# A Phase III, Multicenter, Randomized, Evaluator-blinded, Parallel-Group, Active-controlled Clinical Trial to Evaluate the Efficacy and Safety of Ciprofloxacin 0.3% Plus Fluocinolone Acetonide 0.025% Otic Solution in the Treatment of Acute Otitis Externa

**Protocol No：ZK- CIPRO+FLUO-201911**

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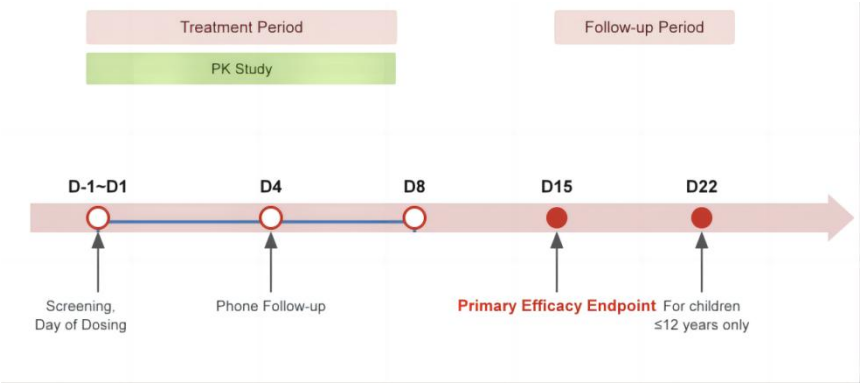
# Abbreviations

| Abbreviations | Definition |
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| AE | Adverse event |
| AOE | Acute otitis externa |
| BLQ | Below the lower limit of quantification |
| CIPRO | Ciprofloxacin |
| CITT | Clinical intent-to-treat population |
| CPP | Clinical per-protocol population |
| eCRF | Electronic case report form |
| FDA | Food and Drug Administration |
| FLUO | Fluocinolone |
| GCP | Good Clinical Practice |
| HCG | Human chorionic gonadotropin |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| LOQ | Limit of quantification |
| LLOQ | Lower limit of quantification |
| MITT | Microbiological intent-to-treat population |
| MPP | Microbiological per-protocol population |
| NMPA | National Medical Products Administration |
| PK | Pharmacokinetics |

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| SAE | Serious adverse event |
| SS | Safety set |

# PROTOCOL SYNOPSIS

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| **Title:** | A Multicenter, Randomized, Evaluator-Blinded, Parallel-Group, Active-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Ciprofloxacin plus Fluocinolone Acetonide Otic Solution in the Treatment of Acute Otitis Externa（AOE） |
| **Study Phase** | III |
| **Indication** | AOE |
| **Number of subjects** | 600 |
| **Objectives** | **Primary objective**<br>• To evaluate the efficacy of ciprofloxacin plus fluocinolone acetonide otic solution compared with ciprofloxacin otic solution in the treatment of AOE.<br>**Secondary objectives**<br>• To evaluate the safety of Ciprofloxacin plus Fluocinolone acetonide otic solution compared with Ciprofloxacin otic solution in the treatment of Acute Otitis Externa.<br>• To determine the plasma concentrations of ciprofloxacin and fluocinolone acetonide following multiple-dose administration of Ciprofloxacin plus Fluocinolone acetonide otic solution in 12 adult patients, and to evaluate the corresponding pharmacokinetic parameters. |

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| **Study design** | This is a multicenter, randomized, evaluator-blind, parallel-group, active-controlled Phase III clinical trial designed to assess the efficacy and safety of Ciprofloxacin plus Fluocinolone acetonide otic solution in the treatment of Acute Otitis Externa, and to evaluate the pharmacokinetic parameters in 12 adult patients.<br>Eligible subjects following screening will be randomized in a 1:1 ratio to either the investigational group or the active-control group, and will receive a 7-day course of treatment with either the investigational product (Ciprofloxacin plus Fluocinolone acetonide otic solution) or the comparator product (Ciprofloxacin otic solution).<br>The study design diagram is as follows： |
| **Study duration** | **The study comprises 5 visits, as follows:**<br>Visit 1 (Day −1 to Day 1): Screening, enrollment, randomization, baseline assessment, and first dosing day (D1). For the subgroup of subjects participating in the pharmacokinetic (PK) study, the first dose will be administered on the afternoon of the day of successful screening (D1), and the baseline pre-dose blood sample will be collected.<br>Visit 2 (Day 4 + 2): Telephone follow-up. The Investigator shall determine, on the basis of clinical judgement, whether rescue medication is to be administered to the subject.<br>Visit 3 (Day 8 + 2): End of Treatment (EOT). For the subgroup of subjects participating in the PK study, blood samples pre- and post-final dose will be collected on the morning of dosing Day 8. If a subject is determined at this visit to have achieved clinical cure, this visit shall be the End-of-Study visit; if the subject is not determined at this visit to have achieved clinical cure, the subject shall continue to Visit 4 (Day 15 + 2) for |

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| | the End-of-Study visit.<br>Visit 4 (Day 15 + 2): End of Study.<br>Visit 5 (Day 22 + 7): Follow-up period. Subjects aged 12 years or younger shall undergo a follow-up audiological assessment. |
| **Eligibility Criteria** | **Inclusion Criteria:**<br>1. Male or female patients aged ≥ 3 years.<br>2. Diagnosis of unilateral or bilateral diffuse Acute Otitis Externa (AOE) within 21 days (3 weeks) prior to screening.<br>3. AOE grading of II–III (see Appendix 1). The subject must simultaneously present with at least Grade 2 edema, Grade 2 ear tenderness (otalgia on palpation), and Grade 1 otorrhea.<br>4. Willingness to take measures during the study period to prevent water from entering the ear canal (e.g., refraining from swimming and wearing a shower cap covering both ears during bathing).<br>5. Subjects must be adequately informed of the contents of the trial prior to its commencement and must voluntarily sign the Informed Consent Form (ICF). For subjects aged ≥ 8 and < 18 years, the ICF must be co-signed by the subject (on the basis of informed understanding and agreement) and the subject's legal guardian. For subjects under 8 years of age, the ICF must be signed by the legal guardian on the subject's behalf.<br>6. Women of childbearing potential (including the female partners of male subjects) must have no plans for pregnancy and must voluntarily adopt effective contraceptive measures from the screening period through 28 days after the last dose.<br>**Exclusion Criteria:**<br>1. Patients unable to undergo otoscopy or otoendoscopy.<br>2. Episode of AOE within 21–28 days prior to screening, or 2 or more episodes of AOE within 21–180 days prior to screening.<br>3. Tympanic membrane perforation (including tympanostomy tubes).<br>4. Known or suspected fungal or viral ear infection, cholesteatoma, otitis media, malignant otitis externa, mastoiditis, seborrheic dermatitis of the external auditory canal, neurodermatitis of the external ear, ear trauma, or other non-infectious suppurative ear conditions.<br>5. Children aged ≤ 6 years with abnormal results on audiological |

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| | assessment using behavioral audiometry, multi-frequency auditory steady-state response (ASSR), auditory brainstem response (ABR), distortion product otoacoustic emissions (DPOAE), play audiometry, or any other non-pure-tone audiometric method.<br>6. History of malignant tumor of the external auditory canal, or currently undergoing radiotherapy or chemotherapy for cancer.<br>7. Concurrent psoriasis, diabetes mellitus, immunodeficiency disease, or history of substance abuse.<br>8. Concurrent severe disease of the cardiovascular, respiratory, urinary, digestive, or nervous system that, after at least 4 weeks of pharmacotherapy, remains unstable and requires further intervention.<br>9. Use within 1 week prior to screening of any systemic or topical antimicrobial agent, corticosteroid, anti-inflammatory or analgesic medication, or any other medication that could affect the evaluation of study results, where the time elapsed has not reached 6 half-lives of the medication.<br>10. Known or suspected hypersensitivity to quinolones, corticosteroids, or any component of the investigational product.<br>11. Participation in any other clinical trial within 3 months prior to screening.<br>12. Pregnant or breastfeeding women.<br>13.Any subject considered unsuitable for participation in this trial in the judgement of the Investigator.<br>Withdrawal Criteria:<br>Investigator-decided withdrawal:<br>The Investigator may decide to withdraw an enrolled subject from the trial if any of the following circumstances arise during the trial that render |

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| | continued participation inappropriate:<br>1) The Investigator considers it medically or ethically necessary to discontinue the trial — for example, where unforeseen circumstances prevent the subject from attending visits.<br>2) Occurrence of an intolerable adverse event or a serious adverse event such that continued participation in the trial is inappropriate.<br>3) The Investigator judges withdrawal from the study to be in the subject's best interest — for example, in the case of treatment failure.<br>4) ： Poor subject compliance, including any of the following:<br>i. The subject does not take the medication or undergo examinations as required.<br>ii. The subject uses other medication(s) that may affect the evaluation of efficacy, safety, or pharmacokinetic results.<br>iii. The subject engages in any other conduct that may affect the trial results.<br>**Subject withdrawal from the study：**<br>Subject-initiated withdrawal: In accordance with the Informed Consent Form, the subject has the right to withdraw from the trial at any time. Subjects who have not formally withdrawn consent but no longer accept dosing or examinations, or who are lost to follow-up for any other reason, are also considered to have withdrawn (also referred to as drop-outs). All such cases shall be documented.<br>**Subjects who withdraw prematurely from the study shall complete the Early Termination assessments within one week of the decision to withdraw.** |
| **Study Medication and Dosage** | **Investigational drug：**<br>Ciprofloxacin HCl plus Fluocinolone acetonide otic solution (0.3% ciprofloxacin + 0.025% fluocinolone acetonide) |

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| | Strength: 0.25 mL/vial, containing ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg<br>Description: clear solution<br>Storage: protected from light at 20-25°C<br>Shelf-life: 2 years<br>Manufacturer: Laboratorios Salvat S.A. (provided by ■■■■■■■■.)<br>**Comparator Products：**<br>Ciprofloxacin otic solution (0.3% ciprofloxacin; brand name: CETRAXAL OTICO®)<br>Strength: 1.2 mg/0.4 mL<br>Description: clear liquid<br>Storage: protected from light at 15-25°C<br>Shelf-life: 2 years<br>Manufacturer: Laboratorios Salvat S.A. (provided by ■■■■■■■■.)<br>**Usage and dosage of the Investigational Product:**<br>Before use, the vial shall be held in the hand for 1 to 2 minutes to warm the otic solution. The cap shall then be twisted off, and the patient shall tilt the head to one side, keeping the affected ear upward. The entire contents of one vial of Ciprofloxacin plus Fluocinolone acetonide otic solution (0.25 mL) shall be instilled into the ear canal, after which the auricle shall be gently pulled upward and outward to allow the solution to flow down into the ear canal. The head shall be kept tilted with the affected ear upward for approximately 5 minutes to prevent the solution from flowing out. The dose shall be administered twice daily (once in the morning and once in the evening, 12 ± 1 hours apart) for 7 consecutive days. See Appendix 2 for details.<br>**Usage and dosage of the Comparator Product:** |

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| | Before use, the vial shall be held in the hand for 1 to 2 minutes to warm the otic solution. The cap shall then be twisted off, and the patient shall tilt the head to one side, keeping the affected ear upward. Five drops of ciprofloxacin otic solution (0.25 mL) shall be instilled into the ear canal. The auricle shall be gently pulled upward and outward to allow the solution to flow down into the ear canal. The head shall be kept tilted with the affected ear upward for approximately 5 minutes to prevent the solution from flowing out. The dose shall be administered twice daily (once in the morning and once in the evening, 12 ± 1 hours apart) for 7 consecutive days. |
| **Rescue Therapy** | On Day 4, Day 5 or Day 6 of dosing (i.e., Visit 2), the Investigator shall reassess, by means of telephone follow-up, the progression of AOE in the study ear. Should symptoms worsen, or should systemic manifestations such as fever appear, the Investigator may administer other treatments, including systemic antibiotic therapy.<br>•Between Visit 1 and Visit 4, the Investigator may provide rescue medication based on the patient's clinical status.<br>•Any subject who receives rescue medication prior to the End-of-Study visit (Visit 4) shall be considered a Treatment Failure.<br>•For subjects aged ≤ 12 years, antibiotic treatment administered after the End-of-Study visit (Visit 4) and after the primary and secondary efficacy endpoints have been collected shall not be considered rescue medication. |
| **Concomitant Medications and Prohibited** | **Permitted Concomitant Therapies During the Study**<br>Medications used to treat other conditions (e.g., hypertension) are permitted during the study, provided that such medications have no therapeutic effect on otitis externa and do not interfere with the evaluation of study results.<br>For enrolled subjects with bilateral infection, the non-study ear may |

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| **Medications** | receive only saline irrigation or other physical therapies, and only at the study center, during the study period.<br>**Prohibited Medications During the Study:**<br>Apart from the investigational products, no other medication for the treatment of otitis externa may be used in this study, including topical and systemic medications and other physical therapies for otitis externa — with the exception of physical therapies administered to the non-study ear of bilaterally infected subjects at the study center. Prohibited medications include, but are not limited to, the following:<br>1) Systemic or topical use of antibiotics or corticosteroids other than the investigational products (e.g., levofloxacin, amoxicillin, cephalosporins, and dexamethasone).<br>2) Medications with anti-inflammatory or analgesic properties. |
| **Selection of Study Ear** | **1. Phase III:**Subjects with unilateral or bilateral infection are eligible. For bilaterally infected subjects, the non-study ear may receive only saline irrigation or other physical therapies, and only at the study center, during the study period.<br>**Selection of bilaterally infected subjects:** The Investigator shall determine whether to enrol a bilaterally infected subject only after assessing the tolerability of the non-study ear.<br>**Criteria for selection of the study ear in bilaterally infected subjects:** If only one ear meets the inclusion criteria, that ear shall be selected as the study ear. **If both ears meet the inclusion criteria, the ear with**<br>2. **Phase III with PK component:** Only subjects with unilateral infection. |
| **Otoscopic examination** | The Investigator shall examine the external auditory canal and tympanic membrane using an ENT video-endoscopy system or an otoscope, and shall assess tympanic membrane integrity, edema of the external auditory canal, otorrhea, and formation of granulation tissue. The degree of ear tenderness (otalgia on palpation) shall be assessed by physical examination.<br>Criterion for tympanic membrane integrity:The tympanic membrane is intact, with no perforation. Methods of examination of tympanic membrane |

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| | integrity:<br>(1) **ENT video-endoscopy system:** If the tympanic membrane is examined by means of an ENT video-endoscopy system and cannot be fully visualized through this system, the Investigator may consider supplementary clinical diagnostic measures (e.g., acoustic impedance) to assist differential diagnosis.<br>(2) **Otoscope:** If the tympanic membrane is examined by means of an otoscope and cannot be fully visualized, the Investigator may consider supplementary clinical diagnostic measures (e.g., acoustic impedance) to assist differential diagnosis.<br>**Notes:**<br>• When choosing between the ENT video-endoscopy system and the otoscope, the Investigator shall give priority to the ENT video-endoscopy system. The otoscope shall be used only if the patient cannot tolerate examination with the ENT video-endoscopy system.<br>• When the ENT video-endoscopy system is used, the Investigator shall capture images and shall print and archive these images.<br>• Irrigation of the ear canal shall not be performed during the study.<br>• Ear-swab sampling from the external auditory canal shall not be performed prior to completion of the otoscopic examination.<br>• The correct sequence of examinations is: otoscopic examination → ear-swab sampling. |
| **Audiological Assessment** | **Subjects > 12 years of age:**<br>Visits at which audiological examination and assessment are required: Visit 1 and Visit 4.<br>Method of audiological examination: Electroaudiometry (i.e., pure-tone audiometry).<br>Assessment grades shall be determined according to the World Health Organization (1997) Grades of Hearing Impairment, based on each subject's air-conduction or bone-conduction values (i.e., average thresholds):<br>Normal (≤ 25 dB), Mild (26–40 dB), Moderate (41–60 dB), Severe |

