

An Investigator Initiated Pilot Study Evaluating the Efficacy of
Efinaconazole 10% Solution (Jublia) For the Treatment of
Onychomycosis with Dermatophytomas

Study Protocol & Statistical Analysis Plan

NCT03098615

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Sponsor: Investigator Initiated

Introduction:

Onychomycosis is a common dermatological disease that traditionally is very difficult to treat. Distal lateral subungual onychomycosis (DLSO), which is the most frequently encountered type of onychomycosis. It is caused by a variety of dermatophyte organisms and usually has a chronic disease course. DLSO is thought to originate from tinea pedis fungal infection with direct extension and invasion of the nail bed over time.

DLSO can cause significant patient morbidity and distress, resulting in discoloration and thickening of the toe nails, subungual debris, onycholysis, and often pain and mobility impairment. Onychomycosis can negatively impact patient's quality of life, and improvement is often appreciated upon successful treatment of the disease.¹

In longstanding DLSO infection, dermatophytomas can develop. Dermatophytomas are thick, adherent fungal masses within and under the nail plate, and these are especially difficult to treat due to their unique morphology.² Dermatophytomas are thought to be particularly resistant to antifungals because they are encased in a thick, protective polysaccharide biofilm that impedes the diffusion of medications to the site of infection.^{2,3} Fungi within the biofilm may also be slower growing, thus further limiting the effectiveness of antifungal medications.

Dermatophytomas are known to be resistant to even long courses of systemic antifungals, and have therefore been excluded from both topical and systemic clinical trials for onychomycosis, including those for Efinaconazole solution. Efinaconazole (Jublia) 10% solution is a new FDA approved topical medication indicated for treatment of DLSO, and the utility of this medication likely exceeds published results.⁴ Efinaconazole solution's novel ability to penetrate into the

subungual space likely accounts for improved treatment results seen in DLSO treated with Jublia.

Recent results from our site demonstrate that Jublia eradicated a dermatophytoma of the toe nail in 12 weeks in one patient (Figure 1). Dermatophytomas are a very common complication seen in DLSO and even long duration treatment with oral terbinafine may not be efficacious. When Jublia is delivered to the subungual site of infection, we posit that Jublia can penetrate into the dermatophyte abscess killing the fungus. Therefore, given the encouraging results seen at our site, we further posit that efinaconazole 10% solution applied to the nail bed and subungual space will be a safe and efficacious treatment for patients with dermatophytomas.

STUDY OBJECTIVES

Primary objective is to determine the efficacy of efinaconazole 10% solution in the eradication of dermatophytomas that occur in DLSO. The primary efficacy outcomes measure will be complete clinical cure of the dermatophytoma. Because a dermatophytoma only involves a section of an onychomycotic nail, resolution of the dermatophytoma will be noted separately from resolution of the active infection.

Primary Objective Measurements:

- Dermatophytoma cure will be measured clinically and time to dermatophytomas resolution will be recorded. Clear nail growth between the proximal nail fold and the dermatophytoma's proximal edge will be measured.

Secondary objective measurements will evaluate the efficacy of efinaconazole in treating DLSO complicated by dermatophytoma, as well as assessing for safety with this treatment.

- Resolution of DLSO will be assessed clinically. Complete clinical cure of onychomycosis will be defined as 0% of nail affected on visual inspection. Percent of nail affected will also be recorded with photographs of all nails and close-up photos of target nail with and without DLSO outlined.

- Mean change in onychomycosis severity index⁶ over the course of the study will be monitored. Responders will be defined by a score of 1-5.
- Healthy nail growth appreciable proximally to the DLSO will be measured in the target nail. The target nail will be notched at baseline thereby allowing subsequent nail growth to be assessed. The nail will be re-notched if the notch grows out.
- Mycological cure will be assessed twice during the study and at the study's conclusion. A negative mycology culture result will define a mycological cure.
- Complete cure will be defined by combined full clinical and mycological cure.
- Adverse effects of efinaconazole 10% solution will be assessed.

STUDY DESIGN

Study Outline

This is an open-label study evaluating the efficacy and adverse effects associated with using efinaconazole 10% solution for the treatment of dermatophytomas of the great toe nail.

Number of Subjects

20 eligible patients will be enrolled. Patients will undergo a screening process for up to 4 weeks, will receive treatment for 52 weeks, and will be followed for safety for 4 weeks post-treatment. All subjects will receive active medication and will apply 10% efinaconazole solution to the nail plate and hyponychium, as per package insert instructions. All patients with concurrent tinea pedis, as determined clinically and by KOH scraping, will be treated with Luliconazole cream 1% for 2 weeks.⁷

Visit Schedule

Screening Period

Patient eligibility will be determined within 28 days prior to enrollment in study. Subjects who meet the inclusion and exclusion criteria may proceed to the first dosing visit.

