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Efficacy and safety of Diclofenac sodium plaster in patients with acute pain of the limbs: a randomized, placebo and active-controlled, double-blind, parallel-group trial

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Abstract. – OBJECTIVE: The aim of the present study was to assess the safety and efficacy of Diclofenac sodium (DS) 140 mg medicated plaster *vs.* Diclofenac epolamine (DIEP) 180 mg medicated plaster and placebo plaster, for the treatment of painful disease due to traumatic events of the limbs.

PATIENTS AND METHODS: This was a multicenter, phase III study involving 214 patients, aged 18-65 years, affected by painful conditions due to soft tissue injuries. Patients were randomized to DS, DIEP or placebo arms and treated with once-daily application of the plaster for a total treatment period of 7 days. The primary objective was first to demonstrate the non-inferior efficacy of the DS treatment when compared to the reference DIEP treatment and second that both, test and reference treatments, were superior with respect to placebo. The secondary objectives included the evaluation of efficacy, adhesion, safety, and local tolerability of DS in comparison to both DIEP and placebo.

RESULTS: The mean visual analog scale (VAS) score decrease for pain at rest was higher in the DS (-17.65 mm) and the DIEP group (-17.5 mm) than in the placebo (-11.3 mm). Both active formulation plasters were associated with a statistically significant pain reduction compared to placebo. No statistically significant differences were observed between DIEP and DS plasters efficacy in relieving pain. Secondary endpoint evaluations supported the primary efficacy results. No serious adverse events (SAEs) were registered, and the most commonly detected adverse events were skin reactions at the application site.

CONCLUSIONS: The results showed that both the DS 140 mg plaster and the reference DIEP 180 mg plaster are effective in relieving pain and present a good safety profile.

Key Words:
Soft-tissue injury, Diclofenac sodium, Patch, plaster, Limbs, Double-blind, Safety.

Introduction

Painful conditions associated to soft-tissue injuries like strains, sprains, and contusions are common in people playing sport and frequently involve upper and lower extremities[1-3]. It is estimated that about 25% of all musculoskeletal system injuries and 50% of all sports-related injuries include ankle injuries[4]. Shoulder disorders are also relatively common: it is estimated that about 30% of people experience at least one episode of shoulder pain in their lives and that about 50% of the population presents shoulder pain annually[5]. In addition, muscular injuries are characterized by a series of events that may contribute to complications, such as recurrences or sequelae, leading to temporary or long-term disability[6]. For this reason, it is crucial to timely adopt appropriate strategies for pain management.

Currently, treatment recommendations for the management of acute pain and inflammation associated to soft tissue injuries include early use of oral non-steroidal anti-inflammatory drugs (NSAIDs)[7] together with rest, ice, compression or elevation (RICE)[8]. However, oral administration of NSAIDs is correlated with the risk of developing gastrointestinal side effects and related organ systems damage due to their high systemic absorption[9,10]. Among alternative approaches to oral NSAIDs administration, topical NSAIDs formulations have been developed to provide pain

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relief in acute conditions such as sprains, strains, and overuse injuries[11], keeping minimal systemic exposure[12].

Literature evidence demonstrated topical Diclofenac – a phenyl acetic acid derivative, non-steroidal anti-inflammatory drug, widely used as a potent anti-inflammatory, analgesic, and antipyretic agent – to be effective and well-tolerated in the management of painful conditions. Specifically, it exerts its analgesic and anti-inflammatory action by blocking prostaglandins (PGs) synthesis in body tissues through the inhibition of cyclo-oxygenase (COX), the enzyme that catalyzes the formation of PGs precursors (endoperoxides) from arachidonic acid[13,14]. Moreover, it was also demonstrated that topical Diclofenac formulations with sodium lotion, lecithin or epolamine gel or plaster have more efficacy with respect to oral Diclofenac formulations, providing significant pain relief in patients suffering from sports and soft tissue injuries involving ankle, knee or shoulder joints[15,16].

