POLICHEM

Clinical Study Report

MULTICENTRE, RANDOMIZED, DOUBLE BLIND WITHIN FREQUENCY OF ADMINISTRATION, PLACEBO CONTROLLED, DOSE-FINDING, PARALLEL-GROUP, EFFICACY AND SAFETY STUDY OF 3 DOSES OF P-3058 NAIL LACQUER (5% o.d., 10% o.d., AND 10% o.w.) GIVEN FOR 52 WEEKS IN PATIENTS WITH ONYCHOMYCOSIS

PROTOCOL NUMBER: PM0731

EUDRACT NUMBER 2008-002707-10

Name of test product:	P-3058 Nail solution
Indication:	Onychomycosis
Study Design:	Multicentre, randomized, double blind, vehicle controlled, parallel-group, dose finding, clinical study
Phase of development:	2b
Sponsor:	POLICHEM SA, Via Senago 42 D, 6912 Lugano Pazzallo, Switzerland
International Scientific Study Coordinator:	[redacted], Nail Disease Centre, 42 rue des Serbes, 06400 Cannes, France
Study Initiation Date: (First Patient First Visit)	23 Mar 2009
Study Completion Date: (Last Patient Last Visit)	14 Nov 2012
Report Date:	Final, 30th June 2014

The trial was performed in compliance with the ICH-Good Clinical Practice (GCP) guideline (CPMP/ICH/135/95) and regulations, including the archiving of essential documents.

2 SYNOPSIS

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

Name of Active Ingredient: Terbinafine hydrochloride

Title of the study: Multicentre, randomized, double-blind within frequency of administration, placebo controlled, dose-finding, parallel-group, efficacy and safety study of 3 doses of P-3058 nail lacquer (5% o.d., 10% o.d. and 10% o.w.) given for 52 weeks in patients with onychomycosis

EudraCT number: 2008-002707-10

Investigators: 37 Principal Investigators in 7 countries (9 in Italy, 1 in Latvia, 10 in Germany, 8 in Czech Republic, 1 in France, 7 in Poland and 1 in Canada)

Study centres: 37 investigational study sites in 7 countries (9 in Italy, 1 in Latvia, 10 in Germany, 8 in Czech Republic, 1 in France, 7 in Poland and 1 in Canada)

Publication (reference): Not applicable

Study period: First patient enrolled: 23 Mar 2009; Last patient completed: 14 Nov 2012 | **Phase of development:** 2

Objectives:

The primary objectives of the study were:

- To assess the effective dose(s) in terms of weekly dose of P-3058 versus vehicle in the treatment of onychomycosis;
- To evaluate the shape and the location of the dose response-curve of the efficacy outcome (responder rate).

The secondary objective of the study was to determine the maximal dose beyond which additional benefit would be unlikely to occur.

Methodology:

This was a multicentre, randomized, double blind within frequency of administration, vehicle-controlled, parallel-group, dose finding, phase II clinical study.

The study used a Central Blinded Evaluator who was responsible to evaluate, under blinded conditions, the eligibility of each patient according to the clinical inclusion criteria: mild-to-moderate distal subungual onychomycosis, involving ≥ 25% to ≤ 60% of the distal nail plate, absence of yellow spikes and/or dermatophytomas, without lunula/matrix involvement. This was done by reviewing photographs taken by the Investigator and using planimetry measurements of the infected target nail area. Moreover, the Central Blinded Evaluator was responsible to evaluate, under blinded conditions, clinical study efficacy endpoints.

The study consisted of five arms comparing P-3058 10% o.d., P-3058 5% o.d., vehicle o.d.,P-3058 10% o.w. and vehicle o.w. nail solution, randomized on a 3:3:2:3:1 ratio.

The duration of the whole study per patient was 80 (+1) weeks: 4 (+1) weeks of screening, 52 weeks of treatment phase and 24 weeks of follow-up phase (from week 52 until week 76).

Number of patients (total and in each arm):

	Randomised	Safety	ITT	MITT	PP
Total	588	585	585	370	224
P-3058 10% o.d.	148	147	147	93	57
P-3058 5% o.d.	147	147	148	94	59
P-3058 10% o.w.	151	150	150	91	51
Vehicle	142	141	140	92	57

Diagnosis and main criteria for inclusion:

Written informed consent before starting any study related procedures; patients aged ≥12 up to 80 years old; males or females; outpatients; patients with established clinical diagnosis of mild-to-moderate distal sub-ungual onychomycosis,

(i.e., involving ≥ 25% to ≤ 60% of the distal bed-adherent nail plate without involvement of the lunula) as assessed by the Central Blinded Evaluator, caused by dermatophytes, affecting at least one big toenail; patients with positive potassium hydroxide (KOH) examination from the target big toenail obtained at screening; patients with positive culture for dermatophytes in screening nail sample.

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

P-3058 nail solution administered at the following concentrations and regimens: Group A: P-3058 5% o.d.; Group B: P-3058 10% o.d.; Group D: P-3058 10% o.w.

Used batches: 5476 (expiry July 2010) and 1002 (expiry March 2013) for P-3058 5%; 5477 (expiry July 2010) and 1003 (expiry March 2013) for P-3058 10%

Duration of treatment: 52 weeks

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

Nail solution vehicle administered at the following regimens: Group C: vehicle o.d.; Group E: vehicle o.w.

Used batches: 5475 (expiry June 2010); 1001 (expiry March 2013)

Criteria for evaluation:

Efficacy

The primary efficacy variable of the study was the Responder Rate at the end of follow-up (76 weeks). The Responder Rate was calculated as the proportion of patients with a diseased target nail area lower than or equal to 10% of the total as evaluated by a central, blinded Assessor, associated with a conversion to negative of culture for dermatophytes and of KOH microscopy.

