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ORIGINAL ARTICLE

An innovative water-soluble biopolymer improves efficacy of ciclopirox nail lacquer in the management of onychomycosis

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Abstract

Background A new 8% ciclopirox-medicated nail lacquer (P-3051), based on a new technology, revealed superior properties in terms of affinity to keratin, nail permeation, and ease of use.

Objective This study aims to assess the efficacy and safety of P-3051 vs. the market 8% ciclopirox nail lacquer.

Methods This is a multicentre, randomized, three-arm, placebo-controlled, parallel groups, evaluator-blinded study. Overall, 467 patients with onychomycosis of at least one big toenail were randomized to receive P-3051, the reference drug or placebo in a 2 : 2 : 1 ratio for a 48-week treatment by daily application, followed by a 12-week follow-up.

Results The study satisfied its objective by demonstrating that P-3051 was both superior to placebo and non-inferior to reference in the complete cure rate after a 48-week active treatment period. Switching the non-inferiority to superiority hypothesis, the superiority of P-3051 vs. reference was nearly significant at week 48 (confirmed at week 52), and it was significant at week 60 (cure rate for P-3051 is 119% higher than reference; $P < 0.05$). Altogether, the results on primary endpoint exceed expectations; superiority test was performed also on secondary endpoints to confirm the superiority trend of the study. At the end of follow-up, percentages of patients who achieved the endpoint 'responder' in the P-3051 group were 66% higher than reference ($P < 0.05$), and those who achieved the endpoint 'decrease of diseased nail' were 40% higher ($P < 0.05$).

Conclusion Ciclopirox 8% hydrolacquer is more active than reference ciclopirox nail lacquer in the treatment of onychomycosis.

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Keywords

ciclopirox, hydroxypropyl chitosan, onychomycosis, water-soluble nail lacquer

Conflicts of interest

None declared.

Introduction

An original technology was developed by Polichem SA (Lugano, Switzerland) for delivery of actives to nails, based on hydroxypropyl chitosan (HPCH), a water-soluble semisynthetic biopolymer, which acts as a film-forming agent. A new 8% ciclopirox nail hydrolacquer (P-3051) based on this new technology revealed superior properties in terms of affinity to keratin, nail permeation, and ease of use.[1–3] In *in vitro* studies, it strengthened the efficacy of antimycotic agents.[2] In long-term treatment, it is expected to be acceptable to patients because of its simple (water rinsing) removal procedure and because it does not need nail filing.

The drug tested in this study, P-3051, is a new hydrolacquer based on hydroxypropyl chitosan technology, which contains 8% ciclopirox as the sole active compound. The content of active principle within the formulation is quantitatively identical to that of the market reference nail varnish formulation (Penlac® in the USA, corresponding to Batrafen® or Mycoster® in Europe). The main difference is the solubility in water of the film-forming agent

in P-3051, which renders the new hydrolacquer permeable to moisture and air and the film non-glossy and non-sticky, whereas the vehicle of the reference drug is based on an insoluble polyvinyl resin.

The nail permeation of ciclopirox from P-3051 was reported to be more efficient than that of market reference in *in vitro* studies.[1–3]

The possible reasons for the greater efficiency of the HPCH vehicle in terms of ciclopirox transfer from the vehicle itself to the keratin membrane has been attributed to a particular affinity of HPCH for the nail matrix, resulting in intimate contact and strong adhesion of the HPCH lacquer to the keratin substrate.[4] Based on those results, it was assumed that a standard ≥ 6-h sleep period after application of P-3051 could allow ciclopirox penetration into the nails in a sufficient amount before possible removal by washing. This assumption has been confirmed by a preliminary nail concentration study on healthy volunteers, which demonstrated that 27% of the applied ciclopirox dose already penetrated in human fingernails within 6 h after the application of P-3051.[5]

Material and methods

Study design

A total of 24 European centres (France, Germany, Italy, Czech Republic, Latvia, Poland) participated in the clinical trial. The study was fully GCP compliant and the protocol was approved by the institutional ethics committees according to the local regulations. All patients enrolled provided their written informed consent before starting any of the protocol procedures.

