CLINICAL TRIAL PROTOCOL

Study Title:	Randomized, Double-blind, Phase III Study of the Efficacy and Safety of Miconazole Oil versus Vehicle Oil in the Treatment of Otomycosis, Followed by an Open-label Safety Evaluation
Study Number:	MZ-0120-ESP3-052
Study Drug:	Miconazole oil
Sponsor:	Hill Dermaceuticals, Inc. 2650 S. Mellonville Ave Sanford, FL 32773
Protocol Date/Version:	14 September 2020 / Version 4 Previous versions: 28 January 2020 / Version 1 (internal only) 04 February 2020 / Version 2 18 May 2020 / Version 3

PROTOCOL APPROVAL

The following individuals approve the 14 September 2020 version of the MZ-0120-ESP3-052 protocol. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Company:	Hill Dermaceuticals, Inc.
Name:	Rosario G. Ramirez, MD
Title:	Medical 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: 2020.09.14 09:13:42 -04'00'

Signature Date

STUDY ACKNOWLEDGEMENT

Protocol number: MZ-0120-ESP3-052 Version 4

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

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

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

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

_____ _____

Investigator's signature Date

_____

Investigator's printed name

SYNOPSIS

Name of Sponsor/Company: Hill Dermaceuticals, Inc.

Name of Finished Product: Miconazole oil

Name of Active Ingredient: 2% miconazole

Study Title:

Randomized, Double-blind, Phase III Study of the Efficacy and Safety of Miconazole Oil versus Vehicle Oil in the Treatment of Otomycosis, Followed by an Open-label Safety Evaluation

Study Number: MZ-0120-ESP3-052

Study Center(s): Up to 20 study centers in the United States (US)

Number of Subjects Planned:

Approximately 390 (estimated); the actual number enrolled will be the number needed to achieve at least 128 subjects eligible to be included in the modified intent-to-treat (MITT) population, defined as all subjects who were randomized with a positive fungal culture at Screening/Baseline, and to achieve at least 300 subjects exposed to miconazole oil for 14 days who are evaluable for safety. Thus, a higher or lower number than estimated may be enrolled, with enrollment continuing until the required numbers of subjects have been achieved.

Phase of Development: 3

Objectives:

- Confirm the efficacy of miconazole oil compared with vehicle over a 14-day treatment duration in subjects with otomycosis
- Assess the safety of miconazole oil over a 14-day treatment duration

Design and Methodology:

This study will be conducted in 2 portions:

1. Enrollment A, which will consist of 2 treatment periods as follows and will be conducted in subjects with otomycosis:
   a. A randomized, double-blind, parallel-group treatment period. This treatment period will be referred to as the “Randomization Period” and will be followed by:
   b. An optional, open-label treatment period with miconazole oil. This treatment period will be referred to as the “Optional Open-label Extension.”
2. Enrollment B, which will consist of open-label treatment with miconazole oil in subjects who will not be required to have signs and symptoms of otomycosis.

<u>Enrollment A</u>

The study will start with Enrollment A, in which an estimated 220 male or female subjects with otomycosis will receive study drug, although this number may be higher or lower depending on the percentage of subjects eligible to be included in the MITT population. Subjects will be randomly assigned in a 1:1 ratio to receive miconazole oil or vehicle, for 14 days. The study drug will be administered as 5 drops per ear at ~30 mg per drop instilled into the external ear canal of the ear(s) affected by otomycosis.

Randomization Period

During the Randomization Period, both the subject and the investigator and study staff will be blinded as to the contents of the study drug.

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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 aural fullness), and an evaluation of medical history. Urine will be obtained for pregnancy screening in female subjects of childbearing potential. Prior and concomitant medications will be reported. Subjects with positive signs and symptoms of otomycosis and who meet all other eligibility criteria will be entered into the study. A fungal culture of the affected ear(s) will be taken, then debris will be cleaned from the affected ear(s) following the site's normal procedures. The subject will be randomized, and study drug will be weighed and dispensed to the subject along with a subject diary. 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 and to complete the subject diary twice per day as instructed. Subjects will be instructed to avoid getting water in the ear, to consider drying excessive water in the ear by using a blow dryer, and to place a Vaseline-impregnated cotton ball over the affected ear(s) to help keep water out of the ear while bathing or showering.

Subjects will return to the clinic on Day 8 for the On Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis, a cleaning of the affected ear(s) (following the site's normal procedures), a review of the subject diary, and an assessment of AEs and concomitant medications will be performed. Subjects will continue to administer the study drug and to complete the subject diary twice per day, up through Day 14, following the same instructions as provided at the Screening/Baseline Visit on Day 1.

Subjects will return to the clinic on Day 15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture. AEs and concomitant medications will also be assessed, and the subject will return all unused study drug along with the completed subject diary.

Subjects will return to the clinic on Day 22 for the Test of Cure Visit, at which time an assessment of clinical signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture. AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential.

Optional Open-label Extension

Subjects who either complete the Randomization Period of the study (up through the Test of Cure Visit), or who are prematurely discontinued from study treatment during the Randomization Period due to worsening of signs and/or symptoms of otomycosis in the judgment of the investigator, will be offered the opportunity to participate in an optional open-label extension, if they have a visual presence of fungal elements in at least one ear treated during the Randomization Period. Only the ear(s) that were treated in the Randomization

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Period will be potentially eligible for treatment during the Optional Open-label Extension.

All subjects in the Optional Open-label Extension will receive miconazole oil for 14 days. No unblinding of the subject's treatment in the Randomization Period will occur at this time.

Before a subject enters the Optional Open-label Extension, all procedures for the Test of Cure Visit will be completed for that subject; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture.

At the first visit of the Optional Open-label Extension (Day OLE1, which will occur while the subject is already onsite for the Test of Cure or Early Termination Visit from the Randomization Period), study drug (miconazole oil) will be weighed and dispensed to the subject along with a subject diary. Subjects or their caregivers will administer the first dose of miconazole oil at the site. AEs and concomitant medications will then be assessed. Subjects will then continue to administer miconazole oil and to complete the subject diary twice per day for a total of 14 days, following the same instructions as provided at the Screening/Baseline Visit on Day 1.

Subjects will return to the clinic on Day OLE15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis will be performed, as well as an assessment of AEs and concomitant medications. A urine pregnancy test will be performed in women of childbearing potential. The subject will return all unused miconazole oil along with the completed subject diary.

Data for Enrollment A will be unblinded after all subjects planned for Enrollment A have completed both the Randomization Period and the Optional Open-label Extension, so that analyses from Enrollment A can be conducted even if Enrollment B is still ongoing (i.e., before the conclusion of Enrollment B).

<u>Enrollment B</u>

Enrollment B may be initiated while Enrollment A is still actively enrolling subjects. An estimated 170 male or female subjects will receive study drug (miconazole oil) in Enrollment B, although this number may be higher or lower depending on the total number of subjects needed to achieve at least 300 subjects who are exposed to miconazole oil for 14 days in the study overall who are evaluable for safety.

At Screening/Baseline (Day B1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a physical examination 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 who meet all eligibility criteria will be entered into the study. Study drug will be weighed and dispensed to the subject along with a subject diary. The subject will then begin treatment with miconazole oil. In subjects who do not have otomycosis, treatment will be in the left ear if both ears are otherwise eligible; if only one ear is eligible, treatment will be in that ear. In subjects who have otomycosis (i.e., any signs and/or symptoms consistent with a clinical diagnosis of otomycosis in the judgment of the investigator), treatment will preferably be in the ear(s) with otomycosis, provided the ear(s) meet all eligibility criteria. If both ears are judged by the investigator to have otomycosis and both meet all eligibility criteria, both ears may be treated. The subject or caregiver will instill the first dose of miconazole oil at the site, under the

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supervision of the investigator or site personnel. AEs will then be assessed. The subject will then leave the clinic and continue to administer miconazole oil and to complete the subject diary twice per day, following the same instructions for miconazole oil administration as in Enrollment A.

Subjects will return to the clinic on Day B15 for the End of Treatment Visit, at which time AEs and concomitant medications will be assessed. Subjects will return all unused miconazole oil along with the completed subject diary. A urine pregnancy test will be performed in women of childbearing potential.

Timing of Subject Recruitment Into Enrollment A and Enrollment B

The study will start with Enrollment A, which will continue until the sponsor determines that a sufficient number of subjects (see Sample Size below) has been recruited to conduct the planned analyses for Enrollment A, at which time the sponsor (or designee) will notify all study sites to terminate further enrollment into the Enrollment A portion of the study.

Recruitment of subjects into Enrollment B will begin when the sponsor (or designee) notifies sites to begin recruiting subjects into Enrollment B, and will end when the sponsor (or designee) notifies study sites to pause or permanently terminate recruitment of subjects into Enrollment B. Enrollment B may occur over one or multiple time periods, each of which will begin and then pause (or permanently end) upon sponsor (or designee) notification to the study sites. The purpose of this mechanism is to allow concurrent enrollment of Enrollment A and Enrollment B at times (such as during the wintertime) when recruitment into Enrollment A is likely to be diminished due to a lower expected incidence of otomycosis, while also allowing the sponsor the flexibility to pause or permanently terminate recruitment into Enrollment B for reasons including (but not limited to) time periods during which a higher incidence of otomycosis is expected (at which times the sponsor may wish for the focus of the study to be on recruitment of subjects into Enrollment A), or evaluation by the sponsor of the number of subjects still needed for Enrollment B (see Sample Size below).

At times when Enrollment A and Enrollment B are concurrently ongoing, if a subject is found to be eligible for both Enrollment A and Enrollment B, the subject should be enrolled into Enrollment A whenever possible.

Study Visits:

Enrollment A

Randomization Period:

- Day 1: Screening/Baseline (1 visit);
- Day 8: On Treatment (1 visit);
- Day 15: End of Treatment (1 visit);
- Day 22: Test of Cure (1 visit)

Optional Open-label Extension:

- Day OLE1 (which will occur while the subject is already onsite for the Test of Cure or Early Termination Visit for the Randomization Period);
- Day OLE15 (1 visit)

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Enrollment B

- Day B1: Screening/Baseline (1 visit);
- Day B15: End of Treatment (1 visit)

Study Duration:

Enrollment A

During Enrollment A, the study duration for each subject who participates only in the Randomization Period will be up to approximately 31 days, which includes up to 1 day for screening (if screening procedures need to be initiated the day before treatment), 14 days of treatment, and 8 days of follow-up, plus a visit window of up to 8 additional days after the scheduled day for the follow-up (Test of Cure) Visit.

The study duration for each subject who participates in both the Randomization Period and the Optional Open-label Extension will be up to approximately 48 days, which includes up to 31 days for the Randomization Period followed by up to 17 days for the Optional Open-label Extension (which includes a visit window of up to 3 additional days after the 14-day treatment to complete the final study visit). This study duration takes into account that the Day OLE1 procedures will occur while the subject is already onsite for the Test of Cure or Early Termination Visit for the Randomization Period.

Enrollment B

In Enrollment B, the study duration for each subject will be up to 19 days, which includes up to 1 day for screening (if screening procedures need to be initiated the day before treatment), 14 days of treatment, and a 1-day final study visit after the 14-day treatment (which has a visit window of up to 3 additional days).

Efficacy Evaluations:

- Clinical signs and symptoms of otomycosis (pruritus; debris; presence of fungal elements; aural fullness)
- Fungal culture

Safety Evaluations:

- AEs

Key Inclusion Criteria:

Enrollment A

Male or non-pregnant, non-lactating females with a clinical diagnosis of uncomplicated otomycosis of the external ear only, with an intact tympanic membrane in the ear(s) to be treated with study drug, 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.

Enrollment B

Male or non-pregnant, non-lactating females with an intact tympanic membrane in the ear(s) to be treated with study drug, who are in general good health as determined by medical examination and medical history, and who are free of clinically significant disease, including

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diabetes mellitus, that is not well-controlled or that could interfere with the study, will be included in the study.
Key Exclusion Criteria: Enrollment A Subjects with any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis or with safety evaluations, 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, in the ear(s) that will be treated with study drug, 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; otomycosis that has been unresponsive to previous antifungal treatment; known hypersensitivity to any of the components in the test formulation; and/or participation in another investigative trial within 28 days of study entry will be excluded from the study. Enrollment B Subjects with any other dermatoses or conditions of the ear that may interfere with safety evaluations, 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; systemic antifungal therapy or warfarin within 28 days of study entry; fever of ≥100°F at study entry; known hypersensitivity to any of the components in the test formulation; and/or participation in another investigative trial within 28 days of study entry will be excluded from the study.
Test Product, Dose, and Mode of Administration: Miconazole oil Active ingredient: 2% miconazole Other ingredients: refined peanut oil, mineral oil, oleth-2, and isopropyl myristate Mode of administration: subjects will be seated and then instructed to tilt their heads so that the affected ear is facing up. The subject or caregiver will then gently pull the ear lobe backward and upward and apply 5 drops of miconazole oil into the ear. The subject will be instructed to keep the head tilted with the ear facing up for approximately 3 to 5 minutes to allow the miconazole oil to penetrate lower into the ear canal. If both ears are being treated, the process will then be repeated for the other ear after a 5-minute wait.

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Reference Product, Dose, and Mode of Administration (Enrollment A Only):
Vehicle oil

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.

Endpoints:

Primary Efficacy Endpoint

- Percentage of subjects with "therapeutic cure," defined as "mycological cure" plus "clinical cure" at the Test of Cure Visit. Mycological cure is defined as a negative mycological culture, and clinical cure is defined as the absence of all otomycosis signs and symptoms according to the scales for each individual sign or symptom.

Secondary Efficacy Endpoints

- Percentage of subjects with mycological cure at the Test of Cure Visit.
- Percentage of subjects with clinical cure at the Test of Cure Visit.

Tertiary Efficacy Endpoints

- Percentage of subjects with "modified therapeutic cure" at the Test of Cure Visit, defined as mycological cure plus a score of 0 for the clinical sign of fungal elements plus a score of 0 or 1 for each of the clinical signs and symptoms of pruritus, debris, and aural fullness.
- Percentage of subjects with "therapeutic improvement" at the Test of Cure Visit, defined as mycological cure plus a score of 0 or 1 for each of the clinical signs and symptoms of fungal elements, pruritus, debris, and aural fullness.

Safety Endpoint

- Percentage of subjects with treatment-emergent adverse events (TEAEs).