The secondary efficacy variables were:

- Responder Rate at week 16, 28, 40, 52 and 64;
- Time to Response, defined as the time (days) to reach the efficacy outcome responder, calculated as time elapsed between first drug administration date and the first date in which the endpoint was reached (for a responder patient) according to the central, blinded Assessor;
- Cure Rate at week 16, 28, 40, 52, 64 and 76. The Cure Rate was calculated as the proportion of patients with a complete replacement of diseased nail with new healthy nail as evaluated by a central, blinded Assessor, associated with a conversion to negative of culture for dermatophytes and KOH microscopy;
- Time to Cure, defined as the time (days) to reach the efficacy outcome cure, calculated as time elapsed between first drug administration date and the first date in which the endpoint was reached (for a cured patient) according to the central, blinded Assessor;
- Mycological Cure Rate, defined as negative KOH microscopy and negative culture for dermatophytes at week 4, 16, 28, 40, 52, 64 and 76;
- Rate of Negative Culture for dermatophytes at week 4, 16, 28, 40, 52, 64 and 76;
- Rate of Negative KOH Microscopy at week 4, 16, 28, 40, 52, 64 and 76;
- Rate of Diseased Nail Area ≤ 10% at week 16, 28, 40, 52, 64 and 76;
- Rate of Clinical Cure, defined as no residual involvement of onychomycosis in the target nail (diseased nail area = 0%) at week 16, 28, 40, 52, 64 and 76;
- Responder Rate by Local Investigator at week 16, 28, 40, 52, 64 and 76;
- Rate of Diseased Nail Area ≤10% by Local Investigator at week 16, 28, 40, 52, 64 and 76;
- Rate of Clinical Cure by Local Investigator at week 16, 28, 40, 52, 64 and 76;
- Rate of Relapse at week 76, calculated as the proportion of responder patients at week 52 with at least one among the following criteria at week 76: diseased target nail area >10%, culture positive for dermatophytes, and KOH microscopy positive;
- Rate of Responders at weeks 64 and 76 among patients non-responders at week 52;
- Growth Rate of healthy nail(s) at week 16, 28, 40, 52, 64 and 76, as evaluated by a central, blinded Assessor, calculated as: 1) [(100% - percentage of surface of the nail involved at each visit) – (100% - percentage of surface of the nail involved at baseline)], and 2) in terms of proximal distance of the notch to the Eponychium (as a percentage of total

nail length) as: [(percentage of proximal distance of the notch to the Eponychium at each visit) – (percentage of proximal distance of the notch to the Eponychium at baseline)];

- Number of toenails/fingernails with clinical evidence of onychomycosis;
- Acceptance of Therapy by patient, based on a 4-point assessment scale: 4 = "very good", 3 = "good", 2 = "moderate", 1 = "poor", collected at the end of treatment visit (week 52);
- Measurements of treatment compliance, evaluated in terms of amount of remaining product in the dispensed bottles: "Bottle empty", "Residual < 25%", "Residual between 25% and 50%", "Residual between 50% and 75%", "Residual > 75%", "Bottle not used", "NA".

Safety

The safety variables of the study were:

- Adverse events (AEs);
- Laboratory parameters (haematology, clinical chemistry and urinalysis);
- Vital signs (weight, heart rate, blood pressure and body temperature);
- ECG;
- Physical examination.

Statistical methods:

The following populations were considered for analysis: safety population/Intention-to-treat (ITT) population, defined as all randomized patients with signed informed consent and with at least one documented application of the investigational drug; modified ITT (MITT) population, defined as all patients in the safety/ITT population with presence of dermatophytes in the nail sample collected at the screening visit and with confirmed clinical eligibility criteria as assessed under blinded conditions by the central, blinded Assessor, namely the International Scientific Study Coordinator (ISSC); per-protocol (PP) population, defined as all patients in the MITT population who completed the follow-up phase of the study without any major protocol violation. The primary efficacy analyses were performed in the MITT population, while supportive analyses were performed in the PP and in the safety/ITT population. The analysis of safety parameters were performed in the safety population.

The results were presented in the form of descriptive statistics, i.e., number of observations, 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 two vehicle groups (o.d. and o.w.) were considered as one group. However, in order to highlight potential efficacy of the vehicle, summary statistics of efficacy outcomes were also presented separately for each vehicle group and the results were also summarized for the comparison of each P-3058 treatment group vs. the vehicle group with the same application frequency.

In the analysis of the results of primary variable (responder rate at the end of follow-up, week 76), a logistic regression model was estimated for the dichotomous dependent variable indicating the responder/non responder outcome, with treatment (P-3058 10% o.w., 5% o.d., 10% o.d. or the vehicle) as the categorical independent variable, and a value = 1 when response was achieved.

The comparison of each dose level versus vehicle was carried out according to the step-down Bonferroni-Holm procedure, that uses the ordering of p-values independently from magnitude of doses, so as to maintain the experiment-wise error α=0.05. Confidence intervals, adjusted according to the Bonferroni method, were provided. Where the variable response had a distribution among treatments with cell frequencies less than five for one of its levels, the results from an exact logistic regression model were considered.

In addition, to investigate the shape of the dose-response curve, another logistic model was estimated treating the weekly dose as a continuous independent variable and testing linear and the quadratic components. The models were also fitted considering weekly dose on the logarithmic scale. Models estimates were presented together with goodness of fit indices. A further inferential analysis by repeated measures logistic regression was performed where variable treatment had 5 levels (i.e., considering each vehicle group separately).

In order to take into account potential efficacy of the vehicle, a logistic model was fitted also considering the two vehicle groups separately and performing the comparison with each P-3058 treatment group vs. the vehicle group with the same application frequency. Absolute and relative frequencies of responders in each treatment group, with asymptotic standard error, asymptotic (Wald) and exact (Clopper-Pearson) 95% confidence limits were also provided (overall and for the subpopulation of patients with at least 28 weeks of treatment).

In the LOCF imputation, results at discontinuation visits were re-allocated to the nearest visit, while in Worst Case, Best

Case and Complete Case approaches used to handle with missing data they were not used.

The analyses for the primary efficacy end-point were also applied to the cure rate at week 76. The comparisons between groups of all the other secondary categorical variables were performed with Chi square tests (or the Fisher Exact test in case of cell frequencies less than 5). Logistic regression models were also estimated in the analysis of responder rate and cure rate at week 64 (also excluding the re-screened Patient 201391) and of rate of negative culture for dermatophytes.

The proportions of responders and cured patients were also computed focusing on patients aged ≤ 70 years, on patients with a diseased area at screening ≤ 50% (+5% tolerability range), on patients aged ≤ 70 years and with a diseased area at screening ≤ 50% (+5% tolerability range).

The results of times to response and time to cure were analyzed by the Kaplan-Meier method. The Log-rank test was used for the comparisons between groups.

The results of growth rate of healthy nail(s) were presented as descriptive statistics. The difference among groups was tested by means of a mixed model for repeated measures, with treatment, visit and interaction between treatment and visit as fixed effects.

