A Randomized, Controlled Trial to Determine the Efficacy of Active Topical Nail Solution versus Placebo Nail Solution for the Treatment of Pedal Onychomycosis

Funding Sponsor:	Marlinz Pharma 15115 Park Row, Suite 100, Houston, TX Telephone 844-398-5656
Study Product:	Topical antifungal solution (Tolcylen™)
Protocol Number:	AFMC16
IND Number:	Not applicable
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List of Abbreviations

AACFAS — Associate American College of Foot and Ankle Surgeons
AE — adverse event
AE/SAE — adverse event/serious adverse event
AFMC — Ankle and Foot Medical Centers of the Delaware Valley
CITI — Collaborative Institutional Training Initiative (CITI Program)
COID — conflict of interest disclosure
COPD — chronic obstructive pulmonary disease
CRF — case report form
DPM — Doctor of Podiatric Medicine
DSM — data safety monitor
DSO — distal subungual onychomycosis
DTM — Dermatophyte Test Medium
EC/IRB — ethics committee/institutional review board
FACFAS — Fellow of the American College of Foot and Ankle Surgeons
FDA — Food and Drug Administration
HIPAA — Health Insurance Portability and Accountability Act of 1996
IRB — institutional review board
KOH — potassium hydroxide
MSCE — Master of Science in Clinical Epidemiology
OnyCOE-t™ — Nail Specific Medical Outcomes Study
PAS — periodic acid-Schiff
QOL — quality of life
SAE — serious adverse event
VNPIS — visible nail plate involvement score

Study Summary

Title	A Randomized, Controlled Trial to Determine the Efficacy of Active Topical Nail Solution versus Placebo Nail Solution for the Treatment of Pedal Onychomycosis
Short Title	Topical Active Nail Solution versus Placebo
Protocol Number	AFMC16
Phase	This study is designed to compare the effects of active topical nail solution versus placebo nail solution in participants with pedal distal subungual onychomycosis (DSO).

Methodology	This is an interventional study comparing active topical nail solution versus placebo nail solution for the treatment of toenail fungal infection. All clinical and mycological examinations will be performed by blinded assessors; and baseline and post-treatment mycological and quality of life measurements will be analyzed in a single-subject paired fashion.
Study Duration	It is estimated that the duration of time necessary for the completion of this protocol (time from the start of screening to the last participant processed and finishing the study) will be 19 months.

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Objectives	The primary aim of this study is to compare the effect of topical active nail solution vs. placebo nail solution alone, for the treatment of pedal onychomycosis. Secondary aims are to compare the effects of the two intervention arms on the quality of life for participants suffering from onychomycosis, and to explain the influence of a number of variables associated with the response to treatment.
Number of Participants	Analyzing for the dichotomous outcome, either cured or not cured, using Fisher's exact test for independent groups (active topical nails solution alone versus placebo nail solution), in a prospective randomized fashion, expressing the alternative hypothesis as two proportions, at $\alpha = 0.05$, and $\beta = 0.80$, with the event rate in controls estimated to be 0.01 and the event rate in cases estimated to be 0.3, and using a 1:1 ratio of cases to controls, 29 participants will be needed in each treatment group in order to identify a statistically significant difference, should one exist. In anticipation of dropouts, limited site enrollment, and center effects and multiple center effects (≥6 clinical sites), an additional 20% will be added in an effort to ensure statistical power. Therefore, a minimum of 70 participants will be enrolled and randomized, subject to the data safety monitor's surveillance and recommendation.
Diagnosis and Main Inclusion Criteria	The main clinical disease under evaluation is toe onychomycosis. Participants will be males and non-pregnant females 18 years of age or older that have been diagnosed with distal subungual onychomycosis (DSO) involving at least one toenail. Diagnosis of this condition is to be made on the basis of history, physical examination, and a mycological inspection that includes a tissue examination for fungal hyphae (PAS stain). Evidence of fungal hyphae will be considered a positive confirmation of the diagnosis of toenail onychomycosis.
Study Product and Regimen	All participants will be randomized to either the active topical nail solution group, antifungal solution treatment, or to the placebo nail solution group. The topical antifungal medication under investigation is *Tolcylen*™. It will be provided by Marlinz Pharma, Houston, TX, the study funding Sponsor. The topical therapy will be applied in accordance with the existing FDA-approved method for use of this cosmetic agent.
Duration of administration	Administration of the interventions, active and placebo, will continue for no longer than nine (9) months. Administration of the topical agent may stop sooner if clinical and mycological evidence of cures are identified prior to nine (9) months.

Reference therapy	Participants in the control group will apply a placebo topical solution to the involved toenail/s. Preparation of the placebo solution, dimethicone 5%, was undertaken with the aim of making it as close as possible to the active topical nail solution in terms of color and texture, and other physical characteristics. The placebo nail solution, like the active topical nail solution, meets the FDA's safe ingredient criteria for an over-the-counter topical agent. The placebo, like the active topical nail solution, will be supplied in three (3) 7.5 ml tubes with a controlled-release applicator mechanism that allows thin coat of the solution to be applied at a time, and the instructions for application specify that only thin coat of solution to be applied daily to under the leading edge, borders of the toenail and the entire surface of the toenail.
Statistical Methodology .	All participants will be followed to the endpoint of the study, in accordance with the proposed timeline (see below). An intention to treat analysis will be used. Data analysis will entail descriptive statistical methods, including mean and standard deviation, or median and quartile, to describe demographic variables; as well as inferential statistical methods that will include two sample tests of the null hypothesis for differences between the two treatment groups both before and after active topical nail solution or placebo application, and for comparisons of pre-treatment and post-treatment results in single participants, for mycological tests and outcomes. The Wilcoxon rank sum (Mann Whitney) test for unpaired data will be used to identify differences between the two intervention groups both before and after active topical nail solution or placebo application, and the Wilcoxon signed rank test for paired data will be used for comparison of pre-treatment and post-treatment results in single participants, mycological tests, and the OnyCOE-t™ and Visible Nail Plate Involvement Scores. Participants will be analyzed as randomized, and the last observation carried forward method will be used if a participant fails to complete the study protocol (lost to follow up for any cause, whether at-random or otherwise). The participants, as well as all observers and outcomes assessors, will be blind to treatment allocation.

Research Protocol

Title of Study: A Randomized, Controlled Trial to Determine the Efficacy of Active Topical Nail Solution versus Placebo Nail Solution for the Treatment of Pedal Onychomycosis

Primary Investigator: Peter Bregman, DPM, FACFAS

Co-Investigators: D. Scot Malay, DPM, MSCE, FACFAS, and Hye R. Kim, DPM, AACFAS

Relevance of this Study: Onychomycosis is a very common clinical entity treated by podiatrists and dermatologists, as well as general practitioners. The condition has been reported to account for as much as 50% of all forms of human onychopathy and has been noted to be responsible for significant medical as well as psychosocial symptomatology (1). In the compromised host, such as the diabetic patient with peripheral neuropathy or the patient suffering with peripheral vascular disease, or the individual with HIV infection or AIDS, as well as in patients with other forms of immunocompromise, onychomycosis predisposes to periungual cutaneous compromise, ulceration and associated morbidity. Although systemic antifungal therapy can be effective in the treatment of onychomycosis, orally administered medications convey the possibility of systemic complications such as adverse drug-to-drug interactions, as well as renal, hematopoietic, and hepatic dysfunction (2-9). Furthermore, systemic antifungal medications may entail a high cost of treatment when compared to local forms of mycotic nail therapy. In an analysis of cost to avoid liver failure with terbinafine, based on the incidence of liver injury, which is 1 case per 50,000 to 120,000 prescriptions according to the Clinical and Research Information on Drug-Induced Liver Injury Database, the total cost to avoid clinically apparent liver injury at a prevalence of 75% was $18.2 to $43.7 million dollars when the diagnosis was made using KOH screening and $37.6 to $90.2 million dollars when PAS STAIN testing was used (9).

