# CLINICAL TRIAL PROTOCOL

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| **Study Title:** | Dose-Ranging Study of the Efficacy and Safety of Miconazole Oil Used for 7 or 14 Days Compared with Vehicle in the Treatment of Otomycosis |
| **Study Number:** | HD-MCZ-PHII-DRF062016 |
| **Study Drug:** | Miconazole oil |
| **Sponsor:** | Hill Dermaceuticals, Inc.<br>2650 S. Mellonville Ave<br>Sanford, FL 32773 |
| **Protocol Date/Version:** | 17 April 2019 / Version 6<br>Previous versions:<br>10 August 2016 / Version 1<br>14 February 2017 / Version 2<br>14 June 2017 / Version 3<br>11 October 2017 / Version 4<br>11 May 2018 / Version 5 |

## PROTOCOL APPROVAL

The following individuals approve the 17 April 2019 version of the HD-MCZ-PHII-DRF062016 protocol. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

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| Company: | Hill Dermaceuticals, Inc. |
| Name: | Rosario G. Ramirez, MD |
| Title: | Medical Director, Research & Development |
| Address: | 2650 South Mellonville Avenue |
| | Sanford, FL 32773 |

Rosario Ramirez

Digitally signed by Rosario Ramirez
DN: c=US, st=FL, l=Sanford, o=Hill Dermaceuticals, Inc, cn=Rosario Ramirez, email=nini.ramirez@hillderm.com
Reason: I am approving this document
Date: 2019.05.09 12:40:09 -04'00'

Signature Date

## STUDY ACKNOWLEDGMENT

Protocol number: HD-MCZ-PHII-DRF062016 Version 6

I have read this protocol and commit to conduct the study as outlined herein. I agree to comply with all applicable regulations and to conduct the study as described in the 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:**

Dose-Ranging Study of the Efficacy and Safety of Miconazole Oil Used for 7 or 14 Day Compared with Vehicle in the Treatment of Otomycosis

**Study Number:** HD-MCZ-PHII-DRF062016

**Study Center(s):** Up to 10 study centers in the United States (US)

**Number of Subjects Planned:** Approximately 75

**Study Period:**

The study duration for each subject will be up to 30 days (up to 14 days of treatment, and 8 days of follow-up, including the visit window of up to 8 additional days after the scheduled day to complete the final visit)

**Phase of Development:** 2

**Objectives:**

- Obtain preliminary evidence of the efficacy and safety of miconazole oil compared with vehicle over a 14-day treatment duration
- Descriptively compare the efficacy and safety of miconazole oil over 7 versus 14 days

**Design and Methodology:**

This study is a randomized, partially masked, multiple-dose, parallel-group design study conducted at up to 10 study centers in the US. Approximately 75 male or female subjects with otomycosis will receive study drug. Subjects will be randomly assigned in a 1:1:1 ratio 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] for 7 or 14 days, or vehicle for 14 days. During the study it is planned to assess treatment allocation to ensure that there is a sufficient number of subjects within each group for the primary analysis. If deemed necessary, future randomizations may be adjusted. For subjects assigned to the 14-day treatment duration with either miconazole oil or vehicle, the contents of the study drug will be masked to both the subject and the investigator and study staff (i.e., double-blind), but the treatment duration assigned to each subject (7 or 14 days) will be unmasked to both the subject and the investigator and study staff.

At Screening/Baseline (Day 1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a physical examination, an assessment of the signs and symptoms of otomycosis (pruritus, debris, visual examination for presence of fungal elements, and pain), 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, and a subject global assessment of disease will be performed. Fungal and bacterial cultures 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 then 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

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| **Name of Sponsor/Company:** Hill Dermaceuticals, Inc. |
| **Name of Finished Product:** Miconazole oil |
| **Name of Active Ingredient:** 2% miconazole |
| 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.<br><br>All subjects will return to the clinic on Day 8. For subjects randomized to the 7-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for that visit below. Subjects randomized to 7-day treatment will not administer study drug on Day 8. For all other subjects, for whom this visit will constitute an On Treatment Visit, a clinical evaluation of the signs and symptoms of otomycosis, a subject global assessment, a cleaning of the affected ear(s) (following the site's normal procedures), and an assessment of AEs and concomitant medications will be performed, and these 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.<br>All subjects will return to the clinic on Day 15. For subjects randomized to the 7-day treatment duration, this visit will constitute the Test of Cure Visit, with procedures performed as described for the Test of Cure Visit below. For subjects randomized to the 14-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for the End of Treatment Visit below.<br>Subjects randomized to the 14-day treatment durations will return to the clinic on Day 22, for the Test of Cure Visit, with procedures performed as described for the Test of Cure Visit below.<br>Procedures performed at the End of Treatment Visit will include an assessment for clinical signs and symptoms of otomycosis, a subject global assessment, and a fungal culture of the affected ear(s). For subjects randomized to the 7-day treatment duration, subjects will have the affected ear(s) cleaned according to the site's normal procedures at this visit, after the efficacy procedures have been completed. AEs and concomitant medications will also be assessed, and the subject will return all unused study drug.<br>Procedures performed at the Test of Cure Visit will include an assessment of clinical signs and symptoms of otomycosis, a subject global assessment, and a fungal culture of the affected ear(s). AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential. |
| **Study Visits:**<br>Screening/Baseline (1 visit); On Treatment (up to 1 visit); End of Treatment (1 visit); Test of Cure (1 visit) |
| **Efficacy Evaluations:**<br>• Clinical signs and symptoms of otomycosis (pruritus; debris; presence of fungal elements; pain)<br>• Fungal culture<br>• Subject global assessment |
| **Safety Evaluations:**<br>• AEs |

**Name of Sponsor/Company:** Hill Dermaceuticals, Inc.

**Name of Finished Product:** Miconazole oil

**Name of Active Ingredient:** 2% miconazole

**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.

**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 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 (7-day and 14-day treatment durations)

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 1 minute 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.

**Reference Product, Dose, and Mode of Administration:**

Vehicle (14-day treatment duration)

Active ingredient: none (vehicle group)

Other ingredients: refined peanut oil, mineral oil, oleth-2, and isopropyl myristate

Mode of administration: same as described for the test product.

**Statistical Analyses:**

The primary and secondary endpoints will be based on the investigator reporting of signs and symptoms. Other efficacy endpoints will be based on the subject reporting of the symptom of pruritus.

Descriptive statistics will be presented for the signs and symptoms of otomycosis for the study ear at each evaluation and will include the number and percentage of subjects in each category. Subject assessments for the study ear for pruritus will also be summarized. No

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| **Name of Sponsor/Company:** Hill Dermaceuticals, Inc. |
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| **Name of Active Ingredient:** 2% miconazole |

imputation will be made for missing data.

The primary efficacy endpoint will be the percentage of subjects at the Test of Cure Visit with "therapeutic cure," defined as a negative mycological culture plus "clinical cure." Clinical cure is defined as the absence of all otomycosis signs and symptoms according to the scales for each individual sign or symptom and with absence defined as a score of 0 on each of the scales for pruritus, debris, fungal elements, and pain.

Other efficacy endpoints will include:

- Percentage of subjects with clinical cure at the Test of Cure Visit
- Percentage of subjects with a negative fungal culture at the Test of Cure Visit
- Percentage of subjects with a negative fungal culture at the Test of Cure visit as well as individual sign or symptom score of 0 or 1 on each of the scales for pruritus and debris and a score of 0 on each of the scales for fungal elements and pain.
- Percentage of subjects with individual signs or symptoms with a score of 0 or 1 on each of the scales for pruritus and debris and a score of 0 on each of the scales for fungal elements and pain.
- Subject global assessments at Baseline and Test of Cure as well as categorical shifts in the subject global assessment scale scores from the Screening/Baseline to the Test of Cure Visit
- If feasible, analyses may also be conducted by fungal organism isolated at Screening/Baseline.

The primary population for all efficacy analyses will be the modified intent-to-treat (MITT) population, defined as all subjects who were randomized, dispensed study drug, and with a clinical diagnosis of otomycosis confirmed by a positive fungal culture.

In cases of bilateral otomycosis, the ear with the worse infection at Screening/Baseline, as assessed by the investigator by taking into account both clinical signs and symptoms and fungal culture results, 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.

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.

All efficacy and safety analyses and comparisons between groups will be descriptive in nature, with no formal hypothesis testing performed.

