Efficacy and Safety of Efinaconazole 10% Solution in the Treatment of Onychomycosis in Diabetic Patients

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1 INTRODUCTION

1.1 Background

Onychomycosis, a common pathology of the toenails, is even more prevalent among diabetic subjects. Nearly 26 million Americans suffer from diabetes, and approximately one-third of subjects with diabetes have toenail onychomycosis. Numerous studies have addressed the efficacy and safety of both topical and oral antifungal treatment options for onychomycosis in diabetic subjects. However, no study to date has specifically addressed the efficacy and safety of efinaconazole among diabetic subjects.

1.2 Potential Pharmacotherapy

Despite the existence of numerous topical antifungal agents for onychomycosis, data investigating the efficacy of topical antifungal agents among exclusively diabetic patient cohorts is limited. Ciclopirox 8% was evaluated in 2007 as a topical solution among a cohort 49 diabetic subjects. The study witnessed clinical improvement in 63.4% of subjects, with 54.3% attaining mycologic cure (Brenner et al., 2007). An earlier, 2001 study of ciclopirox 8% solution summarized the results of a 215-person diabetic subset of subjects. This study was observational, noncomparative, and uncontrolled, thereby limiting the usefulness of the data. The study reported that the mean affected nail area decreased from 64.3% to 25.7% after 6 months of treatment (Seebacher, 2001).

1.3 Efinaconazole 10% Solution Description

Efinaconazole 10% solution is a new triazole antifungal agent. The medication was developed specifically for the topical treatment of distal and lateral subungual onychomycosis (DLSO) (Gupta, 2014). The medication was developed with consideration of the existing triazole antifungals itraconazole and fluconazole, with the formulation developed to more effectively penetrate the nail plate. The preparation was further enhanced with the development of nail lacquers to avoid product build-up and to reduce removal time. The solution is, specifically, an inhibitor of sterol 14alpha-demethylase (14-DM) (Tatsumi, 2013). In broth dilution tests in vitro, the solution was found to be more potent against reference strains than other common antifungals, including terbinafine, ciclopirox, itraconazole, and amorolfine, (Jo Siu, 2013).

1.4 Efinaconazole Safety and Adverse Effects

The safety of efinaconazole has been document in both Phase II and Phase III trials. Treatment associated adverse events have been relatively frequent by incidence, but of low morbidity and of frequency similar to vehicle alone. Two phase III studies noted rates for a single adverse event during treatment to be similar between efinaconazole to vehicle: in one study, 66% versus 61%, and in the second study, 64.5% versus 58.5% (Elewski, 2013). These adverse events included contact dermatitis (2.9% versus 1.9%, 1.4% versus 1.0%), eczema (3.4% versus 3.3%, information not available in the second study), application site dermatitis (3.5% versus 0.0%, information not available in the second study), and application site vesicles (2.0% versus 0.0%, information not available in the second study). Discontinuation of the study as a result of adverse events was low, with 3.2% of treatment versus 0.5% of vehicle in the first study and 1. 9% versus 0.0% in the second.

An additional study investigated if efinaconazole had a relationship with contact sensitization (Del Rosso, 2013). The study involved nine applications of efinaconazole 10% solution versus

vehicle over a three week period, with multiple follow-up applications three weeks later. The study concluded that the cumulative irritation scores were comparable between efinaconazole and vehicle alone.

1.5 Efinaconazole Indications

It is currently indicated for onychomycosis of the toenails (s) due to:

- Trichophyton rubrum
- Trichophyton mentagrophytes

2 STUDY DESIGN

2.1 Study Objective

The objective of this noncomparative, uncontrolled study is to determine the efficacy of topical efinaconazole 10% for toenail onychomycosis among subjects with diabetes mellitus. Specific indicators to measure efficacy of treatment will be the mycological cure rate, complete cure rate, and treatment success. Furthermore, an additional goal of the study is to gain knowledge of safety in the setting of a cohort of diabetic subjects. Safety will be determined by the incidence and nature of treatment associated adverse events. These will be recorded at each follow-up visit.

