# CLINICAL STUDY PROTOCOL

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| **Protocol Title:** | A Phase III, Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Clotrimazole 1% Otic Solution Compared to Placebo for the Treatment of Fungal Otitis Externa (Otomycosis). |
| **Acronym / Protocol Number:** | CLEAR-2 / CLOTOT3-16IA03 |
| **EudraCT Nº:** | 2019-003463-22 |
| **Investigational Product:** | Clotrimazole 1% otic solution (SVT-15652) |
| **Principal Investigator:** | [redacted] |
| **Sponsor:** | Laboratorios Salvat, S.A.<br>Gall 30-36<br>08950 - Esplugues de Llobregat - Barcelona - Spain |
| **Version Nº:** | 2.0 (Amendment 1) |
| **Date:** | 31 October 2019 |

**Previous versions:**

| Version | Date |
|---|---|
| v. 1.1 | 09 September 2019 |

**SPONSOR'S SIGNATURE PAGE**

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| **Sponsor:** | Laboratorios Salvat, S.A. |
| **Clinical Protocol Number:** | CLOTOT3-16IA03 |
| **Investigational product:** | Clotrimazole 1% Otic Solution |
| **Protocol Title:** | A Phase III, Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Clotrimazole 1% Otic Solution Compared to Placebo for the Treatment of Fungal Otitis Externa (Otomycosis). |

This study will be conducted according to the protocol and in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonization, the Declaration of Helsinki, and applicable regulatory requirements

Approved by:

_____ _____

Enrique Jiménez, MD
Medical Director
Laboratorios Salvat, S.A.

Date

_____ _____

Patricia Lois
Clinical Trial Manager
Laboratorios Salvat, S.A.

Date

## INVESTIGATOR'S SIGNATURE PAGE

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| **Sponsor:** | Laboratorios Salvat, S.A. |
| **Clinical Protocol Number:** | CLOTOT3-16IA03 |
| **Investigational Product:** | Clotrimazole 1% Otic Solution |
| **Protocol Title:** | A Phase III, Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Clotrimazole 1% Otic Solution Compared to Placebo for the Treatment of Fungal Otitis Externa (Otomycosis). |

All documentation that has been supplied to me by Laboratorios Salvat, S.A. (the Sponsor) and/or the Sponsor's designee concerning this study, and that has not been previously published, will be kept in the strictest confidence. This documentation includes, but is not limited to, the study protocol, the Investigator's Brochure, and Electronic Data Capture (EDC).

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor or their designee and the IRB/IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and do agree to abide by all the conditions and instructions contained in this protocol.

_____ _____

Signature (Principal Investigator) Date

_____

Printed Name

## PROTOCOL SYNOPSIS

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| **Sponsor:** | Laboratorios Salvat, S.A. |
| **EudraCT number** | 2019-003463-22 |
| **Title:** | A Phase III, Multicenter, Randomized, Double-Blind Clinical Trial to Assess the Efficacy and Safety of Clotrimazole 1% Otic Solution Compared to Placebo for the Treatment of Fungal Otitis Externa (Otomycosis). |
| **Short title:** | Clotrimazole 1% Otic Solution for the Treatment of Otomycosis. |
| **Acronym** | CLEAR-2 |
| **Study Number:** | CLOTOT3-16IA03 |
| **Study Phase:** | III |
| **Study Centers:** | Multi-center study in approximately 17 sites (Bulgaria, Portugal, Romania and Spain). |
| **Study Period** | Planned duration of the study (for each patient): 4 weeks<br>Planned recruitment period: 12 months |
| **Objectives:** | To evaluate the efficacy and safety of topical Clotrimazole 1% otic solution for the treatment of otomycosis.<br>The main efficacy endpoint is proportion of subjects with therapeutic cure (mycological cure and clinical cure) at test-of-cure in MITT population.<br>Mycological cure is defined as eradication (culture does not show growth of any fungal pathogen) or presumed eradication (there is no material to culture and overall clinical outcome is clinical cure). Clinical cure is defined as a total sign/symptoms score (TSSS) of zero on the 4-point severity scale for pruritus, otalgia, ear fullness and otorrhea. |
| **Study Design:** | Multicenter, Randomized, 2-arm parallel-group, double blind, placebo-controlled study in patients suffering from Fungal Otitis Externa (Otomycosis). This study will compare the efficacy and safety of Clotrimazole 1% otic solution to that of Placebo, when administering one vial twice daily during 14 days. |

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| **Study medication, Dosage, and Route of Administration:** | **Test product:** 1 vial of Clotrimazole 1% otic solution in the affected ear(s) twice a day during 14 days.<br><br>**Reference product (placebo):** 1 vial of Saline solution 0.9% in the affected ear(s) twice a day during 14 days.<br><br>A patient study medication kit will contain 6 pouches with 1 strip of 5 vials in each pouch, for a total of 30 vials. Patients with bilateral otomycosis will receive 2 kits with the same treatment. A study staff member will remove 2 vials from the kit and keep them for traceability (if bilateral, remove 2 vials from each kit). The remaining 28 vials will be returned to the kit for dispensation to the patient. The first administration will be at the study site supervised by a study staff member.<br><br>The solution will be warmed by holding the vial for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient will lie with the affected ear upward and 1 vial of the otic solution will be instilled in the ear canal. The patient must remain in the position for 1 minute. Repeat, if necessary, for the opposite ear. |
| **Patient Population:** | Patients of 18 years of age and older, with otomycosis.<br><br>A total of 191 patients will be randomized in a 2:1 ratio (Clotrimazole 1% otic solution: Placebo) to obtain 150 evaluable patients (100 Clotrimazole 1% and 50 Placebo) |
| **Study Rationale:** | Clotrimazole is a broad spectrum antifungal agent that was found to effectively controls fungal isolates attributed to otomycosis (*Aspergillus* and *Candida*) when administered as 1% otic solution twice daily. Each dose consists of approximately 1.7 mg of clotrimazole. The dosing regimen has been shown to be effective in the treatment of otomycosis leading to a negative mycological culture and near total suppression of clinical signs/symptoms (pruritus, otorrhea, ear fullness and otalgia).<br><br>Subjects of 18 years of age and older, with otomycosis will be randomized in a 2:1 ratio to receive treatment with Clotrimazole 1% otic solution or placebo (Saline solution 0.9%). Subjects will be administered one vial of Clotrimazole 1% otic solution or placebo twice daily for 14 days. |

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| **Eligibility Criteria:** | **Inclusion Criteria:**<br>• At least 18 years of age at Visit 1 (Day 1, Screening/Baseline).<br>• Clinical diagnosis of fungal otitis externa (otomycosis) in one or both ears, where topical treatment is indicated.<br>• Presence of at least two of the following symptoms at baseline: pruritus, otalgia and ear fullness.<br>• Presence of debris and/or drainage clinically consistent with a fungal infection, i.e. white or black appearance consistent with *Aspergillus spp*. or *Candida spp*.<br>• Otorrhea/debris sample for bacterial and mycological cultures.<br>• Provide written informed consent.<br>• Willing and able to follow all instructions and attend all study visits.<br>• Females who are not pregnant, not lactating and are not planning a pregnancy during the study. All females of childbearing potential will be able to participate only if they have a negative urine pregnancy test at baseline and if they agree to use adequate birth control methods to prevent pregnancy throughout the study. |
| | **Exclusion Criteria:**<br>• Known bacterial otitis externa or malignant otitis externa.<br>• Tympanic perforation, tympanostomy tubes inserted and post mastoid surgery.<br>• Structural ear anomalies which may difficult the evaluation of the therapeutic response.<br>• Uncontrolled diabetes mellitus.<br>• Known or suspected hypersensitivity to clotrimazole or any component of study medication.<br>• History of an immunosuppressive disorder and/or current immunosuppressive therapy.<br>• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.<br>• Any recent systemic infection within 30 days of the inclusion or any current infection requiring systemic antimicrobial or systemic antifungal therapy. |

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| | • Use of topical therapy with antifungal properties in the target ear within 2 weeks of the inclusion.<br>• Use of systemic antifungal therapy within 1 month of the inclusion.<br>• Concurrent use of any compound, agent or substance that is applied or instilled to the evaluable ear or surrounding area, except non-bacteriostatic saline solution for potential additional cleaning before taking the sample to be cultured.<br>• Concurrent use of analgesic therapy (prescription or over the counter) with anti-inflammatory properties (acetylsalicylic acid for cardiovascular prevention at doses of 325mg or less is allowed). Analgesics without anti-inflammatory properties, such as acetaminophen and anti-inflammatory agents at stable doses at least 30 days prior to enrollment are allowed.<br>• Concurrent use of non-topical antipruritics, except antihistamines at stable doses (at least 30 days prior to enrollment).<br>• Concurrent use of any systemic corticosteroid, except nasal or inhaled corticosteroids at stable doses (at least 30 days prior to enrollment).<br>• Prior participation in this trial unless patient was not randomized.<br>• Participation in other investigational drug or device clinical trials within 30 days prior to the inclusion, or planning to participate in other investigational drug or device clinical trials within 24 days of starting treatment with study medication. |

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| **Study Evaluation:** | **Visit 1 (Baseline; Day 1)**<br>• Informed Consent.<br>• Collection of general patient information: Medical History.<br>• Physical examination (including Ear examination with or without microscope).<br>• Vital signs examination (Temperature, blood pressure and pulse).<br>• Collection of urine for pregnancy test, if the subject is a woman of childbearing potential.<br>• Clinical assessment:<br>  ○ Examination of both ears.<br>  ○ Evaluation of signs and symptoms:<br>  - Pruritus<br>  - Otalgia<br>  - Ear fullness<br>  - Otorrhea<br>• Collection of otorrhea/debris sample for bacterial and mycological cultures.<br>• If bilateral otomycosis is present on exam, culture specimen collection should be performed only on the evaluable ear.<br>• Debridement of the ear(s) (after collection of the culture specimen).<br>• Randomization.<br>• Dispensing study medication and administration of first dose.<br>• Adverse Events Assessment.<br>• Concomitant medication use.<br>• Provide a visit calendar.<br><br>**Visit 2 (During treatment; Day 8-10)**<br>• Vital signs examination (Temperature, blood pressure and pulse).<br>• Clinical assessment:<br>  ○ Examination of both ears.<br>  ○ Evaluation of signs and symptoms:<br>  - Pruritus<br>  - Otalgia<br>  - Ear fullness |

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| | - Otorrhea<br>○ Overall clinical outcome, based on sum of signs and symptoms scores (resolved, improved, not changed, worsened).<br>• Collection of otorrhea/debris sample (if present) for bacterial and mycological cultures.<br>• Debridement of the ear(s), if applicable (after collection of the culture specimen).<br>• Adverse Events Assessment.<br>• Concomitant medication.<br>In the case of patients who report no improvement in otomycosis signs/symptoms, the Investigator will choose one of the two following options for the patient:<br>1. Continue with the study medication and attend Visit 3.<br>2. Discontinue study medication. The Investigator may treat patient with other medication (rescue medication) at their discretion.<br>○ If investigator prescribes rescue medication, the patient will be withdrawn from the study. The clinical outcome for the patient will be recorded as Treatment failure at the End of Study form.<br>○ If investigator does not prescribe any rescue medication, the patient will be expected to return for a clinical and safety evaluation at Visit 3.<br><br>**Visit 3 (End of Treatment; Day 15-17) (EOT)**<br>• Vital signs examination (Temperature, blood pressure and pulse).<br>• Clinical assessment:<br>○ Examination of both ears<br>○ Evaluation of signs and symptoms:<br>- Pruritus<br>- Otalgia<br>- Ear fullness<br>- Otorrhea<br>○ Overall clinical outcome, based on sum of signs and symptoms scores (resolved, improved, not changed, worsened).<br>• Collection of otorrhea/debris sample (if present) for bacterial and mycological cultures. |