During the 1990s, topical administration of Diclofenac has been improved through the formulation of self-adhesive plasters to be applied on the site of painful joint or muscle. This self-adhesive dosage form allows the drug to be delivered through the skin, thus obtaining a local topical effect. Randomized Controlled Trials (RCTs) comparing different Diclofenac formulation plasters *vs.* placebo demonstrated the safety and efficacy of this therapeutic option for the management of acute pain conditions. Medicated plasters containing 140 mg Diclofenac sodium (DS) showed[17-19] to be effective in the treatment of pain due to acute impact injuries. Similarly, the 180 mg Diclofenac epolamine (DIEP) plaster demonstrated to be effective in treating sport injuries and minor soft tissue injuries[20,21] such as sprains, strains, and contusions[22,23]. In the above-mentioned RCTs, Diclofenac plasters were applied for seven consecutive days, or more, twice a day. Up to now, only few clinical studies[24-27] reported a different application regimen. In this scenario, Fidia Farmaceutici S.p.A. has developed a new formulation of DS medicated plaster for the treatment of acute musculoskeletal painful conditions to be used once a day.

DS medicated plaster is a self-adhesive dosage form that, when applied onto intact skin, delivers the drug through it providing a local effect. Specifically, the plaster is composed of three layers: a non-woven fabric backing layer inert to the components of the matrix layer, a self-adhesive matrix layer containing DS, and a mono siliconized paper as a protective liner to be removed prior to use. The self-adhesive matrix layer is a pressure sensitive adhesive prepared from a water-based polymeric dispersion composed by polyacrylate copolymer of methyl- and ethyl- esters of acrylic acid and methacrylic acid (Eudragit NE 40D), without adding organic solvent. The self-adhesive matrix is capable of bonding to the skin surface by applying a light pressure and, when detached, it does not leave any visually noticeable residue.

The aim of the present study was to assess the safety and efficacy of the new DS 140 mg medicated plaster *vs.* the reference DIEP 180 mg medicated plaster, or a placebo plaster, for the treatment of pain caused by acute traumatic events of the limbs.

Patients and Methods

Ethics and Informed Consent

The EQI7-16-02 protocol (EudraCT number: 2017-003526-32) was approved by the reference Ethic Committee of each participating center. The study was conducted following the tenets of the Declaration of Helsinki and in accordance with the guidelines on Good Clinical Practice (GCP).

Prior to being enrolled into the study and before any study-related activity, each patient's written informed consent was obtained following a fully written and verbal explanation of the nature of the study.

Study Population

According to the study protocol, patients aged 18-65 years, affected by painful condition due to acute traumatic events such as limbs injuries or contusions, were included. Presence of pain at rest in the injured area, defined by the patient as $\geq$ 40 mm and $\leq$ 80 mm on a 100-mm visual analog scale (VAS), was a key criterion for study inclusion.

Patients suffering from chronic pain for more than 3 months, experiencing fractures or severe trauma, or not being able to comply with the study requirements were excluded. Other key exclusion criteria were: the presence of concurrent skin disorders or open wounds in the area to be treated; history of allergic reactions or hypersensitivity to Diclofenac and/or to active or inactive excipients; pregnancy, lactation or refusal to use

a highly effective method of contraception; participation in concomitant trial. Pre-treatment of the target area with ice or cooling spray was allowed until 3 hours before the initiation of the study treatment. Use of pain relief drugs such as NSAIDs, oral corticosteroids, and intravenous corticosteroids was allowed if their use was discontinued 1, 2, and 4 weeks before study treatment initiation, respectively. Paracetamol use was required to be discontinued at least 8 hours before plaster application.

Study Design and Treatment

The present prospective randomized, double-blind, parallel-group, phase III clinical study was carried out in 16 investigational centers (based in Germany, Italy, and Hungary). Patient enrollment was completed in six months from May 2018 to October 2018. Eligible patients were equally randomized into three groups: the DS 140 mg medicated plaster (Fidia Farmaceutici S.p.A., Abano Terme, Italy) group, the DIEP 180 mg medicated plaster (IBSA Farmaceutici Italia S.r.l., Lodi, Italy,) group and the placebo plaster group.

The randomization list was prepared using a validated software by Sparc Consulting S.r.l. (Milan, Italy). Treatments (i.e., applications) started at the end of day 1, after baseline assessments and randomization. Treatments were administered once a day for 7 consecutive days, approximately 24 hours after the previous application. The investigator was blind to treatment identity. Except for the first application – which was performed in an open-label fashion by the "open" staff members – following applications were performed independently by the patient. Follow-up visits were performed at day 4 and day 8. RICE therapy was not allowed during the 3 hours prior to day 4 and day 8 visits and, when adopted, they were carefully monitored by investigators, checking patients' diaries. Rescue medication for pain relief (i.e., 500 mg paracetamol tablets), if necessary, were supplied by the Sponsor. The maximum permitted daily dose was 4 tablets.