2.2 Treatment Groups

Adult subjects (18 years or older) with a medical history of controlled type 2 diabetes mellitus will be considered for enrollment. Subjects will be eligible for enrollment if a clinical diagnosis of distal onychomycosis involving at least 20% of one great toenail (GT) has been made and confirmed by nail biopsy. There will be no restriction based on nail involvement; up to 100% of the nail may be involved. Furthermore, there will be no restriction based on toenail plate thickness. The enrollment period will be continued until 48 intention-to-treat subjects have been enrolled in the study.

2.3 Study Duration

The intended enrollment period will be six months, though this may be extended if necessary to achieve 48 intention-to-treat subjects. The treatment period, following enrollment, will be 50 weeks in duration. The intended total study duration, then, will be 76 weeks.

2.4 Efficacy Endpoints

Mycological cure will be defined as negative KOH examination and negative fungal culture of the target toenail sample.

Clinical cure will be defined as 0% clinical involvement of the target toenail. Almost clinical cure will be defined as ≤10% clinical involvement of the target toenail.

Complete cure will be defined as 0% clinical involvement and mycological cure. Treatment success will be defined as ≤10% clinical involvement of the target toenail and mycological cure.

2.4.1 Primary Endpoints

1. The primary efficacy end point will be the proportion of subjects achieving complete cure at week 50.

2.4.2 Secondary Endpoints

1. The secondary efficacy end points will include mycological cure rate, treatment success rate, clinical cure rate, and almost clinical cure rate.

2.4.3 Safety Endpoints

1. Type of Adverse Events
2. Frequency of Adverse Events

2.5 Measurement Methods

At each study visit, the treating podiatrist will visually and physically assess subjects.

3 POTENTIAL RISKS AND BENEFITS

3.1 Adverse effects of Efinaconazole

The following are documented adverse effects of efinaconazole 10% solution, from a large two-armed study (Elewski, 2013):

	Study 1		Study 2	
N (%)	Efinaconazole (N = 653)	Vehicle (N = 213)	Efinaconazole (N = 574)	Vehicle (N = 200)
No. of subjects who reported at least 1 TEAE	431 (66.0%)	130 (61.0%)	370 (64.5%)	117 (58.5%)
Individual TEAEs reported by >2% of subjects in at least 1 study				
Application site dermatitis	23 (3.5%)	0 (0.0%)	-	-
Application site vesicles	13 (2.0%)	0 (0.0%)	7 (1.2%)	0 (0.0%)
Arthralgia	13 (2.0%)	7 (3.3%)	18 (3.1%)	2 (1.0%)
Back pain	16 (2.5%)	6 (2.8%)	19 (3.3%)	7 (3.5%)
Blood creatinine phosphokinase increased	-	-	11 (1.9%)	5 (2.5%)
Bronchitis	8 (1.2%)	4 (1.9%)	14 (2.4%)	3 (1.5%)
Contact dermatitis	19 (2.9%)	4 (1.9%)	8 (1.4%)	2 (1.0%)
Eczema	22 (3.4%)	7 (3.3%)	-	-
Folliculitis	5 (0.8%)	5 (2.3%)	-	-
Headache	15 (2.3%)	5 (2.3%)	25 (4.4%)	7 (3.5%)
Hypertension	17 (2.6%)	10 (4.7%)	11 (1.9%)	5 (2.5%)
Influenza	16 (2.5%)	8 (3.8%)	10 (1.7%)	1 (0.5%)
Ingrowing nail	17 (2.6%)	1 (0.5%)	11 (1.9%)	2 (1.0%)
Nasopharyngitis	78 (11.9%)	25 (11.7%)	63 (11.0%)	15 (7.5%)
Procedural pain	10 (1.5%)	7 (3.3%)	6 (1.0%)	0 (0.0%)
Sinusitis	30 (4.6%)	4 (1.9%)	17 (3.0%)	5 (2.5%)
Tinea pedis	7 (1.1%)	6 (2.8%)	4 (0.7%)	6 (3.0%)
Upper respiratory tract infection	38 (5.8%)	13 (6.1%)	35 (6.1%)	11 (5.5%)
Urinary tract infection	12 (1.8%)	8 (3.8%)	12 (2.1%)	2 (1.0%)

TEAE, Treatment-emergent adverse event.

