Statistical Analysis Plan

Efficacy and Safety of Memantine in the Treatment of Patients With Frequent Symptomatic Atrial Premature Beats: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Adaptive-Design Study (STOP-AP)

Study drug:	Memantine Hydrochloride Tablets
Indications:	Frequent symptomatic atrial premature contractions
Document Type:	Statistical Analysis Plan
Version:	1.0
Release Date:	February 14, 2025

1. Trial Overview

This Statistical Analysis Plan (SAP) provides a detailed description of the statistical analysis methods and data handling principles used to conduct the efficacy and safety of the trial "Efficacy and safety of memantine in the treatment of patients with frequent symptomatic atrial premature beats: a multicenter, randomized, double-blind, placebo-controlled, adaptive-design study". The preparation of the statistical analysis plan was based on the Clinical Research Protocol version 2.2 (09/12/2024).

1.1 Trial Objectives

1.1.1 Primary Objective

To evaluate the efficacy of memantine in treating frequent symptomatic premature atrial contractions (PACs).

1.1.2 Secondary Objective

To assess the safety profile of memantine in patients with frequent symptomatic PACs.

1.2 Endpoints

1.2.1 Primary Endpoints

- The percentage change from baseline in the 24-hour mean number of premature atrial contractions (PACs) at Week 6.

1.2.2 Secondary Endpoints

- The change from baseline in the 24-hour mean number and burden of PACs at Weeks 4, 6, and 8;
- The change from baseline in the 24-hour mean number and burden of non- sustained atrial tachycardia (NSAT) at Weeks 4, 6, and 8;
- The change from baseline in the 24-hour mean episode count of new- onset sustained atrial tachycardia (SAT), atrial fibrillation (AF), and atrial flutter (AFL) at Weeks 4, 6, and 8;
- The incidence of newly onset SAT, AF, and AFL over 72 hours at Weeks 4, 6, and 8.
- The change in SF-36 quality of life scores at Week 6 compared to baseline.
- The occurrence of adverse events (including psychiatric symptoms, seizures, bradycardia, new-onset heart failure, etc.), laboratory abnormalities, and

abnormal electrocardiogram findings.

1.3 Study Design

1.3.1 Overall Design

This study is a multicenter, randomized, double-blind, parallel, placebo-controlled trial with a two-stage adaptive design, designed to enroll 256 patients aged 18 to 80 years with frequent symptomatic PACs.

After an initial eligibility screen, all candidates will undergo 72-hour continuous patch-based ambulatory electrocardiographic monitoring to quantify baseline PAC burden. Participants who meet the inclusion criteria will be randomly assigned on Day 0, in a 1:1 ratio, to receive oral memantine or matched placebo. Randomization will be stratified according to age (≥65 vs. <65 years) and baseline PAC burden (≥5000 vs. <5000 PACs per 24 hours), yielding 128 participants per group (total, 256).

The protocol specifies five visits:

Visit 1 (Screening; ≤7 days before randomization)—Baseline clinical assessments and 72-hour ambulatory ECG monitoring.

Visit 2 (Day 7 ± 2 days)—Telephone contact to assess treatment adherence and solicit adverse events (AEs).

Visit 3 (Day 28 ± 3 days), Visit 4 (Day 42 ± 3 days; end of treatment), and Visit 5 (Day 56 ± 3 days; end of study) — On-site evaluations, each including repeat 72-hour ambulatory electrocardiogram (ECG) monitoring.

A schematic of the study procedures is provided in Figure 1.

