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Ciclopirox Hydroxypropyl Chitosan: Efficacy in Mild-to-Moderate Onychomycosis

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Keywords

Onychomycosis · P-3051 · Post hoc analysis · Antifungals · Randomized controlled trial · Prognostic factors

Abstract

The severity and percentage of nail involvement are usually considered the main prognostic factors for the treatment of onychomycosis. This study investigated the efficacy of P-3051 (ciclopirox [CPX] 8% nail lacquer in hydroxypropyl chitosan technology) in a population subset of the pivotal study, selected according to the criteria used in recent onychomycosis pivotal studies. The original study was a multicenter, randomized, three-arm, placebo-controlled, parallel groups, evaluator-blinded study comparing P-3051 with reference CPX (standard, insoluble 8% CPX nail lacquer) and placebo (P-3051 vehicle) in a 2:2:1 ratio, applied once daily for 48 weeks to 467 patients with onychomycosis, followed by a 12-week follow up. The primary endpoint was complete cure (negative mycology and 100% clear nail) at the end of treatment. Among the secondary endpoints, response rate (negative mycology and ≥90% clear nail) and negative culture were chosen as most representative for a clinical setting. A population subset (modified intention-to-treat population, 302 patients) was selected, excluding those with more severe disease (>50% nail involvement), in line with recent onychomycosis pivotal trials. P-3051 was superior to placebo in all parameters but culture at week 60 and was superior to reference CPX in cure and response rates at week 60. Compared to the overall patient population, efficacy rates in the P-3051 group were higher in the subset excluding patients with nail involvement >50%. Results increased by 33% (from 5.7 to 7.6%) at week 48 and by 19.0% (from 12.7 to 15.1%) at week 60 for cure rate, by 33% (from 24.0 to 31.9%) and 20% (from 28.7 to 34.5%) for response rate, and by 3% (from 89.1 to 91.6%) and 4.0% (from 79.0 to 82.4%) for culture conversion to negative. This post hoc analysis confirms that the severity of onychomycosis is a prognostic factor for responsiveness to antifungal treatments and that this can significantly affect reported efficacy data. The different inclusion criteria should be taken into account when reviewing the efficacy of antifungal agents from different studies.

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Introduction

Onychomycosis is a difficult infection to treat, requiring long-term treatment and good compliance to achieve eradication of the fungus for an acceptable clinical outcome. Comparing the clinical efficacy of different treatments is often difficult. Oral treatments are commonly believed to be more efficacious than topical ones, but the standards of evaluation vary among clinical studies, making comparison even more complex [1].

Efficacy criteria, length of treatment, and severity at baseline are considered the main factors that can affect patients' response to treatment in controlled trials. The criteria for evaluating efficacy in clinical trials used to be the main explanation of differences in results from study to study. Examples can be found in the evaluation of the efficacy of amorolfine between the pivotal study [2], reporting clinical and mycological cure in 45–51% of patients, and a more recent controlled randomized trial with the same drug [3], which reported a cure rate of <1% in an apparently similar patient population, with a similar treatment schedule. Other examples can be found in the literature for ciclopirox (CPX) [4] between the US pivotal studies and non-US studies. Currently, the accepted primary efficacy endpoint in onychomycosis trials is complete cure. Complete cure requires both clinical cure (the nail has a normal appearance) and mycological cure (negative KOH microscopy and negative culture). Clinical effectiveness (also defined as response rate or treatment success) based on negative KOH microscopy and negative culture for dermatophytes, with <10% residual involvement of the target toenail, is another important clinical outcome indicating patients who have responded to therapy.

Several factors (e.g., causative pathogens, clinical features, percentage of nail involvement, severity signs such as lunula involvement and/or yellow spikes, comorbidities) must be taken into consideration when selecting the modality of drug administration [5]. The disadvantages of oral treatments are that they are often limited by drug interactions and potential hepatotoxicity, while topical antifungals require an optimal vehicle and long treatment times. The duration of therapy is in fact 12 weeks for systemic antifungals and at least 48 weeks for topical antifungals. To be efficacious, a drug must reach effective levels in the nail and maintain them for enough time. Nail growth is very slow, especially in elderly populations, and regrowth of a healthy nail free of fungi requires 36–48 weeks.