Statistical Analyses:

Descriptive statistics will be presented for the percentages of subjects by treatment group with therapeutic cure, mycological cure, and clinical cure in the study ear at each evaluation. Descriptive statistics will also be presented for the percentages of subjects by treatment group with success at each secondary and tertiary endpoint, and for each sign or symptom of otomycosis in the study ear at each evaluation. Descriptive statistics will include the number and percentage of subjects in each category.

In Enrollment A 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.

For the primary efficacy endpoint, percentages of subjects with therapeutic cure at the Test of Cure Visit will be compared using a chi-square test with a 2-sided significance level of 0.05. Comparisons will be conducted in a similar manner between the miconazole oil and vehicle oil

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groups for the secondary endpoints of clinical cure and mycological cure. Missing data will be imputed as treatment failures for the primary and secondary efficacy analyses; missing data otherwise will not be imputed.

The primary population for efficacy analyses will be the MITT population, defined as all subjects who were randomized with a positive fungal culture at Screening/Baseline.

Two safety populations will be used for safety analyses. The first will be the Randomization Period safety population, defined as all subjects who received at least one dose of study drug and had at least one post-Baseline safety assessment during the Randomization Period; this population will be used for safety data for the Randomization Period. The second will be the Open Label safety population, defined as all subjects who received at least one dose of miconazole oil and had at least one post-Baseline safety assessment during the Optional Open-label Extension or Enrollment B; this population will be used for safety data for the Optional Open-label Extension and Enrollment B.

All AEs occurring during the study will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported TEAEs, defined as any AE with an onset on or after the date of first study drug application, will be summarized. 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 serious AEs (SAEs) will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug. Descriptive statistics will be presented for all safety data.

Sample Size:

For the Randomization Period of Enrollment A, approximately 128 subjects (~64 in each group) are required to provide 80% power, using a chi-square test with a 2-sided significance level of 0.05, assuming a response rate for the primary efficacy endpoint of 25.0% in the miconazole oil group and 7.1% in the vehicle oil group.

The sample size of 220 subjects for Enrollment A assumes that ~58% of subjects enrolled into Enrollment A will have a positive fungal culture at Screening/Baseline and will therefore be included in the MITT population. This number may be higher or lower depending on the percentage of subjects eligible to be included in the MITT population.

The overall study sample size of ~390 subjects is the total number of study subjects estimated to achieve at least 300 subjects exposed to miconazole oil for 14 days who are evaluable for safety. A higher or lower number of total subjects may be enrolled in order to achieve the required total numbers of subjects for each of Enrollment A and Enrollment B.

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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
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MITT	Modified intent-to-treat
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over the counter
PP	Per protocol
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
US	United States

1 INTRODUCTION

1.1 Background

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

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

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

The mechanisms of action of miconazole against fungi in general appear to be applicable to fungi associated with otomycosis. Data from a recently-completed Phase 2 study of the investigational product (2% miconazole oil; Hill Dermaceuticals, Inc. Study HD-MCZ-PHII-DRF062016) demonstrated 25.0% of subjects with therapeutic cure, defined as a negative fungal culture plus the absence of each of the otomycosis signs and symptoms of pruritus, debris, fungal elements, and pain, compared with 7.1% of subjects treated with control product (vehicle oil), at the final test of cure study visit, following a 14-day treatment regimen. The percentage of subjects with therapeutic cure following a 7-day treatment regimen was 8.3%, supporting the 14-day treatment duration for miconazole.

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

Adverse event (AE) data from the recently-completed Phase 2 study of the investigational study support the acceptable safety of miconazole oil and generally demonstrated a lower percentage of patients with treatment-emergent AEs (TEAEs) in each of the miconazole oil groups (which were treated for either 7 or 14 days) compared with the vehicle oil group (which was treated for 14 days). The most frequently reported TEAEs in the 14-day miconazole oil group in the Phase 2 study were application site pruritus, application site pain, and ear infection fungal (Table 1). In each case except for ear infection fungal, a higher percentage of subjects in the 14-day vehicle oil group compared with the 14-day miconazole oil group reported the TEAE. Similar results were observed for the 7-day miconazole oil group, although a higher percentage of subjects in the 7-day miconazole oil group had the TEAE of application site infection compared with the 14-day miconazole oil and 14-day vehicle oil groups.

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

System Organ Class Preferred Term	Study Group		
	7-Day Miconazole Oil (N=23) n (%)	14-Day Miconazole Oil (N=22) n (%)	14-Day Vehicle Oil (N=20) n (%)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	4 (20.0)
Ear pain	0 (0.0)	0 (0.0)	2 (10.0)
Tympanic membrane perforation	0 (0.0)	0 (0.0)	2 (10.0)
General disorders and administration site conditions	4 (17.4)	6 (27.3)	9 (45.0)
Application site pain	1 (4.3)	2 (9.1)	5 (25.0)
Application site pruritus	3 (13.0)	4 (18.2)	6 (30.0)
Infections and infestations	4 (17.4)	3 (13.6)	2 (10.0)
Application site infection	2 (8.7)	0 (0.0)	0 (0.0)
Ear infection fungal	1 (4.3)	2 (9.1)	1 (5.0)

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

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

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

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

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

1.2 Study Purpose

The purpose of this study is to gather confirmatory data on the efficacy and safety of 2% miconazole oil after topical otic administration in subjects with otomycosis. During the Randomization Period of the Enrollment A portion of the study, a 14-day regimen of twice-daily administration of 2% miconazole oil will be compared with the same treatment regimen using the product vehicle. During the Optional Open-label Extension of the Enrollment A portion and the Enrollment B portion of the study, a 14-day regimen of twice-daily administration of 2% miconazole oil will be administered in an open-label fashion in order to gather safety information in additional subjects.

1.3 Inclusion of Subjects with Peanut Allergy

Miconazole oil contains refined peanut oil. Inclusion in this study of subjects with peanut allergy is justified by studies and publications documenting safe use of the refined peanut oil, as well as 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.

1.4 Compliance with Good Clinical Practice

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

2 STUDY OBJECTIVES

The objectives of the study are to:

- Confirm the efficacy of miconazole oil compared with vehicle over a 14-day treatment duration in subjects with otomycosis
- Assess the safety of miconazole oil over a 14-day treatment duration

3 STUDY DESIGN

This study will be conducted in 2 portions (see also Figure 1 for a schematic diagram of the study design):

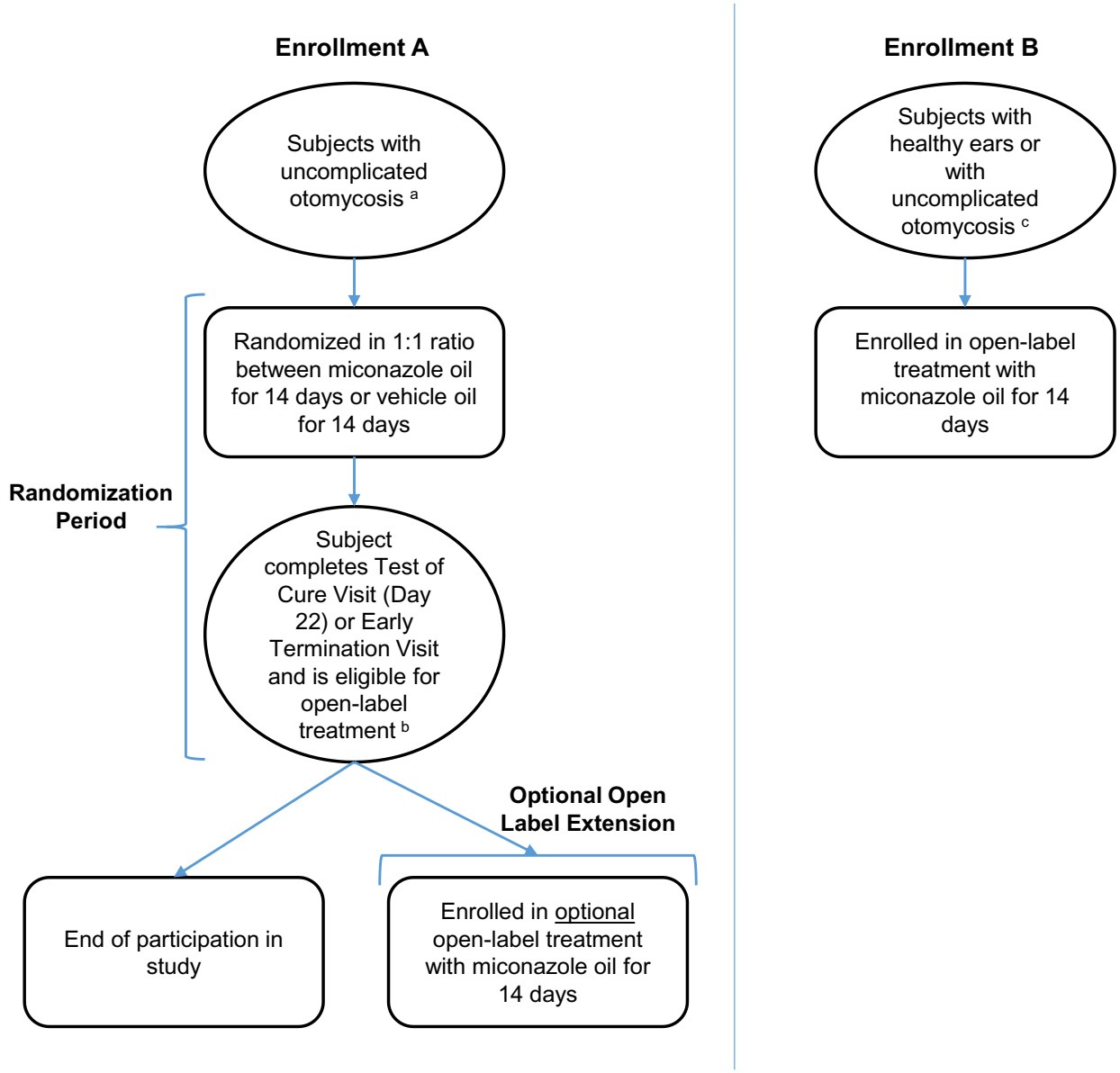
1. Enrollment A, which will consist of 2 treatment periods as follows and will be conducted in subjects with otomycosis:

    a. A randomized, double-blind, parallel-group treatment period. This treatment period will be referred to as the "Randomization Period" and will be followed by:

    b. An optional, open-label treatment period with miconazole oil. This treatment period will be referred to as the "Optional Open-label Extension."

2. Enrollment B, which will consist of open-label treatment with miconazole oil in subjects who will not be required to have signs and symptoms of otomycosis.

Figure 1: Diagram of Study Design



a. Subjects must meet all eligibility criteria in Section 4.1 to be randomized in Enrollment A.
b. Subject must have a visual presence of fungal elements to be enrolled in the Optional Open-label Extension.
c. Subject must meet all eligibility criteria in Section 4.2 to receive treatment with miconazole oil in Enrollment B.

3.1 Enrollment A

The study will start with Enrollment A, in which an estimated 220 male or female subjects with otomycosis will receive study drug, although this number may be higher or lower depending on the percentage of subjects eligible to be included in the modified intent-to-treat (MITT) population (see Section 10.4.2). Subjects will be randomly assigned in a 1:1 ratio to receive miconazole oil or vehicle, for 14 days. The study drug will be administered as 5 drops per ear at ~30 mg per drop instilled into the external ear canal of the ear(s) affected by otomycosis.

3.1.1 Randomization Period

During the Randomization Period, both the subject and the investigator and study staff will be blinded as to the contents of the study drug.

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

Subjects will return to the clinic on Day 8 for the On Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis, a cleaning of the affected ear(s) (following the site's normal procedures), a review of the subject diary, and an assessment of AEs and concomitant medications will be performed. Subjects will continue to administer the study drug and to complete the subject diary twice per day, up through Day 14, following the same instructions as provided at the Screening/Baseline Visit on Day 1.

Subjects will return to the clinic on Day 15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture. AEs and concomitant medications will also be assessed, and the subject will return all unused study drug along with the completed subject diary.

Subjects will return to the clinic on Day 22 for the Test of Cure Visit, at which time an assessment of clinical signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture. 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), and assessments of clinical signs and symptoms of otomycosis. In cases of bilateral otomycosis, both ears will be treated and evaluated by the investigator, but only 1 ear will be used as the study ear for efficacy analyses, the designation of which will be performed at the end of the study in accordance with the following. If only 1 ear has a positive fungal culture at Screening/Baseline, that ear will be used as the study ear for efficacy analyses. If both ears have a positive fungal culture at Screening/Baseline, the ear with the worse infection at Screening/Baseline, as assessed by the investigator by taking into account the clinical signs and symptoms of otomycosis, will be used as the study ear for efficacy analyses. If both ears have a positive fungal culture and 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.

3.1.2 Optional Open-label Extension

Subjects who either complete the Randomization Period of the study (up through the Test of Cure Visit), or who are prematurely discontinued from study treatment during the Randomization Period due to worsening of signs and/or symptoms of otomycosis in the judgment of the investigator, will be offered the opportunity to participate in an optional open-label extension, if they have a visual presence of fungal elements in at least one ear treated during the Randomization Period. Only the ear(s) that were treated in the Randomization Period will be potentially eligible for treatment during the Optional Open-label Extension.

All subjects in the Optional Open-label Extension will receive miconazole oil for 14 days. No unblinding of the subject's treatment in the Randomization Period will occur at this time.

Before a subject enters the Optional Open-label Extension, all procedures for the Test of Cure Visit will be completed for that subject; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture.

At the first visit of the Optional Open-label Extension (Day OLE1, which will occur while the subject is already onsite for the Test of Cure or Early Termination Visit from the Randomization Period), study drug (miconazole oil) will be weighed and dispensed to the subject along with a subject diary. Subjects or their caregivers will administer the first dose of miconazole oil at the site. AEs and concomitant medications will then be assessed. Subjects will then continue to administer miconazole oil and to complete the subject diary twice per day for a total of 14 days, following the same instructions as provided at the Screening/Baseline Visit on Day 1.

Subjects will return to the clinic on Day OLE15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis will be performed, as well as an assessment of AEs and concomitant medications. A urine pregnancy test will be performed in women of childbearing potential. The subject will return all unused miconazole oil along with the completed subject diary.

The purpose of the Optional Open-label Extension is safety and to provide supportive evidence of efficacy. Efficacy assessments will include assessments of clinical signs and symptoms of otomycosis. Safety assessments will include AEs.

3.1.3 Timing of Analysis for Enrollment A

Data for Enrollment A will be unblinded after all subjects planned for Enrollment A have completed both the Randomization Period and the Optional Open-label Extension, so that analyses from Enrollment A can be conducted even if Enrollment B is still ongoing (i.e., before the conclusion of Enrollment B).