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| **Name of Sponsor/Company:** Hill Dermaceuticals, Inc. |
| **Name of Finished Product:** Miconazole oil |
| **Name of Active Ingredient:** 2% miconazole |
| **Sample Size:**<br>The sample size for this study is not based on statistical considerations and is instead intended to be a reasonable number of subjects upon which to gather preliminary information on the efficacy and safety of miconazole oil when administered via the otic route to subjects with otomycosis. |
| **Interim Treatment Allocation Assessment(s):**<br>A subject's MITT status (specifically positive fungal culture at baseline) is determined only following randomization, which may result in imbalance between treatment groups. Therefore, at least one assessment during the conduct of the study is planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. Once at least 10 MITT subjects have been enrolled in the 7-Day active group, the numbers of MITT subjects in the 14-Day active group and the 14-Day vehicle group will be determined by an unblinded statistician; no persons involved in the day to day conduct of the study will be unblinded. Randomization allocation for future subjects may be adjusted if deemed necessary to achieve minimum number of subjects within each arm. |

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## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| IRB | Institutional review board |
| ITT | Intent-to-treat |
| IUD | Intrauterine device |
| LOCF | Last Observation Carried Forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIC | Minimum inhibitory concentration |
| MITT | Modified intent-to-treat |
| OTC | Over the counter |
| PP | Per protocol |
| SAE | Serious adverse event |
| TEAE | Treatment-emergent adverse event |
| US | United States |

# 1 INTRODUCTION

## 1.1 Brief Background Information

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].

The mechanisms of action of miconazole against fungi in general appear to be applicable to fungi associated with otomycosis, in that miconazole has been demonstrated to have activity against some clinical isolates of fungi associated with human otomycosis in the US *in vitro* [Bassiouny 1986; Stern 1988]. 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].

The purpose of this study is to gather preliminary data on the efficacy and safety of 2% miconazole oil after topical otic administration in subjects with otomycosis. A 14-day regimen of

twice-daily administration of 2% miconazole oil will be descriptively compared with the same treatment regimen using the product vehicle. Furthermore, the 14-day regimen of 2% miconazole oil will be compared with a 7-day regimen, to gather preliminary dose-ranging data regarding the duration of treatment. The 2% concentration of miconazole is selected for this study due to the results of an internal study conducted by the sponsor *in vitro* demonstrating greater zones of inhibition against *Candida* and *Aspergillus* using the 2% concentration compared with the 1% concentration. Furthermore, the 2% miconazole concentration is commonly used for dermatophyte infections, and topical application is expected to be ≥1000-fold the minimum inhibitory concentrations (MICs) of the *Candida* and *Aspergillus* organisms most commonly associated with human otomycosis in the US.

## 1.2 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.

## 1.3 Justification of the Study, Risks, Dose, and Inclusion of Subjects with Peanut Allergy

### 1.3.1 Study and Risks

Miconazole has been approved by the US FDA since 1974 and achieved OTC status for some indications when FDA issued a final monograph for miconazole on September 23, 1993. Miconazole is FDA-approved as a prescription for other indications. Approved routes of administration in humans have included systemic (intravenous) routes, as well as a variety of topical routes (dermatologic, intravaginal, and buccal).

Miconazole has not been FDA-approved for otic administration for any indication in humans, but clinical studies in other countries of otically-administered miconazole have been conducted and support the efficacy of miconazole in the treatment of otomycosis [Kiakojuri 2007; Vennewald 2010; Navaneethan 2015]. *In vitro* evidence exists of the susceptibility of clinical isolates from patients with otomycosis to miconazole, including one study of isolates from patients with otomycosis in the US [Bassiouny 1986; Stern 1988]. These results, along with the potential complications of untreated otomycosis, suggest a potential benefit to patients to study miconazole administered otically for the treatment of otomycosis.

The safety of miconazole as a topical dermal application is supported by its OTC approval for dermal conditions. Side effects of topical application to the skin may include blistering, burning, redness, skin rash, or other sign of skin irritation [PubMed Health 2015]. Side effects mentioned in the Monistat 1 consumer information leaflet include burning, itching, irritation, swelling, hives, skin rash, abdominal pain, and abdominal cramping. Other possible local effects of miconazole which may provide benefit in otomycosis may include anti-inflammatory activity at the skin, and possible restoration of skin barrier function in some circumstances of skin injury [Xhauflaire-Uhoda 2006; Liebel 2006].

Evidence supporting the safety of miconazole administered by the otic route comes largely from nonclinical studies. The possibility exists that miconazole could access the middle ear through the tympanic membrane, then diffuse through the round window membrane of the middle ear to reach and damage the cochlea. Miconazole appeared to be non-ototoxic when instilled at a 2% concentration directly into the round window niche of guinea pigs three times over the course of a week [Tom 2000]. Miconazole oil, instilled at 1% and 2% concentrations to guinea pigs twice daily over a period of 14 days in a nonclinical study conducted by the sponsor, also generally failed to demonstrate ototoxicity, although minor hair cell loss was observed in 1 animal in each of the 1% and 2% miconazole groups. Bilateral hearing loss, as assessed by increases in auditory brainstem responses, was observed in all animals in the miconazole vehicle group as well as in each of the 1% and 2% miconazole groups, but not in the saline control group. These results suggest that the hearing loss was due to the miconazole oil vehicle, rather than the miconazole itself. Because this hearing loss was generally not associated with hair cell loss, it is believed that this hearing loss was caused by instillation of a relatively large volume of product in a small animal (resulting in physical blockage of conduction), rather than actual damage to the ear caused by miconazole or the miconazole vehicle. Refer to the Investigator's Brochure (IB) for miconazole oil [Investigator's Brochure for miconazole oil 2016] for more information on the 14-day study of miconazole oil in guinea pigs.

The bilateral hearing loss observed in guinea pigs after a 14-day treatment with miconazole oil and its vehicle is not expected to occur in humans at the doses and volumes of study drug planned for clinical use. The miconazole oil vehicle is almost identical to that of another product manufactured by the sponsor and approved for topical otic administration (DermOtic™, containing 0.01% fluocinolone acetonide and used for the treatment of chronic eczematous external otitis). No subjects randomized to the DermOtic group of the clinical studies reported hearing loss, and no post-marketing reports of hearing loss have been received since DermOtic's approval in 2005.

The non-ototoxicity of the active ingredient, miconazole, is also supported in another species of animal by FDA approval of miconazole in two combination products (Surolan, which contains approximately 2% miconazole, and Easotic, which contains approximately 1.5% miconazole) administered by the otic route for the treatment of canine otitis externa caused by susceptible strains of yeast and bacteria. In the studies of Surolan in which hearing loss was assessed, hearing loss was only reported in 3 of 161 dogs (1.9%) and with apparent reversibility in the 2 dogs for which follow-up information was available and normal hearing was demonstrated at a later date.

Systemic effects of miconazole are generally not expected after topical otic administration. Systemic absorption of miconazole and distribution to locations other than the skin have been demonstrated to be low after topical dermal administration, as has been reported for other miconazole-containing products such as the Vusion™ topical ointment used for the treatment of diaper dermatitis complicated by candidiasis in children. Thus, although some potential systemic effects of miconazole have been reported and the liver has been identified in prior FDA miconazole product approvals to be the main toxicological target of systemic miconazole; these effects are generally not expected after topical otic administration of the doses planned for this study.

### 1.3.2 Dose

The 2% dose was selected for this study based on its widespread use in clinical practice in a variety of antifungal products already approved by FDA, and the larger zones of inhibition of 2% compared with 1% miconazole when incubated with two organisms commonly associated with otomycosis (*Candida albicans* and *Aspergillus niger*) in a sponsor-conducted study *in vitro*. The use of 5 drops of product (at ~30 mg per drop) is based on the estimated volume of the human external ear canal, and the amount believed to be needed to fully coat the canal. The 5 drops planned for this study is the same as that used for DermOtic in the treatment of chronic eczematous external otitis. It is noted that the dose regimen for Floxin™ otic solution (0.3% ofloxacin), an FDA-approved product for the treatment of bacterial otitis externa, is 10 drops in adults and children >13 years. Floxin is aqueous and may not adhere as well to the ear canal as the oil-based miconazole oil. The twice-daily dosing was selected based on evidence that miconazole may not maintain bioactivity in the stratum corneum for a full 24 hours [Pershing 1994].

### 1.3.3 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 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 has been treated 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.

## 2 OBJECTIVES AND RATIONALE

The objectives of the study are to:

- Obtain preliminary evidence of the efficacy and safety of miconazole oil compared with vehicle over a 14-day treatment duration.
- Descriptively compare the efficacy and safety of miconazole oil over treatment durations of 7 versus 14 days.

