CLINICAL TRIAL PROTOCOL

Study Title:	Randomized, Double-blind, Phase III Study of the Efficacy and Safety of Miconazole Oil, Active versus Placebo in the Treatment of Otomycosis
Study Number:	MZ-1015-ESP3-054
Study Drug:	Miconazole oil
Sponsor:	Hill Dermaceuticals, Inc. 2650 S. Mellonville Ave Sanford, FL 32773
Protocol Date/Version:	December 16, 2022 Original
NCT Number	NCT05660382

PROTOCOL APPROVAL

The following individuals approve the December 16, 2022 version of the MZ-1015-ESP3-054 protocol. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Company:	Hill Dermaceuticals, Inc.
Name:	Rosario G. Ramirez, MD
Title:	Medical Officer
Address:	2650 South Mellonville Avenue Sanford, FL 32773

Signature Date

STUDY ACKNOWLEDGEMENT

Protocol number: MZ-1015-ESP3-054

I have read this protocol and commit to conduct the study as outlined herein in accordance with current Good Clinical Practices (cGCPs) and all applicable law.

I agree that I or my designee will completely inform all subjects in this study and their legal representative(s) concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements.

I will be responsible for maintaining the informed consent form signed by each subject or subject's legal representative(s), as applicable, and the assent form signed by each subject, as applicable, and for providing each subject or each subject's legal representative with a signed copy of these forms.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____ _____

Investigator's signature Date

_____

Investigator's printed name

SYNOPSIS

Name of Sponsor/Company: Hill Dermaceuticals, Inc.

Name of Finished Product: Miconazole oil

Name of Active Ingredient: 2% miconazole

Study Title:

Randomized, Double-blind, Phase III Study of the Efficacy and Safety of Miconazole Oil, Active versus Placebo in the Treatment of Otomycosis

Study Number: MZ-1015-ESP3-054

Study Center(s): Up to 8 study centers in the United States (US)

Number of Subjects Planned:

Approximately 110

Study Period:

The study duration for each subject will be up to approximately 24 days, which includes 14 days of treatment and a follow-up visit 7 days after the end of treatment (Test of Cure) visit, including the visit window of 3 additional days after the protocol-specified day to complete the final Test of Cure visit.

Phase of Development: 3

Objectives:

- Confirm the efficacy of miconazole oil (active) compared with mineral oil (placebo) over a 14-day treatment duration in subjects with clinical otomycosis
- Assess the safety of miconazole oil over a 14-day treatment duration in subjects with clinical otomycosis

Design and Methodology:

This study is a randomized, double-blind, parallel-group study to be conducted at up to 8 study centers in the US. Approximately 110 male or female subjects with otomycosis will receive study drug. Subjects will be randomly assigned in a 1:1 ratio within site to receive miconazole oil [administered as 5 drops per ear at ~30 mg per drop instilled into the external ear canal of the ear(s) affected by otomycosis] or mineral oil, for 14 days. Both the subject and the investigator as well as study staff will be blinded as to the contents of the study drug.

At Screening/Baseline (Day 1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a condensed physical examination, an assessment of the signs and symptoms of otomycosis (pruritus, debris, visual examination for presence of fungal elements, and aural fullness), and an evaluation of medical history. Urine will be obtained for pregnancy screening in female subjects of childbearing potential. Prior and concomitant medications will be reported. Subjects with positive signs and symptoms of otomycosis and who meet all other eligibility criteria will be entered into the study. A fungal culture of the affected ear(s) will be taken, then debris will be cleaned from the affected ear(s) following the site's normal procedures. The subject will then begin treatment with study drug. The subject or caregiver will instill the first dose of study drug at the site, under the supervision of the investigator or site personnel. Adverse events (AEs) will be assessed. The subject will then leave the clinic and continue to administer the study drug twice per day as instructed. Subjects will be instructed to avoid getting water in the ear, to consider drying excessive water in the ear by using a blow dryer, and to place a Vaseline-impregnated cotton ball over the affected ear(s) to help keep water out of the ear while bathing or showering.

Name of Sponsor/Company: Hill Dermaceuticals, Inc.
Name of Finished Product: Miconazole oil
Name of Active Ingredient: 2% miconazole
Subjects will continue to administer the study drug twice per day, up through Day 14, following the same instructions as provided at the Screening/Baseline Visit on Day 1. Subjects will return to the clinic on Day 15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis will be performed. AEs and concomitant medications will also be assessed, and the subject will return all unused study drug. Subjects will return to the clinic on Day 22 for the Test of Cure Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed. AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential.
Study Visits: Screening/Baseline (1 visit); End of Treatment (1 visit); Test of Cure (1 visit)
Efficacy Evaluations: • Clinical signs and symptoms of otomycosis (pruritus; debris; presence of fungal elements; aural fullness)
Safety Evaluations: • AEs
Key Inclusion Criteria: Male or non-pregnant, non-lactating females with a clinical diagnosis of uncomplicated otomycosis of the external ear only, with an intact tympanic membrane, who are in general good health as determined by medical examination and medical history, and who are free of clinically significant disease, including diabetes mellitus, that is not well-controlled or that could interfere with the study, will be included in the study. In each ear to be treated with study drug, subjects must have a visual presence of fungal elements and must also have the following signs or symptoms of otomycosis: pruritus ≥2; debris ≥2; and aural fullness ≥2.
Key Exclusion Criteria: Subjects with any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis, including concomitant otic infections (including bacterial infection) that require antimicrobial treatment, disease that has spread beyond the external ear(s), or pre-existing skin atrophy of the affected ear(s); tympanostomy tube or perforated tympanic membrane in the ear(s) that will be treated with study drug; history of prior surgery directly affecting and compromising the external auditory canal and/or tympanic membrane of the ear(s) that will be treated with study drug, except for prior tympanostomy tube(s) that have already been removed and completely healed; use of any topical medicated treatments for otomycosis within 14 days of study entry; use of any systemic antifungal therapy within 28 days of study entry, warfarin within 28 days of study entry, immunosuppressive or immune-stimulating drugs within 28 days of study entry, or systemic steroids within 3 months of study entry; fever of ≥100°F at study entry; recurrent otomycosis that has been unresponsive to previous antifungal treatment; known hypersensitivity to any of the components in the test formulation; and/or participation in another investigative trial within 28 days of study entry will be excluded from the study.
Test Product, Dose and Mode of Administration: Miconazole oil

Name of Sponsor/Company: Hill Dermaceuticals, Inc.
Name of Finished Product: Miconazole oil
Name of Active Ingredient: 2% miconazole
Active ingredient: 2% miconazole Other ingredients: refined peanut oil, mineral oil, oleth-2, and isopropyl myristate Mode of administration: subjects will be seated and then instructed to tilt their heads so that the affected ear is facing up. The subject or caregiver will then gently pull the ear lobe backward and upward and apply 5 drops of miconazole oil into the ear. The subject will be instructed to keep the head tilted with the ear facing up for approximately 3 to 5 minutes to allow the miconazole oil to penetrate lower into the ear canal. If both ears are being treated, the process will then be repeated for the other ear after a 5-minute wait.
Placebo, Dose and Mode of Administration: Mineral oil Active ingredient: none (placebo group) Other ingredients: mineral oil Mode of administration: same as described for the active test product.
Endpoints: **Primary Efficacy Endpoint** • Percentage of subjects with “Clinical Cure,” defined as the score of 0 for fungal elements, and score of 0 for signs and symptoms of otomycosis (pruritus, debris, and aural fullness). **Safety Endpoint** • Percentage of subjects with treatment-emergent adverse events (TEAEs).

Name of Sponsor/Company: Hill Dermaceuticals, Inc.

Name of Finished Product: Miconazole oil

Name of Active Ingredient: 2% miconazole

Statistical Analyses:

Descriptive statistics will be presented for the percentages of subjects by treatment group with Clinical Cure in the study ear at each evaluation. Descriptive statistics will also be presented for the percentages of subjects by treatment group with each sign or symptom of otomycosis in the study ear at each evaluation. Descriptive statistics will include the number and percentage of subjects in each category.

In cases of bilateral otomycosis, the ear with the worse infection at Screening/Baseline, as assessed by the investigator based on clinical signs and symptoms, will be used as the study ear for efficacy analyses. If both ears are determined by the investigator to have the same degree of infection at Screening/Baseline, the left ear will be used as the study ear for the purposes of efficacy analyses.

For the primary efficacy endpoint, percentages of subjects with Clinical Cure at the Test of Cure Visit will be compared using a Cochran-Mantel-Haenszel (CMH) exact test stratified by clinical site with a 2-sided significance level of 0.05. Comparisons will be conducted in a similar manner between the miconazole oil and mineral oil (placebo) groups for the secondary endpoints. Missing data will be imputed as treatment failures for the primary and secondary efficacy analyses; missing data otherwise will not be imputed.

The primary population for all efficacy analyses will be the ITT population, defined as all subjects who were randomized, dispensed study drug, and with a clinical diagnosis of otomycosis.