Clinical assessment of cure should be scheduled 9–12 months after starting treatment, independently of the route of drug administration. This became evident in the first studies on systemic antifungals for onychomycosis, dating back to the 1990s [6, 7], where the protocol included 12 weeks of systemic therapy followed by 36 weeks of follow-up, after which cure was assessed. Those studies showed that the gradual reduction of the percentage of the nail involved by onychomycosis was significantly greater at the end of follow-up (week 48) than at the end of therapy (week 12). Since that time it has become clear that any clinical trial on onychomycosis therapy will need assessment of clinical cure after at least 48 weeks, and in any case much longer than the period of drug administration, bearing in mind the slow nail growth rate.

The same approach was adopted with topical antifungal drugs [3, 4, 8–11]. The adoption of the most stringent criterion of efficacy, namely complete cure (mycological and clinical), reduced the interstudy variability of the results, giving a more reliable measure of the treatment's efficacy. Nevertheless, differences in the design of randomized controlled trials still exist, accounting for differences in the evaluation of efficacy. One of the most important factors is the length of treatment and the need for a follow-up to test the cure [12] so as to avoid false-positive results in mycological assessment, but also to avoid defining as cured those patients who relapse within a short time.

The severity and proportion of target nail involvement remain the main prognostic factors in the treatment of onychomycosis [1]. Therefore, consistency among populations included and assessment parameters is needed to compare the efficacy results of different randomized controlled clinical trials of onychomycosis.

P-3051 (Polichem SA, Lugano, Switzerland), currently marketed in 35 countries worldwide, is an 8% CPX water-soluble nail lacquer based on hydroxypropyl chitosan technology, which has shown superior activity to both reference insoluble CPX [8] and amorolfine [11] commercial nail lacquers in the management of onychomycosis. In the overall evaluation of the pivotal study, 20% of the patients included in the efficacy analysis had severe onychomycosis (proximal involvement, yellow spikes, and/or >65% nail involvement) [8].

Our aim was to investigate the efficacy of P-3051 in a population subset of the pivotal study selected according to the criteria used in the latest onychomycosis pivotal trials [9, 10], namely mild-to-moderate distal subungual onychomycosis, no proximal involvement, and ≤50% nail involvement.

Patients and Methods

Study Design

The study was a prospective, randomized, parallel-group, three-arm study comparing P-3051 with reference CPX (standard, insoluble 8% CPX lacquer) and placebo (P-3051 vehicle). In all, 467 adults with onychomycosis (25–100% nail involvement) with positive KOH and culture were randomized to one of the three treatments with an allocation ratio of 2:2:1 for P-3051, reference CPX, or placebo, respectively, once daily for 48 weeks followed by a 12-week follow-up (at week 60).

Efficacy and Safety Assessments

The scheduled visits were screening and run-in visits (4–8 weeks) before randomization, in-treatment visits at weeks 4, 12, 24, and 36, an end of treatment visit at week 48, and follow-up visits at weeks 52 and 60.

For this post hoc analysis, we considered the following efficacy variables: complete cure rate (100% clear nail, negative KOH microscopy, and negative culture), response rate (≥90% clear nail, negative KOH microscopy, and negative culture), and culture conversion to negative. All parameters were examined at the end of treatment (week 48) and at the end of follow-up (week 60). The clinical evaluation was double-blinded (P-3051 versus placebo) and investigator-blinded (P-3051 versus reference CPX).

Analysis

The modified intention-to-treat (mITT) analysis dataset is a subset of the intention-to-treat (ITT) dataset obtained by excluding patients with baseline involvement >50% and/or severe onychomycosis and/or age >70 years. The safety population is the whole dataset of randomized patients.