3.2 Enrollment B

Enrollment B may be initiated while Enrollment A is still actively enrolling subjects. An estimated 170 male or female subjects will receive study drug (miconazole oil) in Enrollment B, although this number may be higher or lower depending on the total number of subjects needed to achieve at least 300 subjects who are exposed to miconazole oil for 14 days in the study overall who are evaluable for safety.

At Screening/Baseline (Day B1), potentially eligible subjects will provide informed consent, and subjects will undergo screening evaluations to include a physical examination 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 who meet all eligibility criteria will be entered into the study. Study drug will be weighed and dispensed to the subject along with a subject diary. The subject will then begin treatment with miconazole oil. In subjects who do not have otomycosis, treatment will be in the left ear if both ears are otherwise eligible; if only one ear is eligible, treatment will be in that ear. In subjects who have otomycosis (i.e., any signs and/or symptoms consistent with a clinical diagnosis of otomycosis in the judgment of the investigator), treatment will preferably be in the ear(s) with otomycosis, provided the ear(s) meet all eligibility criteria. If both ears are judged by the investigator to have otomycosis and both meet all eligibility criteria, both ears may be treated. The subject or caregiver will instill the first dose of miconazole oil at the site, under the supervision of the investigator or site personnel. AEs will then be assessed. The subject will then leave the clinic and continue to administer miconazole oil and to complete the subject diary twice per day, following the same instructions for miconazole oil administration as in Enrollment A.

Subjects will return to the clinic on Day B15 for the End of Treatment Visit, at which time AEs and concomitant medications will be assessed. Subjects will return all unused miconazole oil along with the completed subject diary. A urine pregnancy test will be performed in women of childbearing potential.

Safety assessments will include AEs.

3.3 Timing of Subject Recruitment Into Enrollment A and Enrollment B

The study will start with Enrollment A, which will continue until the sponsor determines that a sufficient number of subjects (see Section 3.4) has been recruited to conduct the planned

analyses for Enrollment A, at which time the sponsor (or designee) will notify all study sites to terminate further enrollment into the Enrollment A portion of the study.

Recruitment of subjects into Enrollment B will begin when the sponsor (or designee) notifies sites to begin recruiting subjects into Enrollment B, and will end when the sponsor (or designee) notifies study sites to pause or permanently terminate recruitment of subjects into Enrollment B. Enrollment B may occur over one or multiple time periods, each of which will begin and then pause (or permanently end) upon sponsor (or designee) notification to the study sites. The purpose of this mechanism is to allow concurrent enrollment of Enrollment A and Enrollment B at times (such as during the wintertime) when recruitment into Enrollment A is likely to be diminished due to a lower expected incidence of otomycosis, while also allowing the sponsor the flexibility to pause or permanently terminate recruitment into Enrollment B for reasons including (but not limited to) time periods during which a higher incidence of otomycosis is expected (at which times the sponsor may wish for the focus of the study to be on recruitment of subjects into Enrollment A), or evaluation by the sponsor of the number of subjects still needed for Enrollment B (see Section 3.4).

At times when Enrollment A and Enrollment B are concurrently ongoing, if a subject is found to be eligible for both Enrollment A and Enrollment B, the subject should be enrolled into Enrollment A whenever possible.

3.4 Number of Subjects

Approximately 390 total subjects are estimated to be enrolled into the study (~220 subjects estimated for Enrollment A and ~170 subjects estimated for Enrollment B) as described in Section 3.4.1 for Enrollment A and in Section 3.4.2 for Enrollment B.

3.4.1 Enrollment A

An estimated 220 eligible subjects are planned to be enrolled in Enrollment A in order to achieve at least 128 evaluable subjects (i.e., included in the MITT population, defined as those who were randomized with a positive fungal culture at Screening/Baseline). The number of subjects who are enrolled may be higher or lower than 220 depending on the percentage of subjects eligible to be included in the MITT population; enrollment in Enrollment A will continue until the required numbers of subjects have been achieved.

3.4.2 Enrollment B

An estimated 170 eligible subjects are planned to be enrolled in order to achieve at least 300 total subjects in the study (including both Enrollment A and Enrollment B) who are exposed to miconazole oil for 14 days who are evaluable for safety. This number has been estimated on the basis of the following assumptions:

- A total of 220 subjects will be enrolled into the Randomization Period of Enrollment A, with 110 subjects exposed to active treatment with miconazole oil (on the basis of the 1:1 randomization for the Randomization Period), and 110 subjects exposed to the vehicle treatment:

  - Of the 110 subjects exposed to active treatment (miconazole oil) in the Randomization Period, ~90% (100 subjects) will complete the full 14 days of treatment, with the remaining ~10% (10 subjects) completing less than the 14-day treatment course
  - Of the 110 subjects exposed to vehicle treatment in the Randomization Period, ~50% (55 subjects) will opt to participate in the Optional Open-label Extension of Enrollment A, with the other ~50% (55 subjects) concluding participation in the study
- Of the 55 subjects exposed to miconazole oil treatment in the Optional Open-label Extension, ~90% (50 subjects) will complete the full 14 days of treatment, with the remaining ~10% (5 subjects) completing less than the 14-day treatment course
- On the basis of these assumptions, ~150 subjects will have been exposed to miconazole oil for the full 14-day treatment during Enrollment A (100 subjects during the Randomization Period and 50 subjects during the Optional Open-label Extension), and an additional ~150 subjects exposed to miconazole oil for the full 14-day treatment will be needed to achieve the ≥300 total subjects required to be exposed to miconazole oil for the full 14-day treatment
- Assuming ~90% of subjects enrolled into Enrollment B complete the full 14 days of open-label treatment with miconazole oil, ~170 subjects will be required to be enrolled in Enrollment B in order to achieve ~150 subjects who complete the full 14-day treatment with miconazole oil
- Therefore, ~150 subjects from Enrollment A and ~150 subjects from Enrollment B are estimated to be needed for at least 300 total subjects in the study who are exposed to miconazole oil for a full 14 days.

The actual number of subjects enrolled into Enrollment B may therefore be higher or lower than 170 depending on the accuracy of the assumptions as stated above, including the number of subjects who have completed a full 14 days of treatment with miconazole oil in Enrollment A as well as in Enrollment B. Enrollment will continue into Enrollment B until the required number of subjects exposed to miconazole oil for 14 days and evaluable for safety has been achieved.

3.5 Investigators

The study will be conducted at up to 20 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.

3.6 Study Duration

3.6.1 Enrollment A

A diagram of the study duration for each subject participating in Enrollment A is presented in Figure 2.

During Enrollment A, the study duration for a subject who participates only in the Randomization Period of the study will be up to 31 days, which includes up to 1 day for screening (if screening procedures need to be initiated the day before treatment), 14 days for 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 Test of Cure Visit.

The study duration for each subject who participates in both the Randomization Period and Optional Open-label Extension will be up to approximately 48 days, which includes up to 31 days for the Randomization Period followed by up to 17 days for the Optional Open-label Extension (which includes a visit window of up to 3 additional days after the 14-day treatment to complete the final study visit). This study duration takes into account that the Day OLE1 procedures will occur while the subject is already onsite for the Test of Cure or Early Termination Visit for the Randomization Period.

Figure 2: Diagram of Study Duration for Enrollment A

Cumulative Days on Study	Randomization Period of Enrollment A: First and Last Day when Each Study Visit May Occur		Randomization Period of Enrollment A: On-Treatment Days	Optional Open-Label Extension of Enrollment A: First and Last Day when Each Study Visit May Occur		Optional Open-Label Extension of Enrollment A: On-Treatment Days
1	**Screening / Baseline (Day 1)**	*May occur over 2 days*	Day 1			
2			Day 2			
3			Day 3			
4			Day 4			
5			Day 5			
6			Day 6			
7			Day 7			
8			Day 8			
9	**On Treatment (Day 8) Visit Window**	*First allowable day*	Day 9			
10			Day 10			
11			Day 11			
12		*Last allowable day*	Day 12			
13			Day 13			
14			Day 14			
15						
16	**End of Treatment (Day 15) Visit Window**	*First allowable day*				
17						
18						
19		*Last allowable day*				
20						
21						
22						
23	**Test of Cure (Day 22) Visit Window**	*First allowable day*				
24						
25						
26						
27						
28						
29						
30						
31		*Last allowable day*		**Day OLE1**	*must occur*	Day 1
32						Day 2
33						Day 3
34						Day 4
35						Day 5
36						Day 6
37						Day 7
38						Day 8
39						Day 9
40						Day 10
41						Day 11
42						Day 12
43						Day 13
44						Day 14
45				**End of Treatment (Day OLE15) Visit Window**	*First allowable day*	
46						
47						
48					*Last allowable day*	

3.6.2 Enrollment B

A diagram of the study duration for each subject participating in Enrollment B is presented in Figure 3.

In Enrollment B, the study duration for each subject will be up to 19 days, which includes up to 1 day for screening (if screening procedures need to be initiated the day before treatment), 14 days of treatment, and a 1-day final study visit after the 14-day treatment (which has a visit window of up to 3 additional days).

Figure 3: Diagram of Study Duration for Enrollment B

Cumulative Days on Study	Enrollment B: First and Last Day when Each Study Visit May Occur		On-Treatment Days
1	**Day B1 Visit Window**	*May occur over 2 days*	
2			Day 1
3			Day 2
4			Day 3
5			Day 4
6			Day 5
7			Day 6
8			Day 7
9			Day 8
10			Day 9
11			Day 10
12			Day 11
13			Day 12
14			Day 13
15			Day 14
16	**End of Treatment (Day B15) Visit Window**	*First allowable day*	
17			
18			
19		*Last allowable day*	

4 STUDY SUBJECTS

4.1 Enrollment A

4.1.1 Inclusion Criteria

In order to be eligible for Enrollment A, 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 aural fullness, >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.

4.1.2 Exclusion Criteria

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

1. Any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis or with safety evaluations, including concomitant otic infections (including bacterial infection) other than otomycosis 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, in the ear(s) that will be treated with study drug, of any topical medicated treatments for otomycosis within 14 days of study entry:

- Topical corticosteroids prescribed specifically for the treatment of otomycosis are prohibited to be used within 14 days of study entry; however, use of topical corticosteroids for any other reason (e.g., for bacterial otitis externa and/or for control of symptoms in the ear such as itching and/or pain) will not require a 14-day washout
- Alcohol and/or peroxide are prohibited when prescribed/used by a health care provider specifically for the treatment of otomycosis within 14 days of study entry; however, use of these substances for other purposes (e.g., as a drying agent) will not require a 14-day washout
- Use of boric acid for any reason is prohibited 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. 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
10. Participation in the sponsor's previous miconazole oil Study HD-MCZ-PHII-DRF062016 unless the subject was enrolled into either the vehicle or the 7-day miconazole oil group of that study.

4.2 Enrollment B

4.2.1 Inclusion Criteria

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

1. Male or non-pregnant, non-lactating females
2. Presence or absence of uncomplicated otomycosis of the external ear only, with otomycosis defined as the presence of any signs and/or symptoms consistent with a clinical diagnosis of otomycosis in the judgment of the investigator
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 final study visit. 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. In subjects who do not have otomycosis, treatment will be in the left ear if both ears are otherwise eligible. In subjects who have otomycosis, treatment will be in the ear(s) with otomycosis, provided the ear(s) meets all eligibility criteria. If both ears are judged by the investigator to have otomycosis and both meet all eligibility criteria, both ears may be treated.

4.2.2 Exclusion Criteria

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

1. Any other dermatoses or conditions of the ear that may interfere with safety evaluations, including concomitant otic infections (including bacterial infection) other than otomycosis 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 systemic antifungal therapy or warfarin within 28 days of study entry
5. Fever of ≥100°F at study entry
6. Known hypersensitivity to any of the components in the test formulation
7. Participation in another investigative trial within 28 days of study entry
8. Participation in the sponsor's previous miconazole oil Study HD-MCZ-PHII-DRF062016 unless the subject was enrolled into either the vehicle or the 7-day miconazole oil group of that study
9. Previous participation in Enrollment A of this study, unless the subject is known never to received active treatment (miconazole oil) during Enrollment A.

4.3 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
- For subjects participating in Enrollment A, a negative fungal culture at Screening/Baseline (as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal cultures)

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 (Randomization Period) or the End of Treatment Visit (Optional Open-label Extension or Enrollment B) should be performed, and an effort should be made to collect all study drug. A fungal culture is not required for subjects who are prematurely discontinued from the study.

For Enrollment A, 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 are not required to be discontinued from the study, but these subjects will not be included in the primary efficacy analysis. Because the sponsor's goal is to have at least 128 subjects in the MITT population (see Section 10.4.2), the total number of subjects enrolled into Enrollment A may be higher or lower than 220, depending on the percentage of subjects who are eligible to be included in the MITT population.

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 into Enrollment A if it appears that the estimated number of subjects for Enrollment A (approximately 220) is insufficient to meet the sponsor's goal of having at least 128 subjects in the MITT population. After completion of Enrollment A, additional subjects (i.e., exceeding the 390 subjects total for the study) may be enrolled into Enrollment B if it appears that the estimated total number of study subjects is insufficient to achieve at least 300 subjects who have been exposed to miconazole oil for 14 days who are evaluable for safety.

4.4 Subjects Lost to Follow-up

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

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

5 CONCOMITANT THERAPIES

All concomitant therapies must be recorded on the eCRF.

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

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

5.1 Enrollment A

In addition to all concomitant therapies, all therapies within 3 months prior to Day 1 must also be recorded on the eCRF.

5.1.1 Permitted Medications

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

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

5.1.2 Prohibited Medications

Other than the study drug, no other topical medications (including but not limited to antibiotics, alcohol, boric acid, peroxide, and/or corticosteroids) are allowed to be used in the ear(s) being treated with study drug. Other prohibited treatments include systemic antifungal therapy, warfarin, immunosuppressive or immune-stimulating drugs, and systemic steroids. A subject who discontinues study drug during the Randomization Period and who subsequently uses a topical corticosteroid (e.g., to treat an AE such as itching) in the ear(s) that were treated with study drug during the Randomization Period will be eligible for the Optional Open-label Extension if the topical corticosteroid is discontinued in the ear(s) that will be treated with study drug before the start of study drug in the Optional Open-label Extension, and as long as the subject meets all other eligibility criteria for the Optional Open-label Extension.

5.2 Enrollment B

In addition to all concomitant therapies, all therapies within 28 days prior to Day B1 must also be recorded on the eCRF.