The primary population for all safety analyses will be the safety population, defined as all randomized subjects who received at least one dose of study drug and had at least one post-Baseline safety assessment.

All AEs occurring during the study will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent adverse events (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group. Summaries will provide the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported SAEs will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug. Descriptive statistics will be presented for all safety data.

Sample Size:

Approximately 110 subjects (~55 in each group) are required to provide 80% power, using a Fisher's Exact test with a 2-sided significance level of 0.05, assuming a response rate for the primary efficacy endpoint of 35% in the miconazole oil group and 10% in the mineral oil group.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDPE	High density polyethylene
ICH	International Conference on Harmonisation
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open-Label Extension
OTC	Over the counter
PP	Per protocol
RP	Randomization Period
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
US	United States

1 INTRODUCTION

1.1 Background

Miconazole is an imidazole antifungal agent that has been available by prescription and over the counter (OTC), in different formulations, for many years. It is commonly used for different types of fungal skin infections, such as *Candida*, ringworm, jock itch, athlete's foot, nail fungus, vaginal yeast infections, and oropharyngeal candidiasis. Formulations containing up to 4% miconazole nitrate have been approved for OTC use as topical antifungal agents in cream, ointment, powder, or gel dosage forms. The 2% formulation is commonly used for dermatophytic infections.

While antifungal agents including miconazole are used in practice for the treatment of fungal otitis externa (also called otomycosis), there are currently no treatments approved by the United States (US) Food and Drug Administration (FDA) for this indication in humans. Miconazole is currently FDA-approved as a component of two veterinary combination products (Surolan and Easotic) administered otically to dogs for the treatment of canine otitis externa caused by susceptible strains of yeast and bacteria. Each veterinary product contains miconazole in combination with an antibacterial agent and a corticosteroid. The concentration of miconazole present in Surolan (23 mg/mL miconazole nitrate) is similar to the 2% concentration of miconazole planned for use in humans in this study. The concentration of miconazole present in Easotic is 15.1 mg/mL miconazole nitrate, which equates to approximately 1.5% miconazole. While the causative organism of canine otitis externa, *Malassezia pachydermatis*, is not typically associated with human otomycosis in the US, it is expected that human otomycosis, which is most commonly associated with organisms from the *Candida* and *Aspergillus* genera, would respond to concentrations of miconazole similar to those used in dogs.

The mechanisms of action of miconazole when used topically for the treatment of fungal infections involve its actions against the fungal organisms, rather than their human host. Miconazole targets the cytochrome P450-dependent enzyme 14-α-sterol demethylase, an enzyme that is also involved in mammalian cholesterol synthesis, resulting in inhibition of ergosterol biosynthesis in the cell membrane. Because ergosterol is an important component of the cell membrane, inhibition of its synthesis inhibits fungal cell growth [Vandenbosch 2012]. In addition to its activity toward the enzyme 14-α-sterol demethylase, miconazole also leads to increased reactive oxygen species in fungal organisms, which appears to result in fungicidal activity [Vandenbosch 2010; Musaji 2010].

Clinical studies of 2% miconazole conducted outside of the United States also suggest the efficacy of miconazole in the treatment of human otomycosis [Kiakojuri 2007; Vennewald 2010; Navaneethan 2015]. *In vitro* studies of miconazole have also demonstrated activity of miconazole against some clinical isolates of fungi associated with human otomycosis in the US [Bassiouny 1986; Stern 1988].

The mechanisms of action of miconazole against fungi in general appear to be applicable to fungi associated with otomycosis. Data from the completed Phase 2 study of the investigational product (2% miconazole oil; Hill Dermaceuticals, Inc. Study HD-MCZ-PHII-DRF062016) demonstrated 25.0% of subjects with Therapeutic Cure, defined as a negative fungal culture plus

the absence of each of the otomycosis signs and symptoms of pruritus, debris, fungal elements, and pain, compared with 7.1% of subjects treated with control product (vehicle oil), at the final test of cure study visit, following a 14-day treatment regimen. The percentage of subjects with therapeutic cure following a 7-day treatment regimen was 8.3%, supporting the 14-day treatment duration for miconazole.

In the recently completed Phase 3 study (Hill Dermaceuticals, Inc. Study HD-MZ-0120-ESP3-052), 14 of 67 subjects (20.9%) in the Miconazole Oil group achieved the primary endpoint of Therapeutic Cure (both negative fungal culture and no signs or symptoms of otomycosis) at Test of Cure visit, compared to 11 of 64 subjects (17.2%) in the Vehicle Oil group, ($p = 0.589$). Differences between groups in favor of the Miconazole Oil group were greater for the secondary endpoints than for the primary endpoint. For the secondary endpoint of Clinical Cure (score of 0 for visual presence of fungal elements, pruritus, debris and aural fullness) at the Test of Cure visit, an approximately 1.5-fold greater percentage of subjects achieved this endpoint in the Miconazole Oil group (22 of 67 subjects, 32.8%) relative to the Vehicle Oil group (14 of 64 subjects, 21.9%); and for the secondary endpoint of Mycological Cure (negative fungal culture) at the Test of Cure visit, an approximately 1.5-fold greater percentage of subjects achieved this endpoint in the Miconazole Oil group (4 of 67 subjects, 35.8%) relative to the Vehicle Oil group (15 of 64 subjects, 23.4%).

Adverse event (AE) data from the completed Phase 2 and Phase 3 of the investigational studies support the acceptable safety of miconazole oil and generally demonstrated a lower percentage of patients with treatment-emergent AEs (TEAEs) in each of the miconazole oil groups.

The most frequently reported TEAEs in the 14-day miconazole oil group in the Phase 2 study were application site pruritus, application site pain, and ear infection fungal (Table 1). In each case except for ear infection fungal, a higher percentage of subjects in the 14-day vehicle oil group compared with the 14-day miconazole oil group reported the TEAE. Similar results were observed for the 7-day miconazole oil group, although a higher percentage of subjects in the 7-day miconazole oil group had the TEAE of application site infection compared with the 14-day miconazole oil and 14-day vehicle oil groups.

Table 1 Treatment-emergent Adverse Event Preferred Terms Reported in >1 Patient in the Safety Population of Hill Dermaceuticals, Inc. Study HD-MCZ-PHII-DRF062016

System Organ Class Preferred Term	Study Group		
	7-Day Miconazole Oil (N=23) n (%)	14-Day Miconazole Oil (N=22) n (%)	14-Day Vehicle Oil (N=20) n (%)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	4 (20.0)
Ear pain	0 (0.0)	0 (0.0)	2 (10.0)
Tympanic membrane perforation	0 (0.0)	0 (0.0)	2 (10.0)
General disorders and administration site conditions	4 (17.4)	6 (27.3)	9 (45.0)
Application site pain	1 (4.3)	2 (9.1)	5 (25.0)
Application site pruritus	3 (13.0)	4 (18.2)	6 (30.0)

System Organ Class Preferred Term	Study Group		
	7-Day Miconazole Oil (N=23) n (%)	14-Day Miconazole Oil (N=22) n (%)	14-Day Vehicle Oil (N=20) n (%)
Infections and infestations	4 (17.4)	3 (13.6)	2 (10.0)
Application site infection	2 (8.7)	0 (0.0)	0 (0.0)
Ear infection fungal	1 (4.3)	2 (9.1)	1 (5.0)

Source: Study HD-MCZ-PHII-DRF062016 Clinical Study Report Table 18

No serious AEs (SAEs) were reported in the Phase 2 study. AEs leading to discontinuation in the Phase 2 study were observed in a higher percentage of subjects in the 14-day vehicle oil group compared with either the 14-day miconazole oil or 7-day miconazole oil group, providing further evidence of an acceptable safety profile for miconazole oil (Table 2).

Table 2 Treatment-emergent Adverse Event Leading to Permanent Withdrawal of Study Drug and/or Early Discontinuation from the Study in the Safety Population of Hill Dermaceuticals, Inc. Study HD-MCZ-PHII-DRF062016

Preferred Term	Study Group		
	7-Day Miconazole Oil (N=23) n (%)	14-Day Miconazole Oil (N=22) n (%)	14-Day Vehicle Oil (N=20) n (%)
Application site discharge	0 (0.0)	0 (0.0)	1 (5.0)
Application site erosion	0 (0.0)	1 (4.5)	0 (0.0)
Application site infection	1 (4.3)	0 (0.0)	0 (0.0)
Application site pain	0 (0.0)	1 (4.5)	3 (15.0)
Application site pruritus	1 (4.3)	1 (4.5)	1 (5.0)
Dysgeusia	0 (0.0)	1 (4.5)	0 (0.0)
Ear pain	0 (0.0)	0 (0.0)	1 (5.0)
Nausea	0 (0.0)	0 (0.0)	1 (5.0)
Tympanic membrane perforation	0 (0.0)	0 (0.0)	2 (10.0)

Source: Study HD-MCZ-PHII-DRF062016 Clinical Study Report Table 19

In the Phase 3 study, the percentages of subjects who experienced 1 or more TEAEs in the Miconazole Oil group was lower (41 subjects [46.6%]) compared with the Vehicle Oil group (49 subjects [55.1%]) during the Randomization Period (RP; Table 3). During Open Label Extension (OLE) treatment (which consisted of an optional 2 weeks of treatment with miconazole oil in patients who had completed the RP), a total of 1 (3.6%) and 7 (16.7%) subjects who had received prior miconazole oil or who had received prior treatment with vehicle oil, respectively, experienced at least 1 TEAE. In Enrollment B, during which generally healthy subjects who were not required to have otomycosis were treated with open-label miconazole oil for 2 weeks, 13 (6.4%) subjects reported at least 1 TEAE (Table 3). Severe TEAEs were experienced by 3 subjects (3.4%) in the Miconazole Oil group during the Randomization Period and 1 subject (0.5%) in Enrollment B. The number of subjects who experienced 1 or more TEAEs suspected by the investigator to be study drug related were 2 (2.3%), 1 (1.1%), and 8 (3.9%) subjects in the Miconazole Oil, Vehicle Oil, and Enrollment B groups, respectively.