Statistical Analysis

The original primary study objective was to demonstrate the noninferiority of the new drug P-3051 compared to the standard reference CPX with a placebo arm included as internal control. Thus, the primary endpoint (complete cure rate) was evaluated testing the superiority contrast, P-3051 versus placebo, and the noninferiority contrast, P-3051 versus reference CPX, in hierarchical sequence. For the comparison of P-3051 with placebo we employed the Fisher exact test. The null hypothesis of inferiority versus reference CPX would have been rejected if the lower two-tailed 95% confidence interval (CI) of the difference between test drug and reference CPX drug complete cure rates had been more than –10%.

In the new analysis, all three pairwise superiority contrasts were tested (i.e., P-3051 versus placebo, reference CPX versus placebo, and P-3051 versus reference CPX) with the Fisher exact test, considering the superiority comparison, P-3051 versus placebo, the primary one. In addition, two-sided exact 95% CIs for the difference in complete cure rates were calculated and reported for the three pairwise comparisons. Exact CIs were computed using the double binomial test implemented in the NCSS 2007 software.

Response rate and culture conversion to negative were analyzed on the modified ITT set. We used the Pearson χ^2 test to test the three pairwise comparisons, and risk differences in response rates were reported with their two-sided Wald 95% CIs.

A missing value at visit 7 (week 48, i.e., primary endpoint visit) was replaced with the last observation carried forward method, except for data missing for reasons related to treatment safety, which were filled in by default with the negative outcome.

Results

Demography and Baseline Characteristics

In all, 467 patients were randomized to placebo (n = 97), P-3051 (n = 182), or reference CPX (n = 188). All patients were given at least one dose of study medication, but 1 patient assigned to P-3051 was actually switched to reference CPX after 3 months and was thus excluded from the safety dataset. In 12 patients (3 in the placebo, 6 in the P-3051, and 3 in the reference CPX group), post-baseline efficacy data were not available, so they were excluded from the ITT dataset. About two-thirds of the ITT patients (302/454, 66.5%) had baseline involvement ≤50%, mild-to-moderate onychomycosis, and age ≤70 years, and were thus included in the mITT population. Details of the patients, with the types and frequencies of major protocol violations, are summarized by treatment groups in Table 1.

In the population subset of 302 patients in the mITT dataset, 34.1% had more than five onychomycotic nails. The mean proportion of target toenail involvement was 34.9%. The main pathogens were *T. rubrum* in 49.7% of patients and *T. mentagrophytes* in 40.1%. Qualitative and quantitative demographic characteristics of the mITT population were homogeneously distributed over the three arms. Excluding a slightly greater prevalence of the number of toenails involved in the P-3051 group, the baseline data showed no differences between treatment groups.

Efficacy

Efficacy results are reported in Figures 1–3 as the proportion of patients achieving the endpoint. Statistical analysis is reported in Table 2 in terms of relative difference, 95% CI, and p value.

Primary Endpoint Analysis – Complete Cure (Fig. 1). P-3051 was superior to placebo in the complete cure rate after 48 weeks of active treatment. The complete cure rates were 7.6% in the P-3051 group, 3.3% in the reference CPX group, and 0% in the placebo group for the mITT population. These figures indicate a significant difference between P-3051 and placebo (Fisher exact test, p = 0.028). At week 60, there were 15.1% of complete cures in the P-3051 group, 5.8% in the reference CPX

Table 1. Demographic characteristics of the patients included in the mITT population

