Hill Dermaceuticals, Inc.

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STATISTICAL ANALYSIS PLAN

Protocol Number:	MZ-1015-ESP3-054
Title:	Randomized, Double-blind, Phase III Study of the Efficacy and Safety of Miconazole Oil, Active versus Placebo in the Treatment of Otomycosis.
Study Phase:	3
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Table of Contents

1. List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
DM	Data Management
FDA	United States Food And Drug Administration
GCP	Good Clinical Practice
Hill	Hill Dermaceuticals, Inc.
IB	Investigator Brochure
IBC	Institutional Biosafety Committee
ICH	International Conference On Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator site file
MP	Monitoring Plan
PD	Protocol Deviation
PDHP	Protocol Deviation Handling Plan
PI	Principal Investigator
TMF	Trial Master File

2. Introduction

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.

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

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

achieved this endpoint in the Miconazole Oil group (24 of 67 subjects, 35.8%) relative to the Vehicle Oil group (15 of 64 subjects, 23.4%).

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

3. Study Objectives

The objectives of the study are to confirm the efficacy of miconazole oil compared with mineral oil over a 14-day treatment duration in subjects with otomycosis and to further assess the safety of miconazole oil over a 14-day treatment duration.

4. Study Design

4.1. Overall Study Design

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

At Screening/Baseline (Day 1), 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) and 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 supervision of the investigator or site personnel. Adverse events (AEs) will be assessed. The subject will then leave the clinic and continue to administer the study drug twice per day as instructed.

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

Subjects will return to the clinic on Day 22 for the Test of Cure Visit, at which time an assessment of clinical signs and symptoms of otomycosis of the affected ear(s) will be performed (efficacy assessments). AEs and concomitant medications will also be assessed. A urine pregnancy test will be performed in women of childbearing potential.

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

Safety assessments will include AEs.

4.1.1. Schedule of Visits and Assessments

The schedule of assessments can be found in Section 6.1 of the protocol.

4.1.2. Method of Assigning Subjects to Treatment Groups

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

Randomization will be by site.

4.1.3. Blinding

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

If it becomes necessary to unblind a subject's treatment assignment in case of emergency, the investigator should contact the sponsor as per the study Unblinding Plan. A person at the sponsor organization (clinical coordinator) 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.

5. Efficacy and Safety Endpoints

5.1. Efficacy Endpoints

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

5.1.1. Primary Efficacy Endpoints

The primary efficacy endpoint will be:

- Clinical Cure at the Test of Cure visit, with Clinical Cure defined as a score of 0 for fungal elements, and 0 for signs and symptoms of otomycosis (pruritus, debris and aural fullness)

5.1.2. Primary Efficacy Endpoints

The secondary efficacy endpoints are:

- Clinical Cure at the End of Treatment visit, with Clinical Cure defined as a score of 0 for fungal elements, and 0 for each of the signs/symptoms of pruritus, aural fullness and debris based on investigator assessment according to the scales for each individual sign or symptom
- Clinical Clearance at the Test of Cure visit with Clinical Clearance defined as a score of 0 for fungal elements, and a score of 0 or 1 for each sign/symptom of otomycosis (debris, pruritis and aural fullness)
- Clinical Clearance at End of Treatment visit with Clinical Clearance as a score of 0 for fungal elements, and a score of 0 or 1 for each sign/symptom of otomycosis (debris, pruritis and aural fullness)
- Modified Clinical Cure at the Test of Cure visit, with Modified Clinical Cure defined as a score of 0 for fungal elements, and a score of 0 or 1 for each of debris and aural fullness
- Modified Clinical Cure at the End of Treatment visit, with Modified Clinical Cure defined as score = 0 for fungal elements, and score = 0 or 1 for each debris and aural fullness
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5.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Mycological culture results

5.2. Safety Endpoints

The safety endpoints are:

- Treatment-emergent adverse events (TEAEs), with treatment-emergent defined as occurring upon or after administration of the first dose of study drug.

