Statistical Analysis Plan

Version 1.0

Study Title:	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
Investigational Product:	Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution
Sponsor:	[redacted]
Lead Site:	[redacted]
Principal Investigator:	[redacted]
CRO :	[redacted]
Protocol Version:	V3.0 / 2021-03-31
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VERSION HISTORY			
Version	**Date**	**Description of Changes**	**Replacement**
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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AOE	Acute Otitis Externa
CI	Confidence Interval
CIPRO	Ciprofloxacin
CITT	Clinical Intent-To-Treat
CPP	Clinical Per Protocol Set
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
eCRF	Electronic Case Report Form
FLUO	Fluocinoloni Acetonidum
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Microbiological intent-to-treat population
MPP	Microbiological per-protocol population
PK	Pharmacokinetic
PKCS	Pharmacokinetic Concentration Set
PKPS	Pharmacokinetic Parameter Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
WHODD	World Health Organization Drug Dictionaries

1. INTRODUCTION

ZK-CIPRO+FLUO-201911 is a Phase III, multicenter, randomized, evaluator-blind, parallel-group, active-controlled clinical trial designed to evaluate the efficacy and safety of Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution in the treatment of acute otitis externa (AOE), and to assess pharmacokinetic (PK) parameters in 12 adult patients. This Statistical Analysis Plan (SAP) provides a detailed description of the statistical analysis methods and data handling principles for subject baseline characteristics, efficacy, and safety in this trial.

This SAP is written based on Version 3.0 of the ZK-CIPRO+FLUO-201911 clinical study protocol (dated 31 March 2021). In the event that subsequent protocol amendments involve modifications to the original statistical analysis methods, this SAP will be revised accordingly.

The Tables, Listings, and Figures (TLF) shells will be issued in a separate document. Minor updates to the TLF shells may be made during the analysis process to improve clarity or facilitate interpretation of results; such updates do not require revision of the SAP. However, if such updates involve modification of the original statistical analysis methods, the SAP shall be revised accordingly.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the efficacy of Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution versus Ciprofloxacin Otic Solution in the treatment of acute otitis externa.

2.2. Secondary Objectives

- To evaluate the safety of Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution versus Ciprofloxacin Otic Solution in the treatment of acute otitis externa.
- To measure the plasma concentrations of ciprofloxacin and fluocinolone acetonide in 12 adult patients after multiple-dose administration of Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution, and to characterize the corresponding pharmacokinetic parameters.

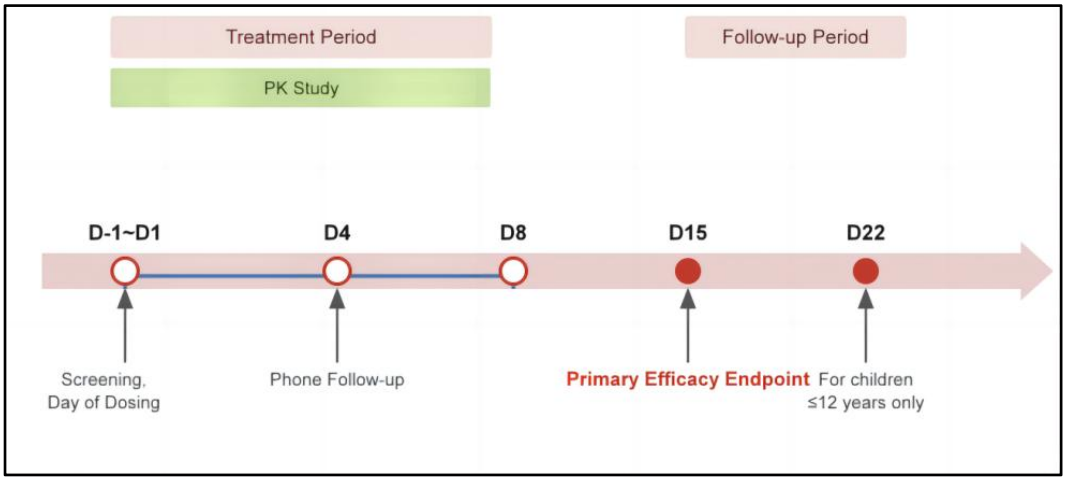
3. STUDY DESIGN

3.1. Overall Study Design

This is a Phase III, multicenter, randomized, evaluator-blind, parallel-group, active-controlled clinical trial designed to evaluate the efficacy and safety of Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution versus Ciprofloxacin Otic Solution in the treatment of AOE, and to assess PK parameters in 12 adult patients.

A total of 600 patients with AOE are planned to be enrolled, with 300 subjects allocated to each of the investigational and control groups.

Eligible subjects 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 the investigational drug (Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution) or the comparator (Ciprofloxacin Otic Solution). A schematic of the study design is shown below:



The study comprises five (5) scheduled visits as follows:

Visit 1 (Day -1 to Day 1): Screening, enrollment, randomization, baseline assessments, and first dosing day (D1). Selected subjects participating in the PK sub-study will receive the first dose on the afternoon of the day they are screened eligible (D1), and a baseline blood sample will be collected prior to the first dose.

Visit 2 (Day 4+2): Telephone follow-up. The investigator will determine whether rescue medication is required for the subject.

Visit 3 (Day 8+2): End of Treatment (EOT). For selected subjects participating in the PK sub-study, blood samples will be collected before and after the final dose on the morning of Day 8. If the investigator deems treatment successful at Visit 3, Visit 3 will be converted to the End-of-Study visit (i.e., no Visit 4 follow-up will be conducted), and all assessments and

procedures of the End-of-Study visit will be completed at that visit.

Visit 4 (Day 15+2): End of Study.

Visit 5 (Day 22+7): Follow-up period. Subjects aged 12 years or younger will undergo a hearing assessment follow-up. The clinical trial schedule of activities is provided in the protocol.

3.2. Randomization and Blinding

This study employs block randomization with a block size of 4, with no stratification factors. Eligible subjects will be randomized in a 1:1 ratio to the investigational group (Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution) or to the active control group (Ciprofloxacin Otic Solution).

This is an evaluator-blind trial. The specific methods for subject randomization and drug randomization are detailed in the Randomization Plan.

4. Sample Size

A re-analysis of a pivotal Phase III clinical trial of Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution (0.3% ciprofloxacin + 0.025% fluocinolone acetonide; trade name CETRAXAL® Plus) conducted in Spain for the treatment of AOE 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 sample size calculation, conservative estimates of 89% and 80% were used as the clinical cure rates for the investigational and control groups, respectively. Assuming that the investigational group is superior to the control group with respect to clinical cure rate, a one-sided significance level of $\alpha = 0.025$, statistical power of $1 - \beta = 80\%$, and a 1:1 allocation ratio, a z-test (unpooled) calculated using PASS 15.0 yielded a total required enrollment of 500 subjects across the two groups. Allowing for a 17% dropout rate, a total of 600 subjects will be enrolled.