Objective and Endpoints

The primary study objective was to demonstrate the non-inferior efficacy of the DS medicated plaster compared to the DIEP medicated plaster and that both active treatments provided greater pain relief than placebo (definition of non-inferiority is provided in the Statistical analysis section below). Treatment efficacy was assessed at day 4 as the mean change from baseline in VAS score for pain at rest (0 mm = no pain; 100 mm = maximum tolerable pain).

Secondary objectives were the evaluation of the efficacy of the 3 treatment arms in relieving pain (pain at rest and on movement), the use of rescue medication, and the global assessment of efficacy by patients. In addition, the adhesion to the site of application, the safety, and the local tolerability of the 3 treatments were compared.

At day 4 and 8, the investigated endpoints were: mean change from baseline in VAS score for pain at rest; the area under the curve (AUC) for pain at rest, calculated by means of the sum of pain intensity difference (SPID) and defining the pain intensity difference as the VAS score for pain at rest at all the post-baseline time points *vs.* baseline; mean change from baseline in VAS score for pain on movement; proportion of responder patients, defined as the ones experiencing a decrease ≥ 50% of baseline VAS score for pain at rest and on movement (a specific standardized movement was identified by the patient and the investigator as the most painful movement according to the injured limb site); global assessment of efficacy performed by patients based on a 7-points Clinical Global Impression – Improvement scale (CGI-I: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse); assessment of the adhesion to the site of application according to a percentage scale performed by both patient and "open" staff of the trial. Moreover, time to resolution (TTR) of pain at rest – defined as the time to achieve a VAS score ≤ 5 mm at each assessment, not followed by a value > 5 mm in the next assessment – and the proportion of patients that used rescue medication, as well as its administration during the entire study period, were detected.

Safety and tolerability endpoints were: summaries of treatment emergent adverse events (TEAEs) defined as adverse events that started during or after the first dose of study treatment; frequency of treatment discontinuation due to AEs; evaluation of symptoms such as local erythema, itching, burning, and pain at baseline, day 4, and day 8 according to a 4-points scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe); the investigator's and patient's opinion on local tolerability rated according to a 4-points scale (0 = poor, 1= fair, 2 = good, 3 = excellent) at day 4 and day 8; change of vital signs (systolic and diastolic

blood pressure, and heart rate) from baseline to day 4 and day 8; abnormalities in the physical examination.

Statistical Analysis

A sample size of 56 patients in each randomization group was calculated taking into account the following assumptions: a difference between the two active groups and the placebo group of 8 mm change in VAS score for pain at rest from baseline to day 4; a standard deviation of 14 mm; a significance level (α) of 0.05; an 85% power; the use of a two-sided *t*-test. Considering a 20% drop-out, a total of 210 patients had to be enrolled in the trial.

Primary and secondary endpoints, except for the safety ones, were evaluated in the intention-to-treat (ITT) cohort, which included all randomized patients who received at least one plaster application and performed at least one post-baseline assessment of efficacy. Primary endpoints were analyzed also in the modified intention-to-treat (mITT) population and in the per-protocol analysis set (PPAS). The mITT group included all patients in the ITT population but excluded all data of pain at rest and pain on movement (VAS) measured within 12 hours from the last intake of rescue medication (i.e., paracetamol). The PPAS group included ITT patients who also met all inclusion/exclusion criteria and who did not have any major protocol deviation. Patients included in the PPAS cohort were analyzed for secondary efficacy endpoints, whereas safety endpoints were evaluated in the safety analysis set (SAF), which included all patients receiving at least one dose of the study medication.

To investigate treatment efficacy based on VAS score change from baseline to day 4 (primary endpoint) and to other follow-up time-points (secondary endpoint), a mixed linear model was used. The analysis was performed considering VAS score change as dependent variable, treatment group and site of application as fixed factors of the model, and baseline VAS value for pain at rest as covariate. The Kenward-Roger method for adjusting degrees of freedom in an unstructured covariance matrix was used to assess the superiority of test and reference plasters over placebo and non-inferiority of test *vs*. the reference product[28]. Hypothesis testing for non-inferiority endpoint was analyzed only after the demonstration of superior efficacy in reducing the pain of both active treatments with respect to placebo ($p < 0.05$). The DS plaster was considered to yield a non-inferior efficacy with respect to DIEP plaster if the upper bound of the 95% confidence intervals (CI) of the difference between the least squares means (LSM) of test and reference plasters was ≤ 8 mm.