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| | • Debridement of the ear(s), if applicable (after collection of the culture specimen).<br>• Adverse Events Assessment.<br>• Concomitant medication use.<br>• Collection of remaining study medication and evaluation of compliance.<br>In the case of patients who report no improvement in otomycosis signs/symptoms, the Investigator will choose one of the two following options for the patient:<br>1. Continue the patient in the study without any treatment for otomycosis (rescue medication) until Visit4. The patient will come to Visit 4.<br>**2.** Prescribe rescue medication and withdraw the patient from the study. The Investigator will withdraw the patient from the study and will treat patient with other medication at their discretion. The clinical outcome for the patient will be recorded as Treatment Failure at the End of Study form.<br><br>**Visit 4 (Test of Cure; Day 24-26) (TOC)**<br>• Vital signs examination (Temperature, blood pressure and pulse).<br>• Clinical assessment:<br>○ Examination of both ears<br>○ Evaluation of signs and symptoms:<br>- Pruritus<br>- Otalgia<br>- Ear fullness<br>- Otorrhea<br>○ Overall clinical outcome, based on sum of signs and symptoms scores (resolved, improved, not changed, worsened).<br>• Collection of otorrhea sample (if present) for bacterial and mycological cultures.<br>• Debridement of the ear(s), if applicable (after collection of the culture specimen).<br>• Adverse Events Assessment.<br>• Concomitant medication.<br>• Completion of the end of study form. |
| **Efficacy Assessments:** | **Efficacy:** Efficacy will be assessed by mycological assessment (fungal culture), AND the sum of signs and |

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| | symptom scores (pruritus, otalgia, ear fulnness and otorrhea).<br>**Primary endpoint:**<br>• Therapeutic cure at test-of-cure (Visit 4) in the MITT population.<br>**Therapeutic cure** is defined as both mycological cure AND clinical cure.<br>**Mycological cure** is defined as eradication (culture does not show growth of any fungal pathogen) or presumed eradication (there is no material to culture and the overall clinical outcome is clinical cure).<br>**Clinical cure** is defined as a total signs/symptoms score (TSSS) of zero on a 4-point scale for pruritus, otalgia, ear fullness and otorrhea.<br>**No Response** is defined as :<br>a positive fungal culture OR<br>sum of signs and symptoms >0.<br>**Secondary endpoints:**<br>• Overall clinical outcome at Visits 2, 3 and 4.<br>• Mycological outcome at Visits 2, 3 and 4.<br>• Therapeutic cure at Visit 2 and 3.<br>• Changes in TSSS at Visits 2, 3 and 4.<br>• Changes in individual signs and symptoms at Visits 2, 3 and 4.<br>In the case of bilateral otomycosis the non-selected ear will also be treated and assessed for its clinical evolution. |
| **Safety Assessments:** | The safety assessments will include adverse events (AEs), and vital signs. All safety data will be summarized separately. Adverse events will be coded and tabulated by system/organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized by relationship to treatment and severity. In addition, serious adverse events (SAEs) and AEs leading to discontinuation will be summarized similarly. |
| **Study Medication Compliance:** | Compliance will be assessed by a review of the number of vials returned. The number of doses the patient actually took during the treatment period will be divided by the number of doses the patient was expected to take during that period. The resulting ratio will be multiplied by 100% to determine percent compliance. Patients will be considered “compliant” if their percent compliance is between 80% and 100%. |

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| **Statistical Methods:** | Analysis will include the following populations:<br>• CITT Population (clinical intent-to-treat): includes all randomized subjects.<br>• Safety Population includes all randomized subjects who received at least one dose of the study treatment.<br>• MITT Population (mycological intent-to-treat): includes all randomized subjects who had a positive baseline fungal culture.<br>• MPP Population (mycological per protocol): includes all randomized subjects who had a positive baseline fungal culture, were compliant with the assigned study treatment, and completed the evaluation at the test-of-cure (evaluation phase) within the designated visit window and have no major protocol violations.<br>All efficacy analyses performed on the MITT population will be repeated on the MPP population.<br>Sample size calculation:<br>Clotrimazole otic solution should be statistically superior to the placebo ($p<0.05$) with regard to the therapeutic cure at the test-of-cure visit, using the MITT population.<br>Assuming a significance level of 5% and a desired statistical power of 95%, a placebo effect of 30%, and a 2:1 allocation schedule, the total number of patients needed to detect a difference of 30% in the therapeutic cure (100% relative increase) is 150 (100 with clotrimazole and 50 with placebo). The suspected dropout rate due to negative mycological culture at baseline is 21% that leads to a required inclusion of 191 patients (127 for the clotrimazole group and 64 patients for the placebo group).<br>As this is a twin trial if the CLEAR-1 study is completed before this study (CLEAR-2) an updated sample size computation will be performed for CLEAR-2 utilizing the results from the CLEAR-1 given the results from the CLEAR-1 will provide a more accurate estimation of the cure rate for treatment and control arms." |

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**List of Abbreviations**

| | |
|---|---|
| AE | Adverse event |
| b.i.d | Twice daily |
| CITT | Clinical intent-to-treat |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| EOT | End-of-treatment |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| IUD | intrauterine device |
| IWRS | Interactive Web Response System |
| LDPE | Low-density polyethylene |
| MPP | Mycolological Per-Protocol |
| MITT | Mycological intent-to-treat |
| PEG | Polyethylene glycol |
| SAE | Serious adverse event |
| TEAE | Treatment-emergent adverse event |
| TOC | Test-of-cure |
| TSSS | Total signs/symptoms score |
| UK | United Kingdom |
| US | United States |

# 1. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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| **Sponsor contact** | Laboratorios Salvat, S.A.<br>Gall, 30-36<br>08950 - Esplugues de Llobregat<br>Barcelona – Spain<br>Enrique Jimenez, MD,<br>Medical Director<br>e-mail: ejimenez@svt.com<br>Telephone: [redacted] |
| **Principal Investigator** | [redacted] |
| **Adverse Event Reporting** | [redacted] Clinical Safety<br>[redacted] Clinical Safety<br>[redacted] SAE reporting line - EU<br>Telephone: [redacted]<br>Fax: [redacted]<br>e-mail: [redacted]<br>SALVAT Pharmacovigilance<br>e-mail: pharmacovigilance@svt.com |
| **Packaging and Distribution of Study Medications** | [redacted] |

# 2. INTRODUCTION

## 2.1 Background

Acute otitis externa, also called "swimmer's ear", is a diffuse inflammation of the external ear canal, which includes the auricle, auditory canal and eardrum (Vennewald et al., 2010)[1]. Inflammation can extend to the pinna distally or to the tympanic membrane proximally (Osguthorpe et al., 2006; Schaefer et al., 2012)[2,3]. Acute otitis externa is characterized by rapid onset and is usually bacterial, rather than fungal, in etiology (Roland et al., 2002)[4]. Otomycosis, or fungal otitis externa, is a fungal infection of the external ear canal. Fungal involvement in acute otitis externa is only found in about 2% of acute otitis externa cases in the United States (US), with 98% of cases being caused by bacteria. However, it has been found to be common in other areas of the world (Schaefer et al., 2012; Roland et al., 2002)[3,4]. Fungi may either be the primary pathogen involved in otomycosis or secondary to bacterial infection (Prasad et al., 2014)[5].

Otomycosis is most often unilateral, with early manifestations including pruritus, otalgia, otorrhea and aural fullness (Pradhan et al., 2003)[6].

Common risk factors for otomycosis include exposure to excess moisture (humid environment, swimming, etc.), trauma, use of hearing aids, quantitative or qualitative changes in earwax, immuno-compromised host, and increased use of topical antibiotic/steroid regimens (Kiakojuri et al., 2015; Prasad et al., 2014)[7,5]. Otomycosis occurs in three stages (Araiza et al., 2006)[8]:

1. Pre-inflammatory stage: The lipid layer of the auditory canal is sloughed off due to excessive moisture or repeated trauma. Edema occurs during this stage, and patients usually report a feeling of ear canal obstruction and itching.
2. Acute inflammatory stage: Edema and erythema is experienced at this stage, accompanied by an odorless discharge. At this stage, inflammation, pain, edema and sero-purulent matter worsens. In more severe cases, the lining of the auditory canal becomes obstructed.
3. Chronic inflammatory stage: Pain is described as intense at this stage. Infection may spread to surrounding soft tissue, lymph nodes and cranial bones.

Diagnosis of otomycosis is based on visual signs of inflammation in the ear canal through otoscopy and biomicroscopy, and mycological exams to evaluate the presence of fungi (Kiakojuri et al., 2015)[7]. Examination of the ear canal reveals fungal growth of either black, gray, bluish green, yellow or white coloring (Ong et al., 2005)[9]. The fungal species that cause otomycosis include molds, yeasts and dermatophytes (Vennewald et al., 2010)[1]. The most common fungal infections are caused by Aspergillus (60-90%) and Candida (10-40%) fungal species, but a wide spectrum of fungal strains can cause otomycosis (Kiakojuri et al., 2015; Ong et al., 2005; Prasad et al., 2014)[7,9,5].

Treatment recommendations include local debridement (microaspiration), local and systemic anti-fungal agents, and discontinuation of topical antibiotics (Anwar et al. 2014)[10]. In some cases, fungal infection may spread to other sites including the middle ear and the mastoids.

Topical treatment of otomycosis with an anti-fungal agent that is active against these species such as clotrimazole is therefore warranted. There is currently no FDA approved anti-fungal otic drug for the treatment of otomycosis, and therefore, this condition is an unmet medical need in the US. As a result, on May 10th, 2016 clotrimazole otic solution was granted an orphan drug designation. The drug is approved in the European Union (EU) and is marketed under CANESTEN (Clotrimazole 1% solution in Polyethylene glycol (PEG) 400) since 1981 and is specifically recommended for "use on hairy skin and in fungal infections of the outer ear (otitis externa) and middle ear (otomycosis)" in the United Kingdom (UK).

Laboratorios Salvat, S.A. (SALVAT) is investigating the use of Clotrimazole 1% otic solution as a treatment for the fungal otitis externa (otomycosis) due to *Aspergillus* or *Candida* species.

Clotrimazole otic solution is a new formulation for an approved drug substance to be used by a new route of administration. The drug substance clotrimazole is a broad-spectrum antifungal that is currently marketed in the US as an oral, topical, and vaginal drug product as prescription and OTC products. The composition of the referred topical solution (reference listed drug: ANDA #074580) is 1% of clotrimazole in PEG 400. The sponsor brings to consideration that there is another product with the same composition (clotrimazole 1% in PEG 400) and the specific indication of otomycosis marketed since 1981 in the UK (CANESTEN 1% solution Summary of Product Characteristics)[11].

There are no clotrimazole otic products approved for human use in the US though clotrimazole solutions and creams are used off-label for otic delivery. Compounded preparations are also used for this indication. One of the vehicles used most often in otic preparations are polyethylene glycols (Pramar, 2012)[12].

The formulation under development is a sterile, preservative-free otic solution of Clotrimazole 1%, supplied in single dose vials. Each vial/application delivers approximately 1.7 mg of clotrimazole.

The contents of 1 vial will be instilled into the affected ear canal twice daily (b.i.d.) for 14 days in the treatment of otomycosis. This dosing regimen will be used for patients of all ages. Clotrimazole is a broad-spectrum antimycotic that belongs to the triazole family of drugs. The mechanism of action of clotrimazole involves binding to ergosterol, an essential sterol located in the cytoplasmic membrane of fungal species. This binding creates a pore in the fungal membrane that causes the leakage of ions (potassium and hydrogen) and other molecules and leads to cell death (Munguia, 2008)[13].

Clotrimazole is used worldwide for treating fungal infections, including the fungal otitis externa (otomycosis).

