2. SYNOPSIS

Company name: ACRAF S.p.A.	**TABULAR FORMAT REFERRING TO**	(For National Authority Use Only)
Name of the finished product: Momendol® 10% gel	Volume:	
Name of the active substance: Naproxen	Page:	

Title of the study: A randomized, multicenter, double-blind study assessing the efficacy and safety of two topical 10% naproxen gel formulations in the treatment of benign soft-tissue injuries.

Investigators: [redacted]

Study centre(s): Multicenter study

Publication (reference): not applicable

Study period (years): 2011-2012 | **Clinical Phase:** IV

Objectives: The aim of the study was to assess the efficacy and safety of Momendol® 10% gel (naproxen 10%) in comparison with the reference marketed product Naprosyn® 10% gel (naproxen 10%) in the treatment of benign soft-tissue injuries.

Methodology: Double-blind, randomized, multicenter, parallel groups study in patients diagnosed for painful benign soft-tissue injuries (sprains, strains and contusions) of upper (including shoulders but excluding fingers) or lower limbs (excluding toes and closed injuries) and tendinitis occurring within the prior 48 h and not requiring hospitalization.

Four visits were scheduled: Screening/baseline visit (V1; day 1), Intermediate visit (V2; day 3 or 4), Final/ETV visit (V3; after 7 days of treatment), and Follow-up visit (V4; 7 days from the last study drug administration)).

Number of subjects (total and per treatment):
149 (77 Momendol® and 72 Naprosyn®) patients were randomised and 147 (75 Momendol® and 72 Naprosyn®) received the allocated treatment.

Diagnosis and inclusion criteria: Patients suffering from benign soft-tiessue injuries. The inclusion criteria were:

1. Male or female subjects aged 18 to 70 years, with no limitation of race. Female patients of childbearing potential were required to have a negative pregnancy test and should not be breastfeeding. Male and female patients must use an appropriate birth control method.
2. Benign soft-tissue injury (closed injuries, sprains, strains and contusions) of upper (including shoulders but excluding fingers and toes) or lower limbs and tendinitis occurred within 48 hours before the randomization, and not requiring hospitalization. Patients included in the study were requested to avoid any solicitation on the injured area including, but not limited to, any kind of mechanical stress. Injured area must be not greater than 250 cm^2.
3. Pain during daily activities ≥ 35 mm on a 100 mm VAS (according to Huskisson method, Huskisson 1974 and 1982), and spontaneous pain at rest ≥ 35 mm on a 100 mm VAS (according to Huskisson method, Huskisson 1974 and 1982 and Esparza 2007).
4. Subjects legally capable to give their consent to participate in a clinical study. A written informed consent to participate to the trial, signed and dated by the patient prior to the inclusion in the study was available.

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Test product, dose, mode of administration: Momendol® 10% gel (naproxen 10%), topical cutaneous administration, bid
Batches no. 00151IP15 (blind batch 2010-9/S01, 2010-9/S02); 00151IP16 (blind batch 2011-7/S02)

Reference therapy, dose, mode of administration: Naprosyn® 10% gel (naproxen 10%) topical cutaneous administration, bid
Batches no. NHOF29 (blind batch 2010-9/S01, 2010-9/S02, 2011-7/S02); NH1D43 (blind batch 2011-7/S02)

Duration of treatment: 7 days

Assessment criteria:
Primary endpoint: change in pain during daily activities after the 7-day treatment period (patient assessment).
Secondary endpoints: change in pain during daily activities at the intermediate and follow up visits (patient assessment), change in pain at rest (patient assessment), change in swelling (Investigator assessment), change in muscle rigidity or stiffness (Investigator assessment), change in functional disability (Investigator assessment), change in pain at full passive motion (Investigator assessment), change in passive isometric contraction (Investigator assessment), change in pain on pressure (Investigator assessment), Global Efficacy Rating (Investigator and patient assessments) and the number of tablets used as rescue medication.
Efficacy variables: Efficacy was assessed by patients' pain assessment during daily activity and at rest using a 100 mm VAS (Huskinsson method, Huskinsson 1974 and 1981). Swelling, muscle rigidity or stiffness, functional disability, pain at full passive motion, passive isometric contraction, pain on pressure were rated as absent, mild, moderate, severe. Global Efficacy was evaluated using the Global Efficacy Rating (*very good, good, fair, poor, very poor)*.
Criteria of safety and tolerability: Safety was assessed by monitoring the frequency of adverse events in each treatment group and by evaluation of the global tolerability using the Global Tolerability Rating (*very good, good, fair, poor, very poor*). In addition, changes from baseline in physical examination, vital signs and laboratory analyses were assessed.

Statistical methods: Demographic characteristics and safety were evaluated on all treated subjects (safety population). All efficacy analyses are referred to the whole efficacy population since no differences in the mITT and PP population was detected The primary efficacy parameter, pain during daily activities was analysed at visit 3 with an analysis of covariance (ANCOVA) applied to the changes in pain from screening/baseline, including screening/baseline measurement as covariate, and the treatment and centres as factors. Interaction terms were examined but the primary model was main effects. The 95% confidence interval (CI) around the least square means was presented. The primary endpoint was accomplished if the lower confidence limit of the difference (test-reference) does not exceed the threshold of -10 mm.