5.2.1 Permitted Medications

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

Oral analgesic medications such as NSAIDs or acetaminophen are permitted.

5.2.2 Prohibited Medications

Prohibited treatments include systemic antifungal therapy and warfarin.

6 STUDY SCHEDULE

6.1 Enrollment A

6.1.1 Study Flow Chart

The study schedule for Enrollment A is presented in Table 3.

Table 3 Study Schedule: Enrollment A

Evaluations and Procedures:	Randomization Period				Optional OLE	
	Screen/ Baseline[a] Day 1	On Treat[b] Day 8	End of Treat[b] Day 15	Test of Cure[c] Day 22[d]	Start of Treat Day OLE1[e]	End of Treat Day OLE15[b]
Informed consent/assent	X					
Inclusion/exclusion criteria	X					
Medical/medication history	X					
Physical examination	X					
Otomycosis signs and symptoms	X	X	X	X		X
Urine pregnancy test[f]	X			X		X
Randomization	X					
Dispensation of study drug	X				X	
Dispensation of subject diary	X				X	
Collection of subject diary		X[g]	X			X
Administration of study drug at site	X				X	
Weighing of study drug	X	X	X		X	X
Collection of study drug			X			X
Fungal culture[h]	X		X	X		
Ear cleaning	X	X				
AE evaluations	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X

a. Procedures for this visit may occur over a 2-day period, if necessary (with Day 1 defined as the first day on which study drug is administered). All procedures for this visit must occur before the first administration of study drug with the exceptions that AE evaluations and review of concomitant medications will also occur after the start of study drug on Day 1.
b. This visit may occur up to 3 days later than the specified day.
c. This visit may occur up to 1 day sooner or up to 8 days later than the specified day.
d. In case of early termination, the assessments planned for the Test of Cure Visit should be performed with the exception of fungal culture, which is not required.
e. This visit will occur on the same day as the final visit of the Randomization Period.
f. Females of childbearing potential only.
g. The subject diary will be returned to the subject after review by study staff for documentation of missed and/or extra study drug doses.
h. Samples will be used for growth and identification of fungal organisms as well as susceptibility testing to miconazole. Fungal cultures are not required to be taken at Day 15 or at Day 22 for subjects known to have a negative fungal culture at Screening/Baseline (assessed after at least 14 days of incubation by the clinical laboratory performing the fungal cultures).

OLE=Open-label Extension; Screen=Screening; Treat=Treatment

6.1.2 Study Visits for the Randomization Period

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 for Enrollment A is presented in Table 3. Details about study procedures and how they are to be performed are presented in Section 7.

6.1.2.1 Screening / Baseline (Day 1)

This visit may be performed over a period of 2 days if necessary for practical reasons (e.g., if study drug cannot reasonably be dispensed until the day after screening procedures are initiated).

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:

- Fungal culture
- 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
- Subjects will be instructed to continue administering study drug and to complete the subject diary twice daily and to bring their bottle of study drug and the diary to the site for their next visit

6.1.2.2 On Treatment (Day 8)

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

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 this visit:

- Otomycosis signs and symptoms

- 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 and return of the subject diary to the subject
- Subjects will be instructed to continue administering study drug and to complete the subject diary twice daily up through Day 14, and to bring their bottle of study drug and the diary to the site for their next visit

6.1.2.3 End of Treatment (Day 15)

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

The following procedures and evaluations will occur during this visit:

- Otomycosis signs and symptoms
- Fungal culture (not required for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture)
- AE evaluation
- Review of concomitant medications
- Collection and review of subject diary
- Collection/weighing of study drug

6.1.2.4 Test of Cure (Day 22)

This visit may occur up to 1 day sooner or up to 8 days later than the specified day.

The following procedures and evaluations will occur during this visit:

- Otomycosis signs and symptoms
- Fungal culture (not required for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture)
- AE evaluation
- Review of concomitant medications
- Urine pregnancy test (in female subjects of childbearing potential only)

In case of early termination from the Randomization Period, the procedures planned for the Test of Cure Visit with the exception of fungal culture should be performed.

Subjects who complete the Test of Cure Visit and who have a visual presence of fungal elements in at least one ear treated during the Randomization Period will be offered the opportunity to participate in the Optional Open-label Extension.

6.1.3 Study Visits for the Optional Open-label Extension

6.1.3.1 Start of Treatment (Day OLE1)

For subjects who opt to participate in the Optional Open-label Extension, this visit will occur on the same day as the final visit of the Randomization Period.

The following procedures and evaluations will occur during this visit:

- Weighing of study drug (miconazole oil), followed by dispensation to subject
- Dispensation of subject diary to subject
- Administration of the first dose of miconazole oil 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 miconazole oil
- Subjects will be instructed to continue administering miconazole oil and to complete the subject diary twice daily for 14 days (i.e., up through Day OLE14) and to bring their bottle of miconazole oil and the diary to the site for their next visit

6.1.3.2 End of Treatment (Day OLE15)

For subjects who opt to participate in the Optional Open-label Extension, this visit may occur up to 3 days later than the specified day.

The following procedures and evaluations will occur during this visit:

- Otomycosis signs and symptoms
- AE evaluation
- Review of concomitant medications
- Collection and review of subject diary
- Collection/weighing of miconazole oil
- Urine pregnancy test (in female subjects of childbearing potential only)

In case of early termination from the Optional Open-label Extension, the procedures planned for the Day OLE15 Visit should be performed if possible.

6.2 Enrollment B

6.2.1 Study Flow Chart

The study schedule for Enrollment B is presented in Table 4.

Table 4: Study Schedule: Enrollment B

Evaluations and Procedures:	Screening/ Baseline[a] Day B1	End of Treatment [b,c] Day B15
Informed consent/assent	X	
Inclusion/exclusion criteria	X	
Medical/medication history	X	
Physical examination	X	X [d]
Urine pregnancy test [e]	X	X
Dispensation of study drug	X	
Dispensation of subject diary	X	
Collection of subject diary		X
Administration of study drug at site	X	
Weighing of study drug	X	X
Collection of study drug		X
AE evaluations	X	X
Concomitant medications review	X	X

a. Procedures for this visit may occur over a 2-day period, if necessary (with Day B1 defined as the first day on which study drug is administered). All procedures for this visit must occur before the first administration of study drug with the exceptions that AE evaluations and review of concomitant medications will also occur after the start of study drug on Day B1.
b. This visit may occur up to 3 days later than the specified day.
c. In case of early termination, the assessments planned for the End of Treatment Visit should be performed if possible.
d. Physical examination of the treated ear(s) will be performed at the End of Treatment Visit; a more extensive physical examination is not required but may be performed if necessary in the judgment of the investigator (e.g., to support evaluation of an AE).
e. Females of childbearing potential only.

6.2.2 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 for Enrollment B is presented in Table 4. Details about study procedures and how they are to be performed are presented in Section 7.

6.2.2.1 Screening / Baseline (Day B1)

This visit may be performed over a period of 2 days if necessary for practical reasons (e.g., if study drug cannot reasonably be dispensed until the day after screening procedures are initiated).

Screening procedures will occur prior to dispensation of study drug (miconazole oil) 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)
- Determination of subject eligibility for the study

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

- Weighing of miconazole oil, followed by dispensation to subject
- Dispensation of subject diary to subject
- Administration of the first dose of miconazole oil 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 miconazole oil
- Subjects will be instructed to continue administering miconazole oil and to complete the subject diary twice daily for 14 days (i.e., up through Day B14) and to bring their bottle of miconazole oil and the diary to the site for their next visit

6.2.2.2 End of Treatment (Day B15)

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

The following procedures and evaluations will occur during this visit:

- AE evaluation
- Review of concomitant medications
- Collection and review of subject diary
- Collection/weighing of miconazole oil
- Urine pregnancy test (in female subjects of childbearing potential only)

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

6.3 Screen Failures

Subjects in both portions of the study who sign informed consent and are then found not to meet all eligibility criteria will be considered screen failures.

6.4 Unscheduled Study Visits

Additional visits may be scheduled in both portions of the study, as necessary, to ensure the safety and well-being of subjects. All additional examinations should be fully documented in the source files and eCRFs, as appropriate. Visits that fall outside the designated scheduled visit

window but that are intended to fulfill scheduled visit requirements will be collected and transcribed to the appropriate scheduled visit eCRF.

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

6.5 Post-study Follow-up

Subjects who require further follow-up for an AE will be followed according to Section 8.4. If a subject requires further follow-up of AEs upon discontinuation or completion of the study, the investigator should schedule post-study follow-up visits, as necessary.

6.6 Missed Visits

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

6.7 Subject Completion

The subject has completed the study when the Test of Cure Visit is completed (Randomization Period of Enrollment A), or when the End of Treatment Visit is completed (Open-label Extension of Enrollment A or Enrollment B). Subjects who require further follow-up for an AE will be followed according to Section 8.4.

6.8 Early Study Termination

The sponsor reserves the right to terminate this study prematurely. If during the study it becomes evident to the sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the investigator, IRB, and FDA, as applicable. The sponsor or designee will instruct the investigator to stop screening/enrolling subjects, to bring all subjects who remain in the study (for example, subjects who are currently receiving treatment or who have completed treatment but have not yet completed the Test of Cure Visit in the Randomization Period, or subjects who have not completed the End of Treatment Visit in the Optional Open-label Extension or in Enrollment B) in for a final study visit as soon as possible, and to arrange for study closeout at the site.

7 STUDY PROCEDURES

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

7.1 Medical/Medication History

At Screening/Baseline, the investigator or designee will interview each subject and obtain a complete medical and medication history, including a history of all surgeries and past medical procedures. The subject must not require any treatment or medication for concurrent illnesses as

specified by the inclusion and exclusion criteria or anticipate the need for any excluded concomitant medications.

7.2 Physical Examination

At Screening/Baseline, the investigator or designee will perform a physical examination to include the following: general appearance; head, eyes, ears, nose, throat; neck; cardiovascular; lungs; abdomen; lymph nodes; extremities; neurological; skin; musculoskeletal; and body temperature. For subjects participating in Enrollment B, a physical examination of the treated ear(s) will also be performed at the End of Treatment Visit; a more extensive physical examination is not required for these subjects at the End of Treatment Visit but may be performed if necessary in the judgment of the investigator (e.g., to support evaluation of an AE).

7.3 Urine Pregnancy Test

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

7.4 Otomycosis Signs and Symptoms

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

7.4.1 Pruritus

Subjects or their caregivers (as appropriate, based on the age of the subject) will be asked by the investigator (or designee) about the severity of itching present in each ear being treated with study drug. Questions such as the following will be used in order to gather information for this assessment:

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

"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 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

7.4.2 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 Aural Fullness

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

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

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

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

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

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

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

7.5 Fungal Culture

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

The central laboratory will grow and identify fungal organisms from the sample provided by the investigator. The central laboratory will also test the susceptibility of the fungal isolates to miconazole.

7.6 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.

7.7 Adverse Event Evaluations

See Section 8.

7.8 Randomization

See Section 9.2.

7.9 Study Drug Administration

See Section 9.1.1.

7.10 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.

7.11 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.

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

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

8.1.1 Definition of a Serious Adverse Event

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

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

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

8.2 Severity of Adverse Events

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

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

8.3 Relationship of Adverse Events to Study Drug

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

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

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 will begin after the subject has signed informed consent and continue up through the Test of Cure Visit (Randomization Period) or up through the End of Treatment Visit (Optional Open-label Extension or Enrollment B). 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 (Randomization Period) or up through the End of Treatment Visit (Optional Open-label Extension or Enrollment B) 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 final study 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 4.1.1 (Enrollment A) and Section 4.2.1 (Enrollment B), must use an effective method of contraception from screening up through the final study visit. Acceptable methods include the use of at least one of the following: 1) IUD; 2) hormonal contraceptives (oral, injectable, implant, or ring); 3) barrier contraceptives (condom or diaphragm) with spermicide; or 4) abstinence.

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

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

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

8.6 Study Contacts

Study contacts will be provided in a separate document.

9 STUDY TREATMENTS

9.1 Description of Study Drug

Miconazole oil contains the active ingredient, 2% miconazole, formulated in an oil vehicle containing refined peanut oil, light mineral oil, oleth-2, and isopropyl myristate. For subjects randomized to the vehicle oil group, the vehicle oil 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 study drug into the ear. The subject will be instructed to keep the head positioned with the ear facing up for approximately 3 to 5 minutes to allow the study drug to coat the ear canal. After this time, the subject can then straighten his/her head, and excess material dripping out of the ear can be gently patted using a clean cotton ball.

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

During the Randomization Period, 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 in the Optional Open-label Extension and subjects in Enrollment B who have signs and/or symptoms of otomycosis may also be given these instructions.

Subjects in both portions will be asked to avoid bathing or showering for at least 30 minutes after applying study drug.

9.2 Randomization

For the Randomization Period, subjects will be randomized in a 1:1 ratio to one of two groups: 1) 14-day treatment with miconazole oil; or 2) 14-day treatment with miconazole oil vehicle. Randomization is not applicable to either the Optional Open-label Extension of Enrollment A or to Enrollment B.

9.3 Blinding/Unblinding

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

If it becomes necessary to unblind a subject's treatment assignment in case of emergency, the investigator should contact the sponsor. A person at the sponsor organization who is not otherwise involved with the study will maintain a randomization list that will enable that person to inform the investigator of the subject's treatment allocation. The treatment allocation is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject.

9.4 Study Drug Handling and Dispensing

9.4.1 Packaging and Labeling

The miconazole oil and the 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.

For the Randomization Period of Enrollment A, 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.

For the Optional Open-label Extension of Enrollment A and for Enrollment B, the study drug will be packaged in a primary bottle that will be dispensed directly to the subject. The dropper bottles will be weighed with the cap on prior to dispensing. If the subject loses a bottle (lost or damaged), a reserve bottle will be dispensed from the study drug inventory packaged for open-label use.

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

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

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

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

10.1 Study Endpoints

10.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the percentage of subjects at the Test of Cure Visit with "therapeutic cure", defined as "mycological cure" plus "clinical cure" for the study ear, at the end of the Randomization Period for each subject. Mycological cure is defined as a negative mycological culture, and 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. 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 (each having been assessed at the end of the Randomization Period for each subject):

- Percentage of subjects with mycological cure at the Test of Cure Visit.
- Percentage of subjects with clinical cure at the Test of Cure Visit.

