**Clinical Study Synopsis for Public Disclosure**

These results are supplied for informational purposes only in the interest of scientific disclosure. The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups. This information is not intended to substitute for informed medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a Healthcare Professional. Before prescribing any product mentioned in this Register, Healthcare Professionals should always refer to the specific approved product labeling information in their country. The results from a single trial may not reflect the overall results and need to be considered in the context of the totality of the available clinical research results for a product.

# 2. SYNOPSIS

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| **NAME OF COMPANY:**<br>GALDERMA | ***For regulatory use only*** |
| **NAME OF FINISHED MEDICINAL PRODUCT:**<br>Not Applicable | |
| **NAME OF ACTIVE INGREDIENT(S):**<br>Amorolfine | |
| **Title of study:** | A multi-centre, randomized, parallel groups, vehicle and active controlled study of amorolfine 4% and 10% nail lacquer new formulation in the topical treatment of distal and lateral subungual toenail onychomycosis |

**METHODOLOGY**

**Study objective(s):** The primary objective was to evaluate the difference in efficacy for amorolfine new formulation (NF) at 4% and 10% concentrations, when compared to its vehicle in the treatment of distal and lateral subungual onychomycosis, without matrix involvement, of the toes after 6 months of treatment. Secondary objectives were to compare efficacy of amorolfine new formulation (4 and 10%) with the current formulation of amorolfine nail lacquer (Loceryl® 5%) assuming primary objective has been met, perform dose ranging evaluation of two new formulation concentrations (4% and 10%) and assess the safety of amorolfine new formulation as compared to its vehicle and current amorolfine formulation.

**Study design and clinical phase:** A Phase 2 multi-centre, prospective, randomized, double-blind vehicle and active controlled, four parallel groups study with a 6 month treatment period and 3 month follow-up period. Study visits were at Screening, Baseline, Day 1, Day 7, Day 14, Day 45, Day 90, Day 135, Day 180, Day 210 and Day 270.

**Study center(s):** A total of 13 centres in Bulgaria, Czech Republic, Germany and Iceland; 10 enrolled, 11 screened and 13 selected subjects

**Number of subjects:**
Planned: 124 subjects
Randomized: 127 subjects

**Diagnosis and Inclusion criteria:** Male or female subjects with distal and lateral subungual onychomycosis due to dermatophytes, involving at least one great toe nail with at least 25% of the nail surface area affected but no involvement of the proximal 1/3 of the nail.

**Study period :**
From 19Sep2006 (first subject in) to 15May2008 (last subject out).

**Investigational products:**

| **Test Product Dosage Form:** | **Amorolfine 10% lacquer** | **Amorolfine % lacquer** | **Vehicle nail lacquer** | **Loceryl® (amorolfine 5% nail lacquer)** |
|---|---|---|---|---|
| Dosage regimen: | Daily for 2 weeks then weekly until 6 months | | | |
| Route of administration: | Topical to the nail | | | |
| Formulation number /Batch/ | 0771.0277 / 2F5 | 771.273 / 2F3 | 771.273P / 2F9 | 6212022 |
| Treatment duration | 6 months | | | |

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**METHODOLOGY (Continued)**

**Criteria for evaluation:**

- **Efficacy**
  - Primary Efficacy Endpoint

Clinical Success was defined as new unaffected target toe nail length superior or equal to 4 mm at the end of the 6 months treatment period as measured by planimetry. The new unaffected nail length was defined as the increase in millimetres in healthy nail growth from the cuticle as compared to baseline.

  - Secondary Efficacy Endpoints

Percentage of subjects achieving:

- Clinical Success at 9 Months
- Clinical cure defined as completely cleared target great toe nail as evaluated by Investigator using the Global Clinical Effectiveness assessment scale.
- Mycological cure defined as Negative Culture.
- Global Success defined as combination of Clinical Success and Mycological Cure.
- Global Cure defined as combination of Clinical Cure and Mycological Cure.

- **Safety**

Adverse events, local safety assessment (examination of the treated toenails and the skin surrounding the treated nails and report any abnormal findings through AE reporting), vital signs, general physical assessment, ophthalmologic examination and laboratory safety tests.

**Principal statistical methods:**

Descriptive statistics were provided to summarize efficacy, safety and other variables.
The subject disposition, demographic variables, baseline characteristics, previous medication, concomitant medication, treatment duration, and study medication usage were summarized. Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) were presented for continuous variables. Frequency distributions (count and percent) were presented for categorical variables.
All efficacy variables were summarized for the ITT population. The primary variable of clinical success rate were analyzed for the PP population to confirm the results from the ITT analyses. All efficacy variables were summarized at each visit (LOCF up to month 6). MedDRA dictionary was used for coding adverse events. Adverse event (AE) occurring the day or after the day of first use were descriptively summarized on the safety population in frequency tables showing incidences and multiplicity, combining different factors, system organ class, preferred term, severity, relationship , seriousness and discontinuation.
Number (n) and percentage (%) of subjects, who experienced at least one AE, as well as the total number of events, were given for the following event categories:

- any event,
- dermatologic adverse events (SOC=Skin and subcutaneous tissues disorders)
- events related to study drug (related events are defined as events possibly, probably or definitely related to study drug),
- serious events,
- events leading to discontinuation,
- death

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**METHODOLOGY (Continued)**

The Intention to treat analysis at end of treatment period was primary, and the last observation carried forward was used to impute missing data until end of treatment period (6 months). The primary endpoint was the success rate defined as the proportion of subjects in the PP population achieving "Clinical Success" defined as new unaffected nail length of at least 4mm. Success rate was submitted to a Cochran-Mantel-Haenszel test, correlation statistic, testing the dose-response relationship between 0%, 4% and 10%. If the test was significant at the 5% significance level, the data from the highest concentration, 10% was removed and the test repeated between 0% and 4%, to determine the smallest effective concentration. Other binary endpoints were analyzed the same way. The new unaffected nail lengths and affected/unaffected nail areas were also analyzed as continuous data using analysis of variance followed by Student's t-tests test versus vehicle.

Tests was two-sided and the 5% level was used to determine significance.

**RESULTS**

■ **Subject Disposition**

A total of 127 subjects with distal and lateral subungual onychomycosis, without matrix involvement, were randomized in this multi-centre, prospective, randomized, double-blind vehicle and active controlled, study conducted in four parallel groups: amorolfine new formulation 10% (NF), amorolfine NF 4%, commercially available Loceryl 5% nail lacquer and vehicle. Study treatment was applied once daily for two weeks and then one weekly up to month six, after which there was a follow-up period up to 9 months. Overall, 109 subjects completed the study.

**Summary Table 1 – Subjects final status - ITT population**

| | | Amorolfine-NF10% | Amorolfine-NF4% | Loceryl® 5% Nail Lacquer | Vehicle | Total |
|---|---|---|---|---|---|---|
| **Randomized** | **Total** | 31 (100.0%) | 30 (100.0%) | 34 (100.0%) | 32 (100.0%) | 127 (100.0%) |
| **Completed the study** | **Normal Completion** | 25 (80.6%) | 26 (86.7%) | 30 (88.2%) | 28 (87.5%) | 109 (85.8%) |
| **Premature discontinuation** | **Total** | 6 (19.4%) | 4 (13.3%) | 4 (11.8%) | 4 (12.5%) | 18 (14.2%) |
| | Lack of Efficacy | 1 (3.2%) | | 1 (2.9%) | | 2 (1.6%) |
| | Lost to Follow-up | 1 (3.2%) | 2 (6.7%) | 1 (2.9%) | 1 (3.1%) | 5 (3.9%) |
| | Other | | 1 (3.3%) | | 2 (6.3%) | 3 (2.4%) |
| | Subject's Request | 4 (12.9%) | 1 (3.3%) | 2 (5.9%) | 1 (3.1%) | 8 (6.3%) |

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**RESULTS (Continued)**

■ **Demographics and Baseline Data**

Demographics and Baseline data of the main efficacy criteria is depicted in Summary Table 2 below.

**Summary Table 2 – Demographics and Baseline Data (ITT population)**

| | | Amorolfine-NF10% | Amorolfine-NF4% | Loceryl® 5% Nail Lacquer | Vehicle | Total |
|---|---|---|---|---|---|---|
| **Age** | **n** | 31 | 30 | 34 | 32 | 127 |
| | **Mean±sd** | 47.2 ± 10.1 | 47.2 ± 11.4 | 47.0 ± 11.5 | 48.0 ± 10.0 | 47.3 ± 10.7 |
| | **Median** | 47 | 49 | 49 | 48 | 48 |
| | **(Min,Max)** | (27,65) | (21,62) | (26,65) | (28,63) | (21,65) |
| **Gender** | **Female** | 13 (41.9%) | 17 (56.7%) | 19 (55.9%) | 19 (59.4%) | 68 (53.5%) |
| | **Male** | 18 (58.1%) | 13 (43.3%) | 15 (44.1%) | 13 (40.6%) | 59 (46.5%) |
| **% target toe nail unaffected surface area** | **Mean±sd** | 61.13 ± 9.2 | 64.21 ± 9.1 | 62.83 ± 10.6 | 61.26 ± 11.9 | 62.35 ± 10.2 |
| | **Median** | 63.78 | 63.52 | 65.71 | 64.53 | 64.32 |
| | **(Min,Max)** | (30.7,76.1) | (43.9,83.5) | (35.5,76.1) | (29.8,77.0) | (29.8,83.5) |
| **Nail length (mm)** | **Mean±sd** | 15.86 ± 2.7 | 16.07 ± 2.4 | 15.11 ± 2.3 | 15.80 ± 2.7 | 15.69 ± 2.5 |
| | **Median** | 16.32 | 16.78 | 15.33 | 16.08 | 16.03 |
| | **(Min,Max)** | (10.8,21.6) | (12.0,19.6) | (10.1,19.3) | (9.0,21.9) | (9.0,21.9) |
| **Number of affected toe nails** | **Mean±sd** | 5.94 ± 3.2 | 4.70 ± 2.9 | 6.12 ± 3.0 | 5.47 ± 3.0 | 5.57 ± 3.0 |
| | **Median** | 7.00 | 4.50 | 6.50 | 6.00 | 6.00 |
| | **(Min,Max)** | (1.0,10.0) | (1.0,10.0) | (1.0,10.0) | (1.0,10.0) | (1.0,10.0) |
| **Onychomycosis Duration (years)** | **Mean±sd** | 7.71 ± 6.3 | 7.03 ± 6.7 | 7.88 ± 7.7 | 6.33 ± 6.2 | 7.24 ± 6.7 |
| | **Median** | 5.00 | 5.00 | 5.00 | 4.50 | 5.00 |
| | **(Min,Max)** | (0.4,20.0) | (0.3,30.0) | (1.0,34.0) | (0.3,25.0) | (0.3,34.0) |