No deaths occurred after the initiation of study drug use. One subject in the Miconazole Oil group experienced SAEs of acute kidney injury and hypotension but completed the study. Overall, 11 subjects discontinued study drug due to TEAEs, including 4 subjects (4.5%) in the Miconazole Oil group, 6 subjects (6.7%) in the Vehicle Oil group, and 1 subject (0.5%) in the Enrollment B portion of the study. The most common TEAEs leading to early discontinuation were the disease under study (fungal ear infection) and application site pain (Table 4). Two additional subjects were discontinued, 1 subject withdrew consent as the primary reason for discontinuation and 1 subject completed the Enrollment A treatment and Randomization Period but discontinued study drug during the OLE.

Table 3 Phase 3 Study - Summary of Treatment-Emergent Adverse Events Characteristics (Randomization Safety Population and Open-label Safety Population)

	Enrollment A						
	Subjects Randomized to Miconazole Oil			Subjects Randomized to Vehicle Oil			
	RP (N=88)	OLE Miconazole Oil (N=28)	Total (N=88)	RP (N=89)	OLE Miconazole Oil (N=42)	Total (N=89)	Enrollment B Miconazole Oil (N=203)
Subjects (%) Reporting At Least One Adverse Event	41 (46.6%)	1 (3.6%)	41 (46.6%)	49 (55.1%)	7 (16.7%)	51 (57.3%)	13 (6.4%)
Subjects (%) Reporting At Least One Serious Adverse Event	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects (%) Who Died	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects (%) Who Discontinued Study Drug Due to Adverse Event	4 (4.5%)	0 (0.0%)	4 (4.5%)	6 (6.7%)	0 (0.0%)	6 (6.7%)	1 (0.5%)
By Subject							
Maximum Severity							
Mild	31 (35.2%)	0 (0.0%)	31 (35.2%)	37 (41.6%)	4 (9.5%)	37 (41.6%)	12 (5.9%)
Moderate	7 (8.0%)	1 (3.6%)	7 (8.0%)	12 (13.5%)	3 (7.1%)	14 (15.7%)	0 (0.0%)
Severe	3 (3.4%)	0 (0.0%)	3 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Strongest Relationship to Study Drug							
Not Suspected	39 (44.3%)	1 (3.6%)	39 (44.3%)	48 (53.9%)	7 (16.7%)	50 (56.2%)	5 (2.5%)
Suspected	2 (2.3%)	0 (0.0%)	2 (2.3%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	8 (3.9%)

OLE = Open-label Extension; RP = Randomization Period.

Treatment-emergent adverse events are those with an onset on or after the date of first study drug application in the Randomization Period of Enrollment A or in Enrollment B or an onset after the date of first study drug application in the Open-label Extension for Enrollment A.

Table 4 Phase 3 Study - Summary of Treatment-Emergent Adverse Events Leading to Permanent Withdrawal of Study Drug and/or Early Discontinuation From Study (Randomization Period Safety Population and Open-label Safety Population)

	Enrollment A						
	Subjects Randomized to Miconazole Oil			Subjects Randomized to Vehicle Oil			
Organ Class[a] Preferred Term	RP (N=88)	OLE Miconazole Oil (N=28)	Total (N=88)	RP (N=89)	OLE Miconazole Oil (N=42)	Total (N=89)	Enrollment B Miconazole Oil (N=203)
Ear and labyrinth disorders	0	0	0	1 (1.1%)	0	1 (1.1%)	0
Tympanic membrane perforation	0	0	0	1 (1.1%)	0	1 (1.1%)	0
General disorders and administration site conditions	3 (3.4%)	0	3 (3.4%)	1 (1.1%)	0	1 (1.1%)	0
Application site irritation	1 (1.1%)	0	1 (1.1%)	0	0	0	0
Application site pain	2 (2.3%)	0	2 (2.3%)	1 (1.1%)	0	1 (1.1%)	0
Infections and infestations	2 (2.3%)	0	2 (2.3%)	7 (7.9%)	0	7 (7.9%)	0
Ear infection fungal	2 (2.3%)	0	2 (2.3%)	6 (6.7%)	0	6 (6.7%)	0
Otitis externa bacterial	0	0	0	1 (1.1%)	0	1 (1.1%)	0
Nervous system disorders	0	0	0	0	0	0	1 (0.5%)
Headache	0	0	0	0	0	0	1 (0.5%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; OLE = Optional Open-label Extension; RP = Randomization Period

[a]Counts reflect numbers of subjects reporting one or more adverse events that map to MedDRA. At each level of summarization (System Organ Class or Preferred Term) subjects are counted once.

Treatment-emergent adverse events are those with an onset on or after the date of first study drug application in the Randomization Period of Enrollment A or in Enrollment B or an onset after the date of first study drug application in the Open-label Extension for Enrollment A.

MedDRA dictionary (23.0).

1.2 Study Purpose

The purpose of this study is to gather confirmatory data on the efficacy and safety of 2% miconazole oil after topical otic administration in subjects with otomycosis, and to fully establish evidence of efficacy for miconazole oil compared to the placebo (mineral oil). A 14-day regimen of twice-daily administration of 2% miconazole oil will be compared with the same treatment regimen using the placebo, mineral oil.

1.3 Inclusion of Subjects with Peanut Allergy

Miconazole oil contains refined peanut oil. Inclusion in this study of subjects with peanut allergy is justified by studies and publications documenting safe use of the refined peanut oil, as well as the FDA approved products containing the refined peanut oil (such as DermOtic, which is the same product as the Derma-Smoothe/FS for which two safety studies were performed in subjects with known hypersensitivity to peanuts) [Yunginger 2001; Paller 2003]. Reports also exist of subjects with known peanut allergy who have continued to safely use products such as Derma-Smoothe/FS even after an anaphylactic reaction to peanuts [Paller 2003]. The refined peanut oil used in the Derma-Smoothe/FS, DermOtic, and miconazole oil products, undergoes refining process to remove the peanut proteins which are generally responsible for allergic reactions to peanuts. Thus, the inclusion of subjects with peanut allergy in this study is not expected to pose an excessive risk to these subjects.

1.4 Compliance with Good Clinical Practice

The investigator and all study staff will conduct the study in compliance with this protocol and FDA regulations, all applicable federal, state, and local laws, rules and regulations relating to the conduct of a clinical study, the ethical principles of the Declaration of Helsinki, and the current International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objectives of the study are to:

- Confirm the efficacy of miconazole oil compared with mineral oil over a 14-day treatment duration in subjects with otomycosis
- Further assess the safety of miconazole oil over a 14-day treatment duration in subjects with otomycosis

2.2 Endpoints

The primary efficacy endpoint is:

- Clinical Cure, defined as score of 0 for fungal elements, and 0 for each of the signs/symptoms of pruritus, aural fullness and debris, at the Test of Cure visit.

The secondary efficacy endpoints are:

- Clinical Cure at the End of Treatment visit with Clinical Cure defined as score = 0 for fungal elements, and score = 0 for each signs/symptoms of otomycosis (debris, pruritus and aural fullness)

- Clinical Clearance at Test of Cure visit with Clinical Clearance defined as score = 0 for fungal elements, and score = 0 or 1 for each signs/symptoms of otomycosis (debris, pruritus and aural fullness)

- Clinical Clearance at End of Treatment visit with Clinical Clearance defined as score = 0 for fungal elements, and score = 0 or 1 for each signs/symptoms of otomycosis (debris, pruritus and aural fullness)

- Modified Clinical Cure at the Test of Cure visit with Modified Clinical Cure defined as score = 0 for fungal elements, and score = 0 or 1 for each of debris and aural fullness

- Modified Clinical Cure at the End of Treatment visit with Modified Clinical Cure defined as score = 0 for fungal elements, and score = 0 or 1 for each debris and aural fullness

The exploratory efficacy endpoint is:

- Mycological culture results through time

2.3 Primary Estimand

The primary estimand will address the following clinical question of interest:

- To establish the efficacy of miconazole oil when taken over a 14-day treatment duration compared with mineral oil in subjects with uncomplicated otomycosis of the external ear only.

