

Clinical Evaluation of Safety and Efficacy of a New Topical Treatment for Onychomycosis

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ABSTRACT

Objective: This clinical study assessed the safety and efficacy of an investigational topical product for the treatment of onychomycosis (nail fungus).

Method: A prospective, multi-center, single-arm, self-controlled clinical investigation was done with adult subjects that met the inclusion criteria, primarily culture-confirmed dermatophyte infection of at least one great toe. Subjects self-treated in a weekly regimen of topical application for six months, with clinical assessment at one, three, and six months. Primary efficacy endpoint was clearance of fungal nail infection after six months of weekly treatment. Primary safety endpoint was freedom from product-related adverse events for the duration of the treatment term.

Results: Fifty males and 13 females, ages 24 to 65, infected with *Trichophyton* (n=62) or *Epidermophyton* (n=1) were enrolled; 53 completed six months of assessment. Sixty percent showed improvement in clinical parameters (nail color, nail plate involvement, onycholysis, thickness, and hyperkeratosis) at six months. Cumulative rates of dermatophyte-negative culture results (test of cure) were 28, 36, and 62 percent of subjects after one, three, and six months of treatment, respectively. Three minor adverse events were device-related, with no unanticipated or serious adverse events.

Limitations: This study was single-arm and self-controlled; 53 of 63 enrolled subjects completed the study.

Conclusion: This study describes a new topical medical device with safety and efficacy profiles that compare favorably to results reported for topically applied onychomycosis drug treatments.

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INTRODUCTION

Onychomycosis, a condition in which fungi infect the nails, is a relatively common disease accounting for up to 50 percent of all nail disorders.¹ Prevalence rises with age, due to diminished blood circulation, longer cumulative time of exposure to fungi, nail trauma, immune compromise such as diabetes and because nails may grow more slowly and thicken with aging, making them more susceptible to infection. This infection can cause changes in one or more nails such as brittleness, discoloration, loss of luster, thickening, distortion, crumbling, or detachment of the nail plate from the nail bed. Additional complications of onychomycosis can include pain, fissuring and secondary infection such as cellulitis.

The causative fungi (dermatophytes) live in warm, moist environments. They can invade the skin through small cuts in the skin or separations between the nail and nail bed. Infection with nail fungus occurs more often in feet than hands due to

confinement in dark, warm, moist environments inside shoes, where fungi can thrive. In addition, the diminished blood circulation and reduced lymphatic drainage in the toes compared with the fingers make it harder for the immune system to detect and eliminate the infection. Nail fungus affects males more than females. Diabetes, psoriasis, and immune deficiency also may increase the risk of developing nail fungus.

Nail fungal infections can be painful and may cause permanent damage to nails. They may also lead to secondary skin infections and other serious infections that can spread beyond the feet. Thickened, discolored nails also may be caused by psoriasis, eczema, lichen planus and other diseases, and therefore accurate diagnosis is critical.

Fungal nail infections are diagnosed by taking a sample of the debris under the nail. The debris can be visualized mi-

croscopically in a potassium hydroxide (KOH) wet mount preparation. Fungal species are easily recognized under the microscope by their characteristic hyphae. However, neither wet-mount nor staining can reliably differentiate between live and dead fungi. Fungal culture, which identifies only live, vegetative organisms, is used to identify the exact species causing the infection. Among the numerous species (nearly one hundred) responsible for onychomycosis, those that are keratinophilic (dermatophytes, antropophilic types) such as *Trichophyton rubrum* and *Trichophyton mentagrophytes* (a.k.a., *Trichophyton interdigitale*) are the most important. Other non-dermatophyte nail pathogens, such as *Scytalidium* species and *Onychocola canadensis*, or geophilic saprophytes (molds), require direct mycological or histological examination to establish their presence.²

The morphological presentation of the infection within the nail plate aids in the choice of treatment agents and in determining prognosis and the need for adjunctive therapy. In most clinical settings, when <75 percent of the nail plate surface area is involved and the lunula is spared, topical therapy may be considered as monotherapy. Systemic therapy is usually recommended when a patient presents with five or more infected nails.³

Current treatment of fungal nail infections can be expensive, long-term, and requires commitment on the part of the patient to continue use of the treatment as prescribed. Even with successful treatment, a recurrence of the infection is common. Both prescription and non-prescription topical antifungal agents have demonstrated marginal effectiveness in treating fungal infections of the nails. The Food and Drug Administration (FDA) has approved a nail lacquer (ciclopirox; Penlac) for fungal nail infections, but it is effective in <10 percent of subjects for complete cure.⁴ There are several effective oral antifungal medications which are incorporated into the nail plate. Some of these medications have significant side effects ranging from skin rashes to hepatotoxicity and may interact adversely with other drugs. Systemic antifungals may require repeated blood studies to track hepatic and hematologic toxicity.⁵