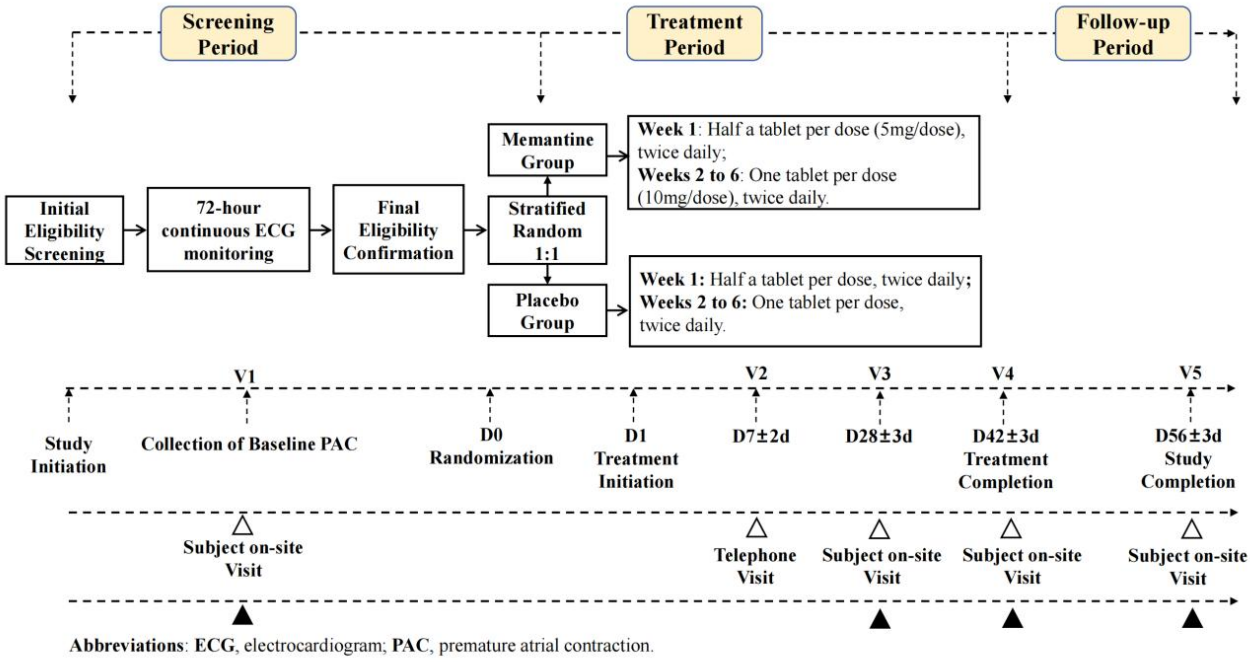


Figure 1 Flow chart of the study protocol

The study drug administration will last for 42 to 45 days. The 72-hour Holter monitoring during visits V3 to V5 will begin on Days 25 to 28 for V3, Days 39 to 42 for V4, and Days 53 to 56 for V5. For the V4 visit, the electrocardiographic monitoring must begin 3 days (72 hours) prior to the end of drug administration. For example, if drug administration ends on Day 42, the 72-hour Holter monitoring must start on Day 39. If the 72-hour Holter monitoring is performed on Day 42, drug administration must continue until Day 45.

Other procedures during visits V3 to V5 must be performed within 2 days before or after completing the 72-hour Holter monitoring, or concurrently.

1.3.2 Sample-Size Determination

Based on the results of our preliminary exploratory single-arm study evaluating the efficacy of memantine in the treatment of PACs, the 24-hour mean reduction in PACs was 75.4%. Considering the robustness of results from the small-sample trial and potential sampling error, we conservatively estimated a 50% reduction in the 24-hour mean burden of PACs following treatment with memantine, while the placebo group is expected to show a 30% reduction, with a standard deviation of 35%. The dropout rate is assumed to be 15.0%. Using EAST 6.5 software for sample size calculation with a one-sided $\alpha = 0.025$ and a 1:1 allocation ratio between the memantine and placebo groups, a total of 256 participants will be enrolled, providing more than 95% power to detect the pre-specified between-group difference.

