POLICHEM

Clinical Study Report

A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUPS, PILOT STUDY TO ASSESS THE EFFECTS OF TWO NEW NAIL LACQUERS, CYCLOSPORINE 5% AND CALCIPOTRIOL 0.005%, IN THE TREATMENT OF NAIL PSORIASIS

PROTOCOL NUMBER: PM0812

EUDRACT NUMBER 2010-019706-16

Name of test product:	Cyclosporine 5% and Calcipotriol 0.005% nail lacquer
Indication:	Nail psoriasis
Study Design:	Randomized, double blind, placebo controlled, parallel groups
Phase of development:	Phase II
Sponsor:	POLICHEM SA, Via Senago 42 D, 6912 Lugano Pazzallo, Switzerland
Co-ordinating Investigator and Centre:	[redacted], 'Azienda Ospedaliera Universitaria Policlinico di Modena', Modena, Italy
Study Initiation Date: (First Patient First Visit)	21 Dec 2010
Study Completion Date: (Last Patient Last Visit)	06 Feb 2013
Report Date:	Final Version, 14th November 2014

This study was performed in compliance with the ICH-Good Clinical Practice (GCP) guideline (CPMP/ICH/135/95) and regulations

2 SYNOPSIS

Name of Sponsor/Company: Polichem SA - Via Senago 42 d CH - 6912 Lugano Pazzallo - Switzerland

Name of Active Ingredient: P-3072 (Cyclosporine 5%) and P-3073 (Calcipotriol 0.005%) Nail Lacquers

Title of the study: A randomized, double blind, placebo controlled, parallel groups, pilot study to assess the effects of two new nail lacquers, cyclosporine 5% and calcipotriol 0.005%, in the treatment of nail psoriasis

EudraCT number: 2010-019706-16

Investigators: 5 Principal Investigators in 2 countries (4 sites in Italy and 1 in Latvia)

Study centres: 5 investigational study sites in 2 countries (4 sites in Italy and 1 in Latvia)

Publication (reference): Not applicable

Study period: First patient enrolled: 21 Dec 2010; Last patient completed: 06 Feb 2013	**Phase of development:** II

Objectives:

The objective of this study was to assess the effects of P-3072 (Cyclosporine 5%) and P-3073 (Calcipotriol 0.005%) nail lacquers in patients affected by mild to moderate psoriasis having nail psoriasis of the nail matrix and / or the nail bed affecting at least one fingernail.

End-points

Primary end-point

The primary end-point of this study was to evaluate the changes of clinical signs of nail bed and of nail matrix of the nails affected by psoriasis by means of NAPSI score at the end of treatment.

Secondary end-points

The secondary end-points of this study were:

- To evaluate the changes versus baseline of clinical signs of nail bed and of nail matrix of the fingernails affected by psoriasis by means of NAPSI score at each study visit and at the end of follow-up period (12 weeks after the end of treatment);
- To evaluate the changes of nail thickness of the affected fingernails by means of 20 MHz ultrasound at the end of treatment, at each study visit and at the end of follow-up period;
- To evaluate the safety profile of P-3072 and P-3073 at each visit and at the end of treatment by means of AE monitoring;
- To evaluate the changes in patients' quality of life by means of NPQ10 (Nail Psoriasis Quality of Life) and DLQI (Dermatology Life Quality Index) questionnaires at the end of treatment, at each study visit and at the end of follow-up period;
- To evaluate the changes in pain due to nail psoriasis by means of a VAS (Visual Analogue Scale);
- To evaluate the changes in discomfort due to nail psoriasis by means of a VAS;
- To evaluate the patient's opinion on the product (effectiveness and acceptability) at the end of treatment and at each study visit.
- To evaluate the blood concentration of cyclosporine at each study visit, at the end of treatment and at the end of the follow-up period and Hydroxypropyl chitosan (HPCH) (contained in the calcipotriol and vehicle samples) at the end of treatment (week 24).

Methodology:

This was a randomized, vehicle controlled, double blind, parallel groups study.