In a review of the literature on otomycosis studies, clotrimazole has shown to be effective and well tolerated for the treatment of otomycosis at different doses (varying between once a day every other day for 10 days and 4 drops three times a day for one month) (Munguia et al, 2008)[13].

The dosing regimen for the clotrimazole solution approved in the UK (CANESTEN) is 2-3 drops of solution in the ear two or three times a day at least 2 weeks (the minimum amount of clotrimazole is 0.74 mg/administration and 1.48 mg/day, and the maximum amount of clotrimazole is 1.11 mg /administration and 3.33 mg/day).

Clotrimazole was also shown to be safe and effective in treating otomycosis with perforated tympanic membrane when administered as a Clotrimazole 1% solution in PEG 400 for up to 3 weeks in 40 patients either delivered using an impregnated Q-tip or an ear wick. Patients were reported to have tolerated both treatments very well. Two patients (11%) had some burning in the first two days of treatment. Itching was gradually relieved over the first week in all patients. The tympanic membrane looked normal in all patients following treatment and perforations closure was noted in 4 out of 40 patients (Abou-halawa et al., 2012)[14].

Overall, clotrimazole is reported to be safe and effective regardless of the route of administration with no ototoxic effects reported in any of the clinical studies.

SALVAT has completed EBEROTIII/11IA01 where safety and efficacy of Eberconazole 1% otic solution was compared with Clotrimazole 1% otic solution (CANESTEN solution) in patients with otomycosis. The study was a multicenter, randomized, parallel-group, double blind phase III non-inferiority study comparing the clinical efficacy and safety of Eberconazole 1% otic solution

compared with Clotrimazole 1% otic solution for the treatment of otomycosis as assessed by mycological evaluation, otoscopic examinations (pruritus, otorrhea and aural fullness), otalgia, and AEs. A total of 190 patients aged 18 years or older were included and treated with either Clotrimazole 1% otic solution (n=95) or Eberconazole 1% otic solution (n=95) 5 drops twice daily for 14 days.

The main efficacy variable consisted of a combination of clinical and mycological evaluation (complete response). The majority of the patients had a complete response to the treatment, with similar percentages in both groups (83.5% in the clotrimazole group and 81.8% in the eberconazole group; p=0.0789; intent-to-treat (ITT) population). These results showed that both drugs are effective in the treatment of otomycosis, although the non-inferiority of eberconazole with respect to clotrimazole was not demonstrated.

The administration of Clotrimazole 1% otic solution, at a dose of 5 drops (1.5 mg) twice a day, was safe and well tolerated throughout the 14 days of treatment and the follow-up phase.

## 2.2 Rationale for the Study

Clotrimazole is a broad spectrum antifungal agent that was found to effectively controls fungal isolates attributed to otomycosis (Aspergillus and Candida) when administered as 1% otic solution twice daily. Each dose consists of approximately 1.7 mg of clotrimazole. The dosing regimen has been shown to be effective in the treatment of otomycosis leading to a negative mycological culture and near total suppression of clinical signs/symptoms (pruritus, otorrhea, otalgia, and aural fullness).

Subjects of 18 years of age and older, with otomycosis will be randomized in a 2:1 ratio to receive treatment with Clotrimazole 1% otic solution or placebo (Saline solution 0.9%). Subjects will be administered one vial of Clotrimazole 1% otic solution or placebo twice daily for 14 days. A follow up evaluation will be conducted on Week 1 (during treatment), after treatment (Week 2) and Week 4 (+/- 4 days).

This study is being conducted to support an application for approval to market Clotrimazole 1% in the US for the indication of otomycosis. The reference (comparator) product in this study, Saline solution 0.9%, is expected to provide a lower efficacy rate when compared to Clotrimazole 1%.

## 2.3 Risk-Benefit Assessment

Clotrimazole is used worldwide for treating fungal infections, including the fungal otitis externa (otomycosis). However, it is important to note that in US there are no clotrimazole otic products approved for human use and clotrimazole solutions and creams are used off-label for otic delivery.

In SALVAT clinical trial (EBEROTIII/11IA01), Clotrimazole 1% otic solution was shown to be safe and effective in otomycosis following a 2-week treatment with Clotrimazole 1% solution formulation with no serious adverse safety events.

The published literature also supports the efficacy and lack of ototoxic effects in humans (Munguia, 2008; Vennewald, 2010)[13,1]. These data indicate that the proposed clinical study does not present an unacceptable risk to patients and the potential for adverse events is very low.

Absorption is expected to be negligible when clotrimazole is applied otically. Clotrimazole is reported to be safe and effective regardless of the route of administration with no topical dermal,

oral or ototoxic effects reported in any of the clinical studies. The extensive clinical experience with clotrimazole confirms that it has low potential for both otic and systemic toxicity.

No significant safety findings are anticipated with clotrimazole. Overall, the current safety data for clotrimazole suggests a well-tolerated drug, with a favorable benefit-risk profile.

# 3. OBJECTIVES

## 3.1 Primary Objective

To demonstrate the superior efficacy of Clotrimazole vs. placebo in the treatment of otomycosis, with respect to the therapeutic cure at test-of-cure (TOC; Visit 4) in the MITT population.

**Therapeutic cure** is defined as both mycological cure AND clinical cure.

**Mycological cure** is defined as eradication (culture does not show growth of any fungal pathogen) or presumed eradication (there is no material to culture and the overall clinical outcome is clinical cure)

**Clinical cure** is defined as a total signs/symptoms score (TSSS) of zero on a 4-point scale for pruritus, otalgia, ear fullness and otorrhea.

No Response is defined as:

a positive fungal culture OR

sum of signs and symptoms >0 on TOC

## 3.2 Secondary Objectives

- Overall clinical cure at Visits 2, 3 and 4.
- Mycological cure at Visits 2, 3 and 4.
- Therapeutic cure at Visit 2 and 3.
- Changes in TSSS at Visits 2, 3 and 4.
- Changes in individual signs and symptoms at Visits 2, 3 and 4.

In the case of bilateral otomycosis the non-selected ear will also be treated and assessed for its clinical evolution.

# 4. OVERALL DESIGN AND PLAN OF THE STUDY

## 4.1 Overview

This is a randomized, parallel-group, double-blinded, active-controlled, multicenter study comparing Clotrimazole 1% otic solution with Placebo in the treatment of fungal otitis externa (otomycosis) in adults. A diagram of the study design is shown in Figure 1, and the schedule of observations and procedures is shown in Table 1 (in Section 8.1).

Patients selected for the study will be male or female, 18 years of age and older, with uncomplicated otomycosis in at least 1 ear. At **Visit 1** (Day 1), patients who have signed the Informed Consent Form (or had it signed by their legally authorized representative) and met the study entry criteria will be randomized in a 2:1 ratio to either the investigational treatment, Clotrimazole 1% otic solution, or the Placebo, Saline solution 0.9%.

At these visits, signs and symptoms of otomycosis will be assessed and a sample of ear exudate (otorrhea or debris if otorrhea is not available) for bacterial and mycological cultures will be collected before onset of treatment and debridement. Debridement of the ear will be preferably done by suction. Patients will be taught to administer study medication and will be instructed to apply it twice daily for 14 days. Patients will receive a 14-day supply of study medication. Patients with bilateral otomycosis will receive the same treatment in both ears. Patients will be instructed to refrain from swimming during the study treatment period and preferably until the final study visit is completed. Patients will also be advised to use a shower cap or neoprene band when bathing.

Day 1 will be the day when the first dose is administered (important when the first dose is administered the day after the baseline visit).

At Visit 1, a urine pregnancy test will be performed in females of childbearing potential.

Patients who show up before day 8 with no improvement or worsening of their signs/symptoms, and the investigator's decision is to discontinue the patient from the study medication, this will be considered as Visit 2, and all the procedures corresponding to this visit will apply.

Patients will attend **Visit 2** on Day 8-10 of study treatment to check on each patient's clinical progress. At this visit, signs and symptoms of otomycosis will be assessed and otorrhea sample will be collected if exudate is present. In the case of patients who report no improvement in otomycosis signs/symptoms at Visit 2 (Day 8-10), the Investigator will choose one of the two following options for the patient:

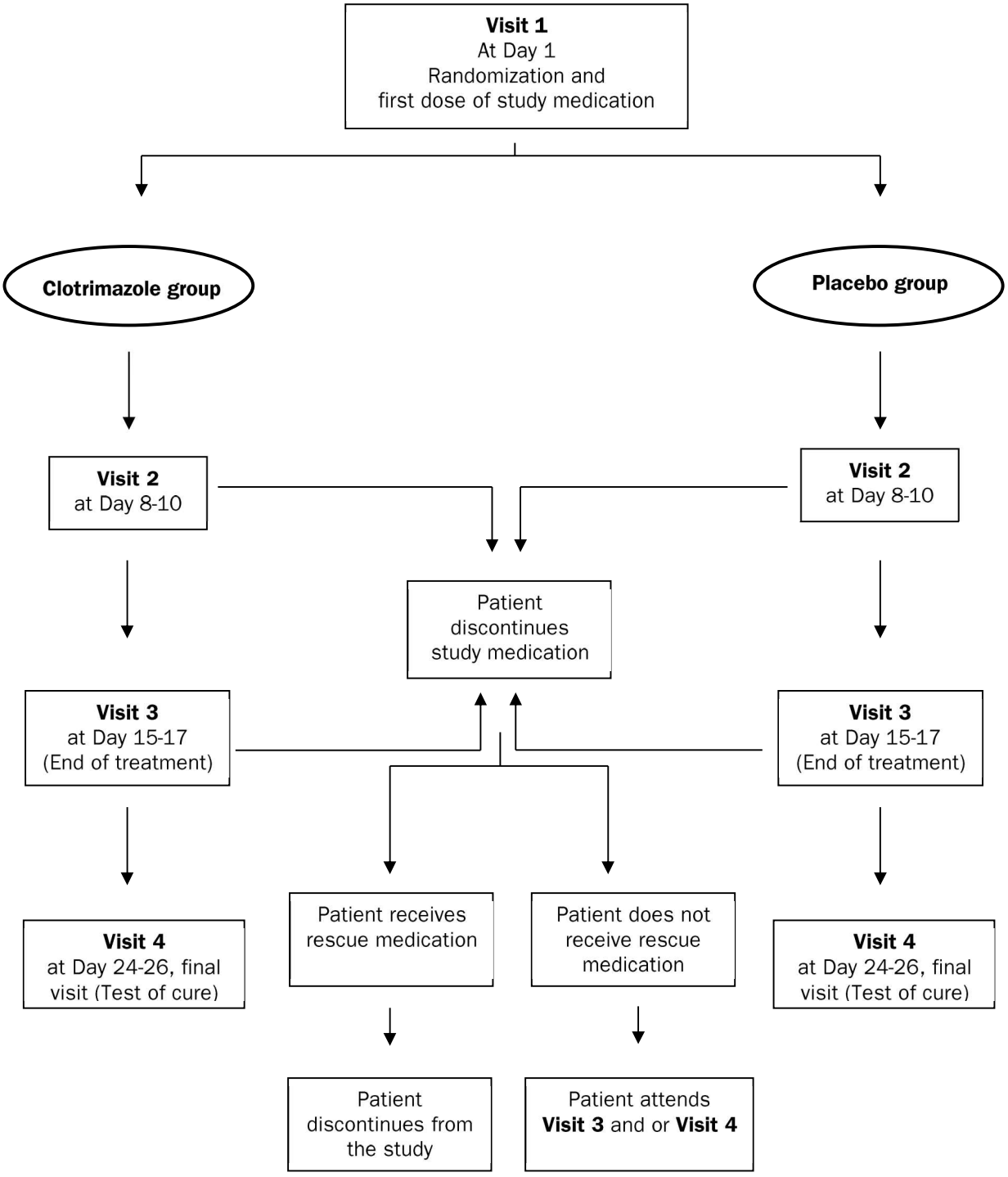
1. Continue with the study medication. Patient continues in the study and attends visit 3
2. Discontinue study medication. The Investigator may treat patient with other medication (rescue medication) at their discretion.
    - If investigator prescribes rescue medication, the patient will be withdrawn from the study. The clinical outcome for the patient will be recorded as Treatment failure at the End of Study form.
    - If investigator does not prescribe any rescue medication, the patient will be expected to return for a clinical and safety evaluation at Visit 3.