# 3 STUDY DESIGN

This study is a randomized, partially masked, multiple-dose, parallel-group design study conducted at up to 10 study centers in the US. Approximately 75 male or female subjects with otomycosis will receive study drug. Subjects will be randomly assigned in a 1:1:1 ratio 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] for 7 or 14 days, or vehicle for 14 days. Interim assessments are planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. If deemed necessary the randomization ratio may be adjusted following the interim assessments; see Section 10.5.5 for details. For subjects assigned to the 14-day treatment duration with either miconazole oil or vehicle, the contents of the study drug will be masked to both the subject and the investigator and study staff (i.e., double-blind), but the treatment duration assigned to each subject (7 or 14 days) will be unmasked to both the subject and the investigator and study staff.

At Screening/Baseline (Day 1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a physical examination, an assessment of the signs and symptoms of otomycosis (pruritus, debris, visual examination for presence of fungal elements, and pain), 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, and a subject global assessment of disease will be performed. Fungal and bacterial cultures 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 then be assessed. The subject will then leave the clinic and continue to administer the study drug twice per day as instructed. While in the study, 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.

All subjects will return to the clinic on Day 8. For subjects randomized to the 7-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for that visit below. Subjects randomized to the 7-day treatment duration will not administer study drug on the day of this visit. For all other subjects, for whom this visit will constitute an On Treatment Visit, a clinical evaluation of the signs and symptoms of otomycosis, a subject global assessment, a cleaning of the affected ear(s) (following the site's normal procedures), and an assessment of AEs and concomitant medications will be performed, and these 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.

All subjects will return to the clinic on Day 15. For subjects randomized to the 7-day treatment duration, this visit will constitute the Test of Cure Visit, with procedures performed as described for the Test of Cure Visit below. For subjects randomized to the 14-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for the

End of Treatment Visit below. Subjects randomized to the 14-day treatment duration will not administer study drug on the day of this visit.

Subjects randomized to the 14-day durations will return to the clinic on Day 22 for the Test of Cure Visit, with procedures performed as described for the Test of Cure Visit below.

Procedures performed at the End of Treatment Visit will include an assessment for clinical signs and symptoms of otomycosis, a subject global assessment, and a fungal culture of the affected ear(s). For subjects randomized to the 7-day treatment duration, subjects will have the affected ear(s) cleaned according to the site's normal procedures at this visit, after the efficacy procedures have been completed. AEs and concomitant medications will also be assessed, and the subject will return all study drug.

Procedures performed at the Test of Cure Visit will include an assessment of clinical signs and symptoms of otomycosis, a subject global assessment, and a fungal culture of the affected ear(s). AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential.

Efficacy assessments will include fungal culture of the affected ear(s), assessments of clinical signs and symptoms of otomycosis, and a subject global assessment. In cases of bilateral otomycosis, both ears will be treated and evaluated by the investigator, but the ear with the worse infection at Screening/Baseline, as assessed by the investigator by taking into account both clinical signs and symptoms and fungal culture results, 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.

Safety assessments will include AEs.

## 3.1 Number of Subjects

Approximately 75 eligible subjects are planned to be enrolled in order to achieve approximately 10 subjects per group (randomized in a 1:1:1 ratio to the 7-day active, 14-day active, and 14-day vehicle treatment groups) with a positive fungal culture at baseline and who have completed the Test of Cure Visit.

## 3.2 Investigators

The study will be conducted at up to 10 investigative sites 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 30 days (including the visit window of up to 8 additional days after the scheduled day to complete the final 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 >0 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 at least two of the following signs or symptoms of otomycosis in each ear to be treated with study drug: pruritus, >1; debris, >1; or pain, >0.
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 Test of Cure 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 both ears meet all study eligibility criteria, the subject will be eligible for the study, both ears may be treated with study drug, 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
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
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.

Due to the time required to obtain fungal culture results from Screening/Baseline, subjects will be enrolled into the study based on a clinical diagnosis of otomycosis (including the visible presence of fungal elements at Screening/Baseline), without a requirement for a positive fungal culture. Subjects who end up with a negative Screening/Baseline fungal culture will not be discontinued from the study, but these subjects will not be included in the primary efficacy analysis. Because the sponsor's goal is to obtain approximately 10 subjects per group who meet both criteria of having a positive fungal culture at Screening/Baseline and completing the Test of Cure Visit, the number of subjects enrolled into the study may be adjusted depending on the rates of negative fungal culture at Screening/Baseline and of discontinuation or loss to follow-up.

Subject discontinuations will be documented clearly on the applicable electronic case report form (eCRF). Subjects who discontinue from the study will not be replaced, but additional subjects may be enrolled and randomized if it appears that approximately 75 subjects is insufficient to meet the sponsor's goal of approximately 10 subjects per group who meet both criteria of having a positive fungal culture at Screening/Baseline and completing the Test of Cure Visit.

## 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 must be placed to the subject at the first missed visit, to attempt to get the subject to complete the visit and to gather as much follow-up data as possible. At least three telephone calls must also be placed to the subject for any subsequent missed visits after an attended visit, to attempt to get the subject to complete the visit and to gather as much follow-up data as possible. Subjects who miss a visit may still be scheduled for a subsequent visit. Subjects who cannot be contacted via three telephone calls to schedule a missed visit may be considered lost to follow-up and discontinued from the study.

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 28 days 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, 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.

## 5.2 Prohibited Medications

Other than the study drug, no other topical medications are allowed to be used in the ears. Other prohibited treatments include systemic antifungal therapy, warfarin, immunosuppressive or immune-stimulating drugs, and systemic steroids.

# 6 STUDY SCHEDULE

## 6.1 Study Flow Chart

The study schedule is presented in Table 1.

**Table 1 Study Schedule**

| Evaluations and Procedures: | Screening/ Baseline Day 1 | On Treatment [a] Day 8 [c] | End of Treatment [a] Day 8 or 15 [d] | Test of Cure [b] Day 15 or 22 [e] |
|---|---|---|---|---|
| Informed consent/assent | X | | | |
| Inclusion/exclusion criteria | X | | | |
| Medical/medication history | X | | | |
| Physical examination | X | | | |
| Otomycosis signs and symptoms | X | X | X | X |
| Urine pregnancy test [f] | X | | | X |
| Randomization | X | | | |
| Dispensation of study drug | X | | | |
| Dispensation of subject diary | X | | | |
| Collection of subject diary | | X | X | |
| Administration of study drug at site | X | | | |
| Weighing of study drug | X | X | X | |
| Collection of study drug | | | X | |
| Subject global assessment | X | X | X | X |
| Microbial culture [g] | X | | X | X |
| Ear cleaning | X | X | X [h] | |
| AE evaluations | X | X | X | X |
| Concomitant medications review | X | 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 8 days later than the specified day.
c. For subjects randomized to the 14-day durations, the Day 8 visit constitutes an On Treatment Visit; for subjects randomized to the 7-day group, the Day 8 visit constitutes the End of Treatment Visit with those procedures performed instead
d. The End of Treatment Visit is scheduled to occur on Day 8 for subjects randomized to the 7-day treatment duration, and on Day 15 for subjects randomized to the 14-day treatment durations
e. The Test of Cure Visit is scheduled to occur on Day 15 for subjects randomized to the 7-day treatment duration, or on Day 22 for subjects randomized to the 14-day treatment durations. In case of early termination, the assessments planned for the Test of Cure Visit should be performed if possible
f. Females of childbearing potential only
g. For both fungi and bacteria at the Screening/Baseline visit and for fungi only at the End of Treatment and Test of Cure visits
h. To be performed in subjects randomized to the 7-day group only, and after all efficacy assessments (otomycosis signs and symptoms, subject global assessment, and microbial culture) have already been performed

## 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/or caregiver's willingness and ability to meet the follow-up requirements of the study will be determined.

The schedule of visits is presented in Table 1. Details about study procedures and how they are to be performed are presented in Section 7.

### 6.2.1 Screening / Baseline

Screening procedures will occur prior to randomization and will include:

- Informed consent and assent (as applicable)
- Medical history
- Prior and concomitant medications
- 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:

- Subject global assessment
- Microbial culture (fungi and bacteria)
- Ear cleaning
- Randomization
- Weighing of study drug, followed by dispensation of study drug to subject
- Dispensation of subject diary 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
- Subject instruction about the date on which they are to stop administering study drug (after all doses have been administered on Day 7 for the 7-day group, and after all doses have been administered on Day 14 for the 14-day groups; subjects will be instructed that study drug should be stopped on the appropriate date regardless of the date for which the next visit is scheduled)

- Subjects will be instructed to bring their bottle of study drug and the diary to the site for their next visit

### 6.2.2 On Treatment

These visits may occur up to 3 days later than the specified day. Subjects randomized to the 7-day group will not have any On Treatment visits and will instead proceed directly to the procedures specified for the End of Treatment Visit. Subjects randomized to the 14-day groups will have one On Treatment visit on Day 8.