To date, there is no published data describing the use of Tolcylen™ antifungal topical solution versus placebo for the treatment of distal pedal onychomycosis. The randomized, placebo-controlled, outcomes assessor-blinded study described in this protocol is designed to critically analyze the efficacy of Tolcylen™ antifungal solution when it is applied topically for the treatment of pedal onychomycosis in the outpatient clinic population.

Funding Source/s: Marlinz Pharma, of Houston, Texas, has agreed to provide support in the form of an unrestricted research grant for this investigation. Marlinz Pharma markets Tolcylen™, which consists of the FDA-approved antifungal medication tolnaftate combined with inactive ingredients that include urea, lactic acid, undecylenic acid, jojoba oil, and vitamin E. The placebo to be used in this investigation will also be provided by Marlinz Pharma, and is a solution

containing only inactive ingredients, specifically dimethicone 5%, and it is prepared so that it mimics the color and texture of the active compound. Both the active topical nail solution and the placebo will be applied using identical, dose-limiting, brush-tip applicators.

Purpose of the Study

This study is designed to critically analyze the efficacy of topical antifungal therapy using Tolcylen™ versus placebo in an outpatient clinic population suffering with pedal onychomycosis.

Research Problem

A large body of literature already exists that describes the importance of identifying and treating onychomycosis (1,10-12). Moreover, the literature already describes orally administered systemic, and topically applied local therapies that are available for the management of onychomycosis (3,4,6,7,13-15). However, there is currently no randomized clinical trial, using blinded outcomes assessors, that compares the effectiveness of topical antifungal therapy using Tolcylen™ to a placebo agent, for the treatment of pedal onychomycosis.

Review of the Literature

Onychomycosis is a very common disorder that affects a large portion of the general population, and a very high percentage of patients seeking podiatric medical care. In North America, the prevalence of onychomycosis has been reported to range from 7% to 14% of a primary care clinic population (16-18). There are several different clinical forms of the condition, including distal and lateral subungual onychomycosis, white superficial onychomycosis, proximal subungual onychomycosis, endonyx onychomycosis, and total dystrophic onychomycosis (19). Fungal infection of the nail typically causes discoloration and thickening of the nail plate, hypertrophy and hyperkeratosis of the nail bed and folds, onycholysis, and the gradual development of flaking and crumbling of the plate and bed (20). Distal subungual onychomycosis is the most common pedal presentation, and *Trichophyton rubrum* is the most common pathogen (21,22). Usually, fungal infection first becomes established in the skin adjacent to the nail, and thereafter fungus invades the nail bed and plate. Subsequent hyperkeratosis and accumulation of subungual debris leads to onycholysis which, in turn, exposes subungual tissues to further contamination. The subungual environment then serves as a reservoir that sequesters fungal pathogens and allows the infection to persist and gradually expand. The presence of digital contraction deformities, including hammertoes and claw toes, has also been associated with fungal propagation into the perionychial tissues (13). Such digital

deformities lead to distal toe tip loading in the stance and swing phases of gait, with resultant mechanically induced hyperkeratosis and nail plate dorsal deflection, onycholysis, and the resultant exposure of the nail bed to fungal and yeast pathogens.

Although dermatophytes predominate, non-dermatophyte fungi and *Candida* species, as well as mixed fungal infections, can also cause onychomycosis. Non-dermatophyte molds account for 11.1% - 20.7%, and *Candida* species 7% - 19.3%, from North America hospital/clinic-based studies that describe the prevalence of onychomycosis. Moreover, non-dermatophyte onychomycosis tends to be more resistant to all forms of treatment (16,17,21,23).

In a systematic review of the prevalence of onychomycosis, the mean prevalence was 4.3% in the general population-based studies and 8.9% in the hospital/clinic-based studies in Europe and North America (22). The condition was noted to increase with age, and patients over 60 years of age were four times more likely to have onychomycosis than were patients under 60 years of age (17). The disease is also more prevalent in men than in women, and more prevalent in the toenail than in the fingernail (22). It has been suggested that the enclosed environment of the shod foot predisposes to fungal infection in toenails. The incidence of onychomycosis has also been observed to be increasing in the elderly, as well as in people infected with the human immunodeficiency virus, individuals with diabetes mellitus, concurrent infection with tinea pedis, obesity, peripheral vascular disease, psoriasis, and family history of onychomycosis (24). Considering the vascular and neurological deficits that often affect the lower extremities of individuals suffering with diabetes mellitus, onychomycosis in the presence of diabetes mellitus poses a serious risk for cutaneous compromise and subsequent limb morbidity (25). Chronic venous insufficiency, as well as occlusive peripheral vascular disease, also show a high correlation with, and may predispose to, the presence of onychomycosis (26,27). Furthermore, the proximal subungual form of onychomycosis is suggestive of immunocompromise and is typically observed in patients suffering with conditions such as HIV infection, peripheral vascular disease, and diabetes mellitus (25,27).

Attention has been directed at the symptoms and morbidity, as well as the psychological and social ramifications, associated with onychomycosis. It has also been shown that onychomycosis significantly affects an individual's quality of life, including physical and social functioning and emotional health (10,12). Patients with onychomycosis were found to be more self-conscious, embarrassed, had fear of spreading the disease, had increased pain, limited physical functioning, and poor general health perception (12,28,29).

There is a wide range of nonfungal forms of nail dystrophy that the clinician must distinguish from onychomycosis. Gupta and coworkers noted that 13.5% of their sample population displayed abnormal-appearing nails, and that only 6.7% of these displayed actual mycological confirmation of onychomycosis (17). Other

forms of onychopathy that mimic mycotic nail changes include psoriasis, mechanically-induced onycholysis, lichen planus, chronic paronychia, alopecia areata, subungual hemorrhage, dysvascular or post-traumatic onychogryphosis, aging, median canalicular dystrophy (pterygium), pincer nail, yellow nail syndrome, subungual melanoma, and subungual squamous cell carcinoma (30). Because it is often difficult to clinically distinguish between nail changes caused by fungal infection and those caused by nonfungal etiologies of nail dystrophy, it is recommended that nail plate and bed tissue fragments be obtained for mycological assessment in an effort to avoid over treatment with topical or systemic antifungal medications (9,31). Interestingly, 28.57% of clinical estimates were incorrect when experienced clinicians made a diagnosis of onychomycosis based solely on their clinical inspection and historical interview, when mycological lab testing was used to ascertain the actual presence of fungal hyphae in toenail fragments (13). It has also been shown that specimens obtained from the deep layers of the nail plate, subungual debris, and nail bed convey different rates of fungal confirmation, with the highest likelihood of confirming the presence of dermatophytes, non-dermatophyte molds, and yeast, coming from samples of the subungual debris (32).

Microscopic inspection of skin and nail scrapings that have undergone potassium hydroxide (KOH) dissolution of keratin is a reliable and simple, as well as relatively inexpensive, technique for rapidly identifying the presence of fungal hyphae. In-office Dermatophyte Test Medium (DTM), on the other hand, is understood to be an unreliable method when compared with independent mycology lab testing. One report describing 100 cases of suspected onychomycosis revealed a positive DTM result in only 50% of cases that displayed positive growth with fungal culture (33). Periodic acid-Schiff (PAS) staining of tissue specimens has been shown to be the most sensitive test when compared to KOH and culture results, with a sensitivity ranging from 61% to 98% (34).