Non-discontinued patients will attend **Visit 3** (EOT: end-of treatment) and **Visit 4** (TOC: test-of-cure) at approximately Day 15 and Day 24, respectively. At these visits, signs and symptoms of otomycosis will be assessed and ear exudate, if present, will be collected for bacterial and mycological cultures. The primary efficacy endpoint will be Therapeutic cure (Clinical cure + Mycological Cure) at Test of Cure.

In the case of patients who report no improvement in otomycosis signs/symptoms at Visit 3 (Day 15-17), the Investigator will choose one of the two following options for the patient:

1. Continue the patient in the study without any rescue medication until Visit 4 (Day 24-26). The patient will come to Visit 4.
2. Prescribe rescue medication and withdraw the patient from the study. The clinical outcome for the patient will be recorded as Treatment Failure at the End of Study form.

**Figure 1 Diagram of Study Design**



### 4.2 Justification for Study Design

The study follows US Food and Drug Administration (FDA) recommendations, and is designed to demonstrate the superiority of an otic solution of Clotrimazole 1% against a matching placebo in the topical treatment of otomycosis.

Clotrimazole is a broad spectrum antifungal agent that was found to effectively controls fungal isolates attributed to otomycosis (*Aspergillus* and *Candida*) when administered as 1% otic solution twice daily. Each dose consists of one vial of approximately 1.7 mg of clotrimazole, which will be sufficient to produce high local concentrations inside the external auditory canal. The dosing regimen has been shown to be effective and well tolerated in the treatment of otomycosis leading to a negative mycological culture and suppression of clinical signs/symptoms (pruritus, otalgia, ear fullness and otorrhea).

The products (investigational product and comparator) will be supplied in translucent single-use vials of the same characteristics. The vials will be wrapped in foil pouches to protect them from the humidity excess. Five (5) vials will be placed into a pouched and heat-sealed foil which will have a label attached. The same label will be applied to all foil pouches to keep the content blinded as much as possible; the only difference among the labels will be the kit number. Six foil pouches will be packaged in a carton box that will also have a label with the kit number.

Subjects of 18 years of age and older, with otomycosis will be randomized in a 2:1 ratio to receive treatment with Clotrimazole 1% otic solution or placebo (Saline solution 0.9%). Subjects will be administered one vial of Clotrimazole 1% otic solution or placebo twice daily for 14 days.

# 5. STUDY POPULATION

## 5.1 Inclusion Criteria

1. At least 18 years of age at Visit 1 (Day 1, Screening/Baseline).
2. Clinical diagnosis of fungal otitis externa (otomycosis) in one or both ears, where topical treatment is indicated.
3. Presence of at least two of the following symptoms at baseline: of pruritus, otalgia and ear fullness.
4. Presence of debris and/or drainage clinically consistent with fungal infection, i.e. white or black appearance consistent with *Aspergillus spp*. or *Candida spp*.
5. Otorrhea/debris sample for bacterial and mycological cultures.
6. Provide written informed consent.
7. Willing and able to follow all instructions and attend all study visits.
8. Females who are not pregnant, not lactating and are not planning a pregnancy during the study. All females of childbearing potential (those who are not premenstrual, not postmenopausal or not surgically sterile) will be able to participate only if they have a negative urine pregnancy test at baseline (prior to randomization), and if they agree to use adequate birth control methods to prevent pregnancy throughout the study.

## 5.2 Exclusion Criteria

1. Known bacterial otitis externa or malignant otitis externa.
2. Tympanic perforation, tympanostomy tubes inserted or post mastoid surgery.
3. Structural ear anomalies which may difficult the evaluation of the therapeutic response.
4. Uncontrolled diabetes mellitus.
5. Known or suspected hypersensitivity to clotrimazole or any component of study medication.
6. History of an immunosuppressive disorder, and/or current immunosuppressive therapy.
7. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
8. Any recent systemic infection within 30 days of the inclusion or any current infection requiring systemic antimicrobial or systemic antifungal therapy.
9. Use of topical therapy with antinfungal properties in the target ear within 2 weeks of the inclusion.
10. Use of systemic antifungal therapy within 1 month of the inclusion.
11. Concurrent use of any compound, agent or substance that is applied or instilled to the evaluable ear or surrounding area, except non-bacteriostatic saline solution for potential additional cleaning before taking the sample to be cultured.
12. Concurrent use of analgesic therapy (prescription or over the counter) with anti-inflammatory

properties (acetylsalicylic acid for cardiovascular prevention at doses of 325mg or less is allowed). Analgesics without anti-inflammatory properties, such as acetaminophen and anti-inflammatory agents at stable doses at least 30 days prior to enrollment are allowed).

13. Concurrent use of non-topical antipruritics, except antihistamines at stable doses (at least 30 days prior to enrollment.
14. Concurrent use of any systemic corticosteroid, except nasal or inhaled corticosteroids at stable doses (at least 30 days prior to enrollment).
15. Prior participation in the trial unless patient was not randomized.
16. Participation in other investigational drug or device clinical trials within 30 days prior to the inclusion, or planning to participate in other investigational drug or device clinical trials within 24 days of starting treatment with study medication.

### 5.3 Withdrawal, Premature Discontinuation of Study Medication, and Replacement of Patients

Patients must be withdrawn from the study if they withdraw consent to participate. Such withdrawal may occur at any time during the study. Patients are not required to state their reasons for withdrawing consent.

Patients who do not experience improvement in signs/symptoms may prematurely discontinue treatment with study medication, but this does not imply termination of study participation. This protocol includes an assessment of whether a patient who experiences no improvement during the study should discontinue study treatment, as described in Section 8.2.2. Moreover, a patient may discontinue study treatment at the Investigator's discretion at any time during the study treatment period. If in these situations the patient receives rescue medication, he/she will also discontinue their study participation.

Patients may be required to discontinue study treatment after discussion with the Sponsor and/or Investigator for any of the following reasons:

- Adverse event(s);
- At the discretion of the Investigator;
- Violation of eligibility criteria; or
- Deviation from the treatment plan specified in the protocol (e.g., incorrect administration of study medication).

In all cases, the reasons for withdrawal or premature discontinuation of study medication must be recorded in the Electronic Data Capture (EDC) and in the patient's medical records. If there is more than one reason for premature discontinuation of study medication, one reason will be listed in the EDC as the primary reason and others will be listed as secondary reasons.

Patients who discontinue the study medication and do not receive any rescue medication will be expected to return for efficacy and safety evaluation at Visits 3 and 4.

If a participant with bilateral otomycosis experiences an adverse event related to the study medication in one ear that leads to the termination of treatment for that ear, the study treatment for the other ear will also be terminated. If the adverse event is not related to the study medication the treatment in the other ear should be maintained.

Patients who withdraw consent or discontinue study medication prematurely will not be replaced.

## 5.4 Planned Sample Size and Study Sites

Planned enrollment is 191 adults. Patients will be randomized in a 2:1 ratio (Clotrimazole 1% otic solution : Placebo), with the aim of including 150 evaluable patients (100 clotrimazole and 50 placebo).

About 17 study sites in Europe (5 in Bulgaria, 2 in Portugal, 5 in Romania and 5 in Spain) will recruit patients. Enrollment will be competitive, i.e., each study site will continue to enroll patients until recruiting the total of 150 evaluable patients.

## 5.5 Patient Identification and Randomization

Patients will be randomized at Visit 1, after signing informed consent and meeting eligibility criteria. Randomization will be conducted through an Interactive Web Response System (IWRS) include blocking. The IWRS will assign a patient number, which will be used to identify the patient during screening and, if applicable, throughout the duration of the study. Patients who do not meet the inclusion and exclusion criteria will be registered as screen failures through the IWRS.

For patients who have bilateral otomycosis, the ear with a higher TSSS (as defined in Section 7.1.1.5) will be considered the evaluable one. If the TSSS is identical in both ears, the left ear will be selected as the evaluable ear. In either case, the non-evaluable ear will receive the same treatment as the evaluable ear.

# 6. STUDY MEDICATION

## 6.1 Identity

**Investigational Medication**

| | |
|---|---|
| Chemical name | Clotrimazole |
| Generic name | Clotrimazole 1% Otic Solution |
| Trade name | Not applicable |
| Dosage form | Auricular solution, sterile |
| Manufacturer | SALVAT |
| Description | Otic solution in single-dose low-density polyethylene (LDPE) translucent vials containing 0.17 mL deliverable volume |

**Reference Medication**

| | |
|---|---|
| Generic name | Saline solution 0.9% |
| Trade name | Not applicable |
| Dosage form | Auricular solution, sterile |
| Manufacturer | SALVAT |
| Description | Otic solution in single-dose low-density polyethylene (LDPE) translucent vials containing 0.17 mL deliverable volume |

## 6.2 Administration

Study medication will be self-administered by the patient. At Visit 1, a study staff member will instruct the patient in how to open the containers and administer study medication, and will supervise the patient during administration of the first dose.

The method of administration for the investigational medication and the comparator medication will be the same: instillation of one vial in the affected ear canal(s) twice a day (morning and evening, preferably 12 hours apart) for 14 consecutive days. Ear wicks may be used at the Investigator's discretion. Use of ear wicks must be documented in the EDC.

Study medication will be supplied in single-dose vials containing 0.20 mL (approximately 0.17 mL deliverable volume) per vial. A patient kit will contain 6 pouches of 5 vials each, for a total of 30 vials and a plastic bag labeled with the kit number.

A study staff member will open one pouch and remove 2 vials. He or she will place the removed vials in a bag provided with the kit, and store the 2 vials at the study site in a secure location. The

remaining 3 vials will be returned to the pouch, which will be returned to the kit for dispensation to the patient. Patient will receive a kit with 28 vials and the first administration will be at the site.

Patients with bilateral otomycosis will receive 2 kits (2 vials will be removed from each kit and only 56 vials will be provided to the patient). The patient will administer the contents of 1 vial twice daily to the affected ear(s) for fourteen days. Each vial will be an intact unit, and the patient will twist off the top of the vial to administer the study medication. The solution should be warmed by holding the vial in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. The outer ear lobe should then be gently pulled upward and outward. This will allow the ear drops to flow down into the ear canal. This position should be maintained for 1 minute. Repeat, if necessary, for the opposite ear.

The planned maximum exposure to the active ingredient is approximately 1.7 mg of clotrimazole per dose (3.4 mg per day, approximately 47.6 mg of clotrimazole over a 14-day period). This quantity will be double in case of bilateral disease.

### 6.3 Packaging, Labeling, and Storage

The primary packaging of study medication will be performed by SALVAT, who will supply the investigational medication as pouches of single-dose vials, as described in Section 6.2. SALVAT will send the pouches directly to [redacted]. Each individual vial will contain 0.17 mL deliverable volume of Clotrimazole 1% otic solution. The vial is made from LDPE and is manufactured via a blow-fill-seal process. This process seals the vials directly after manufacture and contains the solution within a unit-dose vial that is intact until the user twists off the cap to administer the medication.

[redacted] will be responsible for the packaging, labeling and distribution of the study medication. The medication will be packaged in blinded cartons containing labeled pouches with the vials inside.

All study medication supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to the patients, study medication will be stored in a secure area, accessible to authorized personnel only.

Patient must store unused vials in the protective foil pouch.

### 6.4 Blinding and Breaking the Blind

All study medication products (test and placebo) will have the same packaging and labels.