6. Statistical and Analytical Plans

6.1. General Methodology

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

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

Missing efficacy data will be imputed as treatment failures for the primary and secondary efficacy analyses. Missing data otherwise will not be imputed.

The efficacy analysis performed on the intent-to-treat (ITT) population will be considered the primary analysis. The efficacy analysis performed on the per-protocol (PP) population will be considered supportive.

6.1.1. Baseline Definition

Baseline is defined as the last non-missing assessment on or prior to the date of first dose of study drug.

6.1.2. Visit Windowing for Efficacy Assessments

Efficacy data will be summarized based on nominal visit with the exception of data captured at early termination and unscheduled visits which will be summarized based on mapped visit values. If an assessment's mapped visit is a visit at which the subject has data from a scheduled visit present, the data collected at the early termination or unscheduled visit will not be included in analyses.

The analysis windows for early termination and unscheduled visits are presented in the following table.

Analysis Windows for Efficacy Assessments

Scheduled Visit	Target Study Day	Window (Days)
End of Treatment (Day 15)	15	8 to 18
Test of Cure (Day 22)	22	19 to 30

Data collected at early termination and unscheduled visits prior to study day 8 will not be analyzed, with the exception of those identified as baseline values. Data collected at early termination and unscheduled visits after study day 30 will not be included in analyses.

The definition for the study day included in each study window is defined as below:

Study Day prior to Day 1 = Visit Date – Day 1 Date

Study Day on or after Day 1 = Visit Date – Day 1 Date + 1

In the event of multiple values from unscheduled or early termination assessments within an analysis window, the value closest to the scheduled visit target study day will be used for analyses. If two values tie as closest to the time point (for example, one value is before and the other value is after the time point), then the later value will be selected.

Data collected at all visits will be included in the data listings with visit presented as reported by the site.

6.1.3. Adjustments for Covariates

Not applicable to this study.

6.1.4. Handling of Dropouts or Missing Data

Missing data for each efficacy endpoint will be imputed as treatment failures for the primary and secondary efficacy analyses.
Missing data otherwise will not be imputed.

6.1.5. Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study.

6.1.6. Multicenter Studies

Analysis sites will be created as per Section 6.7.5.

6.1.7. Multiple Comparisons/Multiplicity

The overall Type I error will be controlled using a gated sequential approach for the primary and secondary efficacy endpoints. This testing will be performed using the ITT population. The testing process will terminate whenever a statistical test is not significant, i.e., any subsequent test will be considered not significant. The order of testing is:

- Clinical Cure at the Test of Cure visit
- Modified Clinical Cure at the Test of Cure visit
- Clinical Clearance at the Test of Cure visit
- Modified Clinical Cure at the End of Treatment visit
- Clinical Clearance at End of Treatment visit
- Clinical Cure at the End of Treatment visit

6.1.8. Use of an Efficacy Subset of Subjects

Subjects included in the Per Protocol (PP) Population will be included as a subset of the ITT population. Any major protocol deviations will be defined at the time of evaluability evaluation, prior to unblinding.

Excluding subjects who have major protocol deviations is expected to decrease the number of variables impacting the treatment response.

6.1.9. Examination of Subgroups

Descriptive summaries on the primary and secondary endpoints using the ITT population will be included for the following subgroups of gender, age, ethnicity, and race. Age will be summarized as categories of < 18 years, ≥ 18 to < 65 years, and ≥ 65 years.

6.2. Disposition of Subjects

The number of subjects included in each analysis population (ITT and PP) will be summarized by treatment group.

The number of subjects enrolled, completed, and discontinued (including the reasons for discontinuation) will be summarized for each treatment group by each analysis population.

The ear being treated (Left, Right, Both) will be summarized by treatment group.

Subjects who are excluded from an analysis population will be summarized by the reason for exclusion based on primary reason for exclusion.