The results of the number of toenails/fingernails with clinical evidence of onychomycosis were presented as descriptive statistics. Inferential analysis was performed to evaluate the effect of treatment exposure (visit as proxy variable) and of each of the three P-3058 weekly doses versus vehicle on the number of toenails with clinical evidence of onychomycosis considering as covariate the number of toenails with clinical evidence of onychomycosis at baseline.

The proportion of patients per each score of the scale evaluating the acceptance of therapy was provided by treatment group. A Wilcoxon test was applied to test difference between treatment groups.

In the analysis of compliance data, the amount of remaining product in the dispensed bottles was presented with absolute and relative frequency for each level, by dispensed bottle, visit and treatment group.

The incidence of all adverse events, of serious adverse events and of severe adverse events and of adverse events related to study drug was calculated by Preferred Term and System Organ Class (MedDRA dictionary, version 14).

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 (also considering FDA ranges for abnormalities). In addition, shift tables in relation to normal ranges were produced to assess changes at the end of treatment versus 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, 25^{th} and 75^{th} percentiles, minimum and maximum values.

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

Study population:

Of the 1209 screened patients, 585 were included in the safety/ITT population and 370 were included in the MITT population (215 patients did not fulfil the MITT criteria). Of patients in the MITT population, 93 were included in the P-3058 10% o.d. group, 94 in the P-3058 5% o.d. group, 91 in the P-3058 10% o.w. group and 92 in the vehicle o.d./o.w group.

In the overall MITT population 224 patients completed the study (57 in the P-3058 10% o.d. group, 59 in the P-3058 5% o.d. group, 51 in the P-3058 10% o.w. group, and 57 in the vehicle groups), while 146 patients (36 in the P-3058 10% o.d. group, 35 in the P-3058 5% o.d. group, 40 in the P-3058 10% o.w. group, and 35 in the vehicle groups) prematurely discontinued the study. Protocol violation was the most common cause of study discontinuation.

The mean (± SD) age at baseline in the overall safety population was 53.31 ± 12.01 years (range 18-78 years). The overall safety population included more females (62.97%) than males (37.03%). The vast majority of patients were Caucasians. The overall mean percentage of total onychomycotic target nail area (MITT population) was 40.68± 10.80. The overall mean number of affected nails (MITT population) was 6.43 ± 3.26.

Extent of exposure and compliance:

The mean (± SD) extent of exposure was 245.14 ± 158.72 days in the P-3058 10% o.d. group, 229.02 ± 160.36 days in the P-3058 5% o.d. group, 225.25 ± 167.92 days in the P-3058 10% o.w. group, 240.24 ± 158.28 days in the vehicle o.d. group and 255.23 ± 153.64 days in the vehicle o.w. group.

Most of the dispensed bottles were returned empty or with a residual <25%, suggesting a high compliance to treatment by the study patients in all groups. The percentages of bottles returned empty or with a residual <25% in the MITT population were 68.43%, 66.86%, 60.66% and 69.37% in the P-3058 10% o.d. group, P-3058 5% o.d. group, P-3058 10% o.w. group and vehicle groups, respectively.

Efficacy results:

Primary efficacy variable: responder rate at the end of follow-up (76 weeks)

MITT population

The results of responder rate at week 76 in the MITT population with the different used imputations are presented in the table below:

Imputation Used	Response	P-3058 10% o.d. N=93		P-3058 5% o.d. N=94		P-3058 10% o.w. N=91		Vehicle N=92		P value
		N	%	N	%	N	%	N	%	
LOCF	Yes	15	16.13	16	17.02	21	23.08	19	20.65	0.6019
Best	Yes	37	39.78	36	38.30	41	45.05	37	40.22	0.8065
Worst	Yes	15	16.13	14	14.89	18	19.78	19	20.65	0.6886
Complete	Yes	15	21.13	14	19.44	18	26.47	19	25.68	0.7042
	Missing	22		22		23		18		

With the LOCF imputation, the highest rate of response at Week 76 was observed in the P-3058 10% o.w. group (23.08%; exact 95% CI: 14.89-33.09%), while the response rate in the vehicle group (20.65%; exact 95% CI: 12.92-30.36%) was higher than that observed with the once daily regimens, P-3058 10% o.d. (16.13%; exact 95% CI: 9.32-25.20%) and P-3058 5% o.d. (17.02%; exact 95% CI: 10.05-26.16%).

The results observed with the Best Case imputation showed higher rates compared to the LOCF imputation, however again with highest rates in the P-3058 10% o.w. group and lower rates with the two once daily P-3058 groups than with vehicle. With the Worst Case and Complete Case approaches, response rates were higher in the P-3058 10% o.w. group and in the vehicle group than in the P-3058 10% o.d. and the P-3058 5% o.d. groups.

The comparison among all groups of responder rate at week 76 did not show statistically significant differences with any of the tested approaches.

In the logistic regression model, none of the three regimens of P-3058 showed a statistically difference compared to vehicle ($p = 0.4281$ for the P-3058 10% o.d. group, $p = 0.5270$ for the P-3058 5% o.d. group and $p = 0.6915$ for the P-3058 10% o.w. group with the LOCF imputation). The Odds Ratio for P-3058 10% o.w. vs. vehicle was 1.15 (Bonferroni adjusted 95% CI: 0.49-2.72) suggesting a possible, although not statistically significant, treatment effect. No statistically significant differences with any active treatment vs. vehicle were also observed with the Best, the Worst or the Complete approach.

The results of the logistic regression model for repeated measures did not show statistically significant treatment effects. The Odds Ratio for P-3058 10% o.w. versus vehicle with the LOCF imputation was 1.31 (95% CI: 0.72-2.40) suggesting a possible, although not statistically significant, treatment effect. Similar findings were reported with the other approaches.

MITT population with at least 28 weeks of treatment

The results of responder rate at each visit in the MITT population with at least 28 weeks of treatment showed that the proportion of responder rate at week 76 resulted slightly higher than in the MITT population, and (LOCF imputation) was higher in the P-3058 10% o.w. group (25.00%; exact 95% CI: 15.99-35.94%) than in the other groups (which ranged from 17.05% in the P-3058 10% o.d. group to 21.84% in the vehicle. group). The comparison among all groups of responder rate at week 76 did not show statistically significant differences with any approach.