The study consisted in three arms comparing P-3072 (Cyclosporine 5%), P-3073 (Calcipotriol 0.005%) and vehicle. Patients with mild to moderate psoriasis (BSA involvement ≤ 10% or PASI ≤ 10) having nail psoriasis (fingernails) of the nail matrix and / or the nail bed were recruited. A Central Blinded Evaluator (CBE) was in charged to review digital photos taken at each study visit to confirm the local assessment of NAPSI score. The duration of the whole study per patient was 36 weeks: a screening visit, a treatment phase of 24 weeks and a follow-up phase of 12 weeks were foreseen.

Number of patients (total and in each arm):

	Randomised	Safety	FAS	PP
Total	80	78	78	70
P-3072 (Cyclosporine 5%)	31	30	30	27
P-3073 (Calcipotriol 0.005%)	34	34	34	31
Vehicle	15	14	14	12

Diagnosis and main criteria for inclusion:

Written informed consent before starting any study related procedure; patients aged ≥ 18 and ≤ 80 years old; males or females; outpatients; patients with established clinical diagnosis of mild to moderate psoriasis (BSA involvement ≤ 10% or PASI ≤ 10) having nail psoriasis (fingernails) of the nail matrix and/or the nail bed affecting at least one fingernail; presence of at least one clinical sign of nail psoriasis of the matrix (pitting, leukonychia, red spots in lunula, nail plate crumbling) and/or of the nail bed (salmon patch, onycholysis, hyperkeratosis and splinter haemorrhage) in at least one fingernail.

Test product, dose and mode of administration, batch no:

The IMPs were two nail lacquers: P-3072 based on Cyclosporine and P-3073 based on Calcipotriol as active ingredients. Nail lacquer of both IMPs was applied once daily on the evening before going to bed.

Used batch:

Cyclosporine: batch 67605, last expiry 07/2013;

Calcipotriol: batch 7860, last expiry 06/2013.

Duration of treatment: 24 weeks

Reference therapy, dose and mode of administration, batch no:

Nail lacquer vehicle (placebo), applied once daily on the evening before going to bed.

Used batch: 6575, last expiry 06/2013.

Criteria for evaluation:

Efficacy

The primary efficacy parameter was NAPSI score evaluated at the end of treatment (24 weeks) versus baseline.

The secondary efficacy variables were:

- NAPSI score at week 4, 12, 16, 20 and at the end-of follow-up (36 weeks);
- NAPSI score at week 4, 12, 16, 20, 24 (end of treatment) and at the end-of follow-up (36 weeks) by means of central evaluation;
- NAPSI score at week 4, 12, 16, 20, 24 (end of treatment) and at the end-of follow-up (36 weeks) by means of local evaluation;
- Rate of subjects with a decrease of at least 75% in the NAPSI total score at week 4, 12, 16, 20, 24 and 36 weeks;
- Rate of subjects with a decrease of at least 50% in the NAPSI total score at week 4, 12, 16, 20, 24 and 36 weeks;
- Rate of subjects with a decrease of at least 25% in the NAPSI total score at week 4, 12, 16, 20, 24 and 36 weeks;
- Rate of nails with improvement in the NAPSI score at week 4, 12, 16, 20, 24 and 36 weeks;
- Rate of nails with improvement in the NAPSI score at week 4, 12, 16, 20, 24 and 36 weeks by means of local Investigator;
- Rate of nails with improvement in the NAPSI score at week 4, 12, 16, 20, 24 and 36 weeks by means of Central Blinded Evaluator;
- Nail thickness at week 4, 12, 16, 20, 24 (end of treatment) and at the end of follow-up, evaluated by means of the ultrasound scanner Voluson®i (GE Healthcare);
- VAS of pain at week 4, 12, 16, 20, 24 (end of treatment) and at the end of follow-up. The 100 mm VAS of pain measured the amount of pain that a patient felt in fingernail and ranged across a continuum from none to an extreme amount of pain;

- VAS of discomfort at week 4, 12, 16, 20, 24 (end of treatment) and at the end of follow-up. The 100 mm VAS of discomfort measured the amount of discomfort that the patient felt in the nail and ranges from none to an extreme discomfort;
- Evaluation of 10-items Nail Psoriasis Quality of Life (NPQ10) questionnaire;
- Evaluation of 10-items Dermatology Life Quality Index (DLQI) questionnaire;
- Acceptance of therapy by patient at each study visit, based on a 4-point assessment scale: 4=”very good”, 3=”good”, 2=”moderate”, 1=”poor”.