The boxes in which the study medication is packaged, shipped, and dispensed will be identical in appearance. When patients return their used and unused study medication containers to the study site, they will be encouraged to bring them in the original carton.

Mycological and bacterial samples will be processed by a central laboratory under blinded conditions. The central laboratory will be blinded to the treatment assignment of the patient from whom the sample was taken.

Unblinding of study treatment assignment should be an unusual occurrence, and should be done only in case of an emergency when knowledge of the actual treatment becomes medically necessary to affect treatment options. The investigator will be able to break the blind and get the subject's treatment assignment through IWRS at any time, by completing the required information (e.g the user's password, the patient code concerned by the unblinding request, unblinding

code…). The investigator should not share the unblinded information with SALVAT or [redacted] personnel.

### 6.5 Drug Accountability

[redacted] will provide each Investigator with sufficient amounts of the investigational medication (Clotrimazole 1% otic solution) and the placebo (Saline solution 0.9%). The Investigator will confirm receipt of all kits of study medication using the IWRS and will document receipt in the written study files.

The Investigator will dispense the study medication only to patients included in this study and following the procedures described in this study protocol. Each patient will be given only the study medication carrying his/her number. Each dispensing will be documented in the EDC.

Patients will be asked to keep all used and unused study medication vials, and containers and return them to a study staff member at Visit 3 or at last study visit. If patients forget to bring in containers at Visit 3, they must bring them in no later than Visit 4.

All supplies must be accounted for at the end of the study. The Investigator is responsible for ensuring that accurate and adequate records are maintained. These records will include lot numbers, quantities received, dates received, dates dispensed, etc., for the investigational medication (Clotrimazole otic solution) and the placebo (Saline solution). The exact number of vials used in the study must be noted, regardless of whether the study was completed or terminated prematurely. At the time of return, the Investigator must verify that all used and unused supplies of study medication have been returned by the patient and that no remaining supplies are in the patient's possession.

### 6.6 Compliance

Compliance will be assessed by a review of the number of vials returned. The number of doses the patient actually took during the treatment period will be divided by the number of doses the patient was expected to take during that period. The resulting ratio will be multiplied by 100% to determine percent compliance. Patients will be considered "compliant" if their percent compliance is between 80% and 100%.

### 6.7 Concomitant Medications

Any medication the patient takes other than the study medication specified in the protocol is considered a concomitant medication. This includes prescribed medications, over-the-counter medications, herbal remedies, etc. All concomitant medications must be recorded in the EDC.

At Visit 1, patients will be asked what medications they are currently taking or have taken during the last 30 days. At Visits 2, 3, and 4, patients will be asked what concomitant medications they are currently taking or have taken since the last visit.

### *6.7.1 Prohibited Concomitant Medications*

The following medications will be prohibited during the study (unless the subject has prematurely discontinued study treatment):

- Any investigational drug.
- Any systemic antimicrobial or antifungal drug.
- Any compound, agent or substance that is applied or instilled to the evaluable ear or surrounding area, except non-bacteriostatic saline solution for potential additional cleaning before taking the sample to be cultured.
- Any topical antimicrobial or antifungal drug when applied to the non-evaluable ear or surrounding area.
- Any systemic analgesic therapy (prescription or over the counter) with anti-inflammatory properties (acetylsalicylic acid for cardiovascular prevention at doses of 325mg or less is allowed). Analgesics without anti-inflammatory properties, such as acetaminophen and anti-inflammatory agents at stable doses at least 30 days prior to enrollment are allowed.
- Any systemic corticosteroid, except nasal or inhaled corticosteroids at stable doses (at least 30 days prior to enrollment).
- Any non-topic antipruritic agent, except antihistamines at stable doses (at least 30 days prior to enrollment).

### *6.7.2 Rescue Concomitant Medication*

Prohibited medication will be considered rescue medication if they meet both of the following criteria:

- Any otic or systemic treatment administered for reasons associated with otomycosis of the evaluable ear (Note – topical products applied in the non-evaluable ear are NOT considered to be rescue medication)
- Started after Visit 1 but before or at Visit 4 (Note – antifungal given after Visit 4 are NOT considered rescue medications)

### *6.7.3 Recommended Concomitant Analgesics*

For patients who require analgesic medications for otalgia, the recommended medication is acetaminophen (paracetamol). The use of acetaminophen should never be considered as an initial treatment for otalgia, thus will only be administered after confirming that the study medication is not sufficient for pain relief.

# 7. VARIABLES AND METHODS

## 7.1 Efficacy Parameters

### *7.1.1 Clinical Efficacy Parameters*

#### *7.1.1.1 Pruritus*

Pruritus in both ears will be assessed by the investigator at all visits. For consistency, the same individual should perform all the assessments at all visits, if possible. Pruritus will be assessed as:

- Severe (3) if pruritus is marked or intense
- Moderate (2) if pruritus is definitely present
- Mild (1) if pruritus is slight
- Absent (0) if there is complete absence of pruritus

At Visits 2, 3 and 4, pruritus will be considered resolved if the level is 0. Pruritus will be considered improved if the level is lower than the previous pruritus assessment.

#### *7.1.1.2 Otalgia*

Otalgia in both ears will be assessed at all visits. The investigator will ask the patient to assess his or her level of otalgia on the day of the visit. If the patient has taken analgesic medication, he or she will be asked to assess the level of otalgia before taking the analgesic. For consistency, the assessment of otalgia should always be performed before the ear is examined. Assessments will be on the scale described in Blanch 2000.[15] Otalgia will be assessed as:

- Severe (3) if it interferes with activities of daily living;
- Moderate (2) if it causes discomfort but does not interfere with activities of daily living;
- Mild (1) if there is awareness of pain but not much discomfort; or
- Absent (0) if there is total absence of pain.

At Visits 2, 3 and 4, otalgia will be considered resolved if the level is 0. Otalgia will be considered improved if the level is lower than the previous otalgia assessment.

#### *7.1.1.3 Ear fullness*

Ear fullness (aural fullness or ear pressure) in both ears will be assessed by the investigator at all visits. For consistency, the same individual should perform all the assessments at all visits, if possible. Ear fullness will be assessed as:

Severe (3) if ear fullness, is marked or intense

Moderate (2) if ear fullness is definitely present

Mild (1) if ear fullness is slight

Absent (0) if there is complete absence of ear fullness

At Visits 2, 3 and 4, ear fullness will be considered resolved if the level is 0. Ear fullness will be considered improved if the level is lower than the previous ear fullness assessment.

#### *7.1.1.4 Otorrhea*

Otorrhea in both ears will be assessed by the investigator at all visits. For consistency, the same individual should perform all the assessments at all visits, if possible. Otorrhea will be assessed as:

- Severe (3): copious discharge that prevents visualization of the tympanic membrane unless the fluid is suctioned
- Moderate (2): the anterior sulcus is full, but the tympanic membrane is still clearly visible
- Mild (1): little fluid accumulating in the anterior tympanomeatal sulcus but the tympanic membrane is still visible
- Absent (0) absence of fluid

At Visits 2, 3 and 4, otorrhea will be considered resolved if the level is 0. Otorrhea will be considered improved if the level is lower than the previous otorrhea assessment.

#### *7.1.1.5 Overall Clinical Outcome*

Overall Clinical Outcome is based on the TSSS, which is calculated by the sum of pruritus score + otalgia score + ear fullness score + otorrhea score. Patients will be allocated to one of the following categories for Overall Clinical Outcome:

1. Clinical Cure: TSSS is 0, as defined in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.3.
2. Clinical Improvement: TSSS is different than 0 but lower than the previous visit, as defined in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.47.1.1.3.
3. Clinical Failure: TSSS does not meet the definitions of Clinical Cure or Clinical Improvement, as defined in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.4.
4. Not changed: TSSS is different than 0 but unchanged compared to the previous visit.
5. Indeterminate: Discontinued (for reasons other than Clinical Failure) or lost to follow-up.

Patients who take rescue medication (as defined in section 6.7.2) will be considered Clinical Failures.

### ***7.1.2 Mycological Efficacy Parameters***

#### *7.1.2.1 Mycological Outcome*

Samples of ear discharge will be taken at V1, and in addition at visits V2, V3 and V4, when discharge is present. The otorrhea/debris sample will be taken prior to the debridement of the affected ear. A central laboratory will provide exudate sampling kits with standardized instructions for sample preparation (as defined in the Laboratory manual).

The otorrhea/debris sample will be sent to the Central Laboratory for processing. The central laboratory will be blinded to the treatment assignment of the patient from whom the sample was taken.

The central laboratory will use standardized microbiological laboratory procedures to identify fungal and bacterial species.

Susceptibility testing on fungal isolates will be performed according the Clinical and Laboratory Standard Institute methods for clotrimazole and comparator drugs to which the fungal isolates are susceptible.

For any patient with a culture positive for fungi at Visit 1, mycological outcome at Visit 2 will be classified as:

- Eradication if the culture does not show growth of any fungal pathogen;
- Presumed Eradication if there is no material to culture and the Overall Clinical Outcome is Clinical Cure;
- Persistence if any fungal pathogen cultured at Visit 1 is still present;
- Presumed Persistence: if there is no material to culture and the Overall Clinical Outcome is not Clinical Cure;
- Superinfection if a fungal pathogen not present at Visit 1 is now present (presence of a nonpathogenic organism will not be considered Superinfection); or
- Indeterminate if none of the above definitions are met and the mycological outcome cannot be determined.

For any patient with a culture positive for fungi at Visit 1, mycological outcome at Visit 3 will be classified as:

- Eradication if the culture does not show growth of any fungal pathogen;
- Presumed Eradication if there is no material to culture and the Overall Clinical Outcome is Clinical Cure;
- Persistence if any fungal pathogen cultured at Visit 1 is still present;
- Presumed Persistence: if there is no material to culture and the Overall Clinical Outcome is not Clinical Cure;
- Recurrence: if there is reappearance of the fungal pathogen eradicated or presumably eradicated at Visit 2;
- Superinfection if a new fungal pathogen is isolated while the initial pathogen is also present (presence of a nonpathogenic organism will not be considered Superinfection);
- Reinfection: if there is isolation of a new fungal pathogen different from the one eradicated or presumably eradicated at Visit 2: or
- Indeterminate if none of the above definitions are met and the mycological outcome cannot be determined.

For any patient with a culture positive for fungi at Visit 1, mycological outcome at Visit 4 will be classified as:

- Eradication if the culture does not show growth of any fungal pathogen;
- Presumed Eradication if there is no material to culture and the Overall Clinical Outcome is Clinical Cure;
- Persistence if any fungal pathogen cultured at Visit 1 is still present;
- Presumed Persistence: if there is no material to culture and the Overall Clinical Outcome is not Clinical Cure;
- Recurrence: if there is reappearance of the fungal pathogen eradicated or presumably eradicated at Visit 2 and/or 3;
- Superinfection if a new fungal pathogen is isolated while the initial pathogen is also present (presence of a nonpathogenic organism will not be considered Superinfection);
- Reinfection: if there is isolation of a new fungal pathogen different from the one eradicated or presumably eradicated at Visit 2 and/or 3: or
- Indeterminate if none of the above definitions are met and the mycological outcome cannot be determined.

Mycological outcome will be determined for each patient for Visit 2, Visit 3 and for Visit 4 after mycological culture results are made available to the Sponsor or designee.

Mycological cure is defined as eradication (culture does not show growth of any fungal pathogen) or presumed eradication (there is no material to culture and overall clinical outcome is clinical cure).

### *7.1.3 Therapeutic response*

The therapeutic response is a combined assessment of the Overall Clinical Outcome plus the Mycological Outcome. The following categories are defined:

1. Therapeutic cure: TSSS (pruritus + otalgia + ear fullness + otorrhea) = 0 and mycological outcome eradication or presumed eradication.
2. Therapeutic failure:
    - Positive fungal culture, OR
    - TSSS > 0 regardless of mycological outcome.