PP population

With the LOCF approach, the rates of response at Week 76 were higher in the P-3058 10% o.w. group (27.45%; exact 95% CI: 15.89-41.74%) and in the vehicle group (28.07%; exact 95% CI: 16.97-41.54%) than with the once daily regimens, P-3058 10% o.d. (21.05%; exact 95% CI: 11.38-33.89%) and P-3058 5% o.d. (16.95%; exact 95% CI: 8.44-29.97%). The

comparison among all groups did not show statistically significant differences (p = 0.4375). The rates of response at Week 76 with the Best approach, the Worst approach and the Complete approach were similar to those observed with the LOCF approach.

In the logistic regression model (maximum likelihood estimates), none of the three regimens of P-3058 showed a statistically difference compared to vehicle, as well as the treatment interaction in the logistic regression model for repeated measures was not significant. In this latter model, the Odds Ratio for the P-3058 10% o.w. group versus the vehicle group

with the LOCF approach was 1.28 (95% CI: 0.63-2.60) suggesting a possible, although not statistically significant, treatment effect.

Secondary efficacy variables:

Responder Rate at week 16, 28, 40, 52 and 64

In the MITT population, the comparison among all groups on responder rate did not show statistically significant differences at any time point. The maximum rate of P-3058 efficacy was observed at week 64, i.e.,12 weeks after the end of treatment. In the logistic regression model, P-3058 10% o.w. was the most effective dosage at week 64, with an Odds Ratio versus vehicle equal to 2.00 (Bonferroni adjusted 95% CI: 0.77-5.18), whereas for P-3058 10% o.d. and for P-3058 5% o.d. the Odds Ratios versus vehicle were 1.08 (Bonferroni adjusted 95% CI: 0.39-3.04) and 1.07 (Bonferroni adjusted 95% CI: 0.38-3.00). However, none of the three regimens of P-3058 showed a statistically difference compared to vehicle on responder rate at week 64 in the logistic regression model.

In the PP population, the comparison among all groups on responder rate did not show statistically significant differences at any time point, except at Week 16, where a response was observed only in patients in the P-3058 10% o.d. group (5.26%). The results of the logistic regression model in the PP population were consistent with those observed in the MITT population.

In the MITT population with at least 28 weeks of treatment, the comparison among all groups did not show statistically significant differences at any time point. In any case, the figures observed in P-3058 10% o.w. group were clinically relevant: in fact at week 64 the rate of responders was 25% in comparison to 13.79% observed in vehicle group.

Time to response

In the MITT population, a response in 25% of patients was observed at comparable times in the P-3058 10% o.d. group (17.18 months), in the P-3058 5% o.d. group (17.74 months) and in the vehicle groups (17.38 months), while the time of achievement of response in 25% of patients was slightly anticipated in the P-3058 10% o.w. group (15.11 months) compared to the other groups. However, the log-rank model did not show statistically significant differences in the comparisons between any of the three regimens of P-3058 and vehicle. The results of time to response in the PP population were consistent to those observed in the MITT population.

Cure Rate at week 16, 28, 40, 52, 64 and 76

In the MITT population (LOCF approach), the greatest cure rate was observed at week 64 in the P-3058 10% o.w. group(10.99%, exact 95% CI: 5.40-19.28%) and was maintained up to 76 weeks, while the greatest cure rate in all the daily treatment groups was observed at the end of follow-up (76 weeks), and was 8.60% in the P-3058 10% o.d. group (exact 95% CI: 3.79-16.25%) and 8.51% (exact 95% CI: 3.75-16.08) in the P-3058 5% o.d. group. The lowest cure rate was observed in the vehicle group (6.52%; exact 95% CI: 2.43-13.66%). The comparison among all groups did not show statistically significant differences at any time point. The results of cure rate with the Best approach showed that the cure rate at week 76 was higher in the active treatment groups than in the vehicle group, however without statistically significant differences between groups at any time point. Lower cure rates, however higher in the actively-treated groups than in the vehicle group, were observed with the Worst approach and the Complete approach.

In the logistic regression model, the Odds Ratios in the comparisons vs. vehicle were 1.35 (Bonferroni adjusted 95% CI: 0.35-5.17) in the P-3058 10% o.d. group, 1.33 (Bonferroni adjusted 95% CI: 0.35-5.11) in the P-3058 5% o.d. group and 1.77 (Bonferroni adjusted 95% CI: 0.49-6.43) in the P-3058 10% o.w. group, thus suggesting a trend of superiority (although not significantly) of all P-3058 doses in comparison to vehicle. The results of the logistic regression model for repeated measures with the Best approach showed that the treatment interaction was not significant, with the highest Odds Ratio versus the vehicle group observed in the P-3058 10% o.w. group (1.73; 95% CI: 0.95-3.15).

The cure rates at week 76 in the PP population were higher than those observed in the MITT population. The highest cure rate was observed in the P-3058 10% o.w. group (17.65%; exact 95% CI: 8.40-30.87%) than in the other groups (P-3058 10% o.d. group: 10.53, exact 95% CI: 3.96-21.52%; P-3058 5% o.d. group: 10.17, exact 95% CI: 3.62-20.83%; vehicle group: 10.53, exact 95% CI: 3.96-21.52%).As in the MITT population, the results in the PP population in terms of cure rate, in the logistic regression analysis on cure rate at week 64 and 76, and in the logistic regression model for repeated

measures, showed that P-3058 10% o.w. was the most effective treatment, although the difference between groups was not significant.

The comparison among all groups on cure rate at any time point in the MITT population with at least 28 weeks of treatment did not show statistically significant differences at any time point, except at week 28 in the Best approach (p = 0.044), due to a higher cure rate in the P-3058 5% o.d. than in the other groups.

In the logistic regression model (maximum likelihood estimates), none of the three regimens of P-3058 showed a statistically difference compared to vehicle, as well as the treatment interaction in the logistic regression model for repeated measures was not significant. In this latter model, the Odds Ratio for the P-3058 10% o.w. group versus the vehicle group with the LOCF approach was 1.28 (95% CI: 0.63-2.60) suggesting a possible, although not statistically significant, treatment effect.

Secondary efficacy variables:

Responder Rate at week 16, 28, 40, 52 and 64

In the MITT population, the comparison among all groups on responder rate did not show statistically significant differences at any time point. The maximum rate of P-3058 efficacy was observed at week 64, i.e.,12 weeks after the end of treatment. In the logistic regression model, P-3058 10% o.w. was the most effective dosage at week 64, with an Odds Ratio versus vehicle equal to 2.00 (Bonferroni adjusted 95% CI: 0.77-5.18), whereas for P-3058 10% o.d. and for P-3058 5% o.d. the Odds Ratios versus vehicle were 1.08 (Bonferroni adjusted 95% CI: 0.39-3.04) and 1.07 (Bonferroni adjusted 95% CI: 0.38-3.00),. However, none of the three regimens of P-3058 showed a statistically difference compared to vehicle on responder rate at week 64 in the logistic regression model.