This primary estimand is defined as follows:

- Target population: all randomized subjects as defined by the study inclusion / exclusion criteria who are dispensed study drug (ITT population).
- Variable of interest (primary efficacy endpoint): the proportion of subjects who achieve Clinical Cure, defined as score of 0 for fungal elements, and 0 for each of the signs/symptoms of pruritus, aural fullness and debris at the Test of Cure visit
- Intercurrent events (IcE)
  1. Discontinuation of study treatment due to AE unrelated to study drug
  2. Discontinuation of study treatment due to AE related to study drug
  3. Discontinuation of study treatment due to lack of efficacy
  4. Use of rescue medication prior to the Test of Cure visit

  For each above IcE, a composite strategy will be taken where subjects with any of the above IcEs will be considered to have not achieved Clinical Cure.
- Population-level summary: the difference in proportions in Clinical Cure at the Test of Cure visit between the miconazole group and the mineral oil group.

3 STUDY DESIGN

This study is a randomized, double-blind, parallel-group study to be conducted at up to 8 study centers in the US. An estimated 110 male or female subjects with otomycosis will receive study drug. Subjects will be randomly assigned in a 1:1 ratio within study site to receive miconazole oil or mineral oil for 14 days [administered as 5 drops per ear at ~30 mg per drop instilled into the external ear canal of the ear(s) affected by otomycosis]. Both the subject and the investigator and study staff will be blinded as to the contents of the study drug.

At Screening/Baseline (Day 1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a condensed physical examination, an assessment of the signs and symptoms of otomycosis (pruritus, debris, visual examination for presence of fungal elements, and aural fullness), and an evaluation of medical history. Urine will be obtained for pregnancy screening in female subjects of childbearing potential. Prior and concomitant medications will be reported. Subjects with positive signs and symptoms of otomycosis and who meet all other eligibility criteria will be entered into the study. A fungal culture of the affected ear(s) will be taken, then debris will be cleaned from the affected ear(s) following the site's normal procedures. The subject will then begin treatment with study drug. The subject or caregiver will instill the first dose of study drug at the site, under the supervision of the investigator or site personnel. Adverse events (AEs) will be assessed. The subject will then leave the clinic and continue to administer the study drug twice per day as instructed. Subjects will be instructed to avoid getting water in the ear, to consider drying excessive water in the ear by using a blow dryer, and to place a Vaseline-impregnated cotton ball over the affected ear(s) to help keep water out of the ear while bathing or showering.

Subjects will continue to administer the study drug twice per day, up through Day 14, following the same instructions as provided at the Screening/Baseline Visit on Day 1. Subjects will then return to the clinic on Day 15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis will be performed. AEs and concomitant medications will also be assessed, and the subject will return all unused study drug.

Subjects will return to the clinic on Day 22 for the Test of Cure Visit, at which time an assessment of clinical signs and symptoms of otomycosis and fungal culture of the affected ear(s) will be performed. AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential. Results from the fungal culture will not be used to assess primary or secondary efficacy endpoints. All fungal results will be summarized.

Efficacy assessments will include assessments of clinical signs and symptoms of otomycosis. In cases of bilateral otomycosis, both ears will be treated and evaluated by the investigator, but only one ear will be used as the study ear for efficacy analyses, the designation of which will be performed at the end of the study in accordance with the following: (1) If only one ear has clinical signs/symptoms at Screening/Baseline, that ear will be used as the study ear for efficacy analyses; (2) If both ears have clinical signs/symptoms at Screening/Baseline, the ear with the worse infection at Screening/Baseline as assessed by the investigator, will be used as the study ear for efficacy analyses; (3) If both ears are determined by the investigator to have the same

degree of infection at Screening/Baseline, the left ear will be used as the study ear for the purposes of efficacy analyses.

Safety assessments will include AEs.

For subjects who did not improve or had received the placebo, optional rescue treatment may be provided at the end of the study.

3.1 Number of Subjects

An estimated 110 eligible patients are planned to be enrolled and included in the ITT population, defined as those who were randomized, dispensed study drug, and with a clinical diagnosis of otomycosis.

3.2 Investigators

The study will be conducted at up to 8 study centers located in the US.

The study will be conducted by investigators who are determined by the sponsor to be suitably qualified by training and experience to conduct this study in compliance with all applicable GCP and FDA federal regulations or local regulations. Sub-investigators will be identified on the Form FDA 1572.

3.3 Study Duration

The total duration of the study for a subject from screening until the last visit will be up to 25 days (including the visit window of up to 3 additional days after the protocol-specified day to complete the final Test of Cure visit).

4 STUDY SUBJECTS

4.1 Inclusion Criteria

In order to be eligible for the study, subjects must meet all of the following criteria:

1. Male or non-pregnant, non-lactating females
2. Diagnosis of uncomplicated otomycosis of the external ear only, in the ear(s) that will be treated with study drug, with a score for fungal elements of 1 in each ear to be treated with study drug (see Section 7.4 for definitions of the scores for each of the otomycosis signs and symptoms). Subjects must also have the following signs and symptoms of otomycosis in the study ear: pruritus ≥2; debris ≥2; and aural fullness ≥2.
3. General good health as determined by medical examination and medical history, and who are free of clinically significant disease, including diabetes mellitus that is not well-controlled or that could interfere with the study
4. Females of childbearing potential must have had a negative urine pregnancy test at Screening/Baseline and must agree to use an effective method of contraception (as defined in Section 8.5) from Screening/Baseline up through the End of Treatment visit (see Section 6). Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months). Females who are using oral, implanted, or injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential
5. Subjects and/or their caregivers (as appropriate for the age of the subject) must have full legal capacity to volunteer
6. Subjects and/or their caregivers must have completed an appropriately administered institutional review board (IRB)-approved informed consent and assent (as applicable) prior to any study related procedures
7. Subjects and their caregivers (as applicable) must agree to comply with all requirements of the protocol
8. For subjects with only one ear meeting all study eligibility criteria, the subject will be eligible for the study, and the ear meeting all eligibility criteria will be treated with study drug and considered to be the study ear for the purposes of study evaluations. In case of bilateral otomycosis in which at least one ear meet all study eligibility criteria, the subject will be eligible for the study, both ears may be treated with study drug provided that both ears have a score of 1 for fungal elements, and the worse ear will be considered to be the study ear for the purposes of study evaluations. If both ears meet study eligibility criteria and are determined by the investigator to have the same degree of infection at Screening/Baseline, the left ear will be considered to be the study ear for the purposes of study evaluations.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be eligible for the study:

1. Any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis, including concomitant otic infections (including bacterial infection) that require antimicrobial treatment, disease that has spread beyond the external ear(s), or pre-existing skin atrophy of the affected ear(s) that will be treated with study drug
2. Tympanostomy tube or perforated tympanic membrane in the ear(s) that will be treated with study drug
3. History of prior surgery directly affecting and compromising the external auditory canal and/or tympanic membrane of the ear(s) that will be treated with study drug, except for prior tympanostomy tube(s) that have already been removed and completely healed
4. Use of any topical medicated treatments for otomycosis within 14 days of study entry for the ear(s) that will be treated with study drug
5. Use of any systemic antifungal therapy within 28 days of study entry, warfarin within 28 days of study entry, immunosuppressive or immune-stimulating drugs within 28 days of study entry, or systemic steroids within 3 months of study entry
6. Fever of ≥100°F at study entry
7. Recurrent otomycosis that has been unresponsive to previous antifungal treatment within the last 12 months
8. Known hypersensitivity to any of the components in the test formulation
9. Participation in another investigative trial within 28 days of study entry.

4.3 Subject Completion

The subject has completed the study when the Test of Cure Visit is completed. Subjects who require further follow-up for an AE will be followed according to Section 8.4.

4.4 Subject Discontinuation

A subject MAY be withdrawn from the study (at the discretion of the investigator, sponsor, and/or IRB) prior to study completion for any of the following reasons, including, but not limited to:

- A serious adverse event (SAE) occurring during the course of the study which precludes continued follow-up
- Intercurrent illness which may, in the investigator's opinion, significantly affect study assessments
- Failure to follow required study procedures

A subject MUST be discontinued prior to the final study visit for any of the following reasons:

- Whenever the subject decides it is in his/her best interest to withdraw

- Whenever the investigator decides it is in the subject's best interest to be withdrawn

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible. If possible, the assessment schedule for the Test of Cure Visit should be performed, and an effort should be made to collect all study drug.

Subject discontinuations will be documented clearly on the applicable electronic case report form (eCRF).

4.5 Subjects Lost to Follow-up

An effort must be made to contact subjects who do not return for scheduled visits, to schedule the visit and/or obtain as much follow-up data as possible. At least three telephone calls and one certified letter must be placed to the subject after the first missed visit, to attempt to get the subject to complete the visit and to gather as much follow-up data as possible, before a subject may be considered lost to follow-up and discontinued from the study. Subjects who miss a visit may still be scheduled for a subsequent visit.