5. STUDY ENDPOINTS

5.1. Primary Efficacy Endpoint

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse acute otitis externa (AOE) within 21 days prior to screening, with an AOE grade of II–III and concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea.

Target Endpoint: Clinical cure at End of Study (Visit 4, Day 15+2). The investigator will observe and record clinical signs and symptoms using an otoscope or ENT video-endoscopy system. Edema and otorrhea will be assessed for efficacy using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3); ear tenderness (otalgia on palpation) will be assessed by physical examination using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3). Clinical cure is defined as a score of 0 for each of edema, otorrhea, and ear tenderness. A score other than 0 for any of these symptoms is considered a clinical failure.

Intercurrent Events and Handling Strategies:

- For subjects who achieve cure at Visit 3 and complete the study early: a composite strategy will be applied, whereby the efficacy assessment at Visit 3 (cure) will be carried forward as the efficacy assessment at End of Study and included in the analysis.
- For subjects who withdraw from the study early for any other reason: a composite strategy will be applied, whereby missing efficacy assessments at End of Study will be regarded as clinical failure.
- For subjects who receive rescue medication prior to the End-of-Study visit: a composite strategy will be applied, whereby the clinical efficacy assessment at the End-of-Study visit will be regarded as clinical failure.

Population-Level Summary Measure: The difference in clinical cure rate between the investigational and control groups.

5.2. Secondary Efficacy Endpoints

5.2.1. Microbiological Outcome

The microbiological outcome will be classified as Eradication, Presumed Eradication, Persistence, Presumed Persistence, Partial Eradication, Superinfection, or Recurrence; "Recurrence" applies only at Visit 4. At Visits 3 and 4, clinically cured subjects without otorrhea (for whom microbiological cultures cannot be obtained) will be classified as

Presumed Eradication; clinically failed subjects without otorrhea (for whom microbiological cultures cannot be obtained) will be classified as Presumed Persistence.

For statistical analysis, Eradication and Presumed Eradication will be combined to calculate the microbiological success rate; Persistence, Presumed Persistence, Partial Eradication, Superinfection, and/or Recurrence will be combined to calculate the microbiological failure rate. The attributes of the estimand are as follows:

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse AOE within 21 days prior to screening, with an AOE grade of II–III, concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea, and a positive baseline (pre-treatment) bacterial culture.

Target Endpoints:

- Microbiological outcome assessed at Visit 3.
- Microbiological outcome assessed at Visit 4.

The microbiological outcome will be dichotomized as success or failure. Subjects classified as Eradication or Presumed Eradication will be considered microbiological successes; otherwise, they will be considered microbiological failures.

Intercurrent Events and Handling Strategies:

- If a subject receives rescue medication prior to the visit corresponding to the target endpoint: a composite strategy will be applied, and the microbiological outcome at the corresponding endpoint will be regarded as failure.

Population-Level Summary Measure: The difference in microbiological success rate between the investigational and control groups.

5.2.2. Therapeutic Response

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse AOE within 21 days prior to screening, with an AOE grade of II–III, concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea, and a positive baseline (pre-treatment) bacterial culture.

Target Endpoints:

- Therapeutic response assessed at Visit 3.
- Therapeutic response assessed at Visit 4.

The therapeutic response will be dichotomized as therapeutic cure or failure. A subject classified as clinical cure with microbiological Eradication or Presumed Eradication will be

considered a therapeutic cure; all other combinations of outcomes will be considered failures.

Intercurrent Events and Handling Strategies:

- If a subject receives rescue medication prior to the visit corresponding to the target endpoint: a composite strategy will be applied, and the therapeutic response at the corresponding endpoint will be regarded as failure.

Population-Level Summary Measure: The difference in therapeutic cure rate between the investigational and control groups.

5.2.3. Clinical Improvement

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse AOE within 21 days prior to screening, with an AOE grade of II–III and concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea.

Target Endpoints:

- Achievement of clinical improvement at Visit 3.
- Achievement of clinical improvement at Visit 4.

Clinical improvement is defined as an improvement of ≥1 grade in any one of the clinical signs or symptoms (edema, otorrhea, or ear tenderness) relative to baseline (Visit 1), without worsening in the severity of any of the other signs or symptoms.

Intercurrent Events and Handling Strategies:

- For subjects who achieve clinical cure at Visit 3 and complete the study early: a composite strategy will be applied, and the missing Visit 4 value will be regarded as having achieved clinical improvement.
- For subjects who withdraw from the study early for any other reason: a composite strategy will be applied, and missing values at Visit 3 and/or Visit 4 will be regarded as no clinical improvement.
- If a subject receives rescue medication prior to the visit corresponding to the target endpoint: a composite strategy will be applied, and the corresponding endpoint will be regarded as not having achieved clinical improvement.

Population-Level Summary Measure: The difference in clinical improvement rate between the investigational and control groups.

5.2.4. Improvement of Individual Signs or Symptoms

This endpoint includes improvement of edema, otorrhea, and ear tenderness (as assessed by the investigator), defined as the proportion of subjects with an improvement of ≥1 grade at Visit 3 and Visit 4 relative to baseline (Visit 1).

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse AOE within 21 days prior to screening, with an AOE grade of II–III and concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea.

Target Endpoint	Population-Level Summary Measure
Achievement of edema improvement at Visit 3	Difference in edema improvement rate (investigational vs. control)
Achievement of edema improvement at Visit 4	
Achievement of otorrhea improvement at Visit 3	Difference in otorrhea improvement rate (investigational vs. control)
Achievement of otorrhea improvement at Visit 4	
Achievement of ear tenderness improvement at Visit 3	Difference in ear tenderness improvement rate (investigational vs. control)
Achievement of ear tenderness improvement at Visit 4	

Improvement of a clinical sign or symptom is defined as an improvement of ≥1 grade in the corresponding sign or symptom (edema, otorrhea, or ear tenderness) relative to baseline (Visit 1). Edema, otorrhea, and ear tenderness will each be analyzed separately.

Intercurrent Events and Handling Strategies:

- For subjects who achieve clinical cure at Visit 3 and complete the study early: a composite strategy will be applied, and the missing Visit 4 value will be regarded as having achieved clinical improvement.
- For subjects who withdraw from the study early for any other reason: a composite strategy will be applied, and missing values at Visit 3 and/or Visit 4 will be regarded as no clinical improvement.
- If a subject receives rescue medication prior to the visit corresponding to the target endpoint: a composite strategy will be applied, and the corresponding endpoint will be regarded as not having achieved improvement.

5.2.5. Improvement of Granulation Tissue

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse AOE within 21 days prior to screening, with an AOE grade of II–III, concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea, and the presence of granulation tissue at baseline (Visit 1).

Target Endpoints:

- Achievement of granulation tissue improvement at Visit 3.
- Achievement of granulation tissue improvement at Visit 4.

