2 CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor Company	*Name of finished product*	*Name of active ingredient*
Zambon S.p.A.	Z7202 diclofenac diethylamine salt medicated plaster	Diclofenac (2-[(2,6-Dichlorophenyl) amino] benzeneacetic acid diethyl ammonium salt)

Title of the study

EFFICACY, TOLERABILITY AND SAFETY OF Z7202, A ONCE DAILY DICLOFENAC DIETHYLAMINE MEDICATED PLASTER IN THE LOCAL TREATMENT OF PAINFUL CONDITIONS. MULTI-CENTER, MULTINATIONAL, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP STUDY.

EudraCT Number: (2011-000725-69)

Principal Investigators and study sites

Eighteen Principal Investigators at study sites in Estonia (six sites), Lithuania (five sites) and Slovakia (seven sites).

Publication (reference)

Not applicable.

Study Period:	*Phase of Development*
14 September 2011 (First Patient In) to 07 September 2012 (Last Patient Out)	Phase III

Objectives

Primary objective: To assess the clinical efficacy of Z7202 diclofenac diethylamine (DEA) medicated plaster (test), versus placebo on pain intensity on motion related to painful conditions (due to ankle sprains and/or strains), detected by a 100 mm Visual Analogue Scale (VAS), on Day 4 (Patient Diary).

Secondary objectives:

1. To assess the clinical efficacy of Z7202 diclofenac DEA medicated plaster in terms of:
    a. Reduction of pain intensity at rest on Day 4 and 8.
    b. Reduction of pain intensity on motion on Day 8.
    c. Rescue medication consumption.
    d. Global efficacy at the end of treatment.
2. To assess systemic safety and tolerability and local tolerability of Z7202 diclofenac DEA medicated plaster.

Study design and methodology

This was a multi-center, multinational, placebo-controlled, double-blind, randomized, parallel-group Phase III study to assess efficacy, tolerability and safety of Z7202 diclofenac DEA medicated plaster, in comparison with matching placebo, in patients suffering from a painful condition (due to a single localized ankle sprain and/or strain). Patients were screened and randomized on the same day (Visit 1, Day 1). Eligible patients were randomly assigned to two possible treatment groups; either diclofenac DEA medicated plaster or matching placebo plaster group using a 1:1 ratio. The first application of the plaster was done at the clinic (Visit 1) and patients continued the treatment at home for a total of seven consecutive days. Patients returned for a second visit on Day 4 + 1 (Visit 2) and on Day 8 + 1 for the third visit (Visit 3) at the end of treatment. Plasters were applied every 24 hours (h) ± 2 h. A further visit (Visit 4, follow-up) took place on Day 15 ± 2.

Patient population

It was planned to randomize 176 male and female patients (88 in each treatment group).

Number of Patients Randomized:	203 (102 in diclofenac group and 101 in placebo group)
Number of Patient Analyzed for Safety (safety analysis set):	199 (100 in diclofenac group and 99 in placebo group)
Number of Patients Analyzed for Efficacy (full analysis set):	169 (84 in diclofenac group and 85 in placebo group)
Number of Patients Analyzed for Efficacy (per protocol set):	154 (76 in diclofenac group and 78 in placebo group)
Number of Completers:	194 (99 in diclofenac group and 95 in placebo group)

Diagnosis and main criteria for inclusion

Male and female patients between 18 and 70 years old, who had a diagnosis of a single localized painful condition due to an ankle sprain and/or strain: the time between injury/onset of pain and treatment had to be less than 24 h, without any pre-treatment (with the exception of local cold treatment) and with an assessment of pain on motion ≥50 mm on the 100 mm VAS.