Patients with distal subungual, mild-to-moderate onychomycosis of at least one big toenail (target nail) entered the trial. The target nail for efficacy analysis was chosen between the two big toenails, as the most affected within the eligibility criteria. According to the protocol, subjects had an infected area ≥ 25% and ≤ 60% of target nail. Only patients with dermatophyte infection, confirmed by both KOH microscopy and culture, were randomized to treatment. Patients with nail psoriasis, who were positive for yeasts or non-dermatophyte moulds on the nail specimen, and/or who were immunosuppressed were excluded. Local treatment of mycotic infections, with localization other than in the nails, was allowed.

After a run-in period of 4–8 weeks, during which the culture result of nail specimens was obtained, uneven random allocation of treatments (P-3051; market reference, placebo) by blocks of 5 (2: 2 : 1) was performed. Placebo was the matching vehicle of P-3051; thus, the treatment was double blind between the two arms P-3051 and placebo; the third arm (market reference) was open label, both because the appearance of the reference product and the treatment procedure were different from P-3051 and placebo (see below). The final evaluation of the primary and secondary clinical endpoints was centrally made in blind by the International Study Coordinator, who acted as blinded evaluator. Patients were instructed to perform daily application of the nail lacquer for 48 weeks, followed by a 4-week washout and a further 8-week follow-up period.

Treatment procedures

The compositions of the study drugs as declared by the manufacturers were as follows: (i) P-3051 – ciclopirox 80 mg/g, water, ethanol, hydroxypropyl chitosan, cetyl stearyl alcohol, ethyl acetate; (ii) placebo – water, ethanol, hydroxypropyl chitosan, cetyl stearyl alcohol, ethyl acetate; and (iii) reference – ciclopirox 80 mg/g, ethyl acetate, isopropyl alcohol, butylmonoester of poly[methylvinyl ether/maleic acid] in isopropyl alcohol.

The nail lacquers were applied once a day (preferably at bed-time, at least 8 h before washing) to all affected nails with a brush, over the entire nail plate and approximately 5 mm of the surrounding skin and to any exposed nail bed, the hyponychium, and the under-surface of the nail plate.

According to the labelling of the reference nail lacquer, the patients randomized to that treatment were instructed to actively remove once a week the entire week's accumulation of lacquer by means of napkins soaked in 70% isopropyl alcohol and to gently file the nail surface with an emery board provided by the investigator. P-3051 or placebo were simply removed by water and no filing of the nail surface was necessary.

The free edge of the nails had to be trimmed on a regular basis, and any onycholytic material removed.

Assessment procedures

The efficacy variables were evaluated on the target nail and included the KOH microscopy, the fungal culture of the nail specimen and the percentage of the infected nail area on the total nail surface. The primary endpoint was 'Complete cure', defined as conversion to negative of both KOH microscopy and fungal culture, and 100% growth of a healthy nail at week 48 (end of treatment), and confirmed at week 52 (washout). Secondary endpoints were: 'Responder', defined as conversion to negative of both KOH microscopy and fungal culture, and decrease of diseased nail area to ≤ 10% (including zero) of total as assessed by the blinded evaluator; 'Conversion to negative of culture'; and 'Growth rate of healthy nail'. Mycological evaluation and photographic planimetric measurements were performed at screening, at the end of run in (baseline), on a 12 weekly basis during treatment, at the end of treatment, at the washout and at the end of the 12-week follow-up.

The safety variables included overall safety evaluated by means of standard procedures: adverse events recording, vital signs and routine laboratory parameters, and by a specific evaluation of the local irritation potential.

Photographs and planimetry

Colour photographs were taken in standard conditions with a Polaroid Macro SLR 3 camera (Arcisate, VA, Italy). The patients placed the foot on a flat support designed for the purpose, that

blocked the target big toe in the very same position for each picture. Pictures (magnification ×2) were taken at a fixed distance of 13 cm.

At each visit, the local investigators took a picture of the target nail. All pictures were placed by the investigator in an album separated by the case report form (CRF). A transparent tape was put on the target big toenail and drawing of the affected area was made by a pencil, then the tape was placed on the album together with the picture. At the end of study, the albums were sent to a centralized laboratory (DermIng, Monza, Italy) for a computer-assisted, blind planimetric evaluation. All pictures were scanned and subjected to a computerized image analysis by means of a specific software designed for the purpose, according to a validated method.[6] The affected nail area was measured accordingly, based on the discoloration of the nail plate due to onychomycosis. The original pictures, the computer-assisted planimetric evaluation made on photographs and the affected area drawn by the sites on the transparent tape supported the International Scientific Study Coordinator (ISSC) in the blinded assessment of the percentage of affected area at all visits. Thus, the blinded evaluator reviewed for accuracy and for consistency of evaluation among sites, and the final judgement, in case of different opinion, was left to the judgement of the ISSC.