Safety

The safety variables of the study were:

- Adverse events (AEs);
- Laboratory parameters (haematology, clinical chemistry and urinalysis);
- Vital signs (heart rate and blood pressure);
- Physical examination;
- Pregnancy test;
- Severity score of skin irritation.

Statistical methods:

The following populations were considered for analysis:

- Safety population/full analysis set (FAS), defined as all randomized patients with signed informed consent and with at least one documented application of the investigational drug;
- Modified intention-to-treat (MITT) population, defined as all randomized patients with signed informed consent, with at least one documented application of the investigational drug and with the efficacy data at visit 3;
- Per-protocol (PP) population, defined as all randomized patients with signed informed consent, who completed the study fully compliant with the protocol and without any major deviation likely to affect the nail bed or nail matrix assessments.

The results were presented in form of descriptive statistics, i.e. number of observation, mean, standard deviation, median, minimum and maximum, 25^{th} and 75^{th} percentiles for continuous variables, and frequency distributions (number and percentages) for categorical variables.

The comparison between groups of primary variable reduction of NAPSI score from baseline to the end of treatment (24 weeks), as average between local and central evaluation, was performed by using a mixed model for repeated measures, with treatment, visit and treatment*visit interaction as fixed effect. The NAPSI score at baseline was entered in the model as covariate. The two contrasts between the P-3072 and P-3073 versus vehicle at visit 6, end of treatment, were calculated together with the 97.5% confidence limits. Thus, the p-value to be considered as cut-off for significance was 0.025, to maintain the overall alpha level of the study at 0.05.

In the analysis of the results of NAPSI score at the other study visits, of local and central assessment of NAPSI score, of nail thickness, of VAS of pain and VAS of discomfort, and of NPQ10 and DLQI total score, the contrast defined for the primary efficacy analysis was calculated at each study visit applying the model used for primary efficacy evaluation. In the FAS and MITT analysis of NAPSI score and of nail plate thickness, the analyses in prematurely discontinued patients were done using both the last available observation carried forward (LOCF) approach and the sensitivity approach, considering the best and the worst outcome.

A chi-square test (or a Fisher exact text in case of cell frequencies less than 5) was used to compare between groups the proportion of patients with decrease of at least 75%, 50% and 25% in the NAPSI total score, the overall groups of decrease (<25%, between 25% and 50%, between 50% and 75%, >75%) and the proportion of patients with improvement in NAPSI score on each fingernail.

A Kruskall-Wallis test was used in the comparison between groups of the proportion of patients per each score of the scale evaluating the acceptance of therapy.

The incidence of all AEs, of severe AEs and of AEs related to study drug was calculated by Preferred Term (PT) and System Organ Class (SOC) using the MedDRA dictionary (version 13).

Summary tables were produced for each haematology and clinical chemistry parameter, showing the number of observations at each time point, the mean, median, standard deviation, inter-quartile range and the lowest and highest values. For each parameter the proportion of patients who had at least one abnormal value in relation to normal ranges was tabulated by treatment group. In addition, shift tables in relation to normal ranges were produced to assess changes at post-baseline visits versus the baseline value. The results of urinalysis were presented as number and rate of patients with normal

or abnormal findings.

Summary tables were produced for all vital signs showing the number of observations at each time point, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values.

Physical examination and pregnancy test data were described by visit reporting absolute frequencies and percentages of results.

Summary tables were produced for results of the severity score of skin irritation exam. Data were described by visit and treatment group reporting absolute frequencies and percentages of patients with any evidence of irritation and by type of irritation.

Study population:

A total of 83 patients were screened for the study and 80 were randomized to the assigned treatment: 31 patients were randomised to receive P-3072 (cyclosporine 5%), 34 to P-3073 (calcipotriol 0.005%) and 15 to vehicle (placebo).

Overall, 73 patients completed the study (28 in the P-3072 group, 33 in the P-3073 group and 12 in the vehicle group), while other 7 patients overall (3 in the P-3072 group, 1 in the P-3073 group and 3 in the vehicle group) prematurely discontinued the study.

Extent of exposure and compliance:

The mean (± SD) extent of total exposure was 165.40 ± 29.03 days in the P-3072 group, 168.50 ± 18.65 days in the P-3073 group, and 150.29 ± 58.31 days in the vehicle group.