6.3. Protocol Deviations

Protocol deviations will not be entered into the database. Deviations leading to exclusion from analysis populations will be identified before database lock. Protocol deviations will be presented in a by-subject listing.

6.4. Analysis Populations

Subjects will be presented/summarized based on the primary reason for exclusion. The primary reason for exclusion for each population will be assigned based on the order presented in each section below.

6.4.1. Intent-to-Treat (ITT) Population

All subjects who were randomized and dispensed study drug will be included in the ITT population and analyzed according to the treatment group into which they were randomized.

All efficacy analyses will be presented using the ITT population.

6.4.2. Per Protocol (PP) Population

The PP population will be a subset of the ITT population and will include all subjects who complete the Test of Cure visit without any major protocol violations and analyzed according to the treatment each subject actually received. The PP population will include subjects in the ITT 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 doses 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)
- Missed Test of Cure Visit signs and symptoms

Subjects who discontinue from the study due to an adverse event (AE) 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.

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

6.4.3. Safety Population

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

All safety analyses will be performed using the Safety population and analyzed according to the treatment each subject actually received.

6.5. Demographic and Other Baseline Characteristics

Subject demographic and baseline characteristics will be summarized descriptively by treatment for the ITT, PP and safety populations. Demographic data will also be listed.
Sex, race, and ethnicity will be summarized by counts and percentages. Age will be summarized with descriptive statistics and categorically (< 18 years, ≥ 18 to < 65 years, and ≥ 65 years) for subgroup analyses.

Medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and presented in a by-subject listing.

6.6. Prior and Concomitant Medications

Concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the World Health Organization (WHO) Drug dictionary (WHO-DDE).

Medications which start prior to first dose will be considered prior medications. Ongoing medications and medications ending after the date of first dose will be considered concomitant medications. Medications which are both prior and concomitant will be included in both summaries. Incomplete start and end dates which could be either prior to first dose or after first dose will be considered prior to first dose.

A by-subject listing of all prior and concomitant medications and procedures/therapies will be presented.

6.7. Analysis of Efficacy

6.7.1. Primary Efficacy Analysis

The primary population for efficacy analyses will be the ITT population. Efficacy analyses will also be performed on the PP population and will be considered supportive.

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

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

This primary estimand is defined as follows:

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

3. Discontinuation of study treatment due to lack of efficacy, as defined by 'withdrawal by subject' as primary reason for study discontinuation.
4. Use of rescue medication prior to the Test of Cure visit

For IcEs above 1-3, a composite strategy will be taken where subjects will be considered to have not achieved Clinical Cure. For IcE 4, since rescue medication is not specifically defined, a treatment policy strategy will be taken; the data will be used as recorded regardless of other medication. Additionally, any IcEs not explicitly defined here which result in missing data which have not been specified are treated in the same way; missing data at the Test of Cure visit will be considered as not achieving Clinical Cure.

- Population-level summary: the difference in proportions in Clinical Cure at the Test of Cure visit between the miconazole group and the mineral oil group.

The number and percentage of subjects with Clinical Cure at the Test of Cure Visit will be presented.

The primary analysis of Clinical Cure at the Test of Cure Visit will test the following hypothesis:

H0: $pT - pP = 0$

H1: $pT - pP \neq 0$

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

For subjects with bilateral otomycosis in which at least one ear meets all study eligibility criteria, both ears may be treated with study drug provided that both ears have a score of 1 for fungal elements, and the determination of the study ear will be made as described in Section 4.1.

Primary efficacy endpoints will also be presented in a by-subject listing including each component of Clinical Cure and response.

6.7.2. Secondary Efficacy Analysis

The secondary endpoints will be analyzed analogously to the primary endpoint, including the treatment of IcEs and missing data.

- Modified Clinical Cure at the Test of Cure visit
- Clinical Clearance at the Test of Cure visit
- Modified Clinical Cure at the End of Treatment visit
- Clinical Clearance at End of Treatment visit
- Clinical Cure at the End of Treatment visit

A stepwise process will be conducted for testing the secondary efficacy endpoints in order to control for multiplicity; refer to Section 6.1.7.