In the PP population, the comparison among all groups on responder rate did not show statistically significant differences at any time point, except at Week 16, where a response was observed only in patients in the P-3058 10% o.d. group (5.26%). The results of the logistic regression model in the PP population were consistent with those observed in the MITT population.

In the MITT population with at least 28 weeks of treatment, the comparison among all groups did not show statistically significant differences at any time point. In any case, the figures observed in P-3058 10% o.w. group were clinically relevant: in fact at week 64 the rate of responders was 25% in comparison to 13.79% observed in vehicle group.

Time to response

In the MITT population, a response in 25% of patients was observed at comparable times in the P-3058 10% o.d. group (17.18 months), in the P-3058 5% o.d. group (17.74 months) and in the vehicle groups (17.38 months), while the time of achievement of response in 25% of patients was slightly anticipated in the P-3058 10% o.w. group (15.11 months) compared to the other groups. However, the log-rank model did not show statistically significant differences in the comparisons between any of the three regimens of P-3058 and vehicle. The results of time to response in the PP population were consistent to those observed in the MITT population.

Cure Rate at week 16, 28, 40, 52, 64 and 76

In the MITT population (LOCF approach), the greatest cure rate was observed at week 64 in the P-3058 10% o.w. group(10.99%, exact 95% CI: 5.40-19.28%) and was maintained up to 76 weeks, while the greatest cure rate in all the daily treatment groups was observed at the end of follow-up (76 weeks), and was 8.60% in the P-3058 10% o.d. group (exact 95% CI: 3.79-16.25%) and 8.51% (exact 95% CI: 3.75-16.08) in the P-3058 5% o.d. group. The lowest cure rate was observed in the vehicle group (6.52%; exact 95% CI: 2.43-13.66%). The comparison among all groups did not show statistically significant differences at any time point. The results of cure rate with the Best approach showed that the cure rate at week 76 was higher in the active treatment groups than in the vehicle group, however without statistically significant differences between groups at any time point. Lower cure rates, however higher in the actively-treated groups than in the vehicle group, were observed with the Worst approach and the Complete approach.

In the logistic regression model, the Odds Ratios in the comparisons vs. vehicle were 1.35 (Bonferroni adjusted 95% CI: 0.35-5.17) in the P-3058 10% o.d. group, 1.33 (Bonferroni adjusted 95% CI: 0.35-5.11) in the P-3058 5% o.d. group and 1.77 (Bonferroni adjusted 95% CI: 0.49-6.43) in the P-3058 10% o.w. group, thus suggesting a trend of superiority (although not significantly) of all P-3058 doses in comparison to vehicle. The results of the logistic regression model for repeated measures with the Best approach showed that the treatment interaction was not significant, with the highest Odds Ratio versus the vehicle group observed in the P-3058 10% o.w. group (1.73; 95% CI: 0.95-3.15).

The cure rates at week 76 in the PP population were higher than those observed in the MITT population. The highest cure rate was observed in the P-3058 10% o.w. group (17.65%; exact 95% CI: 8.40-30.87%) than in the other groups (P-3058 10% o.d. group: 10.53, exact 95% CI: 3.96-21.52%; P-3058 5% o.d. group: 10.17, exact 95% CI: 3.62-20.83%; vehicle group: 10.53, exact 95% CI: 3.96-21.52%).As in the MITT population, the results in the PP population in terms of cure

rate, in the logistic regression analysis on cure rate at week 64 and 76, and in the logistic regression model for repeated measures, showed that P-3058 10% o.w. was the most effective treatment, although the difference between groups was not significant.

The comparison among all groups on cure rate at any time point in the MITT population with at least 28 weeks of treatment did not show statistically significant differences at any time point, except at week 28 in the Best approach ($p = 0.044$), due to a higher cure rate in the P-3058 5% o.d. than in the other groups.

Time to cure

In the MITT population, a cure in 25% of patients was observed at comparable times in the P-3058 10% o.d. group (18.37 months), in the P-3058 5% o.d. group (18.56 months) and in the vehicle groups (18.20 months), while the time of achievement of cure in 25% of patients was slightly anticipated in the P-3058 10% o.w. group (17.38 months) compared to the other groups. However, the log-rank model did not show statistically significant differences in the comparisons between any of the three regimens of P-3058 and vehicle. The results of time to cure in the PP population were consistent to those observed in the MITT population.

Mycological Cure Rate at week 16, 28, 40, 52, 64 and 76

In the MITT population, the proportion of patients with mycological cure at week 76 was (LOCF approach) 43.01% (exact 95% CI: 32.78-53.69%) in the P-3058 10% o.d. group, 38.30% (exact 95% CI: 28.46-48.90%) in the P-3058 5% o.d. group (proportion already achieved at week 64), 41.76% (exact 95% CI: 31.50-52.57%) in the P-3058 10% o.w. group, and 42.39% (exact 95% CI: 32.15-53.14%) in the vehicle group. In the P-3058 10% o.w. group, the highest proportion of patients with mycological cure was achieved at week 64 (46.15%, exact 95% CI: 35.64-56.92%). The comparison among all groups did not show statistically significant differences at any time point.

The results with the Best approach showed that the mycological cure rate at week 64 was higher in the two active groups with 10% concentration (P-3058 10% o.d. group: 61.29%; P-3058 10% o.w. group: 65.93%) than in the P-3058 5% o.d. group (56.38%) and in the vehicle group (54.35%), with more comparable rates observed across all groups at week 76. The comparison among all groups showed a statistically significant difference at week 4 ($p = 0.0451$), due to a lower rate observed in the vehicle group compared to all the other groups. Lower cure rates were observed with the Worst approach and the Complete approach, with lower rates of mycological cure rate at week 76 in the P-3058 5% o.d. group compared to the other groups.

The results of mycological cure rate in the PP population were consistent to those observed in the MITT population, with a lower rate of patients with mycological cure rate at week 76 in the P-3058 5% o.d. group than in the other groups.