Variable	P-3051 (n = 119)	Reference CPX (n = 120)	Placebo (n = 63)	All patients (n = 302)
Age, years				
Mean ± SD (N)	48.98±12.47 (119)	49.76±11.48 (120)	47.58±12.61 (63)	49±12.1 (302)
Median (min–max)	50.8 (19.3–69.7)	51.55 (21–69.9)	46.6 (18–68.7)	51.05 (18–69.9)
Weight, kg				
Mean ± SD (N)	74.49±13.48 (119)	74.77±13.34 (120)	72.54±12.93 (63)	74.19±13.3 (302)
Median (min–max)	74 (48–118)	72 (50–115)	72 (50–130)	72 (48–130)
Height, cm				
Mean ± SD (N)	171.62±7.65 (119)	170.49±7.62 (120)	169.73±8.78 (63)	170.78±7.89 (302)
Median (min–max)	170 (152–190)	169 (153–192)	170 (150–191)	170 (150–192)
Infected area, %				
Mean ± SD (N)	34.34±10 (119)	33.61±10.66 (120)	33.97±10.21 (63)	33.97±10.28 (302)
Median (min–max)	30 (15–50)	31.5 (5–50)	30 (15–50)	30 (5–50)
Sex, %				
Female	62.2 (74/119)	65.8 (79/120)	77.8 (49/63)	66.9 (202/302)
Male	37.8 (45/119)	34.2 (41/120)	22.2 (14/63)	33.1 (100/302)
Ethnicity, %				
Caucasian	100 (119/119)	100 (120/120)	100 (63/63)	100 (302/302)
Body frame, %				
Large	15.1 (18/119)	8.3 (10/120)	6.3 (4/63)	10.6 (32/302)
Medium	79 (94/119)	87.5 (105/120)	87.3 (55/63)	84.1 (254/302)
Small	5.9 (7/119)	4.2 (5/120)	6.3 (4/63)	5.3 (16/302)
Drug abuse, %	0 (0/119)	0 (0/120)	0 (0/63)	0 (0/302)
Alcohol abuse, %	0 (0/119)	0 (0/120)	0 (0/63)	0 (0/302)
Illness severity, %				
Mild	8.4 (10/119)	14.2 (17/120)	12.7 (8/63)	11.6 (35/302)
Moderate	91.6 (109/119)	85.8 (103/120)	87.3 (55/63)	88.4 (267/302)
Number of involved nails, %				
1–5	61.3 (73/119)	67.5 (81/120)	71.4 (45/63)	65.9 (199/302)
>5	38.7 (46/119)	32.5 (39/120)	28.6 (18/63)	34.1 (103/302)
Causative pathogen, %				
Other	10.1 (12/119)	11.7 (14/120)	7.9 (5/63)	10.3 (31/302)
T. mentagrophytes	37.8 (45/119)	41.7 (50/120)	41.3 (26/63)	40.1 (121/302)
T. rubrum	52.1 (62/119)	46.7 (56/120)	50.8 (32/63)	49.7 (150/302)

CPX, ciclopirox; mITT, modified intention-to-treat.

group, and 1.6% in the placebo group. P-3051 was significantly superior to both placebo (p = 0.004) and reference CPX (p = 0.021).

Response Rates (Fig. 2). The response rates at week 48 were 31.9% in the P-3051 group, 24.2% in the reference CPX group, and 9.5% in the placebo group. At week 60 the response rate was 34.5% in the P-3051 group, 20.8% in the reference CPX group, and 20.6% in the placebo group. P-3051 was significantly superior to placebo at week 48 (p = 0.001) and the difference was close to significance at week 60 (p = 0.052). P-3051 was also significantly superior to reference CPX at week 60 (p = 0.019).

Culture Conversion to Negative (Fig. 3). The rates of negative culture at week 48 were 91.6% in the P-3051 group, 90% in the reference CPX group, and 73% in the placebo group. At week 60, the rates of negative culture were 82.4, 75, and 76.2%, respectively. P-3051 was significantly superior to placebo at week 48 (p = 0.001).

Safety

The safety population of the post hoc analysis was identical to that of the original paper, so the results show no difference from those of the original evaluation. The treatments were generally safe, with a better safety profile in the P-3051 group, as previously reported [8].