The mean (± SD) compliance to study drug was 98.45 ± 4.02 % in the P-3072 group, 97.72 ± 6.96 % in the P-3073 group, and 97.84 ± 5.31 % in the vehicle group.

Efficacy results:

Primary end-point: ***NAPSI score evaluated at the end of treatment (24 weeks)***

FAS population

LOCF approach

The mean (SD) changes from baseline to week 24 were -6.78 (9.52) in the P-3073 group, -2.42 (9.29) in the P-3072 group and -1.11 (5.13) in the vehicle. The comparison between the P-3073 group and the vehicle showed a nearly statistically significant difference (estimated difference -5.7806; 97.5% CI: -12.0895 to 0.5283; p = 0.0395) considering the multiple comparison adjustment (p-value for significance 0.025) but inferior to the conventional threshold of 5% (p-value for significance 0.05). No statistically significant difference between the P-3072 group and the vehicle group was found (estimated difference -1.2254; 97.5% CI: -7.6551 to 5.2044; p = 0.6641).

Worst approach

The mean (SD) changes from baseline to week 24 were -5.46 (12.51) in the P-3073 group, 0.55 (15.89) in the P-3072 group and 5.57 (18.81) in the vehicle group. The comparisons between groups showed a statistically significant difference between the P-3073 group and the vehicle group (estimated difference -11.0355; 97.5% CI: -22.0138 to -0.0572; **p = 0.0243**), while the difference between the P-3072 group and the vehicle group was not statistically significant (estimated difference -5.0151; 97.5% CI: -16.2040 to 6.1738; p = 0.3085).

Best approach

The mean (SD) changes from baseline to week 24 were -7.10 (9.63) in the P-3073 group, -4.78 (12.10) in the P-3072 group and -5.86 (12.64) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

No missing data imputation

The mean (SD) changes from baseline to week 24 were -6.85 (9.66) in the P-3073 group, -2.80 (9.47) in the P-3072 group and -1.46 (5.48) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

PP population

The mean (SD) changes from baseline to week 24 were -5.92 (7.99) in the P-3073 group, -2.94 (9.62) in the P-3072 group and -1.46 (5.48) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

MITT population

With all methods of analysis (LOCF, Best, Worst, no imputation of missing data), the decrease from baseline to week 24 in NAPSI score was more marked in the P-3073 group than in the other two groups. The comparisons between the active groups and the vehicle group did not show statistically significant differences with all approaches.

Secondary end-points

NAPSI score at week 4, 12, 16, 20 and at the end-of follow-up (36 weeks)

FAS population (LOCF approach)

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to smaller changes in the other two groups. Statistically significant differences were observed between the P-3073 group and the vehicle group at week 12 (**p = 0.0241**) and at week 16 (**p = 0.0045**), while the difference at week 20 (p = 0.0280) and at follow-up (week 36) (p = 0.0481) was nearly statistically significant. No statistically significant differences were observed at any time point in the comparison between the P-3072 group and the vehicle group.

PP population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to smaller changes in the other two groups. A statistically significant difference between the P-3073 group and the vehicle group was observed at week 16 (**p = 0.0137**), while the comparisons at the other time points and the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences.

MITT population

The comparisons between groups showed statistically significant differences between the P-3073 group and the vehicle group, in favour of the P-3073 group, at week 12 with the Worst approach (**p = 0.0102**), and at week 16 with the LOCF approach (**p = 0.0093**), with the Best approach (**p = 0.0098**), with the Worst approach (**p = 0.0094**) and with no imputation of missing data (**p = 0.0094**).

NAPSI score at week 4, 12, 16, 20, 24 (end of treatment) and at the end-of follow-up (36 weeks) by means of central evaluation

FAS population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to small changes in the other two groups. The mean (SD) changes from baseline to week 24 were -4.37 (8.98) in the P-3073 group, 1.43 (12.36) in the P-3072 group and 0.18 (8.34) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences with all approaches, except for statistically significant differences between the P-3073 group and the vehicle group at week 16 (**p = 0.0128**) and week 20 (**p = 0.0192**) with the Worst approach, and other nearly statistically significant differences between the same groups with the LOCF and the no missing data imputation approach.