Treatment options for onychomycosis include palliation with mechanical or chemical debridement of the nail, topical antifungal medication, oral antifungal agent, or a combination of topical and oral agents, or topical medication combined with debridement, and laser therapy (35). Poor prognostic factors include immunosuppression, poor peripheral circulation, poorly controlled diabetes mellitus, subungual hyperkeratosis > 2-mm, significant lateral nail fold disease, dermatophytoma (streak or patch), segmental nail involvement > 50% of the transverse area of visible nail plate, the presence of toe nail symptoms > 6 months in duration, current or former cigarette smoking history, slow rate of nail growth, severe onycholysis, total dystrophic onychomycosis, matrix involvement, non-dermatophyte mold, and mixed bacterial/fungal infection (13,36). Orally administered agents perform best when there is intimate nail plate-to-bed adherence, as the active antifungal agent is delivered into the nail plate by means of the blood supply to the root matrix. Severe onycholysis and subungual debris can inhibit transport of orally administered antifungal agent into the keratin

of the nail plate. In the United States, terbinafine and itraconazole are commonly used as orally administered agents for the treatment of onychomycosis. These agents have been observed to be safe in a wide range of patients, including the elderly. Terbinafine was found to have a higher cure rate than azoles and no difference in adverse events or recurrence rates were found in a 2017 Cochran review (15). Despite their generally good safety profile, it is typically recommended that baseline assessment of liver function tests and the patient's blood count be obtained if orally administered agents are to be used to treat onychomycosis. Fluconazole, which was developed to treat candidiasis and cryptococcal meningitis in AIDS patients, is also available for off-labeled oral use for treatment of onychomycosis; however, this agent does not display as high a safety profile as does either terbinafine or itraconazole when used over a time period suitable for the treatment of pedal onychomycosis (37,38).

Topical antifungals are generally recommended for the treatment of distal and lateral subungual onychomycosis with less than 50% of the visible nail plate surface area without matrix involvement, < 2-mm nail plate thickness, and ≤ 4 nails involved (39,40). FDA-approved topical agents that have shown efficacy for antifungal use include ciclopirox nail lacquer, efinaconazole, and tavaborole. According to the package insert for ciclopirox 8% nail lacquer, a complete cure was observed in 5.5% and 8.5% of cases, and the mycologic cure was 29% and 36% (41). Efinaconazole 10% solution had 17.8% and 15.2% complete cure incidences and 55.2% and 53.4% incidences of mycological cure; and tavaborole displayed 6.5% and 9.1% incidences of complete cure rate and 31.1% and 35.9% incidences of mycological cure (41-43). Interestingly, confirmatory mycology testing before treatment in not cost effective with terbinafine whereas it is with efinaconazole (9). Topical therapy can be relatively expensive, with average monthly supply costs of $76.43 for ciclopirox, $687.54 for efinaconazole, and $1885.75 for tavaborole (44-46).

The Tolcylen™ antifungal solution consists of tolnaftate as an active ingredient and undecylenic acid, lactic acid, propylene glycol and urea as delivery system ingredients. The patented low surface tension Tolcylen™ Solution is the first product of its kind to combine FDA-approved antifungal medication with nail renewal, cosmetic and penetration enhancing ingredients. Tolnaftate, a thiocarbamate antifungal, blocks ergosterol biosynthesis, thus inhibiting fungal membrane formation (47). Tolnaftate has been used for superficial mycotic infection, such as tinea pedis due to *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum* (48, 49). The delivery system ingredients in Tolcylen™ also have antifungal properties, and they convey a cosmetic effect in that they improve nail appearance. In a multicenter, randomized, double-blind, placebo-controlled trial, a statistically significantly greater incidence of mycological cure was observed with a topical preparation of urea, propylene glycol and lactic acid compared to placebo; specifically, 27.2% vs. 10.4% placebo for ≤ 50% nail involvement, and 19.1% vs 7.0% placebo for 51-75% nail involvement, after 26 weeks of treatment for distal and lateral

subungual onychomycosis (50). Undecylenic acid has been shown to have efficacy for the treatment of tinea pedis caused by *T. rubrum* and *T. mentagrophytes* (51). Still, further, urea has been shown to improve the penetration of antifungal medication by softening the nail bed (52).

Pharmacological therapy for the treatment of pedal onychomycosis, particularly when topically administered, should be continued until the visible nail plate is replaced by normal growth (53), and failure of pharmacological treatment may be an indication for operative intervention. Debridement, partial and total nail avulsion, partial and total matrixectomy, and skin grafting procedures, can be useful surgical interventions for the treatment of recalcitrant and painful mycotic nails. Typically, avulsion of the offending nail margin or the entire nail plate is recommended for single nail involvement, whereas matrixectomy may be preferable for the surgical management of multiple, painful mycotic nails (54,55).

Research Question

The hypothesis underlying this research study is stated as follows: Participants undergoing topical application of Tolcylen™ antifungal solution, the active topical nail solution, for the treatment of toenail distal and lateral subungual onychomycosis, will display a higher incidence of nail plate improvement, both clinical and mycological, in comparison to participants undergoing application of a topical placebo agent.

Research Design and Methodology

This document describes a protocol for a human research study. This study is to be conducted according to the United States and International Standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures. Moreover, this document describes an interventional study comparing two different interventions, one a known over-the-counter treatment, and the other placebo, for toenail fungal infection. All clinical and mycological examinations will be performed by blinded assessors.

Study Duration

The recruitment and screening period for potential participants will be 12 months (in order to identify 70 eligible participants) following the decision to initiate the protocol. It is expected that 70 participants will be informed and consented, and enrolled in the study, by approximately 12 months. Treatment for each participant will be carried out for a total of 9 months, or less if there is evidence of clinical

and mycological cure prior to that time. The 9-month follow up visit will serve as the primary efficacy endpoint, in keeping with the usual expected minimum 7 to 9 -month duration of time expected for a full replacement of the visible nail plate in a typical adult human. Thereafter, a 3-month period will be allotted for completion of mycological testing and data collection. An additional 3 months will be allotted for completion of the analyses and 3 more months to write the report describing the study and submission of the manuscript for consideration for publication in a refereed journal. It is, therefore, estimated that the duration of time necessary for the completion of this protocol, data analysis, and preparation of the final report, will be approximately 35 months.

Study Centers

This study will be carried out at multiple clinical offices, under the guidance of different CITI-trained investigators, including:

1. Greg Kramer, DPM; Ankle & Foot Associates, (912) 592-0108 (cell) Contact: Self; gkdawgs@gmail.com, 204 Westside Drive Douglas, GA 31533. Site A

2. Ashton Nelsen, DPM; St Cloud Foot & Ankle; (763) 772-4789 (cell) Contact: self; anelsen.dpm@gmail.com 106 Doctors Park, St Cloud, MN 56303. Site B

3. Franklin Polun, DPM; National Foot and Ankle, (301) 529-1575 (cell) Contact: Self; drfpolun@mydamnfoothurts.com, 12400 Park Potomac Avenue, Suite R-2, Potomac, MD 20854. Site C

4. Nancy Quimby, DPM; Family Foot Care, (518) 428-1712 (cell) Contact: Self; nq1108@gmail.com, 6 Maple Ln. S, Valatie, NY 12184. Site D

5. Peter Bregman, DPM (the Principal Investigator); Foot & Ankle Specialists of Nevada, (702) 701-3186 (cell) Contact: Self; docbregman@gmail.com, 7150 West Sunset Road Suite 110, Las Vegas, NV 89135. Site E

6. Kate Johnson, DPM; A Step Ahead Foot and Ankle, (206) 963-5549 (cell) Contact: Self; kateejo1981@gmail.com, 2001 South Shields, Bldg. F, Fort Collins, CO 80526. Site F

7. Sheldon Laps, DPM, Arnold Ravick, DPM; The Division of Podiatry at The GW Medical Faculty Associates, (202)-677-6690) Contact: Office; 1234 19th St NW #900, Washington, DC 20036. Site G.