1.3.3 Randomization and Blinding

Eligible participants will be randomly assigned, in a 1:1 ratio, to receive either memantine or matching placebo. A stratified block design will be used, with randomization stratified by baseline 24-hour PAC burden (≥5000 vs. <5000 PACs per 24 hours) and age (≥65 vs. <65 years). An independent statistician who is otherwise unaffiliated with the study will generate the randomization list and corresponding treatment-allocation list with SAS software (version 9.4 or higher). Both lists will be uploaded to an interactive response technology (IRT) system, which will assign each participant a unique randomization number and the corresponding study-drug kit on Day 0. Randomization and kit numbers, once issued, will not be reused. Participants who withdraw from the study—irrespective of drug exposure—will not be re-enrolled.

2. General Statistical Considerations

2.1 General Principles

Unless otherwise specified, data will be summarized descriptively.

• Continuous variables: number of non-missing observations (n), mean, standard deviation, median, minimum, and maximum.

• Categorical variables: absolute frequency (n) and percentage (%).

2.2 Analysis Sets

• **Full Analysis Set (FAS)** — Includes all randomized participants who receive at least one dose of investigational product; analyzed in the treatment groups to which they were originally assigned (intention-to-treat principle).

• **Per Protocol Set (PPS)** — Comprises all randomized participants who received at least one dose of investigational product, underwent at least one post-baseline efficacy assessment, and had no major protocol deviations that could affect evaluation of the primary efficacy endpoints.

• **Safety Analysis Set (SS)**— Includes all randomized participants who received at least one dose of investigational product; safety endpoints are analyzed according to the treatment actually received.

2.3 Multicenter Design

All trial sites are located in China. Because no clinically meaningful site-to-site heterogeneity is expected, data from all centers will be analyzed in aggregate.

2.4 Multiple Comparisons and Multiplicity

The Lan-Demets approximation of the O'Brien-Fleming boundary, using the consumption function and the CHW method, is employed to strictly control Type I error at a one-sided $\alpha = 0.025$.

3. Data Handling Principles

3.1 Derived Variables

3.1.1 Baseline and Change from Baseline

Unless otherwise specified, baseline is defined as the last non-missing scheduled or unscheduled assessment obtained before the first dose of memantine.

• Change from baseline = baseline value − post-baseline value.

• Percent change from baseline = (baseline value − post-baseline value) / baseline value × 100%.

3.2 Missing data

Unless explicitly stated, missing data will remain missing; no imputation will be performed.

3.2.1 Incomplete or Missing Dates

Imputation of AE Onset Dates

• Year missing (or entire date missing): No imputation will be performed; the AE will be classified as a treatment-emergent adverse event (TEAE).

• Year present, month and/or day missing: Impute according to the hierarchy below. In all cases, the imputed date must not precede the informed-consent date; if it does, use the consent date instead.

(1) Month and day both missing

• If the year matches the year of first study-drug administration, impute the onset date as the first-dose date.

• Otherwise, impute 1 January of the reported year.

(2) Month missing only

• Determine the month using the rule for “month and day both missing.”

(3) Day missing only

• If the reported year and month match those of first dosing, impute the day as the first-dose date.

• Otherwise, impute the day as the first calendar day of the reported month.

If the AE end date is incomplete, it will be filled in as the last day of the month in which the AE ended or the last day of the year (December 31). For death cases, if the imputed

AE end date is later than the death date, the AE end date will be adjusted to the death date. For patients who have not died by the study end date or the cutoff date for data analysis, if the imputed AE end date is later than the most recent known survival date or the cutoff date for data analysis, the AE end date will be adjusted to the most recent known survival date or the cutoff date for data analysis.

Imputation rules for the start and end dates of prior and concomitant medications/non-pharmacological treatments.

If the year is missing—or the complete date is missing—for either the start or end date, no imputation will be performed; the exposure will be classified as concomitant.