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Statistical methods: The secondary efficacy parameters, pain during daily activities and pain at rest were analysed with an ANCOVA applied to the changes in pain from screening/baseline, including the screening/baseline measurement as covariate, and the treatment and centres as factors. Interaction terms were examined but the primary model was main effects. The 95% confidence interval (CI) around the least square means was presented. Other secondary parameters (swelling, muscle rigidity or stiffness, functional disability, pain at full passive motion passive isometric contraction and pain on pressure) were analysed with the Cochran Mantel-Haenszel test. The Wilcoxon rank-sum test was used in the analysis of the number of tablets used as rescue medication, the overall compliance and the extent of exposure.
Global Efficacy Ratings measured at the final visit by Investigators and patients were analysed by the Cochran Mantel-Haenszel test.
Statistical significant level was set at 5% for all comparisons.Statistical significant level setted at 5% was referred only for the comparison of the primary endpoint. The analysis of the secondary endpoint were of exploratory nature.
AEs were coded according to MedDRA dictionary ver. 13.1. Analysis of AEs was based on of the incidence of adverse drug reactions (ADRs) by System Organ Class (SOC) and Preferred Term (PT). ADRs was summarized by numbers and percentages of subjects with each MedDRA PT, nested within SOC; this means that subjects were counted only once in the incidence counts.
Laboratory parameters were evaluated on the basis of the normal range and the Investigator's judgement. Changes from screening/baseline in laboratory tests were analysed at visit 3 with an ANCOVA or ANOVA. Laboratory values at each time point were compared with the relevant reference range and categorized as "Low" (below the lower limit of the reference range), "Normal" (within the limits of the reference range), or "High" (above the upper limit of the reference range). Shift tables were used to present the change in category based on reference ranges from baseline to each post-baseline time point, as appropriate. Global Tolerability Rating filled in by the Investigatorwas analysed by the Cochran Mantel-Haenszel test. Changes from screening/baseline in physical examination were presented by treatment groups. Changes from screening/baseline in vital signs were summarized by descriptive statistics and were evaluated by an ANOVA in order to detect any significant changes.

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SUMMARY – CONCLUSION

Efficacy results:

Primary endpoint: Analysis of the primary endpoint (change in pain during daily activities at the final visit as compared to screening/baseline) demonstrated that seven days of treatment with Momendol® gel was statistically non-inferior to seven days of treatment with Naprosyn® gel. The lower limit of the 95% CI for the mean difference between the two groups (-0.61cm), did not exceed the lower non-inferiority margin (-1 cm).

Secondary endpoints: The results for the secondary endpoints were qualitatively similar to the primary endpoint. No statistically significant differences in the pain during daily activities at the intermediate and follow-up visit and in the pain at rest at any visit were observed between the two treatments.

The patients' and Investigators' global assessment at the final visit were numerically favorable for the Momendol® gel, althought no statistically significant differences between the two groups were shown.

A total of 61/73 (83.5%) patients considered the treatment with Momendol® gel to be very good or good compared to 54/72 (75.0%) patients who applied Naprosyn® gel. The statistical analysis showed no difference between treatment groups.

Both the patients' and the Investigators' global efficacy assessment favoured the treatment with Momendol® gel, as compared to Naprosyn® gel, althought no statistically significant differences were observed between treatments.

No difference in the mean number of tablets used as rescue medication in the Momendol® and Naprosyn® group was observed.

Overall patients treated with Momendol® showed comparable efficacy respect to patients treated with Naprosyn®. This result indicates that Momendol® gel is an effective treatement for pain and disability consequent to soft tissue injuries.

Safety results:

All patients who received at least one dose of investigational product were included in the safety analysis and there were no differences in mean days of exposure between treatment groups.

During the course of the study no serious AE or other significant AEs occurred and no subjects withdrew the study due to an AE. Eight mild-to-moderate AEs occurred in 8 patients, 6 in the Momendol® group and 2 in the Naprosyn® group. Two AEs were judged by the Investigator as drug-related (i.e. highly probable, probable, possible related): a mild dyspepsia a mild headache reported by two patients in the Momendol® arm. Analysis of AEs did not reveal major differences between treatment groups

The safety review of laboratory determinations, vital signs and physical findings did not show a clinical effect of the treatment on any of the parameters. For this reason they are not further discussed in detail.

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Conclusion:

This study compared the efficacy and tolerability two naproxen 10% gel formulations for cutaneous administration, the new ACRAF formulation (Momendol®) and a marketed reference formulation (Naprosyn®) in the treatment of the pain consequent to soft tissue injuries.

As expected a clinically significant decrease in pain during daily activities was observed after treatment with both medications. After a 7-day treatment period, Momendol® gel was statistically non-inferior to Naprosyn® gel. For the secondary efficacy variables, Momendol® presented a good efficacy profile, generally comparable to Naprosyn®, in reducing pain at rest, in improving symptoms as swelling, change in muscle stiffness, functional disability, pain on full passive motion, pain on passive isometric contreaction, pain on pressure, need of rescue medication. Moreover, Momendol® presented a numerically higher global efficacy rates assessed both by patients and Investigators as compared to Naprosyn®, even if the statistical significance was not reached. Momendol® showed a good safety profile, similar to that of Naprosyn®. No SAEs and/or other significant AEs occurred during the studies. There were a very low rates of AEs and clinical findings, with no statistically differences between the two groups. All AEs were minor and resolved without need for intervention. Overall the treatment with Momendol® in patients with pain consequent to soft tissue injuries showed a fully comparable efficacy and tolerability profile with respect to Naprosyn®.

Date of the Clinical Report: October 9th, 2012