Improvement of granulation tissue is defined as the disappearance of granulation tissue at the designated visit. The investigator will observe and record the extent of granulation tissue formation in the external auditory canal using an otoscope or ENT video-endoscopy system, assessed as present or absent (Absent = 0, Present = 1).

Intercurrent Events and Handling Strategies:

- If a subject receives rescue medication prior to the visit corresponding to the target endpoint: a composite strategy will be applied, and the corresponding endpoint will be regarded as not having achieved granulation tissue improvement.

Population-Level Summary Measure: The difference in granulation tissue improvement rate between the investigational and control groups.

5.2.6. Improvement and Time to End of Ear Pain (Patient Self-Assessment)

During the trial, subjects will self-assess the severity of ear pain and the time to end of ear pain using a diary card.

- ✓ Improvement of ear pain: Subjects aged 12 years and older and adults will assess ear pain using a 10-point scale (No pain = 0, Mild = 1–3, Moderate = 4–6, Severe = 7–10); children (≥3 to <12 years) will self-assess using the Wong-Baker FACES Pain Rating Scale (No pain = 0, Mild = 2, Moderate = 4–6, Severe = 8–10). Improvement is defined as an improvement of ≥1 grade in ear pain (using the 4-level categorization from No pain to Severe) at Visit 3 and Visit 4 compared with baseline (Visit 1).

- ✓ Time to end of ear pain: Prior to the end of the study, the time of resolution of ear pain will be recorded on the ear pain resolution record card. If ear pain recurs, the time of each resolution episode must be recorded on the diary card.

Target Population: Male or female patients aged ≥3 years, diagnosed with unilateral or bilateral diffuse AOE within 21 days prior to screening, with an AOE grade of II–III, concurrent presence of Grade 2 edema, Grade 2 ear tenderness, and Grade 1 otorrhea, and ear pain present at baseline (Visit 1) (i.e., ear pain severity is not "No pain").

Target Endpoint	Population-Level Summary Measure (Investigational vs. Control)	Intercurrent Events and Handling (Intercurrent Event: Receipt of Rescue Medication)
Ear pain improvement at Visit 3*	Difference in ear pain	

	improvement rate	On-treatment strategy: Only data prior to receipt of rescue medication will be included in the analysis.
Ear pain improvement at Visit 4*	Difference in ear pain improvement rate	
Time (in days) from first dose to the last resolution of ear pain	Hazard ratio	

*Ear pain improvement is defined as a reduction of ≥1 grade in ear pain severity from baseline (using the 4-level categorization from No pain to Severe).

5.3. Safety Analysis

Safety will be evaluated through adverse events/serious adverse events, physical examination, vital signs, laboratory tests, and hearing assessments.

5.4. Pharmacokinetic Analysis

Pharmacokinetic parameters of ciprofloxacin and fluocinolone acetonide will be calculated in 12 adult patients with unilateral ear infection following multiple-dose administration, including: C_{ss_max}, C_{ss_min}, C_{ss_av}, $t_{1/2}$, AUC_{ss}, T_{max}, DF, CL or CL/F.

6. ANALYSIS SETS

6.1. Statistical Analysis Datasets

(1) Clinical Intent-to-Treat Set (CITT)

The CITT Set includes all randomized subjects who received at least one dose of study medication.

(2) Microbiological Intent-to-Treat Set (MITT)

The MITT Set includes all subjects in the CITT Set with a positive baseline bacterial culture.

(3) Clinical Per-Protocol Set (CPP)

The CPP Set includes subjects in the CITT Set without major protocol deviations who completed Visit 4. If the investigator deems treatment successful at Visit 3, that visit will be converted to the End-of-Study visit (i.e., no Visit 4 follow-up will be conducted), and all assessments and procedures of the End-of-Study visit will be completed at that visit; such subjects will be included in the CPP. The CPP must be jointly confirmed by the principal investigator, the project medical team, and the statistics team prior to the database lock used for the final analysis.

(4) Microbiological Per-Protocol Set (MPP)

The MPP Set includes all subjects in the CPP Set with a positive baseline bacterial culture who underwent bacterial culture (where discharge was available) or microbiological outcome assessment at Visits 3 and 4. If the investigator deems treatment successful at Visit 3, that visit will be converted to the End-of-Study visit, and all assessments and procedures of the

End-of-Study visit will be completed at that visit; such cases will be included in the MPP. The MPP will be jointly confirmed by the principal investigator, the project medical team, and the statistics team prior to the database lock used for the final analysis.

(5) Safety Set (SS)

The SS includes all subjects who received at least one dose of study medication and have safety data available for evaluation.

(6) Pharmacokinetic Concentration Set (PKCS)

The PKCS includes all randomized subjects who received the study drug and have at least one valid plasma concentration measurement during the trial.

(7) Pharmacokinetic Parameter Set (PKPS)

The PKPS includes pharmacokinetic parameter data obtained from subjects who received at least one dose of study medication. This dataset is used for descriptive statistical analysis of subjects' pharmacokinetic parameters. PK parameters from the corresponding dosing cycle will be excluded from statistical analysis under the following circumstances:

a) Subjects with major protocol deviations affecting PK parameter results or for whom parameters cannot be estimated;

b) Subjects with a pre-dose concentration exceeding 5% of Cmax;

c) Subjects who took concomitant medications during the trial that affect PK parameters;

d) Data from subjects whose first post-dose sample is Cmax and for whom early post-dose samples (5–15 minutes post-dose) were not collected.

6.2. Treatment Groups

Statistical tables and figures will be presented and summarized by treatment group (investigational group, control group), with an overall column included where applicable (no overall column is required for efficacy and safety analyses). Each data listing will include the subject's treatment group information.

7. STATISTICAL CONSIDERATIONS

7.1. Data Summary and Rules

7.1.1. General Considerations

All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) or a later version.

The primary efficacy endpoint will be tested using a one-sided test. Unless otherwise specified, all other statistical tests will be two-sided, and a P-value ≤ 0.05 will be considered statistically significant.

In general, continuous (quantitative) variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical (qualitative) variables will be summarized using frequency counts and percentages.

7.1.2. Analysis Visit Windows

Unless otherwise specified, no analysis visit windows are defined for this study. All by-visit summaries will be based on the visits as directly collected on the eCRF. By-visit summaries will generally include scheduled visits only; unscheduled visits will not be presented in summary tables. However, for analyses involving baseline and post-baseline worst-case summaries (e.g., the worst on-treatment clinical significance of laboratory tests), data from both scheduled and unscheduled visits will be included.

7.1.3. Data Presentation

Rules for decimal place reporting: Based on the precision of the raw data, the minimum and maximum will be reported to the same number of decimal places as the raw data; the mean and median will be reported to one more decimal place than the raw data; the SD will be reported to two more decimal places than the raw data. In principle, no summary statistic will be reported to more than five decimal places. Percentages will be reported to one decimal place (percentages will not be calculated when the count is 0). Confidence intervals (CIs) will be reported to one more decimal place than the raw data.