The secondary efficacy endpoints such as AUC for $SPID_{0\text{-}4d}$ and $SPID_{0\text{-}8d}$, change from baseline in VAS score for pain on movement at day 4 and day 8, comparison of the rescue medication consumption, and CGI were analyzed using analysis of variance (ANOVA). This analysis was performed considering treatment, site of treatment, visit, and VAS value at baseline as adjustment factors. The time to resolution (TTR) of pain at rest was analyzed by survival analysis according to Kaplan-Meier method and log-rank test[29,30]. Analysis of responder patients, adhesion, as well as safety variables (AEs, vital signs, tolerability, and physical examinations) were summarized by treatment groups using descriptive statistics. Treatment comparisons were assessed through one-way ANOVA for continuous variables and Chi-Square test or Fisher's exact test for categorical variables. Statistical analyses were performed on SAS statistical program (SAS-PC, version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patient Population

A total of 214 patients was enrolled and equally randomized to DS arm (n=71), DIEP arm (n=72) or placebo arm (n=71). None of the patients discontinued the study.

All randomized patients were included in both the SAF and the ITT datasets. One patient in the DS group and 2 patients in the placebo group applied an unscheduled number of medicated plasters and, therefore, were excluded from mITT dataset, which comprised 70 patients in the DS group, 72 in the reference group, and 69 in the placebo group. One patient in the DS group had major protocol deviations and was excluded from the PPAS dataset, which comprised 70 patients in the DS group, 72 in the reference group and 71 in the placebo group. All the patients were Caucasian and the characteristics at baseline were equally distributed. At baseline, the mean VAS score for pain at rest was 52.6 mm in the DS group, 50.5 mm in the reference group, and 49.6 mm in the placebo group, indicating a pain level of moderate intensity. Regarding patients' medi-

Table I. Characteristics of patients at baseline assessment in ITT set.

			Diclofenac sodium N=71	Diclofenac epolamine N=72	Placebo N=71
Sex	Male	n (%)	32 (45.1%)	38 (52.8%)	36 (50.7%)
	Female	n (%)	39 (54.9%)	34 (47.2%)	35 (49.3%)
Age (years)		Mean (SD)	37.80 (14.22)	39.49 (12.64)	37.59 (13.96)
Time from injury to Visit 1 (hours)		Mean (SD)	394.46 (464.58)	340.32 (415.22)	360.93 (441.52)
Site and side of injury	Right upper limb	n (%)	11 (15.5%)	19 (26.4%)	16 (22.5%)
	Right lower limb	n (%)	32 (45.1%)	26 (36.1%)	18 (25.4%)
	Left upper limb	n (%)	11 (15.5%)	12 (16.7%)	17 (23.9%)
	Left lower limb	n (%)	17 (23.9%)	15 (20.8%)	20 (28.2%)
RICE	No	n (%)	54 (76.1%)	51 (70.8%)	52 (73.2%)
	Yes	n (%)			
VAS, pain at rest (mm)		Mean (SD)	52.6 (9.5)	50.5 (6.7)	49.6 (6.7)
VAS, pain at movement (mm)		Mean (SD)	66.6 (12)	65.1 (9.3)	65.7 (8.7)
Patients with concomitant disease		n (%)	18 (25.4%)	16 (22.2%)	18 (25.4%)
Heart rate (bpm)		Mean (SD)	4.6 (9.4)	71.7 (8.2)	74.6 (9.7)
Systolic Blood Pressure (mmHg)		Mean (SD)	126.2 (12)	126.2 (12.5)	121.8 (12.4)
Diastolic Blood Pressure (mmHg)		Mean (SD)	79.1 (11)	80 (9.5)	78.8 (8.9)

Standard deviation (SD), visual analog scale (VAS).

cal history and clinical condition at baseline, no statistically significant differences were observed among the treated arms (Table I).