10.1.3 Tertiary Efficacy Endpoints

Tertiary efficacy endpoints will include the following (each having been assessed at the end of the Randomization Period for each subject):

- Percentage of subjects with "modified therapeutic cure" at the Test of Cure Visit, defined as mycological cure plus a score of 0 for the clinical sign of fungal elements plus a score of 0 or 1 for each of the clinical signs and symptoms of pruritus, debris, and aural fullness.

- Percentage of subjects with "therapeutic improvement" at the Test of Cure Visit, defined as mycological cure plus a score of 0 or 1 for each of the clinical signs and symptoms of fungal elements, pruritus, debris, and aural fullness.

10.1.4 Safety Endpoint

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

10.2 Hypotheses

The primary efficacy endpoint of the study is percentage of subjects at the Test of Cure Visit with "therapeutic cure", defined as "mycological cure" plus "clinical cure" for the study ear. Mycological cure is defined as a negative mycological culture, and 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.

Analysis is based on the following hypothesis:

H0: $pT - pV = 0$

H1: $pT - pV > 0$.

where H0 is the null hypothesis, H1 the alternative hypotheses, and pT and pV are percentage of subjects with success in the Treatment (miconazole oil) and Vehicle (vehicle oil) groups, respectively. Comparisons between groups for the difference in the percentage of subjects achieving the primary endpoint of therapeutic cure will be conducted using a chi-square test with a 2-sided significance level of 0.05.

Comparisons will also be conducted similarly between the miconazole oil and vehicle oil groups for the secondary endpoints of clinical cure, and mycological cure.

10.3 Sample Size

For the Randomization Period, approximately 128 subjects (~64 in each group) are required to provide 80% power, using a chi-square test with a 2-sided significance level of 0.05, assuming a response rate for the primary efficacy endpoint of 25.0% in the miconazole oil group and 7.1% in the vehicle oil group.

The sample size of 220 subjects for Enrollment A assumes that ~58% of subjects enrolled into Enrollment A will have a positive fungal culture at Screening/Baseline and will therefore be included in the MITT population. This number may be higher or lower depending on the percentage of subjects eligible to be included in the MITT population.

The estimated sample size of 170 subjects for Enrollment B is not based on statistical considerations and is instead based on the achievement of at least 300 subjects who have been exposed to miconazole oil for 14 days who are evaluable for safety (see also Section 3.4.2).

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.

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 in the ITT population with a positive fungal culture at Screening/Baseline. The MITT population will be the primary population to assess efficacy.

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.

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

10.4.4 Safety Population

Two safety populations will be defined.

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

The Open Label safety population will include all subjects who received at least one dose of miconazole oil and had at least one post-Baseline safety assessment during the Optional Open-label Extension or Enrollment B.

Safety analyses for the Randomization Period will be performed using the Randomization Period safety population. Safety analyses for the Optional Open-label Extension and Enrollment B will be combined and presented using the Open Label safety population.

10.5 Statistical Methods

10.5.1 Efficacy Analyses

The primary population for efficacy analyses will be the MITT population (see Section 10.4). Efficacy analyses will also be performed on the ITT and the PP populations and will be considered supportive.

The primary analysis will be conducted once Enrollment A is complete.

The number and percent of subjects who demonstrate a positive outcome for the primary efficacy outcome as well as all secondary and tertiary efficacy outcomes will be presented.

The primary endpoint, defined as the percentage of subjects at the Test of Cure Visit with "therapeutic cure", will be compared between groups using a chi-square test with a 2-sided significance level of 0.05.

The secondary endpoints will be analyzed analogously to the primary endpoint.

In Enrollment A in cases of bilateral otomycosis, if only 1 ear has a positive fungal culture at Screening/Baseline, that ear will be used as the study ear for efficacy analyses. If both ears have a positive fungal culture at Screening/Baseline, the ear with the worse infection at Screening/Baseline, as assessed by the investigator by taking into account clinical signs and symptoms, will be used as the study ear for efficacy analyses. If both ears have a positive fungal culture at Screening/Baseline and are determined by the investigator to have the same degree of infection at Screening/Baseline, the left ear will be used as the study ear for the purposes of efficacy analyses.

Descriptive statistics will be provided for otomycosis signs and symptoms and also for clinical cure, modified therapeutic cure, and therapeutic improvement; each at Day 15 will be summarized using the ITT population for both the Randomization Period and the Optional Open-label Extension.

10.5.1.1 Multiple Comparison/Multiplicity

The overall Type I error will be controlled by requiring the primary efficacy endpoint to be statistically significant. Specifically, failure of the primary efficacy endpoint will invalidate the statistical significance of the secondary efficacy endpoints.

Evaluation of the secondary efficacy endpoints will use a gated sequential procedure in order to control for multiplicity. These tests will be performed for only the MITT population. The testing process will terminate whenever a statistical test for a step is not significant, i.e., any subsequent test will be considered not significant. The order of testing is:

1. Percentage of subjects with mycological cure at the Test of Cure Visit.

2. Percentage of subjects with clinical cure at the Test of Cure Visit.

10.5.2 Safety Analyses

Safety summaries will be conducted using two safety populations (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. 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.

Summaries will be provided separately for the blinded and unblinded portions. Specifically, summaries will be provided by treatment group for the Randomization Period using the Randomization Period safety population, and for all open-label subjects using the Open Label safety population.

All information pertaining to AEs noted during the study will be listed by study portion (Enrollment A or Enrollment B), study period (Randomization or Optional Open-label), as applicable, 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 data will be imputed as treatment failures for the primary and secondary efficacy analyses.

Missing data otherwise will not be imputed.

10.5.5 Sensitivity Analyses

In order to explore the effects of missing data, sensitivity analyses will be performed on the primary endpoint. The first will be a tipping point analysis using the MITT population. The second sensitivity analysis will be analogous to the primary but will be performed on the ITT population.

10.5.6 Subgroup Analyses

Descriptive summaries on the primary and secondary endpoints will be included for the following subgroups of gender, age, ethnicity, race, and fungal organism isolated at Screening/Baseline.

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

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 04 February 2020

The purpose of this amendment was to remove the following secondary endpoints:

- Percentage of subjects with mycological cure at the Test of Cure Visit
- Percentage of subjects with clinical cure at the Test of Cure Visit.

No detailed summary of changes was prepared for Version 2 because the prior version (Version 1, 28 January 2020) was internal only.

13.2 Amendment 2 Version 3 18 May 2020

This amendment reflects updates and revisions to the protocol resulting from an End-of-Phase 2 meeting with FDA and changes in sponsor strategy for the development of miconazole oil. An overview of major changes is as follows.

- An optional open-label extension was added to the study to allow subjects the option to be treated with active drug (miconazole oil) if they have a visual presence of fungal elements in at least one ear following randomized treatment.
- A second portion was added to the study (called Enrollment B), which will commence after completion of the first portion (called Enrollment A) in order to gather safety information for miconazole oil in additional subjects. Because the purpose of Enrollment B is safety, subjects in Enrollment B are not required to have a diagnosis of otomycosis.
- Secondary and tertiary efficacy endpoints were added.

Clarifications and minor changes to study conduct and statistical analyses were also made.

A more complete summary of changes from the prior version is provided below. Insertions are **bolded**. Deletions are ~~struck through~~. For sections that are new or have been completely revised, only a short description is provided.

Location	Change	Rationale
Header	**18 May 2020 / Version 3**~~04 Feb 2020 / Version 2~~	Update to new version and date
Title page, Synopsis (Study Title)	Randomized, Double-blind, Phase III Study of the Efficacy and Safety of Miconazole Oil versus Vehicle Oil in the Treatment of Otomycosis**, Followed by an Open-label Safety Evaluation**	Addition to the study of an optional open-label extension and an open-label Enrollment B portion to gather additional safety information in a greater number of subjects
Title page	**18 May 2020 / Version 3**~~04 February 2020 / Version 2~~ Previous versions: 28 January 2020 / Version 1 (internal only) **04 February 2020 / Version 2**	Update to new version and date

Location	Change	Rationale
Protocol Approval page	**18 May 2020**~~04 February 2020~~	Update to new date
Study Acknowledgement page	**Version 3**~~Version2~~	Update to new version
Synopsis (Study Center(s))	Up to **20**~~15~~ study centers	Allowance for additional study centers
Synopsis (Number of Subjects Planned)	Approximately **390**~~220~~ (estimated); the **actual** number enrolled will be **the number**~~that~~ needed to achieve at least 128 subjects eligible to be included in 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 **at Screening/Baseline, and to achieve at least 300 subjects exposed to miconazole oil for 14 days who are evaluable for safety**. Thus, a higher or lower number **than estimated** may be enrolled**, with enrollment continuing until** ~~depending on~~ the **required numbers**~~percentage~~ of subjects **have been achieved**~~eligible to be included in the MITT population~~.	Addition to the study of an optional open-label extension and an open-label Enrollment B portion; change to definition of MITT population in response to FDA comment at End-of-Phase 2 meeting; clarification that enrollment will continue until the required numbers of subjects have been achieved
Synopsis (Study Period)	~~Study Period:~~ ~~The study duration for each subject will be up to approximately 30 days, which includes 14 days of treatment and 8 days of follow-up, plus a visit window of up to 8 additional days after the scheduled day for the follow-up (Test of Cure) visit.~~	Rename section to Study Duration and move to later in the protocol (after Study Visits) for clarity of presentation
Synopsis (Objectives), Section 2 (Study Objectives)	• Confirm the efficacy of miconazole oil compared with vehicle over a 14-day treatment duration in **subjects**~~patients~~ with otomycosis • Assess the safety of miconazole oil over a 14-day treatment duration ~~in patients with otomycosis~~	Addition to the study of an optional open-label extension and an open-label Enrollment B portion to gather additional safety information in a greater number of subjects (some of whom will not have otomycosis); consistency of terminology throughout protocol
Synopsis (Design and Methodology)	This study **will be conducted in 2 separate, sequential portions:** **1. Enrollment A, which will consist of 2 treatment periods as follows and will be conducted in subjects with otomycosis:** **a. A**~~is a~~ randomized, double-blind, parallel-group **treatment period. This treatment period will be referred to as the "Randomization Period" and will be followed by:** **b. An optional, open-label treatment period with miconazole oil. This treatment period will be referred to as the "Optional Open-label Extension."** **2. Enrollment B, which will commence after**	Addition to the study of an optional open-label extension and an open-label Enrollment B portion

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	completion of Enrollment A and will consist of open-label treatment with miconazole oil in subjects who will not be required to have signs and symptoms of otomycosis. **Enrollment A** **The** study **will start with Enrollment A, in which an**~~to be conducted at up to 15 study centers in the US. An~~ estimated 220 male or female subjects with otomycosis will receive study drug, although this number may be higher or lower depending on the percentage of subjects eligible to be included in the MITT population. Subjects will be randomly assigned in a 1:1 ratio to receive miconazole oil **or vehicle, for 14 days. The study drug will be** ~~[~~administered as 5 drops per ear at ~30 mg per drop instilled into the external ear canal of the ear(s) affected by otomycosis~~]~~. ***Randomization Period*** **During the Randomization Period, both**~~Both~~ the subject and the investigator and study staff will be blinded as to the contents of the study drug.	
Synopsis (Design and Methodology, Randomization Period), Section 3.1.1 (Randomization Period)	A fungal culture of the affected ear(s) will be taken, then debris will be cleaned from the affected ear(s) following the site's normal procedures. **The subject will be randomized, and study drug will be weighed and dispensed to the subject along with a subject diary.** The subject will then begin treatment… The subject will then leave the clinic and continue to administer the study drug **and to complete the subject diary** twice per day as instructed.	Completeness in description of study procedures
Synopsis (Design and Methodology, Randomization Period), Section 3.1.1 (Randomization Period)	Subjects will return to the clinic on Day 8 for the On Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis, a cleaning of the affected ear(s) (following the site's normal procedures), **a review of the subject diary**, and an assessment of AEs and concomitant medications will be performed. Subjects will continue to administer the study drug **and to complete the subject diary** twice per day, …	Completeness in description of study procedures
Synopsis (Design and Methodology, Randomization Period), Section 3.1.1 (Randomization Period)	Subjects will return to the clinic on Day 15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed**; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the**	Elimination of unnecessary fungal culture in situations in which this culture will not contribute to the evaluation of efficacy; completeness in description of study procedures procedure

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	clinical laboratory performing the fungal culture. AEs and concomitant medications will also be assessed, and the subject will return all unused study drug **along with the completed subject diary**.	
Synopsis (Design and Methodology, Randomization Period), Section 3.1.1 (Randomization Period)	Subjects will return to the clinic on Day 22 for the Test of Cure Visit, at which time an assessment of clinical signs and symptoms of otomycosis and a fungal culture of the affected ear(s) will be performed**; however, a fungal culture will not be required at this visit for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal culture**. AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential.	Elimination of unnecessary fungal culture in situations in which this culture will not contribute to the evaluation of efficacy
Synopsis (Design and Methodology, Optional Open-label Extension)	***Optional Open-label Extension*** **Subjects who either complete the Randomization Period of the study (up through the Test of Cure Visit), or who are prematurely discontinued from study treatment during the Randomization Period due to worsening…** **…The subject will return all unused miconazole oil along with the completed subject diary.**	Addition of entire section to reflect addition to the study of an optional open-label extension
Synopsis (Design and Methodology, Enrollment B)	**<u>Enrollment B</u>** **Enrollment B will begin at or after the conclusion of Enrollment A. …** **… A urine pregnancy test will be performed in women of childbearing potential.**	Addition of entire section to reflect addition to the study of Enrollment B portion of study
Synopsis (Study Visits)	**<u>Enrollment A</u>** ***Randomization Period*** • **Day 1:** Screening/Baseline (1 visit); • **Day 8:** On Treatment (1 visit); • **Day 15:** End of Treatment (1 visit); • **Day 22:** Test of Cure (1 visit) ***Optional Open-label Extension:*** • **Day OLE1 (which will occur while the subject is already onsite for the Test of Cure or Early Termination Visit for the Randomization Period);** • **Day OLE15 (1 visit)** **<u>Enrollment B</u>** • **Day B1: Screening/Baseline (1 visit);** • **Day B15: End of Treatment (1 visit)**	Addition to the study of an optional open-label extension and an Enrollment B portion; clarity of presentation
Synopsis (Study	**Study Duration**~~Study Period~~:	Rename section to Study Duration