In general, when 0.0001 ≤ p-value ≤ 0.9999, the p-value will be presented to four decimal places. When the p-value is less than 0.0001, it will be presented as "<0.0001"; when greater than 0.9999, it will be presented as ">0.9999".

7.1.4. Data Transformation

For laboratory tests and other continuous safety variables (e.g., vital signs), raw data not expressed in Système International (SI) units will, unless otherwise specified, be converted to SI units for statistical analysis.

7.1.5. Derived Variables / Definitions

Study Day: Study Day is defined as the number of days that an efficacy or safety assessment/examination occurs relative to the study start date. The date of the first dose of study medication is defined as the study start date and is designated as Day 1.

Study Day is calculated as follows:

- If the assessment/examination occurs on or after the study start date: Study Day = Assessment/Examination Date – Study Start Date + 1;
- If the assessment/examination occurs before the study start date: Study Day = Assessment/Examination Date – Study Start Date.

- **Baseline and Change from Baseline:** Unless otherwise specified, baseline is defined as the last non-missing assessment/examination prior to the first dose of study medication. Change from baseline is calculated as the post-baseline assessment/examination value minus the baseline value.

7.2. Adjustment for Covariates

Adjustment for covariates is not applicable.

7.3. Handling of Missing Data

7.3.1. Missing Efficacy / Safety Data

All subjects who withdraw early without reaching the primary endpoint of the trial, along with the reasons for early withdrawal, will be documented in the final Clinical Study Report (CSR). For these subjects, all available data will be listed and, where applicable, included in the corresponding analyses.

Unless otherwise specified, missing efficacy/safety data will be treated as missing and no imputation will be performed.

7.3.2. Missing or Incomplete Dates

If a date is completely missing, no imputation will be performed.

AE / Concomitant Medication Dates

- If only the year and month of the AE/concomitant medication start date are recorded:
  - If both the year and month match those of the first dose date, the AE/concomitant medication start date will be imputed as the first dose date; or
  - If the year and/or month differ from those of the first dose date, the AE/concomitant medication start date will be imputed as the first day of the

month (Day 1) in which the AE/concomitant medication began.

- If only the year of the AE/concomitant medication start date is recorded:
  - If the year matches that of the first dose date, the AE/concomitant medication start date will be imputed as the first dose date; or

    If the year differs from that of the first dose date, the AE/concomitant medication start date will be imputed as the first day of the year (1 January) in which the AE/concomitant medication began.
- If the AE/concomitant medication end date is incomplete:
  - The AE/concomitant medication end date will be imputed as the last day of the month, or the last day of the year (31 December), in which the AE/concomitant medication ended. If the imputed end date is later than the end-of-study date, it will be replaced by the end-of-study date.

In all date imputations, care will be taken to ensure that the imputed AE/concomitant medication start date is not later than the AE/concomitant medication end date or the date of death (as applicable).

7.4. Interim Analysis

No interim analysis is planned for this study.

7.5. Multicenter Trial

This study is planned to be conducted at 45 investigational sites. Given the large number of participating sites, some sites may enroll relatively few subjects. Therefore, sites with small enrollment will be pooled based on the actual number of subjects enrolled, and center effect analysis will be performed on the pooled centers. The center pooling scheme will be jointly determined by the investigator, the sponsor, and the statistician at the data review meeting prior to database lock.

7.6. Multiple Comparisons / Multiplicity

Multiple comparisons / multiplicity adjustment is not applicable.

7.7. Subgroup Analyses

All subgroup analyses are exploratory and will be performed separately in the CITT, CPP, MITT, and MPP Sets. For the primary efficacy endpoint (clinical cure rate at End of Study, Visit 4, Day 15+2), subgroup analyses will be performed based on the following baseline characteristics:

- Age (<18 years, ≥18 years)
- Gender (Male, Female)
- Baseline microbiological culture result (Negative, Positive)

- AOE grade (Grade II, Grade III)

Analyses will be performed at each level of the subgroup factors using statistical methods consistent with the overall analysis to assess the consistency of the treatment effect across subgroups. Based on data availability, additional exploratory subgroup analyses may also be conducted. Detailed information on subgroup analyses is provided in the Efficacy Analysis section.

8. STATISTICAL ANALYSIS

8.1. Study Population Data

8.1.1. Disposition of Subjects

For all subjects who participated in screening, the number and percentage of subjects who passed and failed screening will be calculated, along with the number and percentage of subjects under each category of screen failure reason.

For all enrolled subjects, the number and percentage of subjects in each analysis set will be summarized by randomized treatment group.

For all randomized subjects, the number and percentage of subjects in each treatment group will be calculated for the following categories:

- Number and percentage of subjects who received study medication
- Number and percentage of subjects who did not receive study medication.
- Number and percentage of subjects who withdrew from the study early
- Number and percentage of subjects who withdrew from the study early, by reason

In addition, the number and percentage of subjects in each group will be summarized separately by investigational site. The distribution of subjects across the analysis sets and the reasons for exclusion from each analysis set will be presented in a listing.

8.1.2. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional departure from, or non-adherence to, the treatment regimens, assessments, or data collection procedures specified in the IRB-approved protocol.

Protocol deviations will be classified as either minor or major. Deviations that have affected subject rights, safety, or benefits, or the integrity, accuracy, and reliability of study data, will be classified as major protocol deviations. All deviations not meeting the criteria for major protocol deviations will be classified as minor. Protocol deviations will be described in detail in the protocol deviation documentation. The decision on whether to exclude a subject from a given analysis set will be jointly determined by the sponsor, principal investigator, and statistician at the data review meeting prior to database lock.

Based on the CITT Set, the number and percentage of subjects with at least one major protocol deviation will be summarized by randomized treatment group. The number and percentage of subjects with at least one major protocol deviation in each deviation category will

also be summarized. All protocol deviations will be presented in a listing, with major protocol deviations flagged.

In addition, major protocol deviations among randomized subjects will be summarized by randomized treatment group and/or investigational site.

8.1.3. Demographic and Baseline Characteristics

Descriptive statistical analyses of the following demographic and baseline characteristics will be performed by treatment group in the CITT, CPP, MITT, and MPP Sets, and between-group comparisons will be conducted. For categorical variables, the Chi-square test p-value and statistic χ^2 will be reported, or the p-value from Fisher's exact test where appropriate. For continuous variables, p-values from the t-test or Wilcoxon rank-sum test will be reported, as appropriate based on the distribution of the data.