PP population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to small changes in the other two groups. The mean (SD) changes from baseline to week 24 were -4.35 (9.16) in the P-3073 group, 1.41 (12.65) in the P-3072 group and 0.18 (8.34) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

MITT population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to small changes in the other two groups. The mean (SD) changes from baseline to week 24 were -4.37 (8.98) in the P-3073 group, 1.43 (12.36) in the P-3072 group and 0.18 (8.34) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences with all approaches, except for statistically significant differences between the P-3073 group and the vehicle group at week 16 (**p = 0.0181**) with the Worst approach, and other nearly statistically significant differences between the same groups with the Best, the Worst and the no missing data imputation approach.

NAPSI score at week 4, 12, 16, 20, 24 (end of treatment) and at the end-of follow-up (36 weeks) by means of local evaluation

FAS population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point from week 4 onwards, compared to overall smaller decreases in the other two groups. The mean (SD) changes from baseline to week 24 were -7.30 (9.22) in the P-3073 group, -5.96 (9.32) in the P-3072 group and -2.75 (6.27) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences with all approaches, except for statistically significant differences between the P-3073 group and the vehicle group at week 12 (**p = 0.0032**) and at week 16 (**p = 0.0086**) with the Worst approach, and other nearly statistically significant differences between the same groups with the LOCF, Best and Worst approach.

PP population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to overall smaller decreases in the other two groups. The mean (SD) changes from baseline to week 24 were -6.45 (7.45) in the P-3073 group, -6.19 (9.43) in the P-3072 group and -2.75 (6.27) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

MITT population

A decrease from baseline in mean NAPSI score was observed in the P-3073 group at any time point, compared to smaller decreases in the other two groups from week 4 onwards. The mean (SD) changes from baseline to week 24 were -7.30 (9.22) in the P-3073 group, -5.96 (9.32) in the P-3072 group and -2.75 (6.27) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences with all approaches, except for statistically significant differences between the P-3073 group and the vehicle group at week 12 (**p = 0.0169**) with the Worst approach.

Rate of subjects with a decrease of at least 75% in the NAPSI total score *(PP population)*

Few patients in all groups had a decrease of at least 75% in the NAPSI total score at any visit. The greatest proportion of patients (22.58%) with a decrease of at least 75% was observed at week 36 (end of follow-up) in the P-3073 group.

Rate of subjects with a decrease of at least 50% in the NAPSI total score *(PP population)*

The proportion of patients with a decrease of at least 50% in the NAPSI total score was higher in the P-3073 group than in the other two groups at any visit. However, the comparisons between groups did not show statistically significant differences at any visit.

The proportion of patients with a decrease between 50% and 75% in the NAPSI total score was higher in the P-3073 group than in the other two groups at any time point up to the end of treatment (week 24). The greatest proportion of patients (29.03%) with a decrease between 50% and 75% was observed at week 24 in the P-3073 group.

Rate of subjects with a decrease of at least 25% in the NAPSI total score *(PP population)*

The proportion of patients with a decrease of at least 25% in the NAPSI total score was higher in the P-3073 group than in the other two groups at any visit. Statistically significant differences between the P-3073 group and the vehicle group were observed at weeks 16 (**p = 0.0193**), 20 (**p = 0.0117**) and 24 (**p = 0.005**), while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences at any visit.

More patients in the P-3073 group than in the other two groups had a decrease between 25% and 50% in the NAPSI total score up to week 24 (end of treatment). The greatest proportion of patients (48.39%) with a decrease between 25% and 50% was observed at week 20 in the P-3073 group.

Rate of subjects with a decrease of at least 75%, at least 50% and at least 25% in the NAPSI total score *(PP population)*

Statistically significant differences between the P-3073 group and the vehicle group were observed at week 16 (**p = 0.0213**), 20 (**p = 0.0045**) and 24 (**p = 0.0023**), due to higher proportion of patients in the P-3073 group with a decrease ≥ 75%, between 50% and 75%, and between 25% and 50%, while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences at any time point.

Rate of nails with improvement in the NAPSI score at week 4, 12, 16, 20, 24 and 36 weeks

FAS population

The proportion of nails with an improvement in the NAPSI total score was higher in the P-3073 group than in the other two groups at any time point. The greatest proportion of nails (37.19%) with improvement was observed at week 36 (end of follow-up) in the P-3073 group. The comparisons between groups showed statistically significant differences between the P-3073 group and the vehicle group at week 16 (**p = 0.0048**), due to higher proportion of nails in the P-3073 group with improvement, while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences at any visit. Furthermore, the difference between the P-3073 group and the vehicle group at week 12 (p = 0.0333) and 36 (p = 0.0407) was nearly statistically significant.