8. Mickey Stapp, DPM; 1416 Wainbrook Drive, Augusta, GA 30909, (706) 312-3668 (706) 825-2392 mickeystapp@comcast.net. Site H

9. (There is no Sit I.)

10. Juan Gonzalez, DPM; 5460 Paredes Line Rd Ste 209, Brownsville, TX 78526, Cell phone: 956-455-7091; Email: jngonzalez@gmail.com. Site J

Each of these centers is directed by a podiatrist that is very familiar with the diagnosis and treatment of pedal onychomycosis. Potential center effects will be considered in the data analyses. All participating investigators will be informed of the details of the protocol, and they will have to disclose any real or potential conflicts of interest and provide a signed conflict of interest disclosure (COID) form (Attachment 12).

Objectives

The primary aim of this study is to compare the effect of the active topical nail solution versus the placebo nail solution alone, for the treatment of pedal onychomycosis. Secondary aims are to compare the effects of the two intervention arms on the quality of life for participants suffering with onychomycosis, and to explain the influence of a number of variables associated with the response to treatment.

Study Population

The study population will consist of males and non-pregnant females 18 years of age or older that have been diagnosed with pedal distal subungual onychomycosis involving at least one toenail. Diagnosis of this condition is to be made based on history, physical examination, and a mycological inspection that includes a tissue examination for fungal structure, namely a periodic acid-Schiff (PAS) staining examination. A positive result on the PAS stain mycological test will be considered confirmation of the diagnosis of pedal onychomycosis, based on the microscopic presence of fungal hyphae. At each study site, as each eligible participant is enrolled into the investigation, the participant will be assigned an alpha-numeric code that designates the study site as well as the participant's number. For instance, at study site A, the first participant will be designated A1, and this will continue in sequential numeric order until n participants (designated A1 to An) have been enrolled. This same process will be used at the remaining study sites, as denoted in Table 1. Enrollment will be driven by each site's recruitment of eligible participants.

Table 1 Topical solution tube site-participant designation*

Site A	Site B	Site C	Site D	Site E	Site F	Site G	Site H	Site J
A1	B1	C1	D1	E1	F1	G1	H1	J1
A2	B2	C2	D2	E2	F2	G2	H2	J2
A3	B3	C3	D3	E3	F3	G3	H3	J3

A4	B4	C4	D4	E4	F4	G4	H4	J4
A5	B5	C5	D5	E5	F5	G5	H5	J5
A6	B6	C6	D6	E6	F6	G6	H6	J6
A7	B7	C7	D7	E7	F7	G7	H7	J7
A8	B8	C8	D8	E8	F8	G8	H8	J8
A9	B9	C9	D9	E9	F9	G9	H9	J9
A10	B10	C10	D10	E10	F10	G10	H10	J10
…An	…Bn	…Cn	…Dn	…En	…Fn	…Gn	…Hn	…Jn

*This designation correlates with the randomization schedule and enables the principal investigator to keep track of active and placebo distribution and use.

A study coinvestigator, not participating at a study site, and not tasked with data analyses, will maintain the random allocation code, which will contain this same information as well as the randomly allocated topical solution, denoted as either the placebo nail solution or the active topical nail solution.

Inclusion and Exclusion Criteria

Inclusion criteria for participation in this study include:

1. Male or female participants aged 18 years or older;
2. If female is of childbearing potential, she must not be pregnant at the time of enrollment and she must be using an accepted form of birth control during the study treatment period (acceptable forms include: post-menopausal, surgical sterility, complete abstinence, sterilized sexual partner, tubal occlusion, copper-T intrauterine device, levonorgestrel-releasing intrauterine device, medroxyprogesterone injections, etonogestrel implants, combined pills, norelgestromin/ethinly estradiol transdermal system, intravaginal device, or Cerazette pill; and for males the use of a condom with spermicide or surgical sterility);
3. Participant has a diagnosis of onychomycosis diagnosed by means of history, physical examination, and positive (evidence of fungal hyphae) mycological tissue examination by periodic acid-Schiff (PAS) staining;
4. At least one toe nail with distal subungual involvement, localized to any toe, with at least 10% involvement and including up to 100% involvement of the visible nail plate, any nail plate thickness, with the index nail being the most involved per inspection by the on-site investigator and agreed upon by the designated co-investigator study doctor (Hye Kim, DPM), who will inspect specific clinical photographs of the involved nail/s (the photographs will be obtained at each study site using a specified method, as demonstrated to site investigators, so that the clinical features are appropriately demonstrated);
5. Participant has an intact protective cutaneous sensation as measured with the Ipswich test for loss of protective sensation (10-gram monofilament);
6. Participant has an intact cutaneous barrier, with or without the presence of hyperkeratotic lesions, with or without concomitant tinea pedis or

interdigital maceration, or with or without a history of previous skin ulceration, but without active or current pedal ulceration;
7. Participant must be a satisfactory candidate for the proposed topical antifungal or placebo intervention;
8. Participant must display the ability to understand and give informed consent to participation, on a voluntary basis, in the research study.

Exclusion criteria for this study are:
1. Presence of dermatophytoma, defined as thick masses of fungal hyphae and necrotic keratin between the nail plate and nail bed;
2. Use of any systemic antifungal therapeutic agents within 7-months before the baseline visit, or topical antifungal agent on the feet within 1 month preceding the baseline measurement visit;
3. Candidate with moccasin tinea pedis involving greater than 50% of either plantar surface;
4. Candidate requires the use of narcotic analgesic or non-steroidal anti-inflammatory drug/s for 48 hours prior to baseline visit or at any follow-up clinical evaluations;
5. Candidate has an active drug/alcohol dependence or abuse history;
6. Candidate has a loss of protective pedal sensation or open cutaneous compromise involving the ipsilateral foot;
7. Candidate has trauma to the nail that resulting in permanent nail plate discoloration or shape;
8. Candidate displays radiographic evidence of abnormal lytic or proliferative bone lesion in the toe/s of interest, including recent or healing of an acute fracture, if clinical inspection indicates the potential presence of subungual exostosis (radiographs will be obtained and paid for in the course of usual and customary care, outside of participation in this study);
9. Candidate has had previous nail matrix ablative surgery, either chemical or cold steel, on any of the involved digits;
10. Candidate presents systemic or local contraindications to the proposed application of the topical antifungal nail solution or the placebo agent, such as an uncontrolled cardiac, neurological, hepatic, renal, metabolic, or hematological disease or impairment that has been identified;
11. Candidate suffers from malignant, or bacterial or viral infectious cause/s of nail plate dystrophy;
12. Candidate has a history of known immunosuppression; use of steroid agent (oral, injectable, and topical, however steroid containing inhalant for COPD/asthma is allowed) 3 months prior to baseline visit or at any follow-up;
13. If diabetic, the candidate has diabetes mellitus with hemoglobin A1c greater than 8% (the Hb A1c value will be determined using the last value in the participant's medical record, up to 3 months prior to enrollment, or procured in the course of the potential participant's subsequent usual and customary medical management);

14. Candidate shows signs of substantial peripheral circulatory insufficiency defined as non-palpable pedal pulses on the involved foot or feet;
15. Candidate is currently participating in another surgical, device, or drug study or has participated in any research study involving an investigational device or drug, or surgical procedure, within the preceding 30 days;
16. Candidate is allergic to any of the study products;
17. Candidate is pregnant or breast feeding;
18. Candidate is unwilling or unable to comply with the study procedures;
19. Candidate is affiliated with the investigator or persons working at a study site, or patient who is an employee of the sponsor's company;
20. Candidate is institutionalized because of legal or regulatory order; or
21. Candidate is unable to provide informed consent.