All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable eCRFs will be completed. The date a subject will be considered lost to follow-up will be the date of the last non-missing visit.

5 CONCOMITANT THERAPIES

All concomitant therapies must be recorded on the eCRF. All therapies within 3 months prior to Day 1 must also be recorded on the eCRF.

Every effort should be made to keep concomitant therapy and dosing constant during the study. Any changes in concomitant therapies during the study must be recorded on the eCRF at each visit. The reason for any change in concomitant therapies should be reported as, or in conjunction with, an AE except as noted below:

- Prophylactic therapies, such as vaccines or prophylactic analgesics, must be recorded on the eCRF but should not be reported as AEs.
- Changes in therapy for pre-existing conditions that are not related to a worsening of the condition must be reported on the eCRF but should not be reported as AEs. The condition must be reported on the eCRF as part of the subject's medical history.

5.1 Permitted Medications

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Screening/Baseline may be continued.

Oral analgesic medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are permitted. Such medications may be helpful for the management of pain caused by otomycosis and/or study procedures such as ear cleaning and administration of study drug.

5.2 Prohibited Medications

Other than the study drug, no other topical medications are allowed to be used in any ear that is being treated with study drug. Other prohibited treatments during the study include systemic antifungal therapy, warfarin, immunosuppressive or immune-stimulating drugs, antibiotics, and systemic steroids.

6 STUDY SCHEDULE

6.1 Study Flow Chart

The study schedule is presented in Table 5.

Table 5 Study Schedule

Evaluations and Procedures:	Screening/ Baseline Day 1	End of Treatment [a] Day 15	Test of Cure Day 22 [b, c]
Informed consent/assent	X		
Inclusion/exclusion criteria	X		
Medical/medication history	X		
Condensed physical examination	X		
Otomycosis signs and symptoms	X	X	X
Fungal Culture	X		X
Photographs of ear[d]	X[e]	X	X
Urine pregnancy test [f]	X		X
Randomization	X		
Dispensation of study drug	X		
Ear cleaning prior to administration of study drug	X		
Administration of study drug at site	X		
Weighing of study drug	X	X	
Collection of study drug		X	
AE evaluations	X	X	X
Concomitant medications review	X	X	X

a. This visit may occur up to 3 days later than the specified day.
b. This visit may occur up to 1 day sooner or up to 3 days later than the specified day.
c. In case of early termination, the assessments planned for the Test of Cure Visit should be performed if possible.
d. Only applicable to designated site(s).
e. Prior to ear cleaning at this visit.
f. Females of childbearing potential only.

6.2 Study Visits

Prior to the signing of informed consent and assent (as applicable), the investigator or designee will explain the purpose of the study, procedures, and subject responsibilities to the potential study subject and/or caregiver (as applicable). The subject's (and caregiver's, as appropriate) willingness and ability to meet the follow-up requirements of the study will be determined.

The schedule of visits is presented in Table 5. Details about study procedures and how they are to be performed are presented in Section 7.

6.2.1 Screening / Baseline (Day 1)

Screening procedures will occur prior to randomization and will include:

- Informed consent and assent (as applicable)
- Medical history
- Prior and concomitant medications
- Condensed physical examination
- Urine pregnancy test (in female subjects of childbearing potential only)
- Otomycosis signs and symptoms
- Determination of subject eligibility for the study

Subjects who are eligible for the study will undergo the following additional procedures, in the order listed:

- Photography of the affected ear(s) prior to ear cleaning and culture. Photography will be limited to designated site(s).
- Fungal culture of the affected ear(s) prior to ear cleaning
- Ear cleaning prior to study drug administration
- Randomization
- Weighing of study drug, followed by dispensation of study drug to subject
- Administration of the first dose by the subject or caregiver under the supervision of the investigator or other study personnel
- Collection of AE information, with the time of AEs to be reported as occurring either before or after the first dose of study drug
- Subjects will be instructed to continue administering study drug twice daily and to bring their bottle of study drug to the site for their next visit

6.2.2 End of Treatment (Day 15)

This visit may occur up to 3 days later than the specified day, in the order listed.

The following procedures and evaluations will occur during this visit:

- Photography of the affected ear(s). Photography will be limited to designated site(s).
- Otomycosis signs and symptoms
- AE evaluation
- Review of concomitant medications
- Collection/weighing of study drug

6.3 Test of Cure (Day 22)

This visit may occur up to 1 day sooner or up to 3 days later than the specified day.

The following procedures and evaluations will occur during this visit, in the order listed:

- Photography of the affected ear(s) prior to fungal culture. Photography will be limited to designated site(s).
- Otomycosis signs and symptoms
- Fungal culture of the affected ear(s)
- AE evaluation
- Review of concomitant medications
- Urine pregnancy test (in female subjects of childbearing potential only)

In case of early termination, the procedures planned for the Test of Cure Visit should be performed if possible.

6.4 Unscheduled Study Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional examinations should be fully documented in the source files and eCRFs, as appropriate. Visits that fall outside the designated scheduled visit window but that are intended to fulfill scheduled visit requirements will be collected and transcribed to the appropriate scheduled visit eCRF.

If a subject is seen for multiple visits during a given visit time frame, the data from the visit(s) that are intended to meet the protocol requirements for the scheduled visit should be captured on the visit eCRF. Any other data from any additional visits within a scheduled visit interval will be captured elsewhere on the eCRF.

6.5 Post-study Follow-up

If a subject requires further follow-up of AEs upon discontinuation or completion of the study, the investigator should schedule post-study follow-up visits, as necessary.

6.6 Missed Visits

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

6.7 Subject Completion

The subject has completed the study when the Test of Cure Visit is completed. Subjects who require further follow-up for an AE will be followed according to Section 6.5.

6.8 Early Study Termination

The sponsor reserves the right to terminate this study prematurely. If during the study it becomes evident to the sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the investigator, IRB, and FDA, as applicable. The sponsor or designee will instruct the investigator to stop randomizing subjects, to bring all subjects who remain in the study (for example, subjects who are currently receiving treatment or who have completed treatment but have not yet completed the Test of Cure Visit) in for a Test of Cure Visit as soon as possible, and to arrange for study closeout at the site.

7 STUDY PROCEDURES

The required study procedures are detailed in this section. The timeline for these procedures is presented in Section 6.

7.1 Medical/Medication History

At Screening/Baseline, the investigator or designee will interview each subject and obtain a complete medical and medication history, including a history of all surgeries and past medical procedures. The subject must not require any treatment or medication for concurrent illnesses as specified by the inclusion and exclusion criteria or anticipate the need for any excluded concomitant medications.

7.2 Condensed Physical Examination

At Screening/Baseline, the investigator or designee will perform a physical examination to include the following: general appearance; head, eyes, ears, nose, throat; neck; cardiovascular; lungs; abdomen; lymph nodes; extremities; neurological; skin; musculoskeletal; and body temperature.

7.3 Urine Pregnancy Test

The urine pregnancy test (performed in females of childbearing potential only) must have a minimum sensitivity of 25 mIU of β-hCG/mL of urine.

7.4 Otomycosis Signs and Symptoms

The signs and symptoms of otomycosis will be assessed according to the scales for pruritus (see Section 7.4.1), debris (see Section 7.4.2), presence of fungal elements (see Section 7.4.3), and aural fullness (see Section 7.4.4). The same evaluator should assess each subject for signs and symptoms of otomycosis at each visit throughout the subject's participation in the study, if possible.

7.4.1 Pruritus

Subjects or their caregivers (as appropriate, based on the age of the subject) will be asked by the investigator (or designee) about the severity of itching present in each ear being treated with study drug. Questions such as the following will be used in order to gather information for this assessment, with careful consideration given to distinguish between a nonspecific occasional itch and itching from the infection:

"Over the last 24 hours, have you had itching in your ear?"

"Over the last 24 hours, did itching interfere with your daily activities?"

"Over the last 24 hours, has your itching been bad enough to keep you awake?"

"Over the last 24 hours, would you describe your itching as intolerable or constant?"

The investigator will then score the symptom of pruritus for each ear being treated with study drug, taking into consideration the subject's and/or caregiver's answers and the investigator's observations of the subject. Scores will be according to the following scale:

Score	Category	Description
0	None	No itching; occasional nonspecific itch
1	Mild	Occasional itching, not interfering with daily activities
2	Moderate	Fairly persistent itching, partially tolerated; sleep is not interrupted
3	Severe	Intolerable, constant itching; sleep is interrupted

7.4.2 Debris

Upon otoscopic examination, the investigator will score the amount of debris present in each ear being treated with study drug. Debris would consist of earwax, fungal elements or microorganisms, skin cells, and sometimes exudates. Scores will be according to the following scale:

Score	Category	Description
0	None/Normal	No debris, normal earwax present
1	Scant	Debris minimally present, but with no notable occlusion of external ear canal
2	Moderate	Debris present with partial occlusion of external ear canal; tympanic membrane can be visualized
3	Heavy	Complete occlusion of ear canal; tympanic membrane cannot be visualized

7.4.3 Presence of Fungal Elements

Upon otoscopic examination, the investigator will assess the presence of fungal elements in each ear being treated with study drug. Visual inspection of the ear canal with otoscope may show presence of white filaments in debris; black, gray, bluish, yellow, or white discharge; white debris with hyphae; or moist white plugs with black debris; or other observations that in the investigator's judgment are indicative of macroscopic fungal presence.