Test product, dose and mode of administration, batch number

	Diclofenac DEA medicated plaster	Comparator/placebo
Dosage	162.4 mg/plaster (corresponding to 140 mg diclofenac–sodium)	n/a
Duration of the therapy	7 days (Day 1 to Day 8)	7 days (Day 1 to Day 8)
Mode of administration	Topically (once daily)	Topically (once daily)
Batch number	P1280D0	P1225M9
Expiry date	April 2013	April 2013

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Criteria for Evaluation

Efficacy:

Change in pain intensity, at rest and on motion; proportion of patients achieving at least 50% pain relief on motion and proportion of patients achieving 20, 50 and 70% pain relief on motion were evaluated using a 100 mm VAS. Global efficacy was assessed by the Investigator using individual 8-point scales of score for Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C) and was assessed by the patient using a 7-point scale of score for Patient Global Impression of Change (PGIC).

Safety and tolerability:

Systemic safety and tolerability were evaluated on a 4-point scale and local tolerability was evaluated on a separate 4-point tolerability scale (Investigator and patient). Vital signs and incidence of adverse events (AEs), with particular attention to local reactions (i.e. erythema, itching and burning) were assessed.

Statistical methods

Primary analysis:

The primary analysis was performed using an Analysis of Covariance (ANCOVA) for each time point, with baseline pain intensity on motion as a covariate and treatment and country as factors in the model. The country-by-treatment interaction was not included in the primary analysis model, but was investigated in an exploratory model separately. Least square means were presented for each of the two treatment groups. In addition, an estimate of the treatment effect (diclofenac minus placebo) was presented together with a two-sided 95% confidence interval for the difference and a p-value for the test for significance of the difference.

Secondary analysis:

The change in pain intensity at rest and on motion was analyzed using ANCOVA, as for the primary analysis. In addition, descriptive statistics of the actual values and of the changes from baseline in VAS score were presented by time point and treatment group. The Wilcoxon Rank Sum test was used for analysis of the CGI-S, CGI-C and PGIC assessments and for the amount of rescue medication. For the CGI-C and PGIC assessments, the number and percent of patients falling into each category (score) were summarized by treatment group. A shift table was produced for the CGI-S scores, by treatment group. Proportion of patients achieving: at least 50% pain relief on motion, patients achieving 20%, 50%, 70% pain relief on motion, patients using rescue medication and withdrawal due to treatment failure were analyzed by the number and percent of patients reaching each endpoint and were presented by treatment group. The proportion of patients reaching each endpoint was compared between the two treatment groups using Fisher's Exact test. Analysis of time to 50% pain relief on motion, first rescue medication and withdrawal due to treatment failure were summarized descriptively using Kaplan-Meier estimates by treatment group.

Safety data:

Systemic safety and treatment tolerability and presence of erythema, itching and burning were analyzed by the number and percent of patients falling into each score category and summarized by time point and treatment group. In addition, for each time point, the systemic safety and treatment tolerability scores were compared between treatment groups using a Wilcoxon Rank Sum test.

Adverse events: Only treatment-emergent AEs (TEAEs) were reported and were summarized by relationship to investigational medicinal product, as well as by severity. All summaries presented for TEAEs were repeated for treatment-emergent serious AEs and TEAEs of special interest. All AEs were listed. There were no statistical comparisons for AEs between the two treatment groups.

Vital signs and other observations related to safety: Physical examinations, including the assessment of physical abnormalities and vital signs (blood pressure and heart rate [HR]), were performed. Vital sign data was presented by summaries of actual values and change from baseline by parameter and time point. There were no statistical comparisons between the two treatment groups. Physical examination and pregnancy test data were listed only.

Sample size calculation:

A sample size of 70 patients in each treatment group was calculated to give 90% power to detect a difference in mean VAS score of 10 mm, assuming a common standard deviation of 18 mm, using a two sided treatment t-test at the 5% two-sided significance level. Allowing for 20% drop out rate, it was planned to recruit a total of 88 patients in each treatment group, in order to provide 70 completers per group. Therefore the total number to be recruited in the study was 176 patients, expecting a total of 140 completers.