Local irritation potential

Skin irritation potential of P-3051, reference drug and placebo was evaluated by following the classification proposed by Berger *et al.*[7] referred to in the US Food and Drug Administration guideline.[8]

Statistical analysis

The estimated sample size consisted of 410 evaluable patients randomly allocated in a 2 : 2 : 1 ratio for P-3051, market reference and placebo, respectively. If a patient completed at least 6 months of treatment, the data collected were to be used in the analyses [both the common LOCF (last observation carried forward) and Schaffer's multiple imputation method]. With this sample size, the statistical power was 80% for the non-inferiority contrast 'P-3051 vs. reference' and 85% for the superiority contrast 'P-3051 vs. placebo'. Considering 10% as a reasonable figure for dropout, the drawn sample had to be no less than 460 patients.

Deviations from protocol were noticed by the ISSC in about 20% of patients as a result of his blinded evaluation of photographs, with proximal nail involvement and/or > 60% affected area (until 100%) at baseline. Before unblinding, it was decided to include all those patients into intent-to-treat (ITT) and per protocol (PP) populations. The primary parameter, complete cure rate, has been evaluated testing the superiority contrast, P-3051 vs. placebo, and the non-inferiority contrast, P-3051 vs. reference drug, in hierarchical sequence. The null hypothesis of inferiority had to be rejected if the lower two-tailed 95% confidence limit of the difference between P-3051 and reference drug complete cure rates was greater than –10%. We used the Fisher exact test for the comparison of P-3051 with placebo. Homogeneity of treatment difference among centres has been tested by means of the Breslow–Day test. The primary analysis was made on the ITT population; a confirmatory analysis was performed on the PP population.

Interpretation of non inferiority as superiority of P-3051 vs. reference drug was foreseen by the protocol in case the actual data justified the switch from non-inferiority to superiority, according to the CPMP/EWP/482/99.[9] Switching the non-inferiority to superiority hypothesis did not require any supplementary statistical analysis, considering that superiority was tested directly using the confidence limits calculated for non-inferiority objective. If the 95% confidence interval of the treatment difference not only lied entirely above –10%, but also above zero, then there was evidence of superiority of P-3051 vs. reference in terms of statistical significance at the 5% level ($P < 0.05$).

For the following secondary parameters – responder rate, decrease of diseased nail area to ≤ 10% of total, conversion to negative of culture – the 95% confidence interval of the rate difference was calculated for the contrast P-3051 vs. reference while the Fisher exact test was used to compare P-3051 with placebo.

For the growth rate of healthy nail, the analysis was conducted on the ITT analysis set only. Using treatment as a fixed effect and time as a random effect, a treatment by time interaction effect was estimated using the longitudinal models of Laird and Ware. ITT data in this approach were analysed as observed cases. Descriptive statistics were used to summarize the safety parameters.

Results

Demography and baseline characteristics

The actual number of randomized patients were 467; namely, 182 in the P-3051 group, 188 in the reference group and 97 in the placebo group. All patients were Caucasian, and there was a higher proportion of females compared to males in all groups. The three groups were similar with respect to sex, age and weight (Table 1). The three groups were also similar in the number of affected toenails (mean of about 4/patient), and in causative pathogen (i.e. *Trichophyton rubrum* in about 50–54% of cases, *Trichophyton mentagrophytes* in 37–39%, and *Epidermophyton floccosum* in 1–3% of cases).

The percentage of diseased target nail area – on average 43 – 44% in all groups – is consistent with a population of moderately to severely affected patients (Table 1). The patients with proximal involvement and/or > 60–100% affected nail area at baseline were 40 (22.1%) in P-3051, 38 (20.2%) in reference and 20 (20.6%) in placebo group.