There is a need for a safe, topically-applied product that can inhibit the growth of the dermatophytes that cause nail fungus. The product described here does not contain a drug and so does not achieve its intended therapeutic effect through any chemical, pharmaceutical, metabolic or immunological means. It is not designed to have a direct action on the microorganism. Instead, the product is painted on the nail and the resulting polymer product (solvents vaporize after application) adheres to the nail plate and contiguous skin to create a waterproof, but vapor-permeable protective covering. The film creates a change in the micro-environment of the fungus and the conditions allowing growth are no longer present or become inadequate for continued growth. The micro-envi-

ronment is changed because the product forms a protective barrier to water, but not a vapor barrier, and therefore keeps the nail plate and underlying nail bed dry. The results of a multi-center, single-arm, self-controlled clinical investigation to evaluate acute safety and efficacy of, Chesson Laboratory Associates, Inc., treatment for onychomycosis are described.

METHODS

Clinical Study

This study was done under a community Investigational Review Board-approved protocol, with Investigator Agreements at each site. All sites were licensed and state-certified dermatology or podiatry practices or medical research centers. The study was managed by a clinical research organization, not by the sponsor. Each subject provided informed consent before enrollment in the study. This was a prospective, single-arm study at four centers to evaluate safety and efficacy of the investigational product for treatment of onychomycosis. Each subject served as their own treatment control. Subjects were assessed before treatment and at one, three and six month time points by visual and culture methods. Due to the nature of the product, there was no blinding of the application procedure. Samples from each subject were numbered for traceability. A single, nationally-accredited core microbiology lab (Laboratory Corporation of America; Raritan, NJ), blind to all other aspects of the study, was used for all mycology culture and wet-mount KOH with calcofluor white preparations.

The primary efficacy endpoint was clearance of fungal nail infection, defined by negative culture, within the six-month treatment phase. Since KOH tests can produce a false positive result from nonviable hyphae, from normal flora, or from fungi that are not causative for onychomycosis, these tests were used for information only and not as a test of cure. The primary safety endpoint was freedom from unanticipated or major device-related adverse events (AEs) for the duration of the treatment phase (six months). Anticipated minor AEs were sensitivity to the product causing redness to the surrounding skin, minor stinging on application, or discoloration of affected area. Safety of the product in this non-comparative study was determined by comparing the incidence of AEs with the investigational product to those reported in the scientific literature for other topical application products for treatment of onychomycosis.

Subject Population

Adults, 18 to 65 years of age, with positive KOH tests and dermatophyte culture results were considered, regardless of gender, race, or ethnicity. For inclusion in the study, candidates had to meet all of the following criteria: nail fungal infection of at least one great toe (per visual assessment, positive KOH preparation, and positive dermatophyte culture) with 20–65 percent nail surface area involvement, no lunula involvement, and nail thickness <3 mm. All subjects had to be physically able to reach

their toes to clean them and apply product, to discontinue use of other nail fungus treatment products and nail cosmetic products for the duration of the trial, and to return for follow up.

Subjects were excluded if they were pregnant, nursing, or of childbearing age and unwilling to use contraception, had known hypersensitivity or allergy to the product materials, or were enrolled in another investigational product protocol that would interfere with this clinical trial. Potential subjects were excluded if use of other topical or pharmaceutical treatments for the condition was continued; a wash-out period of at least four weeks after discontinuation of a topical product or 180 days after discontinuation of an oral product for treatment of nail fungus was required. Chronic disease, including diabetes, psoriasis, immune deficiency, severe foot injury, chronic vascular disease, or any other condition that would decrease circulation to the extremities was documented and inclusion in the trial was left to the discretion of the investigator.

Device Description

The investigational product is a biocompatible, polymeric suspension that forms a uniform film when applied to the nail. The polymer product is dispersed in organic solvents that vaporize rapidly upon application, allowing the suspended polymer to adhere to the contours of the nail to form a flexible, waterproof barrier over the nail. The film is colorless, transparent and possesses good moisture vapor permeability. The product has been shown biocompatible per ISO 10993 in cytotoxicity, sensitization, irritation, acute system toxicity and implantation assays.

