CLINICAL STUDY REPORT

A double-blind, randomised, parallel group, active controlled, multicentre study to assess the therapeutic non-inferiority of SKP-021, a 0.3% ketoprofen patch, versus diclofenac sodium patch in patients with painful and inflammatory conditions (e.g.: back pain, bruise, contusion, sprain, strains)

Study ID: SKP-021-01-11

Sponsor	**PROMO INTERNATIONAL srl** **(Legal representative in Italy of Sato Pharmaceutical Co. Ltd.)**
Phase	III
EudraCT Number	2011-005661-20
Version and Date	FinalV1, 25-Jul-2014

1. TITLE PAGE

Study Title	A double-blind, randomised, parallel group, active controlled, multicentre study to assess the therapeutic non-inferiority of SKP-021, a 0.3% ketoprofen patch, versus diclofenac sodium patch in patients with painful and inflammatory conditions (e.g.: back pain, bruise, contusion, sprain, strains)
Study ID	SKP-021-01-11
Sponsor	Promo International srl Viale Campania 5 - 20133 Milan, Italy
Investigational Product	SKP-021: a 0.3% ketoprofen patch
Indication	Painful and inflammatory conditions
Design of clinical investigation	Phase III, double blind, randomized, parallel group, active controlled, multicentre investigation performed in 12 Italian investigational centres. ▪ Group 1: SKP-021 patch, ketoprofen 30 mg. ▪ Group 2: Voltadol® patch, diclofenac sodium 140 mg. The test and control drugs were to be applied, one patch at one time twice daily, for 5 to 7 days.
Phase	III
FSFV	4-Sep-2012
LSFV	17-Jun-2013
LSLV	24-Jun-2013
Coordinating Centre and Coordinating Investigator	Pier Carlo Sarzi Puttini, MD Reumatology Unit "L. SACCO" Hospital Via G.B. Grassi, 74 - 20157 Milan, Italy
The study was conducted in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.	
Clinical Study Report (CSR)	
CSR version and date	V1, 25-Jul-2014
Sponsor signatory	Carlo Fornara – Managing Director Promo International srl for SATO Pharmaceutical Co. Ltd.
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2. SYNOPSIS

Name of Sponsor: Promo International srl for SATO Pharmaceutical Co. Ltd.	**Name of Finished Product:** SKP-021	**Name of Active Ingredient:** ketoprofen 30 mg
Title of the study:	*A double-blind, randomised, parallel group, active controlled, multicentre study to assess the therapeutic non-inferiority of SKP-021, a 0.3% ketoprofen patch, versus diclofenac sodium patch in patients with painful and inflammatory conditions (e.g.: back pain, bruise, contusion, sprain, strains)*	
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Studied Period: **FPFV:** **LPLV:**	10 months 4-Sep-2012 24-Jun-2013
Phase of Development:	III
Objectives:	To evaluate the efficacy and safety of SKP-021 (medicated patch containing ketoprofen as an active ingredient) in a double blind study in