Efficacy Results

The decrease in the mean VAS score for pain at rest between baseline and day 4 (primary endpoint) was higher in DS (-17.65 mm) and in the DIEP (-17.5 mm) arms than in the placebo arm (-11.32 mm). Both active formulation plasters were associated with a significant pain reduction compared to placebo plaster (DS $p < 0.0098$; DIEP $p < 0.0096$). Comparison between DIEP and DS mean score change at day 4 showed no statistically significant difference (0.133 mm, $p = 0.96$). Since the upper bound of the 95% CI of the difference between adjusted means (i.e., 4.99 mm) was lower than the pre-specified limit of 8 mm, the DS had non-inferior efficacy with respect to the reference formulation (Table II). The results obtained in the other datasets were consistent with those observed in the ITT population.

Table III summarizes the results of secondary efficacy endpoints evaluated at day 4 and day 8 time-points. The AUC for $SPID_{0\text{-}4d}$ and $SPID_{0\text{-}8d}$ for pain at rest supported the results of the pri-

Table II. Primary efficacy endpoints: adjusted mean change of VAS score (mm) from baseline to day 4 in ITT population.

		Superior efficacy analysis			Non-inferior efficacy analysis		
	N	Adjusted mean change (95% CI)	Adjusted mean of difference (95% CI)	*p*-value	Adjusted mean change 95% CI	Adjusted mean of difference 95% CI	*p*-value
Diclofenac sodium	71	-17.65 (-21.56, -13.74)*	-6.33 (-11.1, -1.55)°	0.0098	-17.4 (-21.92, -12.87)*	0.133 (-4.72, 4.99)$^{+}$	0.96
Diclofenac epolamine	72	-17.5 (-21.15, -13.85)*	-6.18 (-10.84, -1.52)^	0.0096	-17.53 (-21.6, -13.45)*		
Placebo	71	-11.32 (-14.98, -7.66)*					

N: number; **p*-value < 0.0001; °Adjusted mean of difference between Test and placebo; ^Adjusted mean of difference between reference and placebo; $^{+}$Adjusted mean of difference between test and reference.

Table III. Secondary efficacy endpoints evaluated at day 4 and 8 after start of treatment in ITT population.

		Diclofenac sodium N = 71	Diclofenac epolamine N = 72	Placebo N = 71
AUC for pain at rest, SPID (mm)				
Day 4	Mean (SD)	-716.94 (997)	-695.10 (946.35)	-424.14 (908.52)
Day 8	Mean (SD)	-2,825.72 (2,621.75)	-3,044.40 (2,340.29)	-1,916.36 (2,531.16)
VAS for pain on movement (mm)*				
Day 4	Mean (SD)	-21.2 (19.5)	-22.3 (15.9)	-18.0 (16.3)
Day 8	Mean (SD)	-33.5 (22.8)	-37.9 (20.6)	-28.5 (19.1)
Responder patients				
Day 4	n (%)	15 (21.1%)	11 (15.3%)	9 (12.7%)
Day 8	n (%)	31 (43.7%)	45 (62.5%)	26 (36.6%)
Global assessment of efficacy°				
Day 4				
Improvement	n (%)	51 (71.8%)	68 (94.4%)	51 (71.8%)
No change	n (%)	20 (28.2%)	3 (4.2%)	18 (25.4%)
Worsening	n (%)	-	1 (1.4%)	2 (2.8%)
Day 8 Improvement	n (%)	56 (78.9%)	68 (94.4%)	54 (76.1%)
No change	n (%)	14 (19.7%)	4 (5.6%)	15 (21.1%)
Worsening	n (%)	1 (1.4%)	-	2 (2.8%)
Patch adhesion (%)^				
Day 4	Mean (SD)	76.94 (21.80)	86.48 (21.96)	80.67 (21.50)
Day 8	Mean (SD)	78.13 (24.28)	85.36 (20.93)	78.96 (23.09)

*VAS for pain on movement score changes from baseline; °CGI-I 7-points scale was summarized in 3 categories: improvement (including very much improved, much improved, minimally improved), No change and worsening (minimally worse, much worse, very much worse); ^evaluation of adhesion by "open" staff member were reported. Area under the curve (AUC), sum of pain intensity difference (SPID), visual analog scale (VAS).