8.1.3.1. Demographic Characteristics

- Age (years)
- Age group 1 (≤12 years, >12 to 64 years, >64 years)
- Age group 2 (<18 years, ≥18 years)
- Gender (Male, Female)
- Ethnicity (Han, Other)
- Height (cm)
- Weight (kg)

8.1.3.2. Baseline Disease Characteristics

- Site of infection (Left ear, Right ear)
- Study ear (Left ear, Right ear)
- AOE grade [Grade II (Moderate), Grade III (Severe)]
- Tympanic membrane integrity (Intact, Not intact)
- Severity of external auditory canal edema (2 = Moderate, 3 = Severe)
- Severity of otorrhea (1 = Mild, 2 = Moderate, 3 = Severe)

- Ear tenderness (2 = Moderate, 3 = Severe)
- Granulation tissue formation (Absent, Present)
- Baseline microbiological culture result (Negative, Positive)

8.1.4. Medical History

Based on the CITT Set, medical history (excluding AOE) will be coded using MedDRA. The number and percentage of subjects with medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment group.

8.1.5. Prior and Concomitant Medications

Medications other than the study drug are classified as prior or concomitant medications, defined as follows:

- Prior medication: medication used only before the trial (i.e., medication ended prior to the first administration of the study drug).
- Concomitant medication: medication used during the trial, including: (a) medication started before the first administration of the study drug and ended on or after the first dose, or still ongoing; and (b) medication started on or after the first administration of the study drug.

If the timing of medication relative to the first dose of study drug cannot be determined, the medication will be considered concomitant.

Based on the CITT Set, prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). The number and percentage of subjects with prior and concomitant medications will be summarized by treatment group, by ATC Level 2 code (sorted by descending frequency) and Preferred Term (sorted by descending frequency).

8.1.6. Prior and Concomitant Non-Pharmacological Therapies

Non-pharmacological therapies are classified as prior or concomitant, defined as follows:

- Prior non-pharmacological therapy: non-pharmacological therapy used only before the trial (i.e., therapy ended prior to the first administration of the study drug).
- •Concomitant non-pharmacological therapy: non-pharmacological therapy used during the trial (using the same rules as for concomitant medications).

If the timing of a non-pharmacological therapy relative to the first dose of study drug cannot be determined, it will be considered a concomitant non-pharmacological therapy. Based on the CITT Set, non-pharmacological therapies will be coded using MedDRA, and the number and percentage of subjects with prior and concomitant non-pharmacological therapies will be

summarized by SOC and PT for each treatment group.

8.2. Efficacy Analyses

8.2.1. Primary Efficacy Endpoint

At Visit 1, Visit 3, and Visit 4, the investigator will assess the subject's clinical signs and symptoms via otoscopy. Edema and otorrhea will be assessed using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3); ear tenderness will be assessed by physical examination using the same 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3). Clinical efficacy will be assessed as either "clinical cure" or "clinical failure".

The primary efficacy endpoint of this trial is the clinical cure rate at End of Study (Visit 4, Day 15+2). Analyses of the primary endpoint will be conducted on the CITT and CPP Sets.

8.2.1.1. Primary Analysis

Based on the clinical assessment at End of Study (Visit 4, Day 15+2), the number and proportion of subjects classified as "clinical cure" and "clinical failure" will be calculated for each treatment group. The clinical cure rate will be compared between groups using a Chi-square test at a one-sided significance level of $\alpha = 0.025$; the Chi-square test p-value and statistic χ^2 will be reported. The difference in cure rate between the investigational and control groups will be calculated together with its two-sided 95% Wald confidence interval. Superiority will be concluded if the difference is statistically significant and the lower bound of the 95% CI is greater than 0.

The following potential intercurrent events will be considered in this analysis:

- For subjects who achieve cure at Visit 3 and complete the study early: a composite strategy will be applied, and the clinical efficacy at End of Study will be regarded as clinical cure.

  For subjects who withdraw from the study early for any other reason: a composite strategy will be applied, and the efficacy at End of Study (Visit 4) will be regarded as clinical failure.

- For subjects who receive rescue medication prior to the End-of-Study visit: an on-treatment strategy will be applied, and only the clinical efficacy assessment recorded at the End-of-Study visit prior to receipt of rescue medication will be included in the analysis.

8.2.1.2. Sensitivity Analyses

Sensitivity Analysis I:

If the End-of-Study visit (Visit 4, Day 15+2) assessment is missing because the subject completed the study early or withdrew early for any reason, the missing assessment will be imputed using the Last Observation Carried Forward (LOCF) method. The clinical cure rate will then be analyzed using the same statistical method as in the primary analysis. Intercurrent events will not be considered in this analysis.

Sensitivity Analysis II:

Clinical cure for the primary endpoint will be analyzed using logistic regression, with intercurrent events handled in the same manner as in the primary analysis. The regression model will include the center effect; centers with an effective sample size of less than 4 (the block size used in block randomization) will be pooled before being included in the analysis. Given the large number of centers and the fact that the block randomization scheme employed in this trial does not produce by-center imbalances in treatment allocation, the center-by-treatment interaction will not be considered. The analysis will output the odds ratio (investigational group : control group) to characterize the between-group difference in clinical cure rate.

8.2.1.3. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint will be performed in accordance with the subgroups defined in Section 7.7, based on the CITT, CPP, MITT, and MPP Sets, using the same statistical methods as the primary analysis. Forest plots will be presented to assess the consistency of the treatment effect across subgroups. In subgroup analyses based on the MITT and MPP Sets, the "baseline microbiological culture result" subgroup will be omitted.

Potential intercurrent events will be handled in the same manner as described in Section 8.2.1.1.

Given that some subgroups may have small sample sizes, the following adjustments will be applied in the subgroup analyses:

- If all expected frequencies in the 2×2 table are ≥5 and the total sample size N is ≥40, the standard Chi-square test will be used, and the p-value and statistic χ^2 will be reported;
- If at least one expected frequency is between 1 and <5 and N is ≥40, the continuity-corrected Chi-square test will be used, and the p-value and statistic χ^2

will be reported;

- If any expected frequency is <1 or N is <40, Fisher's exact test will be used and the p-value will be reported. When the sample size meets the requirements for Fisher's exact test, the confidence interval for the rate difference will be calculated as an exact 95% CI based on the risk-difference score statistic. Otherwise, the 95% CI for the rate difference will be calculated as a Wald CI.

8.2.2. Secondary Efficacy Endpoints

Unless otherwise specified, analyses of the secondary efficacy endpoints will be based on the CITT and CPP Sets. The secondary endpoints include microbiological outcome, therapeutic response, clinical improvement, improvement of individual signs or symptoms, granulation tissue improvement, ear pain improvement, and time to end of ear pain.

Unless otherwise specified, between-group hypothesis tests for binary endpoints will use either the Chi-square test or Fisher's exact test, selected based on the actual data according to the criteria below. The test method used will be specified in the footnote of the analysis table:

- If all expected frequencies in the 2×2 table are ≥5 and N is ≥40, the Chi-square test p-value and statistic χ^2 will be reported;
- If at least one expected frequency is between 1 and <5 and N is ≥40, the continuity-corrected Chi-square test p-value and statistic χ^2 will be reported;
- If any expected frequency is <1 or N is <40, Fisher's exact test p-value will be reported. When the sample size meets the requirements for Fisher's exact test, the confidence interval for the rate difference will be calculated as an exact 95% CI based on the risk-difference score statistic. Otherwise, the 95% CI for the rate difference will be calculated as a Wald CI.

