2. CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor Company **Zambon SpA**	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
Name of finished product Z7202	PART: [……]	
Name of active ingredient Diclofenac diethylamine (DEA)	VOLUME: [……] PAGE: [……]	

Title of the study

EFFICACY, TOLERABILITY AND SAFETY OF Z7202, DICLOFENAC MEDICATED PLASTER IN COMPARISON WITH MARKETED DICLOFENAC MEDICATED PLASTER IN THE LOCAL TREATMENT OF POST-TRAUMATIC PAINFUL CONDITIONS

Study Code: Z7202L02 EudraCT number: 2010-022736-37

Principal Investigators and study sites

The study was conducted at 30 clinical sites in Czeck Republic, Slovakia and Hungary. Principal Investigator and overall study coordinator: Dr. Neumann in Czech Republic. A complete list of the clinical sites is found in Appendix 16.1.4 to this clinical trial report (CTR).

Publication (reference)

Unpublished (2012)

Study Period:	***Phase of Development***
19 April 2011 (First Subject In) / 07 October 2011 (Last Subject Out)	Phase III

Objectives

Primary Objective:

To assess the clinical efficacy of diclofenac DEA medicated plaster (test), versus diclofenac HEP medicated plaster (reference), on spontaneous pain intensity at rest related to post-traumatic painful conditions (due to sprains/strains/contusions), detected by a 100 mm Visual Analogue Scale (VAS), on Day 5 (Patient Diary).

Secondary Objectives:

- to assess the clinical efficacy of diclofenac DEA plaster in terms of:
  - reduction of spontaneous pain at daily activities on Day 8
  - reduction of spontaneous pain at rest on Day 8
  - rescue medication consumption
- to assess global efficacy of the therapy at the end of the treatment
- to assess systemic safety and tolerability of the therapy
- to assess local tolerability of the study treatments.

Study design and Methodology

Multi-centre, multinational, active-controlled, single-blind, randomised, parallel-group study

Patients with a diagnosis of single localised post-traumatic painful conditions in the previous 24h were randomised to either diclofenac DEA (test) or diclofenac HEP (reference) treatment group, according to the study randomisation list. The two medicated plasters were applied for 7 days: diclofenac DEA once daily (o.d.) and diclofenac HEP twice daily (b.i.d.). Patients were not aware of the study medication received and completed a patient's diary for 8 days to evaluate pain intensity, PGIC score, systemic and local tolerability to the product. Patients were requested to return to the clinical centre for study visits on day 5 and day 8 (end of treatment), and then after one week for a follow-up visit. Additional evaluations for secondary endpoints were reported in the case report form (CRF) by the investigator.

Subject population

Number of Subjects Planned:	*348*
Number of Subjects Randomised:	359 (253 Males/106 Females)
Number of Subject Analysed for Safety:	359 (181 in Test Group and 178 in Reference Group).
Number of Subjects Analysed for Efficacy (Full Analysis Set):	356 (180 in Test Group and 176 in Reference Group)
(Per Protocol Set):	333 (169 in Test Group and 164 in Reference Group)
Number of Completers:	353 (179 in Test Group and 174 in Reference Group)

Diagnosis and main criteria for inclusions

Diagnosis: Single localised post-traumatic painful condition.

Main inclusion criteria: Male or female patients, 18-70 years old inclusive with a diagnosis of single localised post-

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traumatic painful condition (the time between injury and treatment had to be less than 24 h, without any pre-treatment, with the exception of local cold treatment); spontaneous pain at rest ≥ 50 mm on the 100 mm VAS.

Main exclusion criteria: Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients including to adhesives; history of anaphylaxis to drugs or allergic reactions, in particular, history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) to aspirin or other non steroidal anti-inflammatory drugs (NSAIDs) and to acetaminophen (paracetamol); patients with neuropathic pain (e.g. neuropathic low back pain, diabetic neuropathy, post-herpetic nevralgia), osteoarthritis pain, fibromyalgia; history of psychosis (e.g. schizophrenia or psychotic depression) or major depression (requiring treatment); diagnosis including dementia, anxiety, mental retardation; multiple sclerosis, Parkinson's disease, restless legs syndrome; significant kidney or liver disease; history of gastrointestinal ulcer or bleeding; blood coagulation disorders; skin conditions affecting the site of application (e.g. wound, eczema, weeping dermatitis); open lesion or serious injury, including a fracture, nerve injury and a tear of ligament, muscle or cartilage; use of paracetamol within 24 h before the inclusion; use of aspirin or NSAIDs within 36 h before the inclusion; use of topical medications applied to the painful region within 7 days before the inclusion; use of opioids within 7 days before the inclusion; use of corticosteroid drugs by any route of administration within 30 days before the inclusion; use of myorelaxant drugs within 24 h before the inclusion; use of any physical therapy (physiotherapy and kinesis-therapy) apart local cold application within 48 h before the inclusion; pregnant or lactating women, or women of childbearing age not using a reliable method of contraception, or women of not child-bearing potential if not permanently sterilised or if not in post-menopausal status for at least two years.