### *7.1.4 Primary Efficacy Endpoint*

Based on the definitions in Section 7.1.1.5, 7.1.2 and 7.1.3, the primary efficacy endpoint will be the proportion of patients with Therapeutic cure at Test of Cure (Visit 4) in the mycological intended- to-treat (MITT) population.

### *7.1.5 Secondary Efficacy Endpoints*

Based on the definitions in Sections 7.1.1, 7.1.2 and 7.1.3, the secondary efficacy endpoints will be:

- Overall clinical cure at Visits 2, 3 and 4.
- Mycological cure at Visits 2, 3 and 4.
- Therapeutic cure at Visit 2 and 3.
- Changes in TSSS at Visits 2, 3 and 4.
- Changes in individual signs and symptoms at Visits 2, 3 and 4.

In the case of bilateral otomycosis the non-selected ear will also be treated and assessed for its clinical evolution.

## 7.2 Safety Parameters

Safety will be assessed by AEs and physical examination. In addition, a urine pregnancy test for females of childbearing potential will be performed at Visit 1.

Adverse events will be recorded throughout the study and at early termination, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

### *7.2.1 Adverse Events*

#### *7.2.1.1 Definitions*

An AE is any untoward medical event that occurs in a patient or subject who has received an investigational product, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the study product.

An illness present at entry to the study is considered a pre-existing condition and will not be considered an AE. However, if a pre-existing condition worsens during the study, this may be considered an AE. Pre-existing conditions will be documented in the EDC. If pre-existing signs and signs/symptoms of otomycosis (pruritus, otalgia, ear fullness and otorrhea) worsen during the study, this will be considered a treatment failure instead of an AE. All AEs, including intercurrent illnesses, that occur during the study (i.e., between Informed Consent Form (ICF) signature and Visit 4) must be reported and documented as described below.

#### *7.2.1.2 Timing*

Adverse events will be assessed from the time the subject provides informed consent.

Serious adverse events should be collected for up to 30 days after the last dose of study medication.

At study termination, subjects with ongoing AEs/SAEs should be followed up by the Investigator for as long as medically indicated. The Sponsor retains the right to request additional information for any subject with ongoing AEs/SAEs at the end of the study, if judged necessary.

#### *7.2.1.3 Recording Adverse Events*

Volunteered, observed, and elicited AEs will be recorded. This includes AEs the patient reports spontaneously, those the Investigator observes, and those the elicited in response to questions from the study staff. Patients will be asked open-ended questions, such as "How have you been feeling since your last visit?", at each study visit. If a patient reports any pain or illness during or after administration of the eardrops (i.e itching), the pain or illness experienced by the patient should be recorded as an AE.

All AEs that occur during the study must be recorded in the Adverse Events page of the EDC. All Adverse Event EDC entries should contain a brief description of the event, date and time of onset, duration, intensity, treatment required, relationship to study medication, action taken with regard to study medication, outcome, and whether the event is classified as serious.

#### *7.2.1.4 Assessment of Adverse Event*

Each AE will be assessed by the Investigator with regard to the following categories.

##### 7.2.1.4.1 Serious Adverse Event

International Conference on Harmonization (ICH) Guidelines and federal regulations define a SAE as any untoward medical occurrence that at any dose results in any of the following outcomes:

- death;
- life-threatening. This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- requires or prolongs patient hospitalization (any hospitalization except observational admissions of less than 24 hours);
- results in persistent or significant disability or incapacity; or
- congenital anomaly or birth defect.
- important medical events that may not result in death, be life threatening, or require hospitalization may be considered as an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the Sponsor or Sponsor's designee as described in Section 7.2.1.3.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard of care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g. for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject.
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

#### 7.2.1.4.2 Severity

The severity of each AE must be assessed by the Investigator and recorded on the Adverse Events EDC as mild, moderate, or severe according to the following definitions:

- Mild: An AE that does not interfere with usual activities;
- Moderate: An AE that interferes with usual activities; or
- Severe: An AE that is intense or debilitating and interferes with usual activities.

**Note:** The terms serious and severe are not synonymous. Serious criteria as defined in Section 7.2.1.4.1 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/adverse outcome. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

#### 7.2.1.4.3 Relationship to Study Medication

The relationship of each AE to study medication must be assessed and recorded on the Adverse Events EDC as one of the following:

- Not related: an AE which is not related to the use of the study medication.
- Possibly related: an AE for which an alternative explanation is more likely, e.g. concomitant medication(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.
- Probably related: an AE which might be due to the use of the study medication. An alternative explanation, e.g. concomitant medication(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- Definitely related: an AE which is related to the use of the study medication.

### *7.2.1.5 Reporting Serious Adverse Events*

#### 7.2.1.5.1 Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the final dose of study drug must be reported to [redacted] Clinical Safety no later than 24 hours of the knowledge of the occurrence, regardless of relationship to study medication.

To report the SAE, investigators have to complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form will be completed, [redacted] Safety personnel will be notified automatically by the EDC system and will retrieve the form.

If the investigator is not able to access the EDC system and the event meets serious criteria, the investigator will send an e-mail to [redacted] Safety at [redacted] or call the [redacted] SAE reporting line (phone number listed below), and fax/e-mail the completed paper SAE form to Medpace (fax number listed below) no later than 24 hours of awareness. When the EDC system becomes available, the investigator will enter the SAE information in the EDC no later than 24 hours of the system becoming available.

Safety Contact Information: [redacted] Clinical Safety

[redacted] **SAE reporting line - EU**

Telephone: [redacted]

Fax: [redacted]

E-mail: [redacted]

#### 7.2.1.5.2 Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. This follow-up may extend after the end of the study.

In no later than 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system. If there is any supporting documentation (eg, patient

discharge summary or autopsy reports) this has to be submitted to [redacted]Safety via fax or e-mail to the above listed contact details. If it is not possible to access the EDC system, the procedures outlined above for initial reporting of SAEs have to be followed.

The Investigator and the Sponsor (or Sponsor's designee) will review each SAE report and evaluate the relationship of the SAE to study medication. Based on the Investigator's and Sponsor's assessment of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new SAE related to the study medication raises concern over the safety of continued administration of the study medication to patients, the Sponsor (or Sponsor's designee) will take immediate steps to notify the FDA/other regulatory authorities and all Investigators participating in clinical studies of the study medication.

Further action that may be required includes the following:

- Modification of the protocol;
- Discontinuation or suspension of the study;
- Modification of the existing consent form and informing current study participants of new findings; or
- Addition of any newly identified study medication-related AEs to the list of expected AEs.

#### *7.2.1.6 Reporting Safety Information*

The Sponsor or Sponsor's designee will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to regulatory authoritiesand in any case no later than 7 days after Sponsor or Sponsor's designee knowledge. Within no later than 8 additional days a follow-up report will be sent to the regulatory authorities with the new relevant retrieved information, if applicable, or stating that no new information is available.

All other suspected unexpected serious adverse reactions will be reported to the regulatory authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor or Sponsor's designee.

The Sponsor or Sponsor's designee will also inform all study Investigators as required about the new relevant safety information retrieved.

The Investigator must promptly report to his or her Institutional Review Board (IRB) or Independent Ethics Committee (IEC) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs assessed as possibly, probably, or definitely related to the study medication, and any other events required to be reported by the IRB/IEC.

#### *7.2.1.7 Protocol Deviations Due to an Emergency or Adverse Event*

In the case of an emergency or AE, departures from the protocol may be necessary. Such protocol deviations will be determined as allowable on a case-by-case basis. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency. The Medical Monitor and the Investigator will confer to decide whether the patient should continue to receive study medication. All protocol deviations and the reasons for such deviations must be noted in the EDC.

### 7.2.2 *Pregnancy Reporting*

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator will stop dosing with study drug(s) immediately and the patient will be withdrawn from the study. Early termination procedures will be implemented at that time.

A pregnancy is not considered to be an adverse event or SAE; however, nevertheless it must be reported to [redacted] Clinical Safety no later than 24 hours of knowledge of the pregnancy. [redacted] Clinical Safety will then provide the Investigator/site the Pregnancy form (Exposure In Utero form) for completion. The Investigator/site must complete the Pregnancy form and fax or e-mail it back to [redacted] Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient (the father) is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator must notify [redacted] Clinical Safety as described above by using the Pregnancy form.

The pregnancy should be followed until the outcome of the pregnancy. Once the outcome of the pregnancy is known, the Pregnancy form has to be completed and faxed/e-mailed to [redacted] Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator must follow the procedures for reporting an SAE.

### 7.2.3 *Physical Examination*

Physical examination will be performed at V1. A directed examination of the ears (external inspection and examination (with or without microscope) of the external auditory canal), head, nose and oropharynx will be performed.

Vital signs (temperature, blood pressure, and pulse) will be assessed at all visits.

### 7.2.4 *Pregnancy Test*

A urine pregnancy test will be performed at Visit 1 for female patients of childbearing potential (females who have had menarche and are not premenstrual, not postmenopausal or not surgically sterile). This test will be performed at the study site. A negative result is required before the patient can be randomized.

Moreover, females must have agreed to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods included topical, hormonal-oral, implantable or injectable contraceptives; mechanical-spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner (must be $\geq$ 6 months post vasectomy). For non-sexually active females, abstinence will be regarded as an adequate method of birth control; however, if the patient becomes sexually active during the study, she must have agreed to use adequate birth control methods as defined above for the remainder of the study.

# 8. STUDY CONDUCT

## 8.1 Schedule of Observations

A schedule of observations and assessments to be performed during the study is provided in Table 1.

**Table 1 Schedule of Observations**

| Evaluation | Visit 1 Screening (Study Entry) | Visit 2 On treatment | Visit 3 End of Treatment | Visit 4 Post-Treatment Follow-Up |
|---|---|---|---|---|
| **Study Day** | **1** | **8-10** | **15-17** | **24-26** |
| Informed Consent | X | | | |
| Inclusion/exclusion criteria | X | | | |
| Medical history | X | | | |
| Concurrent symptoms/conditions | X | | | |
| Urine pregnancy test[a] | X | | | |
| Physical examination[b] | X | | | |
| Vital signs[c] | X | X | X | X |
| Pruritus | X | X | X | X |
| Otalgia | X | X | X | X |
| Ear fullness | X | X | X | X |
| Otorrhea | X | X | X | X |
| Overall Clinical Outcome | | X | X | X |
| Bacterial and Mycological cultures of ear discharge | X | X[d] | X[d] | X[d] |
| Debridement of the ear | X | X[d] | X[d] | X[d] |
| Randomization through IWRS | X | | | |
| Dispense study medication and explain its use | X | X[e] | | |
| Provide a visit calendar | X | | | |
| Collect used and unused study medication containers | | | X[f] | |
| Concomitant medications | X | X | X | X |
| Adverse events | X | X | X | X |

[a] For female patients of childbearing potential.
[b] To include a directed examination of the ears, head, nose and oropharynx.
[c] To include temperature, blood pressure, and pulse rate.
[d] If no discharge (otorrhea or debris) is present, no attempt to culture will be made.
[e] If patient with unilateral otomycosis at baseline becomes bilateral prior to Visit 3 a resupply study medication kit (with the same medication) will be dispensed for the non-evaluable ear.
[f] If patients forget to bring in containers at this visit, they must bring them in no later than Visit 4.

## 8.2 Observations by Visit

### *8.2.1 Visit 1*

Patients who may be eligible to participate in the study will be offered the opportunity to participate. The study will be explained to them and questions about the study will be answered. Patients who elect to participate will sign the Informed Consent Form (or have it signed by their legally authorized representative), before any study procedures may be performed. The IWRS will assign a patient number, which will be used to identify the patient during screening and, if applicable, throughout the duration of the study. Patients who do not meet the inclusion and exclusion criteria will be registered as screen failures through the IWRS. Patients who have provided consent and met the inclusion and exclusion criteria will be enrolled and randomized through the IWRS.