8.2.2.1. Microbiological Outcome

Analysis of the microbiological outcome will be based on the MITT and MPP Sets. Based on the microbiological culture results at Visit 1, Visit 3, and Visit 4, subjects will be classified as microbiological successes or failures, and the number and proportion of subjects in each treatment group will be calculated by microbiological outcome category.

The microbiological success rate at Visit 3 and Visit 4 will be compared between groups using either the Chi-square test or Fisher's exact test. The number and proportion of subjects classified as microbiological successes in the investigational and control groups will be calculated at each visit. The 95% CI for the microbiological success rate will be

calculated using the Clopper-Pearson method. The difference in microbiological success rate (investigational vs. control) will be calculated with its 95% Wald CI (or Exact CI). For subjects who achieved clinical cure at Visit 3 and completed the study early, the missing microbiological outcome at Visit 4 will be imputed using LOCF (i.e., carried forward from the Visit 3 observation). In all other cases, missing microbiological outcomes at Visit 3 and Visit 4 will be uniformly imputed as failure (i.e., microbiological failure). Superinfection at Visits 3 and 4 and recurrence at Visit 4 will be analyzed separately (recurrence will be further analyzed in two subcategories: i. clinical cure with bacterial eradication at Visit 3; and ii. clinical failure with bacterial eradication at Visit 3). The number and proportion of subjects with superinfection and recurrence at each visit will be calculated, along with the difference in incidence between the investigational and control groups. The 95% CIs for the corresponding incidence rates and the rate difference will be calculated using the Clopper-Pearson method.

The microbiological outcome analysis will employ an on-treatment strategy to handle efficacy assessments affected by rescue medication: only microbiological outcomes recorded prior to receipt of rescue medication will be included in the analysis. If the result at Visit 3 or Visit 4 is missing, the missing value will be imputed or handled as described above.

Antimicrobial susceptibility test results for AOE pathogens (excluding fungi) at Visit 1, Visit 3, and Visit 4 will be presented in listings, including:

1. Disk diffusion susceptibility test results (reporting the susceptibility of AOE pathogens to ciprofloxacin, levofloxacin, piperacillin, or azithromycin; results will be categorized according to the 30th Edition (2020) CLSI standards; for results not interpretable under CLSI standards, the measured inhibition zone diameter will be provided).
2. In vitro antimicrobial activity test results (the MIC range, MIC_{50}, and MIC_{90} of ciprofloxacin hydrochloride, ciprofloxacin, levofloxacin, piperacillin, and azithromycin against clinical pathogen isolates, as determined by the dilution method at the central laboratory, will be tabulated).

8.2.2.2. Therapeutic Response: Therapeutic Cure Rate

Analysis of the therapeutic response will be based on the MITT and MPP Sets. The number and proportion of subjects classified as "therapeutic cure" and "failure" will be calculated for each treatment group based on the therapeutic response assessments at Visit 3 and Visit 4. The therapeutic

cure rate at Visit 3 and Visit 4 will be analyzed and compared between groups using the same statistical methods as for the microbiological success rate. For subjects who achieved clinical cure at Visit 3 and completed the study early, the missing therapeutic response at Visit 4 will be imputed using LOCF (i.e., carried forward from the Visit 3 observation). In all other cases, missing therapeutic response assessments at Visit 3 and Visit 4 will be uniformly imputed as "failure".

The therapeutic response analysis will employ an on-treatment strategy to handle efficacy assessments affected by rescue medication: only therapeutic response assessments recorded prior to receipt of rescue medication will be included in the analysis. If the result at Visit 3 or Visit 4 is missing, the missing value will be imputed or handled as described above.

8.2.2.3. Clinical Improvement

At Visit 1, Visit 3, and Visit 4, the investigator will assess the subject's clinical signs and symptoms via otoscopy, evaluating edema, otorrhea, and ear tenderness using a 4-point scale (Absent = 0, Mild = 1, Moderate = 2, Severe = 3). Descriptive analyses of the grade score for each clinical sign or symptom will be performed by treatment group at each visit. For post-baseline visits, descriptive analyses of the change from baseline in each clinical sign or symptom will also be performed by treatment group.

Clinical improvement is defined as an improvement of ≥1 grade in any one of the clinical signs or symptoms (edema, otorrhea, or ear tenderness) relative to baseline (Visit 1), without worsening in the severity of either of the other two signs or symptoms. The clinical improvement rate at Visit 3 and Visit 4 will be analyzed using the same statistical methods as for the microbiological success rate.

The following potential intercurrent events will be considered in this analysis:

- For subjects who achieve cure at Visit 3 and complete the study early: a composite strategy will be applied, and Visit 4 will be regarded as having achieved clinical improvement.
- For subjects who withdraw from the study early for any other reason: a composite strategy will be applied, and missing values at Visit 3 and/or Visit 4 will be regarded as no clinical improvement.
- For subjects who receive rescue medication prior to Visit 3 or Visit 4: an on-treatment strategy will be applied, and only the assessments of clinical signs or symptoms recorded prior to receipt of rescue medication will be used to determine clinical improvement.

8.2.2.4. Improvement of Individual Signs or Symptoms

Improvement of an individual sign or symptom is defined as improvement in edema, otorrhea, or ear tenderness (as assessed by the investigator), i.e., an improvement of ≥1 grade relative to baseline (Visit 1). Subjects with the corresponding symptom at baseline will be selected, and the improvement rate for each sign or symptom at Visit 3 and Visit 4 will be analyzed using the same statistical methods as for the microbiological success rate.

For the analyses of improvement in edema, otorrhea, and ear tenderness, the following potential intercurrent events will be considered:

- For subjects who achieve cure at Visit 3 and complete the study early: a composite strategy will be applied, and the sign or symptom at Visit 4 will be regarded as having improved.
- For subjects who withdraw from the study early for any other reason: a composite strategy will be applied, and missing values at Visit 3 and/or Visit 4 will be regarded as no improvement.

For subjects who receive rescue medication prior to Visit 3 or Visit 4: an on-treatment strategy will be applied, and only the assessments of each clinical sign or symptom recorded prior to receipt of rescue medication will be used to determine whether improvement was achieved.

8.2.2.5. Improvement of Granulation Tissue

Granulation tissue improvement is defined as a clinical assessment of "absent" for granulation tissue formation.

This endpoint applies only to subjects with granulation tissue formation at baseline. Based on the clinical assessment of granulation tissue formation at each visit, the number and proportion of subjects with "present" and "absent" granulation tissue in each treatment group will be calculated. The granulation tissue improvement rate at Visit 3 and Visit 4 will be analyzed separately using the same statistical methods as for the microbiological success rate. For subjects who achieved clinical cure at Visit 3 and completed the study early, the granulation tissue status at Visit 4 will be imputed using LOCF (i.e., carried forward from the Visit 3 observation).