mary endpoints. The mean value of $SPID_{0\text{-}4d}$ was higher in DS and DIEP groups than in the placebo group, showing a greater pain decrease from baseline, but not in a statistically significant manner. Differently, a statistically significant higher value of $SPID_{0\text{-}8d}$ was detected for DS ($p = 0.0313$) and DIEP ($p = 0.0075$) groups when compared to placebo. No statistically significant difference was observed between DS and reference plaster groups. Mean change in VAS score for pain at rest from baseline to any time-point assessment, other than day 4, showed greater pain reduction at every evaluation in all arms. Specifically, a statistically significant decrease from day 4 to day 8 in DS arms compared to placebo ($p < 0.0001$), as well as from day 3 to day 8 in DIEP arms compared to placebo ($p < 0.0001$) was recorded. At day 8, mean change in VAS score was -26.8 ± 19.4, -29.8 ± 17.5, and -21.2 ± 17.6 for DS, DIEP, and placebo plasters, respectively. Except for day 7, no statistically significant difference was observed between DS and DIEP plaster during the treatment period (Figure 1).

The adjusted mean VAS score for pain on movement significantly decreased from baseline to both day 4 and day 8 assessments in all treatment groups ($p < 0.0001$), reflecting mean score reduction of pain at rest. At day 4, the adjusted mean difference between the DS and the placebo group was -3.4410 mm (95% CI, -8.3630 to 1.4811 mm, $p = 0.1695$), whereas the adjusted mean difference between the DIEP and the placebo group was -5.4786 mm (95% CI, -10.3549 to -0.6023 mm, $p = 0.0279$) (Figure 2). At day 8, the adjusted mean difference between the DS and the placebo group was -5.2973 mm (95% CI,

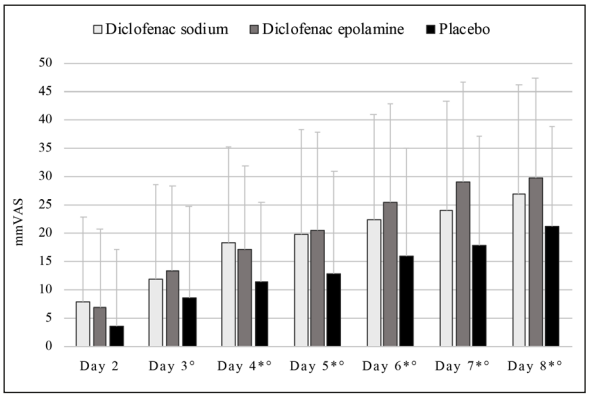

Figure 1. Results of VAS reduction from baseline for pain at rest in the ITT population. Mean and standard deviation (SD) were reported in bars. *p-value <0.05 between DS and placebo; °p-value <0.05 between DIEP and placebo.

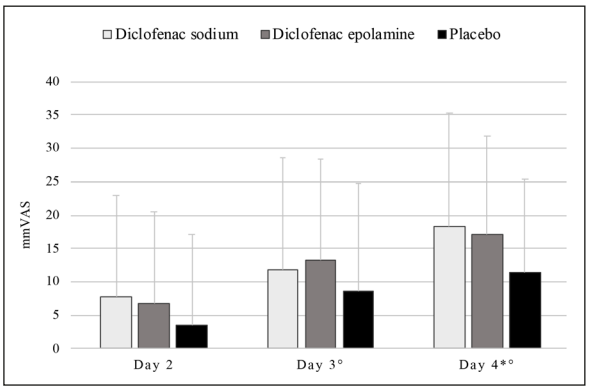

Figure 2. Results of VAS reduction from baseline for pain at rest in the ITT population. Mean and standard deviation (SD) were reported in bars. *p-value <0.05 between DS and placebo; °p-value<0.05 between DIEP and placebo.

-11.2589 to 0.6642 mm, $p = 0.0813$), whereas the adjusted mean difference between the DIEP and the placebo group was -10.6762 mm (95% CI, -16.5823 to -4.7700 mm, $p = 0.0005$). No statistically significant differences were highlighted between DS and DIEP plaster at both day 4 and day 8.

The proportion of responder patients at day 4 was slightly higher in the DS group than in the DIEP and placebo groups ($p = 0.3781$), whereas the proportion of responder patients at day 8 in the DIEP group was significantly higher than in the DS and placebo groups ($p = 0.0053$).