Scores will be according to the following scale:

Score	Category	Description
0	Absent	No fungal elements present on visual inspection with otoscope
1	Present	Fungal elements present on visual inspection with otoscope, such as visualization of white filaments in debris; black, gray, bluish, yellow, or white discharge; white debris with hyphae; or moist white plugs with black debris; or other observations that in the investigator's judgment are indicative of the presence of fungus

7.4.4 Aural Fullness

Subjects or their caregivers (as appropriate, based on the age of the subject) will be asked by the investigator (or designee) whether aural fullness is present in each ear being treated with study drug. Aural fullness can be defined as a sensation of blockage in the ear, or sound is muffled. Questions such as the following will be used in order to gather information for this assessment:

"Over the last 24 hours, have you had a feeling of fullness in your ear?"

"Over the last 24 hours, has a feeling of fullness in your ear interfered with your daily activities?"

"Over the last 24 hours, has a feeling of fullness in your ear been bad enough to keep you awake?"

"Over the last 24 hours, would you describe a feeling of fullness in your ear as intolerable?"

The investigator will then score the symptom of aural fullness for each ear being treated with study drug, taking into consideration the subject's and/or caregiver's answers and the investigator's observations of the subject. Scores will be according to the following scale:

Score	Category	Description
0	None	Not present
1	Mild	Present but not affecting daily activities
2	Moderate	Present and affecting daily activities but tolerable
3	Severe	Intolerable and severely disrupting daily activities; sleep is interrupted

7.5 Fungal Culture

At designated visits, the investigator or designee will obtain a sample from the external ear to be sent to a central laboratory for fungal culture. Techniques for obtaining and handling the sample and sending it to the laboratory will be described in a separate laboratory manual. If both ears will be treated with the study drug, both ears will be cultured.

The central laboratory will grow and identify fungal organisms from the sample provided by the investigator. Susceptibility testing will not be performed.

The results of fungal cultures will not be blinded as they do not affect the primary efficacy endpoint analysis.

7.6 Ear Cleaning

There will be only one ear cleaning which will occur at Screening/Baseline after the fungal culture has been taken and prior to the first application of the study drug. No other ear cleaning will be done during the study.

7.7 Adverse Event Evaluations

See Section 8.

7.8 Randomization

See Section 9.2.

7.9 Study Drug Administration

See Section 9.1.1.

7.10 Photography of the Ear

Designated site(s) will be provided with, and trained on, photography equipment appropriate for use in capturing images of the ear canal. Alternatively, site may use existing equipment that is approved by the sponsor. Investigators may take as many images of each affected ear as they

deem appropriate to reflect the condition of the ear. Missing photography of an ear or a visit, will not constitute a protocol deviation.

7.11 Treatment Compliance

Subjects or their caregivers (as appropriate) will be given the study drug. Additionally, each bottle of study drug will be weighed by the investigator or designee before dispensing to the subject and at the last visit in which the used bottle is brought to the site.

7.12 Protocol Deviations

The IRB-approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects.

The date of, nature of, and reason for deviations, will be documented and explained by the investigator in all cases. Significant or major protocol deviations impacting the safety of the subject or the integrity of the study must be reported by the investigator to the sponsor and/or its designee and to the IRB immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB.

All changes to the protocol will be made by the sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation. New or altered consent forms required by the IRB due to a protocol revision must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

8 ADVERSE EVENTS

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a study drug and which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational or marketed study drug, whether or not considered related to the investigational or marketed study drug. AEs include any illness, sign, or symptom that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study drug. Study drug includes the investigational drug under evaluation and the comparator placebo.

Medical conditions/diseases present before signing the informed consent form are only considered AEs if they worsen after the informed consent form is signed.

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. At each examination or visit, study personnel will ask each subject the following question, "Have you had any problems since we last spoke?" If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms.

The worsening or reoccurrence as compared to any previous visit in a subject of any symptom of otomycosis (including any increase in numerical score for pruritus and/or aural fullness according to the scales presented in Section 7.4, and/or any other symptom of otomycosis that worsens but is not captured in the scales presented in Section 7.4) should be reported as an AE. The diagnosis of the underlying disease or disorder should be reported as the AE, if known. For example, if the worsening symptom is believed to be due to otomycosis, the AE should be reported as "worsening of disease under study." If the worsening symptom is believed to be due to some other cause (such as bacterial infection), that underlying illness or disorder should be reported as the AE.

Debris and fungal elements are considered signs (manifestations) of otomycosis and minor changes are expected as a natural progression of the disease; therefore, minor changes in debris and fungal elements scores may not necessarily be captured as AEs if the changes are not clinically significant in the judgment of the investigator. If, however, in the investigator's judgment there is a clinically significant worsening of debris and/or fungal elements, an AE of "worsening of disease under study" should be recorded.

8.1.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment may jeopardize the patient/subject or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above). Examples of such events include but are not limited to: allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasia or convulsions that do not result in inpatient hospitalization; the development of drug dependency or drug abuse.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that has not worsened since the start of the study, is not considered an SAE.

8.2 Severity of Adverse Events

The severity of an AE will be determined by the investigator according to the following definitions:

- **Mild:** Awareness of event, but easily tolerated and does not disrupt usual activity
- **Moderate:** Discomfort sufficient to cause interference with usual activity
- **Severe:** Incapacitating, with inability to perform usual activities

8.3 Relationship of Adverse Events to Study Drug

The relationship of AEs to the study drug will be assessed by the investigator according to the following definitions:

- **Not suspected:** The temporal relationship of the event to the study drug makes a causal relationship unlikely, or, other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
- **Suspected:** The temporal relationship of the event to the study drug makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

A temporal relationship is the timing between a factor and an outcome which can be used to assign causality to a relationship.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE, then the AE should be considered “suspected.”

If the relationship between the AE and the study drug is determined by the sponsor to be "suspected," the event will be considered to be related to the study drug for the purposes of expedited regulatory reporting.

8.4 Documentation of Adverse Events

All AEs must be completely recorded on the Adverse Events section of the eCRF. The collection of AE information should begin after the subject has signed informed consent and continue up through the Test of Cure Visit. Subjects experiencing AEs that cause interruption or discontinuation of study drug, or those experiencing AEs that are present at the end of their participation in the study or that resulted in permanent discontinuation will receive follow-up as appropriate until the AEs have either resolved or have stabilized.

For each AE, the Investigator will evaluate and report the following:

- Onset (date);
- Resolution (date);
- Severity grade (mild, moderate, severe);
- Relationship to study drug (not suspected, suspected);
- Action taken (none, study drug temporarily interrupted, study drug permanently discontinued, concomitant medication taken, hospitalization/prolonged hospitalization, other);
- Serious (yes/no);
- Whether the AE occurred at the study drug application site (yes/no);
- For AEs of the ear, which ear (left, right, or both) was affected.

8.4.1 Additional Reporting Requirements for Serious Adverse Events

All SAEs that occur from the time the subject has signed the informed consent until the Test of Cure Visit will be reported. Additionally, any SAEs "suspected" to be related to the study drug and discovered by the investigator at any time after the study should be reported. Each of these SAEs must be reported to the sponsor's designee within 24 hours of the occurrence of the SAE, or within 24 hours of learning of the SAE. Information on recurrent episodes, complications, or progression of the initial SAE must also be reported within 24 hours of the investigator receiving the information.

Reporting may be by telephone, confirmed facsimile transmission, or confirmed email to the medical monitor. The investigator must assess the relationship of the SAE to study drug and must complete the SAE form. If only limited information is initially available, follow-up reports are required. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy (with the subject's personal information removed and with the subject identified only by subject number) will be sent by confirmed facsimile transmission or confirmed email to the medical monitor. In the event of death, if an autopsy is performed, a copy of the report (with the subject's personal information removed and with the subject identified only by subject number) should be sent to the medical monitor.

As required and after the sponsor's review and determination of causality, the sponsor and/or designee will notify investigators of all AEs that are serious, unexpected, and considered by the investigator to have a suspected relationship to the study drug. This notification will be in the form of an update to the Investigator's Brochure (i.e., "15-day letter"). An AE, whether serious or non-serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and immediately submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Follow-up reports should be submitted when requested or when pertinent information becomes available.

The sponsor will report all SAEs to the US FDA on the appropriate schedule depending on the event's expectedness and relationship to study drug based on the available information as presented in the Investigator's Brochure.

Any SAE occurring after the Test of Cure Visit and which is not considered to be of "suspected" relationship to study drug does not need to be reported.