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Duration)	**Enrollment A** **During Enrollment A, the**~~The~~ study duration for each subject **who participates only in the Randomization Period** will be up to approximately **31**~~30~~ days, which includes **up to 1 day for screening (if screening procedures need to be initiated the day before treatment),** 14 days of treatment**,** and 8 days of follow-up, plus a visit window of up to 8 additional days after the scheduled day for the follow-up (Test of Cure) **Visit**~~visit~~. **The study duration for each subject who participates in both the Randomization Period and the Optional Open-label Extension will be up to approximately 48 days, which includes up to 31 days for the Randomization Period followed by up to 17 days for the Optional Open-label Extension (which includes a visit window of up to 3 additional days after the 14-day treatment to complete the final study visit). This study duration takes into account that the Day OLE1 procedures will occur while the subject is already onsite for the Test of Cure or Early Termination Visit for the Randomization Period.** **Enrollment B** **In Enrollment B, the study duration for each subject will be up to 19 days, which includes up to 1 day for screening (if screening procedures need to be initiated the day before treatment), 14 days of treatment, and a 1-day final study visit after the 14-day treatment (which has a visit window of up to 3 additional days).**	and move to after the Study Visits section of Synopsis for clarity of presentation; allowance for 1 additional day at screening for investigator flexibility in initiating screening procedures; addition to the study of an optional open-label extension and an Enrollment B portion
Synopsis (Key Inclusion Criteria)	**Enrollment A** Male or non-pregnant, non-lactating females with a clinical diagnosis of uncomplicated otomycosis of the external ear only, with an intact tympanic membrane **in the ear(s) to be treated with study drug**, who are in general good health… **Enrollment B** **Male or non-pregnant, non-lactating females with an intact tympanic membrane in the ear(s) to be treated with study drug, who are in general good health…**	Addition of entire subsection to reflect the addition to the study of an Enrollment B portion with different eligibility criteria; clarification as to ear(s) for which intact tympanic membrane is required
Synopsis (Key Exclusion Criteria)	**Enrollment A** Subjects with any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis **or with safety evaluations**, including concomitant otic	Clarity; addition of entire subsection to reflect the addition to the study of an Enrollment B portion with different eligibility criteria; clarification of exclusion criterion

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	infections…~~recurrent~~ otomycosis that has… **Enrollment B** **Subjects with any other dermatoses or conditions of the ear that may interfere with safety evaluations, including concomitant otic infections...**	about otomycosis that has been unresponsive to previous antifungal treatment
Synopsis (Reference Product…)	Reference Product, Dose, and Mode of Administration **(Enrollment A Only)**:	Clarification that this section is now only applicable to Enrollment A
Synopsis (Endpoints)	**Secondary Efficacy Endpoints** • **Percentage of subjects with mycological cure…** **Tertiary Efficacy Endpoints** • **Percentage of subjects with "modified therapeutic cure" at the Test of Cure Visit, defined as…**	Addition of secondary and tertiary efficacy endpoints
Synopsis (Statistical Analyses)	Descriptive statistics will also be presented for the percentages of subjects by treatment group with **success at each secondary and tertiary endpoint, and for** each sign or symptom…	Addition of secondary and tertiary efficacy endpoints
Synopsis (Statistical Analyses)	In **Enrollment A in** cases of bilateral otomycosis, the ear with…	Clarification that this statement is now only applicable to Enrollment A
Synopsis (Statistical Analyses)	For the primary efficacy endpoint, percentages of subjects with therapeutic cure at the Test of Cure Visit will be compared using a chi-square test with a 2-sided significance level of 0.05. **Comparisons will be conducted in a similar manner between the miconazole oil and vehicle oil groups for the secondary endpoints of clinical cure and mycological cure. Missing data will be imputed as treatment failures for the primary and secondary efficacy analyses; missing data otherwise will not be imputed.**	Addition of secondary and tertiary efficacy endpoints; addition for completeness of statement about the handling of missing data
Synopsis (Statistical Analyses)	The primary population for ~~all~~ efficacy analyses will be the MITT population, defined as all subjects who were randomized with a positive fungal culture at Screening/Baseline.	Addition of an optional open-label extension for which the ITT population will be used for efficacy analyses
Synopsis (Statistical Analyses)	**Two**~~The primary population for all~~ safety **populations will be used for safety** analyses**. The first** will be the **Randomization Period** 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 **during the Randomization Period; this population will be used for safety data for the Randomization Period. The second will be the Open Label safety population, defined as all subjects who received at least one dose of miconazole oil and had at least one post-Baseline safety assessment during the Optional Open-label Period; this**	Change to presentation of safety information because of the addition of an optional open-label extension and an open-label Enrollment B portion of the study

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	population will be used for safety data for the Optional Open-label Extension and Enrollment B.	
Synopsis (Statistical Analyses)	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~~. … All reported **serious AEs (SAEs)**~~SAEs~~will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug. Descriptive statistics will be presented for all safety data.	Change to presentation of safety information because of the addition of an optional open-label extension and an open-label Enrollment B portion of the study; corrections to use of abbreviations
Synopsis (Sample Size)	**For the Randomization Period of Enrollment A, approximately**~~Approximately~~ 128 subjects (~64 in each group) are required to provide 80% power,… The sample size of 220 subjects for **Enrollment A**~~this study~~ assumes that ~58% of subjects enrolled into **Enrollment A**~~the study~~ will have a positive fungal culture at Screening/Baseline	Clarification that this statement is now only applicable to the Randomization Period of Enrollment A
Synopsis (Sample Size)	**The overall study sample size of ~390 subjects is the total number of study subjects estimated to achieve at least 300 subjects exposed to miconazole oil for 14 days who are evaluable for safety. A higher or lower number of total subjects may be enrolled in order to achieve the required total numbers of subjects for each of Enrollment A and Enrollment B.**	Addition to the study of an optional open-label extension and an open-label Enrollment B portion
List of Abbreviations	~~LOCF Last observation carried forward~~	Change to method for handling missing data in response to FDA comment at End-of-Phase 2 meeting
Section 1.2 (Study Purpose)	**During the Randomization Period of the Enrollment A portion of the study, a**~~A~~ 14-day regimen of twice-daily administration of 2% miconazole oil will be compared with the same treatment regimen using the product vehicle. **During the Optional Open-label Extension of the Enrollment A portion and the Enrollment B portion of the study, a 14-day regimen of twice-daily administration of 2% miconazole oil will be administered in an open-label fashion in order to gather safety information in additional subjects.**	Addition to the study of an optional open-label extension and an open-label Enrollment B portion
Section 3 (Study Design)	This study **will be conducted in 2 separate, sequential portions (see also Figure 1 for a schematic diagram of the study design):**	Addition to the study of an optional open-label extension and an open-label Enrollment B portion

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	1. Enrollment A, which will consist of 2 treatment periods as follows and will be conducted in subjects with otomycosis: **a. A**~~is a~~ randomized, double-blind, parallel-group **treatment period. This treatment period will be referred to as the "Randomization Period" and will be followed by:** **b. An optional, open-label treatment period with miconazole oil. This treatment period will be referred to as the "Optional Open-label Extension."** **2. Enrollment B, which will commence after completion of Enrollment A and will consist of open-label treatment with miconazole oil in subjects who will not be required to have signs and symptoms of otomycosis.**	
Section 3 (Study Design)	**Figure 1 Diagram of Study Design…**	Addition of figure and footnotes for clarity about study design incorporating the addition to the study of an optional open-label extension and Enrollment B portion
Section 3 (Study Design)	**3.1 Enrollment A** **The** study **will start with Enrollment A, in which an**~~to be conducted at up to 15 study centers in the US. An~~ estimated 220 male or female subjects with otomycosis will receive study drug, although this number may be higher or lower depending on the percentage of subjects eligible to be included in the modifed intent to treat **(**MITT) population (see Section 10.4.2). Subjects will be randomly assigned in a 1:1 ratio to receive miconazole oil **or vehicle, for 14 days. The study drug will be** ~~[~~administered as 5 drops per ear at ~30 mg per drop instilled into the external ear canal of the ear(s) affected by otomycosis~~]~~. **3.1.1 Randomization Period** **During the Randomization Period, both**~~Both~~ the subject and the investigator and study staff will be blinded as to the contents of the study drug.	Addition to the study of an optional open-label extension and an open-label Enrollment B portion
Section 3 (Study Design)	**3.1.2 Optional Open-label Extension** **Subjects who either complete the Randomization Period of the study (up through the Test of Cure Visit), or who are prematurely discontinued from study treatment during the Randomization Period due to worsening…** **…The purpose of the Optional Open-label Extension is safety and to provide supportive evidence of efficacy. Efficacy assessments will**	Addition of entire section to reflect addition to the study of an optional open-label extension

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	include assessments of clinical signs and symptoms of otomycosis. Safety assessments will include AEs.	
Section 3 (Study Design)	**3.2 Enrollment B** **Enrollment B will begin at or after the conclusion of Enrollment A. …** **…Safety assessments will include AEs.**	Addition of entire section to reflect addition to the study of Enrollment B portion of study
Section 3.3 (Number of Subjects)	**3.3**~~3.1~~ Number of Subjects **Approximately 390 total subjects are estimated to be enrolled into the study (~220 subjects estimated for Enrollment A and ~170 subjects estimated for Enrollment B) as described in Section 3.3.1 for Enrollment A and in Section 3.3.2 for Enrollment B.** **3.3.1 Enrollment A** An estimated 220 eligible subjects are planned to be enrolled **in Enrollment A** in order to achieve at least 128 evaluable subjects (i.e., included in the MITT population, defined as those who were randomized~~, dispensed study drug, and~~ with a ~~clinical diagnosis of otomycosis confirmed by a~~ positive fungal culture **at Screening/Baseline**). The number of subjects who are enrolled may be higher or lower than 220 depending on the percentage of subjects eligible to be included in the MITT population**; enrollment in Enrollment A will continue until the required numbers of subjects have been achieved**.	Addition to the study of an optional open-label extension and an open-label Enrollment B portion; change to definition of MITT population in response to FDA comment at End-of-Phase 2 meeting; clarification that enrollment in Enrollment A will continue until the required numbers of subjects have been achieved
Section 3.3 (Number of Subjects)	**3.3.2 Enrollment B** **An estimated 170 eligible subjects are planned to be enrolled in order to achieve at least 300 total subjects in the study…** **… Enrollment will continue into Enrollment B until the required number of subjects exposed to miconazole oil for 14 days and evaluable for safety has been achieved.**	Addition of entire section to reflect addition to the study of Enrollment B portion of study
Section 3.4 (Investigators)	**3.4**~~3.2~~ Investigators The study will be conducted at up to **20**~~15~~ investigative sites located in the US.	Allowance for additional investigative sites
Section 3.5 (Study Duration)	**3.5**~~3.3~~ Study Duration **3.5.1 Enrollment A** **A diagram of the study duration for each subject participating in Enrollment A is presented in Figure 2.** **During Enrollment A, the**~~The~~ study duration for each subject **who participates only in the Randomization Period of the study** will be up to approximately **31**~~30~~ days, which includes **up to 1 day for screening (if screening procedures need to be initiated the day**	Allowance for 1 additional day at screening for investigator flexibility in initiating screening procedures; addition to the study of an optional open-label extension

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	before treatment), 14 days for 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 **Test of Cure Visit**~~visit)~~. **The study duration for each subject who participates in both the Randomization Period and Optional Open-label Extension will be up to approximately 48 days, which includes up to 31 days for the Randomization Period followed by up to 17 days for the Optional Open-label Extension (which includes a visit window of up to 3 additional days after the 14-day treatment to complete the final study visit). This study duration takes into account that the Day OLE1 procedures will occur while the subject is already onsite for the Test of Cure or Early Termination Visit for the Randomization Period.**	
Section 3.5 (Study Duration)	**Figure 2: Diagram of Study Duration for Enrollment A…**	Addition of figure to clarify study duration after addition to the study of an optional open-label extension
Section 3.5 (Study Duration)	**3.5.2 Enrollment B** **A diagram of the study duration for each subject participating in Enrollment B is presented in Figure 3.** **In Enrollment B, the study duration for each subject will be up to 19 days, which includes up to 1 day for screening (if screening procedures need to be initiated the day before treatment), 14 days of treatment, and a 1-day final study visit after the 14-day treatment (which has a visit window of up to 3 additional days).**	Addition to the study of an Enrollment B portion; allowance for 1 additional day at screening for investigator flexibility in initiating screening procedures
Section 3.5 (Study Duration)	**Figure 3: Diagram of Study Duration for Enrollment B…**	Addition of figure to clarify study duration after addition to the study of an Enrollment B portion
Section 4 (Study Subjects)	**4.1 Enrollment A** **4.1.1**~~4.1~~ Inclusion Criteria In order to be eligible for **Enrollment A**~~the study~~, subjects…	Addition to the study of an optional open-label extension and an open-label Enrollment B portion
Section 4 (Study Subjects)	**4.1.2**~~4.2~~ Exclusion Criteria Subjects meeting any of the following criteria will not be eligible for **Enrollment A**~~the study~~: 1. Any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis **or with safety evaluations**, including concomitant otic infections (including bacterial infection) **other than otomycosis** that require antimicrobial treatment, disease that has	Addition to the study of an optional open-label extension and an open-label Enrollment B portion; clarification of exclusion criteria #1 and #7; addition of exclusion criterion #10

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	spread beyond the external ear(s), or pre-existing skin atrophy of the affected ear(s) that will be treated with study drug… 7. **Otomycosis**~~Recurrent otomycosis~~ that has been unresponsive to previous antifungal treatment… **10. Participation in the sponsor's previous miconazole oil Study HD-MCZ-PHII-DRF062016 unless the subject was enrolled into either the vehicle or the 7-day miconazole oil group of that study.**	
Section 4 (Study Subjects)	**4.2 Enrollment B** **4.2.1 Inclusion Criteria** **In order to be eligible for Enrollment B…** **…** **4.2.2 Exclusion Criteria** **Subjects meeting any of the following criteria…** **…9. Previous participation in Enrollment A of this study, unless the subject is known never to received active treatment (miconazole oil) during Enrollment A.**	Addition of entire section to reflect addition to the study of Enrollment B portion of study
Previous Section 4.3 (Subject Completion)	~~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.~~	Deletion of redundant section (presented also in Section 6.7)
Section 4.3 (Subject Discontinuation)	**4.3**~~4.4~~ Subject Discontinuation A subject MAY be withdrawn from the study… • Failure to follow required study procedures • **For subjects participating in Enrollment A, a negative fungal culture at Screening/Baseline (as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal cultures)** …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 **(Randomization Period) or the End of Treatment Visit (Optional Open-label Extension or Enrollment B)** should be performed, and an effort should be made to collect all study drug. **A fungal culture is not required for subjects who are prematurely discontinued from the study.** **For Enrollment A, due**~~Due~~ to the time required to obtain fungal culture results from Screening/Baseline, subjects will be enrolled	Provision for subjects with a negative fungal culture to be discontinued from the study; addition to the study of an optional open-label extension and an open-label Enrollment B portion; elimination of unnecessary fungal culture in situations in which this culture will not contribute to the evaluation of efficacy