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| | (61–80 dB), Profound or Total Deafness (≥ 81 dB).<br>**Pediatric subjects aged 6 to 12 years (inclusive):**<br>Visits at which audiological examination and assessment are required: Visit 1, Visit 4, and Visit 5.<br>Method of audiological examination: Electroaudiometry (i.e., pure-tone audiometry).<br>Assessment grades shall be determined according to the World Health Organization (1997) Grades of Hearing Impairment, based on each subject's air-conduction or bone-conduction values (i.e., average thresholds):<br>Normal (≤ 25 dB), Mild (26–40 dB), Moderate (41–60 dB), Severe (61–80 dB), Profound or Total Deafness (≥ 81 dB).<br>**Pediatric subjects aged ≤ 6 years:**<br>Visits at which audiological examination and assessment are required: Visit 1, Visit 4, and Visit 5.<br>Methods of audiological examination: Electroaudiometry (i.e., pure-tone audiometry), behavioral audiometry, multi-frequency auditory steady-state response (ASSR), auditory brainstem response (ABR), distortion product otoacoustic emissions (DPOAE), play audiometry, or any other non-pure-tone audiometric method.<br>If pure-tone audiometry is used, assessment grades shall be determined according to the World Health Organization (1997) Grades of Hearing Impairment, based on each subject's air-conduction or bone-conduction values (i.e., average thresholds):<br>Normal (≤ 25 dB), Mild (26–40 dB), Moderate (41–60 dB), Severe (61–80 dB), Profound or Total Deafness (≥ 81 dB).<br>If any other audiometric method is used, the assessment grades shall be: Normal or Abnormal. |

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| **Microbiological Examination** | **1. Specimen collection:**<br>Microbiological examination shall be performed on all subjects at Visit 1 and on subjects with otorrhea still present on clinical observation at Visit 3 and Visit 4. The examination shall include bacterial culture, bacterial isolation and identification, antimicrobial susceptibility testing, and in vitro antibacterial activity testing of the investigational products.<br>**2. Bacterial culture and identification:**<br>Clinical specimens shall be inoculated onto blood agar and chocolate agar at primary isolation culture, and AOE pathogens shall be routinely isolated.<br>All clinical isolates shall be identified to the species and genus level.<br>**3. Antimicrobial susceptibility testing:**<br>Each study site shall preserve all clinical isolates obtained, including fungi and non-AOE-pathogenic species.<br>Each study site shall perform disc diffusion susceptibility testing on the clinical AOE pathogen isolates obtained (excluding fungi), and shall preserve the isolates. Two tubes of each isolate shall be preserved: one tube shall be sent to the central laboratory, and the other shall be retained at the respective sub-site. The timing of shipment of isolates to the central laboratory shall be determined by each site based on the storage temperature: isolates stored at −20 °C to −70 °C shall be shipped to the central laboratory between 3 and 6 months after collection; isolates stored at ≤ −70 °C shall be shipped to the central laboratory between 6 and 12 months after collection. Each study site shall determine the shipping schedule for its isolates based on actual conditions. Upon receipt of the sub-site isolates, the central laboratory shall perform confirmatory identification and Minimum Inhibitory Concentration (MIC) determination on the sub-site clinical |

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| | isolates.<br>**1） Disc diffusion susceptibility testing:**<br>For the common AOE pathogens in this study, the disc diffusion (Kirby–Bauer) susceptibility test shall include ciprofloxacin, levofloxacin, piperacillin, and azithromycin.<br>**2） In vitro antibacterial activity testing:**<br>At the central laboratory, the dilution method shall be used to determine the Minimum Inhibitory Concentrations (MICs) of the investigational drug (Ciprofloxacin) and the comparator drugs (ciprofloxacin, levofloxacin, piperacillin, and azithromycin) against the clinical pathogen isolates (excluding fungi). The reported parameters shall include MIC range, MIC50, and MIC90.<br>Detailed procedures for specimen collection, culture and identification, susceptibility testing, and MIC determination are provided in the central laboratory's Standard Operating Procedures (SOPs). |
| **Efficacy Assessments** | ● **Primary Efficacy Endpoint**<br>The primary efficacy endpoint is clinical cure at End of Study (Day 15 + 2).<br>**Definition of clinical cure:**<br>Definition of clinical cure: The Investigator shall observe and record the clinical symptoms using an otoscope or ENT video-endoscopy system. Edema and otorrhea shall be assessed for efficacy using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3); ear tenderness shall be assessed for efficacy by physical examination using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3).<br>**Clinical cure is considered to have been achieved when the scores for edema, otorrhea, and ear tenderness are all 0.** |

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| | ✓ Edema (severity): The Investigator shall observe and record the extent to which edema of the external auditory canal obscures the tympanic membrane.<br>• Absent (0) = No edema of the external auditory canal.<br>• Mild (1) = Edema of the external auditory canal is present, but the tympanic membrane remains fully and clearly visible.<br>• Moderate (2) = Localized edema of the external auditory canal and/or edema obscuring < 25% of the tympanic membrane.<br>• Severe (3) = Diffuse edema of the external auditory canal with edema obscuring ≥ 25% of the tympanic membrane.<br>✓ Otorrhea (severity):<br>• Absent (0) = External auditory canal and tympanic membrane are dry.<br>• Mild (1) = Surface of the external auditory canal and/or tympanic membrane is moist.<br>• Moderate (2) = Only a small amount of discharge is present in the external auditory canal, not affecting or only partially affecting visualization of the tympanic membrane.<br>• Severe (3) = Substantial fluid is present in the external auditory canal, completely obscuring visualization of the tympanic membrane.<br>✓ Ear tenderness (severity):<br>• Absent (0) = No tenderness.<br>• Mild (1) = Awareness of pain, but no painful facial expression or withdrawal on palpation. |

• Moderate (2) = Painful facial expression and/or withdrawal on palpation.

• Severe (3) = Refusal to allow palpation, or startled movement, on palpation or with mild traction.

**Definition of clinical failure: Clinical failure is defined as any one of the primary efficacy assessments being other than 0.**

- **Secondary Efficacy Endpoints**

1. Microbiological efficacy parameters: Microbiological examination shall be performed on all subjects at Visit 1 and on subjects with otorrhea still present on clinical observation at Visit 3 and Visit 4. Microbiological efficacy shall be classified as microbiological success or microbiological failure.

Microbiological efficacy classifications: Eradication, Presumed Eradication, Persistence, Presumed Persistence, Partial Eradication, Superinfection, and Recurrence. "Recurrence" applies only at Visit 4. At Visit 3 and Visit 4, subjects with clinical cure for whom microbiological examination was not performed owing to absence of otorrhea shall be classified as Presumed Eradication; subjects with clinical failure for whom microbiological examination was not performed owing to absence of otorrhea shall be classified as Presumed Persistence.

For statistical analysis, Eradication and Presumed Eradication shall be pooled to calculate the eradication rate (i.e., the microbiological success rate); Persistence, Presumed Persistence, Partial Eradication, Superinfection, and/or Recurrence shall be pooled to calculate the microbiological failure rate.

Superinfection and Recurrence at Visit 4 shall be analyzed and assessed separately.

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| | 2. Therapeutic Response (overall therapeutic outcome): To be assessed at Visit 3 and Visit 4.<br>The therapeutic response shall be classified as Therapeutic Cure or Therapeutic Failure, and shall be assessed only in subjects with positive baseline microbiological cultures (excluding fungi). A subject classified as clinically cured and bacteriologically Eradicated or Presumed Eradicated shall be classified as a Therapeutic Cure. All other combinations of outcomes shall be classified as Therapeutic Failure.<br>3. Clinical improvement: To be assessed at Visit 3 and Visit 4.<br>Clinical improvement is defined as improvement of at least 1 grade in any clinical sign or symptom (edema, otorrhea, or ear tenderness) compared with baseline (Visit 1).<br>4. Improvement in individual signs and symptoms: This includes improvement (by ≥ 1 grade compared with baseline, Visit 1) in edema, otorrhea, and ear tenderness (as assessed by the Investigator) at Visit 3 and Visit 4, expressed as the proportion of subjects with such improvement.<br>5. Improvement in granulation tissue: The Investigator shall observe and record the degree of granulation tissue formation in the external auditory canal by means of an otoscope or ENT video-endoscopy system, assessed dichotomously (Absent = 0, Present = 1). The endpoint shall be the proportion of subjects with resolution of granulation tissue at Visit 3 and Visit 4 compared with baseline (Visit 1).<br>6. Improvement in otalgia (patient self-assessment) and time to end of pain: The patient shall self-assess the severity of ear pain and the time at which ear pain ends, using a diary card. |

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| | ✓ Improvement in otalgia: For subjects aged ≥ 12 years and adults, ear pain shall be assessed using a 10-point scale (No pain = 0, Mild = 1–3, Moderate = 4–6, Severe = 7–10); for pediatric subjects (aged ≥ 3 to 12 years), self-assessment shall be performed using the Wong-Baker FACES Pain Rating Scale (No pain = 0, Mild = 2, Moderate = 4–6, Severe = 8–10). Improvement is defined as improvement of at least 1 grade in otalgia at Visit 3 and Visit 4 compared with baseline (Visit 1), where the grades are: No pain, Mild, Moderate, and Severe.<br>✓ Time to end of ear pain : Prior to the End of Study, the patient or legal guardian (where the patient is aged ≥ 3 and < 12 years) shall record on the diary card the time of cessation of ear pain, measured from the first day of dosing. Where recurrence of ear pain occurs, the time of cessation of each episode shall be recorded on the diary card. |
| **Safety Assessment** | Safety shall be assessed by means of adverse events / serious adverse events, physical examination, vital signs, laboratory tests, and audiological assessment. |
| **Pharmacokinetic Assessment (Subgroup of Adult Patients)** | **At designated study sites, 12 adult patients (≥ 18 years) with unilateral ear infection shall be screened for the collection of PK data. The design of the pharmacokinetic study is as follows:**<br>Venous blood shall be collected at the following 7 time points: pre-dose of the first dose (D1) at 0 h (within 60 min before dosing); pre-dose of the final dose at Visit 3 (D8) at 0 h (within 60 min before dosing); and 15 min, 30 min, 1 h, 2 h, and 4 h post-dose. At each collection, approximately 1.0 mL of blood shall be discarded, after which approximately 4 mL of blood shall be drawn into labelled, pre-chilled EDTA-K2 anticoagulant vacuum |

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| | collection tubes. Following centrifugation, the plasma sample shall be divided into two aliquots and stored in a freezer at ≤ −60 °C for pharmacokinetic analysis of ciprofloxacin and fluocinolone acetonide.<br>**Permissible time deviations during blood sampling are provided in Appendix 5.**<br>Detailed procedures for sample handling are provided in the Sample Operations Manual issued by the bioanalytical laboratory.<br>Bioanalytical methods are provided in the bioanalytical laboratory's Sample Analysis Method document.<br>Should any revision relating to the pharmacokinetic study be required, approval need only be obtained from the Ethics Committee of the designated study site, with filing accordingly. |
| **Statistical Analysis** | • **Efficacy Analysis**<br>1、 **Primary efficacy endpoint: Clinical cure rate at End of Study (Day 15 + 2).**<br>The clinical cure rate shall be analyzed using the chi-squared test, with a one-sided $\alpha = 0.025$. The between-group difference and the two-sided 95% confidence interval (CI) shall be calculated. Superiority shall be concluded where the difference is statistically significant (i.e., the lower bound of the 95% CI > 0).<br>**2、 Secondary efficacy endpoints:**<br>The microbiological success rate shall be compared between treatment groups using the chi-squared test or Fisher's exact test. Subjects whose bacterial cultures yield fungal infection shall be classified as Not Evaluable in the statistical analysis.<br>Therapeutic response: Therapeutic cure rate. Subjects who are clinically cured at Visit 3 and Visit 4 and who are bacteriologically Eradicated or |

Presumed Eradicated shall be classified as Therapeutic Cure. Between-group comparisons shall be made using the chi-squared test.

Clinical improvement: The chi-squared test shall be used for between-group comparison of the proportion of subjects with improvement of ≥ 1 grade in any clinical sign or symptom (edema, otorrhea, or ear tenderness) at Visit 3 and Visit 4 compared with baseline (Visit 1).

Improvement in individual signs and symptoms: The chi-squared test shall be used for between-group comparison of the proportion of subjects with improvement of ≥ 1 grade in edema, otorrhea, and ear tenderness (as assessed by the Investigator) at Visit 3 and Visit 4 compared with baseline (Visit 1).

Improvement in granulation tissue: The chi-squared test shall be used for between-group comparison of the proportion of subjects with resolution of granulation tissue at Visit 3 and Visit 4 compared with baseline (Visit 1).

Improvement in otalgia: Improvement is defined as patient-self-assessed improvement of ≥ 1 grade in ear pain at Visit 3 and Visit 4 compared with baseline (Visit 1). Between-group comparisons shall be made using the chi-squared test.

Time to end of ear pain: The Kaplan–Meier method shall be used to estimate the median time to end of ear pain in each group together with the corresponding 95% CI. Between-group comparison shall be performed using the log-rank test. The time to end of ear pain used in the statistical analysis shall be the time of cessation of the last episode of ear pain for the subject.

- **Safety Analysis**

Safety analyses shall be performed on the Safety Set. All subjects who have received at least one dose of the investigational product and have had

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| | at least one post-dose safety assessment shall be included in the safety data summaries and listings. Adverse events shall be coded by System Organ Class and Preferred Term (MedDRA). The types, numbers, severity, and relationship to the investigational product of adverse events shall be tabulated, and the incidence rates of adverse events shall be calculated. Cases of study discontinuation due to adverse events and cases of serious adverse events shall be described.<br>● **Pharmacokinetic Analysis**<br>The following pharmacokinetic parameters shall be calculated for ciprofloxacin and fluocinolone acetonide following multiple-dose administration in the 12 adult patients with unilateral ear infection: $C_{ss_max}$, $C_{ss_min}$, $C_{ss_av}$, $t_{1/2}$, $AUC_{ss}$, $T_{max}$, DF, CL or CL/F。 |

# Diagram of Study Design

| Study phase | Screening/Base line/First Dose | Treatment Period | | End of Study | Follow-up Period （Subjects aged ≤12） | Early Termination |
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| **Visit** | **V1** | **V2** | **V3[11]** | **V4** | **V5** | **withdrawal** |
| **Study Day** | **D-1~D1[10]** | **D4（+2）** | **D8（+2）** | **D15（+2）** | **D22（+7）** | **date（+7）** |
| **Collection of subject baseline data** | | | | | | |
| Signing of ICF | X | | | | | |
| Confirmation of inclusion/exclusion criteria | X | | | | | |
| Collection of demographic data | X | | | | | |
| Height and weight | X | | | | | |
| Medical and medication history | X | | | | | |
| History of substance abuse, allergies | X | | | | | |
| Concomitant diseases and concomitant medications | X | X | X | X | X | X |
| **Efficacy assessment** | | | | | | |
| AOE grading assessment[1] | X | | | | | |
| Primary efficacy assessment (edema, otorrhea, tenderness)[2] | X | | X | X | | X |
| Granulation tissue[3] | X | | X | X | | X |
| Microbiological examination[4] | X | | X | X | | X |
| Therapeutic response assessment | | | X | X | | X |

| | | | | | | |
|---|---|---|---|---|---|---|
| Time to end of ear pain (diary card) | X | X | X | X | | X |
| Ear pain severity (diary card) | X | X | X | X | | X |
| **Safety assessment** | | | | | | |
| Physical examination | X | | X | X | | X |
| Vital signs | X | | X | X | | X |
| Audiological assessment[5] | X | | | X | X | X |
| Urine/blood pregnancy test[6] | X | | | X | | X |
| Laboratory tests (CBC, biochem)[7] | X | | | X | | X |
| Adverse event recording[8] | X | X | X | X | X | X |
| **Pharmacokinetic study (12 adult patients)** | | | | | | |
| PK blood sampling[9] | X | | X | | | |
| **Randomization and medication** | | | | | | |
| Randomization | X | | | | | |
| Drug dispensing/return record | X | | X | | | X |
| Medication record (diary card) | X | X | X | X | | X |

**Notes:**

[1] Criteria for selection of the study ear in bilaterally infected subjects: If only one ear of the subject meets the inclusion criteria, that ear shall be selected as the study ear. If both ears meet the inclusion criteria, the ear with the more severe condition shall be selected.