Efficacy

The data on the primary endpoint are summarized in Fig. 1. The statistical analysis of the primary and secondary endpoints is summarized in Table 2. The study attained its primary objectives:

Table 1 Demography and baseline characteristics of randomized patients

Variable	Placebo (*n* = 97)	P-3051 (*n* = 181)	Reference (*n* = 188)	All patients (*n* = 466)
Gender				
Female (%)	73.2	58.6	62.8	63.3
Male (%)	26.8	41.4	37.2	36.7
Age (years)				
Mean ± SD	49.5 ± 12.43	49.47 ± 12.44	50.38 ± 11.09	49.84 ± 11.89
Weight (kg)				
Mean ± SD	73.88 ± 13.81	75.69 ± 13.62	75.31 ± 13.59	75.16 ± 13.64
Ethnicity				
Caucasian (%)	100	100	100	100
Positive KOH at baseline				
Percentage of patients	100	100	100	100
Positive culture at baseline				
Any dermatophyte (%)	100	100	100	100
Trichophyton mentagrophytes (%)	39.2	36.8	37.8	37.7
Trichophyton rubrum (%)	52.6	54.4	50.5	52.5
Trichophyton spp.(%)	5.1	5.5	6.9	6.0
Epidermophyton floccosum (%)	1.0	1.6	2.7	2.1
Other dermatophytes (%)	2.1	1.7	2.1	1.9
Total number of toenails with onychomycosis				
Mean ± SD	3.98 ± 2.44	4.36 ± 2.55	4.09 ± 2.54	4.17 ± 2.52
Percentage of diseased target nail area				
Mean ± SD	43.4 ± 18.8	44.5 ± 19.9	44.1 ± 18.8	44.1 ± 19.2

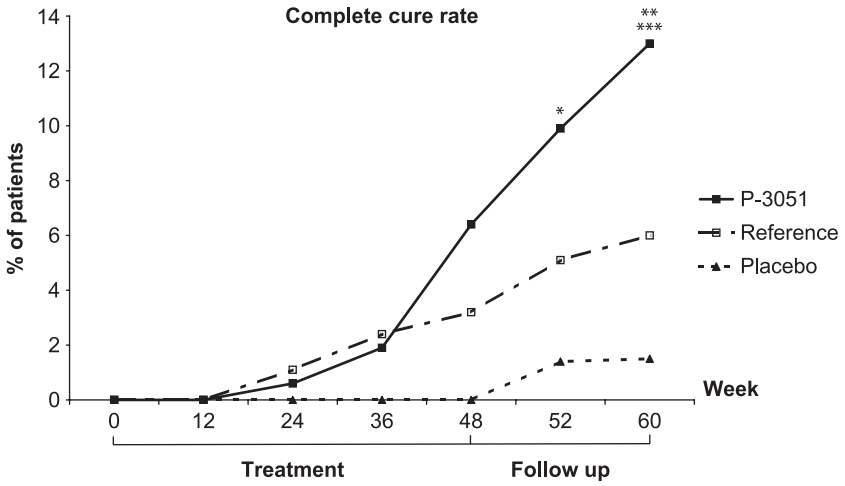

Figure 1 Complete cure rate during the active treatment period and follow-up. *P-3051 vs. Placebo *p*-value = 0.0143; **P-3051 vs. Placebo *p*-value = 0.0029; ***P-3051 vs. Reference *p*-value < 0.05 for the superiority comparison.

the P-3051-treated subjects obtained complete cure in 10/175 ITT and 10/167 PP subjects, compared to 0/94 ITT and 0/89 PP patients in the placebo group (Fisher exact test, $P = 0.0165$ in ITT and 0.0166 in PP). Reference-treated subjects obtained complete cure in 6/185 ITT and 6/177 PP patients.

Therefore, during the treatment period, P-3051 resulted definitely superior to placebo and not inferior to reference with a consistent trend to superiority for P-3051 vs. reference drug. Furthermore, at the end of follow-up (week 60), percentages of patients with complete cure, in P-3051 group, further increased compared to reference group, being 119% higher for cure rate ($P < 0.05$). This effect, due to continuous growth of healthy nail after the end of treatment, was not unexpected and was more evident in the P-3051 group.