Subjects will be advised to contact study coordinators if they notice signs of any of the aforementioned adverse effects.

3.2 Contraindications to Efinaconazole administration

- Known hypersensitivity to efinaconazole

3.3 Benefits of Study

The potential benefits of treating onychomycosis have been well-documented; these benefits are only heightened in the setting of diabetes mellitus. A recent report investigated the impact of successful treatment with efinaconazole 10% solution among a group of subjects with onychomycosis. The study found a statistically greater improvement in all investigated aspects of quality of life compared to a controlled vehicle group (Tosti, 2014). Furthermore, the risk profile of the topical medication have been documented and represent qualitatively small levels of risk.

It is believed that the potential benefits of this study outweigh the potential risks.

4 SUBJECT SELECTION

Prior to enrollment, an informed consent must be obtained. Eligibility will be determined by the established inclusion and exclusion criteria. Assuming a 50% screen rate, it is anticipated that a total of 96 subjects will need to be screened to reach 48 intention-to-treat subjects. Using an estimate of 55% for mycologic cure, 48 subjects will yield a 95% confidence interval of 0.281.

4.1 Informed Consent/Screening Visit

Subjects will complete a written informed consent prior to enrollment. This will be administered by the investigators at the study site in the patient's preferred language (English or Spanish). The informed consent must be signed and dated. Each subject will be assigned a number in ascending order beginning from 01. A screening log of all the subjects will be obtained for each written informed consent . The screening log includes: screening number, first and last name, age, gender, eligibility status or reason for ineligibility. This information will be stored in a locked security box, and kept in a locked cabinet at the Arrowhead Regional Medical Center. This will be accessible only by specifically designated study personnel.

4.1.1 Medical History Screening

Subject eligibility will be determined by the inclusion/exclusion criteria. Record if the subject does or does not meet the criteria.

1. Record date of visit, subject enrollment number, and subject initials
2. Verify subject eligibility based on inclusion and exclusion criteria. Adherence to criteria will be noted.
3. Record subject demographics, including date of birth, gender, race, and weight, and if there were any treatments attempted prior to enrollment.

4.1.2 Physical Assessment Screening

Subject eligibility will be determined by the inclusion and exclusion criteria. Subject adherence to inclusion or exclusion criteria will be recorded. Screening will include reviewing and obtaining informed consent, reviewing inclusion/exclusion criteria, and the initial (complete) physical examination.

4.1.2.A Criteria for Diagnosis of Onychomycosis

To establish diagnosis, a positive potassium hydroxide (KOH) wet mount is required, along with a fungal culture positive for a dermatophyte species.

4.2 Inclusion Criteria

To be considered for inclusion, clinical diagnosis will need to be confirmed through positive KOH stain or positive mycologic culture findings. Involvement of at minimum 20% of the target great toenail will be required for inclusion. A negative pregnancy screen will be required among women of child-bearing age. These women will be required to be on oral contraceptive throughout the study duration.

Subjects will be recruited from Arrowhead Regional Medical Center.