[2] Clinical efficacy assessment: At Visit 1, Visit 3, and Visit 4, the Investigator shall observe and record the clinical symptoms by means of an otoscope or ENT video-endoscopy system. Edema and otorrhea shall be assessed for efficacy using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3); ear tenderness shall be

assessed for efficacy by physical examination using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3). Clinical cure is considered to have been achieved when the scores for edema, otorrhea, and ear tenderness are all 0.

[3] Granulation tissue formation shall be assessed dichotomously (Absent = 0, Present = 1).

[4] Microbiological examination: Microbiological examination shall be performed on all subjects at Visit 1 and on subjects with otorrhea still present on clinical observation at Visit 3 and Visit 4. The examination shall include bacterial culture, bacterial isolation and identification, antimicrobial susceptibility testing, and in vitro antibacterial activity testing of the investigational products. Subjects who withdraw early and who have undergone microbiological examination within 3 days prior to withdrawal need not repeat the examination at withdrawal.

[5] Audiological assessment: For subjects aged > 6 years, electroaudiometry shall be used. For subjects aged ≤ 6 years, the audiological assessment shall be performed using the audiometric method routinely used at the study site for clinical care.

[6] Urine/blood pregnancy test: To be performed at screening and at End of Study, in women of childbearing potential only.

[7] Laboratory tests: To be performed at screening, Visit 4, and Early Termination, comprising the following: Complete Blood Count: white blood cell count (WBC), neutrophil percentage (NE%), lymphocyte percentage (LY%), absolute neutrophil count (NE#), absolute lymphocyte count (LY#), red blood cell count (RBC), hemoglobin (HGB), and platelets (PLT); Blood Biochemistry: direct bilirubin (DBIL), total bilirubin (TBIL), urea/blood urea nitrogen (UREA/BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and blood glucose (GLU).

Requirements for biochemistry sampling: As the target indication, AOE, has an acute onset and causes considerable clinical discomfort, non-fasting blood biochemistry testing

shall be accepted at the screening visit. However, fasting samples remain required for blood biochemistry testing at the End-of-Study visit.

[8] Period of adverse event collection: From the implementation of Protocol V3.0 onwards, adverse events shall be collected from the time of the first administration of the investigational product through to the End of Study.

[9] PK blood sampling: Venous blood shall be collected at the following 7 time points: pre-dose of the first dose at 0 h (within 60 min before dosing); pre-dose of the final dose at Visit 3 (D8) at 0 h (within 60 min before dosing); and 15 min, 30 min, 1 h, 2 h, and 4 h post-dose. At each collection, approximately 1.0 mL of blood shall be discarded, after which approximately 4 mL of blood shall be drawn into labelled, pre-chilled EDTA-K2 anticoagulant vacuum collection tubes. Following centrifugation, the plasma sample shall be divided into two aliquots and stored in a freezer at ≤ −60 °C for pharmacokinetic analysis of ciprofloxacin and fluocinolone acetonide.

[10] The window period "D−1 to D1" for screening, randomization, baseline, and the first dosing day represents the time span "D−1, D0, D1".

[11] If a subject is determined at Visit 3 to have achieved clinical cure, Visit 3 shall be the End-of-Study visit; if the subject is not determined at Visit 3 to have achieved clinical cure, the subject shall continue in the trial.

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# 1 INTRODUCTION

Acute otitis externa (AOE), also known as swimmer's ear, is an acute diffuse inflammation of the skin or subcutaneous tissue of the external auditory canal, mainly caused by Pseudomonas aeruginosa or Staphylococcus aureus, and may sometimes involve the auricle or tympanic membrane. It has an acute onset, with ear canal inflammation developing rapidly within 3 weeks, usually within 48 hours. Clinical manifestations may include ear pain, pruritus, aural fullness, or otorrhea, with or without hearing loss due to obstruction of the external auditory canal or ear pain during chewing. Typical signs include tragal tenderness or pain on traction of the auricle. It commonly occurs in children older than 2 years and in adults. The annual incidence is 1.3% in females and 1.2% in males. Incidence is highest in children aged 7-12 years and adults aged 65-74 years; AOE is rare in children younger than 2 years. AOE occurs more frequently in summer, possibly because increased humidity or participation in water activities such as swimming allows water to enter the ear canal. Excessive cleaning of the ear canal or use of alkaline ear drops may also cause AOE. In most patients, symptoms resolve as the infection resolves, but in a minority of patients the infection may spread to tissues surrounding the ear.

According to published data, [1] almost all cases of AOE in North America (98%) are caused by bacterial infection. The most common pathogens are Pseudomonas aeruginosa (20%-60%) and Staphylococcus aureus (10%-70%), often occurring as polymicrobial infection. Other pathogens are mainly Gram-negative bacteria other than Pseudomonas aeruginosa; in large clinical series, each Gram-negative bacterium accounted for no more than 2%-3%. Fungi are rare in the early stage of AOE infection but are more common in chronic otitis externa or after topical antibiotic treatment of external ear canal infection. Clinically, topical antibacterial agents are generally used for AOE, and systemic

medications are considered only when other severe symptoms are present.

The 2014 clinical practice guideline on AOE issued by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [1]clearly states that topical antibacterial agents are more effective than oral antibiotics. Approximately 20%-40% of AOE patients receive oral antibiotics in addition to topical anti-inflammatory treatment; however, the selected antibiotics are often ineffective against Pseudomonas aeruginosa and Staphylococcus aureus, leading to increased bacterial resistance and possible adverse effects due to extensive systemic distribution of antibiotics[2-3]. In addition, studies have shown that treatment with penicillins, macrolides, or cephalosporins may prolong the disease course (rate ratio 1.56-1.91), and cephalosporins may increase recurrence (rate ratio 1.28; 95% CI, 1.03-1.58)[4]. The advantage of topical antibacterial treatment for AOE is that it can achieve very high antibacterial concentrations at the site of infection, usually 100 to 1000 times higher than systemic antibiotic therapy[1], thereby substantially improving efficacy and reducing bacterial resistance.

Quinolone antibiotics were approved by the US FDA as topical antibiotics in 2004 and are characterized by broad antibacterial activity, strong tissue penetration, and good safety and tolerability. International consensus holds that, for uncomplicated AOE and otorrhea caused by acute otitis media with tympanostomy tubes (AOMT), topical antibiotic treatment is more advantageous than systemic therapy. Quinolone ear drops can achieve local drug concentrations 1000 times higher than oral antibiotics[5-6], which can significantly improve efficacy and reduce bacterial resistance. In its recommendations for topical therapy for bacterial AOE, Nationwide Children's recommends quinolone antibacterial agents as first-line topical therapy for pediatric AOE, and recommends 0.3% ciprofloxacin + 0.1% dexamethasone (Ciprodex) as the preferred topical therapy for AOE with granulation tissue or active bleeding[7].

Ciprofloxacin is a second-generation quinolone antibacterial agent. It acts on the A subunit of bacterial DNA gyrase, inhibiting DNA synthesis and replication and thereby causing bacterial death. Because of its broad-spectrum antibacterial activity and potent and rapid bactericidal effect, it is widely used clinically for systemic infections such as respiratory tract and urinary tract infections, and for local infections such as ear and eye infections. Ciprofloxacin has the strongest antibacterial activity among quinolones against Pseudomonas aeruginosa and also has strong activity against other Gram-negative bacteria and staphylococci. It can effectively eradicate the main pathogens of AOE, including Pseudomonas aeruginosa and Staphylococcus aureus.

Fluocinolone acetonide, like other topical corticosteroids, has anti-inflammatory, analgesic, and capillary vasoconstrictive effects and is classified as a low- to medium-potency corticosteroid. Addition of a corticosteroid to an otic antibacterial preparation may help relieve the inflammatory response accompanying bacterial infection and reduce the formation of granulation tissue.

ciprofloxacin plus fluocinolone acetonide multidose otic solution (0.3% ciprofloxacin [CIPRO] + 0.025% fluocinolone acetonide [FLUO]), developed by Laboratorios Salvat S.A. in Spain and marketed as CETRAXAL® Plus, has been approved in more than 40 countries since its initial approval in 2002 for the treatment of AOE caused by ciprofloxacin-susceptible bacteria and AOMT in children aged 6 months and older and in adults. In April 2016, the single-dose formulation of CIPRO+FLUO otic solution was approved for marketing in the United States, followed by approvals in Canada and several EU countries.

The ciprofloxacin plus fluocinolone acetonide otic solution (0.3% ciprofloxacin [CIPRO] + 0.025% fluocinolone acetonide [FLUO]) licensed by Laboratorios Salvat S.A. to our company for domestic development and

marketing (trade name: CETRAXAL® Plus) is a single-dose formulation, supplied in individual sterile preservative-free packaging and administered by the otic route. The strength is 0.25 mL per vial; each vial contains ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg. This product is the first topical otic fixed-dose combination of a fluoroquinolone and a corticosteroid in China, and according to the new registration classification of chemical drugs (2016 No. 51) should be classified as Chemical Drug Category 5.1.

# 2 Study Objectives

This is a Phase III clinical study designed to investigate the efficacy and safety of Ciprofloxacin plus Fluocinolone acetonide otic solution compared with Ciprofloxacin otic solution in the treatment of Acute Otitis Externa, and to collect plasma pharmacokinetic (PK) data in a subgroup of adult patients.

- **Primary objective**

To evaluate the efficacy of ciprofloxacin plus fluocinolone acetonide otic solution compared with ciprofloxacin otic solution in the treatment of AOE.

- **Secondary objectives**

1) To evaluate the safety of Ciprofloxacin plus Fluocinolone acetonide otic solution compared with Ciprofloxacin otic solution in the treatment of Acute Otitis Externa.
2) To determine the plasma concentrations of ciprofloxacin and fluocinolone acetonide following multiple-dose administration of Ciprofloxacin plus Fluocinolone acetonide otic solution in 12 adult patients, and to evaluate the corresponding pharmacokinetic parameters.

# 3 Study Design and Implementation

This is a multicenter, randomized, evaluator-blind, parallel-group, active-controlled Phase III clinical trial designed to assess the efficacy and safety

of Ciprofloxacin plus Fluocinolone acetonide otic solution compared with Ciprofloxacin otic solution in the treatment of Acute Otitis Externa, and to collect plasma pharmacokinetic data in a subgroup of adult patients.

In order to ensure balance among enrolled cases and the scientific integrity of the study data, this clinical study shall be conducted across multiple clinical investigator sites and shall adopt a randomized, evaluator-blind, parallel-group, active-controlled design with a view to minimizing bias as far as possible.

## 3.1 Determination of the Randomization Method

This study shall employ block randomization. Subjects eligible following screening shall be randomized in a 1:1 ratio to either the investigational group (Ciprofloxacin plus Fluocinolone acetonide otic solution) or the active-control group (Ciprofloxacin otic solution).

This study is an evaluator-blind trial. Randomization shall be performed by means of an Interactive Web Response System (IWRS). At each study site, the drug manager shall, in accordance with the requirements of the protocol and the medication number assigned by the IWRS, dispense the corresponding medication to the subject according to that medication number.

The independent Evaluator-Investigator shall examine the external auditory canal and tympanic membrane using an ENT video-endoscopy system or an otoscope, and shall assess tympanic membrane integrity, edema of the external auditory canal, otorrhea, and formation of granulation tissue. The degree of ear tenderness (otalgia on palpation) shall be assessed by physical examination. The Evaluator shall remain blinded to the investigational product administered to the subject.

**Requirements for blinded conduct of this study:**

1.The independent Evaluator (i.e., the Efficacy Evaluator-Investigator) shall possess sufficient clinical experience to independently assume responsibility for

efficacy assessment.

2.For any given subject, efficacy data assessments should, to the extent possible, be performed by the same Efficacy Evaluator-Investigator.

### 3.2 Number of Subjects

A total of 600 patients with Acute Otitis Externa are planned to be enrolled during this study, comprising 300 subjects in the investigational group and 300 subjects in the active-control group.

## 4 Study Population

### 4.1 Inclusion Criteria

1. Male or female patients aged ≥ 3 years.

2. Diagnosis of unilateral or bilateral diffuse Acute Otitis Externa (AOE) within 21 days (3 weeks) prior to screening.

3. AOE grading of II–III (see Appendix 1). The subject must simultaneously present with at least Grade 2 edema, Grade 2 ear tenderness (otalgia on palpation), and Grade 1 otorrhea.

4. Willingness to take measures during the study period to prevent water from entering the ear canal (e.g., refraining from swimming and wearing a shower cap covering both ears during bathing).

5. Subjects must be adequately informed of the contents of the trial prior to its commencement and must voluntarily sign the Informed Consent Form (ICF). For subjects aged ≥ 8 and < 18 years, the ICF must be co-signed by the subject (on the basis of informed understanding and agreement) and the subject's legal guardian. For subjects under 8 years of age, the ICF must be signed by the legal guardian on the subject's behalf.

6. Women of childbearing potential (including the female partners of male subjects) must have no plans for pregnancy and must voluntarily adopt effective contraceptive measures from the screening period through 28 days after the last

dose.

## 4.2 Exclusion Criteria

1. Patients unable to undergo otoscopy or otoendoscopy.

2. Episode of AOE within 21–28 days prior to screening, or 2 or more episodes of AOE within 21–180 days prior to screening.

3. Tympanic membrane perforation (including tympanostomy tubes).

4. Known or suspected fungal or viral ear infection, cholesteatoma, otitis media, malignant otitis externa, mastoiditis, seborrheic dermatitis of the external auditory canal, neurodermatitis of the external ear, ear trauma, or other non-infectious suppurative ear conditions.

5. Children aged ≤ 6 years with abnormal results on audiological assessment using behavioral audiometry, multi-frequency auditory steady-state response (ASSR), auditory brainstem response (ABR), distortion product otoacoustic emissions (DPOAE), play audiometry, or any other non-pure-tone audiometric method.

6. History of malignant tumor of the external auditory canal, or currently undergoing radiotherapy or chemotherapy for cancer.

7. Concurrent psoriasis, diabetes mellitus, immunodeficiency disease, or history of substance abuse.

8. Concurrent severe disease of the cardiovascular, respiratory, urinary, digestive, or nervous system that, after at least 4 weeks of pharmacotherapy, remains unstable and requires further intervention.

9. Use within 1 week prior to screening of any systemic or topical antimicrobial agent, corticosteroid, anti-inflammatory or analgesic medication, or any other medication that could affect the evaluation of study results, where the time elapsed has not reached 6 half-lives of the medication.

10. Known or suspected hypersensitivity to quinolones, corticosteroids, or any component of the investigational product.

11. Participation in any other clinical trial within 3 months prior to screening.

12. Pregnant or breastfeeding women.

13.Any subject considered unsuitable for participation in this trial in the judgement of the Investigator.