Method for Assigning Participants to Treatment Groups

After enrollment into the study, participants will be randomly allocated to either the placebo nail solution or the active topical nail solution. Randomization will be carried out by means of electronic random number generation under the authority of a co-investigator (HRK), who will prepare sealed, sequentially numbered envelopes for each study site, and mail the envelopes to the designated coordinator for each study site (A-J) (Table 1). In each sealed envelope will be a tube of the topical solution, either the active topical nail solution or the placebo nail solution, consistent with the random number list, which will determine whether or not the placebo or active topical nail solution is contained in the tube. Each tube will be numbered in sequential numeric order from 1 to n, and recorded in the investigator's master list, which will serve to record the random allocation code, detailing whether or not the placebo nail solution or the active topical nail solution was dispensed in the designated tube. Furthermore, each block of tubes will be designated with a letter, A to J, to represent the distinct study sites. The labeled tubes will be mailed to the study sites in blocks of 10, and replenished based on the prevalence of enrolment at each site. At each study site, the investigator will open, in sequential numeric order, a sealed envelope and dispense the labeled tube to the eligible participant in consecutive order. Neither the study doctors responsible for assessing the results of the intervention, nor the participants themselves, will know which of the treatment groups the participant will be in (until after completion of the analyses, when the randomization code will be revealed if a participant or investigator desires to know, and participants randomized to the placebo group will also have the opportunity to receive, from the study sponsor, and free of charge, a course of the active topical nail solution with the Tolcylen™ Fungal Eradication Nail/Skin Renewal Kit, which includes Tolcylen™ Antifungal/Nail Renewal Solution, Tolcylen™ Antifungal Skin Cream, and Tolcylen™ Antimicrobial Shoe Spray (up

to 2 kits)). The nail solution with its envelope will be stored in a secure medicine supply cabinet or at the site investigator's office at a secure location.

Diagnosis of Primary Outcome

The clinical disease under evaluation is pedal onychomycosis. Onychomycosis will be confirmed if fungal hyphae are observed on periodic acid-Schiff (PAS) stain examination of nail plate/bed tissue fragments. The fungal cell wall is composed of layers of chitin, glucan mannoproteins, and glycosylphosphatidylinositol, and the periodic acid-Schiff reaction colors these polysaccharides in the cell walls of fungi magenta. PAS staining of nail clippings is more sensitive than potassium hydroxide (KOH) and fungal culture for the diagnosis of onychomycosis (56). The PAS stain examination will be conducted by a certified microbiology laboratory of the site investigator's choice (their usual and customary practice) or an independent lab that has contracted with the sponsor to conduct the PAS test in support of the investigation. Each site investigator, or the contracted microbiology lab, will forward the results of the PAS tests for each participant. The payment for the baseline PAS stain will be handled by the patient's insurance, in the usual and customary fashion, since this is the typical requirement for standard treatment of mycotic toenails. Once again, anyone randomized to placebo nail solution will receive the active topical nail solution, Tolcylen™, at the end of the treatment as described elsewhere in this protocol, if the participant desires. The PAS stain examination will be repeated at the termination of the intervention period, at either 3, 7 or 9 months after initiation of the intervention, and will be collected for the purposes of the investigation. As such, PAS assessments after the baseline test are not necessarily part of the clinician's usual and customary practice, since standard therapy usually does not entail a second mycology assessment if therapy has been successful. If, however, nail dystrophy persists, then a follow up PAS stain would be considered a reasonable component of standard therapy. To be fair to our participants, the cost of this final PAS assessment will be covered by the study sponsor. We will also randomly allocate a number of participants to either the active or placebo topical solution even if they do not have a PAS stain positive for fungal elements at baseline, in an effort to ascertain the influence that the active solution might have on non-mycotic dystrophic toenails. The investigation will not be powered *a priori* to see a statistically significant difference in this secondary analysis.

Study Product, Dose, Route and Regimen

All participants will be undergoing one of two interventions. Participants in the control group will apply the placebo nail solution to the involved toenail/s. Preparation of the placebo nail solution (dimethicone 5%, a skin protectant and emollient) was undertaken with the aim of making it as close as possible to the active treatment agent in terms of color and texture, and the gross physical

appearance of the solution. The placebo nail solution, like the active topical nail solution, meets the FDA's safe ingredient criteria for an over-the-counter topical agent. The placebo nail solution, like the active topical nail solution, will be supplied in three (3) 7.5 ml tubes with a controlled-release applicator mechanism that allows thin coat of the solution to be applied at a time, and the instructions for application specify that only thin coat of solution to be applied daily to under the leading edge, borders of the toenail and the entire surface of the toenail. It is expected that use of the controlled-release applicator tube will last on average 4 to 5 months when used on two toenails, and therefore each participant will be provided with three (3) tubes of the randomly allocated solution as needed during each follow up visit of their participation in the investigation. The tube containing the topical solution is also designed to prevent evaporation of the agent, and the base terminal of the tube will have a crimped seal labeled with an imprinted code that designates the ingredient as either placebo or active topical solution contained in the tube. Three tubes will be dispensed in order to provide enough of the randomly allocated solution to minimize the potential need to supply more product. If a tube is lost by the participant, or if for any reason the participant runs out of the randomly allocated topical solution, then the PI will ascertain the precise agent (placebo or active topical nail solution) and a replacement tube (also with the base terminal of the tube labeled with an imprinted code that designates the ingredient contained in the tube as either placebo or active topical solution) of the randomly allocated topical solution will be forwarded directly to the study site and dispensed to the participant.

It should be noted that the method of supply and application of both the placebo and the active topical nail solution is consistent with the standard method of use approved by the FDA monograph for use of an over-the-counter topical cosmetic agent, in accordance with the existing FDA monograph approved method for the treatment of dystrophic nails (see Tolcylen™ label, Attachment 1). Participants in each group will be verbally instructed in the proper method of application of the topical solution and will also receive written instructions describing the study regimen and application technique (Attachment 2).

Upon arrival to the clinic for follow-up evaluation and care, the study participant will meet with a blinded investigator in the treatment room. The blinded investigator will review the study protocol and discuss any questions that the participant may have. The blinded investigator will inspect the participant's affected toes and procure the required information (clinical and photographic data) as delineated in this protocol.

Duration of Administration

For participants in both groups, maintenance of topical application of the assigned solution on the mycotic toenail/s will continue for a period of up to 9 (nine) months, for the purposes of the study. This duration of application is based

on an average adult nail growth rate of 9 months for emergence from the proximal nail fold to the distal margin of the nail bed. Follow-up inspections will take place at 3, 7, and 9 months, following randomization and initiation of the treatment process. If participant shows clinical and mycological clearance prior to 9 months follow up, the participant may discontinue application of the topical nail solution if desired, in keeping with general clinical practice. The primary efficacy endpoint will occur at the minimum duration of 7-9 months, in keeping with the aforementioned and subsequently reviewed, proposed study timeline.