When the year is present but the month and/or day are missing, dates will be imputed as follows:

- Start date recorded as year + month only: impute the first day of that month.
- Start date recorded as year only: impute 1 January of that year.
- End date recorded as year + month only: impute the last day of that month.
- End date recorded as year only: impute 31 December of that year.
- For death cases, if the imputed end date is later than the death date, the end date will be adjusted to the death date. For patients who have not died by the study end date or the cutoff date for data analysis, if the imputed end date is later than the most recent known survival date or the cutoff date for data analysis, the end date will be adjusted to the most recent known survival date or the cutoff date for data analysis.

3.2.2 Handling of Missing Adverse Event Data

In cases where data on the causality, severity, or outcome of an adverse event are missing, a worst-case imputation approach will be applied:

- If the causality of the adverse event is missing, it will be assumed to be related to memantine hydrochloride tablets.
- If the severity is missing, the event will be assigned the most severe grade according to the Common Terminology Criteria for Adverse Events (CTCAE).
- If the outcome is missing and no end date is available, the event will be

considered as "not recovered."

4. Statistical Analysis Methods

4.1 Study Population

4.1.1 Participant Disposition

All screened participants (i.e., those who signed the informed-consent form) will be included in the disposition analysis.

Screening failures: the number of participants who were not successfully randomized, together with the reasons for screen failure, will be reported.

Treated population: for all randomized participants, the number and percentage who received ≥ 1 dose of study medication will be summarized by treatment group.

Completion status: for all randomized participants, the number and percentage who completed treatment, completed the study, and discontinued treatment or withdrew from the study—overall and by each prespecified reason—will be summarized by treatment group.

Analysis sets: among all randomized participants, the number and percentage included in the full analysis set, per-protocol set, and safety analysis set will be summarized by treatment group.

A detailed tabular listing of subject disposition will be provided.

4.1.2 Protocol Deviations

A complete listing of participants with protocol deviations—including a classification of deviation severity—will be prepared and finalized before database lock.

Within the FAS, major protocol deviations will be summarized by treatment group and deviation category; counts and percentages will be tabulated.

4.1.3 Demographic and Baseline Characteristics

Using the FAS, demographic variables and baseline clinical characteristics will be summarized descriptively for each treatment group and presented in tabular form.

4.1.3.1 Demographics

Descriptive statistics will be generated for continuous variables—age (years), height (cm), weight (kg), body- mass index (BMI, kg/m²), and waist circumference.

Categorical variables will be summarized as counts and percentages: age group (≥65 yr vs. <65 yr), 24- hour mean PAC count (≥5000 vs. <5000 beats per 24 hr), sex,

race/ethnicity, and educational attainment. BMI will be calculated as baseline weight (kg) divided by the square of baseline height (m).

4.1.3.2 Baseline Medical History

Counts and percentages will be reported for categorical baseline variables, including history of smoking, alcohol use, and documented allergies.

4.1.4 PAC Assessment

Using the FAS, the presence or absence of additional cardiac arrhythmias will be summarized descriptively by treatment group. PAC burden will be characterized with descriptive statistics for each group, and a participant-level listing of PAC diagnoses will be provided.

4.1.5 Prior and Concurrent Medical Conditions

Within the FAS, all additional medical conditions present before or at baseline will be summarized descriptively by treatment group. Conditions will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by System Organ Class (SOC) and Preferred Term (PT), with participant counts and corresponding percentages reported. SOCs and PTs will be ordered by overall frequency in descending order; ties will be resolved alphabetically. A complete participant-level listing of all prior and ongoing conditions will be provided.

• Prior medical history — conditions that resolved before the first study dose (i.e., the end date precedes the first-dose date).

• Ongoing medical history — conditions that were active on or after the first-dose date.

4.1.6 Prior and Concomitant Medications

Within the FAS, prior and concomitant medications will be summarized descriptively by treatment group. All treatments will be coded with the WHO Drug Dictionary Global and tabulated by Anatomical Therapeutic Chemical (ATC) level-2 category and Preferred Name (PN). ATC level-2 categories and PNs will be ranked in descending order of overall frequency, with alphabetical ordering applied to ties. A participant-level listing of every prior and concomitant medication will be provided.