## 4.3 Selection of Unilateral/Bilateral Ears

**1. Phase III:** Subjects with unilateral or bilateral infection are eligible. For bilaterally infected subjects, the non-study ear may receive only saline irrigation or other physical therapies, and only at the study center, during the study period.

**Selection of bilaterally infected subjects:**The Investigator shall determine whether to enrol a bilaterally infected subject only after assessing the tolerability of the non-study ear.

**Criteria for selection of the study ear in bilaterally infected subjects:** If only one ear meets the inclusion criteria, that ear shall be selected as the study ear. **If both ears meet the inclusion criteria, the ear with the more severe condition shall be selected.**

1. **Phase III with PK:** Subjects with unilateral ear infection are included.

## 4.4 Subject Withdrawal Criteria

All subjects who sign the ICF and enter the study after screening have the right to withdraw from the study at any time without condition. If a subject does not complete protocol-specified safety and efficacy observations, the subject is considered to have discontinued the study and is a dropout case. The time and reason for discontinuation shall be recorded in the eCRF.

- **Investigator-decided withdrawal:**

The Investigator may decide to withdraw an enrolled subject from the trial if any of the following circumstances arise during the trial that render continued

participation inappropriate:

2) The Investigator considers it medically or ethically necessary to discontinue the trial — for example, where unforeseen circumstances prevent the subject from attending visits.

2) Occurrence of an intolerable adverse event or a serious adverse event such that continued participation in the trial is inappropriate.

3) The Investigator judges withdrawal from the study to be in the subject's best interest — for example, in the case of treatment failure.

4) ： Poor subject compliance, including any of the following:

i. The subject does not take the medication or undergo examinations as required.

ii. The subject uses other medication(s) that may affect the evaluation of efficacy, safety, or pharmacokinetic results.

iii. The subject engages in any other conduct that may affect the trial results.

- **Subject withdrawal from the study：**

Subject-initiated withdrawal: In accordance with the Informed Consent Form, the subject has the right to withdraw from the trial at any time. Subjects who have not formally withdrawn consent but no longer accept dosing or examinations, or who are lost to follow-up for any other reason, are also considered to have withdrawn (also referred to as drop-outs). All such cases shall be documented.

**Subjects who withdraw prematurely from the study shall complete the Early Termination assessments within one week of the decision to withdraw.**

# 5 Study drug

## 5.1 Drug category

- Investigational drug：Ciprofloxacin plus Fluocinolone acetonide otic solution (0.3% ciprofloxacin + 0.025% fluocinolone acetonide)

Strength: 0.25 mL/vial, containing ciprofloxacin 0.75 mg and fluocinolone acetonide 0.0625 mg

Description: clear solution

Storage: protected from light at 20-25°C

Shelf-life: 2 years

Manufacturer: Laboratorios Salvat S.A. (provided by ■■■■■■■■■.)

- Comparator Products：Ciprofloxacin otic solution (0.3% ciprofloxacin; brand name: CETRAXAL OTICO®)

Strength: 1.2 mg/0.4 mL

Description: clear liquid

Storage: protected from light at 15-25°C

Shelf-life: 2 years

Manufacturer: Laboratorios Salvat S.A. (provided by ■■■■■■■■■.)

## 5.2 Management of Study Drug

### 5.2.1 Receipt

Study drugs delivered by the sponsor to each site must be received by designated site personnel and signed for by at least one responsible person.

### 5.2.2 Registration

The investigational product dispensed to each study site shall be managed by a designated individual who shall be responsible for the following:

- Maintaining inventory records of all study medication.
- Ensuring that all study medication is dispensed and used in accordance with the requirements of this protocol.
- Recording the dates and quantities of study medication dispensed to, and returned by, each subject.
- Ensuring that drug inventory quantities reconcile with the quantities of drug received, dispensed, and expired. Any discrepancy shall be explained in the remarks.

- Ensuring that the quantity of drug dispensed reconciles with the quantity used and the quantity returned. Any discrepancy shall be explained in the remarks.

#### 5.2.3 Storage

The study medication shall be stored in accordance with the requirements stated on the label, and temperature records shall be maintained at regular intervals.

- The study medication shall not be supplied to any person other than the subjects participating in this study.
- The study medication shall be stored in a locked and secure storage facility, either in the pharmacy or under other controlled storage conditions, and shall be accessible only to personnel authorized by the Investigator to dispense the study medication.
- Should a temperature excursion occur during storage of the investigational product at the study site, the medication may continue to be used and need not be quarantined if the stability data of the investigational product support its acceptability within the duration of the excursion.

#### 5.2.4 Return and Destruction of the Study Medication

All unused medication and used product shall be collected upon completion of the study, returned to the Sponsor, and destroyed centrally.

# 6 STUDY MEDICATION

## 6.1 6.1Subject Randomization

After signing the ICF, eligible subjects who meet all inclusion criteria and none of the exclusion criteria may be randomized into the study in a 1:1 ratio to the investigational group or active-control group.

## 6.2 Administration

Both the investigational product and the comparator product shall be

administered twice daily (once in the morning and once in the evening, 12 ± 1 hours apart) for 7 consecutive days.

**Interval between consecutive doses = time of current dose − time of previous dose.**

Following randomization and enrollment, the Investigator shall inform the subject or the subject's legal guardian of the posology.

Usage and dosage of the Investigational Product:

Before use, the vial shall be held in the hand for 1 to 2 minutes to warm the otic solution. The cap shall then be twisted off, and the patient shall tilt the head to one side, keeping the affected ear upward. The entire contents of one vial of Ciprofloxacin plus Fluocinolone acetonide otic solution (0.25 mL) shall be instilled into the ear canal, after which the auricle shall be gently pulled upward and outward to allow the solution to flow down into the ear canal. The head shall be kept tilted with the affected ear upward for approximately 5 minutes to prevent the solution from flowing out. For detailed administration procedures, see Appendix 2 (Administration Instructions for Ciprofloxacin plus Fluocinolone acetonide Otic Solution).

**Usage and dosage of the Comparator Product:**

Before use, the vial shall be held in the hand for 1 to 2 minutes to warm the otic solution. The cap shall then be twisted off, and the patient shall tilt the head to one side, keeping the affected ear upward. Five drops of ciprofloxacin otic solution (0.25 mL) shall be instilled into the ear canal. The auricle shall be gently pulled upward and outward to allow the solution to flow down into the ear canal. The head shall be kept tilted with the affected ear upward for approximately 5 minutes to prevent the solution from flowing out. The dose shall be administered twice daily (once in the morning and once in the evening, 12 ± 1 hours apart) for 7 consecutive days.

All investigational products shall be supplied free of charge by the Sponsor, and shall have been verified as conforming to specifications.

In actual use, the volume administered for both the investigational and comparator products shall approximate to 0.25 mL.

## 6.3 Concomitant Medications

During the study, subjects shall truthfully record concomitant medications in the diary card.

Any other treatments received concurrently by the subject during the study shall also be recorded in the source documents and the eCRF.

Medications used to treat other conditions (e.g., hypertension) are permitted during the study, provided that such medications have no therapeutic effect on otitis externa and do not interfere with the evaluation of study results.

**For enrolled subjects with bilateral infection, the non-study ear may receive only saline irrigation or other physical therapies, and only at the study center, during the study period.**

## 6.4 Prohibited Medications

Apart from the investigational products, no other medication for the treatment of otitis externa may be used in this study, including topical and systemic medications and other physical therapies for otitis externa — with the exception of physical therapies administered to the non-study ear of bilaterally infected subjects at the study center. Prohibited medications include, but are not limited to, the following:

- Systemic or topical use of antibiotics or corticosteroids other than the investigational products (e.g., levofloxacin, amoxicillin, cephalosporins, and dexamethasone).
- Medications with anti-inflammatory or analgesic properties.

Should a subject use any prohibited medication during the trial, the

Investigator shall promptly notify the monitor and report the protocol deviation.

## 6.5 Treatment Compliance and Duration of Treatment

### 6.5.1 Treatment Compliance

Following the commencement of treatment, at each visit the Investigator shall confirm the dose actually taken by the subject by asking the subject whether the medication has been correctly administered daily and by reviewing the subject's diary card.

Method for calculating subject treatment compliance: Treatment compliance shall be calculated as the proportion of doses actually taken to doses expected to be taken, in accordance with the following formula:

- Compliance (%) = (number of doses actually taken / number of doses expected to be taken) × 100%
- Compliance between 80% and 120% shall be considered to constitute good compliance.

### 6.5.2 Duration of Treatment

During the study, subjects shall receive a treatment course of sufficient duration (7 days), corresponding to 80% to 120% of the treatment course specified in the protocol (expressed in number of vials for the investigational group and in number of drops for the comparator group).

## 6.6 Rescue Medication

On Day 4, Day 5 or Day 6 of dosing (i.e., Visit 2), the Investigator shall reassess, by means of telephone follow-up, the progression of AOE in the study ear. Should symptoms worsen, or should systemic manifestations such as fever appear, the Investigator may administer other treatments, including systemic antibiotic therapy.

•Between Visit 1 and Visit 4, the Investigator may provide rescue

medication based on the patient's clinical status.

- Any subject who receives rescue medication prior to the End-of-Study visit (Visit 4) shall be considered a Treatment Failure.
- For subjects aged ≤ 12 years, antibiotic treatment administered after the End-of-Study visit (Visit 4) and after the primary and secondary efficacy endpoints have been collected shall not be considered rescue medication.

# 7 Study Procedures

The study will include 5 visits. Otoscopic examination and bacteriological examination are special examinations required during the study.

- **Otoscopic examination**

The Investigator shall examine the external auditory canal and tympanic membrane using an ENT video-endoscopy system or an otoscope, and shall assess tympanic membrane integrity, edema of the external auditory canal, otorrhea, and formation of granulation tissue. The degree of ear tenderness (otalgia on palpation) shall be assessed by physical examination.

**Criterion for tympanic membrane integrity:The tympanic membrane is intact, with no perforation. Methods of examination of tympanic membrane integrity:**

(1)ENT video-endoscopy system: If the tympanic membrane is examined by means of an ENT video-endoscopy system and cannot be fully visualized through this system, the Investigator may consider supplementary clinical diagnostic measures (e.g., acoustic impedance) to assist differential diagnosis.

(2)Otoscope: If the tympanic membrane is examined by means of an otoscope and cannot be fully visualized, the Investigator may consider supplementary clinical diagnostic measures (e.g., acoustic impedance) to assist differential diagnosis.

**Notes:**

•When choosing between the ENT video-endoscopy system and the otoscope, the Investigator shall give priority to the ENT video-endoscopy system. The otoscope shall be used only if the patient cannot tolerate examination with the ENT video-endoscopy system.

•When the ENT video-endoscopy system is used, the Investigator shall capture images and shall print and archive these images.

•Irrigation of the ear canal shall not be performed during the study.

•Ear-swab sampling from the external auditory canal shall not be performed prior to completion of the otoscopic examination.

•The correct sequence of examinations is: otoscopic examination → ear-swab sampling.

- **Microbiological Examination**

**（1）Specimen collection**

Microbiological examination shall be performed on all subjects at Visit 1 and on subjects with otorrhea still present on clinical observation at Visit 3 and Visit 4. The examination shall include bacterial culture, bacterial isolation and identification, antimicrobial susceptibility testing, and in vitro antibacterial activity testing of the investigational products

**（2）Bacterial culture and identification**

Clinical specimens shall be inoculated onto blood agar and chocolate agar at primary isolation culture, and the common AOE pathogens shall be routinely isolated.

All clinical isolates shall be identified to the species and genus level.

The common pathogenic bacteria of AOE are as follows, among which Pseudomonas aeruginosa and Staphylococcus aureus account for the vast*.

*Pseudomonas aeruginosa* *

*Escherichia coli*

*Proteus mirabilis*

*Serratia marcescens*

*Haemophilus influenzae*

*Staphylococcus aureus**

*Enterococcus faecalis*

*Streptococcus pneumoniae*

*Other organisms clinically established as being associated with AOE, including Pseudomonas spp., Enterobacteriaceae, Acinetobacter spp., coagulase-negative staphylococci, Corynebacterium spp., and fungi.*

**（3）Antimicrobial susceptibility testing**

Each site shall retain all clinical isolates obtained, including fungi and non-AOE pathogens.

Sites shall perform disk diffusion susceptibility testing on clinical AOE pathogens except fungi and retain two tubes of each isolate: one sent to the central laboratory and one stored at the site.Transport timing depends on storage temperature: isolates stored at -20 ℃ to -70 ℃ must be transported within 3 to 6 months after collection; isolates stored at ≤ -70 ℃ must be transported within 6 to 12 months.The central laboratory will perform confirmatory identification and MIC testing.

**a) Disc diffusion susceptibility testing**

In this study, the disc diffusion (Kirby–Bauer) susceptibility test for the common AOE pathogens shall include ciprofloxacin, levofloxacin, piperacillin, and azithromycin. Interpretation criteria for the disc diffusion susceptibility test for common organisms shall refer to the 30th edition of the CLSI standards (2020). Where susceptibility test results for AOE pathogens against ciprofloxacin, levofloxacin, piperacillin, or azithromycin are not provided in the 30th edition of

the CLSI standards (2020), the inhibition zone diameter shall be recorded directly as the result of the susceptibility test.

Susceptibility test results in this study shall be reported as Susceptible (S), Intermediate (I), Resistant (R), or Other (inhibition zone diameter).

**b) In vitro antibacterial activity testing**

At the central laboratory, the dilution method shall be used to determine the Minimum Inhibitory Concentrations (MICs) of the investigational drug (Ciprofloxacin) and the comparator drugs (ciprofloxacin, levofloxacin, piperacillin, and azithromycin) against the clinical pathogen isolates (excluding fungi). The reported parameters shall include MIC range, MIC50, and MIC90.

Detailed procedures for specimen collection, culture and identification, susceptibility testing, and MIC determination are provided in the central laboratory's

## 7.1 Visit 1 (Day −1 to Day 1: Screening / Baseline, First Dosing Day, Pharmacokinetic Study in a Subgroup of Adult Patients)

The Investigator shall select suitable subjects based on the patient's medical history. Prior to any study-related procedure, the Investigator must obtain the subject's informed consent and have the Informed Consent Form signed (for subjects aged ≥ 8 and < 18 years, the ICF must be co-signed by the subject — on the basis of informed understanding and agreement — and the subject's legal guardian; for subjects under 8 years of age, the ICF shall be signed by the legal guardian on the subject's behalf).

**Once the written Informed Consent Form has been obtained, the following examinations / procedures shall be performed:**

1) Verify, item by item, that the subject satisfies the inclusion criteria and does not meet any exclusion criterion.

2) Collect the subject's demographic data, including date of birth, sex, and ethnicity.
3) Perform a physical examination, and measure vital signs (blood pressure, pulse, respiration, and temperature) as well as height and weight.
4) Enquire as to past medical history, prior medications, history of substance abuse, and history of allergies (prior medications used from 3 months prior to study commencement up to the time of randomized drug dispensing), and concomitant diseases and concomitant medications.
5) By means of an otoscope or ENT video-endoscopy system, examine the external auditory canal and complete the baseline assessment of edema, otorrhea, granulation tissue, and tympanic membrane integrity; perform the assessment of ear tenderness by physical examination; and complete the assessment of AOE grade.
6) Obtain an ear-swab sample and perform bacterial culture.
7) Assess baseline auditory function.
8) Perform laboratory tests (complete blood count and blood biochemistry; see Appendix 4 for details).
9) Urine or blood HCG pregnancy test (in women of childbearing potential).
10) For subjects who are eligible following screening, the Investigator shall log into the IWRS, in the order of subject presentation, to obtain the randomization number and the medication number, and shall dispense the study medication to the subject in accordance with the medication number.
11) Issue the patient diary card, and instruct the patient to take the medication on the day of randomization, to record daily the medication administered and any concomitant medications, the severity of ear pain, the time at which ear pain ceases, and to record at any time any discomfort that arises.
12) Schedule the date of the next visit.