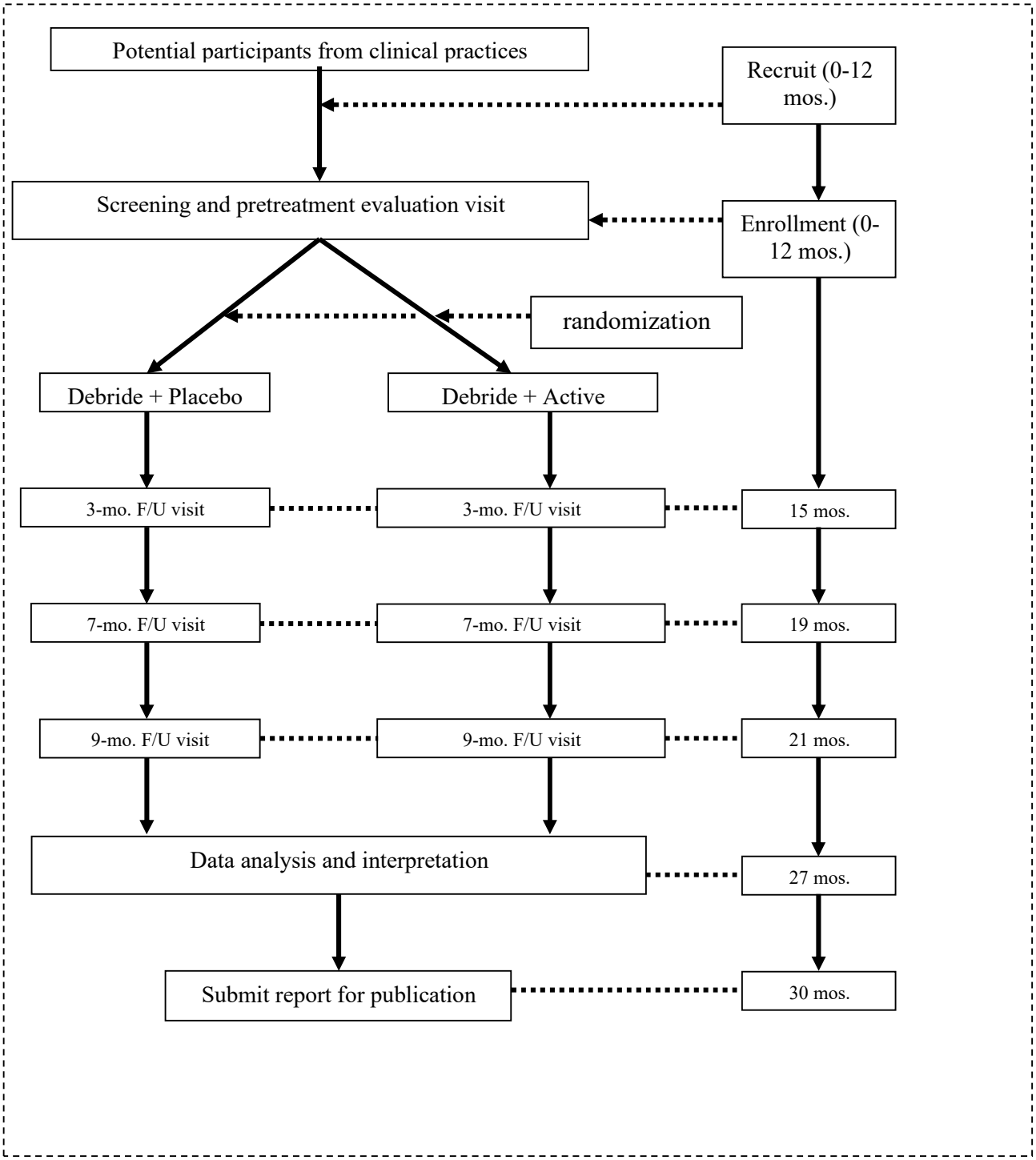
Timeline

The general design of this study is that of a randomized, controlled trial, wherein the intervention arms of the study consist of the application of either placebo or active topical nail solution, to be performed on volunteer human participants. The proposed study timeline is denoted in Table 2 and Fig. 1, below.

Table 2. Research Study Timeline

Milestone	Months
Screening visit and enrollment	12
3-month follow up visit	15
7-month follow up visit	18
9-mont follow up visit	21
Data analysis	27
Submit for publication	30

Fig. 1 Protocol flow diagram



Reference Intervention

Reference intervention in this study will be the application of a placebo nail solution. The 3-month initial interval for follow-up was selected in order to comply with standard clinical practice guidelines which generally suit patient needs relative to mycotic toenail care. As mentioned above, the placebo nail solution was prepared with the aim of making it as close as possible in appearance and texture to the active topical nail solution. The placebo nail solution, like the active topical nail solution, meets the FDA's safe ingredient criteria for an over-the-counter topical, cosmetic agent. The placebo nail solution, like the active topical nail solution, will be supplied in three (3) 7.5 ml tubes with a controlled-release applicator mechanism that allows only a thin coat of the solution to be applied at a time, which is precisely the same as the active topical nail solution will be administered.

Quality of Life Assessment

The OnyCOE-t™ quality of life questionnaire (57,58) will be used to document differences, if any, between the quality of life (QOL) health concepts before, during, and after toenail intervention, and between the study groups (see Attachment 3). The OnyCOE-t is composed of 7, including: a 7-item toenail symptom assessment, which comprises both symptom frequency and symptom bothersomeness scales; an 8-item appearance problems scale; a 7-item physical activities problems scale; a 1-item overall problem scale; a 7-item stigma scale; and a 3-item treatment satisfaction scale. This assessment questionnaire will be used under license from the proprietor IQVIA™ (IQVIA RDS, Inc., Durham, North Carolina), and the fee paid by the study sponsor.

Visible Nail Plate Involvement Score (VNPIS)

A visible nail plate involvement score (Table 3, below) will be used to assess the clinical appearance of an involved toenail, at baseline and then repeated at each follow up visit. This score was designed to provide a continuous numeric value to rate the gross clinical appearance of dystrophic and/or mycotic toenails. The score ranges from a low of 7 to a maximum of 27, with a lower score indicative of a more normal appearing toenail and a higher score indicative of more advanced toenail dystrophy based on gross clinical inspection. This scoring scale was deemed reliable when tested for inter- and intra-rater reliability; wherein, 4 observers rated 40 nails on two separate occasions 3 weeks apart (Pearson's product-moment correlation coefficients for inter-rater reliability ranged from

0.8849 to 0.9609 and the intra-rater reliability ranged from 0.8768 to 0.9687). Pearson's product-moment correlation coefficients range from −1 (100% negative association, or perfect inversion) to +1 (100% positive association, or perfect agreement), with a value of zero indicative of the absence of an association. In general, correlation coefficients with absolute values ranging from 0.60 to 1.00 are considered strong, and those <0.40 are considered weak. Our assessment of this scoring scale for visible toenail involvement indicated strong positive agreements for between and within rater correlations. The index toenail will be rated either by the blind site investigator, or submitted as a photograph for blind study coinvestigators to score. A decrease in the VNPIS of ≥ 60% at any follow up visit will be considered a clinical cure.