4.3 Exclusion Criteria

Subjects will be excluded if any of the following exclusion criteria are met:

- Diagnosis of a nondermatophyte fungus infection, diagnosis of proximal subungual onychomycosis, diagnosis of superficial white onychomycosis
- Diagnosis of peripheral arterial disease or anatomic abnormalities of the target toenail
- Inability to follow through with all requisite office visits
- Routine use of a systemic corticosteroid, routine use of a systemic immunomodulator, or history of systemic antifungals within the prior five years.
- Active interdigital tinea pedis refractory to topical antifungal treatments
- Known hypersensitivity to efinaconazole
- Use, within the month preceding screening, of: topical antifungal agents, topical anti-inflammatory agents to the toes
- Any history of oral systemic antifungal with known activity against dermatophytes

4.4 Method of Subject Assignment to Treatment Groups

Subjects will be enrolled into the study after verification of eligibility according to the inclusion and exclusion criteria. Written informed consent will also be obtained from subjects.

5 STUDY PROCEDURES

5.1 Initial Visit

5.1.1 Enrollment

Refer to section 4.

5.1.2 Medical History

1. Record date of visit, subject enrollment number, and subject initials.
2. Verify subject eligibility based on inclusion and exclusion criteria. Adherence to criteria will be noted.

5.1.3 Physical Examination

- The complete history and physical will be performed at screening. At the first visit, the examination will be limited to a problem focused examination.
- Digital assessment of the great toe/planimetry.
- Vital signs.
- Clinical assessment of the toenails.

5.1.4 Procedures

5.1.5 Adverse Events Pre-screen

Subjects' health status will be studied for the purpose of recording adverse events in the future.

5.1.6 Treatment

- Eligible subjects will be given efinaconazole 10% solution, and instructed to apply the solution to the great toenail (GT). If more toenails are affected, the solution may be applied in the same manner to all affected toenails as directed by the investigator and desired by the patient.

5.2 Follow-up Visits

Subjects will be assessed at the screening, at baseline, and at every 10 weeks until week 50 (at weeks 10, 20, 30, 40, and 50). The final assessment (week 50) will include a complete history and physical examination, replacing the lower extremity focused physical examination.

5.2.1 Medical History

1. Date of visit, subject enrollment number, and subject initials will be recorded at each follow-up visit.
2. Subject eligibility will be verified based on inclusion and exclusion criteria. Adherence to criteria will be noted.

5.2.2 Physical Examination

- Digital assessment of the great toe/planimetry
- Lower extremity focused physical examination for visits at weeks 10, 20, 30, 40. A complete history and physical examination at week 50.

- Vital signs
- Clinical assessment of the toenails

5.2.3 Procedures

- KOH wet mount and fungal culture at final office visit
- Additional safety laboratory studies will be ordered as needed
- Debridement of target toenail
- Debridement of other toenails as needed

5.2.4 Adverse Events

- Each follow-up visit will include careful monitoring for adverse events

5.3 Administration of Efinaconazole Methods

All subjects will be self-administering the medication. All related questions will be answered and concerns addressed.

5.3.1 Storage and Handling of Efinaconazole

Efinaconazole will be stored by the subjects themselves, without requirement of freezing or refrigeration .

5.3.2 Subject Education

Subjects will be informed of all beneficial and adverse effects of efinaconazole during the written and oral consent process (refer to sections 3.1 and 4)

5.3.3 Subject Compensation

Subjects will be compensated a stipend for each attended office visit following screening. The amount of compensation will be of reasonable amount, and not excessively large as to inappropriately motivate subjects.

6 SUBJECT COMPLETION OR DISCONTINUATION

6.1 Subject Completion
The subject will be considered to have completed the study after completed the week 50 follow-up evaluation.

6.2 Subject Discontinuation
The subject will be discontinued from the study if the subject withdraws, is withdrawn due to an adverse event, or is no longer able to be located. Any reason for discontinuation must be documented along with information about the health of the subject at the time of withdrawal. All attempts to contact subject must be documented. After 3 documented attempts of contact, the subject will be considered discontinued.

6.3 Early Termination Appointment
If the subject elects to discontinue the study prior to completion, the subject will be asked to attend an early termination appointment. This early termination appointment will replace the final office visit. It will include the procedures of a follow-up office visit, with the addition of a complete history and physical. Subjects will be provided increased, but not excessive, financial compensation as motivation for attending this appointment.