More than 70% of all patients reported a CGI-I improvement in terms of efficacy at both day 4 and day 8. Globally, at day 4, a judgment of 'no change' was reported by less than 30% of patients and none of them reported worsening judgments. At day 8, 19.7% of patients in the DS group, 5.6% in DIEP group, and 21.1% in the placebo group reported a "no change" impression compared to baseline. Only 1.4% of patients in the DS group, none of patients in the reference group, and 2.8% in the placebo group had a judgment of 'minimally worse'. In all the treated arms, an improvement was associated to the day 8 evaluation ($p < 0.0001$) and no statistically significant differences were observed among the groups for the efficacy assessment.

As reported in Table III, evaluation of adhesion performed by patients was in line with the one performed by "open" members of the staff.

A better trend was detectable in the TTR of pain at rest for the DS treated patients, showing earlier and wider pain resolution than DIEP and placebo arms. Patients who achieved resolution of pain at rest were 11 (15.5%), 8 (11.1%), and 7 (9.9%) for DS, DIEP, and placebo groups, respectively ($p = 0.62$).

In ITT population, the number of patients using rescue medication in the entire study period was higher in both reference (10 patients, 13.9%) and placebo groups (10 patients, 14.1%) than in the DS group (5 patients, 7.0%). The difference among groups was not statistically significant ($p = 0.3298$). The results obtained in mITT and PPAS datasets were consistent with those observed in the ITT population.

Adverse Events and Tolerability

Overall, 25 TEAEs were recorded in 13 patients. Among them, treatment related TEAEs were reported in 5 patients (7.0%) in the DS group, in 3 (4.2%) in the reference group and in 4 (5.6%) in the placebo group. No serious adverse events (SAEs) or severe TEAEs were reported and none of the patients discontinued the study due to TEAEs. The most common treatment related TEAEs, involving 4 patients (5.6%) in DS arms, 2 (2.8%) in DIEP arms, and 3 (4.2%) in placebo arms, were skin burning sensation and pruritus in the site of application.

In all treatment groups, no statistically significant changes were detected from baseline to both day 4 and day 8 in erythema, itching, and burning rating. No patients experienced severe events. At baseline, most patients in all groups had no evidence of irritation (90.1% of patients in the DS group, 87.5% in the reference group, and 87.3% in the placebo group). Itching and burning were present at baseline in less than 10% of patients in any treatment group.

Regarding the evaluation of pain, in all groups, an improvement in pain relief from baseline to both day 4 and day 8 was found. In the DS group, 52.1% and 62% of patients expressed a pain score of 0 (absent) at day 4 and day 8, respectively. For the reference group, absence of pain was described in 56.9% of patients at day 4 and 77.2% of patients at day 8. As per DS and reference group, increasing results were highlighted for placebo (52.1% day 4, 62% day 8).

Overall, investigators and patients expressed concordant opinions on local tolerability of the treatment. Indeed, approximately 90% of both patients and investigators reported tolerability as excellent or good (Table IV). Both the DS and the DIEP plasters were considered well tolerated since no significant differences were found in terms of changes in vital signs and physical

Table IV. Investigator's and patient's opinion on local tolerability during the study in SAF population. Data were reported as number and percentage

	Diclofenac sodium (N = 71)		Diclofenac epolamine (N = 72)		Placebo (N = 71)	
	Investigator	Patient	Investigator	Patient	Investigator	Patient
Day 4						
Poor	1 (1.4%)	0 (0%)	2 (2.8%)	2 (2.8%)	2 (2.8%)	2 (2.8%)
Fair	5 (7.0%)	8 (11.3%)	4 (5.6%)	4 (5.6%)	4 (5.6%)	6 (8.5%)
Good	30 (42.3%)	28 (39.4%)	26 (36.1%)	31 (43.1%)	30 (42.3%)	30 (42.3%)
Excellent	35 (49.3%)	35 (49.3%)	40 (55.6%)	35 (48.6%)	35 (49.3%)	33 (46.5%)
Day 8						
Poor	2 (2.8%)	1 (1.4%)	1 (1.4%)	2 (2.8%)	3 (4.2%)	4 (5.6%)
Fair	5 (7.0%)	4 (5.6%)	3 (4.2%)	4 (5.6%)	7 (9.9%)	7 (9.9%)
Good	31 (43.7%)	36 (50.7%)	22 (30.6%)	19 (26.4%)	26 (36.6%)	24 (33.8%)
Excellent	33 (46.5%)	30 (42.3%)	46 (63.9%)	47 (65.3%)	35 (49.3%)	36 (50.7%)

examinations from baseline to day 4 and day 8 (data not shown). For all safety endpoints, the results in the SAF group were consistent with those observed in the ITT population.