Table 3 Visible Nail Plate Involvement Score (VNPIS)

Nail plate characteristics		Point/s
Type of apparent onychomycosis [select one]	White superficial	1
	Distal subungual	2
	Proximal subungual	3
	Any combination of above	4
Longitudinal segmental involvement of visible nail plate (location of gross visible nail plate involvement) [select one]	≤ Distal half	2
	> Distal half, excluding lunula	3
	Extending proximal to lunula	4
Apparent percentage involvement of visible nail plate [select one]	≤ 25%	2
	> 25% ≤ 50%	3
	> 50% ≤ 75%	4
	> 75%	5
Overt gross appearance of involved nail. For thickness, inspect distal margin of visible nail plate and bed (including hyperkeratosis of nail bed attached to plantar surface of nail plate) compared to other toenails [select all that pertain]	Overtly thickened nail plate	2
	Lytic, overtly lifted from nail bed	3
	Onychauxis, gryphosis, clubbed, ram's horn shape	4
	Split, canaliformis, fragmented	5
	TOTAL SCORE (range 7 to 27)	

S**tudy Visits and Procedures**

Investigators participating in this clinical trial will undergo a thorough review of the protocol via teleconference prior to initiation of the investigation. Participating site personnel and the study sponsor, as well as the PI, have already engaged in teleconference in regard to preparation of the study materials and planned involvement. Study visits and procedures will proceed as follows:

1. Screening and Pre-treatment Evaluation
2. Initiation of Study Treatment
3. 3-Month Follow-up Visit
4. 7-Month Follow-up Visit
5. 9-Month Follow-up Visit

When and How to Withdraw Participants

Participation in this research study is voluntary, and any participant can withdraw from the study at any time of their own choice. Although it is desired that all participants, once randomized into a treatment arm, remain in the study until completion of the follow-up visits, it may be necessary to discontinue a volunteer's participation if the participant fails to adhere to the protocol requirements, worsening of fungal infection to the involved toenail or if the participant withdraws his or her consent. Beyond the routine potential complications related to topical application of active topical nail solution, participation in this research project conveys no foreseeable safety hazards. If the volunteer desires, or if the study staff decides, to discontinue a volunteer's participation, it can be done on an immediate basis without the need for a tapered withdrawal period. Participants who choose not to continue with the study protocol until the end of the follow-up period, due to the development of a complication related to their participation in the study, or for any other reason, will be censored, and their last observed data carried forward in the statistical analyses.

Data Collection and Follow-up for Withdrawn Participants

In the event that a participant withdraws from the study prior to the termination of the designated follow-up period, every attempt will be made to inquire as to the rationale that the participant used in deciding to withdraw. Moreover, permission will be sought to collect at least survival (time to event) data. In light of the importance of complete follow-up, in relation to the integrity of the research study, the following steps will be taken prior to concluding that a participant is definitely lost to follow-up:

1. Three separate telephone calls on three separate days, each to the participant's home and place of work.
2. A letter sent to the participant's residence via certified mail, asking the individual to contact the study center to discuss their progress and participation in the study.
3. A telephone call to the participant's next of kin, to inquire as to the participant's whereabouts and participation in the study.

Statistical Plan

Power and Sample Size Determination

Analyzing for the dichotomous outcome, either cured or not cured, using Fisher's exact test for independent groups (active topical nail solution and placebo), in a prospective randomized fashion, expressing the alternative hypothesis as two proportions, at $\alpha = 0.05$, and $\beta = 0.08$, with the event rate in controls as 0.01 and the that in cases as 0.3, and using a 1:1 ratio of cases to controls, we will need 29 participants in each treatment group, or 58 participants overall, to be able to detect a statistically significant difference between the treatment arms. In anticipation of dropouts, limited site enrollment and center effects and multiple center effects (6 clinical sites), an additional 20% will be added in an effort to ensure statistical power. Therefore, a total of 70 participants will be enrolled and randomized, subject to the data safety monitor's surveillance and recommendation.

Statistical Methods

The primary endpoint in this study is the mycological presence or absence of fungal hyphae in fragments of the index toenail as viewed on the microscopic PAS stain, following the application of active topical nail solution, or placebo nail solution, to participant's mycotic toenails.

Secondary endpoints are changes in the participants' toenail-related quality of life, as measured using the OnyCOE-t™ quality of life questionnaire (56,57), and changes in the appearance of the index toenail as measured using the visible nail plate involvement score. Additional demographic exposure variables will also be collected and analyzed in order to describe the participants in the study. Specifically, the participant's age, sex, body mass index (BMI), comorbidities and medications, as well as the number of mycotic toe nails, the duration of onychomycosis based on the participant's history, the presence of pedal digital deformity (hammer toe, claw toe, if present), and any local or systemic complication/s that may arise during the course of the investigation.

All participants will be followed to the endpoint of the study, in accordance with the proposed timeline. The data will be considered based on type and distribution. An intention-to-treat analysis will be used, and it will entail descriptive statistical methods, including mean and standard deviation, or median and quartile, to describe demographic variables; as well as tests of the null hypothesis that will include 2-sample Student's *t*-tests, or Wilcoxon rank sum tests, for differences between the two study groups both before and after intervention, and paired *t*-tests, or Wilcoxon signed ranks tests, for comparison of pre- and post-treatment results in single participants, for continuous data, depending on the distribution of the data. The statistician will be blind to treatment allocation, which will be denoted as "A" or "B" until the results are computed, after which time the precise nature of the allocation will be revealed.

Participant Population(s) for Analysis

The specific population to be included in this intention-to-treat analysis will be the all-randomized population (any participant randomized into the study, regardless of whether they underwent topical application of active topical nail solution or the placebo). This population will be subjected to primary and secondary endpoint analyses. For any participant lost to follow, their last observation will be carried forward for the subsequent evaluations in accordance with the study timeline.

Safety and Adverse Events

Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are adverse events if the abnormality:

- results in study withdrawal;
- is associated with a serious adverse event;
- is associated with clinical signs or symptoms;
- leads to additional treatment or to further diagnostic tests; and
- is considered by the investigators to be of clinical significance.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal;
- life-threatening;
- requires or prolongs hospital stay;
- results in persistent or significant disability or incapacity;
- a congenital anomaly or birth defect; and
- an important medical event.

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the participant and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality;
- The abnormality suggests a disease and/or organ toxicity; and
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of a drug, more frequent follow-up assessments, further diagnostic investigation, and the like.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events

At each contact with the participant, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the appropriate adverse event module of the source document and case report form (CRF) (Attachments 4-7), and in the adverse event-serious adverse event form (Attachment 8). All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document and grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed to determine the outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported.

Reporting of Serious Adverse Events

- **Study Sponsor Notification by Investigator**

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. The Adverse Event/Serious Adverse Event (AE/SAE) form, Attachment 8, form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a

copy of this SAE form on file at the study site. Serious adverse events will be reported by phone to the pharmacovigilance services of Marlinz Pharma, at:

Perry Forrester
Marlinz Pharma
15115 Park Row, Suite 100, Houston, TX
Telephone 844-398-5656

At the time of the initial report, the following information should be provided:

- Study identifier
- Study clinic address
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information related to an ongoing serious adverse event should also be provided promptly to the study sponsor.