8.5 Pregnancy

Females of childbearing potential, as defined in Section 4.1, must use an effective method of contraception from screening up through the Test of Cure Visit. Acceptable methods include the use of at least one of the following: 1) IUD; 2) hormonal contraceptives (oral, injectable, implant, or ring); 3) barrier contraceptives (condom or diaphragm) with spermicide; or 4) abstinence.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form and sent by confirmed facsimile or confirmed email to the medical monitor, as well as documented in the eCRF. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug product may have interfered with the effectiveness of a contraceptive medication.

In the event of pregnancy that is detected during treatment with study drug, the subject must be withdrawn from further treatment with study drug. The subject may continue to participate in the study on a case-by-case basis after discussion between the investigator and the sponsor and/or the sponsor's designee.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study and/or study drug.

8.6 Study Contacts

Study contacts will be provided in a separate document.

9 STUDY TREATMENTS

9.1 Description of Study Drug

Miconazole oil contains the active ingredient, 2% miconazole, formulated in an oil vehicle containing refined peanut oil, light mineral oil, oleth-2, and isopropyl myristate. For subjects randomized to the placebo group, the placebo is plain mineral oil.

Study drug will be supplied in bottles containing ~20 grams (20 mL) of product. The dispensing tip will deliver approximately 30 mg of product per drop.

9.1.1 Administration

Subjects will be seated or lying on one side with the head positioned so the ear being treated is facing up. If both ears are being treated, the ear that appears to have less severe disease will be treated first. The subject or caregiver will gently pull the ear lobe backward and upward and apply 5 drops of study drug into the ear. The subject will be instructed to keep the head positioned with the ear facing up for approximately 3 to 5 minutes to allow the oil to coat the ear canal. After this time, the subject can then straighten his/her head, and excess material dripping out of the ear can be gently patted using a clean cotton ball.

If both ears are being treated, the subject will then wait at least 5 minutes, then repeat this procedure for the second ear.

While on study treatment, subjects will be instructed to avoid getting water in the ear, to consider drying excessive water in the ear by using a blow dryer, and to place a Vaseline-impregnated cotton ball over the affected ear(s) to help keep water out of the ear(s) while bathing or showering. Subjects will be asked to avoid bathing or showering for at least 30 minutes after applying study drug.

9.2 Randomization

Subjects will be randomized in a 1:1 ratio to one of two groups: 1) 14-day treatment with miconazole oil; or 2) 14-day treatment with mineral oil.

Randomization will be by site.

9.3 Blinding/Unblinding

The contents of the study drug (miconazole oil versus mineral oil) will be blinded to both the investigator (and all study staff) and the subject. Randomized study drug will be packaged in identical bottles and will be labeled with a randomization number rather than the contents of the bottle.

If it becomes necessary to unblind a subject's treatment assignment in case of emergency, the investigator should contact the sponsor. A person at the sponsor organization who is not otherwise involved with the study will maintain a randomization list that will enable that person to inform the investigator of the subject's treatment allocation. The treatment allocation is to be

obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject.

9.4 Study Drug Handling and Dispensing

9.4.1 Packaging and Labeling

The miconazole oil and the mineral oil will be processed and labeled by Hill Dermaceuticals, Inc. It will be packaged in dropper bottles, each of which will contain ~20 grams (20 mL) of study drug. The dropper bottle will dispense approximately 30 mg per drop.

The active drug and mineral oil will be packaged in a 1 ounce HDPE bottle with a dispensing tip and provided in identical study drug kits. Each kit will contain the investigational drug product (or placebo product), reserve identical drug product (or placebo product), bag of cotton balls, and Vaseline jelly. The subject will be dispensed the kit (minus the reserve product) at Baseline only. The dropper bottles will be weighed with the cap on prior to dispensing. If the subject loses a bottle (lost or damaged), the reserve bottle will be dispensed using a replacement process as defined in the randomization plan. Each drug kit dispensed will be documented on the drug accountability log. Labels on the drug kit will contain the following information:

- Protocol number
- Subject number
- Space for entry of the subject initials
- Space for entry of date dispensed
- A statement reading, “For otic use only. Avoid contact with eyes and lips”
- A statement reading, “Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F)”
- A statement indicating the sponsor, Hill Dermaceuticals
- A statement indicating the quantity of product (20 g/ 20 mL)
- A statement reading, “Caution: New Drug - Limited by Federal Law to Investigational Use”
- A statement reading, “Keep out of Reach of Children”

9.4.2 Storage

The study drug is to be stored at room temperature (20°C to 25°C, or 68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). All investigational study drug must be stored in a secure facility, with access limited to the investigator and authorized staff.

9.5 Accountability

The investigator or designee (e.g., study coordinator or pharmacist) is responsible for ensuring storage as per the label on the study drug and adequate accountability of all used and unused study drug. Adequate accountability includes acknowledgment of receipt of each shipment of study drug (quantity and condition), records of administration (including container number, date administered, subject number, and the initials of the person administering the drug), and documentation of quantities returned to the sponsor (or designee).

At time points during the course of the study and/or upon completion of the study, the sponsor or designee will review and verify the investigator's accountability records.

9.6 Return and Destruction

At the completion of the study, following verification of the investigator’s accountability records by the sponsor and/or designee, all study drug must be returned to the sponsor or designee. This would include study drug returned by the subjects at the completion of the study, and reserve products that were not used.

10 STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage of subjects at the Test of Cure Visit with Clinical Cure defined as score of 0 for fungal elements, and 0 for each of the signs/symptoms of otomycosis (debris, pruritus and aural fullness) based on investigator assessment according to the scales for each individual sign or symptom. See Section 7.4 for the scales for each otomycosis sign and symptom.

10.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will consist of the following:

a) Clinical Cure at the End of Treatment visit with Clinical Cure defined as score = 0 for fungal elements, and score = 0 for each signs/symptoms of otomycosis (debris, pruritus and aural fullness)

b) Clinical Clearance at Test of Cure visit with Clinical Clearance defined as score = 0 for fungal elements, and score = 0 or 1 for each signs/symptoms of otomycosis (debris, pruritus and aural fullness)

c) Clinical Clearance at End of Treatment visit with Clinical Clearance defined as score = 0 for fungal elements, and score = 0 or 1 for each signs/symptoms of otomycosis (debris, pruritus and aural fullness)

d) Modified Clinical Cure at the Test of Cure visit with Modified Clinical Cure defined as score = 0 for fungal elements, and score = 0 or 1 for each of debris and aural fullness

e) Modified Clinical Cure at the End of Treatment visit with Modified Clinical Cure defined as score = 0 for fungal elements, and score = 0 or 1 for each debris and aural fullness

10.1.3 Exploratory Endpoints

The results of the mycological cultures will be summarized over time.

10.1.4 Safety Endpoints

A safety endpoint will be the percentage of subjects with treatment-emergent AEs (TEAEs), with treatment-emergent defined as occurring upon or after administration of the first dose of study drug.

10.2 Hypotheses

The primary efficacy endpoint of the study is percentage of subjects at the Test of Cure Visit with “clinical cure”, defined as score of 0 for fungal elements, and 0 for signs/symptoms of

otomycosis based on investigator assessment according to the scales for each individual sign or symptom.

Analysis is based on the following hypothesis:

H0: pT – pP = 0

H1: pT - pP ≠ 0.

where H0 is the null hypothesis, H1 the alternative hypotheses, and pT and pP are percentage of subjects with success in the Treatment (miconazole oil) and Placebo (mineral oil) groups, respectively. Comparisons between groups for the difference in the percentage of subjects achieving the primary endpoint of clinical improvement will be conducted using a Cochran-Mantel-Haenszel (CMH) exact test stratified by clinical site with a 2-sided significance level of 0.05.

10.3 Sample Size

Approximately 110 subjects (~55 in each group) provide 80% power, using a Fisher's Exact test chi-square test with a 2-sided significance level of 0.05, assuming a response rate for the primary efficacy endpoint of 35% in the miconazole oil group and 10% in the mineral oil group. These assumptions are consistent with the findings from the first Phase 3 study for the miconazole oil group, and with conservative assumptions for the mineral oil group.

10.4 Study Populations

10.4.1 Intent-to-treat Population

The intent-to-treat (ITT) population will be defined as all subjects who were randomized and dispensed study medication. The ITT population will be the primary population to assess efficacy.

10.4.2 Per Protocol Population

The per protocol (PP) population will be a subset of the ITT population and will include all subjects who complete the Test of Cure visit without any major protocol violations. The PP population will exclude subjects from the ITT population that met any of the following criteria:

- Violated the inclusion/exclusion criteria
- Used an interfering concomitant medication
- Did not attend the Test of Cure visit
- Did not attend the End of Treatment visit
- Have not been compliant with the dosing regimen (i.e., subjects must have received 80%-120% of the expected applications of study medication in the study ear during participation in the study)
- Out of visit window at the Test of Cure Visit (-1/+8 days)

Subjects who discontinue from the study due to an adverse event related to study treatment, documented lack of treatment effect, or worsening of condition will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

All efficacy analyses will be performed using the PP population in a supportive manner.

10.4.3 Safety Population

The safety population will include all randomized subjects who received at least one dose of study drug and had at least one post-Baseline safety assessment.