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	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 **are**~~will~~ not **required to** be discontinued from the study, but these subjects will not be included in the primary efficacy analysis. Because the sponsor's goal is to have at least 128 subjects in the MITT population (see Section 10.4.2), the total number of subjects enrolled into **Enrollment A**~~the study~~ may be higher or lower than 220, depending on the percentage of subjects who are eligible to be included in the MITT population.	
Section 4.3 (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 **into Enrollment A** if it appears that the estimated number of subjects **for Enrollment A** (approximately 220) is insufficient to meet the sponsor's goal of having at least 128 subjects in the MITT population. **After completion of Enrollment A, additional subjects (i.e., exceeding the 390 subjects total for the study) may be enrolled into Enrollment B if it appears that the estimated total number of study subjects is insufficient to achieve at least 300 subjects who have been exposed to miconazole oil for 14 days who are evaluable for safety.**	Addition to the study of an optional open-label extension and an open-label Enrollment B portion
Section 4.4 (Subjects Lost to Follow-up)	**4.4**~~4.5~~ Subjects Lost to Follow-up	Renumbering of section due to revisions above
Section 5 (Concomitant Therapies)	All concomitant therapies must be recorded on the eCRF.~~ All therapies within 3 months prior to Day 1 must also be recorded on the eCRF.~~ **5.1 Enrollment A** **In addition to all concomitant therapies, all therapies within 3 months prior to Day 1 must also be recorded on the eCRF.** **5.1.1**~~5.1~~ Permitted Medications Therapies… **5.1.2**~~5.2~~ Prohibited Medications Other than…	Reorganization of information because of addition to the study of an Enrollment B portion
Section 5 (Concomitant Therapies)	**5.2 Enrollment B** **In addition to all concomitant therapies…** **…Prohibited treatments include systemic antifungal therapy and warfarin.**	Addition of entire section because of addition to the study of an Enrollment B portion

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Section 6 (Study Schedule)	6.1 **Enrollment A**~~Study Flow Chart~~ **6.1.1 Study Flow Chart** The study schedule **for Enrollment A** is presented in Table 3. Table 3: Study Schedule**: Enrollment A**	Addition to the study of an Enrollment B portion
Section 6 (Study Schedule)	See revised Table 3 below and footnotes	Allowance for 1 additional day at screening for investigator flexibility in initiating screening procedures; addition to the study of an optional open-label extension and an Enrollment B portion; clarification for completeness about return of the subject diary to the subject after review on Day 8 of Enrollment A; elimination of unnecessary fungal culture in situations in which this culture will not contribute to the evaluation of efficacy
Section 6 (Study Schedule)	**6.1.2**~~6.2~~ Study Visits **for the Randomization Period** …The schedule of visits **for Enrollment A** is presented in Table 3.	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 6 (Study Schedule)	**6.1.2.1**~~6.2.1~~ Screening / Baseline **(Day 1)** **This visit may be performed over a period of 2 days if necessary for practical reasons (e.g., if study drug cannot reasonably be dispensed until the day after screening procedures are initiated).**	Renumbering of section; allowance for 1 additional day at screening for investigator flexibility in initiating screening procedures; addition of visit day (Day 1) for clarity of presentation
Section 6.1.2.1 (Screening/Baseline (Day 1))	• Subjects will be instructed to continue administering study drug **and to complete the subject diary** twice daily and to bring their bottle of study drug and the diary to the site for their next visit	Mention of subject diary for completeness
Section 6 (Study Schedule)	**6.1.2.2**~~6.2.2~~ On Treatment **(Day 8)**	Renumbering of section; addition of visit day (Day 8) for clarity
Section 6.1.2.2 (On Treatment (Day 8))	• Review of subject diary **and return of the subject diary to the subject** • Subjects will be instructed to continue administering study drug **and to complete the subject diary** twice daily up through Day 14, and to bring their bottle of study drug and the diary to the site for their next visit	Mention of subject diary and its return to the subject for completeness
Section 6 (Study Schedule)	**6.1.2.3**~~6.3~~ End of Treatment **(Day 15)**	Renumbering of section; addition of visit day (Day 15) for clarity
Section 6.1.2.3 (End of Treatment (Day 15)), Section 6.1.2.4 (Test of Cure (Day 22))	• Fungal culture **(not required for subjects known to have a negative fungal culture at Screening/Baseline, as assessed after at least 14 days of incubation by the clinical laboratory performing the fungal**	Elimination of unnecessary fungal culture in a situation in which this culture will not contribute to the evaluation of efficacy

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	culture)	
Section 6 (Study Schedule)	**6.1.2.4~~6.4~~** Test of Cure **(Day 22)**	Renumbering of section; addition of visit day (Day 22) for clarity
Section 6.1.2.4 (Test of Cure (Day 22))	In case of early termination **from the Randomization Period**, the procedures planned for the Test of Cure Visit **with the exception of fungal culture** should be performed ~~if possible~~. **Subjects who complete the Test of Cure Visit and who have a visual presence of fungal elements in at least one ear treated during the Randomization Period will be offered the opportunity to participate in the Optional Open-label Extension.**	Addition to the study of an optional open-label extension and an Enrollment B portion; elimination of unnecessary fungal culture in a situation in which this culture will not contribute to the evaluation of efficacy
Section 6 (Study Schedule)	**6.1.3 Study Visits for the Optional Open-label Extension**	Addition of entire section to reflect addition to the study of optional open-label extension
Section 6 (Study Schedule)	**6.2 Enrollment B** **…**	Addition of entire section to reflect addition to the study of Enrollment B portion
Section 6 (Study Schedule)	**6.3 Screen Failures** **Subjects in both portions of the study who sign informed consent and are then found not to meet all eligibility criteria will be considered screen failures.**	Addition of entire section to indicate how patients who sign informed consent but then do not meet all eligibility criteria will be handled
Section 6 (Study Schedule)	**6.4~~6.5~~** Unscheduled Study Visits Additional visits may be scheduled **in both portions of the study**, as necessary, to ensure…	Renumbering of section; addition to the study of an open-label Enrollment B portion
Section 6 (Study Schedule)	**6.5~~6.6~~** Post-study Follow-up **Subjects who require further follow-up for an AE will be followed according to Section 8.4.** If a subject requires…	Renumbering of section; reorganization of information
Section 6 (Study Schedule)	**6.6~~6.7~~** Missed Visits	Renumbering of section
Section 6 (Study Schedule)	**6.7~~6.8~~** Subject Completion The subject has completed the study when the Test of Cure Visit is completed **(Randomization Period of Enrollment A), or when the End of Treatment Visit is completed (Open-label Extension of Enrollment A or Enrollment B)**. Subjects who require further follow-up for an AE will be followed according to Section **8.4~~6.6~~**.	Renumbering of section; addition to the study of an optional open-label extension and an Enrollment B portion; reorganization of information
Section 6 (Study Schedule)	**6.8~~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	Renumbering of section; addition to the study of an optional open-label extension and an Enrollment B portion

Location	Change	Rationale
	applicable. The sponsor or designee will instruct the investigator to stop **screening/enrolling**~~randomizing~~ subjects, to bring all subjects who remain in the study (for example, subjects who are currently receiving treatment or who have completed treatment but have not yet completed the Test of Cure Visit **in the Randomization Period, or subjects who have not completed the End of Treatment Visit in the Optional Open-label Extension or in Enrollment B) in for a final study visit**~~) in for a Test of Cure Visit~~ as soon as possible, and to arrange for study closeout at the site.	
Section 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; musculoskeletal; and body temperature. **For subjects participating in Enrollment B, a physical examination of the treated ear(s) will also be performed at the End of Treatment Visit; a more extensive physical examination is not required for these subjects at the End of Treatment Visit but may be performed if necessary in the judgment of the investigator (e.g., to support evaluation of an AE).**	Clarification of extent of physical examination; addition to the study of an Enrollment B portion
Section 8.1 (Definition of an Adverse Event)	**The worsening or reoccurrence as compared to any previous visit in a subject of any symptom of otomycosis (including any increase in numerical score for pruritus and/or aural fullness…** **…If, however, in the investigator's judgment there is a clinically significant worsening of debris and/or fungal elements, an AE of "worsening of disease under study" should be recorded.**	Addition of 2 paragraphs to clarify how adverse events that could be considered signs and symptoms of otomycosis should be reported
Section 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 **will**~~should~~ begin after the subject has signed informed consent and continue up through the Test of Cure Visit **(Randomization Period) or up through the End of Treatment Visit (Optional Open-label Extension or Enrollment B)**.	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 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 **(Randomization Period) or up through the End of Treatment Visit (Optional Open-label Extension or Enrollment B)** will be reported…	Addition to the study of an optional open-label extension and an Enrollment B portion

Location	Change	Rationale
	… Any SAE occurring after the **final study visit**~~Test of Cure Visit~~ and which is not considered to be of "suspected" relationship to study drug does not need to be reported.	
Section 8.5 (Pregnancy)	Females of childbearing potential, as defined in **Section 4.1.1 (Enrollment A) and Section 4.2.1 (Enrollment B)**~~Section 4.1~~, must use an effective method of contraception from screening up through the **final study visit**~~Test of Cure Visit~~.	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 9.1.1 (Administration)	The subject or caregiver will gently pull the ear lobe backward and upward and apply 5 drops of **study drug**~~miconazole oil~~ into the ear. The subject will be instructed to keep the head positioned with the ear facing up for approximately 3 to 5 minutes to allow the **study drug**~~miconazole oil~~ to coat the ear canal.	Clarification to accommodate vehicle comparator
Section 9.1.1 (Administration)	**During the Randomization Period, while**~~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 in the Optional Open-label Extension and subjects in Enrollment B who have signs and/or symptoms of otomycosis may also be given these instructions.** Subjects **in both portions** will be asked to avoid bathing or shower for at least 30 minutes after applying study drug.	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 9.2 (Randomization)	**For the Randomization Period, subjects**~~Subjects~~ will be randomized in a 1:1 ratio to one of two groups: 1) 14-day treatment with miconazole oil; or 2) 14-day treatment with miconazole oil vehicle. **Randomization is not applicable to either the Optional Open-label Extension of Enrollment A or to Enrollment B.**	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 9.3 (Blinding/Unblinding)	The contents of the study drug (miconazole oil versus vehicle) will be blinded to both the investigator (and all study staff) and the subject **during the Randomization Period of Enrollment A**.	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 9.4.1 (Packaging and Labeling)	**For the Randomization Period of Enrollment A, the**~~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	Addition to the study of an optional open-label extension and an Enrollment B portion

Location	Change	Rationale
	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. **For the Optional Open-label Extension of Enrollment A and for Enrollment B, the study drug will be packaged in a primary bottle that will be dispensed directly to the subject. The dropper bottles will be weighed with the cap on prior to dispensing. If the subject loses a bottle (lost or damaged), a reserve bottle will be dispensed from the study drug inventory packaged for open-label use.** Each drug kit dispensed will be documented on the drug accountability log. Labels on the drug kit will contain the following information:	
Section 10 (Statistical Considerations)	**All statistical processing will be performed using Statistical Analysis System (SAS®) Version 9.4 or higher. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.** **Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, and standard deviation, median, minimum, and maximum.** **Full details of statistical analyses will be provided in a separate statistical analysis plan.** 10.1 Study Endpoints…	Reorganization of information (text moved from the previous Section 10.5 Statistical Methods to the beginning of Section 10)
Section 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 **"mycological cure"**~~a negative mycological culture~~ plus "clinical cure" for the study ear**, at the end of the Randomization Period for each subject**. **Mycological cure is defined as a negative mycological culture, and clinical**~~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.	Addition to the study of an optional open-label extension and an Enrollment B portion; consistency of presentation throughout protocol
Section 10.1.2 (Secondary Efficacy	**10.1.2 Secondary Efficacy Endpoints** **Secondary endpoints will include…**	Addition of entire section due to addition to protocol of new

Location	Change	Rationale
Endpoints)		secondary endpoints
Section 10.1.3 (Tertiary Efficacy Endpoints)	**10.1.3 Tertiary Efficacy Endpoints** **Tertiary endpoints will include…**	Addition of entire section due to addition to protocol of new tertiary endpoints
Section 10.1.4 (Safety Endpoint)	**10.1.4~~10.1.2~~** Safety Endpoint	Renumbering of section
Section 10.2 (Hypotheses)	The primary efficacy endpoint of the study is percentage of subjects at the Test of Cure Visit with "therapeutic cure", defined as **"mycological cure"**~~a negative mycological culture~~ plus "clinical cure" for the study ear. **Mycological cure is defined as a negative mycological culture, and clinical**~~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.	Consistency of presentation throughout protocol
Section 10.2 (Hypotheses)	**Comparisons will also be conducted similarly between the miconazole oil and vehicle oil groups for the secondary endpoints of clinical cure, and mycological cure.**	Addition to protocol of secondary endpoints
Section 10.3 (Sample Size)	**For the Randomization Period, approximately**~~Approximately~~ 128 subjects (~64 in each group) are required to provide 80% power… The sample size of 220 subjects for **Enrollment A**~~this study~~ assumes that ~58% of subjects enrolled into **Enrollment A**~~the study~~ will have a positive fungal culture at Screening/Baseline… **The estimated sample size of 170 subjects for Enrollment B is not based on statistical considerations and is instead based on the achievement of at least 300 subjects who have been exposed to miconazole oil for 14 days who are evaluable for safety (see also Section 3.3.2).**	Addition to the study of an optional open-label extension and an Enrollment B portion
Section 10.4.2 (Modified Intent-to-treat Population)	The MITT population will include subjects **in the ITT population**~~who were randomized, dispensed study drug, and~~ with a ~~clinical diagnosis of otomycosis confirmed by a~~ positive fungal culture **at Screening/Baseline**.	Modification to definition of MITT population in response to FDA comment at End-of-Phase 2 meeting
10.4.4 Safety Population	**Two safety populations will be defined.** The **Randomization Period** 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 **during the Randomization Period**. **The Open Label safety population will include all subjects who received at least one dose of miconazole oil and had at least one post-Baseline safety assessment during the**	Modification to presentation of safety information due to addition to the study of an optional open-label extension and an Enrollment B portion