The other analyses show consistent results. Conversion to negative of mycology culture was reached already at 12-week visit in 77% of patients in both P-3051 and reference drug, and 48% with placebo. Negative culture was then reached by about 90% of patients at the next time point, 24 weeks, and this performance was maintained until the end of treatment and 4-week washout.

Table 2 Statistical analysis on primary and secondary efficacy endpoints (intent-to-treat population)

Variable	P-3051	Reference	Placebo	P-3051 vs. placebo*	P-3051 vs. reference†
Primary endpoint					
Complete cure rate					
Week 48 (confirmed at week 52)	5.7 (10/175)	3.2 (6/185)	0 (0/94)	$P = 0.0165$	$P = 0.6834$
Week 60	12.7 (20/157)	5.8 (9/156)	1.3 (1/75)	$P = 0.0029$	$P < 0.05$‡
Secondary endpoints					
Rate of conversion to negative of culture					
Week 48	89.1 (156/175)	90.8 (168/185)	69.1 (65/94)	$P = 0.0001$	–1.7 (–7.9 ÷ 4.5)
Week 60	79 (124/157)	79.7 (126/158)	72.4 (55/76)	$P = 0.3204$	–0.8 (–9.7 ÷ 8.2)
Responder rate					
Week 48	24 (42/175)	17.3 (32/185)	6.4 (6/94)	$P = 0.0002$	6.7 (–1.6 ÷ 15.1)
Week 60	28.7 (45/157)	17.3 (27/156)	14.7 (11/75)	$P = 0.0217$	$P < 0.05$ ‡
Decrease of diseased nail rate					
Week 48	28 (49/175)	18.9 (35/185)	10.6 (10/94)	$P = 0.0011$	9.1 (0.4 ÷ 17.8)
Week 60	36.3 (57/157)	21.8 (34/156)	16.2 (12/74)	$P = 0.0020$	$P < 0.05$‡

Data are reported as the percentage and the absolute frequency vs. the number of valuable patients [% (n/N)]. Primary endpoint data are referred to week 48 confirmed at week 52. Secondary endpoints data are referred to week 48 if data are available or to the last recorded visit for discontinued patients (LOCF) and to week 60.

*Fisher exact test for the planned comparison P-3051 vs. placebo; †Risk difference with associated two-sided 95% confidence interval; ‡superiority comparison P-3051 vs. reference (Fisher exact test).

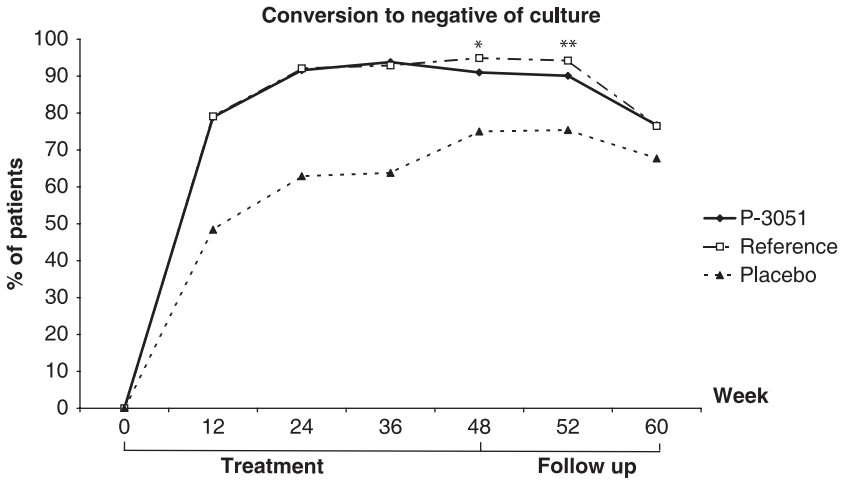

Figure 2 Conversion to negative of culture during the active treatment period and follow-up. *P-3051 vs. Placebo p-value = 0.0001; **P-3051 vs. Placebo p-value = 0.0162.

At the end of 12-week follow-up, negativity of culture was still present in 76% of patients who applied P-3051 or reference (Fig. 2).

At the end of treatment, the percentage of responders, in the P-3051 group, was consistently higher than in the reference group (Fig. 3). At the end of follow-up, percentages of responder patients in the P-3051 group further increased compared to the reference group, being 66% higher for responder rate ($P < 0.05$) in ITT population.