Prior medication — any medication that was discontinued before the first study dose (i.e., the stop date precedes the first-dose date).

Concomitant medication — any medication that meets either of the following criteria: initiated on or after the first- dose date, or initiated before the first- dose date and continuing on or after that date.

Missing or incomplete start- or stop- date information will be imputed according to the procedures outlined in Section 3.2.

4.1.7 Prior and Concomitant Non- Pharmacologic Therapies

Based on the FAS, prior and concomitant non-pharmacologic therapies will be summarized descriptively by treatment group. All therapy names will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT). SOCs and PTs will be sorted in descending order of overall frequency; items with equal frequencies will be ordered alphabetically. In addition, a complete listing of all prior and concomitant non-pharmacologic therapies will be provided.

The timing definition for prior and concomitant non-pharmacologic therapies will follow the criteria used for prior and concomitant medications.

4.2 Efficacy Analysis

Efficacy will be evaluated in the FAS, with participants analysed according to their randomized treatment assignment. Analyses in the PPS will be performed as sensitivity assessments, and comprehensive listings of all efficacy end points will be provided.

For each efficacy end point, percent change from baseline will be calculated as

$$(Baseline\ value - Post\text{-}baseline\ value) \div Baseline\ value \times 100\ \%$$

4.2.1 Primary Efficacy Analysis

Based on the full analysis set FAS, a single interim analysis of the primary endpoint will be conducted in this study. If the interim analysis results in a sample size re-estimation, the final analysis will employ the CHW method to calculate the test statistic. The formula for the CHW test statistic used in the final analysis is as follows:

$$Z^{*}_{2,chw} = \frac{\sqrt{w^{(1)}}Z^{*(1)} + \sqrt{w^{(2)}}Z^{*(2)}}{\sqrt{w^{(1)} + w^{(2)}}}$$

Where $Z^*_{2,chw}$ denotes the cumulative CHW test statistic at the final analysis, combining data from both Stage 1 and Stage 2, $Z^{*(1)}$ is the test statistic from Stage 1 based on the actual sample size at the time of the interim analysis, and $Z^{*(2)}$ represents the incremental test statistic from Stage 2, calculated using the additional data collected after the interim analysis. $w^{(1)}$ and $w^{(2)}$ are the pre-specified weights assigned to Stage 1 and Stage 2, respectively:

$$w^{(1)} = \frac{n^{(1)}}{n_2}$$

$$w^{(2)} = \frac{n^{(2)}}{n_2}$$

$n^{(1)}$ denotes the planned sample size for Stage 1 (interim analysis), pre-specified as 128 participants, $n^{(2)}$ represents the planned increase in sample size for Stage 2 (final analysis) relative to the planned sample size at interim. n_2 is the total planned sample size at the time of the final analysis, pre-specified as 256 participants. By definition, $n^{(1)} + n^{(2)} = n_2$.

Details of the Statistical Analysis

The computation for the primary analysis is as follows:

Each stage of the analysis will begin with an analysis of covariance (ANCOVA) model to assess the percentage change from baseline in the 24-hour average number of PACs at Week 6. The treatment group will be included as a fixed effect, while age and baseline 24-hour average APB count will be included as covariates. A one-sided p-value comparing the treatment and control groups will be obtained, from which a corresponding z-statistic will be derived using inverse normal transformation. The Stage 1 z-statistic and the CHW statistic at the final analysis will be compared with the pre-specified superiority boundaries (see Section 5.1).

Point estimates of the between-group difference, along with the 95% confidence interval and nominal p-value, will also be reported.

A trend plot of the least squares means for the percent reduction in 24-hour average APB count at each visit will be presented for both groups.