Subjects will be instructed not to administer any study drug on the day of this visit until after the visit has occurred, if the visit is scheduled for the morning. If the visit is scheduled for the afternoon, subjects will be instructed that the morning dose of the study drug can be administered prior to the visit.

The following procedures and evaluations will occur during the On Treatment visits:

- Otomycosis signs and symptoms
- Subject global assessment
- Ear cleaning
- AE evaluation
- Review of concomitant medications
- Weighing of study drug and return of the bottle of study drug to the subject
- Review of subject diary.
- Subject reminder to continue to administer their assigned study drug twice daily up through the date on which they are to stop administering study drug (after all doses have been administered on Day 14; study drug should be stopped on the appropriate date regardless of the date for which the next visit is scheduled)
- Subjects will be instructed to bring their bottle of study drug and the diary to the site for their next visit

## 6.3 End of Treatment

This visit may occur up to 3 days later than the specified day. Subjects randomized to the 7-day group will have the End of Treatment Visit on Day 8, and subjects randomized to the 14-day groups will have the End of Treatment Visit on Day 15.

The following procedures and evaluations will occur during the End of Treatment visits:

- Otomycosis signs and symptoms
- Subject global assessment
- Microbial (fungal) culture
- Ear cleaning (in subjects randomized to the 7-day group only)
- AE evaluation
- Review of concomitant medications
- Collection of subject diary
- Collection/weighing of study drug

## 6.4 Test of Cure

This visit may occur up to 1 day sooner or up to 8 days later than the specified day. Subjects randomized to the 7-day group will have the Test of Cure Visit on Day 15, and subjects randomized to the 14-day groups will have the Test of Cure Visit on Day 22.

The following procedures and evaluations will occur during the Test of Cure Visit:

- Otomycosis signs and symptoms
- Subject global assessment
- Microbial (fungal) culture
- 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.

## 6.5 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.

## 6.6 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.

## 6.7 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.

## 6.8 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 6.6.

## 6.9 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 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 Physical Examination

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

## 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 pain (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

#### 7.4.1.1 Subject Assessment

Subjects or their caregivers (as appropriate, based on the age of the subject) will be handed a questionnaire for each ear being treated with study drug and asked to indicate the choice that most closely reflects the severity of itching in the ear over the last 24 hours. Choices and scores will be according to the following scale:

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

#### 7.4.1.2 Investigator Assessment

After subjects have completed the questionnaire described in Section 7.4.1.1, 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:

"Have you had itching in your ear over the last day or so?"

"Over the last 24 hours, has your itching interfered 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 same scale as described in Section 7.4.1.1.

### 7.4.2 Debris

Upon otoscopic examination, the investigator will score the amount of debris present in each ear being treated with study drug. Scores will be according to the following scale:

| Score | Category | Description |
|---|---|---|
| 0 | None | No debris 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. 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 Pain

Subjects or their caregivers (as appropriate, based on the age of the subject) will be asked by the investigator (or designee) whether pain is 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:

"Over the last 24 hours, has your ear hurt?"

"Over the last 24 hours, has your pain been constant?"

"Over the last 24 hours, would you characterize your pain as more dull or sharp?"

"Over the last 24 hours, have you had pain when your earlobe or the front part of your ear is touched?"

"Over the last 24 hours, have you felt pain inside your ear?"

"Over the last 24 hours, have you felt pain on the outside of your ear?"

The investigator will then score the symptom of pain 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 | Absent | No pain |
| 1 | Present | Pain present, easily tolerated to intolerable |

## 7.5 Subject Global Assessment

Subjects or their caregivers (as appropriate, based on the age of the subject) will be asked to choose among the following three options to assess the overall level of discomfort in each ear being treated with study drug. Subjects or their caregivers will be handed a questionnaire for each ear being treated with study drug and asked to indicate the choice that most closely reflects the subject's situation with the ear. Choices and scores will be according to the following scale:

| Score | Category | Description |
|---|---|---|
| 0 | None | My ear is not causing me any discomfort and is not stopping me from my normal activities |
| 1 | Minor | My ear is slightly uncomfortable, but it is not for the most part stopping me from my normal activities |
| 2 | Moderate | My ear is uncomfortable, and it is stopping me from at least some of my normal activities |

## 7.6 Microbial Culture

At designated visits, the investigator or designee will obtain a sample from the external ear to be sent to a laboratory for microbial culture (for both fungi and bacteria at the Screening/Baseline visit and for fungi only at the End of Treatment and Test of Cure visits). 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 study drug, both ears will be cultured.

## 7.7 Ear Cleaning

At designated visits, the investigator or designee will clean the ear(s) that are being/have been treated with study drug, according to the site's normal procedures. Ear(s) being treated will be cleaned at the designated visits even if they appear clear of debris. In cases in which the investigator would normally not clean the ear because it appears to be clear, this cleaning may be minimal. All ear cleaning will be documented in the eCRF.

## 7.8 Adverse Event Evaluations

See Section 8.

## 7.9 Randomization

See Section 9.2.

## 7.10 Study Drug Administration

See Section 9.1.1.

## 7.11 Treatment Compliance

Subjects or their caregivers (as appropriate) will complete a diary documenting each study drug administration. Additionally, each bottle of study drug will be weighed by the investigator or designee before dispensation to the subject and at each 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 subject 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 (including a clinically significant abnormal laboratory finding), 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 product.

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.

### 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.

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.

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.

## 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 14-day groups, 2% miconazole oil will be compared descriptively against the oil vehicle, which will not contain miconazole and will instead contain a greater amount of refined peanut oil and mineral oil to account for the absence of the miconazole.

Study drug will be supplied in bottles containing ~20 grams 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 miconazole oil into the ear. The subject will be instructed to keep the head positioned with the ear facing up for approximately 1 minute to allow the miconazole oil to coat the ear canal. After 1 minute, 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 shower for at least 30 minutes after applying study drug.

## 9.2 Randomization

Subjects will be randomized in a 1:1:1 ratio to one of three groups: 1) 7-day treatment with miconazole oil; 2) 14-day treatment with miconazole oil; or 3) 14-day treatment with miconazole oil vehicle. Interim assessments are planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. If deemed necessary the randomization ratio may be adjusted following the interim assessments; see Section 10.5.5 for details.

## 9.3 Masking/Unmasking

The duration of treatment will not be masked. For subjects randomized to the 14-day treatment durations, the contents of the study drug (miconazole oil versus vehicle) will be masked. Randomized study drug will be packaged in identical bottles and will be labeled with a randomization number rather than the contents of the bottle.

For subjects randomized to the 14-day durations, if it becomes necessary to unmask 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 oil vehicle will be manufactured, packaged and labeled by Hill Dermaceuticals, Inc. It will be packaged in dropper bottles, each of which will contain ~20 grams of study drug. The dropper will dispense approximately 30 mg per drop.

The Study drug and Vehicle will be packaged in primary bottle 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 grams)
- 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

The primary and secondary endpoints will be based on the investigator reporting of signs and symptoms for the study ear. Other efficacy endpoints will be based on the subject reporting of the symptom of pruritus.

Descriptive statistics will be presented for the signs and symptoms of otomycosis for the study ear at each evaluation and will include the number and percentage of subjects in each category. Subject assessments for the study ear for pruritus will also be summarized. No imputation will be made for missing data.

### 10.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage of subjects at the Test of Cure Visit with "therapeutic cure," defined as a negative mycological culture plus "clinical cure" for the study ear. Clinical cure is defined as the absence of all otomycosis signs and symptoms based on Investigator assessment according to the scales for each individual sign or symptom and with absence defined as a score of 0 on each of the scales for pruritus, debris, fungal elements, and pain). See Section 7.4 for the scales for each otomycosis sign and symptom.

### 10.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will include the following:

- Percentage of subjects with clinical cure at the Test of Cure Visit
- Percentage of subjects with a negative fungal culture at the Test of Cure Visit
- Percentage of subjects with a negative fungal culture at the Test of Cure visit as well as individual sign or symptom score of 0 or 1 on each of the scales for pruritus and debris and a score of 0 on each of the scales for fungal elements and pain.
- Percentage of subjects with individual signs or symptoms with a score of 0 or 1 on each of the scales for pruritus and debris and a score of 0 on each of the scales for fungal elements and pain.
- Subject global assessments at Baseline and Test of Cure as well as categorical shifts in the subject global assessment scale scores from the Screening/Baseline to the Test of Cure Visit.
- If feasible, analyses may also be conducted by fungal organism isolated at Screening/Baseline.