7 SAFETY ASSESSMENTS
A safety evaluation will be conducted at every visit.

7.1 Safety Evaluation
Safety will be assessed by recording the nature, intensity, and duration of treatment related adverse events. Safety analyses will be performed on both an intention-to-treat and per-protocol analysis basis. The intention-to-treat population will include each patient receiving at least one dose of the medication, with at least one post-baseline assessment.

7.2 Adverse Events
An adverse event may be any unintended clinical, radiographic, or laboratory result associated with the use of treatment modality. An adverse event does not necessarily have causal relationship with the treatment intervention.

Information collected during subject screening serves to determine if an adverse event started before or during the course of study and to monitor its progression throughout the course of the study. Follow-up evaluation and treatment will continue until the adverse event has resolved.

7.2.2 Adverse Events Causality
Adverse events will be assessed for causality. The event is considered related to the treatment intervention if there is a reasonable possibility that the treatment could have contributed to the event. Evidence supporting the relation between treatment and adverse event can be derived from scientific and medical facts, observation, and professional opinion.

7.3 Serious Adverse Events
An adverse event is considered serious if:

- it results in death
- it is life threatening
- it requires hospitalization
- it results in disability or incapacity
- it jeopardizes the health of the subject

7.4 Documentation and Reporting of Adverse Events
Adverse events will be documented. Serious adverse events will be completely reported to the study grant sponsor, the institutional review board (IRB), and to the University Compliance Office, within 24 hours of becoming aware of the serious adverse event.

8 SUBJECT PROTECTION REQUIREMENTS

The Principal Investigator is required to provide an Institutional Review Board (IRB)/Ethics Committee with necessary materials. The study cannot commence until the IRB/Ethics Committee provides written

approval of the proposed pilot study. Appropriate reports of progress of this study will be provided to the IRB/Ethics Committee in agreement with the policy established by the grant sponsor.

Changes to an approved protocol may only be made by the grant sponsor with IRB authorization, except in instances deemed necessary to eliminate immediate harm to the subjects or when the change involves only administration or logistics.

Significant deviation from the protocol without appropriate approval will be regarded as a protocol violation.

9 REGULATORY REQUIREMENTS

This study will be conducted in accordance with the principles consistent with Good Clinical Practice (GCP).

10 RESPONSIBILITIES OF THE INVESTIGATORS

10.1 Obtaining Subject Informed Consent

Information about the study in a language fully understandable by the eligible subject (English or Spanish) will be given in written and oral form by the investigator. It will be explained to subjects that they are free to refuse entry into the study and free to withdraw at any time. Written consent forms will

be approved by the grant sponsor. The original consent form is placed in the subject's study records and a copy is provided to the subject.

10.2 Subject Confidentiality

The investigators will ensure that privacy of all subjects is maintained. Investigators will assure subjects that their personal identity and all personal medical information will be safeguarded. In all documents submitted to the sponsor, subjects will be identified by a unique identification code. All personal medical information will always be treated as confidential and in compliance with HIPAA regulations.

10.3 Access to Data/Documents

The investigators will have access to data and documents obtained from subjects during the course of the study. Personal medical information may be studied for the purpose of verifying data recorded and subject eligibility and is only accessible to the investigators

10.4 Product Delivery, Storage, and Returns

The investigator is responsible for ensuring that deliveries of all material involved with the study are correctly received and handled. Materials will be properly labeled and safely stored. All unopened materials will be returned to the study grant sponsor.

10.5 Data Handling

All data collected will be included in a report to be submitted to the study grant sponsor. The data will be scanned and sent through secure electronic mail (e-mail). The report will be legible. Any errors will be corrected with a single line strike-through that does not obscure the original entry and annotated with the investigator's initials and current date. No data will be withheld from the report and any missing data will be noted with the reason for why it is missing. Frequency of case report submissions to the grant sponsor will be decided between the investigator and grant sponsor.

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