**Randomization is permitted in this study before the bacterial culture report is available. Should the culture result be negative, the subject's data shall not be included in the final therapeutic response analysis; only the clinical efficacy and safety analyses shall be performed.**

- **Pharmacokinetic Study (Subgroup of Adult Patients)**

The 12 adult subjects with unilateral ear infection participating in the PK study shall receive the first dose of the investigational product on the afternoon of the day of successful screening (D1) (i.e., the PK subjects must belong to the investigational group), and baseline PK data shall be collected prior to the first dose, as follows:

1) Verify the subject's demographic data, including date of birth, sex, and ethnicity.
2) Verify past medical history, prior medications, history of substance abuse, and history of allergies (prior medications used from 3 months prior to study commencement up to the time of randomized drug dispensing), and concomitant diseases and concomitant medications.
3) Perform a physical examination, and measure pre-dose 0 h (within 60 min before dosing) vital signs (blood pressure, pulse, respiration, and temperature).
4) Collect the pre-first-dose 0 h (within 60 min before dosing) PK blood sample.
5) Measure vital signs at 1 h post-dose (± 15 min), and record adverse events occurring from the time of the first dose onwards.
6) Schedule the date of the next PK sampling.

## 7.2 Visit 2 (Day 4 + 2, Telephone Follow-Up / Rescue Medication)

The Investigator shall conduct a telephone follow-up on Day 4, Day 5 or Day 6 of the study, enquiring as to treatment compliance and **reviewing**

**photographs of the patient's diary card**, to ascertain the severity of ear pain, the time at which ear pain ceased, any change in condition, adverse events, concomitant diseases, and concomitant medications.

Should the subject's condition show no improvement or even worsen, the Investigator shall reassess the patient. Where necessary, the subject may be given alternative treatment regimens, such as systemic antibiotic therapy. Any subject who receives rescue medication prior to End of Study shall be considered a Treatment Failure.

## 7.3 Visit 3 (Day 8 + 2, End of Treatment / PK Blood Sampling)

This visit shall be scheduled for Day 8 of the study, with a visit window of +2 days.

Patients shall complete the final dose of the entire study before the morning of treatment Day 8.

1) The Investigator shall ask the subject whether the medication has been correctly administered daily, and shall record the number of days of correct administration.

2) Enquire whether the severity of ear pain and the time at which ear pain ceased have been recorded daily.

3) Perform a physical examination and measure vital signs (blood pressure, pulse, respiration, and temperature).

4) By means of an otoscope or ENT video-endoscopy system, examine the external auditory canal and complete the assessment of edema, otorrhea, granulation tissue formation, and tympanic membrane integrity; complete the assessment of ear tenderness by physical examination.

5) For patients with otorrhea still present only, obtain an ear-swab sample and send it for bacterial culture.

6) Once the bacterial culture results are available, complete the assessment of

microbiological efficacy and therapeutic response.

7) Enquire as to any concomitant diseases and record any changes in concomitant medications.

8) Ask whether the subject has experienced any adverse events, and record any adverse events observed by the Investigator or reported by the subject.

9) Collect and reconcile the unused medication and packaging returned by the subject.

10) Review the patient diary card.

11) Visit 3 (Day 8 + 2) is the End-of-Treatment visit (for the subgroup of subjects participating in the PK study, pre- and post-final-dose blood samples shall be collected on the morning of dosing Day 8).

**If a subject is determined at this visit to have achieved clinical cure, this visit shall be the End-of-Study visit; if the subject is not determined at this visit to have achieved clinical cure, the subject shall continue to Visit 4 (Day 15 + 2) for the End-of-Study visit.**

**The timing of the assessment of microbiological efficacy and therapeutic response at this visit shall be determined by the time at which each site's bacterial culture results become available, and shall be independent of the date of Visit 3.**

- **Pharmacokinetic Study (Subgroup of Adult Patients)**

The 12 adult subjects participating in the PK study shall undergo venous blood collection at 6 time points on Day 8, namely: pre-dose of the final dose of the investigational product at 0 h (within 60 min before dosing), and 15 min, 30 min, 1 h, 2 h, and 4 h post-dose. At each collection, approximately 1.0 mL of blood shall be discarded, after which approximately 4 mL of blood shall be drawn into labelled, pre-chilled EDTA-K2 anticoagulant vacuum collection tubes. Following centrifugation, the plasma sample shall be divided into two aliquots

and stored in a freezer at ≤ −60 °C for pharmacokinetic analysis of ciprofloxacin and fluocinolone acetonide. Adverse events, concomitant diseases, and concomitant medications occurring during this period shall be recorded. Permissible time deviations during blood sampling are provided in Appendix 5.

Vital signs of the subject (blood pressure, pulse, respiration, and temperature) shall be recorded within 1 h before dosing and at 1 h (± 15 min), 2 h (± 30 min), and 4 h (± 30 min) after dosing. A safety assessment shall be performed in the subject following completion of the trial. Should any adverse event occur during the trial, the subject shall be followed up until the adverse event resolves, stabilizes, has been adequately explained, the subject is lost to follow-up, or the subject dies.

## 7.4 Visit 4 (Day 15 + 2, End of Study)

This visit shall be scheduled for Day 15 of the study, with a visit window of +2 days.

1) Enquire whether the severity of ear pain and the time at which ear pain ceased have been recorded daily.
2) Perform a physical examination, measure vital signs (blood pressure, pulse, respiration, and temperature), and assess auditory function.
3) By means of an otoscope or ENT video-endoscopy system, examine the external auditory canal and complete the assessment of edema, otorrhea, granulation tissue formation, and tympanic membrane integrity; complete the assessment of ear tenderness by physical examination.
4) For patients with otorrhea still present on clinical observation, obtain an ear-swab sample and send it for bacterial culture.
5) Once the bacterial culture results are available, complete the assessment of microbiological efficacy and therapeutic response.
6) Perform laboratory tests (complete blood count and blood biochemistry).

7) Urine or blood HCG pregnancy test (in women of childbearing potential).
8) Enquire as to any concomitant diseases and record any changes in concomitant medications.
9) Ask whether the subject has experienced any adverse events, and record any adverse events observed by the Investigator or reported by the subject.
10) Review the patient diary card.

**The timing of the assessment of microbiological efficacy and therapeutic response at this visit shall be determined by the time at which each site's bacterial culture results become available, and shall be independent of the date of Visit 4.**

### 7.5 Visit 5 (Day 22 + 7, Follow-Up Period)

This visit shall be scheduled for Day 22 of the study, with a visit window of +7 days. Audiological assessment shall be performed only in subjects aged 12 years or younger. Enquiries shall be made as to any concomitant diseases, and any changes in concomitant medications and any adverse events that have occurred shall be recorded; adverse events observed by the Investigator and those reported by the subject shall be recorded.

## 8 Efficacy Assessment

### 8.1 Primary Efficacy Endpoint

Clinical cure at study end (Day 15 + 2 days) is the primary efficacy endpoint.

**Definition of Clinical Cure:**

The Investigator shall observe and record the clinical symptoms using an otoscope or ENT video-endoscopy system. Edema and otorrhea shall be assessed for efficacy using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3); ear tenderness shall be assessed for efficacy by physical examination using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3). Clinical cure is

considered to have been achieved when the scores for edema, otorrhea, and ear tenderness are all 0.

- ✓ Edema (severity): The Investigator shall observe and record the extent to which edema of the external auditory canal obscures the tympanic membrane.
  - Absent (0) = No edema of the external auditory canal.
  - Mild (1) = Edema of the external auditory canal is present, but the tympanic membrane remains fully and clearly visible.
  - Moderate (2) = Localized edema of the external auditory canal and/or edema obscuring < 25% of the tympanic membrane.
  - Severe (3) = Diffuse edema of the external auditory canal with edema obscuring ≥ 25% of the tympanic membrane.
- ✓ Otorrhea (severity):
  - Absent (0) = External auditory canal and tympanic membrane are dry.
  - Mild (1) = Surface of the external auditory canal and/or tympanic membrane is moist.
  - Moderate (2) = Only a small amount of discharge is present in the external auditory canal, not affecting or only partially affecting visualization of the tympanic membrane.
  - Severe (3) = Substantial fluid is present in the external auditory canal, completely obscuring visualization of the tympanic membrane.
- ✓ Ear tenderness (severity):
  - Absent (0) = No tenderness.
  - Mild (1) = Awareness of pain, but no painful facial expression or withdrawal on palpation.

- Moderate (2) = Painful facial expression and/or withdrawal on palpation.
- Severe (3) = Refusal to allow palpation, or startled movement, on palpation or with mild traction.

Definition of Clinical Failure: Clinical failure is defined as any one of the primary efficacy assessments being other than 0.

**Table 1. 4-Point Scale for Clinical Efficacy Assessment**

| Symptom | Grade | | | |
|---|---|---|---|---|
| | Absent | Mild | Moderate | Severe |
| **Edema** | 0 | 1 | 2 | 3 |
| **Otorrhea** | | | | |
| **Ear tenderness** | | | | |

## 8.2 Secondary Efficacy Endpoints

### 8.2.1 Microbiological Efficacy Endpoints

Microbiological examination shall be performed on all subjects at Visit 1 and on subjects with otorrhea still present on clinical observation at Visit 3 and Visit 4. Microbiological efficacy shall be classified as microbiological success or microbiological failure.

Microbiological efficacy classifications: Eradication, Presumed Eradication, Persistence, Presumed Persistence, Partial Eradication, Superinfection, and Recurrence. "Recurrence" applies only at Visit 4.

**At Visit 3 and Visit 4, subjects with clinical cure for whom microbiological examination was not performed owing to absence of otorrhea shall be classified as Presumed Eradication; subjects with clinical**

**failure for whom microbiological examination was not performed owing to absence of otorrhea shall be classified as Presumed Persistence.**

1. Eradication: The original causative pathogen is absent at End of Treatment.

2. Presumed Eradication: For subjects who achieve clinical cure, where culture has not been performed or cannot be performed because the improvement in clinical symptoms has resulted in reduced otorrhea such that a suitable specimen cannot be obtained for culture and evaluation, the microbiological outcome shall be recorded as "Presumed Eradication".

3. Persistence: The original causative pathogen remains present at End of Treatment.

4. Presumed Persistence: For subjects with clinical failure, where culture has not been performed or cannot be performed, the microbiological outcome shall be recorded as "Presumed Persistence".

5. Partial Eradication: At End of Treatment, one or more — but not all — of the originally present causative pathogens have been eliminated; other causative pathogens remain present.

6. Superinfection: At End of Treatment, a new causative pathogen is isolated on culture of the ear specimen.

7. Recurrence: The originally present causative pathogen has been eradicated at Visit 3 but reappears at Visit 4.

For statistical analysis, Eradication and Presumed Eradication shall be pooled to calculate the eradication rate (i.e., the microbiological success rate); Persistence, Presumed Persistence, Partial Eradication, Superinfection, and/or Recurrence shall be pooled to calculate the microbiological failure rate.

Superinfection and Recurrence at Visit 4 shall be analyzed and assessed separately.

Fungi shall not be subjected to microbiological efficacy assessment.

Where the microbiological examination results at Visit 1, Visit 3, or Visit 4 of this study yield fungi, the Investigator shall, in conjunction with the subject's clinical symptoms, determine whether the fungus is the causative pathogen of the AOE, the causative pathogen of another ear condition, or does not support any clinical determination. Where the fungus is the causative pathogen of the AOE or does not support any clinical determination, the study site need only record the fungus. Where the fungus is the causative pathogen of another ear condition, the Investigator shall determine, on the basis of the visit at which the fungus was detected, whether to record it as part of the medical history or as an adverse event.

### 8.2.2 Therapeutic Response Endpoint

The therapeutic response shall be classified as Therapeutic Cure or Therapeutic Failure, and shall be assessed only in subjects with positive baseline microbiological cultures (excluding fungi). A subject classified as clinically cured and bacteriologically Eradicated or Presumed Eradicated shall be classified as a Therapeutic Cure. All other combinations of outcomes shall be classified as Therapeutic Failure.

### 8.2.3 Clinical Improvement: Assessment at Visit 3 and Visit 4

Clinical improvement is defined as improvement of at least 1 grade in any clinical sign or symptom (edema, otorrhea, or ear tenderness) compared with baseline (Visit 1).

### 8.2.4 Improvement in Individual Signs and Symptoms

Improvement in individual signs and symptoms shall include improvement (by ≥ 1 grade compared with baseline, Visit 1) in edema, otorrhea, and ear tenderness (as assessed by the Investigator) at Visit 3 and Visit 4, expressed as the

proportion of subjects with such improvement.

### 8.2.5 Improvement in Granulation Tissue

The Investigator shall observe and record the degree of granulation tissue formation in the external auditory canal by means of an otoscope or ENT video-endoscopy system, assessed dichotomously (Absent = 0, Present = 1). The endpoint shall be the proportion of subjects with resolution of granulation tissue at Visit 3 and Visit 4 compared with baseline

### 8.2.6 Improvement in Otalgia (Patient Self-Assessment) and Time to End of Pain

The patient shall self-assess the severity of ear pain and the time at which ear pain ends, using a diary card.

Improvement in otalgia: For subjects aged ≥ 12 years and adults, ear pain shall be assessed using a 10-point scale[9] (No pain = 0, Mild = 1–3, Moderate = 4–6, Severe = 7–10); for pediatric subjects (aged ≥ 3 to 12 years), self-assessment shall be performed using the Wong-Baker FACES Pain Rating Scale[10] (No pain = 0, Mild = 2, Moderate = 4–6, Severe = 8–10); see Appendix 3 for details. Improvement is defined as improvement of at least 1 grade in otalgia at Visit 3 and Visit 4 compared with baseline (Visit 1), where the grades are: No pain, Mild, Moderate, and Severe.

Time to end of ear pain : Prior to the End of Study, the patient or legal guardian (where the patient is aged ≥ 3 and < 12 years) shall record on the diary card the time of cessation of ear pain, measured from the first day of dosing. Where recurrence of ear pain occurs, the time of cessation of each episode shall be recorded on the diary card.

# 9 Safety Assessment

## 9.1 Physical Examination, Vital Signs and Audiological Assessment

### 9.1.1 Physical Examination and Vital Signs

At Visit 1, Visit 3, and Visit 4, the Investigator shall record the patient's physical examination findings and vital signs (blood pressure, pulse, respiration, and temperature) at baseline, at End of Treatment, and at End of Study.

### 9.1.2 Audiological Assessment

**Subjects > 12 years of age:**

Visits at which audiological examination and assessment are required: Visit 1 and Visit 4.

Method of audiological examination: Electroaudiometry (i.e., pure-tone audiometry).

Assessment grades shall be determined according to the World Health Organization (1997) Grades of Hearing Impairment, based on each subject's air-conduction or bone-conduction values (i.e., average thresholds):

Normal (≤ 25 dB), Mild (26–40 dB), Moderate (41–60 dB), Severe (61–80 dB), Profound or Total Deafness (≥ 81 dB).

**Pediatric subjects aged 6 to 12 years (inclusive):**

Visits at which audiological examination and assessment are required: Visit 1, Visit 4, and Visit 5.

Method of audiological examination: Electroaudiometry (i.e., pure-tone audiometry).

Assessment grades shall be determined according to the World Health Organization (1997) Grades of Hearing Impairment, based on each subject's air-conduction or bone-conduction values (i.e., average thresholds):

Normal (≤ 25 dB), Mild (26–40 dB), Moderate (41–60 dB), Severe (61–80

dB), Profound or Total Deafness (≥ 81 dB).