### 10.1.3 Other Efficacy Endpoints

Other efficacy endpoints based on subject reporting of pruritus will include the following:

- Subject therapeutic cure (defined as a negative mycological culture plus clinical cure) at the Test of Cure visit for the study ear based on subject assessment of pruritus. Clinical cure is defined as the absence of all otomycosis signs and symptoms according to the scales for each individual sign or symptom and with absence defined as a score of 0 on each of the scales for pruritus, debris, fungal elements, and pain.

### 10.1.4 Safety Endpoints

Safety endpoints will be the percentage of subjects with treatment-emergent AEs, with treatment-emergent defined as occurring upon or after administration of the first dose of study drug.

## 10.2 Hypotheses

No formal hypotheses will be tested in this study. Descriptive comparisons will be made between the miconazole oil and the oil vehicle groups for subjects randomized to the 14-day groups. Additionally, descriptive comparisons will be made between the 7-day and 14-day groups for subjects randomized to the miconazole oil treatment.

## 10.3 Sample Size

The sample size for this study is not based on statistical considerations and is instead intended to be a reasonable number of subjects upon which to gather preliminary information on the efficacy and safety of miconazole oil when administered via the otic route to subjects with otomycosis.

## 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.

### 10.4.2 Modified Intent-to-treat Population

The modified intent-to-treat (MITT) population will be a subset of the ITT population. The MITT population will include subjects who were randomized, dispensed study drug, and with a clinical diagnosis of otomycosis confirmed by a positive fungal culture

### 10.4.3 Per Protocol Population

The per protocol (PP) population will be a subset of the MITT population and will include all subjects who complete the Test of Cure visit without any major protocol violations. The PP population will include subjects in the MITT population who did not meet 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.

### 10.4.4 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.

## 10.5 Statistical Methods

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

### 10.5.1 Efficacy Analyses

The primary population for all efficacy analyses will be the MITT population (see Section 10.4). Efficacy endpoints will also be summarized for the PP population and will be considered supportive.

The sample size N, frequency, and percent of subjects who demonstrate a positive outcome for each efficacy endpoint will be presented for the primary efficacy parameter as well as all secondary efficacy parameters.

In cases of bilateral otomycosis, the ear with the worse infection at Screening/Baseline, as assessed by the investigator by taking into account both clinical signs and symptoms and fungal culture results, 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.

### 10.5.2 Safety Analyses

Safety summaries will be conducted using the safety population (see Section 10.4.4). 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 MITT, PP, and Safety populations and will be supported with individual subject data listings.

### 10.5.4 Missing Data

Missing values from the Test of Cure visit from which the dichotomized Therapeutic Cure is derived will be imputed using last observation carried forward (LOCF) method.

### 10.5.5 Interim Treatment Allocation Assessment(s)

A subject's MITT status (specifically positive fungal culture at baseline) is determined only following randomization, which may result in imbalance between treatment groups. Therefore, at least one assessment during the conduct of the study is planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. Once at least 10 MITT subjects have been enrolled in the 7-Day active group, the numbers of MITT subjects in the 14-Day active group and the 14-Day vehicle group will be determined by an unblinded statistician; no persons involved in the day to day conduct of the study will be unblinded. Randomization allocation for future subjects may be adjusted if deemed necessary to achieve minimum number of subjects within each arm.

Full details will be provided in the SAP.

# 11 ADMINISTRATIVE CONSIDERATIONS

## 11.1 Institutional Review Board

The protocol, informed consent documents, 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. Data reconciliation will be performed between the EDC data and the external data reported by the central laboratory. Any discrepancies in the data will be queried first with the clinical site and second with the central laboratory.

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.

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# 13 SUMMARY OF PROTOCOL AMENDMENTS

## 13.1 Amendment 1 Version 2 14 February 2017

This amendment reflects updates and revisions based on comments and feedback received from the Agency. In addition, corrections to inconsistencies throughout the protocol, minor changes to study conduct, and administrative changes (i.e., typographical/grammatical, abbreviations) have been made based on CRO and Investigator feedback.

As summary of changes is provided below. New/changes in text are **bolded**. Deletions are ~~struck through~~. Sections that are new or have been completely revised only a short description is provided.

### Global Changes:

Administrative changes for typographical / grammatical errors, updates to list of abbreviations and abbreviations throughout text

### Title, Protocol Approval, and Study Acknowledgment Pages:

Updated to reflect protocol version and date change

### Synopsis

Study Number: **HD-MCZ-PHII-DRF062016**

Study Period:

The study duration for each subject will be up to ~~29~~ **30** days (up to 14 days of treatment, and ~~7~~ **8** days of follow-up, including the visit window of up to 8 additional days after the scheduled day to complete the final visit)

Design and Methodology:

…..Subjects will be randomly assigned in a 1:1:1 ratio to receive miconazole oil [administered as 5 drops per ear at ~30 ~~µL~~ **mg** per drop instilled into the external ear canal of the ear(s) affected by otomycosis] for 7 or 14 days, or vehicle for 14 days….

**…..**

At Screening/Baseline (Day 1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a physical examination, an assessment of the signs and symptoms of otomycosis (pruritus, debris, visual examination for presence of fungal elements, and pain), and an evaluation of ~~adverse events (AEs).~~ **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, and a subject global assessment of disease will be performed. ~~A culture~~ **Fungal and bacterial cultures** of the affected ear(s) will be taken, then debris will be cleaned from the affected ear(s) following the site's normal procedures……

**……**

All subjects will return to the clinic on Day 8. For subjects randomized to the 7-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for that visit below. **Subjects randomized to 7-day treatment will not administer study drug on Day 8.**

**……**

Procedures performed at the End of Treatment Visit will include an assessment for clinical signs and symptoms of otomycosis, a subject global assessment, and a **fungal** culture of the affected ear(s).

**…..**

Procedures performed at the Test of Cure Visit will include an assessment of clinical signs and symptoms of otomycosis, a subject global assessment, and a **fungal** culture of the affected ear(s).

Key Exclusion Criteria:

**….**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; **….**

Test Product, Dose, and Mode of Administration:

Miconazole oil (**7-day and** 14-day treatment ~~duration~~ **durations**)

Statistical Analyses:

**The primary and secondary endpoints will be based on the investigator reporting of signs and symptoms. Other efficacy endpoints will be based on the subject reporting of the symptom of pruritus.**

**Descriptive statistics will be presented for the signs and symptoms of otomycosis for the study ear at each evaluation and will include the number and percentage of subjects in each category. Subject assessments for the study ear for pruritus will also be summarized. No imputation will be made for missing data.**

The primary efficacy endpoint will be the percentage of subjects at the Test of Cure Visit with "therapeutic cure," defined as a negative mycological culture plus "clinical cure." Clinical cure is defined as the absence of all otomycosis signs and symptoms according to the scales for each individual sign or symptom and with absence defined as ~~scores~~ **a score** of 0 ~~or 1~~ on each of the scales for pruritus ~~and~~, debris, ~~and scores of 0 on each of the scales for~~ fungal elements, and pain.

Other efficacy endpoints will include:

- Percentage of subjects with clinical cure at the Test of Cure Visit
- Percentage of subjects with a negative fungal culture at the Test of Cure Visit
- Percentage of subjects with a **negative fungal culture at the Test of Cure visit as well as individual sign or symptom** score of 0 or 1 **on each of the scales** for pruritus **and debris and a score of 0 on each of the scales for fungal elements and pain.** ~~at the Test of Cure Visit~~
- ~~Percentage of subjects with a score of 0 or 1 for debris at the Test of Cure Visit~~
- Percentage of subjects with **individual signs or symptoms with a score of 0 or 1 on each of the scales for pruritus and debris and a score of 0 on each of the scales for fungal elements and pain** ~~the fungal elements at the Test of Cure Visit~~
- ~~Percentage of subjects with a score of 0 for pain at the Test of Cure Visit~~
- **Subject global assessments at Baseline and Test of Cure as well as categorical shifts in the subject global assessment scale scores from the Screening/Baseline to the Test of Cure Visit**
- ~~Percentages of subjects with categorical shifts on the subject global assessment scale from the Screening/Baseline to the Test of Cure Visit~~
- If feasible, analyses may also be conducted by fungal organism isolated at Screening/Baseline.

