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.[1,2]

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.[3]

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