Rate of negative culture for dermatophytes at week 16, 28, 40, 52, 64 and 76

In the MITT population, the largest rate of conversion to negative culture for dermatophytes at week 76 (LOCF approach) was achieved in the P-3058 10% o.d. group (73.12%; exact 95% CI: 62.92-81.79%), with comparable rates in the other groups. At week 64, the highest proportion of conversion to negative culture was observed in the P-3058 10% o.w. group (74.73%; exact 95% CI: 64.53-83.25%). Statistically significant differences between groups were observed at week 4 ($p<0.0001$), week 16 ($p = 0.0012$), week 40 ($p = 0.0166$) and week 52 ($p = 0.0064$), due to higher rates of conversion in the actively-treated groups compared to the vehicle group. The results with the Best, Worst and Complete approach were comparable to those observed with the LOCF approach (however with a trend towards higher rates with the Best approach and lower rates with the Worst approach). Statistically significant treatment effects for all actively-treated groups vs. vehicle at weeks 4, 16, 40 and 52 were also observed in the logistic regression analysis.

The results of the logistic regression model for repeated measures showed a statistically significant treatment effect ($p = 0.0004$) and a statistically significant treatment-visit interaction ($p = 0.0365$). The Odds Ratios (95% confidence limits) of treated groups versus vehicle were 2.29 (1.47-3.58) for the P-3058 10% o.d. group, 2.03 (1.31-3.15) for the P-3058 5% o.d group and 2.10 (1.34-3.27) for the P-3058 10% o.w. group.

The results of the pairwise comparisons of rate of negative culture for dermatophytes at each visit in the MITT population showed that the difference between all actives and vehicle was significant at week 16, 40 and 52 (end of treatment).

In the PP population, statistically significant differences between groups were observed at week 4 ($p = 0.0013$) and week 52 ($p = 0.0068$), due to higher rates of conversion in the actively-treated groups compared to the vehicle group. The largest rate of conversion to negative culture for dermatophytes at week 76 was achieved in the P-3058 10% o.d. group (77.19%), although the difference between groups was not statistically significant. At week 64, the highest proportion of conversion to negative culture was observed in the P-3058 10% o.w. group (78.43%).

Rate of Negative KOH Microscopy at week 4, 16, 28, 40, 52, 64 and 76

In the MITT population, the greatest proportions of patients with a conversion to negative KOH microscopy were observed (LOCF approach) in the P-3058 10% o.w. group at week 64 (49.45%; exact 95% CI: 38.80-60.14%). At week 76, the rate

of patients with negative KOH microscopy was comparable in all actively-treated groups and in the vehicle group. The comparison among all groups did not show statistically significant differences at any time point.

The results with the Best, Worst and Complete approach did not show differences between groups at any time point. With all the tested approaches, the rate of patients with negative KOH microscopy at week 76 was lower in the P-3058 5% o.d. group than in the other groups.

The results of rate of negative KOH microscopy in the PP population were consistent with those observed in the MITT population.

Rate of Clinical Cure at week 16, 28, 40, 52, 64 and 76

In the MITT population, the greatest proportions of patients with clinical cure were observed at week 76 in all groups. The rate (LOCF approach) at week 76 observed in the P-3058 10% o.w. group (16.48%; exact 95% CI: 9.53-25.73%) and in the vehicle group (16.30%; exact 95% CI: 9.42-25.46%) was higher than that observed in the P-3058 10% o.d. group (15.05%; exact 95% CI: 8.48-23.97%) and in the P-3058 5% o.d. group (12.77%; exact 95% CI: 6.77-21.24%). The comparison among all groups did not show statistically significant differences at any time point.

The results of rate of clinical cure with the Best, Worst and Complete approach did not show differences between groups at any time point, except at week 16 ($p = 0.0392$) and week 28 ($p = 0.0359$) in the analysis with the Best approach, due to higher rates in the P-3058 5% o.d. group and in the P-3058 10% o.w. group compared to the P-3058 10% o.d. group and the vehicle group. With all the tested approaches, the rate of patients with clinical cure at week 76 was higher in the P-3058 10% o.w. group than in the other groups.

In the PP population, the rate of clinical cure at week 76 (LOCF approach) was higher in the P-3058 10% o.w. group (25.49%) than in the other groups (P-3058 10% o.d. group: 15.79%; P-3058 5% o.d. group: 15.25%; vehicle group: 21.05%). The comparison among all groups did not show statistically significant differences at any time point, except at week 64 ($p = 0.0319$), due to a higher rate in the P-3058 10% o.w. group (21.57%) and a lower rate in the in the P-3058 10% o.d. group (3.51%) compared to the P-3058 5% o.d. group (10.17%) and the vehicle group (12.28%).The results of clinical cure rate with the Best, Worst and Complete approach were consistent with those observed with the LOCF approach.

Rate of Relapse at week 76

In the MITT population, relapse at week 76 among responder patients at week 52 was observed in 5/7 patients (71.43%) in the P-3058 10% o.d. group, in 3/4 patients in the P-3058 5% o.d. group (75.00%), in 5/7 patients (71.43%) in the P-3058 10% o.w. group and in 4/7 (57.14%) patients in the vehicle group. The difference between groups was not statistically significant ($p = 1.000$).The results of rate of relapse at week 76 with the Best, Worst and Complete approach did not show differences between groups at any time point, as well as no statistically significant differences between groups being observed in the PP population.

Rate of Responders at weeks 64 and 76 among patients non-responders at week 52

In the MITT population, the greatest proportion of responders among non-responders at week 52 was observed at the end of follow-up (76 weeks) in all groups, and (LOCF approach) was higher in the P-3058 10% o.w. group (19.05%; exact 95% CI: 11.30-29.08%) and in the vehicle group (17.65%; exact 95% CI: 10.23-27.43%) than in the P-3058 10% o.d. group (11.63%; exact 95% CI: 5.72-20.35%) and in the P-3058 5% o.d. group (14.44%; exact 95% CI: 7.92-23.43%). The comparison among all groups did not show statistically significant differences at both week 64 and week 76. The results with the Worst and Complete approach were consistent with those observed with the LOCF approach, while the results observed with the Best approach showed a higher rate at week 76 observed in the P-3058 10% o.w. group (33.33%) than in the other groups (26.03% in the P-3058 10% o.d. group, 25.33% in the P-3058 5% o.d. group and 23.19% in the vehicle group), although without statistically significant differences between groups.

The results of responders at weeks 64 and 76 among non-responders at week 52 in the PP population were consistent with those observed in the MITT population, although without statistically significant differences between groups with any of the tested approaches.