All secondary efficacy analyses will be presented using the ITT population. Analyses will also be presented in a supportive manner using the PP population. All efficacy data will be included in by-subject listings.

6.7.3. Sensitivity Efficacy Analysis

Sensitivity analyses consist of repeating analyses for the primary and secondary endpoints using the PP population.

6.7.4. Exploratory Efficacy Analysis

Results of the fungal cultures which are taken at designated visits are recorded in the eCRFs and will be presented using descriptive statistics.

6.7.5. Analysis Sites

The study is intended to be conducted in a manner such that a minimum of 5 subjects will be enrolled in each treatment arm for any Investigator site. In the event that there are too few subjects in a treatment arm for a site, then this site's data will be combined with the site with the largest enrollment. If there is a further need to combine data, then the data of the site with the second smallest enrollment will be combined with the site's data which had the second largest enrollment and so on. This process will continue for all sites who did not randomize a minimum of 5 subjects per treatment arm. The process of combining sites that have insufficient subjects per treatment arm will result in redefining sites for the purpose of statistical analyses. These will be referred to as 'analysis sites' in the statistical analyses.

6.8. Safety Evaluation

6.8.1. Extent of Exposure

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of doses, number of missed doses and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the expected number of doses while enrolled in the study.

Days of exposure = Date of Last Dose – Date of First Dose + 1

Total Number of Doses:

> 2*(Date of Last Dose - Date of First Dose + 1) – (Number of study ear doses missed as collected on the case report form (CRF)) + (Number of study ear extra doses as collected on the CRF)

Total Number of Expected Doses = 28

If a subject discontinues from the study early before the End of Treatment Visit, the number of expected doses will be calculated to the later of the last visit date or date of last dose. If the total number of expected doses exceeds 28 then the total number of expected doses will be set to 28.

Compliance will be calculated as a percentage as 100 times the total number of doses divided by the total number of expected doses.

Extent of exposure summaries will be provided using the Safety population.

6.8.2. Medical History

Medical history results will be presented in a by-subject listing.

6.8.3. Adverse Events

Safety summaries will be conducted using the Safety population.

All adverse events (AEs) occurring during the study will be recorded and classified using terminology from MedDRA.

All reported TEAEs, defined as any AE occurring upon or after administration of the first dose of study drug, 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.

All information pertaining to AEs noted during the study will be listed by 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.

6.8.4. Physical Examination

Physical examination data will be presented in a by-subject listing.

6.8.5. Pregnancy Testing

Pregnancy testing results will be presented in a by-subject listing.

7. Determination of Sample Size

Approximately 110 subjects (55 per group) provide ~80% power, using a Fisher's Exact test with a 2-sided significance level of .05, to demonstrate a difference between the miconazole oil group and mineral oil group, assuming a response rate of 35% in the miconazole oil group and 10% in the mineral oil group and a chi-square test with alpha of 0.05. These assumptions are consistent with the findings from the first Phase 3 study for the miconazole oil group, and with conservative assumptions for the mineral oil group.

8. Changes from the Protocol in the Planned Analyses

The approach to testing of the secondary endpoints has been added in the SAP.
Intercurrent events are specified in more detail in the SAP.
The protocol erroneously includes the word 'Exact'; the primary endpoint will be tested using a CMH test stratified by analysis site.
No mention of multiplicity strategy toward the testing of secondary endpoints was made in the protocol. The SAP lays out the approach in Section 6.1.7.

9. Revision History

Version	Change Control No.	Effective Date
0	CC-5391	11/05/24
1	CC-5546	02/06/25

Appendix 1: Otomycosis Signs and Symptoms

The signs and symptoms of otomycosis will be assessed according to the scales for pruritus, debris, presence of fungal elements and aural fullness as outlined below.

Pruritus

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

Debris

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

Presence of Fungal Elements

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

Aural Fullness

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