At end of treatment, the percentage of patients with decrease of diseased nail area to ≤ 10% of the total nail surface, was consistently higher in the P-3051 group than in the reference group (Fig. 4). At the end of follow-up, percentages in the P-3051 group further increased compared to the reference group, being 67% higher for responder rate ($P < 0.05$) in ITT population.

The estimates of weekly growth of healthy nail obtained by fitting straight lines to data of active treatment period were: +0.7‰ with placebo, +2.9‰ with P-3051 and +1.9‰ with reference. Only the comparison between P-3051 vs. placebo was found statistically significant ($P = 0.0015$) (Fig. 5).

Safety

Treatment-emergent adverse events (TEAE) occurred in about 23% of patients belonging to the safety data set ($n = 466$) and were equally distributed in the three treatment arms. In 1.1% of patients, TEAE were classified as definitely/possibly/probably

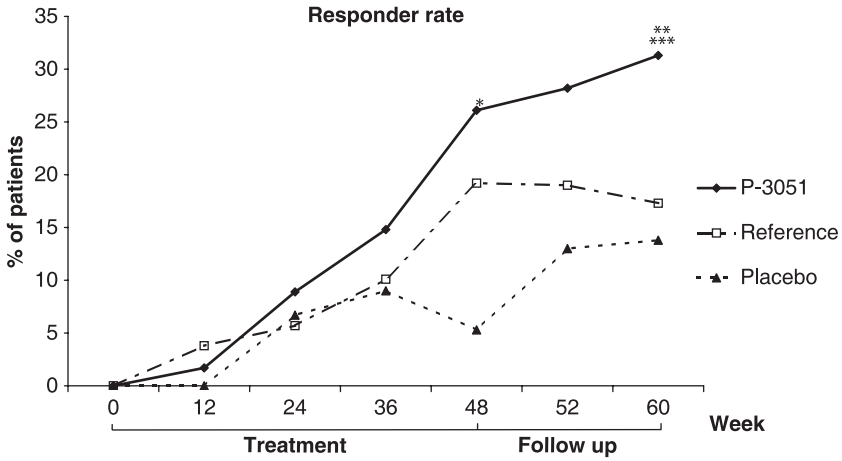

Figure 3 Responder rate during the active treatment period and follow-up.
*P-3051 vs. Placebo *p*-value = 0.0002;
**P-3051 vs. Placebo *p*-value = 0.0217;
***P-3051 vs. Reference *p*-value < 0.05 for the superiority comparison.

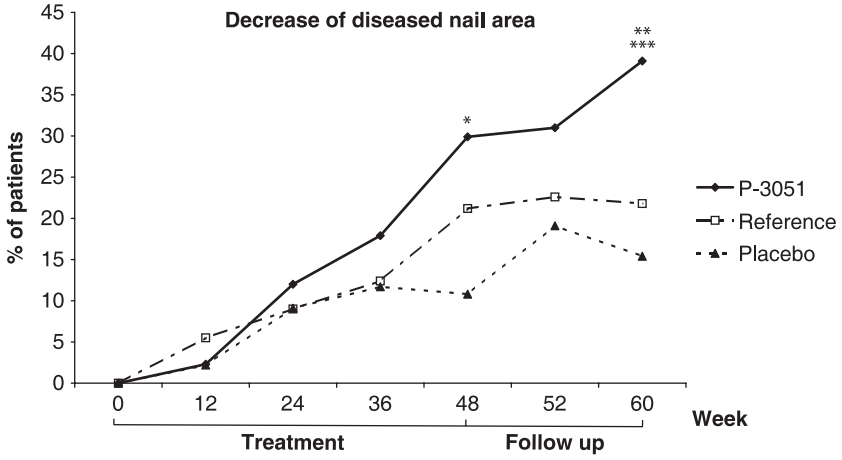

Figure 4 Decease of diseased nail area to 10% of the total nail surface during the active treatment period and follow-up.
*P-3051 vs. Placebo *p*-value = 0.001;
**P-3051 vs. Placebo *p*-value = 0.002;
***P-3051 vs. Reference *p*-value < 0.05 for the superiority comparison.