Application Procedure

Detailed, written instructions for use were provided to each subject. The multi-use packaging system (glass bottles with screw top and swab applicator) is designed for convenient storage and application of the product. Product is stored at normal room temperature and humidity. For use, nails are cleaned with acetone (nail polish remover). Product is applied to affected nail plate (in entirety), proximal and lateral nail folds and the distal nail tip using the supplied application swab. Nails are allowed to air-dry before applying socks or footwear. For this trial, the product was applied once a day before bedtime, Monday through Friday. On Saturday, nails were to be cleaned thoroughly with acetone. Product was not applied on Saturday or Sunday. Subject management also included all treatments typical for fungal infections of the nail and basic hygiene, including regular washing and clipping of the nail, removing foreign matter and dead tissue, and minimizing further infection.

Clinical Assessments

Wet-mount KOH with calcofluor white preparations and fungal cultures were performed to identify infection and determine causative organisms before enrollment and at one, three and six month time points. The affected nail plate of the great toe

was clipped and the nail bed was scraped to remove dead skin cells and the causative organism. The nail bed scrapings and nail clippings were sent to a single core microbiology laboratory for KOH preparations and culture. Contents of the culture were examined under a microscope weekly to detect growth and identify the growing fungi. No growth of dermatophytes of interest after four weeks in culture was defined as a negative mycology. Dermatophytes of interest were specified as *Trichophyton*, *Epidermophyton* and *Microsporum* species per clinical literature for U.S. trials of this indication.⁶

Unlike its comparators, this new topical product does not contain a pharmaceutical agent, it is not absorbed by the body, and it is not dependent upon being metabolized to achieve its intended purpose.

RESULTS

Baseline Characteristics

Sixty-three subjects were enrolled at four clinical sites over a one-year period (Table 1). This report includes the available data from 53 subjects enrolled (Intent to Treat population) and treated with the investigational product for six months per protocol. There was no randomization in the single-arm protocol, as subjects served as their own comparator pre- and post-treatment. Since there was no randomization, intent to treat analysis was not applicable; safety and efficacy analysis was done on all subjects that completed the six-month treatment period.

Fifty-six percent of subjects had previously used OTC treatments or taken prescription medications for the condition. In every case, these had been discontinued for the appropriate period before the subject enrolled in the current clinical trial.

Safety Analysis

There were a total of 17 treatment-emergent adverse events (TEAEs) reported through the six-month follow-up visit. Of the AEs, only three were categorized by the investigators as probably or definitely product-related (Table 2). There were no unanticipated device-related AEs and no product malfunctions were reported. There were no serious adverse events (SAEs).

Efficacy: Visual Assessment

More than half the subjects (60% averaged across all parameters) showed an improvement in the total visual assessments after six months of treatment (Table 3). The remainder of subjects showed no change (17%) or deterioration (23%). There was an average 20 percent improvement for all subjects in all

TABLE 1.

Subject Baseline Characteristic Summary

Age	24 to 65 years; average 51 years			
Gender	Male (50)		Female (13)	
Percent Nail Involvement (#)	0-19% (0)	20-35% (11)	36-50% (30)	51-65% (22)
Positive KOH & Positive Culture (#, %)	63 (100%)			
Dermatophyte cultured (#)	<i>Trichophyton sp.</i> (62)		<i>Epidermophyton sp.</i> (1)	
Nail thickness (#)	≤1 mm (1)	1-2 mm (14)	2-3 mm (48)	≥3 mm (0)
2 mm clear nail proximally (#, %)	63 (100%)			

TABLE 2.

Device-Related Adverse Event Description Summary

Adverse Event	Device Related*	SAE / AE
Tingles a little when product applied; no pain	1	AE
Mild stinging at distal nail plate	2	AE
Dry cracking skin on rt great toe	1	AE

*1=definitely product related, 2=probably product related

visual parameters (color 10%, onycholysis 30%, all others 20%) over the six months of the study. There was no correlation of infection severity by visual assessment and time to clearance of infection by dermatophyte culture.

Efficacy: KOH Test and Dermatophyte Culture

All KOH tests and fungal cultures were performed by an independent core lab. At baseline screening, 100 percent of the enrolled subjects were positive in both the KOH wet mount with calcofluor for microscopic visualization of fungal hyphae and in the dermatophyte culture, per inclusion criteria. Throughout the six-month treatment and follow-up period, in all cases where KOH was negative (no hyphae observed), the dermatophyte culture results were also negative; i.e., there were no "false negatives." However, in nearly half of the samples (76 of 159; 48%), KOH produced a false positive result, from dead hyphae or from organisms that were normal flora or not causative for onychomycosis. For this reason, KOH tests were not used to verify "test of cure."