Test product, dose and mode of administration, batch number

	Test product	**Comparator (Reference)**
Study product	Diclofenac DEA* plaster	Diclofenac HEP* plaster
Dose active ingredient/plaster	162.4 mg corresponding to 140 mg diclofenac sodium	180 mg corresponding to 140 mg diclofenac sodium
Dosage	Once a day	Twice a day
Duration of the therapy	7 days	7 days
Mode of administration	Cutaneous	Cutaneous
Batch number	P1280D0	1005111
Expiry date:	April 2013	May 2013

*Note: * DEA: diethylamine; HEP: Hydroxyethylpyrrolidine (epolamine)*

Criteria for Evaluation

Efficacy

Primary Endpoint: Comparison of the DEA medicated plaster (test) versus diclofenac HEP medicated plaster (reference) in terms of change in spontaneous pain intensity at rest, from baseline to Day 5, evaluated by using a 100 mm VAS.

Secondary Endpoints: Comparison between treatments in terms of :

- change in spontaneous pain intensity at daily activities from baseline to Day 8, evaluated using a 4-point scale ;
- change in spontaneous pain intensity at rest from baseline to Day 8, evaluated using a 100 mm VAS;
- time to 50% pain relief;
- proportion of patients achieving 50% pain relief (i.e. responders);
- time to first rescue medication and total amount of rescue medication;
- proportion of withdrawn patients and time to withdrawal due to treatment failure;
- global efficacy evaluation by both investigator and patient at the end of the treatment (Day 8);

Safety Endpoints:

1. systemic safety and tolerability assessed by both the investigator (visit 2, 3 and 4) and the patient at Day 5 and Day 8;
2. local tolerability assessed by the patient (erythema, itching and burning) every day during the treatment period and by the investigator (erythema) on Visit 3 and Visit 4;
3. incidence of adverse events

Statistical methods

Primary analysis: The VAS change from baseline (Day 1) to Day 5 was compared between treatments by ANCOVA, with the factors treatment and centre as fixed effects and the baseline pain intensity at rest as covariate. Non-inferiority of the Test in comparison with the Reference treatment was assumed if the lower confidence limit of the 95% two-sided confidence interval of the residual difference between treatments was greater than, or equal to, the value $-\Delta$ (- 6mm).

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Analysis was perfomed on the Full Analysis Set (FAS) and Per Protocol (PP) population. In the FAS, missing data were replaced by the multiple imputation (MI) method under missing at random (MAR) assumption (primary analysis) and by the worst case (WC) method (sensitivity analysis).

Secondary analysis: VAS change from baseline (Day 1) to Day 8 was compared between treatments by ANCOVA as detailed for the primary analysis. Non-inferiority test was performed as described above. Spontaneous pain at daily activities, CGI and PGIC scores were compared between treatments by Wilcoxon rank-sum test. The proportion of responders was compared between treatments using Fischer exact test. Time to 50% pain relief and time to rescue medication were compared between treatments using Kaplan-Meier survival analysis (with a log-rank test).

Safety data: Pretreatment adverse events and treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Authorities (MedDRA) version 14.1 and listed. TEAEs were summarised in frequency tables, by treatment, seriousness and severity. Systemic safety/tolerability scores and local tolerability scores were summarised in tables by treatment and study day. Score distribution was compared between treatments by Wilcoxon rank-sum test. Clinical laboratory results were summarised in shift tables. Vital sign results were summarised by descriptive statistics.