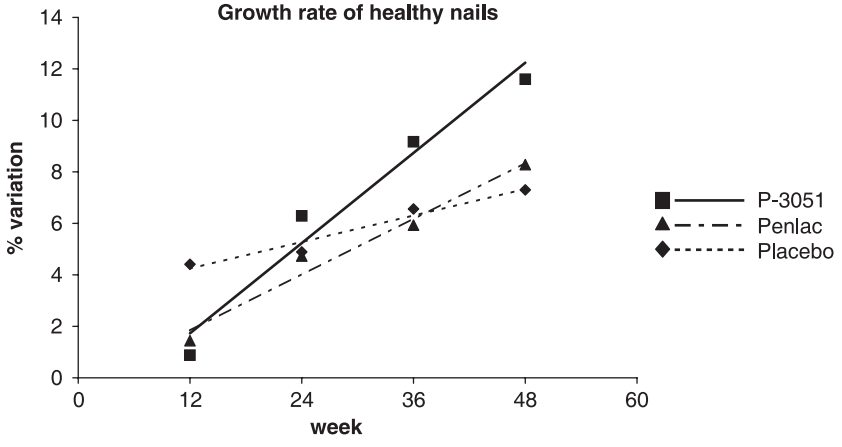

Figure 5 Growth rate of healthy nail during the active treatment period ($P < 0.05$ vs. placebo).

study drug related. No patients in P-3051 group experienced any TEAE drug related. Conversely, in 5 patients (2 patients in the reference group and 3 patients in the placebo group), drug-related TEAE were recorded. Among the drug-related TEAE, none was serious, severe or cause of dropout.

Only few signs and symptoms were recorded during the study without any increase on time. The subjective symptoms were short lasting after product application. Overall, signs were three times more frequent with reference drug (8.6%) than with P-3051 (2.8%), and symptoms were twice more frequent with reference

Table 3 Local safety at the application site. Categorical variables are summarized as percentage and absolute frequency vs. the number of patients belonging to the safety population [% (n/N)]

Variable	Placebo ($n = 97$)	P-3051 ($n = 181$)	Reference ($n = 188$)	All patients ($n = 466$)
Objective signs	**7.2 (7/97)**	**2.8 (5/180)**	**8.6 (16/187)**	**6.0 (28/464)**
Definite oedema	1 (1/97)	0 (0/181)	0 (0/188)	0.2 (1/466)
Definite erythema	3.1 (3/97)	0.6 (1/181)	2.1 (4/188)	1.7 (8/466)
Minimal erythema	3.1 (3/97)	2.2 (4/181)	6.4 (12/188)	4.1 (19/466)
Any symptoms occurred	**12.4 (12/97)**	**7.8 (14/180)**	**16 (30/187)**	**12.1 (56/464)**
Itching	7.2 (7/97)	2.8 (5/180)	1.6 (3/187)	3.2 (15/464)
Burning	4.1 (4/97)	2.8 (5/180)	10.7 (20/187)	6.3 (29/464)
Pain	2.1 (2/97)	1.7 (3/180)	3.2 (6/187)	2.4 (11/464)
Erythema	0.0 (0/97)	0.0 (0/180)	2.1 (4/187)	0.8 (4/464)
Other (not related)	2.1 (2/97)	1.1 (2/180)	3.2 (6/187)	2.2 (10/464)

(16%) than with P-3051 (7.8%). In the placebo group, 7.2% signs and 12.4% symptoms were recorded. The most frequent sign observed by the investigator was erythema (2.8% in P-3051 group, and 8.6% in reference group); redness was additionally reported by a further 2.1% of patients in the reference group. The most frequent symptom was burning, reported by 2.8% of patients in the P-3051 group and by 10.7% of patients in the reference group (Table 3).

No treatment-related systemic adverse event was recorded in any group.

Discussion

More females than males were included in our study, which is inconsistent with North American onychomycosis studies[10] and with many epidemiology studies[11] reporting that onychomycoses are more prevalent in men than in women. A possible explanation is that onychomycosis is a largely under-evaluated illness by patients, many of them still considering it as a cosmetic problem rather than as an infection. This could have led more females than males to visit doctors and require treatment in our study. The situation with the USA is different, because patients are paid in that country to participate in a clinical study (payment of patients to take part in a clinical trial is prohibited in Europe), and payment could represent a similar or higher incentive for men compared to women.