Medical history, concurrent symptoms and conditions, and concomitant medications will be recorded, and a physical examination (as described in Section 7.2.3) will be performed. Female patients of childbearing potential will have a urine pregnancy test.

Pruritus, otalgia, ear fullness and otorrhea will be evaluated as described in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.4. A sample of ear discharge will be obtained for bacterial and mycological cultures as described in Section 7.1.2 prior to the debridement of the ear.

The patient will be given a medication kit containing a 14-day supply of study medication. The blind will be maintained as described in Section 6.4. A member of the study staff will instruct the patient on how to open the vials and administer study medication, and will supervise the patient during administration of first dose. Day 1 will be the day when the first dose is administered (important if due to unforeseen circumstances the first dose is administered the day after the baseline visit).

Patients will be instructed to refrain from swimming during the study treatment period and preferably until the final study visit is completed. Patients will also be advised to use a shower cap or neoprene head band when bathing.

A visit calendar will be provided to the patient.

If any AEs occur during Visit 1, they will be recorded in the Adverse Events page of the EDC.

### *8.2.2 Visit 2*

Visit 2 will take place on Day 8-10. AEs and concomitant medications will be recorded and vital signs will be assessed.

Pruritus, otalgia, ear fullness and otorrhea will be evaluated as described in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.4. Overall Clinical Outcome will be evaluated by the Investigator as described in Section 7.1.1.5. A sample of ear discharge will be obtained for bacterial and mycological cultures as described in Section 7.1.2 prior to the debridement of the ear.

In the case of patients who report no improvement in otomycosis signs/symptoms, the Investigator will choose one of the two following options for the patient:

1. Continue with study medication. The patient will continue taking study medication without interruption and will come to Visit 3.

2. Discontinue study medication. The Investigator will may treat patient with other medication (rescue medication) at their discretion.
   - If rescue medication (see section 6.7.2) is prescribed the following actions have to be implemented:
     - Collection of remaining study medication and evaluation of compliance
     - Completion of the end of study form. The clinical outcome for the patient will be recorded as Treatment failure for the remaining visits.
   - If no rescue medication is prescribed the patient will be expected to return for clinical and safety evaluation at Visit 3.

If patient has unilateral otomycosis at Visit 1, but at Visit 2 is found to have an otomycosis also in the other ear, then the investigator will obtain a second kit number (with the same medication) through the IWRS.

Patients who show up before day 8 with no improvement or worsening of their signs/symptoms, and the investigator's decision is to discontinue the patient from the study medication, this will be considered as Visit 2, and all the procedures corresponding to this visit will apply.

### *8.2.3 Visit 3*

Visit 3 will take place on Day 15-17. AEs and concomitant medications will be recorded vital signs will be assessed.

Pruritus, otalgia, ear fullness and otorrhea will be evaluated as described in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.4. Overall Clinical Outcome will be evaluated by the Investigator as described in Section 7.1.1.5. A sample of ear discharge will be obtained for bacterial and mycological cultures as described in Section 7.1.2 prior to the debridement of the ear.

If the patient took rescue medication (see section 6.7.2) prior to this visit, the patient will be considered Treatment Failure, and no further ear discharge sample will be collected for study purposes.

Used and unused study medication containers will be collected from the patient by a member of the study staff.

In the case of patients with a TSSS greater than 2 on a 4-point scale, the Investigator will choose one of the two following options for the patient:

1. Continue the patient in the study (without receiving any further treatment for the signs/symptoms of otomycosis). The patient will come to Visit 4.
2. Prescribe rescue medication and withdraw the patient from study.

   The clinical outcome for the patient will be recorded as Treatment failure at the End of Study form.

### *8.2.4 Visit 4*

Visit 4 will take place on Day 24-26. A member of study staff will contact the patient on the previous days to remind the patient to attend this visit.

Adverse events and concomitant medications will be recorded and vital signs will be assessed.

Pruritus, otalgia, ear fullness and otorrhea will be evaluated as described in Sections 7.1.1.1, 7.1.1.2, 7.1.1.3 and 7.1.1.4. Overall Clinical Outcome will be evaluated by the Investigator as described in Section 7.1.1.5. A sample of ear discharge will be obtained for mycological culture as described in Section 7.1.2 prior to the debridement of the ear.

If the patient took rescue medication (see section 6.7.2) prior to this visit, the patient will be considered Treatment Failure, and no further ear discharge sample will be collected for study purposes.

Upon completing Visit 4, the patient will have completed his or her participation in the study.

### *8.2.5 Study Termination*

If the Sponsor or their designee, the Investigator, or the Medical Monitor discovers conditions arising during the study that indicate the study should be halted, the study may be terminated. Conduct of the study may also be terminated at a particular study site while the study continues at other sites. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study;
- Failure of the Investigator to enter patients at an acceptable rate;
- Insufficient adherence to protocol requirements; or
- A decision on the part of the Sponsor to suspend or discontinue development of the study medication.

# 9. DATA HANDLING AND RECORD KEEPING

## 9.1 Data Quality Assurance

The Sponsor (or Sponsor's designee) will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of his or her responsibilities and the procedures for ensuring adequate and correct documentation.

An Investigator Meeting or training extensive site initiation visits will be held to introduce Investigators and their personnel to the study protocol, EDC, procedures, and regulatory requirements.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the EDC for this study must be consistent with the patient's source documentation (e.g., medical records).

During the course of the study, a monitor will make site visits to review protocol compliance, compare EDC with individual patients' medical records, assess study medication accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. Entries in the EDC will be verified against source documents. The review of medical records will be performed in a manner that ensures patient confidentiality is maintained.

Regulatory authorities of certain countries, the IRB/IEC, and/or the Sponsor's or designee's Clinical Quality Assurance Group may perform source data checks and/or on-site audit inspections. Investigators and their institutions will provide direct access to source data and documents to these authorities. The Investigator assures the Sponsor and their designee of the necessary support at all times.

## 9.2 Case Report Forms and Source Documentation

Electronic Data Capture (EDC) will be used in this study. The Sponsor or designee will provide a password to each staff member who has the authorization to implement the EDC.

The electronic data for each patient will be checked against source documents at the study site by the site monitor. Any information recorded directly into the EDC (i.e., information for which there is no prior written or electronic record) will be considered source data. A copy of the EDC with audit trail and final data of the EDC including data management changes will be placed in the Investigator's study file.

A Screening Log will be maintained, listing all patients screened, including patients who do not qualify for enrollment.

Instances of missing data will be discussed with the Investigator for resolution. If necessary, data query forms will be generated and sent to the site for further clarifications or corrections. The Sponsor or designee will perform a quality control review on the database. If a self-evident correction document is generated during the study, the document must be approved and signed by each principal investigator.

### 9.3 Archiving Study Records

Essential documents should be retained for a minimum of 25 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or at least 25 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable laws. The Sponsor or designee must be notified in writing if the Investigator moves or if the storage location of documents is changed.

### 9.4 Sample Retention

Samples may be used for purpose related to research. The samples may be stored until the sponsor has determined that the specimens are no longer needed, and the decision has been made that there are no samples to be re-assayed. In addition, identifiable sample can be destroyed at any time at the request of the subject.

# 10. STATISTICAL METHODS

## 10.1 General Statistical Methods

All data collected in the database will be presented in the data listings.

Continuous data will be summarized by treatment group using descriptive statistics (n, mean, standard deviation, standard error of the mean, median, minimum, and maximum). Categorical data will be tabulated by treatment group and category.

All analyses and summaries will be based on the mycological intent-to-treat (MITT) and mycological per-protocol (MPP) populations. MITT population will be the primary population for efficacy analysis. Efficacy analyses will also be conducted on the Clinical intent-to-treat (CITT) population. Safety summaries will be based on the Safety population. These populations are defined in Section 10.1.4.

### *10.1.1 Sample Size*

Planned enrollment is 191 patients randomized in 2:1 ratio (Clotrimazole 1% otic solution: Placebo) to obtain 150 evaluable patients (100 Clotrimazole 1% and 50 Placebo).

Clotrimazole otic solution should be statistically superior to the placebo ($p<0.05$) with regard to the therapeutic cure at the test-of-cure visit, using the MITT population.

Assuming a significance level of 5% and a desired statistical power of 95%, a placebo effect of 30%, and a 2:1 allocation schedule, the total number of patients needed to detect a difference of 30% in the therapeutic cure (100% relative increase) is 150 (100 with clotrimazole and 50 with placebo). The suspected dropout rate due to negative mycological culture at baseline is 21% that leads to a required inclusion of 191 patients (127 for the clotrimazole group and 64 patients for the placebo group).

As this is a twin trial if the CLEAR-1 study is completed before this study (CLEAR-2) an updated sample size computation will be performed in order to have a more accurate picture of treatment and control arm success probabilities.

### *10.1.2 Interim Analyses*

No interim analyses are planned.

### *10.1.3 Missing, Unused, and Spurious Data*

Patients with missing efficacy data or indeterminate outcomes will be considered as treatment failures for efficacy analyses.

For the primary and secondary endpoints, patients who discontinue for lack of efficacy or rescue medication will be considered as treatment failures.

All data, whether summarized or not, will be presented in the data listings.

Spurious data, such as unscheduled visit collections, laboratory tests not specified in the protocol, or Investigator comments, will be presented in the data listings. These data will be excluded from the summary tables.

In order to limit patient drop-out during the post-treatment phase, a study staff member will contact patient to promote attendance at Visit 4.

### *10.1.4 Analysis Populations*

There will be 4 populations defined for this study: Safety, Clinical intent-to-treat (CITT), Mycological intent-to-treat (MITT), and Mycological per-protocol (MPP).

The **Safety population** will include all patients who received any study medication.

The **CITT population** will include all patients who were randomized.

The **MITT population** will include all CITT patients who had a positive baseline fungal culture for *Aspergillus spp* and/or *Candida spp*.

The **MPP population** will include all randomized patient who had positive baseline culture for *Aspergillus spp* and/or *Candida spp* and who:

- Satisfied all inclusion and exclusion criteria;
- Did not receive any prohibited concomitant medications (except if it is considered rescue medication);
- Did not have any other major protocol violations;
- Completed Visit 2, Visit 3 and Visit 4 (unless the subject was deemed a clinical failure at an earlier visit than Visit 4) with the designated visit window
- Had compliance rates between 80% and 100% as defined in Section 10.1.8 (patients who are deemed Clinical Failures are to be included if they had compliance rates between 80% and 100% during the first 3 days of study treatment).
- Had mycological results (when subject has material to culture) from Visit 1, Visit 2, Visit 3 and/or Visit 4 unless the subject was deemed a clinical failure at an earlier visit than Visit 4.

For the CITT and MITT populations, the treatment group of a patient will be determined by the treatment group to which the patient was randomized.

For the Safety and MPP populations, the treatment group of a patient will be determined by the treatment the patient received, not necessarily the group to which he or she was randomized. The Safety population will be used for all safety analyses.

The primary populations for efficacy analyses will be the MITT population.

The populations to be used for each of the secondary efficacy endpoints will be detailed in the Statistical Analysis Plan.

### *10.1.5 Patient Disposition*

The numbers of patients in each treatment group who completed the study and who terminated early will be tabulated. For patients who terminated early, primary and secondary reasons for termination will be tabulated. Patients who were excluded from each of the study populations defined in Section 10.1.4, and their reasons for exclusion, will be listed.

### *10.1.6 Demographics and Baseline Characteristics*

Continuous demographic and baseline characteristics, such as age, will be summarized by treatment group with descriptive statistics (n, mean, standard deviation, standard error of the mean, median, minimum, and maximum). Categorical demographic and baseline characteristics such as gender and race will be tabulated (frequency and percent) by treatment group and category. Demographic and baseline characteristic tables will be presented for all study populations.