The primary population for all efficacy analyses will be the modified intent-to-treat (MITT) population, defined as all subjects **who were randomized, dispensed study drug, and** with a clinical diagnosis of otomycosis ~~and~~ **confirmed by** a positive fungal culture ~~at Screening/Baseline who received at least one dose of study drug.~~

**….**

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.** ~~Safety analyses will include the percentages of subjects with treatment-emergent AEs, classified on the basis of Medical Dictionary for Regulatory Affairs (MedDRA) terminology. Treatment-emergent AEs will be defined as those occurring upon or after administration of the first dose of study drug.~~

**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.**

### 1.3.2. Dose

**……**The use of 5 drops of product (at ~30 ~~µL~~ **mg** per drop) is based on the estimated volume of the human external ear canal, and the amount believed to be needed to fully coat the canal. **…..**

## 3 Study Design

**…..**

At Screening/Baseline (Day 1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a physical examination, an assessment of the signs and symptoms of otomycosis (pruritus, debris, visual examination for presence of fungal elements, and pain), and an evaluation of ~~adverse events (AEs).~~ **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, and a subject global assessment of disease will be performed. ~~A culture~~ **Fungal and bacterial cultures** of the affected ear(s) will be taken, then debris will be cleaned from the affected ear(s) following the site's normal procedures**……**

All subjects will return to the clinic on Day 8. For subjects randomized to the 7-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for that visit below. **Subjects randomized to the 7-day treatment duration will not administer study drug on the day of this visit. ….**

**…..**For subjects randomized to the 14-day treatment duration, this visit will constitute the End of Treatment Visit, with procedures performed as described for the End of Treatment Visit below. **Subjects randomized to the 14-day treatment duration will not administer study drug on the day of this visit.**

**…..**

Procedures performed at the End of Treatment Visit will include an assessment for clinical signs and symptoms of otomycosis, a subject global assessment, and a **fungal** culture of the affected ear(s). **….**AEs and concomitant medications will also be assessed, and the subject will return all ~~unused~~ study drug.

**…..**

Procedures performed at the Test of Cure Visit will include an assessment of clinical signs and symptoms of otomycosis, a subject global assessment, and a **fungal** culture of the affected ear(s). **…**

Efficacy assessments will include **fungal** culture of the affected ear(s), assessments of clinical signs and symptoms of otomycosis, and a subject global assessment.

### 3.1 Study Duration

The total duration of the study for a subject from screening until the last visit will be up to ~~29~~ **30** days (including the visit window of up to 8 additional days after the scheduled day to complete the final visit).

### 4.2 Exclusion Criteria

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

### 4.4 Subject Discontinuation

**…..**

**…..**If possible, the assessment schedule for the Test of Cure Visit should be performed, and an effort should be made to collect all ~~unused~~ study drug.

…..

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

### 5.2 Prohibited Medications

Other than the study drug, no other topical medications are allowed to be used in the ears. Other prohibited treatments include **systemic antifungal therapy,** warfarin, immunosuppressive or immune-stimulating drugs, and systemic steroids.

### Table 1 Study Schedule

*Addition of:*

Dispensation of subject diary to Screening/Baseline Day1
Collection of subject diary to On Treatment Day 8 and End of Treatment Day 8 or 15

*Change in assessments:*

Collection of ~~unused~~ study drug
~~Fungal~~**Microbial** culture, and addition of footnote g. for this assessment: **For both fungi and bacteria at the Screening/Baseline visit and for fungi only at the End of Treatment and Test of Cure visits**

*Change to footnotes:*

a. This visit may occur up to ~~1 day sooner or up to~~ 3 days later than the specified day.
h. To be performed in subjects randomized to the 7-day group only, and after all efficacy assessments (otomycosis signs and symptoms, subject global assessment, and ~~fungal~~**microbial** culture) have already been performed

### 6.2.1 Screening/Baseline

**….**

Subjects who are eligible for the study will undergo the following additional procedures:

- **….**
- ~~Fungal~~**Microbial** culture **(fungi and bacteria)**
- **….**
- **Dispensation of subject diary to subject.**
- **….**
- Subject instruction about the date on which they are to stop administering study drug **(after all doses have been administered on** Day 7 for the 7-day group, and a**fter all doses have been**

**administered on** Day 14 for the 14-day groups; subjects will be instructed that study drug should be stopped on the appropriate date regardless of the date for which the next visit is scheduled)
- Subjects will be instructed to bring their bottle of study drug **and the diary** to the site for their next visit

### 6.2.2 On Treatment

These visits may occur ~~up to 1 day sooner or~~ up to 3 days later than the specified day. Subjects randomized to the 7-day group will not have any On Treatment visits and will instead proceed directly to the procedures specified for the End of Treatment Visit. Subjects randomized to the 14-day groups will have one On Treatment visit on Day 8.

Subjects will be instructed not to administer any study drug on the day of this visit until after the visit has occurred**, if the visit is scheduled for the morning. If the visit is scheduled for the afternoon, subjects will be instructed that the morning dose of the study drug can be administered prior to the visit.**

The following procedures and evaluations will occur during the On Treatment visits:

- …..
- Ear cleaning ~~(on Day 8 only)~~
- ….
- **Weighing of study drug and return of the bottle of study drug to the subject**
- ~~Collection of unused study drug~~
- ~~Dispensation of study drug~~
- ~~For subjects randomized to the 14-day groups,~~
- **Review of subject diary.**
- Subject reminder to continue to administer their assigned study drug twice daily up through the date on which they are to stop administering study drug (**after all doses have been administered on** Day 14; study drug should be stopped on the appropriate date regardless of the date for which the next visit is scheduled)
- Subjects ~~randomized to the 14-day groups~~ will be instructed to bring their bottle of study drug **and the diary** to the site for their next visit

## 6.3 End of Treatment

This visit may occur ~~up to 1 day sooner or~~ up to 3 days later than the specified day. Subjects randomized to the 7-day group will have the End of Treatment Visit on Day 8, and subjects randomized to the 14-day groups will have the End of Treatment Visit on Day 15.

The following procedures and evaluations will occur during the ~~On~~**End of** Treatment visits:

- …..
- ~~Fungal~~**Microbial (fungal)** culture
- …..
- Collection of ~~unused study drug~~**subject diary**
- **Collection/weighing of study drug**

## 6.4 Test of Cure

The following procedures and evaluations will occur during the Test of Cure Visit:

- **….**
- ~~Fungal~~**Microbial (fungal)** culture
- ~~Ear cleaning (in subjects randomized to the 7-day group only)~~

### 7.4.1 Pruritus

*Text revised and updated including addition of:*

*Section 7.4.1.1 Subject Assessment*

*Section 7.4.1.2 Investigator Assessment*

**7.4.3 Presence of Fungal Elements**

*Score 1 updated:*

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**

**7.4.3 Pain**

*Text and sample questions revised*

**7.5 Global Assessment**

….Subjects or their caregivers will be handed a questionnaire for each ear being treated with study drug and asked to indicate the choice that most closely reflects the ~~(or their dependent's, as appropriate)~~**subject's** situation with the ear.

**7.6 ~~Fungal~~ Microbial Culture**

At designated visits, the investigator or designee will obtain a sample from the external ear to be sent to a laboratory for ~~fungal culture.~~**microbial culture (for both fungi and bacteria at the Screening/Baseline visit and for fungi only at the End of Treatment and Test of Cure visits).** Techniques for obtaining and handling the sample and sending it to the laboratory will be described in a separate laboratory manual.

**7.11 Treatment Compliance**

Subjects or their caregivers (as appropriate) will complete a diary ~~of~~ documenting ~~the time and amount of~~ each study drug administration.

**8.1 Definition of Adverse Events**

**….**

Medical conditions/diseases present before signing the informed consent form are only considered AEs if they worsen after the informed consent form is signed. ~~Abnormal or out-of-range laboratory test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.~~

**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 ~~final visit (Day 8).~~**Test of Cure Visit.**

**9.1 Description of Study Drug**

**….**For subjects randomized to the 14-day groups, 2% miconazole oil will be compared descriptively against the oil vehicle, which will not contain miconazole and will instead contain a greater amount of refined peanut oil **and mineral oil** to account for the absence of the miconazole.

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

**9.4.1 Packaging and Labeling**

The miconazole oil and the oil vehicle will be manufactured, packaged and labeled by Hill Dermaceuticals, Inc. It will be packaged in dropper bottles, each of which will contain ~20 ~~mL~~**grams** of study drug. The dropper will dispense approximately 30 ~~µL~~**mg** per drop.