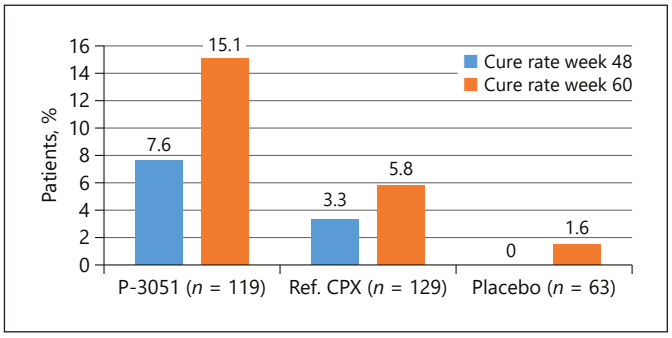

Fig. 1. Primary endpoint post hoc analysis: cure rate at the end of treatment (week 48) and at the end of follow-up (week 60) (100% clear nail, negative KOH microscopy, and negative culture). CPX, ciclopirox.

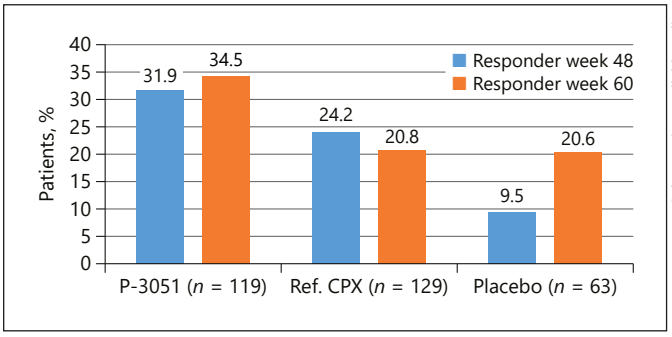

Fig. 2. Secondary endpoint post hoc analysis: response rate at the end of treatment (week 48) and at the end of follow-up (week 60) (≥90% clear nail, negative KOH microscopy, and negative culture). CPX, ciclopirox.

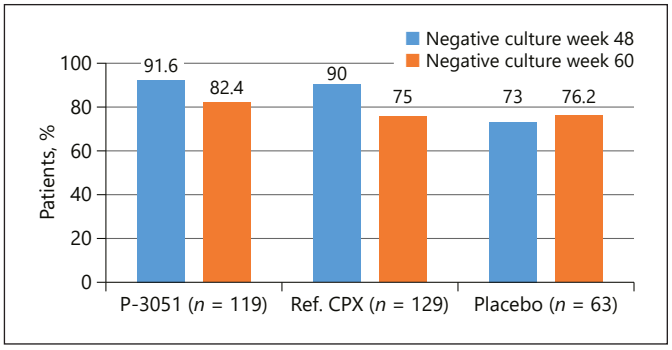

Fig. 3. Secondary endpoint post hoc analysis: culture conversion to negative at the end of treatment (week 48) and at the end of follow-up (week 60). CPX, ciclopirox.

Discussion

Onychomycosis is a chronic, hard-to-treat infection of the nails that can have a significant impact on patients' quality of life [13]. Therapeutic guidelines for treatment do exist [14], but they are not yet up to date on the latest scientific knowledge. Besides the classic treatments, oral terbinafine and itraconazole as well as topical CPX and amorolfine, other topical treatments have been proposed in recent years, including efinaconazole and tavaborole [9, 10]. In efinaconazole pivotal studies, complete cure was reported in 18 and 15% of patients, respectively. Comparing the patient populations in those studies and in previous pivotal studies on topical treatment of onychomycosis [3, 4, 8], the efinaconazole and tavaborole studies clearly included a population with milder disease than those on CPX insoluble, CPX water soluble (P-3051), and terbinafine nail lacquer. This might account for the apparently better efficacy of efinaconazole in comparison with other topical treatments in controlled randomized trials of distal subungual onychomycosis. This might also be confirmed by the apparently better results with placebo in efinaconazole studies, namely 3 and 6% complete cure rate [9] compared to placebo in the CPX water soluble pivotal study, and 0% at the end of treatment and 1.3% at the end of follow-up [8].