Missing-Data Handling

Missing values for the Week 6 primary end point will be addressed with multiple imputation.

- **Imputation Procedure** Twenty complete data sets will be generated separately within each treatment group with a Markov chain Monte Carlo (MCMC) algorithm (PROC MI, SAS; seed = 20240716).
- **Imputation Model Covariates** Age, baseline 24-hour mean PAC count, and the 24-hour mean PAC count at every post-baseline visit.

After imputation, the data sets from both treatment groups will be combined. Each imputed data set will be analyzed with the prespecified ANCOVA model for the primary end point. Results will be pooled according to Rubin's rules with PROC MIANALYZE (SAS) to yield the final least-squares mean treatment difference with its two-sided 95% CI and P value.

Sensitivity Analysis:

A mixed-effects model for repeated measures (MMRM) will be applied to the primary end point as a prespecified sensitivity analysis. The model will include treatment group, visit, and the treatment-by-visit interaction as fixed effects and age and the baseline 24-hour mean PAC count as covariates. Parameters will be estimated with restricted maximum likelihood, and denominator degrees of freedom will be determined with the Kenward–Roger approximation.

Within-participant variability will be modeled with an unstructured covariance matrix. If the model fails to converge, alternative covariance structures will be evaluated sequentially—heterogeneous Toeplitz, heterogeneous first-order autoregressive, heterogeneous compound symmetry, Toeplitz, first-order autoregressive, and compound symmetry—until convergence is achieved; the first structure that converges will be retained.

Results will be presented as the least-squares mean treatment difference with the corresponding two-sided 95% CI.

4.2.2 Secondary Efficacy Endpoints

Descriptive statistics will be performed for the following secondary efficacy endpoints:

- Change from baseline in the 24-hour average number and burden of PACs at Weeks 4, 6, and 8.
- Change from baseline in the 24-hour average number and burden of NSAT episodes at Weeks 4, 6, and 8.
- Number of episodes of SAT, AF, and AFL over a 24-hour period at Weeks 4, 6, and 8.
- Incidence of newly onset SAT, AF, and AFL over 72 consecutive hours at Weeks 4, 6, and 8.
- Change from baseline in the SF-36 quality of life score at Week 6.

4.2.3 Subgroup Analysis

Subgroup analyses of the primary endpoint will be performed using the same analytical approach as the primary analysis. Subgroups will include, but are not limited to, the following:

- Sex (male, female)
- Mean number of premature atrial beats in 24 hours (≥5000 beats/24h,< 5000 beats/24h)
- Age (≥65 years,< 65 years)

And forest plots will be drawn for the results of subgroup analysis.

4.3 Safety Analysis

4.3.1 Drug exposure

Based on the SS, the following information will be summarized by treatment group and presented in tabular form for all study drug administration data:

- Exposure duration (days) = Last dose date during the treatment period - First dose date during the treatment period + 1
- Actual total dose administered (mg) = Total dose actually administered during the study period
- Actual dose intensity (mg/day) = Actual dose administered (mg) / Exposure duration (days)
- Compliance (%) = (Actual dose intensity (mg/day) / Planned dose intensity (mg/day)) × 100%

➢ Planned dose intensity (mg/day) = (7 × 10 mg + 35 × 20 mg) / 42

- The prescribed dose (mg) refers to the dose adjusted by the physician based on the participant's clinical condition, corresponding to the intended dosing recorded in the EDC system.

4.3.2 Adverse Events (AE)

AEs will be summarized by treatment group in the safety population. Events will be coded with the MedDRA and classified by severity (mild, moderate, or severe). A TEAE is any AE that begins after the first study dose or worsens in severity relative to its pre-dose state; events with an indeterminate temporal relationship to dosing will also be considered TEAEs. All TEAEs will be individually listed, and their incidence will be tabulated and summarized descriptively.