SUMMARY

Efficacy results

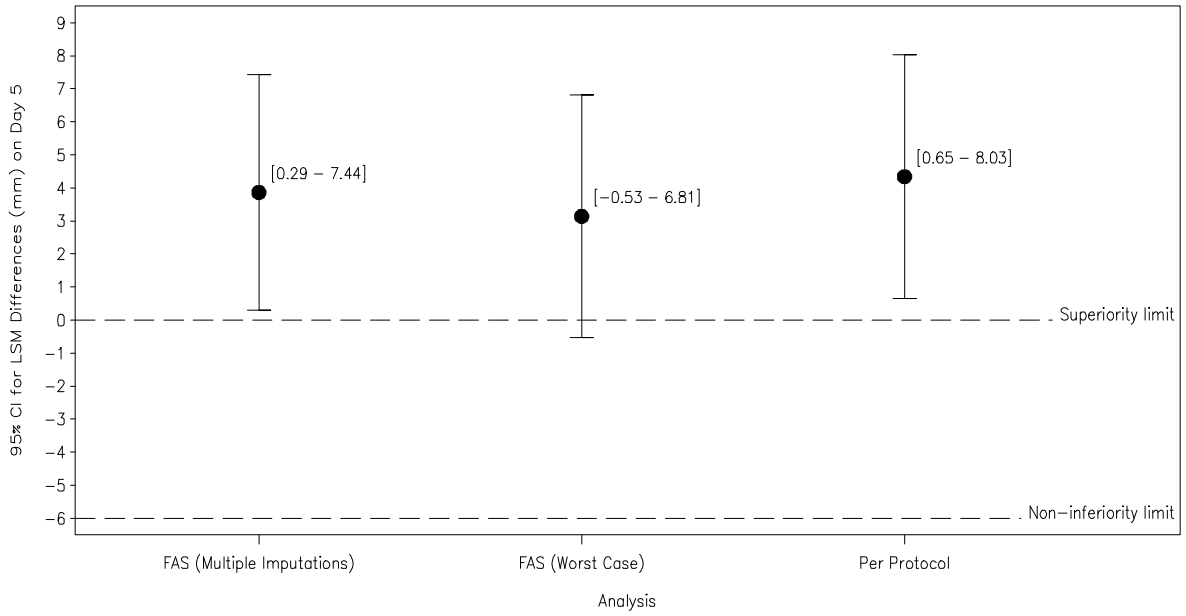
Primary endpoint:

Mean (±SD) VAS values on Day 1, Day 5 (Primary Endpoint), Day 8 (Secondary Endpoint) and changes from baseline are summarised by treatment for the Full Analysis Set (FAS) and Per Protocol (PP) population in the table below:

Table 1 Pain intensity at rest (100 mm VAS) – Change from baseline to Day 5 and Day 8

Population	Assessment time	Diclofenac DEA		Diclofenac HEP	
		Mean±SD	Change	Mean±SD	Change
Full Analysis Set	Day 1 (baseline)	72.6±10.3	-	73.5±10.1	-
	Day 5	31.5±21.7	41.0±22.3	35.2±23.3	38.4±22.7
	Day 8	14.4±18.4	58.4±20.5	18.6±21.8	55.1±21.4
Per Protocol	Day 1 (baseline)	72.6±10.2	-	73.7±10.2	-
	Day 5	31.3±21.8	41.4±22.3	35.5±23.3	38.2±22.7
	Day 8	14.1±18.5	58.8±20.3	18.6±21.9	55.1±21.4

A decrease in pain intensity at rest from baseline (Day 1) to Day 5 and to study end was clearly observed in both treatment groups and both populations. The 95% Confidence Intervals for least square mean differences between diclofenac DEA and diclofenac HEP on Day 5 are presented in the figure below:



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The non-inferiority test was fully satisfied. In fact, change in spontaneous pain from baseline to Day 5 for Test was not inferior, or was even superior, to that of the Reference. The analysis performed on the FAS and on the PP population resulted in superiority of diclofenac DEA with respect to diclofenac HEP (95% CI: [0.29-7.44] p=0.0341 and [0.65-8.03] p=0.0211, respectively). The test performed on the FAS for the sensitivity analysis resulted in non-inferiority of diclofenac DEA versus diclofenac HEP (95% CI:[-0.53-6.81] p=0.0932).

Secondary endpoints:
Results of the analysis on pain intensity at rest in the FAS and in the PP population showed the superiority of diclofenac DEA on diclofenac HEP change from baseline to the end of treatment (95% CI: [1.54-8.22] p=0.0043 and [1.68-8.59] p=0.0037, respectively). Sensitivity analysis in the FAS confirmed non-inferiority of Test vs. Reference (95% CI: [-0.94-6.15] p=0.1490) also after 7 days of treatment.

Number of responders (FAS: 87.2% vs. 81.3%, diclofenac DEA and diclofenac HEP respectively) and time to 50% pain relief (mean values FAS: 3.53±1.96 vs. 3.68±1.85 days diclofenac DEA and diclofenac HEP respectively) did not significantly differ between treatment groups and showed a median value of time to 50% pain relief of 3.02 and 3.91 days in the respective groups.

Assessment of spontaneous pain at daily activities using a 4-point scale showed that in both treatment groups there was an increased frequency of no pain and mild pain, and a decreased frequency of moderate and severe pain, at Day 5 and Day 8 compared with baseline. In the FAS, no statistically significant difference in score frequency between treatment groups was observed at any assessment time. In the PP population, on Day 2 difference in score frequency was statistically significant (p=0.0312), with a slightly higher frequency of moderate and mild scores for diclofenac DEA and of severe scores for diclofenac HEP.