*Addition of text describing study drug packaging and labeling*

### 9.5 Accountability

…..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 ~~either~~ returned to the sponsor (or designee~~) or destroyed~~**).**

### 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 ~~unused~~ study drug must ~~either~~ be returned to the sponsor or designee~~, or destroyed according instructions from~~. **This would include study drug returned by** the ~~sponsor or designee~~**subjects at the completion of the study, and reserve products that were not used.**

### 10.1 Study Endpoints

Addition of new text describing primary and secondary endpoints

### 10.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint will be the percentage of subjects at the Test of Cure Visit with "therapeutic cure," defined as a negative mycological culture plus "clinical cure" **for the study ear.** Clinical cure is defined as the absence of all otomycosis signs and symptoms **based on Investigator assessment** according to the scales for each individual sign or symptom and with absence defined as ~~scores of 0 or 1 on each of the scales for pruritus and debris, and scores~~**a score** of 0 on each of the scales for **pruritus, debris**, fungal elements, and pain). See Section 7.4 for the scales for each otomycosis sign and symptom.

### 10.1.2 Secondary Efficacy Endpoints

- ……
- Percentage of subjects with a **negative fungal culture at the Test of Cure visit as well as individual sign or symptom** score of 0 or 1 **on each of the scales** for pruritus **and debris and a score of 0 on each of the scales for fungal elements and pain.** ~~at the Test of Cure Visit~~
- ~~Percentage of subjects with a score of 0 or 1 for debris at the Test of Cure Visit~~
- Percentage of subjects with **individual signs or symptoms with a score of 0 or 1 on each of the scales for pruritus and debris and a score of 0 on each of the scales for fungal elements and pain** ~~the fungal elements at the Test of Cure Visit~~
- ~~Percentage of subjects with a score of 0 for pain at the Test of Cure Visit~~
- **Subject global assessments at Baseline and Test of Cure as well as categorical shifts in the subject global assessment scale scores from the Screening/Baseline to the Test of Cure Visit**
- ~~Percentages of subjects with categorical shifts on the subject global assessment scale from the Screening/Baseline to the Test of Cure Visit~~

### 10.1.3 Other Efficacy Endpoints *(new section)*

*Addition of description of other efficacy endpoints*

### 10.4.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will be defined as all subjects~~ with a clinical diagnosis of otomycosis at Screening/Baseline who received at least one dose of study drug~~**who were randomized and dispensed study medication.**

### 10.4.2 Modified Intent-to-Treat Population

The modified intent-to-treat (MITT) population will be **a subset of** the ~~primary~~**ITT** population~~ for all efficacy analyses and~~ **. The MITT population** will ~~be defined as all~~**include** subjects **who were**

**randomized, dispensed study drug, and** with a clinical diagnosis of otomycosis ~~and~~**confirmed by** a positive fungal culture ~~at Screening/Baseline who received at least one dose of study drug.~~

### 10.4.3 Per Protocol Population

*Revised description of per protocol population including specific criteria*

### 10.4.4 Safety Population

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

### 10.5.1 Efficacy Analysis

The primary population for all efficacy analyses will be the MITT population (see Section 10.4). Efficacy ~~parameters~~**endpoints** will **also** be ~~assessed secondarily~~**summarized** for the PP population **and will be considered supportive**

### 10.5.2 Safety Analysis

*Revised description of safety analysis*

### 10.5.3 Subject Demographics and Baseline Characteristics

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

### 10.5.4 Missing Data

*Addition of description of process for handling missing data*

### 11.1 Institutional Review Board

**….**

**…..**The investigator should also provide the miconazole oil Investigator's Brochure ~~and a copy of the Monistat 1 Consumer Information Leaflet~~ to the IRB.

### 11.6 Case Report Form Requirements

*Revised description of CRFs including addition of eCRFs*

## 13.2 Amendment 2 Version 3 14 June 2017

This amendment changes the inclusion criteria to require subjects to have a score of >0 for the otomycosis sign of fungal elements in each ear to be treated with study drug, in addition to having at least two of the following signs or symptoms of otomycosis in each ear to be treated with study drug: pruritus, >1; debris >1; or pain >0. Clarifications have also been added in multiple places to further emphasize the existing wording contained in Section 4.4 (Subject Discontinuation) indicating that the Test of Cure procedures should be performed for subjects who prematurely discontinue from the study if possible. A clarification has also been added to Section 7.6 to emphasize that if both ears will be treated with study drug, both ears will be cultured.

As summary of changes is provided below. New/changes in text are **bolded**. Deletions are ~~struck through~~.

**Title, Protocol Approval, and Study Acknowledgment Pages:**

Updated to reflect protocol version and date change and to remove the second signature block on the Protocol Approval page

**Section 4.1 Inclusion Criteria**

2. Diagnosis of uncomplicated otomycosis of the external ear only, in the ear(s) that will be treated with study drug, with ~~the subject score for at least two of the signs or symptoms of otomycosis to be elevated, defined as scores of the following (see Section 7.4 for definitions of the scores): pruritus, >1; debris, >1; fungal elements, >0; or pain, >0.~~ **a score for fungal elements of >0 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 at least two of the following signs or symptoms of otomycosis in each ear to be treated with study drug: pruritus, >1; debris, >1; or pain, >0.**

**Table 1 Study Schedule Footnote e**

e. The Test of Cure Visit is scheduled to occur on Day 15 for subjects randomized to the 7-day treatment duration, or on Day 22 for subjects randomized to the 14-day treatment durations**. In case of early termination, the assessments planned for the Test of Cure Visit should be performed if possible**

**Section 6.4 Test of Cure**

This visit may occur up to 1 day sooner or up to 8 days later than the specified day. Subjects randomized to the 7-day group will have the Test of Cure Visit on Day 15, and subjects randomized to the 14-day groups will have the Test of Cure Visit on Day 22.

The following procedures and evaluations will occur during the Test of Cure Visit:

- Otomycosis signs and symptoms
- Subject global assessment
- Microbial (fungal) culture
- 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.**

**Section 7.6 Microbial Culture**

At designated visits, the investigator or designee will obtain a sample from the external ear to be sent to a laboratory for microbial culture (for both fungi and bacteria at the Screening/Baseline visit and for fungi only at the End of Treatment and Test of Cure visits). 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 study drug, both ears will be cultured.**

## 13.3 Amendment 3 Version 4 11 October 2017

This amendment changes and clarifies the exclusion criteria. Exclusion criterion #3 was changed to, "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**," to clarify the type of surgery that will disqualify a subject from the study. Clarification has also been added to Section 4.4 (Subject Discontinuation) to emphasize that the visible presence of fungal elements at Screening/Baseline is required, to be enrolled into the study.

The summary of changes is provided below. New/changes in text are **bolded**. Deletions are ~~struck through~~.

**Header, Title, Protocol Approval, and Study Acknowledgment Pages:**

Updated to reflect protocol version and date change.

**Synopsis**

Key Exclusion Criteria:

…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**…

**Section 3 STUDY DESIGN**

…**While in the study, subjects** ~~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…

**Section 4.2 Exclusion Criteria**

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**

**Section 4.4 Subject Discontinuation**

Due to the time required to obtain fungal culture results from Screening/Baseline, subjects will be enrolled into the study based on a clinical diagnosis of otomycosis **(including the visible presence of fungal elements at Screening/Baseline)**, without a requirement for a positive fungal culture. Subjects who end up with a negative **Screening/Baseline** fungal culture will not be discontinued from the study, but these subjects will not be included in the primary efficacy analysis.

## 13.4 Amendment 4 Version 5 11 May 2018

This amendment increases the number of subjects planned, from 36 to 75. This change is being implemented to account for a lower than planned percentage of subjects who meet both parameters of having a positive fungal culture at Screening/Baseline and completing the Test of Cure visit. This amendment also makes corrections to the Study Schedule (Table 1) and to the description of study procedures to be performed at Screening/Baseline (Section 6.2.1) to indicate that study drug is to be weighed at the Screening/Baseline visit before dispensing study drug to the subject; these corrections are for consistency with the Treatment Compliance section (Section 7.11) which requires the study drug to be weighed by the investigator or designee before dispensation to the subject.

A summary of changes is provided below. New/changes in text are **bolded**. Deletions are ~~struck through~~.

**Header, Title, Protocol Approval, and Study Acknowledgment Pages:**

Updated to reflect protocol version and date change.

**Synopsis**

Number of Subjects Planned

Approximately ~~36~~**75**

Design and Methodology

This study is a randomized, partially masked, multiple-dose, parallel-group design study conducted at up to 10 study centers in the US. Approximately ~~36~~**75** male or female subjects with otomycosis will receive study drug….

**Section 3 STUDY DESIGN**

This study is a randomized, partially masked, multiple-dose, parallel-group design study conducted at up to 10 study centers in the US. Approximately ~~36~~**75** male or female subjects with otomycosis will receive study drug….