Discussion

Topical NSAIDs showed to be effective in treating acute musculoskeletal painful conditions, providing analgesic effect at the application site while maintaining low systemic circulation[16,31]. Plasters are self-adhesive medicated bandages that allow the maintenance of stable plasma levels of the active substance and, in contrast to the traditional topical creams, gels, or solutions, enable a continuous drug release[32].

The results of this randomized, double-blind, parallel-group, placebo-controlled, multinational, multicenter trial show that 140 mg DS medicated plaster is safe and effective for treating mild-to-moderate acute pain due to soft tissue injuries of the limbs. It has been demonstrated that a daily application of DS plaster for one week is associated with a statistically significant pain reduction compared to placebo ($p < 0.0098$) and has comparable efficacy to a reference 180 mg DIEP plaster ($p = 0.9576$). DS, as well as DIEP plasters, provided a greater pain relief at rest after 4 days from initial treatment than placebo (DS: -17.65 mm, DIEP: -17.5 mm, placebo: -11.32 mm in the VAS scale). Significant pain reduction at rest, assessed from day 4 to the end of treatment for patients treated with DS, supports the results of the primary endpoints. Both, the AUC decrease evaluated by means of SPID at day 4 and day 8 and the mean decrease in VAS score of pain at movement, confirmed the action of DS plaster application on pain relief. Importantly, during the treatment period, only 7% of patients in the DS arms took rescue medication (i.e., paracetamol), whereas, in the DIEP and the placebo arms, rescue medications were taken in the 13.9% and 14.1% of patients, respectively.

The results of the present study are consistent with those of previously published studies[17-20,23,33] comparing Diclofenac medicated plasters with placebo, showing superior efficacy of the drug and an overall pain reduction at day 7 ranging between 26% and 88%, according to a VAS scale. These studies[17-20,23,33] demonstrated that Diclofenac topical treatments, both DS and DIEP, were effective in the treatment of soft tissue injuries when administrated twice daily (every 12 hours) for a total treatment period of 7 or 14 days. Differently, the medical benefits reported in the present study were obtained with a once-daily application of DS plaster. A single application per day is advantageous for patients because it increases patients' compliance to treatment, and it allows saving costs and time.

Regarding safety, topical Diclofenac therapy, as well as other NSAIDs, presents a low incidence of systemic adverse events. The most common treatment-related adverse events are mild and transient local skin reactions[34]. In the present study, the DS plaster was well tolerated and demonstrated a placebo-like safety profile. No SAEs were registered and the most common treatment-related TEAEs were skin-related disorders involving less than 6% of patients. Literature[20] review on adverse events related to the

use of Diclofenac medicated plaster twice-daily shows an incidence rate of 14%. They are described as mainly represented by skin-related adverse events but, especially in the case of treatments lasting 14-days, they might include also gastrointestinal reactions or symptoms[33,35]. Of note, in the present study, safety results of DS medicated plaster were reported independently by investigators and patients. Approximately 90% of both patients and investigators described a constant local tolerability as excellent or good.

Conclusions

The newly developed 140 mg Diclofenac sodium medicated plaster is effective in reducing pain, caused by traumatic events, when applied once a day for one week. Moreover, it is a safe and well-tolerated option for treating sprains, strains and contusions of the limbs. Overall, the benefits derived from the treatment of soft tissue injuries with DS medicated plaster overcome the fully reversible potential risk. Future trials characterized by longer follow-ups would be useful to investigate long-term efficacy of DS medicated plasters and their possible application for chronic pain management.

Conflict of Interest

The authors declare that they have no conflict of commercial interest. Beatrice Barbaro and Nicola Giordan are employees of Fidia Farmaceutici S.p.A. All authors state, however, that Fidia Farmaceutici S.p.A. did not participate in the collection, analysis, or interpretation of data, or in the writing of the manuscript.

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Ethics Approval

The EQI7-16-02 protocol (EudraCT number: 2017-003526-32) was approved by the reference Ethic Committee of each participating center. The study was conducted following the tenets of the Declaration of Helsinki and in accordance with the guidelines on Good Clinical Practice (GCP).

Informed Consent

Prior to being enrolled into the study and before any study-related activity, each patient's written informed consent was obtained following a fully written and verbal explanation of the nature of the study.

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