- **EC/IRB Notification by Investigator**

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB (ethics committee/ institutional review board) within 10 working days. If the serious adverse events involved death must be submitted to the EC/IRB within 3 working days. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder. Serious adverse events will be reported by Email or phone and facsimile to:

Jessica Kelly | IRB Operations Specialist
WCG IRB
1019 39th Ave SE, Suite 120
Puyallup, WA 98374
o/ +1 855.818.2289
d/ +1 984.227.6166 (Eastern Time)
jkelly@cgirb.com | www.wcgirb.com

Unblinding Procedures

It is not likely that any AE or SAE will develop in relation to this study, since the intervention in question is already an established method of treatment of pedal dystrophic toenail, with a longstanding record of safety and widespread use in the United States. If, however, an adverse event develops in a participant, wherein there is serious risk of morbidity or mortality, there is no conceivable way that knowing whether or not the participant received topical active nail solution or placebo nail solution will make any difference in the management of the participant. If, however, it becomes necessary to unblind a blinded treating doctor or study staff member, this responsibility lies with the Principal Investigator and the Sponsor charged with oversight of the research investigation. The Blind Randomization Schedule Master List for this protocol (Marlinz Pharma #IIT-6042-04-002) will be secured by a co-investigator (HRK), and in the Office of Scientific and Medical Affairs, at;

Marlinz Pharma
15115 Park Row, Suite 100, Houston, TX
Telephone 844-398-5656

This information will remain only with these two individuals, the coinvestigator (HRK) and the science officer, or his/her direct appointee assigned to this task and will not be accessible to any clinical researchers employed at Marlinz Pharma. Moreover, the secured information will not be available to investigators or participating clinical sites during the extent of the investigation, with the exception of the member of the investigational team responsible for assuring that participants are assigned to the appropriate treatment group (in accordance with the randomized allocation schedule), namely the coinvestigator (HRK). In the event of an emergency, the investigators may contact:

Hye R. Kim, DPM
3801 Market Street, MAB 111
Penn Presbyterian Medical Center
Philadelphia, PA 19104
215-662-9664

Perry Forrester
Marlinz Pharma
15115 Park Row, Suite 100, Houston, TX
Telephone 844-398-5656

If there is a need to obtain the Blind Schedule, prior authorization will be required. The decode procedure for blinding will be strictly adhered to. Unblinding will be documented in the source documents and CRFs, and notification of the sponsor will take place within 24 hours by Email, text

message or telephone or telefax, followed by a written narrative of the event within 48 hours.

Data and Safety Monitor (DSM)

This study will be monitored by a Data and Safety Monitor, should any adverse or serious adverse events arise. The details of the organization and operation of the DSM are described in Attachment 9, appended to this protocol.

Stopping Rules

It is not anticipated that this study will impart a high or unreasonable risk to the participants. Nonetheless, a Data Safety Monitor (DSM) will have oversight of the progress and make recommendations related to participant safety and progress. The DSM will have the authority to dictate stopping rules, based on his/her analysis of the results of the study at predetermined times along the course of the investigation. The details of the organization and operation of this DSM are described in Attachment 9, appended to this protocol.

Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. Safety monitoring will include assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data Handling and Record Keeping

Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study;
- Who will have access to that information and why;
- Who will use or disclose that information; and

- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period. A copy of the HIPAA Authorization is included with this protocol (see Attachment 10).

Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial, and these data are contained in source documents. All entries will be entered in the electronic form or printed legibly in black ink on a paper form and returned to a coinvestigator at the study headquarters (D. Scot Malay, 2314 Waverly Street, Philadelphia, PA 19146; D.Malay@pennmedicine.upenn.edu), who will tabulate the data. Examples of these data records include clinical and office charts, laboratory reports, case report forms and photographs.

Case Report Forms

The study case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded. All missing data must be explained. If a space on a CRF is left blank because the procedure was not done or the question was not asked, “N/D” will be written. If the item is not applicable to the individual case, “N/A” will be written. All entries will be entered in the electronic form or printed legibly in black of blue ink on a paper form. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes must be initialed and dated. Investigators will be instructed as follows: “1) DO NOT ERASE OR WHITE OUT ERRORS on the Case Report Forms. 2) For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.” Copies of CRFs are included with this protocol, as Attachments 3-8. The CRFs will be mailed to the distinct study sites, and used to collect study data. Once completed, the forms will be returned to the study headquarters (D. Scot Malay, 2314 Waverly Street, Philadelphia, PA 19146; D.Malay@pennmedicine.upenn.edu)) using preaddresses and postage paid stamped envelopes provided specifically for this purpose. It is also acceptable for the site investigator to photograph or scan the forms and to return them electronically.

Records Retention

The study will be registered with a public registry. It is the investigator's responsibility to retain essential study documents for at least 7 years after publication of the results of this study. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Study Monitoring, Auditing, and Inspecting

Study Monitoring Plan

This study will be monitored according to the monitoring plan described in Attachment 9. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer/s is/are given access to all the above noted study-related documents and study related facilities (e.g. clinics, etc.), and has adequate space to conduct the monitoring visit.

Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and the DSM of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities, the Institutional Review Board, and the Sponsor, for purposes of quality assurance and compliance.

Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the

sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliations to the Sponsor.

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. See Attachment 11 for a copy of the Information and Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a participant, using the EC/IRB-approved consent form, must be obtained before that participant is submitted to any study procedure. This consent form must be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Study Finances

Funding Source

This study is financed through a research grant from Marlinz Pharma, 15115 Park Row, Suite 100, Houston, TX; telephone 844-398-5656.

Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the organization's conflict of interest policy. Attachment 12 is the Conflict-of-Interest Disclosure (COID) form to be used by all members of the investigation team.

Participant Stipends or Payments

Participants will not receive any monetary remuneration for participation in this study. There is no participant stipend or payment for participation in this research project. Participants randomly allocated to the placebo arm of the study will have the option to receive the active topical nail solution, Tolcylen™ for up to nine months (or two 7.5ml tubes), Tolcylen™ Antifungal Skin Cream, and Tolcylen™ Antimicrobial Shoe Spray (up to 2 kits), provided by the study sponsor free of charge, with instructions as to proper use. This option will be described to potential participants during the informed consent process.

Study Site Stipends or Payments

Each study site coinvestigating director will be paid $300.00 by the study sponsor, Marlinz Pharma, for each participant enrolled that completes 7-9

months study at each study site. This payment is aimed at reimbursing the site director and his/her staff for the work required to appropriately conduct this clinical experiment in accordance with United States and International Standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.

The principal investigator and statistician-coinvestigator will be paid by the study sponsor, Marlinz Pharma, $43,750 to oversee the execution of this clinical trial, to analyze the data, and to prepare a written report of the findings with the intention of submitting the final report to a peer-reviewed journal for consideration for publication.

Publication Plan

D. Scot Malay, DPM, MSCE, FACFAS, is a coinvestigator and statistician responsible for the completion of this research project. Moreover, Dr. Malay holds the primary responsibility for preparation of a report for submission to a journal for consideration for publication of the results of this study. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. Neither the complete results of this study, nor any part thereof, carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be passed on to any third party without the consent of the study sponsor, with the exception of the final report, which is to be submitted to a peer-reviewed scientific journal with the intent of publication. The choice of the journal to which the written manuscript will be submitted, remains with the PI and co-investigator (DSM), who will discuss the matter with the coauthors of the report. The report will be authored by the PI and selected investigators, as determined by the PI, and in accordance with standard requirements for authorship. The study sponsor, Marlinz Pharma of Houston, TX, cannot prohibit or block submission of the manuscript of the final report, or its publication, except for a temporary embargo of ≤ 3 months. The PI agrees to delay submission of the report for a period not to exceed three months, at the request of the sponsor, should the sponsor determine that a temporary embargo on submission of the report is in their best interest.

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Attachments

Attachment 1 Tolcylen™ label
Attachment 2 Study regimen and application technique
Attachment 3 OnyCOE-t™ quality of life questionnaire
Attachment 4 Baseline
Attachment 5 3-month follow-up
Attachment 6 7-month follow-up
Attachment 7 9-month follow-up
Attachment 8 AE/SAE Report
Attachment 9 Data safety monitor
Attachment 10 HIPAA
Attachment 11 Consent
Attachment 12 Conflict of Interest Disclosure

Tables

Table 1 Topical solution participant and tube designation
Table 2 Research study timeline
Table 3 Visible nail plate involvement score (VNPIS)

Figures

Fig. 1 Study flow diagram