Evaluation of safety profile, pharmacokinetics and clinical benefit of an innovative terbinafine transungual solution (P-3058): a phase I, study in patients with mild-to-moderate distal subungual onychomycosis

1Ilona Hartmane, 1Ingmars Mikazans, 1Andra Derveniece, 2Linda Frisenda, 2Maurizio Caserini, 2Federico Mailland

1Clinical Centre of Skin and STD, Riga - Latvia  
2Scientific Department, Polichem S.A. Lugano - Switzerland
Introduction

A new terbinafine nail solution (P-3058) has been developed, based on a patented film-forming Hydroxypropyl chitosan technology, well known to improve penetration of actives through nails.

Two different concentrations (5% and 10%) and two different dosage schedules (once a day versus once a week) have been tested in this phase I study carried out in patients with mild-to-moderate onychomycosis.

Aim of this phase I study was the evaluation of the safety profile, pharmacokinetics and any clinical benefit of the tested concentrations/dosage schedules.
Methods

Study design
- Phase I, randomized, open-label, parallel groups study
- Sixty adult patients with mild-to-moderate big toenail onychomycosis (25% to 60% nail-involvement, matrix uninvolved)
- Positive KOH microscopy and dermatophytes culture at baseline
- Treatment period of 24 weeks followed by a 24-week follow up

Dosage schedule
- P-3058 5% once daily application
- P-3058 10% once daily application
- P-3058 10% once weekly application
Methods

Study endpoints

- **Safety** ⇒ AEs recording and local tolerability
- **PK** ⇒ Terbinafine concentration in:
  - Blood samples (12, 24, 36 and 48 wks)
  - Target Nail (day 2, wk 4, 8, 12, 16, 20, 24, 36 and 48)
- **Efficacy** ⇒ Mycology and Clinical outcome.
  Descriptive statistics only, being the sample size not calculated for efficacy purpose.
Results

Patient disposition

Overall, 60 patients were randomized in the study and included in the safety population (20 patients per treatment group).
Fifty-seven patients (95%) with confirmed clinical-mycological eligibility criteria were included in the MITT population as follows:

- N° 18 in the 5% o.d. group (90%)
- N° 19 in the 10% o.d. group (95%)
- N° 20 in the 10% o.w. group (100%)
Results

Safety: Treatment Emergent Adverse Events - Treatment Related N (%)

<table>
<thead>
<tr>
<th></th>
<th>5%od</th>
<th>10%od</th>
<th>10%ow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>N=20</td>
<td>N=20</td>
<td>N=20</td>
</tr>
<tr>
<td>With AEs</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>With SAEs</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>With Severe AEs</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
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<tr>
<td>Discontinued due to AEs</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
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All three dose regimens were safe and well tolerated
No patients discontinued due to adverse events
No patients experienced any adverse drug reaction
Results

Terbinafine plasma concentrations in MITT population after P-3058 treatment resulted three orders of magnitude lower than the oral administration whose Cmax (μg/ml) = 1.70 ± 0.77*

Results

Terbinafine nail concentrations after P-3058 treatment were over three orders of magnitude (up to 18,000 fold) higher than those achieved by the oral administration (about 1 μg/g)*. Steady state was reached after 4 wks in the o.d. group and after 12 wks in the o.w. group.

Results

Mycology outcome at end of treatment (wk 24)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Negative culture</th>
<th>Negative KOH</th>
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<tbody>
<tr>
<td>5% o.d.</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
<td>10% o.d.</td>
<td>84%</td>
<td>68%</td>
</tr>
<tr>
<td>10% o.w.</td>
<td>90%</td>
<td>75%</td>
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</table>
The pooled data of the three P-3058 dose regimens (MITT population) showed a statistically significant decrease of the diseased target nail area at the end of treatment (p<.0001) and at the end of wash-out (p<.0001) versus baseline.
Conclusion

- P-3058 showed to be very safe after long term application to nails of patients with onychomycosis and indeed the systemic absorption was very negligible, being less than 1% of the total administered dose. Local tolerability was excellent.

- Terbinafine in P-3058 formulation showed to penetrate the nail in concentrations well above the MIC for dermatophytes and in fact both mycological and clinical benefit have been observed.

- P-3058 at the tested concentrations (5%-10%) is a promising candidate for a larger and longer Phase II study.