### *10.1.7 Protocol Deviations*

Protocol deviations are defined as violations from the procedures outlined in the protocol. **Major** protocol deviations are protocol violations likely to affect the study results and leading to the exclusion of the subject from the MPP.

Once the database has been completed and considered as “clean”, a data blind review will be conducted before the database lock in order to identify all major protocol violations and assign subjects into each of the analysis sets as defined in section 10.1.4.

Patients with protocol deviations will be presented in the data listings. Protocol violations will be tabulated by treatment group and violation.

The protocol deviations are considered critical (or very serious) and major (or severe), according to the following definitions:

- **Critical or very serious:** Deviations affecting / they have adversely affected the rights, safety or welfare of subjects and / or the quality and integrity of data
- **Major or serious:** Deviations that may affect / have adversely affected the rights, safety or welfare of subjects and / or the quality and integrity of data.

The Sponsor or designee will report the protocol deviations to the Health Authorities according to local rules and regulations.

### *10.1.8 Compliance with Study Medication*

Compliance will be assessed by a review of the number of vials returned. The number of doses the patient actually took during the treatment period will be divided by the number of doses the patient was expected to have taken. The resulting ratio will be multiplied by 100% to determine percent compliance. Patients will be considered “compliant” if their percent compliance is between 80% and 100%. The proportion of patients who were compliant and non-compliant during the treatment period will be tabulated by treatment group.

### *10.1.9 Concomitant Medications*

Concomitant medications will be tabulated by treatment group.

### *10.1.10 Efficacy Analyses*

For the efficacy analyses, only the assessments from the evaluable ear will be used.

*10.1.10.1 Primary efficacy endpoint*

Primary analysis of the primary endpoint

The primary endpoint for efficacy will be the proportion of subjects with therapeutic cure at test-of-cure (Visit 4).

**Therapeutic cure** is defined as both mycological cure and clinical cure.

**Mycological cure** is defined as eradication (culture does not show growth of any fungal pathogen) or presumed eradication (there is no material to culture and the overall clinical outcome is clinical cure).

**Clinical cure** is defined as a TSSS of zero on a 4-point scale for pruritus, otalgia, ear fullness and otorrhea.

Therapeutic cure at Visit 4 will be compared between treatment groups by using a chi-square test, under a two-sided 5% significance level. The 95% confidence intervals based on the normal approximation to the binomial distribution will be presented for the between-treatment group differences in the therapeutic cure rate. For each treatment group, the 95% confidence intervals of the therapeutic cure rate using the Clopper-Pearson method will also be presented.

For the main objective of the study, the statistical analysis of the primary endpoint will be performed in the MITT population.

Secondary analyses of the primary endpoint

The efficacy analyses of the primary endpoint conducted on the MITT population will be repeated on the MPP and CITT populations.

Sensitivity Analyses of the primary endpoint

- The proportion of subjects with therapeutic cure at Visit 4 will be analyzed using the standardized estimator (Steingrimsson, 2017)[16].
- The proportion of subjects with therapeutic cure at Visit 4 will be analyzed using multiple imputation method to define missing data.
- The proportion of subjects with therapeutic cure at Visit 4 will be analyzed using worst case scenario to define missing data, in which missing endpoints for treatment arm patients are set to therapeutic failure and missing endpoints for control arm patients are set to clinical cure.

*10.1.10.2 Secondary efficacy endpoints*

Analysis of the secondary efficacy endpoints will be supportive only:

- Overall clinical cure at Visits 2, 3 and 4.
- Mycological cure at Visits 3 and 4.
- Therapeutic cure at Visit 2 and 3.
- Changes in signs/symptoms at Visits 2, 3 and 4.

  Changes in each sign/symptom (pruritus, otorrhea, ear fullness and otalgia) and in the overall clinical outcome (TSSS) will be analyzed as:

- 2-level approach: resolved/not resolved.
- 3-level approach: resolved/improved/not improved
- mean change in rating from the baseline assessment

The proportion of patients with clinical, mycological and therapeutic cure, the 2-level approach for changes in sign/symptoms and the overall clinical outcome will be summarized by visit and treatment group. For each visit, the proportions of patients will be compared between the treatment groups by using a chi-square test.

For Visits 2, 3 and 4, the proportion of patients with a response of Resolved and Not Improved will be compared between the treatment groups by using a Chi-square test.

#### 10.1.10.2.1 Mycological outcome

The proportion of patients with a response of Eradication or Presumed Eradication at Visit 2, Visit 3 (EOT) and Visit 4 (TOC) will be compared between the Clotrimazole 1% otic solution and the Placebo treatment groups by using a chi-squared test.

Mycological outcome will be summarized by treatment group and visit in terms of proportion in each category at each visit.

If a patient took rescue medication prior to Visit 3, the response will be considered a failure at Visit 3. Similarly, if a patient took rescue medication prior to Visit 4, the response will be considered a failure at Visit 4.

Responses will be summarized in terms of a 3-level response. Responses of Eradication or Presumed Eradication will be categorized at favorable. Responses of Persistence, Presumed Persistence, Superinfection, Reinfection, and Recurrence will be categorized at unfavorable. Indeterminate responses will be categorized as indeterminate. The proportion of patients with a favorable response at Visit 2, Visit 3 and Visit 4 will be compared between the Clotrimazole and Placebo treatment groups by using the same chi-squared test as the primary efficacy endpoint.

Mycological outcome will also be presented by pathogen.

#### 10.1.10.2.2 Changes in signs/symptoms

The frequency of patients (n,%) with signs/symptoms (pruritus, otalgia, ear fullness and otorrhea) assessed by the investigator as “Absent”, “Mild”, “Moderate” or “Severe” will be summarized at V1, V2, V3, and V4.

The change from V1 in each sign and symptom will be assessed and classified as follows:

- **“Resolved”** at V2, V3 and V4 if that sign/symptom is assessed by the investigator as “Absent”
- **“Improved”** at V2, V3 and V4 if that sign/symptom is assessed by the investigator as:
  - “Mild” and was assessed as “Severe” or “Moderate” at V1 or
  - “Moderate” and was assessed as “Severe” at V1.
- **“Remain Absent”** at V2, V3 and V4 if the eardrum edema is assessed by the investigator as “Absent” and was assessed as “Absent” at V1
- **“Not improved”** otherwise

The frequency of patients (n,%) with a change from V1 in each sign/symptom considered as "Resolved", "Improved" or "Not improved" will be summarized at V2, V3 and V4 and will be compared between treatment groups by using a chi-square test.

The frequency of patients (n,%) with each sign/symptom considered as "Resolved" or "Not resolved" will be summarized at V2, V3, and V4 and will be compared between treatment groups by using a chi-square test.

#### *10.1.10.3 Additional analysis*

##### 10.1.10.3.1 Antimycological susceptibility

Antifungal susceptibility against clotrimazole and comparators will be tested. Interpretation of antimycological susceptibility by baseline pathogen will also be provided.

### *10.1.11 Safety Analyses*

All safety analyses will be based on the Safety population.

Adverse events, the data analyzed with respect to incidence as well as severity and potential relationship of the AEs to study medication will be monitored during the study. Safety will be assessed by reports of AEs and physical examination findings. Adverse events with onset on, or after the first dose of study medication or with onset prior to the first dose of study medication that increase in severity on, or after the first dose of study medication will be considered treatment-emergent. All treatment-emergent AEs (TEAEs) will be coded and tabulated by body system, preferred term, and treatment group. Tabulations of AEs by body system, preferred term, treatment group, and severity, and by body system, preferred term, treatment group, and relationship to study medication will also be provided. Listings of AEs, SAEs, deaths, and AEs leading to discontinuation will be produced. Adverse events will be tabulated for the following subsets:

1. All AEs;
2. Adverse events leading to discontinuation from the study and from the study medication;
3. Adverse events resulting in death;
4. Serious AEs; and
5. Adverse events related to study medication.

Patients reporting the same AE more than once will be counted only once for this event in the AE summary table. For tabulation by severity, the AE with the greatest severity reported by the patient will be included in the table. Similarly, for tabulation by relationship to study medication, the AE with the closest relationship to study medication will be included in the table.

Summary statistics will be provided for vital signs. Physical examination results will be tabulated with frequency counts.

## 10.2 Changes in Statistical Methods

Any deviation(s) from the original Statistical Analysis Plan will be described and justified in the final study report.

# 11. ETHICS, LEGAL, AND ADMINISTRATIVE ASPECTS

## 11.1 Good Clinical Practice

The procedures described in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice (GCP) guidelines of the ICH and of the Declaration of Helsinki (shown in Appendix 1). The study also will be performed in keeping with local legal requirements. The Investigator's signature on this protocol constitutes acceptance of these guidelines.

## 11.2 Informed Consent

Before being admitted to the study, each patient, or patient's legally authorized representative, will provide informed consent according to the regulatory and legal requirements of the participating country. The Investigator will not undertake any procedure specifically required for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the EDC. One or two original Informed Consent Forms (ICF) must be signed and dated by the individual administering consent according to local rules and regulations. Original signed ICF will be retained by the Investigator as part of the study records.

The Principal Investigator or Sub-Investigator will provide one original signed ICF or a copy to the patient or legal representative, according to local rules and regulations.

Should a protocol amendment be made, the ICF may be revised to reflect the changes in the protocol. If the ICF is revised, it is the responsibility of the Investigator to ensure that the amended ICF is reviewed and approved by the IRB/IEC, and that it is signed by all patients currently in the study and all patients subsequently entered in the study (or by their legally authorized representatives).

## 11.3 Approval of Study Protocol

Before the start of the study, the study protocol and other appropriate documents will be submitted to the IRB/IEC. Written approval from the IRB/IEC must be obtained before any patients are screened. The study protocol and other appropriate documents will be submitted to other authorities as required by local legal requirements.

## 11.4 Amending the Protocol

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from all persons who approved the original protocol, and receive IRB/IEC approval prior to implementation. Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug application, and other applications, if any, under which the study is being conducted. Administrative changes (minor changes that do not affect the patient benefit/risk ratio) may be made by the Sponsor without any further approvals.

All amendments and administrative changes will be distributed to all protocol recipients with instructions to append them to the protocol.

### 11.5 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on EDC and other documents submitted to the Sponsor or designee by their patient number, and/or birth date, or in such other way as may be required by local data protection regulations. Documents not to be submitted to the Sponsor or designee that identify the patient (e.g., the ICF, the initials) must be maintained in confidence by the Investigator.

### 11.6 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements, without prejudice to the liability insurance corresponding to the Investigator, the persons instructed by the Investigator, and the hospital, practice, or institute in which they are employed. The civil liability of the Investigator, the persons instructed by him, and the hospital, practice, or institute in which they are employed and the liability of the Sponsor in respect of financial loss due to personal injury and other damage that may arise as a result of the performance of this study are governed by the applicable law.

### 11.7 Publication Policy

The clinical study report will be a presentation of the pooled results, which will be prepared by the Sponsor with the assistance of some or all of the investigators.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having obtained written approval from the Sponsor prior to submission for publication or presentation.

The above policy applies to information from a prematurely discontinued or other non-completed study as well as from a completed study. Results from Investigators shall not be made available to any third party by the investigating team outside the publication procedure as described above.

The Sponsor will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

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## 13. APPENDICES

### Appendix 1
### Declaration of Helsinki

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**

**Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

**PREAMBLE**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

**GENERAL PRINCIPLES**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven

interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**RISKS, BURDENS AND BENEFITS**

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**VULNERABLE GROUPS AND INDIVIDUALS**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**RESEARCH ETHICS COMMITTEES**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**PRIVACY AND CONFIDENTIALITY**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**INFORMED CONSENT**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics

committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**USE OF PLACEBO**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

**POST-TRIAL PROVISIONS**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports

of research not in accordance with the principles of this Declaration should not be accepted for publication.

**UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.