Nail samples taken from each subject at baseline and at follow-up visits after one, three and six months of treatment were cultured for mycological identification by the core lab. At baseline, 47 (89%) of the cultures were positive for *Trichophyton rubrum*, three (6%) for *Trichophyton mentagrophytes*, two (4%) for *Trichophyton tonsurans* and one (2%) subject had *Epidermophyton floccosum*. A few secondary fungal organisms also were observed throughout the test period; all of these were

normal flora or were not causative organisms for the condition of interest. Increasing numbers of subjects had dermatophyte-negative culture results with longer period of treatment (Table 4). The subjects reported here are only those that remained culture-negative through the six-month treatment period.

DISCUSSION

There was no single "most common" AE in this clinical trial. The only reported AEs likely related to the device were mild stinging at distal nail plate and dry cracking skin on right great toenail. There were no unanticipated AEs. The AE rate in this clinical trial was 5.6 percent, which is similar to the rates observed with other topical pharmaceutical products for this indication. The following summaries are supplied for general comparison only, since each trial may have important differences (e.g., site at which study was conducted, population studied, protocol used, evaluators for the study, etc.) and as a result direct comparison of AE rates from individual studies are not valid.⁷

Treatment-emergent adverse events (TEAEs) were reported in nine percent of patients treated with ciclopirox Topical Solution and seven percent of patients treated with vehicle; eight percent and four percent of subjects in the ciclopirox and vehicle groups reported at least one AE, respectively.⁴ The most common were rash-related AEs: periungual erythema and erythema of the proximal nail fold were reported more frequently in patients treated with ciclopirox (5%) than in patients treated with vehicle (1%). Other TEAEs thought to be causally related included nail disorders such as shape change, irritation, ingrown toenail and discoloration. Other reported studies with this topical solution contain no information on AE rates, noted no AEs, or reported that no patient exhibited intense side effects.⁷⁻⁹

Causative organisms of onychomycosis have changed markedly over the years and show distinct patterns in different parts of the world.¹⁰ In the current study, *Trichophyton* species were cultured from nearly all of the subjects, with *T. rubrum* as the dominant organism. Foster et al. reported *T. tonsurans* as the causative agent in 96 percent of the patients in a U.S. study.¹¹ Current results are similar to those from recent European

TABLE 3.**Change in Visual Assessment Parameters from Baseline to Six-Month Follow-Up Visit**

Visual Parameter	Color	Nail Involvement	Onycholysis	Thickness	Subungual Hyperkeratosis
Change from baseline to 6 months	Number (percentage) of total subjects				
Deterioration	7 (13)	6 (11)	5 (9)	2 (4)	8 (15)
No change	30 (57)	21 (40)	28 (53)	33 (62)	25 (47)
Improvement	16 (30)	26 (49)	20 (38)	18 (34)	20 (38)

TABLE 4.**Cumulative Totals for Subjects that Remained Dermatophyte-Culture Negative**

Follow-up Visit	Culture-Negative for Causative Dermatophyte	
	Subject #	Subject %
Screen	0	0 (all were positive)
1 month	15	28
3 months	19	36
6 month	33	62

studies in which the most isolated organisms causing onychomycosis were *T. rubrum* (83%, 53%) and *T. mentagrophytes* (12%, 35%), respectively.^{8,12}

In comparison of cure rates, different assessment measures have complicated the interpretation of benefit in clinical trials to control onychomycosis.² Mycologic cure has predominantly been defined as negative microscopy and culture. Unlike mycologic cure, clinical measures have been variably defined, and subjective terms, such as "cure" or "markedly improved," have been used. Studies have measured the distance between the proximal nail fold and a notch in the nail plate, at the junction between the diseased and normal-appearing nail, or in some cases estimated the diseased nail plate involvement. In others, negative KOH test and negative culture have been used to define test of cure.

The differences in positive KOH wet mounts (94%) and dermatophyte culture (55%) results in the current study are similar to those reported in the literature. The apparent sensitivities of the potassium hydroxide preparations (KOH, 80%) and other staining methods such as Periodic Acid-Schiff's (PAS, 90%) are generally higher than dermatophyte or mycotic culture (60%).¹³ However, culture remains the gold standard since only live, vegetative organisms can be used to identify the exact species causing the infection and verify test of cure.

The only topical treatment approved by the FDA for the management of nail fungus in the U.S. is ciclopirox (e.g., Penlac).