Location	Change	Rationale
	Optional Open-label Extension or Enrollment B. **Safety**~~All safety~~ analyses **for the Randomization Period** will be performed using the **Randomization Period safety population. Safety analyses for the Optional Open-label Extension and Enrollment B will be combined and presented using the Open Label** safety population.	
Section 10.5 (Statistical Methods)	10.5 Statistical Methods ~~All statistical processing will be performed using Statistical Analysis System (SAS®) Version 9.4 or higher. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.~~ ~~Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, and standard deviation, median, minimum, and maximum.~~ ~~Full details of statistical analyses will be provided in a separate statistical analysis plan.~~	Reorganization of information (text moved to the beginning of Section 10)
Section 10.5.1 (Efficacy Analyses)	The primary population for ~~all~~ efficacy analyses will be the MITT population (see Section 10.4). Efficacy analyses will also be performed **on the ITT and**~~for~~ the PP **populations**~~population~~ and will be considered supportive.	Modification to populations used for efficacy analyses in response to FDA comment at End-of-Phase 2 meeting; addition of an optional open-label extension for which the ITT population will be used for efficacy analyses
Section 10.5.1 (Efficacy Analyses)	**The primary analysis will be conducted once Enrollment A is complete.**	Specification of when analysis will be conducted given the addition to the study of an optional open-label extension and an Enrollment B portion
Section 10.5.1 (Efficacy Analyses)	The number and percent of subjects who demonstrate a positive outcome for the primary efficacy outcome **as well as all secondary and tertiary efficacy outcomes** will be presented. … **The secondary endpoints will be analyzed analogously to the primary endpoint.**	Addition to protocol of secondary and tertiary endpoints
Section 10.5.1 (Efficacy Analyses)	In **Enrollment A in** cases of bilateral otomycosis…	Addition to the study of an Enrollment B portion
Section 10.5.1 (Efficacy Analyses)	Descriptive statistics will be provided for otomycosis signs and symptoms **and also for clinical cure, modified therapeutic cure, and therapeutic improvement; each at Day 15 will be summarized using the ITT population**	Modification to populations used for efficacy analyses in response to FDA comment at End-of-Phase 2 meeting; addition of an optional open-label extension for which the

Location	Change	Rationale
	for both the Randomization Period and the Optional Open-label Extension.	ITT population will be used for efficacy analyses
Section 10.5.1.1 (Multiple Comparison/Multiplicity)	**Section 10.5.1.1 Multiple Comparison/Multiplicity** **The overall Type I error will be controlled…**	Addition of entire section due to addition to protocol of secondary endpoints
Section 10.5.2 (Safety Analyses)	Safety summaries will be conducted using **two**~~the~~ safety **populations**~~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 be provided separately for the blinded and unblinded portions. Specifically, summaries will be provided by treatment group for the Randomization Period using the Randomization Period safety population, and for all open-label subjects using the Open Label safety population.** All information pertaining to AEs noted during the study will be listed by **study portion (Enrollment A or Enrollment B), study period (Randomization or Optional Open-label), as applicable,** 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.	Modification to presentation of safety information due to addition to the study of an optional open-label extension and an Enrollment B portion
Section 10.5.4 (Missing Data)	Missing data will be imputed **as treatment failures for the primary and secondary efficacy analyses**~~according to the last observation carried forward (LOCF) method. Sensitivity analyses including a tipping point analysis will also be conducted~~. **Missing data otherwise will not be imputed.**	Change to method for handling missing data in response to FDA comment at End-of-Phase 2 meeting; addition to the protocol of secondary efficacy endpoints; reorganization of information regarding sensitivity analyses into a new section
Section 10.5.5 (Sensitivity Analyses)	**10.5.5 Sensitivity Analyses** **In order to explore the effects of missing data, sensitivity analyses…**	Addition of entire section for reorganization of information; modification to sensitivity analyses in response to FDA comment at End-of-Phase 2 meeting
Section 10.5.6 (Subgroup Analyses)	**10.5.6 Subgroup Analyses** **Descriptive summaries on the primary and secondary endpoints will be included for the following subgroups of gender, age, ethnicity,**	Addition of entire section to describe subgroup analyses for this Phase 3 study

Location	Change	Rationale
	race, and fungal organism isolated at Screening/Baseline.	
Section 11.6 (Case Report Form Requirements)	**Source**~~Paper source~~ documents will be created and retained at the clinical site.	Flexibility with regard to format of source documents
Section 13 (Summary of Protocol Amendments)	**13 SUMMARY OF PROTOCOL AMENDMENTS** **…**	Addition of entire section to include a summary of protocol amendments

Revised Table 3 Study Schedule**: Enrollment A**

	Randomization Period				**Optional OLE**	
Evaluations and Procedures:	~~Screening~~ **Screen**/ Baseline[a] Day 1	On ~~Treatment~~ ~~a~~**Treat** [b] Day 8	End of Treat [~~a~~**ab**] Day 15	Test of Cure [~~b~~**bc**] Day 22 [~~c~~**cd**]	**Start of Treat Day OLE1**[e]	**End of Treat Day OLE15**[b]
Informed consent/assent	X					
Inclusion/exclusion criteria	X					
Medical/medication history	X					
Physical examination	X					
Otomycosis signs and symptoms	X	X	X	X		**X**
Urine pregnancy test [~~d~~**df**]	X			X		**X**
Randomization	X					
Dispensation of study drug	X				**X**	
Dispensation of subject diary	X				**X**	
Collection of subject diary		X [g]	X			**X**
Administration of study drug at site	X				**X**	
Weighing of study drug	X	X	X		**X**	**X**
Collection of study drug			X			**X**
Fungal culture [~~e~~**eh**]	X		X	X		
Ear cleaning	X	X				
AE evaluations	X	X	X	X	**X**	**X**
Concomitant medications review	X	X	X	X	**X**	**X**

a. Procedures for this visit may occur over a 2-day period, if necessary (with Day 1 defined as the first day on which study drug is administered). All procedures for this visit must occur before the first administration of study drug with the exceptions that AE evaluations and review of concomitant medications will also occur after the start of study drug on Day 1.

~~a~~**b**. This visit may occur up to 3 days later than the specified day.

~~b~~**c**. This visit may occur up to 1 day sooner or up to 8 days later than the specified day.

~~c~~**d**. In case of early termination, the assessments planned for the Test of Cure Visit should be performed **with the exception of fungal culture, which is not required**.

e. This visit will occur on the same day as the final visit of the Randomization Period.

~~d~~**f**. Females of childbearing potential only.

g. The subject diary will be returned to the subject after review by study staff for documentation of missed and/or extra study drug doses.

~~e~~**h**. Samples will be used for growth and identification of fungal organisms as well as susceptibility testing to miconazole. **Fungal cultures are not required to be taken at Day 15 or at Day 22 for subjects known to have a negative fungal culture at Screening/Baseline (assessed after at least 14 days of incubation by the clinical laboratory performing the fungal cultures).**

OLE=Open-label Extension; Screen=Screening; Treat=Treatment

13.3 Amendment 3 Version 4 14 September 2020

This amendment revises the timing of the study so that Enrollment B may be conducted over multiple time periods, including times when Enrollment A and Enrollment B may be concurrently ongoing. This amendment also clarifies prohibited topical medications prior to and during Enrollment A.

A more complete summary of changes from the prior version is provided below. Insertions are **bolded**. Deletions are ~~struck through~~. For sections that are new or have been completely revised, only a short description is provided.

Location	Change	Rationale
Header	**14 Sep 2020 / Version 4**~~18 May 2020 / Version 3~~	Update to new version and date
Title page	**14 Sep 2020 / Version 4**~~18 May 2020 / Version 3~~ Previous versions: 28 January 2020 / Version 1 (internal only) 04 February 2020 / Version 2 **18 May 2020 / Version 3**	Update to new version and date
Protocol Approval page	**14 September 2020**~~18 May 2020~~	Update to new date
Study Acknowledgement page	**Version 4**~~Version 3~~	Update to new version
Synopsis (Design and Methodology), Section 3 (Study Design)	This study will be conducted in 2 ~~separate, sequential~~ portions… 1. Enrollment A, which will… …2. Enrollment B, which ~~will commence after completion of Enrollment A and~~ will consist of open-label treatment with miconazole oil in subjects who will not be required to have signs and symptoms of otomycosis.	Change in timing of Enrollment B relative to Enrollment A
Synopsis (Design and Methodology)	Subjects will return to the clinic on Day OLE15 for the End of Treatment Visit, at which time a clinical evaluation of the signs and symptoms of otomycosis will be performed, as well as an assessment of AEs and concomitant medications. A urine pregnancy test will be performed in women of childbearing potential. The subject will return all unused miconazole oil along with the completed subject diary. **Data for Enrollment A will be unblinded after all subjects planned for Enrollment A have completed both the Randomization Period and the Optional Open-label Extension, so that analyses from Enrollment A can be conducted even if Enrollment B is still ongoing (i.e., before the conclusion of Enrollment B).**	Change in timing of Enrollment B relative to Enrollment A
Synopsis (Design and Methodology), Section 3.2 (Enrollment B)	Enrollment B **Enrollment B may be initiated while Enrollment A is still actively enrolling subjects.**~~Enrollment B will begin at or after the conclusion of Enrollment A. Data for Enrollment A will be unblinded after all subjects participating in Enrollment A have completed both the Randomization Period and the Optional Open-label Extension, so that~~	Change in timing of Enrollment B relative to Enrollment A

Location	Change	Rationale
	~~analyses from Enrollment A can be conducted before and/or during the conduct of Enrollment B.~~ An estimated 170 male or female subjects will receive study drug (miconazole oil) in Enrollment B, although this number may be higher or lower…	
Synopsis (Design and Methodology)	Subjects will return to the clinic on Day B15 for the End of Treatment Visit, at which time AEs and concomitant medications will be assessed. Subjects will return all unused miconazole oil along with the completed subject diary. A urine pregnancy test will be performed in women of childbearing potential. **Timing of Subject Recruitment Into Enrollment A and Enrollment B** **The study will start with Enrollment A, which will continue until the sponsor determines that a sufficient number of subjects (see Sample Size below) has been recruited to conduct the planned analyses for Enrollment A, at which time the sponsor (or designee) will notify all study sites to terminate further enrollment into the Enrollment A portion of the study. …** **…At times when Enrollment A and Enrollment B are concurrently ongoing, if a subject is found to be eligible for both Enrollment A and Enrollment B, the subject should be enrolled into Enrollment A whenever possible.**	Addition of several paragraphs regarding the change in timing of Enrollment B relative to Enrollment A
Synopsis (Key Exclusion Criteria, Enrollment A)	Subjects with any other dermatoses or conditions of the ear that may interfere with the evaluation of otomycosis or with safety evaluations, 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**, in the ear(s) that will be treated with study drug,** of any topical medicated treatments for otomycosis within 14 days of study entry; use of any systemic antifungal therapy	Clarification that topical medicated treatments for otomycosis within 14 days of study entry are only exclusionary if used in the ear(s) that will be treated with study drug
Synopsis (Sample Size)	For the Randomization Period of Enrollment A, approximately 128 subjects (~64 in each group) are required to provide 80% power, ~~using a~~	Correction of clerical error

Location	Change	Rationale
	using a chi-square test…	
Figure 1	See revised Figure 1	Figure updated to reflect change in timing of Enrollment B relative to Enrollment A
Figure 1 (footnotes)	a. Subjects must meet all eligibility criteria in Section 4.1 to be randomized in Enrollment A. b. Subject must have a visual presence of fungal elements to be enrolled in the Optional Open-label Extension. ~~c. Enrollment B can only commence after all subjects participating in Enrollment A have completed both the Randomization Period and Optional Open-label Extension.~~ **c.**~~d.~~ Subject must meet all eligibility criteria in Section 4.2 to receive treatment with miconazole oil in Enrollment B.	Consistency with the updated Figure 1 reflecting the change in timing of Enrollment B relative to Enrollment A
Section 3.1.3 (Timing of Analysis for Enrollment A)	See Section 3.1.3	Entire section added to reflect change in timing of Enrollment B relative to Enrollment A
Section 3.3 (Timing of Subject Recruitment Into Enrollment A and Enrollment B)	See Section 3.3	Entire section added to reflect change in timing of Enrollment B relative to Enrollment A
Sections 3.4 (Number of Subjects), 3.5 (Investigators), and 3.6 (Study Duration)	Renumbering of these sections to accommodate the addition of Section 3.3	Addition of Section 3.3
Section 4.1.2 (Exclusion Criteria)	4. Use**, in the ear(s) that will be treated with study drug,** of any topical medicated treatments for otomycosis within 14 days of study entry**:**	Clarification that topical medicated treatments for otomycosis within 14 days of study entry are only exclusionary if used in the ear(s) that will be treated with study drug
Section 4.1.2 (Exclusion Criterion #4)	• **Topical corticosteroids prescribed specifically for the treatment of otomycosis are prohibited to be used within 14 days of study entry; however, use of topical corticosteroids for any other reason (e.g., for bacterial otitis externa and/or for control of symptoms in the ear such as itching and/or pain) will not require a 14-day washout** • **Alcohol and/or peroxide are prohibited when prescribed/used by a health care provider specifically for the treatment of otomycosis within 14 days of study entry; however, use of these substances for other purposes (e.g., as a drying agent) will not require a 14-day washout** • **Use of boric acid for any reason is prohibited within 14 days of study entry**	Addition of several paragraphs to clarify commonly-used topical treatments that are exclusionary within 14 days of study entry for the ear(s) that will be treated with study drug
Section 5.1.2 (Prohibited	Other than the study drug, no other topical	Clarification that topical medications

Location	Change	Rationale
Medications)	medications **(including but not limited to antibiotics, alcohol, boric acid, peroxide, and/or corticosteroids)** are allowed to be used in the **ear(s) being treated with study drug**~~ears~~. Other prohibited treatments include systemic antifungal therapy, warfarin, immunosuppressive or immune-stimulating drugs, and systemic steroids. **A subject who discontinues study drug during the Randomization Period and who subsequently uses a topical corticosteroid (e.g., to treat an AE such as itching) in the ear(s) that were treated with study drug during the Randomization Period will be eligible for the Optional Open-label Extension if the topical corticosteroid is discontinued in the ear(s) that will be treated with study drug before the start of study drug in the Optional Open-label Extension, and as long as the subject meets all other eligibility criteria for the Optional Open-label Extension.**	are prohibited only in the ear(s) being treated with study drug; clarification regarding use of topical corticosteroid to treat an AE in relation to subject eligibility for the Optional Open-label Extension
Section 13.3 (Amendment 3 Version 4 14 September 2020)	See Section 13.3	Addition of entire section to describe Amendment 3