Overall, treatment groups were well balanced at Baseline for demographics as well as for Baseline disease characteristics.

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**RESULTS (Continued)**

■ Efficacy

The study could not confirm that the rate of subjects achieving at least 4 mm of increase from Baseline to month 6 in unaffected nail length (clinical success) were achieved with amorolfine new formulation at doses of 4 or 10%. In addition no numerical trend was observed in favour of amorolfine NF versus vehicle on this parameter. Overall, none of the planned statistical tests performed on clinical endpoints were significant in the expected direction (i.e. favouring the active treatments versus vehicle).
A dose response relationship with amorolfine NF was observed on mycological cure and is significant at month 7 only.
Per protocol analyses confirmed ITT analyses. No added value to amorolfine 5% nail lacquer could be demonstrated. The independent centralized photographic assessment was performed at the end of the study by an expert in dermatology and the results from the independent review confirmed those from the main in-study assessments.

■ Safety

Overall, 37 (29.1%) of 127 of the subjects experienced a total of 51 AEs: 7 (22.6%) subjects in the amorolfine NF 10%, group, 11 (36.7%) subjects in the amorolfine NF 4% group, 12 (35.3%) subjects in the Loceryl 5% group and 7 (21.9%) subjects in the vehicle group.

**Summary Table 3- Overview of Subjects Reporting Adverse Events (Safety population)**

| | Amorolfine NF 10% | | | Amorolfine NF 4% | | | Loceryl® 5% Nail Lacquer | | | Vehicle | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N AEs | N subj* | % subj | N AEs | N subj* | % subj. | N AEs | N subj* | % subj | N AEs | N subj.* | % subj |
| **All AEs** | 11 | 7 | 22.6 | 18 | 11 | 36.7 | 14 | 12 | 35.3 | 8 | 7 | 21.9 |
| **All serious AEs** | 0 | 0 | 0 | 3 | 3 | 10.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Deaths** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Related AEs(*)** | 0 | 0 | 0 | 1 | 1 | 3.3 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Related serious AEs** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **All AEs leading to discontinuation** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Related AEs leading to discontinuation** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Severe AEs** | 0 | 0 | 0 | 1 | 1 | 3.3 | 0 | 0 | 0 | 0 | 0 | 0 |
| **All dermatologic AEs (**)** | 0 | 0 | 0 | 2 | 2 | 6.7 | 2 | 2 | 5.9 | 0 | 0 | 0 |
| **Related dermatologic AEs(**)** | 0 | 0 | 0 | 1 | 1 | 3.3 | 0 | 0 | 0 | 0 | 0 | 0 |

Adverse events are defined as events that occurred on the day of, or after, the first use of medication
N subjects = Number of subjects with at least one event
(**) Dermatological AEs = All AEs related to system organ class = skin and subcutaneous disorders

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No deaths occurred during the study and 3 (2.7%) subjects reported SAEs (all in amorolfine NF 4% treatment group: pyelonephritis, radius fracture and cryptogenic organizing pneumonia). There were no treatment related SAEs or AEs leading to study discontinuation.

One (3.3%) subject, experienced a related AE (soft nails) coded in nail disorder which started 3 months after starting the treatment with Amorolfine NF 4% group, One (3.3%) subject, in the amorolfine NF 4% group, experienced an AE of severe intensity (radius fracture).

Four subjects had dermatological AEs: 2 (6.7%) subjects in the amorolfine NF 4% group (eczema and nail disorder) and 2 (5.9%) subjects in the Loceryl 5% group (folliculitis and onychomadesis).

No changes in laboratory were considered related to study treatment. In the ophthalmologic examination none of the changes in LOCSII scale examination were considered clinically significant.

**CONCLUSION**

The superiority of amorolfine NF at concentrations of 4 and 10% over its vehicle could not be demonstrated.

Amorolfine NF at concentrations of 4 and 10% as well as Loceryl® 5% nail lacquer was safe and well tolerated.