Penlac's original product labeling cited the following cure rates in the intent-to-treat population, at week 48: Complete Cure (8.5%), 10 percent nail involvement and negative mycology (12%), negative KOH and negative culture (36%).⁴ In a randomized study with 96 subjects, a lacquer solution containing an extract of *A. pichinchensis* or a control lacquer solution containing 8% ciclopirox was administered topically for six months. Mycological effectiveness was achieved in 59 percent and 64 percent of the experimental and control group, respectively.⁹ In a study, 967 European patients with distal subungual onychomycosis that were culture positive for dermatophytes were randomized to two ciclopirox nail lacquers in different vehicles or to the two placebo vehicles.⁸ Patients underwent 48-week treatment by daily application and a 12-week follow-up period. At week 60, mycological cure rate in the treatment groups were five percent and 14 percent versus three percent in the vehicle control group. Data from the 10 studies conducted worldwide show a meta-analytic mean mycologic cure rate of 53 percent with Penlac.⁷

CONCLUSION

In the current clinical investigation with a new topical product, mycological cure rate was 62 percent after six months of treatment. Unlike its comparators, this new topical product does not contain a pharmaceutical agent, it is not absorbed by the body, and it is not dependent upon being metabolized to achieve its intended purpose. This product was shown to be safe, with no cross reactions and minimal adverse effects. This study, therefore, supports a safe, topically applied product that can effectively treat onychomycosis.

Limitations

The results of this study should be interpreted in the context of several limitations. First, the sample size was too small to allow statistically valid assessment of potentially confounding covariates (e.g., baseline infection severity, duration of infection, subject age, or compliance with follow-up visits) on study outcomes. The number of subjects at some sites was too small to define differences between sites, if any. Long-term follow-up assessment at one year (six months after treatment end) was voluntary and therefore was not available for all subjects, so recurrence rates could not be determined

for the entire population. Because of the nature of the product, the study could not be blinded. The six-month follow-up was too short to make a final determination of effect on long-term visual improvement. Some of the subjects have potentially confounding factors that were evident from the list of medications that they were taking at screening (e.g., Lyrica for peripheral neuropathy). These conditions and disease states were not captured for this clinical trial and no diagnostic details are available. Despite these limitations, the findings constitute important observations that support safety and effectiveness of the product for this use.

DISCLOSURES

This study was funded by Chesson Laboratory Associates, Inc. Dr. Nasir was a site principal investigator and received compensation for services. Dr. Goldstein was the principal investigator and received compensation for services. Dr. van Cleeff was a site principal investigator and received compensation for services. Dr. Swick is an employee of Chesson Labs and received compensation for services.

REFERENCES

- Ghannoum MA, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. *J Am Acad Dermatol.* 2000;43(4):641-648.
- Scher RK, Tavakkol A, Sigurgeirsson B, et al. Onychomycosis: Diagnosis and definition of cure. *J Am Acad Dermatol.* 2007;56(6):939-944.
- Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia.* 2008;166(5-6):353-367. Epub May 14, 2008.
- Penlac [package insert]. Berwyn, PA: Dermik Laboratories – A Division of Aventis Pharmaceuticals; 2005.
- Gupta AK, Chwetzoff E, Del Rosso J, et al. Hepatic safety of itraconazole. *J Cutan Med Surg.* 2002;6(3):210-213. Epub April 15, 2002.
- Oyeka and Ugwu. Fungal flora of human toe webs. *Mycoses.* 2002;45(11-12):488-491.
- Gupta AK, Shear NH. A risk-benefit assessment of the newer oral antifungal agents used to treat onychomycosis. *Drug Saf.* 2000;22(1):33-52.
- Mailland F, Baran R. Sensitivity of *Trichophyton rubrum* versus other dermatophytes to ciclopirox nail lacquers in patients with onychomycosis. *J Am Acad Derm.* 2008;58(2):AB90-AB90 Suppl.
- Romero-Cerecero O, Zamilpa A, Jiménez-Ferrer JE, et al. Double-blind clinical trial for evaluating the effectiveness and tolerability of *Ageratina pichinchensis* extract on patients with mild to moderate onychomycosis. A comparative clinical trial with ciclopirox. *Planta Med.* 2008;74(12):1430-1435. Epub July 31, 2008.
- Seebacher C, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. *Mycopathologia.* 2008;166(5-6):335-352. Epub May 14, 2008.
- Foster KW; Ghannoum MA; Elewski BE. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. *J Am Acad Dermatol.* 2004;50(5):748-752.
- Tietz HJ, Kunzelmann V, Schönian G. Changes in the fungal spectrum of dermatomycoses. *Mycoses.* 1995;38(suppl 1):33-39.
- Lilly KK, Koshnick RL, Grill JP, et al. Cost-effectiveness of diagnostic tests for toenail onychomycosis: A repeated-measure, single-blinded, cross-sectional evaluation of 7 diagnostic tests. *J Am Acad Dermatol.* 2006;55(4):620-626. Epub June 13, 2006.

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