**Section 3.1 Number of Subjects**

Approximately ~~36~~**75** eligible subjects are planned to be enrolled in order to achieve approximately 10 subjects per group (randomized in a 1:1:1 ratio to the 7-day active, 14-day active, and 14-day vehicle treatment groups) with a positive fungal culture at baseline and who have completed the Test of Cure Visit.

**Section 4.4 Subject Discontinuation**

Subject discontinuations will be documented clearly on the applicable electronic case report form (eCRF). Subjects who discontinue from the study will not be replaced, but additional subjects may be enrolled and randomized if it appears that approximately ~~36~~**75** subjects is insufficient to meet the sponsor's goal of approximately 10 subjects per group who meet both criteria of having a positive fungal culture at Screening/Baseline and completing the Test of Cure Visit.

**Table 1 Study Schedule**

An "X" has been added to the row "Weighing of study drug" under the "Screening/Baseline/Day 1" column to indicate that study drug is to be weighed at this visit.

**Section 6.2.1 Screening / Baseline**

- Randomization ~~and dispensation of study drug~~
- **Weighing of study drug, followed by** dispensation of study drug **to subject**
- Dispensation of subject diary to subject.

## 13.5 Amendment 5 Version 6 17 April 2019

This amendment contains the inclusion of an interim analysis to ensure that there is a sufficient number of subjects within each group for the primary analysis. A subject's MITT status (specifically positive fungal culture at baseline) is determined only following randomization, which may result in imbalance between treatment groups. Therefore, at least one assessment during the conduct of the study is planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. Once at least 10 MITT subjects have been enrolled in the 7-Day active group, the numbers of MITT subjects in the 14-Day active group and the 14-Day vehicle group will be determined by an unblinded statistician; no persons involved in the day to day conduct of the study will be unblinded. Randomization allocation for future subjects may be adjusted if deemed necessary to achieve minimum number of subjects within each arm. Full details will be provided in the SAP.

A summary of changes is provided below. New/changes in text are **bolded**. Deletions are ~~struck through~~.

**Header, Title, Protocol Approval, and Study Acknowledgment Pages:**

Updated to reflect protocol version and date change.

**Synopsis**

**Design and Methodology**

This study is a randomized, partially masked, multiple-dose, parallel-group design study conducted at up to 10 study centers in the US. Approximately 75 male or female subjects with otomycosis will receive study drug. Subjects will be randomly assigned in a 1:1:1 ratio 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] for 7 or 14 days, or vehicle for 14 days. **During the study it is planned to assess treatment allocation to ensure that there is a sufficient number of subjects within each group for the primary analysis. If deemed necessary, future randomizations may be adjusted.** For subjects assigned to the 14-day treatment duration with either miconazole oil or vehicle, the contents of the study drug will be masked to both the subject and the investigator and study staff (i.e., double-blind), but the treatment duration assigned to each subject (7 or 14 days) will be unmasked to both the subject and the investigator and study staff.

**Interim Treatment Allocation Assessment(s)**

**A subject's MITT status (specifically positive fungal culture at baseline) is determined only following randomization, which may result in imbalance between treatment groups. Therefore, at least one assessment during the conduct of the study is planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. Once at least 10 MITT subjects have been enrolled in the 7-Day active group, the numbers of MITT subjects in the 14-Day active group and the 14-Day vehicle group will be determined by an unblinded statistician; no persons involved in the day to day conduct of the study will be unblinded. Randomization allocation for future subjects may be adjusted if deemed necessary to achieve minimum number of subjects within each arm.**

**List of Abbreviations**

~~MCMC Markov Chain Monte Carlo~~

**LOCF Last Observation Carried Forward**

**Section 3 Study Design**

This study is a randomized, partially masked, multiple-dose, parallel-group design study conducted at up to 10 study centers in the US. Approximately 75 male or female subjects with otomycosis will receive study drug. Subjects will be randomly assigned in a 1:1:1 ratio 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] for 7 or 14 days, or vehicle for 14 days. **Interim assessments are planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. If deemed necessary the randomization ratio may be adjusted following the interim assessments; see Section 10.5.5 for details.** For subjects assigned to the 14-day treatment duration with either miconazole oil or vehicle, the contents of the study drug will be masked to both the subject and the investigator and study staff (i.e., double-blind), but the treatment duration assigned to each subject (7 or 14 days) will be unmasked to both the subject and the investigator and study staff.

**Section 9.2 Randomization**

Subjects will be randomized in a 1:1:1 ratio to one of three groups: 1) 7-day treatment with miconazole oil; 2) 14-day treatment with miconazole oil; or 3) 14-day treatment with miconazole oil vehicle. **Interim assessments are planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. If deemed necessary the randomization ratio may be adjusted following the interim assessments; see Section 10.5.5 for details.**

**Section 10.5.4 Missing Data**

Missing **values from the** Test of Cure **visit** from which the dichotomized Therapeutic Cure is derived will be **imputed using last observation carried forward (LOCF) method.**~~estimated by Markov Chain Monte Carlo (MCMC). The pattern of missing observations in each treatment group cannot influence the missing value estimation in the other because the imputation will be conducted independently for each treatment group.~~

~~Multiple imputation and subsequent summarization will involve 4 principal tasks:~~

~~Calculate the number of missing Test of Cure values to be estimated by MCMC in each treatment group. Let nmiss be the maximum number of missing Test of Cure values among the treatment groups. For each treatment group, create a data set containing subjects with observed values and those needing estimation by MCMC. The missing Therapeutic Cure values in each data set will be filled in using the MCMC method '5 x nmiss' times to generate '5 x nmiss' data sets. The resulting data set for each treatment group will be combined into 1 complete data set for each imputation.~~

~~Syntax (14 day treatment groups) :~~
~~proc mi data=datain out=dataout seed=&seed. nimpute=5xnmiss <options>;~~
~~where trtpn=(2 or 3);~~
~~mcmc chain=multiple;~~
~~var baseline, Day 8, Day 15, Day 22);~~
~~run;~~

~~Syntax (7 day treatment groups) :~~
~~proc mi data=datain out=dataout seed=&seed. nimpute=5xnmiss <options>;~~

~~where trtpn=(1);~~
~~memc chain=multiple;~~
~~var baseline, Day 8, Day 15);~~
~~run;~~

~~For each complete data set, the dichotomous success rate will be computed.~~

~~The results from each complete dataset will be averaged and presented.~~

~~A total of 15 random seeds will be needed to impute Therapeutic Cure for the three treatment groups. Those 15 random seeds have been pre-specified by using a random number generator:~~

~~Culture; Miconazole oil 7-day: Seed=1673675075~~

~~Culture; Miconazole oil 14-day: Seed=1973865476~~

~~Culture; Vehicle 14-day: Seed=1984342934~~

~~Pruritus; Miconazole oil 7-day: Seed= 1032756100~~

~~Pruritus; Miconazole oil 14-day: Seed=548516766~~

~~Pruritus; Vehicle 14-day: Seed= 1352599714~~

~~Debris; Miconazole oil 7-day: Seed=90285723~~

~~Debris; Miconazole oil 14-day: Seed=739430049~~

~~Debris; Vehicle 14-day: Seed=143241952~~

~~Fungal elements; Miconazole oil 7-day: Seed=1177358335~~

~~Fungal elements; Miconazole oil 14-day: Seed=521921209~~

~~Fungal elements; Vehicle 14-day: Seed=131606110~~

~~Pain; Miconazole oil 7-day: Seed=665476352~~

~~Pain; Miconazole oil 14-day: Seed=476181336~~

~~Pain; Vehicle 14-day: Seed=1305387803~~

~~If multiple imputation is impaired due to not sufficient missing data to allow for multiple imputation to be performed, multiple imputation may be performed on the computed endpoint rather than the individual efficacy assessments. If multiple imputation is still not possible, other sensitivity methods may be used such as imputing failure for any missing Therapeutic Cure determinations.~~

### Section 10.5.5 Interim Treatment Allocation Assessment(s)

**A subject's MITT status (specifically positive fungal culture at baseline) is determined only following randomization, which may result in imbalance between treatment groups. Therefore, at least one assessment during the conduct of the study is planned to ensure that there is a sufficient number of subjects within each group for the primary analysis. Once at least 10 MITT subjects have been enrolled in the 7-Day active group, the numbers of MITT subjects in the 14-Day active group and the 14-Day vehicle group will be determined by an unblinded statistician; no persons involved in the day to day conduct of the study will be unblinded. Randomization allocation for future subjects may be adjusted if deemed necessary to achieve minimum number of subjects within each arm.**

**Full details will be provided in the SAP.**