**Pediatric subjects aged ≤ 6 years:**

Visits at which audiological examination and assessment are required: Visit 1, Visit 4, and Visit 5.

Methods of audiological examination: Electroaudiometry (i.e., pure-tone audiometry), behavioral audiometry, multi-frequency auditory steady-state response (ASSR), auditory brainstem response (ABR), distortion product otoacoustic emissions (DPOAE), play audiometry, or any other non-pure-tone audiometric method.

If pure-tone audiometry is used, assessment grades shall be determined according to the World Health Organization (1997) Grades of Hearing Impairment, based on each subject's air-conduction or bone-conduction values (i.e., average thresholds):

Normal (≤ 25 dB), Mild (26–40 dB), Moderate (41–60 dB), Severe (61–80 dB), Profound or Total Deafness (≥ 81 dB).

If any other audiometric method is used, the assessment grades shall be: Normal or Abnormal.

### 9.1.3 Notes

Safety assessments for the subgroup of adult subjects participating in the PK study are detailed in the Study Procedures.

During the study, all physical examination, vital signs, and audiological assessment results shall be recorded in the electronic Case Report Form (eCRF), with particular attention to any clinically significant abnormal findings identified at any visit relative to baseline.

## 9.2 Laboratory Tests

At Visit 1 and Visit 4, the Investigator shall record the patient's laboratory test results (complete blood count and blood biochemistry; see Appendix 4 for

details) at baseline and at End of Study, as well as the urine or blood pregnancy test result.

During the study, laboratory test results shall be recorded in the eCRF, with particular attention to any clinically significant abnormal findings identified at any visit relative to baseline.

## 9.3 Adverse Events

### 9.3.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject who has been administered the investigational product. An AE may manifest as a sign or symptom, a disease, or an abnormal laboratory finding, but does not necessarily have a causal relationship with the investigational product. An adverse event may therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the (investigational) product, whether or not related to the product. All adverse events — irrespective of severity or of relationship to the treatment — must be recorded in the Case Report Form.

During the study, the worsening of the pre-existing signs and symptoms of acute otitis externa (ear tenderness / otalgia, edema, granulation tissue, and otorrhea) shall be considered as treatment failure and not as an AE.

### 9.3.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence in a subject who has been administered the investigational product that results in death, is life-threatening, results in persistent or significant disability or incapacity, requires inpatient hospitalization or prolongs an existing hospitalization, or constitutes a congenital anomaly or birth defect.

- Any of the following constitutes a serious adverse event:

1） Results in death.

2） Is life-threatening.

3） Requires inpatient hospitalization or prolongs an existing hospitalization.

4） Results in persistent or significant disability or incapacity.

5） Constitutes a congenital anomaly or birth defect.

6） Other important medical events: These are adverse events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the outcomes listed above. Whether such an event constitutes an SAE shall be determined on the basis of medical and scientific judgement.

### 9.3.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected and unexpected serious adverse reaction the nature or severity of whose clinical manifestations is not consistent with the existing reference information for the product, including the Investigator's Brochure for an investigational product, the package insert for a marketed product, or the Summary of Product Characteristics.

### 9.3.4 Assessment of AE/SAE

**1) Severity grading**

The severity of adverse events shall be graded in accordance with NCI-CTCAE Version 5.0. For adverse events not listed in CTCAE 5.0, the following criteria shall apply:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate): Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

- Grade 3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4 (Life-threatening): Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to the AE.

**2) Causality Assessment in Relation to the Study Medication**

Causality assessment for adverse events occurring during the clinical trial shall be performed by the authorized Investigator. In addition to determining whether a causal relationship exists with the investigational product, the Investigator shall, to the extent possible, document the basis for that determination. Causality shall be assessed using the following 5-level classification: Definitely Related, Probably Related, Possibly Related, Probably Not Related, and Definitely Not Related.

- Definitely Related

  Evidence exists that the investigational product has been administered; the temporal sequence between administration of the investigational product and the occurrence of the adverse event is plausible; explanation of the adverse event by the investigational product is more reasonable than alternative explanations; positive dechallenge response; positive rechallenge; and the pattern of the adverse event is consistent with prior knowledge of this product or class of products.

- Probably Related

  Evidence exists that the investigational product has been administered; the temporal sequence between administration of the investigational product and the occurrence of the adverse event is plausible; explanation

of the adverse event by the investigational product is more reasonable than alternative explanations; positive dechallenge response.

- Probably Not Related

  Evidence exists that the investigational product has been administered; the temporal sequence between administration of the investigational product and the occurrence of the adverse event is plausible; the adverse event may have been caused either by the investigational product or by other causes; positive dechallenge response.

- Probably Not Related

  Evidence exists that the investigational product has been administered; the adverse event is more likely to have been caused by other factors; the dechallenge response is negative or equivocal; the rechallenge result is negative or equivocal.

- Definitely Not Related

  The subject did not receive the investigational product; or the temporal sequence between administration of the investigational product and the occurrence of the adverse event is not plausible; or there are other clear causes that can explain the adverse event.

### 9.3.5 Recording and Follow-Up of AE/SAE

From the implementation of Protocol V3.0 onwards, adverse events in this study shall be collected from the time of the first administration of the investigational product through to the End of Study. All AEs and SAEs shall be followed up until the event resolves, the subject's status stabilizes, the event has been adequately explained, the subject is lost to follow-up, or the subject dies.

Recording of AEs and SAEs shall include, but is not limited to, the following:

- Term

The term used for an adverse event should preferentially be a medical diagnosis. That is, where multiple symptoms, signs, and abnormal laboratory values can be attributed to a single disease or injury, they shall be recorded as a single adverse event. Where a definitive diagnosis cannot be made, the symptoms / signs shall be recorded. Once a definitive diagnosis is subsequently established, the record shall be updated, replacing the previously recorded symptoms / signs with the diagnosis.

- Onset Time

  The onset time of the adverse event shall be recorded as the "time of onset of symptoms". **Where an adverse event progresses to a serious adverse event, the onset time of the serious adverse event shall be the date on which the adverse event was upgraded to a serious adverse event.**

- End Date

  The end date of the adverse event shall be the time at which the adverse event resolves, the status stabilizes, the event has been adequately explained, or the subject is lost to follow-up. The date should, wherever possible, be recorded with year, month, and day precision; if information is incomplete, the year and month should at least be specified. Where the subject has died and an end date has not been obtained for an adverse event that was not the direct cause of death but that remains ongoing, the end date for that adverse event shall be left blank and the status shall be recorded as "Ongoing". Where an adverse event is determined to be the direct or principal cause of "Death", the end date shall be the time of death of the subject.

- Outcome: Recovered / Resolved; Ongoing; Improving; Worsening;

Recovered / Resolved with Sequelae; Death; Unknown.

- Concomitant Medications

  Concomitant medications administered for an adverse event shall be reflected in the source medical record. The name of the medication and the details of its use (such as the start and end dates, dose, route of administration, and dosing frequency) shall be clearly recorded; it is recommended that any such concomitant medication be annotated to indicate that it has been administered for the treatment of a specified adverse event or serious adverse event.

- Severity
- Causality Assessment

### 9.3.6 Reporting of Serious Adverse Events (SAEs)

Should a serious adverse event occur during the study, irrespective of its relationship to the study treatment, the Investigator must immediately institute appropriate treatment measures, and must report all SAEs to the Sponsor in writing within 24 hours of becoming aware of the event (Email: [redacted]; Telephone: [redacted]). The Investigator shall subsequently provide a detailed written follow-up report in a timely manner. The initial SAE report and any follow-up reports shall identify the subject by the subject identification code used in the clinical trial, rather than by the subject's actual name, citizenship identification number, address, or other identifying information.

In the case of reports involving a fatal outcome, the Investigator shall provide the Sponsor and the Ethics Committee with such other information as may be required, such as the autopsy report and the final medical report.

For all SAEs, the Investigator is responsible for follow``ing up and for providing information to the Sponsor within the reporting timeframes specified

above. In addition, the Sponsor may request the Investigator to expedite the collection of specified supplementary information, which may be more detailed than the information recorded on the SAE report form. Such information shall generally include a detailed description of the SAE, to enable a complete medical evaluation of the event and an initial independent assessment of its possible causes. Information shall also be provided concerning other possible causes, such as concomitant medications and concomitant diseases.

Upon receipt of an SAE report, the Sponsor shall immediately analyze and assess the SAE, including its seriousness, its relationship to the investigational product, and whether it constitutes an expected event. Should the event be classified as a SUSAR, the Sponsor shall expeditiously report it to all investigators and clinical investigator institutions participating in the clinical trial, and to the Ethics Committee. The Sponsor shall, at the same time, report the SUSAR to the drug regulatory authority (via the electronic gateway) and to the health authority (Email of the National Health Commission: [redacted]).

All SUSARs occurring during the clinical trial shall be reported on an expedited basis to the national drug evaluation authority within the prescribed timeframes. The expedited reporting period commences on the date of clinical trial approval or on the date of commencement of tacit authorization by the national drug evaluation authority, and ends on the date of the last subject follow-up visit in China. SUSARs occurring between the end of the clinical trial or follow-up and the issuance of the evaluation and approval conclusion shall likewise be subject to expedited reporting.

Timeframes for expedited reporting: For SUSARs that are fatal or life-threatening, the Sponsor shall report as soon as possible after initially becoming aware of the event, but in any case no later than 7 days, and shall report and complete the follow-up information within the subsequent 8 days. For

SUSARs that are neither fatal nor life-threatening, the Sponsor shall report as soon as possible after initially becoming aware of the event, but in any case no later than 15 days (note: the day on which the applicant first becomes aware of the event is counted as Day 0).

### 9.3.7 Management of Pregnancy Events

- Should a subject experience a pregnancy event during the trial, the Investigator shall communicate with the subject scientifically and rigorously on the basis of medication information, informing her or him of the possible effects and risks of the investigational product on the pregnant woman and the fetus, and the subject shall determine personally whether to terminate or continue the pregnancy.
- Where a female subject becomes pregnant during the trial, the Investigator shall, upon becoming aware of the pregnancy event, first discontinue the subject's clinical trial participation. Where the protocol specifies that pregnancy must be terminated, the Investigator shall, in the first instance, notify the subject and shall consult with her concerning the termination of pregnancy. Where there is no scientific support requiring termination of the pregnancy, the pregnancy shall be closely monitored until termination (induced abortion, spontaneous abortion, or labor induction) or until 28 days post-delivery.
- For male subjects whose sexual partner becomes pregnant during the trial, the subject shall continue to participate in the clinical trial; the pregnancy event shall, however, be reported, and the partner shall be followed up to termination of pregnancy or throughout the course of the pregnancy and until 28 days post-delivery.
- Within 24 hours of confirmation of a pregnancy event in a subject (or in the subject's sexual partner), the Investigator shall complete the initial Pregnancy

Report Form and shall report in accordance with the SAE reporting procedure

- Upon receipt of the Pregnancy Report Form, the Sponsor's pharmacovigilance specialist shall, in the event of an uneventful pregnancy, retain the report on a long-term basis. In the event of any congenital abnormality or malformation of the fetus or neonate (SAE), spontaneous abortion (SAE), or termination of pregnancy for medical reasons (SAE), the case shall be processed as an expedited report.

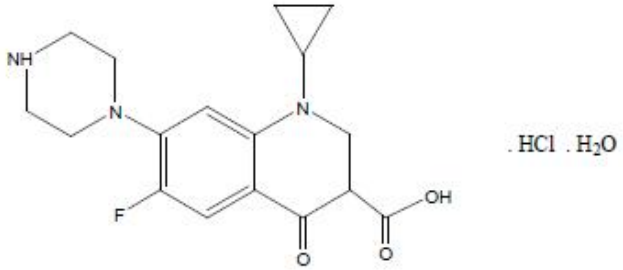
# 10 Pharmacokinetic Assessment

The Ciprofloxacin plus Fluocinolone acetonide otic solution developed by the Sponsor is a single-dose presentation, the principal components of which are ciprofloxacin hydrochloride and fluocinolone acetonide. The strength is 0.25 mL per vial; each vial contains 0.75 mg ciprofloxacin and 0.0625 mg fluocinolone acetonide. The product is supplied in single-use, sterile, preservative-free unit-dose containers, and is administered into the ear. Following instillation into the ear, an aural bath of approximately 5 minutes shall be maintained. The dose shall be administered twice daily (once in the morning and once in the evening, 12 ± 1 hours apart) for 7 consecutive days.

## 10.1 Principal Components and Chemical Characteristics

1） **Chemical name: Ciprofloxacin hydrochloride**

Chemical structural formula:

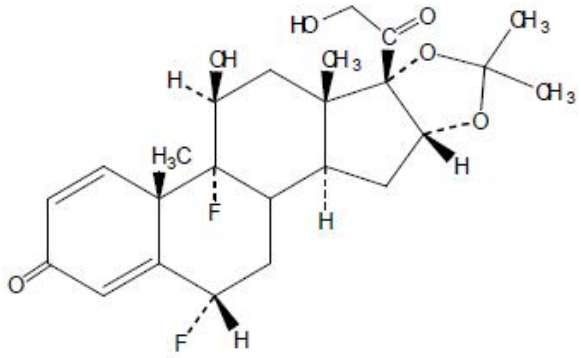



Molecular formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular weight: 385.8

2） **Chemical name: Fluocinolone acetonide**

Chemical structural formula:



Molecular formula: $C_{24}H_{30}F_2O_6$

Molecular weight: 452.49

## 10.2 Pharmacokinetic Studies of Ciprofloxacin and Fluocinolone acetonide

### 10.2.1 Pharmacokinetic Studies of Ciprofloxacin

In a number of published studies in pediatric and adult ear conditions, ciprofloxacin has been applied to the ear canal at concentrations of 0.2%, 0.3%, or 0.5%, and blood samples have been collected to determine plasma ciprofloxacin concentrations. In all cases, plasma ciprofloxacin concentrations were below the limit of detection. This indicates that, in patients with or without tympanic membrane perforation, systemic absorption following otic administration of ciprofloxacin at concentrations in the range of 0.2% to 0.5% is negligible. No published studies on the systemic absorption of fluocinolone acetonide following otic administration have, to date, been identified. It is generally considered that corticosteroids are only minimally absorbed through large areas of smooth skin. Following topical application of fluocinolone

acetonide to intact skin, only very small amounts of drug reach the dermal layer, and systemic absorption is minimal to negligible.

In one study, designed to measure plasma ciprofloxacin levels in children with diffuse otitis externa following topical administration of 0.3% ciprofloxacin, blood samples were collected from 12 children aged 3 to 11 years on the last day of an 8-day course of 0.3% ciprofloxacin for diffuse otitis externa[10]. Patients received 5 drops in the infected ear three times daily (tid). Liquid chromatography with a lower limit of detection of 5 ng/mL was used to determine serum ciprofloxacin concentrations. Ciprofloxacin concentrations were below the limit of detection in all samples.

- Absorption

Following oral administration of 250 mg ciprofloxacin, peak concentrations are reached approximately 0.81 hours post-dose, with a mean maximum plasma concentration (Cmax) of 0.94 mg/L and a mean area under the curve (AUC) of 1.013 L/h·kg. Following topical otic instillation of 0.3% ciprofloxacin, peak concentrations are reached approximately 0.92 hours post-dose, with a mean Cmax of 1.33 ng/mL[12].

The oral bioavailability of ciprofloxacin reported by the United States FDA is 70%–80%.

- Distribution

The distribution of ciprofloxacin in humans conforms to a three-compartment model, with a central compartment volume of approximately 0.161 L/kg and a total volume of distribution of 2.00–3.04 L/kg.