Growth Rate of healthy nail/s at week 16, 28, 40, 52, 64 and 76

Surface of the nail involved at each visit

In the MITT population, the mean values of onychomycotic target nail area progressively decreased from screening up to week 76 in all groups. The extent of the absolute decrease from screening to week 76 was more marked in the P-3058 10% o.w. group than in all the other groups. The results in the PP population were consistent with those observed in the MITT population.

Proximal distance of the notch to the Eponychium

In the MITT population, the mean values of proximal distance of the notch to the Eponychium increased from screening

up to week 76 in all groups. The extent of the absolute increase from screening to week 76 was more marked in the P-3058 10% o.w. group than in all the other groups. The results in the PP population were consistent with those observed in the MITT population.

Growth rate of the surface of the healthy nail

In the MITT population, the mean values of growth rate of the surface of the healthy nail increased from week 4 up to week 76 in all groups. The extent of the absolute increase from week 4 to week 76 was more marked in the P-3058 10% o.w. group and in the vehicle group than in the P-3058 10% o.d. group and in the P-3058 5% o.d. group. The comparison between groups with the logistic regression model for repeated measures showed a statistically significant treatment effect in the comparison between the P-3058 10% o.d. group and the vehicle group ($p = 0.0130$), and statistically significant treatment-visit interaction effects in the comparison between the P-3058 10% o.d. group and the vehicle group at week 16 ($p = 0.0441$), week 52 ($p = 0.0174$), week 64 ($p = 0.0449$) and week 76 ($p = 0.0073$), as well as in the comparison between the P-3058 5% o.d. group and the vehicle group at week 76 ($p = 0.0228$). The results in the PP population were consistent with those observed in the MITT population.

Growth rate of the proximal distance of the notch to the Eponychium

In the MITT population, the mean values of growth rate of the proximal distance of the notch to the Eponychium increased from week 4 up to week 76 in all groups. The extent of the absolute increase from week 4 to week 76 was slightly more marked in the P-3058 10% o.w. group and in the vehicle group than in the P-3058 10% o.d. group and in the P-3058 5% o.d. group. The comparison between groups with the logistic regression model for repeated measures did not show statistically significant treatment effects or treatment-visit interactions. The results in the PP population were consistent with those observed in the MITT population. However, the logistic regression model for repeated measures showed statistically significant treatment-visit interaction effects in the comparison between the P-3058 10% o.d. group and the vehicle group at week 40 ($p = 0.0310$).

Number of toenails/fingernails with clinical evidence of onychomycosis

In the MITT population, the mean values of total number of toenails with evidence of onychomycosis was lower at week 76 compared to the screening visit in all groups. The comparison between groups with the logistic regression model for repeated measures showed a statistically significant treatment effect in the comparison between the P-3058 5% o.d. group and the vehicle group ($p = 0.0449$), as a result of a better outcome observed in the former group (mainly up to week 28), and statistically significant treatment-visit interaction effects in the comparison between the P-3058 5% o.d. group and the vehicle group at week 16 ($p = 0.0202$), week 28 ($p = 0.0102$) and week 40 ($p = 0.0218$), as well as in the comparison between the P-3058 10% o.w. group and the vehicle group at week 16 ($p = 0.0231$), again due to a better result in the actively-treated groups (mainly up to week 28).

The mean number of fingernails at week 76 was comparable to that at the screening visit. Therefore, the results of the total nails (toenails and fingernails) with evidence of onychomycosis were consistent with those of toenails.

The results in the PP population were consistent with those of the MITT population. However, the comparison between groups of number of toenails with evidence of onychomycosis with the logistic regression model for repeated measures (Section 14, Table 2.3.14.2-2) did not show statistically significant treatment effects but showed statistically significant treatment-visit interaction effects in the comparison between the P-3058 5% o.d. group and the vehicle group at week 16 ($p = 0.0264$) and at week 52 ($p = 0.0214$), due to better results in the P-3058 5% o.d. group (mainly up to week 28).

Acceptance of therapy

In the MITT population, $\geq 90\%$ of patients in all groups reported a moderate to very good acceptance of therapy at end of treatment (week 52): rates were 90.00% in the P-3058 10% o.d. group, 93.51% in the P-3058 5% o.d. group, 93.59% in the P-3058 10% o.w. group, 93.88% in the vehicle o.d. and 100.00% in the vehicle o.w. group. There were no statistically significant differences between treatment groups and vehicle groups. The results of acceptance of therapy in the PP population were consistent with those observed in the MITT population.

Assessments by local investigator

The assessment of the secondary efficacy end-points evaluated by the local Investigator (responder rate, rate of diseased nail area $\leq 10\%$ and rate of clinical cure) were in general consistent to those of central assessment, although rates from the assessment of the local Investigator were lower than those of the Central Blinded Assessor.

Subgroup analyses

Patients aged ≤ 70 years

As in the overall MITT population, the highest rate of response at Week 76 was observed in the P-3058 10% o.w. group (23.26%), while the response rate in the vehicle group (22.35%) was higher than that observed with the once daily regimens, P-3058 10% o.d. (16.28%) and P-3058 5% o.d. (17.98%). The highest responder rate was observed in the P-3058 10% o.w. group at week 64 (24.42%).The highest rate of cure at Week 76 was observed in the P-3058 10% o.w. group (10.47%), while the response rate observed with the once daily regimens, P-3058 10% o.d. (8.14%) and P-3058 5% o.d. (8.99%) was

comparable to that observed in the vehicle group (7.06%). The highest responder rate was observed in the P-3058 10% o.w. group at week 64 (11.63%).

Disease target nail area ≤ 50%

The highest rate of response at Week 76 was observed in the P-3058 10% o.w. group (25.00%), while the response rate in the P-3058 10% o.d. group (15.48%) and in the P-3058 5% o.d. group (19.05%) was comparable to that observed in the vehicle group (18.60%). The responder rate in the P-3058 10% o.w. group at week 76 was already observed at week 64.

The highest rate of cure at Week 76 was observed in the P-3058 10% o.w. group (11.25%), while the response rate in the P-3058 10% o.d. group (8.33%) and in the P-3058 5% o.d. group (9.52%) was slightly higher than that observed in the vehicle group (6.98%). The cure rate in the P-3058 10% o.w. group at week 76 was already observed at week 64.

Patients aged ≤ 70 years and disease target nail area ≤ 50%

The highest rate of response at Week 76 was observed in the P-3058 10% o.w. group (25.33%), while the response rate in the P-3058 5% o.d. group (20.00%) and in the in the vehicle group (20.25%) was higher than that observed in the P-3058 10% o.d. group (15.58%). The highest responder rate was observed in the P-3058 10% o.w. group at week 64 (26.67%).