	patients with painful and inflammatory conditions (e.g.: back pain, bruise, contusion, sprain, strains), using Voltadol® as a control drug.	
Methodology:	Patients who fulfilled the inclusion and exclusion criteria were randomized in a double blind manner to Group 1 (SKP-021) or 2 (Voltadol®), with a ratio of 1:1. SKP-021 or the control drug were to be applied, one patch at one time twice daily, for a minimum of five days and a maximum of 7 days. Patients were evaluated at visit 1 (enrolment and randomization) and Visit 2 (end of treatment) and were requested to fill in a daily diary during the treatment period at home.	
Number of patients:	**Planned:** 311 completed patients per each group in order to show the non inferiority of tested drug in comparison with the standard. Considering an 11% drop-out rate the number of randomized patients per group was increased to 350 and the overall number of patients to be included in the trial was 700.	**Analysed:** 697 patients have been randomized and treated (348 in Diclofenac and 349 in Ketoprofen group). According to the investigator's judgement 592 patients were defined as having completed the study as per protocol but, according to the analysis, 561 patients completed the study without major protocol deviations.
Diagnosis and main criteria for inclusion:	**BEFORE Amendment #1, dated 14-Nov-2012:** Out-patients of both sexes, aged between 18-65 years, able to give informed consent and to complete the diary were to be included if they had traumatic disease (e.g.: bruise, contusion, sprain, etc.), presenting frank symptoms of inflammation, such as pain (VAS ≥50mm), myalgia and swelling, within 2 days from trauma; if the patient had more than one affected site, only one was to be treated regardless of severity. Patients were to be excluded mainly if: the affected site was too wide, needed anti-inflammatory analgesic other than the study drug for the underlying disease, were obese, with history of drug allergy or with aspirin-induced asthma, with a skin wound or skin disease at the test site, pregnant or lactating women. **AFTER Amendment #1, dated 14-Nov-2012:** Out-patients of both sexes, aged between 18-75 years, able to give informed consent and to complete the diary were to be included if they had an inflammatory condition (e.g.: back pain, bruise, contusion, sprain, etc.), presenting frank symptoms of acute inflammation, such as pain (VAS ≥50mm), myalgia and/or swelling; if the patient had more than one affected site, only one was to be treated. Patients were to be excluded mainly if: the affected site was too wide to be treated with the patch; needed other anti-inflammatory analgesic other than the study drug for the underlying disease or for other diseases; were obese; had history of drug allergy or had aspirin-induced asthma; had a skin wound or skin disease at the test site; were pregnant or lactating women.	
Test product: dose and mode of administration, batch number:	SKP-021 patch: ketoprofen 30 mg one patch twice daily Batch numbers: B287MA (clinical batch: DP04/12_03) and B284MA	
Reference therapy: dose and mode of administration, batch number:	Voltadol® patch: diclofenac sodium 140 mg one patch twice daily Batch number: C2011P (clinical batch: DP04/12_03)	

Duration of treatment:	5 to 7 days
Criteria for evaluation:	**Efficacy variables:** **Primary response variable:** Number of patients with reduction of VAS (Visual Analogue Scale) score of at least 50% versus baseline condition (responders). **Secondary response variables:** • Time needed to reach the status of responder • Overall changes in VAS score • Improvement of clinical symptoms related to the disease • Changes in the MPAC (Memorial Pain Assessment Card) scale with particular attention to the mood profile • Overall physician and patient rating on the treatment result **Safety variables:** • Adverse events • Vital signs • Physical examination
Statistical methods:	After the data base lock, a blind randomization list was provided to the statistician, the treatment groups being identified only by the A/B letters. The code was opened when the statistical analysis was completed. All clinical data are presented by individual subject listings, sorting by treatment Group, centre, Subject within centre and time-point, as appropriate. Descriptive summary statistics: mean, standard deviation (SD), median, minimum and maximum, 95% Confidence Interval (95%CI), are presented for continuous data. Categorical data are summarised by frequencies and percentages. The summaried results are presented according to the treatment group (either ketoprofen or diclofenac). The statistical analysis was performed with the package SAS® System version 9.3 at a 5% significance level ($\alpha = 0.05$, two-sided). At each planned visit, continuous variable are presented by descriptive statistics (mean, SD, median, lower and upper 95% confidence limit); categorical variables are summarized by frequencies and percentages.
Summary - Conclusions	The two groups were homogenous at baseline for demographics and baseline characteristics. **Efficacy Results:** As concerns the **primary efficacy endpoint**, the response rate of the two experimental treatments was of similar extent. The Ketoprofen-Diclofenac differences in response rates do not exceed the non-inferiority margin. Therefore the non-inferiority of the Test product (SKP-021, 0.3% ketoprofen patch) has been demonstrated. The patterns of all **secondary efficacy endpoints** were similar in the two groups. **Safety Results:** There was no safety concern associated with the patch applications. The Adverse Events which occurred to 65 subjects in Diclofenac (18.7%) and 59 subjects in Ketoprofen (16.9%) group were mild to moderate, no serious adverse events have been reported. The incidence of events of the SOC "Skin and subcutaneous tissue disorders" was significantly lower in the Ketoprofen group (10.6% in the Diclofenac; 4% in the Ketoprofen; $p<0.001$).

	Conclusions: This study has demonstrated the non-inferiority in terms of efficacy of the Test product (SKP 021, 0.3% ketoprofen patch) compared with the Reference product (diclofenac patch). The Test product was at least as safe as the Reference product.
Date of report:	25-Jul-2014