- Metabolism

Ciprofloxacin is metabolized principally via the CYP1A2 enzyme. The principal metabolites are oxociprofloxacin and sulfociprofloxacin, each accounting for 3%–8% of the total dose. Other minor metabolites are desethylene

ciprofloxacin and formylciprofloxacin. These four metabolites together account for approximately 15% of the total oral dose. To date, no data are available on the enzymes and reaction types involved in the formation of the above metabolites.

Following oral administration of 250 mg ciprofloxacin, the mean half-life is 4.71 hours; following intravenous administration of a 100-mg dose, the mean half-life is 3.65 hours. Following topical instillation of the 0.3% ciprofloxacin + 0.1% dexamethasone fixed-dose otic solution, the half-life of ciprofloxacin is 3.0 ± 1.2 hours[12].

Published studies indicate that, following oral or intravenous administration of ciprofloxacin, the metabolic process in humans exhibits a concentration-dependent linear relationship, and that the steady-state plasma concentration is not significantly increased compared with that following the first dose[13].

- Excretion

Following oral administration of 250 mg ciprofloxacin, the mean renal clearance is 5.08 mL/min·kg. Following intravenous administration of 100 mg, the mean total clearance is 9.62 mL/min·kg, the mean renal clearance is 4.42 mL/min·kg, and the mean non-renal clearance is 5.21 mL/min·kg.

The proportions of parent drug and metabolites in serum correspond to those in urine, and the metabolites are almost entirely excreted within 24 hours after administration.

### 10.2.2 Pharmacokinetic Studies of Fluocinolone acetonide

No published studies on the systemic absorption of fluocinolone acetonide following otic administration have been identified.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the mediation and integrity of the epidermal barrier. Topical corticosteroids may be absorbed through normal intact

skin. In addition, cutaneous inflammation and/or other disease processes may increase percutaneous absorption. In one study comparing systemic levels of dexamethasone following oral administration of 0.5 mg and otic administration of 0.1% (as dexamethasone), the serum levels of dexamethasone from the topical product were 7-fold lower than those from oral administration.

Although topical corticosteroids may produce systemic effects, this is associated with specific conditions of use, such as application over large surface areas, use at higher doses, prolonged use, or use under occlusive dressings. Actual absorption of topical (forearm skin) steroids is likely to be less than 1%. In general, corticosteroids are only minimally absorbed through large areas of smooth skin. Absorption of topical fluocinolone acetonide is generally low and varies according to the site of application. Fluorinated corticosteroids such as fluocinolone acetonide are absorbed to a lesser extent than hydrocortisone. Following topical application to intact skin, only very small amounts of drug reach the dermal layer, and in this respect systemic absorption is minimal.

### 10.2.3 Pharmacokinetic Design for the Ciprofloxacin plus Fluocinolone acetonide Otic Solution

The pharmacokinetic design of this study refers to a 2008 published pharmacokinetic study of a single topical dose of 0.3% ciprofloxacin + 0.1% dexamethasone otic solution (CIPRODEX®, Bayer) for the treatment of pediatric (aged 1–14 years) chronic otitis media following tympanostomy tube placement [12]. In that study, subjects received 4 drops of the investigational drug per ear via tympanostomy tubes, for a total dose of 840 μg ciprofloxacin and 280 μg dexamethasone. Sampling time points were pre-dose 0 h and 0.25 h, 0.5 h, 1 h, 2 h, 4 h, and 6 h post-dose. The results demonstrated very low systemic exposure following topical administration of ciprofloxacin: of 25 subjects, only 4 had plasma concentrations above the lower limit of detection. The Cmax of

ciprofloxacin was 1.31 ± 0.96 ng/mL, with a Tmax of approximately 1 hour post-dose. The range of ciprofloxacin peak concentrations was < 0.5 ng/mL (below the limit of quantification) to 3.45 ng/mL.

**Table 2. Pharmacokinetic Parameters of Ciprofloxacin Following a Single Dose of Ciprofloxacin/Dexamethasone**

| | **$C_{max}$ (ng/mL)** | **$T_{max}$ (h)** | **$AUC_{0-6}$ (ng.h/mL)** | **$AUC_{0-inf}$ (ng.h/mL)** | **$t_{1/2}$ (h)** |
|---|---|---|---|---|---|
| N | 25 | 19 | 8 | 7 | 7 |
| Mean ± SD | 1.33±0.96 | 0.92±0.69 | 6.63±2.75 | 9.49±2.84 | 3.0±1.2 |
| Range | [a](BLQ-3.45) | (0.25-2.23) | (3.14-10.8) | (4.86-13.3) | (1.8-5.3) |

Note: [a]BLQ = Below the Limit of Quantification (LOQ = 0.50 ng/mL). BLQ values were calculated as one-half of the Lower Limit of Quantification (LLOQ) of mean Cmax (0.50 / 2 = 0.25 ng/mL).

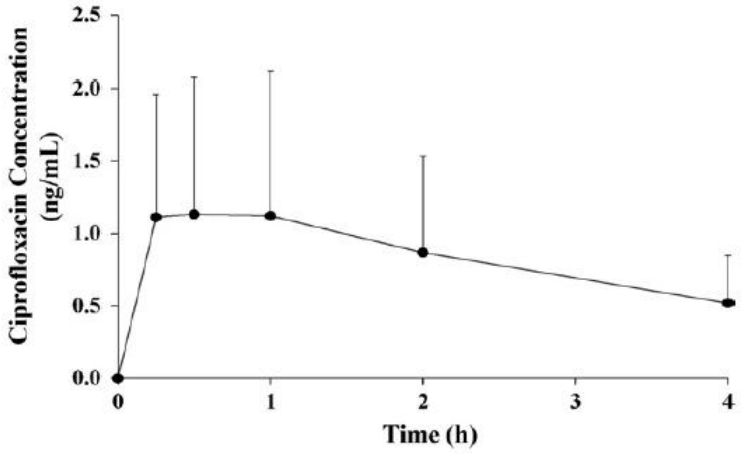



**Figure 1. PK Profile of Ciprofloxacin Following a Single Dose of Ciprofloxacin/Dexamethasone Suspension.**

**Note: The plasma concentration of ciprofloxacin at 6 hours post-dose was below the limit of quantification and is therefore not depicted in this figure.**

In summary[10–11], ciprofloxacin exhibits linear pharmacokinetic

characteristics, with a half-life of 3 to 4 hours; in healthy subjects, the multiple-dose pharmacokinetic results following oral or intravenous administration show that the steady-state plasma concentration is not significantly increased compared with that following the first dose, indicating no accumulation after multiple-dose administration. The pharmacokinetic study of the present trial is therefore designed to be conducted in adult subjects (aged ≥ 18 years) with unilateral ear infection. Twelve adult patients with unilateral ear infection treated with the investigational product shall be screened for the collection of multiple-dose pharmacokinetic data.

Venous blood shall be collected at the following 7 time points: pre-dose of the first dose (D1) at 0 h (within 60 min before dosing); pre-dose of the final dose at Visit 3 (D8) at 0 h (within 60 min before dosing); and 15 min, 30 min, 1 h, 2 h, and 4 h post-dose. At each collection, approximately 1.0 mL of blood shall be discarded, after which approximately 4 mL of blood shall be drawn into labelled, pre-chilled EDTA-K2 anticoagulant vacuum collection tubes. Following centrifugation, the plasma sample shall be divided into two aliquots and stored in a freezer at ≤ −60 °C for pharmacokinetic analysis of ciprofloxacin and fluocinolone acetonide.

Detailed procedures for sample handling are provided in the Sample Operations Manual issued by the bioanalytical laboratory.

Bioanalytical methods are provided in the bioanalytical laboratory's Sample Analysis Method document.

Permissible time deviations during blood sampling are provided in Appendix 5.

Should any revision relating to the pharmacokinetic study be required, approval need only be obtained from the Ethics Committee of the designated study site, with filing accordingly.

# 11 Data Management

## 11.1 Data Management Tools

This study shall use an Electronic Data Capture (EDC) system for the collection and management of study data. The EDC platform employed is the Taimei eCollect V system, which fully satisfies the United States FDA "21 CFR Part 11" requirements concerning electronic signatures and audit trails.

## 11.2 Construction of the Electronic Case Report Form (eCRF)

Prior to the commencement of the study, the data manager and the relevant technical personnel shall construct the eCRF on the EDC platform for completion by the Investigators. The data manager shall draft data range checks and logical checks based on the value ranges and inter-relationships of the parameters in the Case Report Form, and shall write the corresponding computer programs on the EDC platform so as to enable real-time logical checking during eCRF completion and to control errors in eCRF entry. Back-end logical-checking programs shall likewise be written, to enable back-end logical checking on data that have been exported following entry. The entire EDC platform — including the database, the eCRF, and the real-time logical-checking programs — shall be used only after multiple rounds of testing have confirmed its correctness.

## 11.3 Access Rights Management

The system account administrator shall create accounts for each of the various roles (such as Investigator, Monitor, Data Entry Personnel, Data Manager, and Auditor) and shall grant different levels of access to the EDC system, on a role-by-role basis. For example, investigators at each site shall be able to view only the contents of their own site. Data entry personnel shall have data entry, modification, and query-resolution privileges. Investigators shall have modification, viewing, query-resolution, and review privileges. The Principal Investigator shall have, in addition to the investigator's privileges, electronic

signature privileges. Monitors shall have viewing, query issuance / closure, and Source Data Verification (SDV) privileges. Data managers shall have viewing, query issuance / closure, data freezing, data locking, and Data Management (DM) verification privileges.

## 11.4 Data Entry

This study uses an EDC system, and no paper-CRF-to-database data entry process is required. Prior to the commencement of the study, the data manager shall thoroughly understand the contents of the protocol and the Case Report Form, shall standardize the coding of each data field, and shall establish the EDC back-end database. Following the commencement of the study, the Investigator or sub-investigator shall enter the source data into the eCRF in a timely, complete, accurate, and truthful manner.

## 11.5 Data Queries and Resolution

Once data have been entered into the EDC database, the system shall, in accordance with the edit checks established by the Data Validation Plan, automatically perform data checks; queried data shall automatically generate system queries. The Monitor shall, on the EDC platform, confirm that all Case Report Form entries are correct and complete and are consistent with the source documents. Where errors or omissions are identified, the Monitor may at any time raise queries online, requiring the Investigator or data entry personnel to confirm and respond on the eCRF in a timely manner, and to correct erroneous data where necessary, until the queries are resolved. The EDC platform shall maintain an audit trail of all data changes, including the identity of the person making the change and the time of the change. The data manager shall conduct verification either online via the EDC platform or following data export, and shall require the Investigator or data entry personnel to respond to any issues identified. Where the response does not resolve the query, the data manager and the Monitor may issue

further queries on the data point in question. All records shall be retained in the EDC database.

### 11.6 Database Lock and Export

Once all subjects have completed the trial and all data have been reviewed without error, the data manager shall lock the data in accordance with the Database Lock Agreement. Should any modification be required after the database has been locked, an application must be made, and may be implemented only after discussion and written sign-off by the Sponsor, the Investigator, the data entry personnel, the Monitor (including the Medical Monitor), and the data manager. Once all data have been locked, the data manager shall import them into the designated database and shall provide them to the statistical personnel for statistical analysis. Following completion of the study, the eCRF and EDC audit trail report from the EDC platform shall be printed or archived as required. The Investigator shall retain the clinical trial records for five years after the investigational product has been approved for marketing. The Sponsor shall retain the clinical trial records for five years after the investigational product has been approved for marketing. However, where prevailing regulations or agreements with the Sponsor so require, these records shall be retained for a longer period. The Sponsor shall notify the Investigator in writing of the time at which such records will no longer be required to be retained.

## 12 Statistical Analysis

### 12.1 Sample Size Determination

A reanalysis of a pivotal Phase III clinical study of Ciprofloxacin plus Fluocinolone acetonide otic solution (0.3% ciprofloxacin + 0.025% fluocinolone acetonide; brand name CETRAXAL® Plus) for the treatment of Acute Otitis Externa (AOE) conducted in Spain[14] showed a clinical cure rate of 89.3% in the investigational group (0.3% ciprofloxacin + 0.025% fluocinolone acetonide) and

79.6% in the control group (0.3% ciprofloxacin). For the purpose of sample size estimation, a conservative estimate of the trial cure rates was applied: a cure rate of 89% in the investigational group and 80% in the control group. The following assumptions were made: the investigational group is superior to the control group with respect to the clinical cure rate; one-sided significance level $\alpha = 0.025$; statistical power $1 - \beta = 80\%$; the number of subjects in the investigational group and the control group is 1:1; Using the z-test (unpooled) in PASS 15.0, a total of 500 subjects must be enrolled across the two groups. Allowing for a 17% drop-out rate, a total of 600 subjects must be enrolled.

## 12.2 Analysis Sets for Statistical Analysis

1) Clinical Intent-to-Treat (CITT) population: This shall include all subjects who have been randomized and have received at least one dose of treatment.
2) Microbiological Intent-to-Treat (MITT) population: This shall include all subjects in the CITT population who have a positive baseline bacterial culture.
3) Clinical Per-Protocol (CPP) population: This shall include subjects in the CITT population who have no major protocol deviations and have completed the trial.

Where the Investigator assesses treatment as successful at the Visit 3 follow-up, that visit shall be converted to the End-of-Study visit, and the patient shall complete all examinations and procedures of the End-of-Study visit; the case shall be included in the CPP analysis set and shall be treated as a case of successful treatment.

4) Microbiological Per-Protocol (MPP) population: This shall include subjects in the CPP population who have a positive baseline bacterial culture and who have undergone bacterial culture at Visit 3 and Visit 4 (where otorrhea is present).

Where the Investigator assesses treatment as successful at the Visit 3 follow-up, that visit shall be converted to the End-of-Study visit, and the patient shall complete all examinations and procedures of the End-of-Study visit; the case shall be included in the MPP analysis set and shall be treated as a case of successful treatment.

5) Safety Set (SS): All subjects who have received at least one dose of treatment and who have safety data available for assessment.
6) Pharmacokinetic Concentration Set (PKCS): All subjects who have been randomized, have received the investigational product, and have had at least one valid plasma concentration data point during the trial.
7) Pharmacokinetic Parameter Set (PKPS): This shall include the pharmacokinetic parameter dataset obtained from subjects who have received at least one dose of the investigational product. The purpose of this dataset is the descriptive statistical analysis of subjects' pharmacokinetic parameters. The parameters for the corresponding period shall not be included in the statistical analysis for subjects in any of the following circumstances:
   a) Subjects whose enrollment involves a major protocol deviation that affects the PK parameter results, or for whom parameters cannot be estimated.
   b) Subjects whose pre-dose concentration exceeds 5% of $C_{max}$.
   c) Subjects who use concomitant medications during the trial that affect the PK parameters.
   d) Subjects in whom the first post-dose sample is the $C_{max}$ and early (5–15 min post-dose) samples have not been collected.

## 12.3 Statistical Analysis Methods

Following finalization of the trial protocol, the statistical professional shall, in consultation with the Principal Investigator, be responsible for preparing the

Statistical Analysis Plan. The statistical analyses shall be performed using SAS version 9.4 or higher and WinNonlin version 8.0 or higher.

## 12.4 General Statistical Considerations

The primary efficacy endpoint shall be analyzed using a one-sided test. All other statistical tests, unless otherwise specified, shall be two-sided, and P≤0.05 shall be considered to indicate a statistically significant difference.

Quantitative data shall be described, according to their normality, by mean, standard deviation, median, minimum, and maximum, etc. Categorical data shall be described by frequency and percentage.

