically experience vomiting with their headaches or with hemiplegic or basilar migraines.
6. Subjects known to have any significant and unstable medical disease that would compromise the subject's welfare or confound the study results, or any disease or condition that compromises the function of those body systems that could result in altered absorption, excess accumulation or impaired metabolism or excretion of the test medication.

Investigational drug, doses and mode of administration, batch number:

Study medication was supplied by Almirall, free of charge, as tablets containing 12.5mg of Almotriptan malate or their corresponding placebo tablets.

STUDY MEDICATION: ALMOTRIPTAN 12.5mg TABLETS

Substance:	Almotriptan
Chemical name:	3-(2-dimethylaminoethyl)-5-(1-pyrrolidinylsulphonylmethyl)-1H-indole D,L hydrogen malate)
Dosage:	12.5mg
Dosage form:	Tablet
Administration route:	Oral
Batch Number:	021F0036
Manufacture date:	31 Aug 2004
Expiry date:	36 months (31 Aug 2007)

Relabelling (new ex. date): 31 Oct 2008
Medical Control Number: MCN104
Manufacturer: ALMIRALL PRODESFARMA S.A.

Study treatments, time and mode of administration.

The IMP, consisting of either 12.5 mg Almotriptan malate or matching placebo in identically-appearing tablets, was self administered at the onset of the first menstrual migraine attack occurring during the specified window (day - 2 to + 3) of the menstrual cycle. Participants took one tablet of study medication orally to treat the attack when pain was still mild and in the first hour from pain onset.

Reference therapy:

REFERENCE MEDICATION: Placebo Tablets

Substance: Placebo
Dosage: --
Dosage form: Tablet
Administration route: Oral
Batch Number: 003F0035
Manufacture date: 31 Aug 2004
Expiry date: 36 months (31 Aug 2007)
Relabelling (new exp. date): 31 Oct 2008
Medical Control Number: MCN104
Manufacturer: ALMIRALL PRODESFARMA, S.A.

Duration of treatment:

The planned duration of treatment was four months: one single menstrual migraine attack per menstrual cycle was treated in four different menstrual cycles. One out of the first two of the four attacks is placebo-treated. Each attack was treated with one single dose of IMP.

For each subject the duration of participation in the study was supposed to be five months including the open follow-up phase.

Criteria for evaluation:

Efficacy:

Primary endpoint

Percentage of patients being pain free 2 hours after IMP administration.

Secondary endpoints.

- Percentage of patients being pain free at 0.25, 0.5, 1, 1.5 and 24 hours after IMP administration
- Number and percentage of patients being sustained pain free, defined as pain free from 2 h to 24 and no rescue medication use
- Rescue medication use patients' percentage
- Duration of migraine attack in hours
- Attack recurrence within 48 h patients' percentage
- Evolution of migraine associated symptoms: patients' percentage with nausea, vomiting, phonophobia, or photophobia, each assessed at 0.25, 0.5, 1, 1.5, 2, and 24 hours after study drug intake
- Time loss in hours

Safety:

- Adverse events occurrence
- Vital signs (blood pressure and pulse rate)
- Physical examination

Statistical methods:

The evaluation of the primary end-point (pain free at 2 hours) was performed by means of a logistic regression model with generalized estimating equations (GEE). The model effects were: the treatment sequence (Almotriptan-placebo and placebo-Almotriptan), the treatment (Almotriptan and placebo) and the period (first and second). Being this a Cross-Over trial a compound symmetry variance-covariance matrix was employed in order to take into account clustered data (repeated measures). Results were reported as Odds Ratio (OR) with associated 95% Confidence Limits (CL) and two-tailed p-values. The main analyses were performed on the Intention To Treat population (ITT population). Per Protocol population (PP population) was analyzed with the aim of ensuring that protocol violations/deviations and drop-outs or withdrawals did not affect the results. All statistical computations was carried-out using SAS version 9.1.

Results: 147 patients were randomized to Almotriptan-Placebo (n=74) or Placebo-Almotriptan (n=73). 122 patients completed the double-blind phase as follow: Almotriptan-Placebo (n=63) and Placebo-Almotriptan (n=59) and 105 completed the additional open follow-up phase (two further attacks). All patients are Caucasian and no statistical significant differences have been found comparing age, height and weight. The commonest past documented illnesses are surgical interventions which occurred in about 34% of randomized patients. All the other past documented illnesses and concomitant documented illnesses are sparsely distributed without appreciable differences between the two sequences of treatment and with incidences constantly lower than 5%.

At inclusion visit about 73% of the recorded concomitant treatments were classified as rescue medication. This percentage decreases to 43% and 57% during treatment with Almotriptan and Placebo, respectively.

When grouped by System Organ Class (SOC), the almost totality of concomitant medications was associated to “Vascular Disorder” indication. The three commonest documented concomitant medications were: ibuprofen, indometacin and nimesulide . About 5% of the recorded concomitant medications were classified as ongoing.

Descriptive statistics highlight that: 1) about half of the migraine attacks occurred between the first and second day of menstrual period, 2) moderate headache occurred in 50% to 60% of migraine attacks and 3) an association with other symptoms (nausea, vomiting, etc) was present in about 90% of patients.

Considering that around 30% of the patients were able to treat migraine attack during its mild phase a post-hoc analysis was conducted to assess the efficacy of Almotriptan in comparison with placebo in the sub-groups of patients both with moderate/severe and mild pain intensity (according to the IHS criteria). Assessment of active treatment (Almotriptan) consistency in two further attacks in the open follow-up phase was also performed. Data confirmed the results obtained in primary and secondary endpoint analysis.

Efficacy: The study has reached the main objective to demonstrate the superiority of Almotriptan compared to Placebo in terms of percentage of patients being pain free at 2 hours. The percentages of patients pain free at 2 hours are 49.1% and 23.6% for Almotriptan and placebo respectively (PP Population n=110), with a risk ratio of 2.02 (95%CI; 1.37 - 2.99; p = 0.0004 and 48.4% and 26.2% for Almotriptan and placebo, respectively (mITT Population n=122), with a risk ratio of 1.81 (95%CI; 1.28 - 2.57; p = 0.0008).

All other items examined as secondary endpoints also demonstrate the superiority of Almotriptan compared to Placebo.

Safety: Treatment-emergent adverse events (TEAE) occurred in about 6% of patients belonging to the Safety dataset during Almotriptan and Placebo treatment. All the treatment-emergent adverse events are sparsely distributed without appreciable differences between the two treatments and with incidences constantly lower than 5%. 42% of TEAE were classified as definitely/possibly/probably study drug related, none TEAE were graded as severe or led to study discontinuation during the double-blind phase. No treatment-emergent serious adverse events (TESAE) occurred during the study.

Conclusions: The menstrually-related migraine population is a particularly difficult one to treat. The results of this double-blind, placebo controlled study showed an excellent efficacy of Almotriptan on all symptoms and the hypothesis of a superior efficacy of the compound was confirmed.
Almotriptan was well tolerated and considering its efficacy one can conclude that it can be considered a first choice treatment for mild and moderate/severe pain in Menstrually-Related Migraine (MRM).

Date of the report: 18 June 2009