All safety analyses will be performed using the safety population.

10.5 Statistical Methods

All statistical processing will be performed using Statistical Analysis System (SAS®) Version 9.4 or higher. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, and standard deviation, median, minimum, and maximum.

Full details of statistical analyses will be provided in a separate statistical analysis plan.

10.5.1 Efficacy Analyses

The primary population for the primary estimand analysis and all efficacy analyses will be the ITT population (see Section 10.4). Efficacy analyses will also be performed for the PP population and will be considered supportive.

The number and percent of subjects who demonstrate a positive outcome for the primary efficacy outcome will be presented.

The primary endpoint, defined as the percentage of subjects at the Test of Cure Visit with “Clinical Cure”, will be compared between groups using a Cochran-Mantel-Haenszel (CMH) exact test stratified by analysis center with a 2-sided significance level of 0.05.

Secondary endpoints will be analyzed analogously to the primary endpoint.

The exploratory endpoint will be summarized by visit.

In cases of bilateral otomycosis, if only 1 ear has clinical signs/symptoms of otomycosis at Screening/Baseline, that ear will be used as the study ear for efficacy analyses. If both ears have clinical otomycosis at Screening/Baseline, the ear with the worse infection at

Screening/Baseline, as assessed by the investigator, will be used as the study ear for efficacy analyses. If both ears are determined by the investigator to have the same degree of infection at Screening/Baseline, the left ear will be used as the study ear for the purposes of efficacy analyses.

Descriptive statistics will be provided for otomycosis signs and symptoms.

10.5.2 Safety Analyses

Safety summaries will be conducted using the safety population (see Section 10.4.3). All AEs occurring during the study will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent adverse events (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group. Summaries will provide the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported SAEs will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug.

All information pertaining to AEs noted during the study will be listed by treatment group and subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who report an SAE.

10.5.3 Subject Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized descriptively for the ITT, PP, and safety populations and will be supported with individual subject data listings.

10.5.4 Missing Data

If a subject has missing efficacy data at the Test of Cure visit, the subject will be considered as a treatment failure for the primary and secondary efficacy analyses.

Missing data otherwise will not be imputed.

10.5.5 Pooling of Sites

The study is intended to be conducted in a manner such that a minimum of 5 Subjects will be enrolled in each treatment arm for any Investigator. In the event that there are too few Subjects in a treatment arm for an Investigator, then this Investigator's data will be combined to achieve the desired sample size minimum per arm. The combining of Investigator's data will be accomplished by taking the Investigator with the smallest enrollment and combining it with the Investigator with the largest enrollment. If there is a further need to combine data, then the data

of the Investigator with the second smallest enrollment will be combined with the Investigator's data which had the second largest enrollment and so on. This process will continue for all Investigators who did not have a minimum of 5 Subjects per treatment arm. The process of combining Investigator data that have insufficient Subjects per treatment arm will result in redefining the groups of Investigators for the purposes of statistical analyses. These combined groups will be referred to as "analysis centers" in the statistical analyses.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Institutional Review Board

The protocol, informed consent documents including photography consent, any information provided to subjects, recruitment advertisements and any amendments to these items will have IRB approval prior to their use in the study.

Before study initiation, this protocol, the miconazole oil Investigator's Brochure, the informed consent form, any other written information given to subjects, and any advertisement for subject recruitment must have IRB approval. Documentation of IRB approval must be sent to the sponsor or designee before study drug will be shipped to the site. The investigator should also provide the miconazole oil Investigator's Brochure to the IRB.

The investigator must provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements and Institution procedures. The IRB must be notified of completion or termination of the study.

Copies of all correspondence with the IRB regarding this study must be sent to the sponsor or its designee. Additionally, the clinical site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

11.2 Ethics

The investigator and all study staff will conduct the study in compliance with this protocol and compliance with FDA regulations, all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study, the ethical principles of the Declaration of Helsinki, and the current ICH GCP guidelines.

The rights, safety, and wellbeing of the study subjects are the most important considerations and prevail over the interests of science and society.

All personnel involved in the conduct of this study must be qualified by education, training and/or experience to perform their assigned responsibilities.

11.3 Informed Consent and Assent

Voluntary informed consent and assent (as applicable) will be given by every subject and/or the subject's legal representative (as applicable) prior to the initiation of any study related

procedures. The IRB-approved consent and assent forms must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements. Sample informed consent and assent forms containing the required elements of informed consent or assent (as applicable) will be provided by the sponsor or designee. Any changes made to this sample must be approved by the sponsor or its designee prior to submission to the IRB. After approval by the sponsor or its designee, the informed consent and assent forms must be submitted to and approved by the IRB.

The informed consent and assent forms must be written in a language in which the subject is fluent. Regulations require that foreign language informed consent and assent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation. The investigator must forward a copy of the consent form, the certified foreign language translation, and an IRB approval letter to the sponsor.

The investigator/designee will explain the study to each potential subject and/or the subject's legal representative (as applicable) prior to the screening evaluation, and the subject and/or the subject's legal representative (as applicable) must indicate voluntary consent by signing and dating the approved informed consent form. The consent process will be conducted prior to the start of any study-related procedure. The investigator must retain the original and provide the subject and/or the subject's legal representative (as applicable) with a copy of the consent form(s).

The investigator will maintain documentation that informed consent and assent (as applicable) was obtained prior to the initiation of any study-related procedures.

11.4 Confidentiality of Subject Information

Subject data recorded on eCRFs during the study will be documented in a coded fashion, and all communications and reports regarding this study will identify subjects only by their subject numbers. Complete subject identification will be kept by the investigator for purposes of long-term follow-up, if needed. This information, as well as all medical information resulting from a subject's participation in this study, will be treated with strict adherence to professional standards of confidentiality. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

Data generated for the study should be stored in a limited-access file area and be accessible only to the investigator and authorized personnel, the sponsor and its designee(s), the IRB, and FDA or other relevant regulatory authorities. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare, but no information that can be related to a specific individual subject will be released or used in any fashion without the signed written consent of that subject.

11.5 Study Monitoring

Representatives of the sponsor and designee(s) must be allowed to visit all study sites, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff

and to verify that the investigator, study staff and facilities remain acceptable for the conduct of the study. Representatives of government regulatory authorities (i.e. FDA) may also evaluate the study records, source documents, investigator, study staff and facilities. All data generated during this study and the medical records/documents from which they originated are subject to inspection by the sponsor, its designee(s), the FDA, and other regulatory agencies.

Prior to the start of the study, the sponsor and/or its designee will review the protocol, eCRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, during the course of the investigation to verify the following:

- the rights and well-being of subjects are protected
- the conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB requirements
- the integrity of the data, including adequate study documentation
- the facilities remain acceptable
- the investigator and site personnel remain qualified and able to conduct the study
- study drug accountability

The investigator must immediately notify the sponsor of any audits by any regulatory agency, and must promptly provide copies of any audit reports.

11.6 Case Report Form Requirements

Paper source documents will be created and retained at the clinical site.

Electronic case report forms (eCRFs) will be used to record subject data during the course of the study. The investigator and study site personnel will be responsible for completing the eCRFs. The investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be entered, including subject identification, date(s), assessment values, etc. Any omission or discrepancy will require explanation.

The sponsor or designee will review the data recorded in the eCRFs utilizing original source documentation, as applicable. Discrepant findings will be queried within the electronic data capture (EDC) system. The investigator and study site personnel will be responsible for answering all queries.

A copy of the eCRFs or archive of eCRFs will be retained by the investigator, who must ensure that it is stored in a secure place.

11.7 Quality Assurance Audits

Representatives from the sponsor and/or a third party selected by the sponsor or designee may conduct a quality assurance audit of this study at any time during or after completion of the study. The Investigator will be given adequate notice if he/she is selected for an audit. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authority, the investigator must give the inspector direct access to relevant documents and discuss any findings with the inspector. If an inspection is requested by a regulatory authority and/or IRB, the investigator must inform the sponsor immediately that this request has been made.

11.8 Records Retention

The investigator must retain all study-related records for at least 2 years after a marketing application is approved for the drug. If an application is not approved for the drug, the investigator must retain all study-related records until at least 2 years after shipment and delivery of the drug for investigational use is discontinued, and FDA or regulatory agencies have been so notified.

The investigator must contact the sponsor prior to destroying any records associated with this study.

If the location of the study files changes from the address noted on the Form FDA 1572, written notification of the new location must be given to the sponsor. In the event the investigator withdraws from participation in the study, study records will be transferred to a mutually agreed upon designee. The investigator must provide written notice to the sponsor of such transfer.

11.9 Publication of Results

All information concerning miconazole oil including study data and sponsor operations including but not limited to formulation information, manufacturing processes, basic scientific data, and patent applications will be regarded as confidential and will remain the sole property of the sponsor. The investigator agrees to use this information solely for the purposes of accomplishing this study and agrees not to use it for any other purposes without the written consent of the sponsor.

Study-related information must not be published or presented by the investigator without prior consultation with and written agreement from the sponsor.

12 REFERENCES

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