The granulation tissue improvement analysis will employ an on-treatment strategy to

handle efficacy assessments affected by rescue medication: only granulation tissue assessments recorded prior to receipt of rescue medication will be included in the analysis. If the result at Visit 3 or Visit 4 is missing, the missing value will be imputed or handled as described above.

8.2.2.6. Improvement of Ear Pain

Ear pain improvement is defined as a patient-reported improvement of ≥1 grade in ear pain severity. The ear pain improvement rate at Visit 3 and Visit 4 will be analyzed using the same statistical methods as for the microbiological success rate. Because ear pain severity is collected daily via the diary card rather than assessed at scheduled visits, the following visit windows are defined:

Visit 3: Days 8 to 10 (D8–D10)

Visit 4: Days 15 to 17 (D15–D17)

If multiple records fall within the same visit window, the earliest record will be used as the assessment for that visit. If no valid record falls within the visit window, LOCF will be applied: the latest valid post-baseline value up to (and including) the current visit day (D8 for Visit 3, D15 for Visit 4) will be used as the imputed value for that visit.

This analysis will employ an on-treatment strategy to handle ear pain assessments affected by rescue medication: only ear pain records falling within the visit window and recorded prior to receipt of rescue medication will be used to determine improvement. If, after this filtering, the result at Visit 3 or Visit 4 is missing, the missing value will be imputed or handled as described above.

8.2.2.7. Time to End of Ear Pain

This endpoint applies only to subjects with ear pain at baseline (i.e., the pain severity on the first day of the ear pain record is not "No pain"). Time to end of ear pain is defined as the time from the first dose to the resolution of ear pain. The time of resolution is taken from the "Time of Ear Pain Resolution" record form; when multiple resolution records are available (e.g., due to recurrent ear pain), the time of the last resolution will be used. If a subject still has ear pain at the end of the study, the observation will be censored. The principles for handling event/censoring dates are as follows:

- Event: Resolution of ear pain, defined as the latest time of ear pain resolution recorded on the "Time of Ear Pain Resolution" record form;
- Censoring:

- If ear pain is still present: censored at the date of the last valid assessment on the ear pain record form;
- If no ear pain records are completed after dosing and no entries are made on the "Time of Ear Pain Resolution" record form: censored at the date of the first dose.

Calculation formula: Time to End of Ear Pain (days) = Resolution/Censoring Date – First Dose Date + 1.

The median time to end of ear pain and its 95% CI, as well as the Q1 and Q3 quartiles and their corresponding 95% CIs, will be estimated using the Kaplan-Meier method for each group. The hazard ratio (investigational group : control group) will be estimated using Cox regression.

This analysis will employ an on-treatment strategy to handle ear pain resolution affected by rescue medication: if the latest time of ear pain resolution in the source data is later than the time of first receipt of rescue medication, the subject's ear pain will be regarded as not resolved, and the observation will be censored at the time of first receipt of rescue medication.

8.3. Safety Analyses

Safety analyses will be based on the Safety Set (SS). Subjects will be analyzed according to the treatment they actually received.

Unless otherwise specified, when multiple measurements or assessments are available at the same visit, the last measurement/assessment will be included in the statistical analysis, while all results from all visits will be included in the data listings.

8.3.1. Drug Exposure, Compliance, and Duration of Treatment

Descriptive analyses will be performed for each subject's actual exposure to study medication during the trial, including exposure quantity, duration of exposure (days), exposure compliance rate, actual duration of treatment, and duration-of-treatment compliance rate. The number and proportion of subjects with exposure compliance and duration-of-treatment compliance >120%, 80%–120%, and <80% will also be calculated.

In addition, the number of instances, frequency, and reasons for dose interruption and dose reduction during the trial will be summarized.

Investigational Drug: Ciprofloxacin Hydrochloride and Fluocinolone Acetonide Otic Solution, twice daily (once in the morning and once in the evening, at intervals of 12 ± 1 hours), for 7 consecutive days.

- Exposure quantity (number of vials) = Sum of all doses actually administered;
- Duration of exposure (days) = Date of last dose – Date of first dose + 1;

- Exposure compliance rate (%) = Exposure quantity (number of vials) / Planned exposure quantity (number of vials) × 100%. The planned exposure is 1 vial per dose; planned exposure will be calculated based on the date and time of the first and last doses.
- Duration-of-treatment compliance rate (%) = Actual duration of treatment (days) / Planned duration of treatment (7 days) × 100%. The actual duration of treatment will be derived from the actual number of doses administered, with each dose equivalent to 0.5 days of treatment.

Comparator: Ciprofloxacin Otic Solution, twice daily (once in the morning and once in the evening, at intervals of 12 ± 1 hours), for 7 consecutive days.

- Exposure quantity (number of drops) = Sum of all doses actually administered;
- Duration of exposure (days) = Date of last dose – Date of first dose + 1;
- Exposure compliance rate (%) = Exposure quantity (number of drops) / Planned exposure quantity (number of drops) × 100%. The planned exposure is 5 drops per dose; planned exposure will be calculated based on the date and time of the first and last doses.
- Duration-of-treatment compliance rate (%) = Actual duration of treatment (days) / Planned duration of treatment (7 days) × 100%. The actual duration of treatment will be derived from the actual number of doses administered, with each dose equivalent to 0.5 days of treatment.

8.3.2. Adverse Events (AEs)

Adverse events (AEs) will be coded using MedDRA (Chinese version 23.0 or the latest version) and graded using NCI CTCAE Version 5.0.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs on or after the first administration of study drug. If the timing of an AE relative to the first administration of study drug cannot be determined, the AE will be considered a TEAE.

AE summaries in this study will be based on TEAEs; non-TEAEs will be listed only. TEAE summaries will provide the number of events, number of subjects, and incidence rate. When calculating TEAE incidence rates, each subject will be counted at most once within each SOC and within each PT. When summarizing TEAE severity, for the same TEAE occurring multiple times in the same subject, the worst CTCAE grade will be used. If the severity of all occurrences of the same TEAE in a subject is missing, no imputation will be performed, and

"missing" will be used as a category in the summary.

According to the criteria for assessing the causal relationship between drug and TEAE, the relationship of a TEAE to the study drug will be classified into five categories: Definitely related, Probably related, Possibly related, Unlikely related, and Not related. All TEAEs assessed by the investigator as definitely related, probably related, possibly related, or with missing causality will be classified as drug-related TEAEs.

AE summary tables will be sorted by descending incidence in the investigational group, first by SOC incidence, and then by PT incidence within each SOC. If the incidence in the investigational group is the same, sorting will proceed by descending incidence in the control group using the same rule. If the incidence remains tied, the entries will be sorted alphabetically by the Chinese pinyin of the term.