PP Population

The results in the PP population were consistent with those observed in the FAS population. The proportion of nails with an improvement in the NAPSI total score was higher in the P-3073 group than in the other two groups at any time point. The greatest proportion of nails (36.94%) with improvement was observed at week 36 (end of follow-up) in the P-3073 group. The comparisons between groups showed statistically significant differences between the P-3073 group and the vehicle group at weeks 16 **(p = 0.0083**), due to higher proportion of nails in the P-3073 group with improvement, while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences at any visit. Furthermore, the difference between the P-3073 group and the vehicle group at week 36 (p = 0.0472) was nearly statistically significant.

MITT population

The results in the MITT population were consistent with those observed in the FAS and in the PP populations.

Nail thickness at week 4, 12, 16, 20, 24 (end of treatment) and at the end of follow-up, evaluated by means of the ultrasound scanner Voluson®i (GE Healthcare)

FAS population

A small decrease from baseline in mean nail thickness was observed in all the three groups. The mean (SD) changes from baseline to week 24 were -1.31 (2.91) in the P-3073 group, -2.60 (4.36) mm in the P-3072 group and -2.44 (2.87) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences with all approaches (LOCF, Best and Worst, no missing data imputation).

PP population

A small decrease from baseline in mean nail thickness was observed in all the three groups. The mean (SD) changes from baseline to week 24 were -1.61 (2.49) in the P-3073 group, -2.64 (4.45) mm in the P-3072 group and -2.44 (2.87) in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

MITT population

The results in the MITT population were consistent with those observed in the FAS and in the PP populations.

VAS of pain at week 4, 12, 16, 20, 24 (end of treatment) and at the end of follow-up *(PP population)*

An overall decrease from baseline in mean VAS score was observed in the vehicle group, compared to less evident changes in the two active groups. The mean (SD) changes from baseline to week 24 were 1.63 (22.14) mm in the P-3073 group, -0.85 (25.60) mm in the P-3072 group and -5.75 (27.64) mm in the vehicle group. The comparisons between the active groups and the vehicle group did not show statistically significant differences.

VAS of discomfort at week 4, 12, 16, 20, 24 (end of treatment) and at the end of follow-up *(PP population)*

The mean VAS score decreased from baseline to any time point in all treatment groups. The extent of the decrease was higher in the two active treatment groups than in the vehicle group up to the end of treatment, being the highest decreases observed in the P-3073 group. The mean (SD) changes from baseline to week 24 were -29.02 (33.51) mm in the P-3073 group, -26.04 (29.44) mm in the P-3072 group and -12.42 (43.10) mm in the vehicle group. The comparisons between groups showed statistically significant differences between the P-3073 group and the vehicle group at week 16 (**p = 0.0033**) and week 20 (**p = 0.0109**), in favour of the P-3073 group, while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences at any visit.

NPQ10 questionnaire *(PP population)*

The mean NPQ10 questionnaire total score decreased from baseline to any time point in the P-3073 group, compared to less evident changes in the other two groups (except for a marked decrease in the vehicle group at week 4). The mean (SD) changes from baseline to week 24 were -1.72 (10.37) in the P-3073 group, -1.35 (11.71) in the P-3072 group and 3.43 (9.62) in the vehicle group. The comparisons between groups did not show statistically significant differences between the two actively-treated groups and the vehicle group at any time point. However, the difference between the P-3073 group and the vehicle group at week 36 (end of follow-up) (p = 0.0425) was nearly statistically significant.

DLQI questionnaire *(PP population)*

The mean DLQI questionnaire total score decreased from baseline to any time point in the P-3073 group, compared to less marked decreases in the other two groups (except for a marked decrease in the vehicle group at week 4). The mean (SD) changes from baseline to week 24 were -3.83 (3.52) in the P-3073 group, -2.67 (4.16) in the P-3072 group and -2.42 (5.16) in the vehicle group. The comparisons between groups showed statistically significant differences between the P-3073 group and the vehicle group at week 12 (**p = 0.0025**) and at week 36 (end of follow-up) (**p = 0.0033**), in favour of the P-3073 group, while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences, except at week 4 (**p = 0.0088**), in favour of the vehicle group. Furthermore, the difference between the P-3073 group and the vehicle group at week 20 (p = 0.0470) was nearly statistically significant.