In our post hoc analysis on a population subset of the original CPX P-3051 pivotal study, excluding patients with >50% nail involvement and other markers of disease severity at baseline, the efficacy results with P-3051 are better both in terms of complete cure and response rates. P-3051 was superior to or close to superiority over placebo and to reference CPX in complete cure and response rates at the end of follow-up – the most reliable and robust efficacy endpoints for an antimycotic agent in terms of mycological and clinical parameters. Compared to the overall patient population, efficacy rates were better in the subset excluding patients with nail involvement >50% in P-3051. Results increased by 33% (from 5.7 to 7.6%) at week 48 and by 19% (from 12.7 to 15.1% at week 60) for cure rate, by 33% (from 24.0 to 31.9%) and 20% (from 28.7 to 34.5%) for response rate, and by 3% (from 89.1 to 91.6%) and 4% (from 79 to 82.4%) for culture conversion to negative. Most important, the significant superiority of P-3051 over placebo and reference CPX was maintained in almost all parameters considered, even though the size of the subset and the statistical power were lower than those planned in the original protocol.

In the CPX study, there was an effect of placebo on the culture conversion to negative. This is a typical effect of

Table 2. Statistical analysis on complete cure rate (by Fisher exact test) and on the secondary efficacy parameters (by Pearson χ^2 test) in the mITT population

	P-3051 versus placebo		P-3051 versus reference CPX	
	RD (95% CI)	*p* value	RD (95% CI)	*p* value
Complete cure week 48	7.6 (1.2 to 14.2)	0.028	4.2 (–1.8 to 11.0)	0.167
Complete cure week 60	13.5 (5.2 to 21.5)	0.004	9.3 (1.5 to 17.6)	0.021
Responder week 48	22.4 (11.3 to 33.5)	0.001	7.8 (–3.6 to 19.1)	0.181
Responder week 60	13.8 (0.7 to 27)	0.052	13.6 (2.4 to 24.8)	0.019
Negative culture week 48	18.6 (6.5 to 30.6)	0.001	1.6 (–5.7 to 8.9)	0.669
Negative culture week 60	6.2 (–6.4 to 18.7)	0.321	7.4 (–3.0 to 17.7)	0.165

CI, confidence interval; CPX, ciclopirox; mITT, modified intention-to-treat; RD, relative difference.

hydroxypropyl chitosan, which, when applied onto the nail surface, reduces the penetration of the dermatophyte hyphae [15]. Interestingly, the effect of placebo was maintained and even increased during the follow-up, most probably due to the persistence of hydroxypropyl chitosan in the nail holes in the nails for a long time. This would be the reason why the superiority of P-3051 versus placebo was no longer significant at the end of follow-up.

The efficacy of P-3051 in this population subset is now in the range of that reported in efinaconazole studies [9]. This post hoc analysis confirms that the severity of the illness is a predictive factor for responsiveness to antifungal treatments for onychomycosis. The different inclusion criteria should be taken into account when reviewing the efficacy of antifungal agents from different studies. Eligibility criteria greatly affect the efficacy results in onychomycosis trials and may have a marked impact on efficacy outcomes. Our post hoc analysis is an example: between the overall population in the original design [8] and our mITT subset, the comparisons of the three treatment groups (test, reference, and placebo) did not change in terms of respective efficacy. Instead, the absolute figures changed, as they were better in the milder subset than in the overall population. A further example is given by a post hoc analysis on the pooled population of efinaconazole studies, confirming that patients with ≤25% nail involvement at baseline had an even larger complete cure compared to patients with >25% involvement [16]. No comparison with P-3051 is possible on this population as patients with ≤25% nail involvement at baseline were not included in the pivotal study of this product [9]. In conclusion, our post hoc analysis indicates that controlled randomized trials are needed to compare the efficacy of different drug treatments, since indirect comparisons of different trials are unreliable, as with a population suffering from milder disease better figures can be expected in terms of efficacy.

Statement of Ethics

Patients gave their written informed consent before starting any protocol procedure. The protocol was approved by the ethics committees of all the centers.

Disclosure Statement

The authors declare no conflict of interest.

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