8.3.2.1. TEAE Overview

The number of events, number of subjects, and incidence rate of subjects reporting at least one TEAE will be summarized in a single table for each treatment group, according to the following categories:

- All TEAEs and CTCAE grades
- Drug-related TEAEs and CTCAE grades
- TEAEs of CTCAE Grade 3 or higher in severity
- Drug-related TEAEs of CTCAE Grade 3 or higher in severity
- Serious adverse events (SAEs)
- Drug-related SAEs
- TEAEs leading to dose reduction of study drug
- TEAEs leading to interruption of study drug
- TEAEs leading to permanent discontinuation of study drug
- TEAEs leading to withdrawal from the study
- Drug-related TEAEs leading to withdrawal from the study
- TEAEs leading to death
- Drug-related TEAEs leading to death

8.3.2.2. TEAE

The number of subjects, incidence rate, and number of events for each of the following AE categories, in subjects experiencing at least one such event, will be summarized by SOC and PT:

- TEAE
- Drug-related TEAEs
- TEAEs with an incidence of ≥10% in either treatment group
- Drug-related TEAEs with an incidence of ≥10% in either treatment group

For the following AE categories, the number of subjects and incidence rate will be further summarized by SOC and PT according to the worst CTCAE grade:

- TEAE
- Drug-related TEAEs

8.3.2.3. TEAEs of Grade 3 or Higher in Severity

The number of subjects, incidence rate, and number of events for each of the following AE categories, in subjects experiencing at least one such event, will be summarized by SOC and PT:

- TEAEs of Grade 3 or higher in severity
- Drug-related TEAEs of Grade 3 or higher in severity

8.3.2.4. Serious Adverse Events and Other Significant Adverse Events

The number of subjects, incidence rate, and number of events for each of the following AE categories, in subjects experiencing at least one such event, will be summarized by SOC and PT:

- Serious adverse events (SAEs)
- Drug-related SAEs
- TEAEs leading to dose reduction of study drug
- TEAEs leading to interruption of study drug
- TEAEs leading to permanent discontinuation of study drug
- TEAEs leading to withdrawal from the study
- Drug-related TEAEs leading to withdrawal from the study
- TEAEs leading to death
- Drug-related TEAEs leading to death

8.3.2.5. AE Listings

Detailed listings of all adverse events, drug-related adverse events, serious adverse events, and adverse events leading to withdrawal from the study will be provided by treatment group. The listings will include the AE term, start date, severity, SAE status and category, relationship to study drug, action taken with study drug, other actions taken, end date, outcome, and other relevant information.

8.3.3. Laboratory Tests

Laboratory tests include hematology and blood biochemistry; all laboratory test results will be converted to SI units.

Descriptive statistics will be presented for the observed values and changes from baseline of laboratory test results by treatment group, visit, and test category. For parameters that can be graded according to CTCAE 5.0, CTCAE grades will be derived from the test results, and a shift table from baseline to the worst on-treatment CTCAE grade will be generated.

For all laboratory parameters, results will also be categorized as "Normal", "Abnormal, not clinically significant", or "Abnormal, clinically significant" based on the investigator's assessment. A separate shift table will summarize the change from baseline to the worst on-treatment result in clinical significance ("Abnormal, clinically significant" being considered worse than "Abnormal, not clinically significant").

All laboratory test results will be listed by treatment group in the data listings.

If a laboratory result contains symbols such as "<", ">", ">=", or "<=", the numerical portion will be extracted for analysis. For example, if the result is "> 0.1", then "0.1" will be used in the analysis, while the original value "> 0.1" will be presented in the listing.

8.3.4. Vital Signs

Vital signs include blood pressure, pulse rate, body temperature, and respiratory rate.

Vital signs will be summarized by treatment group and visit, with tables presenting observed values and changes from baseline at each on-treatment visit. Vital signs will also be categorized based on the investigator's assessment as "Normal", "Abnormal, not clinically significant", or "Abnormal, clinically significant". A shift table from baseline to the worst on-treatment result will be presented ("Abnormal, clinically significant" being considered worse than "Abnormal, not clinically significant").

8.3.5. Physical Examination

For all physical examination items, results will be categorized as "Normal", "Abnormal, not clinically significant", or "Abnormal, clinically significant". Separate shift tables will summarize the change from baseline to each visit and to the worst on-treatment result in clinical significance ("Abnormal, clinically significant" being considered worse than "Abnormal, not clinically significant").

8.3.6. Hearing Assessment

In this trial, hearing in subjects aged over 6 years will be assessed by pure-tone audiometry at Visit 1 and Visit 4. Subjects aged ≤6 years will be assessed using the hearing testing methods routinely employed at the investigational site. At Visit 5, subjects aged ≤6 years will likewise be assessed using the routine hearing testing methods of the investigational site. Hearing assessment results will be presented in listings.

8.4. Pharmacokinetic Analyses

In this trial, 12 adult patients (aged ≥18 years) with unilateral ear infection will be screened at designated investigational sites for PK data collection. The PK study design is as follows:

Venous blood will be collected at the following 7 time points for pharmacokinetic analysis of ciprofloxacin and fluocinolone acetonide: 0 h before the first dose on Day 1 (within 60 minutes pre-dose), and 0 h before the last dose at Visit 3 (Day 8, within 60 minutes pre-dose), and 15 min, 30 min, 1 h, 2 h, and 4 h post-dose.

8.4.1. Plasma Concentration Analysis

The plasma concentration analysis will be performed on the Pharmacokinetic Concentration Set (PKCS). Descriptive statistics will be presented for plasma concentrations at each scheduled sampling time point by treatment group, including the sample size, number of BLQ (below limit of quantification) values, arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation.

Mean plasma concentration-time curves will be plotted using the sampling time points. The plasma concentration-time curves will be displayed on both linear and semi-logarithmic scales, with the arithmetic mean plasma concentration plotted against time (± SD on the linear plot; no SD on the semi-logarithmic plot).

The following plasma concentration-time plots will be generated for each treatment group:

- Mean (SD) plasma concentration-time profile by treatment group (linear scale);
- Mean plasma concentration-time profile by treatment group (semi-logarithmic scale)

8.4.2. Pharmacokinetic Parameter Analysis

Based on the Pharmacokinetic Parameter Set (PKPS), pharmacokinetic parameters will be calculated using non-compartmental analysis with Phoenix WinNonlin (Version 6.4 or higher). The pharmacokinetic parameters of ciprofloxacin and fluocinolone acetonide will be

calculated in 12 subjects, including: Css_max, Css_min, Css_av, t1/2, AUCss, Tmax, DF, and CL or CL/F.

The arithmetic mean, standard deviation, coefficient of variation, median, maximum, minimum, geometric mean, and geometric coefficient of variation of each parameter will be calculated by treatment group. All pharmacokinetic parameter values will be presented in the listings.

9. CHANGES FROM THE PROTOCOL-SPECIFIED STATISTICAL ANALYSIS

This Statistical Analysis Plan does not introduce any changes to the analyses planned in the protocol.

10. APPENDICES

None. The statistical analysis table shells and programming specifications will be provided in a separate document.