The rate of cure at Week 76 was higher in the P-3058 5% o.d. group (10.00%) and in the P-3058 10% o.w. group (10.67%) than in the P-3058 10% o.d. group (7.79%) and in the in the vehicle group (7.59%). The highest cure rate was observed in the P-3058 10% o.w. group at week 64 (12.00%).

Safety results:

Adverse events:

Out of the 585 patients included in the Safety Population, 174 patients overall (29.74%) reported at least one adverse event (all causalities).

The rate of patients with adverse events was lower in the P-3058 10% o.w. group than in all the other groups. Adverse events were reported in 51 patients (34.69%) in the P-3058 10% o.d. group, in 50 (34.01%) in the P-3058 5% o.d. group, in 30 (20.00%) in the P-3058 10% o.w. group, in 27 (28.72%) in the vehicle o.d. group and in 16 (34.04%) in the vehicle o.w. group. Infections and infestations and nervous system disorders were the most commonly involved SOCs. Headache and nasopharyngitis were the most commonly reported adverse events by preferred term.

Eight patients overall (1.37%), 4 (2.72%) in the P-3058 10% o.d. group, 2 (1.36%) in the P-3058 5% o.d. group, 1 (0.67) in the P-3058 10% o.w. group, and 1 (1.06%) in the vehicle o.d. group had serious adverse events. None of the serious adverse events was fatal.

Treatment-related adverse events were reported in 6 patients overall (1.03%), and were reported in 1 patient (0.68%) in the P-3058 10% o.d. group, in 2 (1.33%) in the P-3058 10% o.w. group, in 1 (1.06%) in the vehicle o.d. group and in 2 (4.26%) in the vehicle o.w. group. Apart from one case of nervousness in 1 patient in the P-3058 10% o.w. group, all treatment-related adverse events consisted of local reactions at the site of application.

Overall, 4 patients (0.68%) discontinued the study due to adverse events, 2 (1.36%) in the P-3058 10% o.d. group and 2 (1.36%) in the P-3058 10% o.w. group. None of these events was treatment-related.

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. Importantly, there was no evidence of alteration in hepatic functions (that is a potential side effect of oral terbinafine) in any treatment group. The results of laboratory parameters in form of shift tables based on low/normal/high values with respect to normal range from baseline to the last available post-baseline value showed that, in all groups, most of patients had normal values in all parameters at both baseline and the last post-baseline visit, or values that did not change category between the baseline and the last post-baseline visit. Moreover, the proportion of patients with normal values at baseline and abnormal values at the last post-baseline visit was comparable to that of patients with abnormal values at baseline that were normalised at the last post-baseline visit.

Vital signs:

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

ECG:

Although performed in a minority of patients, there were no clinically relevant post-baseline ECG abnormalities in any group.

Physical examination:

In all groups, the proportion of patients with abnormal findings at the end of treatment (week 52), at the end of follow-up (week 76) or at the discontinuation visit was generally lower than that observed at baseline for all the examined body

districts.

Conclusions:

- The results of the primary efficacy variable showed that responder rate at the end of follow-up (week 76) was higher in the P-3058 10% o.w. group than in the once daily P-3058 10% and P-3058 5% groups and in the vehicle group.
- Although no tested dose regimen was significantly superior at week 76 to P-3058 vehicle, a trend of superiority emerged for the 10% once weekly dosage regimen and the observed response rate in the P-3058 10% o.w. group (23.08%) can be considered clinically relevant when compared to published pivotal data from recently approved topical antimycotic drugs..
- The results on primary outcome using the LOCF imputation clearly show that the maximum rate of P-3058 efficacy is already achieved three months after the end of treatment. In particular, in the P-3058 10% o.w. group the highest rate of response (23.08%) was observed at week 64 and was maintained for a further three months (last observation time-point).
- The results of the sub-analysis carried out in patients aged ≤ 70 years and with ≤ 50% disease involvement of the target nail at baseline at week 64 were in general the most clinically relevant among those observed in the other population analysed (MITT, MITT with at least 28 weeks of treatment, MITT with disease target nail area ≤ 50% and MITT with patients aged ≤ 70 years).
- In the PP population (LOCF imputation), although no statistically significant differences versus vehicle were achieved, the rate of responders and cured patients in the P-3058 10% o.w. group at week 64 were numerically clinically relevant. In fact, the figures were 29.4% and 15.7% respectively. When patients are adherent to treatment, the results of the study PM0731 are consistent with effect sizes in two efinaconazole pivotal studies reported by Elewski in 2013, the most recent antimycotic drug approved by FDA. Moreover, in the treated population the effect size comparison for P-3058 10% o.w vs. vehicle in responder rate was 13.6%, closely comparable to the 14% value reported for oral terbinafine administered daily for 12 weeks at a dosage of 250 mg vs. vehicle (Svejgard, 1997).
- The results of most of the secondary endpoints (e.g., cure rate, time to response, time to cure, mycological cure rate, clinical cure, evaluations performed by the local Investigator, growth rate of healthy nails) showed that, overall, P-3058 10% o.w. was the most effective treatment dosage, although the comparisons between groups did not show statistically significant differences. As expected, analyses of the MITT population found statistically significant differences between the P-3058 vehicle and each of the 3 active P-3058 treatments with respect to the negative dermatophytes culture rates.
- P-3058 10% administered once weekly exposes the patients to negligible terbinafine systemic exposure in comparison to once daily dosage schedule.
- All the P-3058 formulations and regimens were well tolerated in terms of local and general adverse reactions, and of systemic safety.
- P-3058 10% o.w. was shown to be more effective than the two once daily formulations in the primary and in most of the secondary efficacy endpoint. Moreover, the efficacy of P-3058 10% o.w. at week 64 relative to vehicle was even better in the subgroup of patients aged ≤ 70 years and with ≤ 50% disease involvement of the target nail at baseline.

Considering the more pronounced efficacy rate in the population aged ≤ 70 years and with ≤ 50% disease involvement of the target nail at baseline observed three months after the end of treatment, the low drug exposure among the three P-3058 treatments dosage tested, the convenience of switching to once weekly administration and the excellent safety profile, P-3058 10% o.w, preceded by a loading dose of 4 weeks daily application, is the most appropriate candidate for Phase 3 trials in the treatment of mild-to-moderate distal subungual onychomycosis due to dermatophytes.