In our study, the effect of P-3051 and reference active treatments on mycological findings was similar, with about 90% conversion to negative of culture at the end of treatment. On the other hand, the composed mycological + clinical endpoints largely exceeded the expectations, with about better efficacy of P-3051 by over 100% in terms of cure rate and almost 70% in terms of responder rate compared to the reference. The actual results allowed the superiority analysis of P-3051 vs. the reference product, performed at the last time point in line with the CPMP/EWP/482/99,[9] which in fact confirmed the superiority of P-3051 vs. reference on cure rate ($P < 0.05$), responder rate ($P < 0.05$) and decrease of diseased nail area ($P < 0.05$). The continuous and increasing efficacy during the 12 weeks after the end of treatment on primary and secondary parameters – cure rate, responder rate and decrease of diseased nail – was not so unexpected, keeping in mind the continuous growth of clear nail in patients who, at 48-week time point, already reached the definitive mycology cure, but not the complete growth of new healthy nail. This effect was more evident in the P-3051 than in the reference group, and it was consistent with the growth rate of healthy nail parameter, where only the difference of P-3051 vs. placebo resulted statistically significant ($P = 0.0015$).

The rate of responsiveness of patients treated with the reference drug, in our experience, was consistent with published data of that product[10]: 18% of patients in our study reached the ≤ 10% involved area in presence of negativity to both culture and microscopy KOH examination.

Although significantly better than reference, the approximately 13% complete cure rate of P-3051 is still quite low. The inclusion of severe and proximal onychomycoses (homogeneously distributed into the three groups) may have contributed to this low cure rate. In a comparable patient population, oral terbinafine, which is considered the gold standard in the treatment of patients with onychomycosis, had an efficacy rate of about 38%.[12] Itraconazole and fluconazole, also widely used as oral treatments of onychomycosis, are even less effective than terbinafine.[13,14] None of those drugs is devoid of rare, serious adverse events (sometimes fatal, due to liver toxicity of terbinafine[12] and fluconazole[15] and to cardiac toxicity of itraconazole[16]) and drug–drug interactions (due to the extensive metabolism and inhibitory activity of P-450 isoenzymes).[12,15,16] Thus, there is still a strong medical need for active and safe treatments of onychomycosis, and mainly elderly people may benefit from the new treatment with P-3051. On the other hand, the efficacy rates in our study are consistent with the most recent literature concerning controlled studies,[10] which define endpoints as selective and rigorous as those used in our study. It is not surprising that higher efficacy rates are reported when choosing endpoints defined with less restrictive criteria.[17]

A recent paper by Scher *et al.*[18] reports a definition of onychomycosis cure, which responds to the absence of clinical signs or the presence of negative nail culture and/or microscopy results,

with one or more of minor clinical signs, including minimal distal subungual hyperkeratosis and nail-plate thickening. According to that paper, although nail appearance will usually continue to improve after cessation of therapy, the nails may have a persistent abnormal appearance even in cases where treatment has been effective. This corresponds to what has been defined as 'responder' in our study, and given that criterion the cure rate of patients in the P-3051 group of our study would have been approximately 29%, which is a more comfortable result of efficacy in this difficult-to-eradicate disease.

Overall, P-3051 was very well tolerated. The absence of systemic side-effects of the reference drug is known from the labelling of that product, and has been confirmed by the present investigation. P-3051 was also devoid of any systemic effect.

Local signs (erythema) were three times more frequent with reference than with P-3051 and symptom (burning) was four times more frequent with reference drug than with P-3051. As those effects were also less frequent in the placebo group compared to reference drug, it is concluded that the larger part of the minimal local irritation caused by the reference drug is due to the composition in inactive ingredients. These differ from P-3051 and reference drug in that the former contains a water-soluble film-forming agent (namely, hydroxypropyl chitosan) that has a much better local safety profile compared to the polyvinyl resin contained in the reference drug.

It is concluded that ciclopirox, formulated in the new hydrolacquer technology, besides being much easier to apply without needing any bothersome removal procedures, is far more active and better tolerated than the reference ciclopirox nail lacquer in the long-term treatment of onychomycosis. Thus, the availability of the new product P-3051 may represent a real therapeutic progress in the treatment of this difficult-to-eradicate and often recurring illness.

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