Acceptance of therapy

The proportion of patients with very good or good opinion of acceptance of therapy was higher in the two actively treated groups than in the vehicle group at any visit, and was higher in the P-3073 group than in the P-3072 group from week 12 onwards. At the end of treatment (week 24), the number and rate with very good or good opinion of acceptance of therapy was 25 (80.65%) in the P-3073 group, 18 (66.67%) in the P-3072 group and 6 (50.00%) in the vehicle group.

The results comparisons between groups showed statistically significant differences between the P-3073 group and the vehicle group at week 12 (**p = 0.0072**), in favour of the P-3073 group, while the comparisons between the P-3072 group and the vehicle group did not show statistically significant differences. Moreover, the difference between the P-3073 group and the vehicle group at week 20 (p = 0.0360) and between the P-3072 group and the vehicle group at week 4 (p = 0.0260) were nearly statistically significant.

Safety results:

Adverse events:

The rate of patients with AEs was lower in the vehicle group (8 patients, 57.14%) than in the P-3073 group (27 patients, 79.41%) and in the P-3072 group (24 patients, 80.00%). However, treatment-related AEs (i.e. those AEs with a probable or possible correlation with study drug) were reported in 1 patient (2.94%) in the P-3073 group, in 3 (10.00%) in the P-3072 group and in 1 (7.14%) in the vehicle group.

Adverse events of severe intensity were reported in 2 patients (6.67%) in the P-3072 group and in 2 (14.29%) in the vehicle group. None of patients in any group had serious adverse events or adverse events that led to temporary or definite discontinuation, or dose reduction, of the study drug.

Headache (16 patients overall, 20.51%) and rhinitis (11 patients, 14.10) were the most reported AEs by preferred term.

Laboratory parameters:

The results of laboratory parameters (haematology, blood chemistry and urinalysis) did not show changes in mean values from baseline to the end of treatment, as well as there were no treatment-related clinically significant abnormalities.

The results of haematology and blood chemistry in form of shift tables based on low/normal/high values with respect no normal range from baseline to post-baseline visits showed that, in all groups, most of patients had normal values of all parameters at both baseline and post-baseline visits, or values that did not change category between the baseline and the post-baseline visits.

Vital signs:

The results of vital signs (heart rate, blood pressure, body weight) di not show changes in mean values from baseline to the end of treatment.

Physical examination

Very few patients had abnormal findings at the screening visit and at the end of treatment (week 24).

Pregnancy test

None of female patients that performed the pregnancy test during the study had positive results.

Skin irritation

Very few patients in all groups had evidence of irritation in fingernails at the post-baseline visits.

Conclusions:

- The study has attained its primary objective, showing superiority in reducing NAPSI score of at least one active versus vehicle (placebo). The results of the primary efficacy variable of the study NAPSI score evaluated at the end of treatment (24 weeks) showed a superior efficacy of P-3073 over vehicle (placebo) when the conventional threshold of 5% is considered, while the difference between the P-3072 group and the vehicle group was not statistically significant.
- Consistently with the primary end point, P-3073 was able to improve several secondary end-points. The results of other secondary efficacy variables, such as the NAPSI score at the other visits, the proportion of patients with a decrease of NAPSI score ≥ 75%, ≥ 50% and ≥ 25%, the proportion of nails with improvements in NAPSI score, the severity of discomfort, the quality of life and the opinion on acceptance of therapy, all were indicative of a better efficacy of P-3073 compared to vehicle, while there was no evidence of superiority of P-3072 over vehicle in all parameters.
- Both P-3072 and P-3073 were well tolerated in terms of local and general adverse reactions, and of systemic safety.
- As P-3073 (Calcipotriol 0.005%) was shown to be more effective than the vehicle (placebo) in the primary and in most of the secondary efficacy endpoints, and taking into consideration its excellent safety profile, this nail lacquer formulation is the most appropriate candidate for further development in the treatment of patients with mild to moderate nail psoriasis.