## 12.5 Study Population Data

### 12.5.1 Enrollment and Completion

Patient disposition information shall be summarized by analysis population. The number of patients in each analysis population shall be tabulated. For the CITT population, the patients' demographic and baseline characteristics shall be summarized. Patient demographic characteristics shall include age, height, weight, etc.; baseline characteristics shall include medical history, physical examination, etc.

## 12.6 Efficacy Analysis

### 12.6.1 Baseline

Baseline disease severity grading shall be described separately, with calculation of the number of cases, mean, standard deviation, minimum, maximum, median, and percentage. Continuous data may be analyzed using either the t-test or the Wilcoxon rank-sum test; categorical data may be compared between groups using the chi-squared test.

### 12.6.2 Efficacy Analysis

1、 Primary efficacy endpoint: Clinical cure rate at End of Study (Day 15 + 2).

The clinical cure rate shall be analyzed using the chi-squared test, with a one-sided $\alpha = 0.025$. The between-group difference and the two-sided 95% confidence interval (CI) shall be calculated. Superiority shall be concluded where the difference is statistically significant (i.e., the lower bound of the 95% CI > 0).

**2、 Secondary efficacy endpoints:**

The microbiological success rate shall be compared between treatment groups using the chi-squared test or Fisher's exact test.

Therapeutic response: Therapeutic cure rate. Subjects who are clinically cured at Visit 3 and Visit 4 and who are bacteriologically Eradicated or Presumed Eradicated shall be classified as Therapeutic Cure. Between-group comparisons shall be performed using the chi-squared test.

Clinical improvement: The chi-squared test shall be used for between-group comparison of the proportion of subjects with improvement of ≥ 1 grade in any clinical sign or symptom (edema, otorrhea, or ear tenderness) at Visit 3 and Visit 4 compared with baseline (Visit 1).

Improvement in individual signs and symptoms: The chi-squared test shall be used for between-group comparison of the proportion of subjects with improvement of ≥ 1 grade in edema, otorrhea, and ear tenderness (as assessed by the Investigator) at Visit 3 and Visit 4 compared with baseline (Visit 1).

Improvement in granulation tissue: The chi-squared test shall be used for between-group comparison of the proportion of subjects with resolution of granulation tissue at Visit 3 and Visit 4 compared with baseline (Visit 1).

Improvement in otalgia: Improvement is defined as patient-self-assessed improvement of ≥ 1 grade in ear pain at Visit 3 and Visit 4 compared with baseline (Visit 1). Between-group comparisons shall be performed using the chi-squared test.

Time to end of ear pain : The Kaplan–Meier method shall be used to estimate

the median time to end of ear pain in each group together with the corresponding 95% CI. Between-group comparison shall be performed using the log-rank test. The time to end of ear pain used in the statistical analysis shall be the time of cessation of the last episode of ear pain for the subject.

### 12.7 Safety Analyses

Safety analyses shall be performed on the Safety Set. All subjects who have received at least one dose of the investigational product and have had at least one post-dose safety assessment shall be included in the safety data summaries and listings. Adverse events shall be coded by System Organ Class and Preferred Term (MedDRA). The number, severity, and relationship to the investigational product of adverse events shall be tabulated, and the incidence rates of adverse events shall be calculated. Cases of study discontinuation due to adverse events and cases of serious adverse events shall be described.

### 12.8 Pharmacokinetic Analysis

The following pharmacokinetic parameters shall be calculated for ciprofloxacin and fluocinolone acetonide following multiple-dose administration of the investigational product in the 12 adult patients with unilateral ear infection：$C_{ss_max}$, $C_{ss_min}$, $C_{ss_av}$, $t_{1/2}$, $AUC_{ss}$, $T_{max}$, DF, CL or CL/F。

## 13 Quality Control and Quality Assurance

During the conduct of this study, clinical monitors designated by the Sponsor shall make periodic on-site monitoring visits to the study hospitals to ensure strict adherence to all elements of the protocol and the accurate completion of the study records.

1）Personnel participating in the study shall undergo standardized training, with uniform methods of recording and criteria of assessment.

2）The entire clinical study shall be conducted in strict accordance with this protocol.

3）The Investigator shall, in accordance with the requirements for completion of the electronic Case Report Form, record the contents of the eCRF truthfully, in detail, and conscientiously, so as to ensure that the contents of the eCRF are accurate and reliable.

4）The criteria for determining abnormality of laboratory test results shall be the normal reference ranges of the testing institution.

5）All observations and findings in the clinical study shall be verified, in order to ensure the reliability of the data and to ensure that all conclusions of the clinical study are derived from the source data. Corresponding data management measures shall be in place during both the clinical study and data processing phases.

6）Active measures shall be taken in respect of possible drop-outs, so that the case drop-out rate is controlled to within 10%.

# 14 Ethical Requirements and Informed Consent

This clinical study must be conducted in accordance with the ethical principles for medical research involving human subjects set forth in the Declaration of Helsinki (2013 version) and the Good Clinical Practice (GCP) for Pharmaceutical Products, together with applicable Chinese clinical research standards and regulations. Prior to commencement of the trial, the protocol must be reviewed and approved by the medical ethics committee of each study site before implementation.

Prior to the enrollment of each subject in this study, the Investigator is responsible for providing the subject or the subject's legal representative, in written form, with a complete and comprehensive explanation of the purpose, procedures, and potential risks of this study. Subjects shall be informed that they have the right to withdraw from the study at any time. A written Informed Consent Form must be provided to each subject prior to enrollment. The

Investigator is responsible for obtaining the signed Informed Consent Form before each subject enters the study and for retaining it in the study records.

# 15 Records Retention and Ownership

To enable the evaluation and oversight by the National Medical Products Administration (NMPA) and the Sponsor, the Investigator shall agree to retain all study records, including the identification of all enrolled subjects (in a manner that effectively permits cross-referencing of different records such as the eCRF and hospital source records), all originally signed Informed Consent Forms, all eCRFs, and detailed records of drug dispensing and return. Essential documents shall be retained for at least 5 years after the investigational product has been approved for marketing.

Ownership of the records of this clinical study vests in [redacted] Save as required by the National Medical Products Administration, the Investigator shall not provide such records in any form to any third party without the prior written consent of the Sponsor.

# 16 References

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# Appendix 1. Clinical Grading of Acute Otitis Externa (AOE)

The clinical grading of Acute Otitis Externa shall refer to the Brighton grading, which classifies the clinical symptoms of AOE into 4 grades (I–IV), with certain grading details adjusted accordingly.

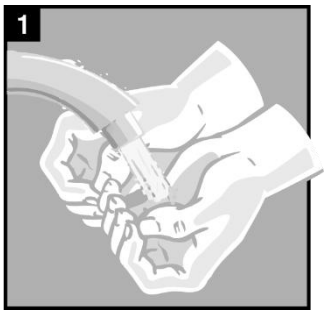
| AOE Grade | Illustration | Description |
|---|---|---|
| **Grade I (Mild)** |  | ● **Tympanic membrane visible and intact**<br>● **No obvious edema of the external auditory canal**<br>● **No otorrhea**<br>● **No granulation tissue formation** |
| **Grade II (Moderate)** |  | ● **Localized edema of the external auditory canal**<br>● **Tympanic membrane partially visible owing to canal edema** |
| **Grade III (Severe)** |  | ● **Diffuse edema of the external auditory canal**<br>● **Tympanic membrane often obscured by canal edema and not visible**<br>● **No systemic infection** |

| | | |
|---|---|---|
| **Grade IV**<br>**(Very Severe)** |  | ● **Diffuse edema of the external auditory canal**<br>● **Perichondritis (auricular cellulitis)**<br>● **With systemic infection** |

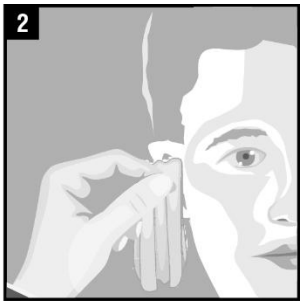
Lindisfarne ME, Berwick J, Das P. Clinical Review: Acute Otitis Externa.Available from:https://www.gponline.com.

## Appendix 2. Administration Instructions for Ciprofloxacin plus Fluocinolone acetonide Otic Solution

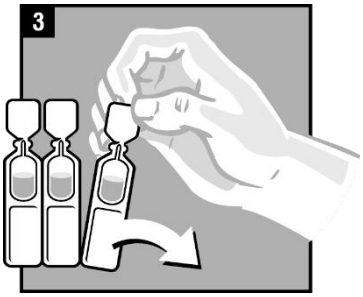
1. The person responsible for administering the medication shall wash the hands with soap and clean water.



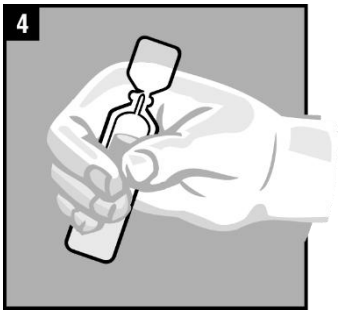

2. Gently clean any discharge that can be readily removed from the outer ear. Do not insert any object or cotton swab into the ear canal.



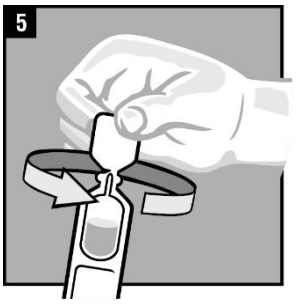

3. Remove the single-dose vial from the packaging.



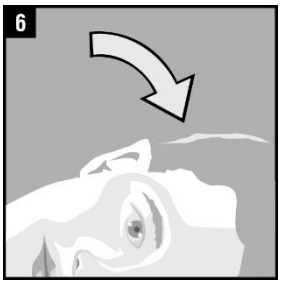

4. Hold the single-dose vial in the hand for 1 to 2 minutes to warm the otic solution.



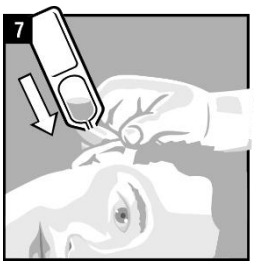

5. Twist off the cap of the single-dose vial.



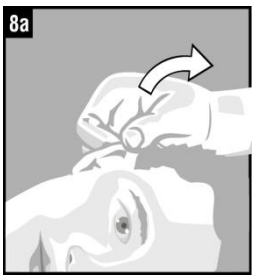
6. Tilt the head of the patient or the patient's child to one side, keeping the infected ear facing upward.




7. Administer the entire contents of the single-dose vial into that ear.




8. Gently pull the auricle upward and outward. This will allow the otic solution to flow down into the ear canal.




9. Keep the patient's head tilted, with the affected ear facing upward, for approximately 5 minutes, so that the medication has sufficient time to penetrate into the ear. When applying the otic drops, avoid raising the head to an upright position or moving it too quickly, so as to prevent the solution from leaking out of the ear canal and failing to cover the entire ear canal.




10. If administration to the other ear is required, repeat the above steps.

## Appendix 3. Pain Rating Scales

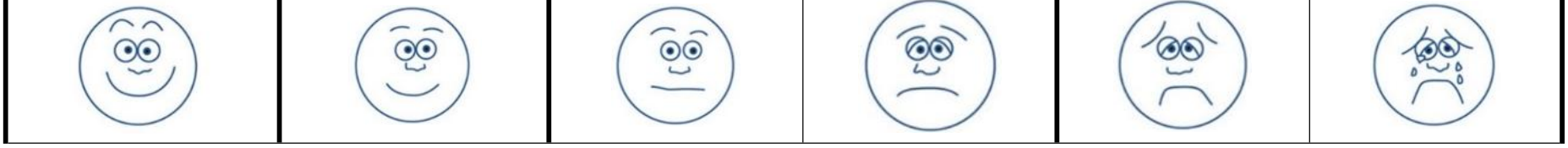
1. Pain Rating Scale for Subjects Aged ≥ 12 Years and Adults (Patient Self-Assessment)

**Patient name：** _____ **Date：** _____ **Pain score：** _____

| **0** **No sensation** | **1** **Very slight** | **2** **Discomfort** | **3** **Tolerable** | **4** **Pain** | **5** **Mildly painful** | **6** **Very painful** | **7** **Severely painful** | **8** **Extremely painful** | **9** **Unbearable** | **10** **Indescribable pain** |
|---|---|---|---|---|---|---|---|---|---|---|
| **No pain** | **Mild** | | | **Moderate** | | | **Severe** | | | |
| Feels normal | Uncomfortably painful but tolerable; most activities of daily living are not yet affected | | | Cannot adapt to the pain; daily life is severely disrupted, but the patient can still manage self-care | | | Unbearable pain; unable to manage self-care; normal life is not possible | | | |

2. Pain Rating Scale for Children Aged ≥ 3 to 12 Years (Wong-Baker FACES® Pain Rating Scale) (Patient Self-Assessment)

**Patient name：** _____ **Date：** _____ **Pain score：** _____



| | | | | | |
|---|---|---|---|---|---|
| **0**<br>**No sensation** | **2**<br>**Uncomfortable** | **4**<br>**Painful** | **6**<br>**Very painful** | **8**<br>**Extremely painful** | **10**<br>**Pain too severe to speak** |
| **No pain** | **Mild** | **Moderate** | | **Severe** | |

# Appendix 4. Clinical Laboratory Tests

| **Blood Biochemistry** | **Complete Blood Count** |
|---|---|
| *（To be tested at Screening and Visit 4)* | *(To be tested at Screening and Visit 4)* |
| Direct Bilirubin (DBIL) | White Blood Cell Count (WBC) |
| Total Bilirubin (TBIL) | Neutrophil Percentage (NE%) |
| Urea / Blood Urea Nitrogen (UREA / BUN) | Lymphocyte Percentage (LY%) |
| Creatinine (Cr) | Absolute Neutrophil Count (NE#) |
| Aspartate Aminotransferase (AST) | Absolute Lymphocyte Count (LY#) |
| Alanine Aminotransferase (ALT) | Red Blood Cell Count (RBC) |
| Blood Glucose (GLU) | Hemoglobin (HGB) |
| | Platelets (PLT) |

## Appendix 5. Permissible Time Deviations for Blood Sampling

In the pharmacokinetic study, PK blood samples shall be collected within the permitted time windows.

The permissible time deviations during blood sampling are set out in the table below.

Any failure to comply with the permitted blood sampling time windows shall be immediately recorded on the relevant source data form. During the course of multiple blood samplings, an indwelling catheter shall be flushed with 3–5 mL of physiological saline solution and shall remain in situ in the forearm vein throughout; accordingly, the saline-containing blood shall be discarded prior to each blood draw. Blood sampling shall be performed using single-use sterile syringes and needles.

**Blood Sampling Time Windows**

| Sampling Time Point | Sampling Time Window (min) |
|---|---|
| Pre-dose 0 h | Within 60 min before dosing |
| 15min | ±30s |
| 30min | ±1min |
| 1h | ±1min |
| 2h | ±1.5min |
| 4h | ±1.5min |

## Appendix 6. Methods for Determining Drug Half-Life

**In cases where Exclusion Criterion 9 of this study is invoked, the half-life of a drug shall be determined by reference to the package insert of that drug.**

# Appendix 7. World Health Organization (1997) Grades of Hearing Impairment

| Grade of Hearing Impairment | Average Hearing Threshold (dB HL) | Daily Functional Performance |
|---|---|---|
| Normal | ≤25 | Able to hear whispered speech |
| Mild | 26-40 | Able to hear and repeat speech at normal volume at a distance of 1 m |
| Moderate | 41-60 | Able to hear and repeat speech at raised volume at a distance of 1 m |
| Severe | 61-80 | Able to hear some words when shouted into the better ear |
| Profound or Total Deafness | ≥81 | Unable to hear or understand even shouted speech |