For both treatments (FAS), according to CGI-S assessment, differences between treatment groups were not statitically significant. Overall, for 59.2% patients in the diclofenac DEA group and 51.2% patients in the diclofenac HEP group, pain very much improved on Day 8 compared with baseline. Difference in frequency of CGI-C scores between treatments was statistically significant in the FAS (p=0.0445), but not in the PP population (p=0.0621), whereas difference in frequency of PGIC scores between treatments was statistically significant in both populations (p=0.0437 for FAS and p=0.0224 for PP), with a slightly higher frequency of "Better and definite improvement" and "A great deal better and considerable improvement" scores in diclofenac DEA than diclofenac HEP group. No patients withdrew from the study for treatment failure.

Time to rescue medication was 18.1±36.8 hours for diclofenac DEA (20.0% of patients) and 20.4±41.0 hours for diclofenac HEP (26.7% of patients) in the FAS. Kaplan-Meier survival curves show a better trend for diclofenac DEA than diclofenac HEP in time to rescue medication during the study period, although the differences observed were not statistically significant (log-rank test p-value≥0.1448). No significant difference in the amount of rescue medication at Day 5 and at the end of the study was observed for the FAS, while in the PP population a higher amount was taken by the patients in the diclofenac DEA group with a statistically significant difference between treatments at Day 5 (p=0.0490).

Safety results

Ninety three (93) treatment-emergent AEs (TEAEs) were experienced by 50 (27.6%) patients in diclofenac DEA group; 121 TEAEs were experienced by 60 (33.7%) in diclofenac HEP group; 75 (21.5%) of the TEAEs reported in diclofenac DEA group and 96 (27.0%) in diclofenac HEP group were deemed related to study treatment. The most common related TEAEs (> 10.0%) were with diclofenac DEA and diclofenac HEP: "application site pruritus" (17.1% and 19.1% patients, respectively), "application site erythema" (11.6% and 11.8% patients, respectively) and "skin burning sensation" (4.4% and 12.4% patients, respectively) from local tolerability scores reported by the patients in the daily diary. The majority of TEAEs were mild. One serious TEAE was reported for one patient (0.6%) in diclofenac HEP group: bone sarcoma was diagnosed during patient's examination and led to study discontinuation. An additional patient discontinued the study in diclofenac HEP group for skin irritation and burning.

No significant differences between treatments in frequency of local erythema scores were found by the investigators. Similarly, patients' assessment did not result in significant differences in erythema and itching scores. However, distribution of burning scores was significantly different between the two plasters on Day 2 (p=0.0160), Day 5 (p=0.0094), and Day 7 (p=0.0269), due to a higher frequency in the diclofenac HEP group.

Systemic safety and tolerability of the applied plasters was rated as "Excellent" and "Good" for the majority of the patients. The difference in frequency scores between treatments was not significant according to the investigators' assessment. As for the patients' assessment, difference between groups was statistically significant both at Day 5 and Day

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8 ($p \leq 0.0456$), with more patients in the diclofenac DEA group rating safety and tolerability as "Excellent" and more patients in diclofenac HEP group rating it as "Good".

Clinical laboratory test results were in general within normal ranges or judged not clinically significant by the investigators. A few clinically significant abnormalities in clinical laboratory tests were already present at screening or were associated to concomitant diseases (e.g infections) assessed as unrelated to study treatment. Only one increase in ALT value was observed in one patient in the diclofenac HEP group at final visit, and was reported by the investigator as related to study treatment. Overall, clinical laboratory results did not give rise to any safety concern.

Conclusions

The present study in subjects with localised post-traumatic painful conditions (sprain/strain/contusion) has demonstrated the non-inferioritiy (or even the superiority) of the diclofenac DEA medicated plaster in comparison with the diclofenac HEP plaster, in terms of pain reduction from baseline to Day 5 and to the end of the treatment (Day 8). A comparable efficacy of the two plasters was confirmed by all the study assessments. Notably, diclofenac DEA results have been obtained with a single daily dose versus a twice daily dose regimen of the marketed reference.

The tolerability profile of the two plasters was good, confirming the results observed in other studies with topical NSAIDs formulations.

The clinical efficacy results, together with the favourable tolerability profile, suggest that the novel diclofenac DEA medicated plaster could offer a valid alternative for the treatment of localised injuries, reducing the number of applications per day, thus increasing patients' compliance and adherence to treatment, and avoiding the gastrointestinal side effects associated with the oral administration.

Date of the report

19 October 2012