SUMMARY

Efficacy results

- For the primary endpoint of change in pain intensity on motion from baseline to Day 4, no statistically significant difference was observed between the diclofenac and placebo groups.
- For change in pain intensity on motion from baseline to Day 8 and change in pain intensity at rest from baseline to Days 4 and 8, no statistically significant difference was observed between the diclofenac and placebo groups.
- For the proportion of patients achieving at least 50% pain relief on motion by Day 4, no statistically significant differences were observed between the diclofenac and placebo groups.
- For the proportion of patients achieving at least 50% pain relief on motion at any point during the study, no statistically significant differences were observed between the diclofenac and placebo groups. A difference was observed between the two treatment groups on Days 2 and 3, with a higher proportion of responders reported in the diclofenac group compared to the placebo group on both days, however, the observed differences on Days 2 and 3 have not been statistically tested. At later time points, the proportions of responders for at least 50% pain relief on motion were either similar between the two treatment groups or higher in the placebo group.
- For time to achieve 50% pain relief on motion during the study, a higher proportion of patients achieving 50% pain relief was observed after 1 day and after 2 days. At later time points, the proportion of patients achieving 50% pain relief on motion was lower in the diclofenac group.
- For proportion of patients achieving at least 20% and at least 70% pain relief on motion during the study, there were no marked differences between the diclofenac and placebo groups.

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- For rescue medication consumption, no statistically significant differences were observed between the diclofenac and placebo groups for total amount of rescue medication used and a similar proportion of patients in each treatment group used rescue medication during the study. The time to first rescue medication was also similar in each treatment group.
- For Investigator and patient assessments of global efficacy at the end of treatment, no statistically significant differences were observed between the diclofenac and placebo groups for any of the analyzed parameters; change in CGI-S, CGI-C and PGIC.
- Only one patient withdrew prematurely from the study due to treatment failure. The patient was in the placebo group and withdrew due to treatment failure 2 days after randomization.

Safety results

A slightly lower proportion of patients were reported with TEAEs in the diclofenac group compared with the placebo group during the study. Overall, the most commonly reported TEAEs by System Organ Class (SOC) were general disorders and administration site conditions, with a lower proportion of patients in the diclofenac group than in the placebo group reported with TEAEs within this SOC. Overall, the most commonly reported TEAEs were application site pruritus, application site burning and application site erythema, and these TEAEs were reported with similar incidences in both treatment groups, with the exception of application site erythema, which was reported in a higher proportion of patients in the placebo group compared with the diclofenac group.

The proportion of patients reported with at least one treatment-related TEAE was similar in both treatment groups. The most commonly reported treatment-related TEAEs were application site pruritus, application site burning and application site erythema. For application site erythema, there was a lower proportion of patients in the diclofenac group who reported a treatment-related TEAE, compared to the placebo group. For application site pruritus and application site burning, the proportions of patients with treatment-related TEAEs were similar in each of the two treatment groups.

Only one patient prematurely discontinued the study due to a TEAE. The patient with the TEAE leading to study discontinuation was in the placebo group and was reported for blister, which was mild in severity.

The majority of TEAEs were mild in severity. All TEAEs of moderate severity were in the SOC general disorders and administration site conditions, with a lower proportion of patients in the diclofenac group reported with moderate TEAEs within this SOC. One patient in the diclofenac group was reported with a severe TEAE (application site erythema) and no severe TEAEs were reported in the placebo group.

No patients in either treatment group were reported with TEAEs leading to death, serious TEAEs or with TEAEs of special interest during the study.

There were no notable differences in changes from baseline at any time point for vital signs parameters for either of the treatment groups. Only one patient reported a TEAE related to vital signs parameters (diclofenac group; increased HR).

Physical examination data was listed only. Abnormal physical examinations, which were either new or aggravated since baseline, were reported in three patients during the study (two patients in the diclofenac group and one patient in the placebo group). No pregnancies were reported during the study.

Conclusions

The results of this study indicate that Z7202, a diclofenac DEA medicated plaster suitable for once daily application, did not have an effect greater than placebo for the primary analysis endpoint. No statistically significant difference was observed between the two treatment groups for change in pain intensity on motion from baseline to Day 4, nor in any of the secondary endpoints for either the Investigator or patient assessments during or at the end of the 7-day treatment period. The high placebo effect is believed to be the only suitable explanation to explain the results of this study.

Z7202 was safe and well tolerated in this study.

Date of the report

24 April 2013