Study Visit

Subjects will report to the clinic site monthly for the first 3 months, followed by 8-week intervals, with the final visit at week 52. Patients nails will be wiped clean prior to evaluation and the target nail will be clipped at each visit.

Follow-Up Visits

Subjects will return to the investigational site for a follow-up visit at 1 month after cessation of therapy.

Discontinuation of the Study

The study may be discontinued at the discretion of the investigator at any time.

STUDY ENTRY CRITERIA

Study Inclusion Criteria

To be eligible to participate in this study, candidates will meet the following eligibility criteria at the time of enrollment:

Inclusion criteria:

- Age over 18
- Give written informed consent prior to any study procedures being conducted, and candidates will authorize the release and use of protected health information (PHI)
- Clinically diagnosed with DLSO of at least 1 great toe by positive KOH. A culture will be collected but not required for inclusion in the study. All cultures will be sent to University of Texas per the fee for service agreement that is in place. Cultures for patients with a previous positive fungal test can be waived at the discretion of the investigator.
- Dermatophytoma present in the target great toe nail as determined by the clinical appearance of the nail infection

- Suitable for application of topical antifungal therapy, in the opinion of the investigator
- Target toenail thickness of 3mm or less as measured by digital caliper
- Women of childbearing potential will be required to use birth control and a negative urine pregnancy test must be documented prior to initiating treatment

Exclusion

- Female patients of childbearing potential who are unable to use two forms of effective contraception throughout the length of the study and 28 days following the last dose
- Unable to comply with the protocol (as defined by the Investigator; i.e. drug or alcohol abuse or history of noncompliance)
- Concurrent onychomycosis of the finger nails
- Severe tinea pedis infection
- Concomitant pseudomonas or other bacterial infection involving the toenails
- History of immunosuppression or concurrent use of immunosuppressant drugs
- History of uncontrolled diabetes mellitus
- History of psoriasis or any other condition that might interfere with the toenail evaluation
- Patients who cannot refrain from toe nail polishes for the length of the study
- Any subject who, in the opinion of the investigator, will be uncooperative or unable to comply with duty procedures

STUDY PROCEDURES & TREATMENT PLAN GUIDELINES

Informed Consent:

A written, signed informed consent form (ICF) and written authorization to release and use PHI, will be obtained prior to performing any tests or evaluations under this protocol. Patients will have the option to ask questions and will be given at least 24 hours to review the ICF before signing. Patients will be allowed to waive the 24 hour review time, if travel or work schedule impedes participation.

See Protocol Flowchart for detailed timing of tests and evaluations.

General Concomitant Therapy:

Subjects should advise the investigator if they start taking any new medications, including over the counter and complementary and alternative medications.

Concomitant onychomycosis therapy

Patients will not be permitted to use any concomitant medications for the treatment of onychomycosis. Patients need to discontinue all treatment for onychomycosis 4 weeks prior to randomization and initiation of treatment in this trial.

SAFETY PLAN

Clinical Safety Assessments

The following clinical safety assessments will be performed: (See study flowchart)

- Physical examinations
- Vital signs (temperature, heart rate, and blood pressure)
- Monitoring for adverse events
- Monitoring for concomitant therapy

Laboratory Safety Assessments

The following laboratory tests will be performed at screening:

- Urine pregnancy test, if applicable.

Jublia	Screening	Treatment									Follow Up
		Visit 1	2	3	4	5	6	7	8	9	
Test / Evaluation	Within 28 Days Prior to Day 1	Wk 1	Wk 4	Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	WK 48	Wk 52	Wk 56
Informed Consent	X										
Medical History	X	X									
Physical Exam	X	X					X			X	X
Vital Signs	X	X					X			X	X
Urine pregnancy test	X										
Assess for resolution of dermatophytoma		X	X	X	X	X	X	X	X	X	X
Onychomycosis severity index	X	X			X		X			X	X
Measure nail growth		X	X	X	X	X	X	X	X	X	X
Photos of nails*		X			X		X			X	
Mycology evaluation	X				X		X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X

*Nail photos will be taken when clinical improvement is noted regardless of whether or not photos were scheduled to occur on the given visit.

References

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Statistical Analysis Plan NCT03098615.

The statistical analysis plan included descriptive statistics on the proportion of patients with negative culture at week 56 and proportion of patient's cure of the toenail as described by less than 10% target nail involvement.

Mean improvement in the OASIS score for patients with cure and non-cure was also reported.