4.3.2.1 TEAE Summary Table

The number and percentage of participants experiencing at least one treatment-emergent adverse event (TEAE) will be summarized. In addition, the number and percentage of participants experiencing the following categories of TEAEs will be reported:

- All TEAEs
  - Drug-related TEAEs (defined as those assessed as "possibly related," "probably related," or "definitely related" to the study drug; TEAEs with missing relationship data will also be considered drug-related)
- TEAEs of moderate severity or greater
  - Drug-related TEAEs of moderate severity or greater
- Serious Adverse Events (SAEs)
  - Drug-related SAEs
  - SAEs of moderate severity or greater
  - Drug-related SAEs of moderate severity or greater
- TEAEs resulting in death
  - Drug-related TEAEs resulting in death
- TEAEs leading to permanent discontinuation of the study drug
  - Drug-related TEAEs leading to permanent discontinuation of the study drug
- TEAE leading to withdrawal from the study
  - Drug-related TEAEs leading to withdrawal from the study

4.3.2.2 TEAE Analysis by SOC and PT

The number and percentage of participants experiencing the following treatment-emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT):

- All TEAEs
  - Drug-related TEAEs
- TEAEs of moderate severity or greater
  - Drug-related TEAEs of moderate severity or greater
- SAEs
  - Drug-related SAEs
- TEAEs leading to death
  - Drug-related TEAEs leading to death
- TEAEs resulting in permanent discontinuation of study medication
  - Drug-related TEAEs resulting in permanent discontinuation of study medication
- TEAEs leading to study withdrawal
  - Drug-related TEAEs leading to study withdrawal

In addition, the number and percentage of participants with all TEAEs and drug-related TEAEs will be summarized by MedDRA SOC, PT, and severity. If a participant experiences multiple TEAEs with the same SOC or PT, they will be counted only once at that SOC or PT level, using the highest CTCAE grade observed.

When summarizing adverse events, SOCs will be listed in descending order of total number of events. In the case of ties, SOCs will be sorted alphabetically. Within each SOC, PTs will also be ordered by descending frequency; PTs with the same frequency will be sorted in alphabetical order.

4.3.3 Laboratory Evaluations

Analysis population: SS

Panels: Complete blood count, serum chemistry, thyroid-function tests, urine pH

For each treatment group at every scheduled visit, summary statistics (n, mean ± SD, median [IQR], minimum, maximum) will be presented for observed values and change from baseline.

Each result will be graded by the investigator as Normal, Abnormal — not clinically significant (NCS), or Abnormal — clinically significant (CS). A shift table will display baseline status versus the worst post-baseline status (scheduled + unscheduled assessments); the severity hierarchy is CS > NCS > Normal.

4.3.4 Vital signs

Analysis population: SS

Parameters: Body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure

Observed values and change-from-baseline data will be summarized as described above. Baseline-to-worst shift tables (Normal/NCS/CS) will be compiled using the same severity hierarchy.

4.3.5 12-Lead ECG

Analysis population: SS

Parameters: Heart rate, PR interval, QRS duration, QT and QTc intervals

For each scheduled visit, observed values and change from baseline will be summarized. Each tracing will be classified as Normal, NCS, or CS, and baseline-to-worst shift tables will be generated (scheduled + unscheduled recordings).

4.3.6 Symptom Assessment

Analysis population: SS

Instrument: Protocol-specified, validated symptom scale (s)

Observed scores and change-from-baseline values will be summarized with the same set of descriptive statistics.

4.3.7 NYHA Functional Class

A NYHA functional class will be summarized in the SS by treatment group and scheduled visit; descriptive statistics will be reported for the class distribution at each visit and for changes from baseline.

4.3.8 SF-36 Health Survey

Analysis population: SS

Instrument: Short Form-36 (SF-36) questionnaire

For each visit, domain and summary scores—both observed values and change from baseline—will be summarized (n, mean ± SD, median [IQR], minimum, maximum).

5. Planned Analyses

5.1 Interim Analysis

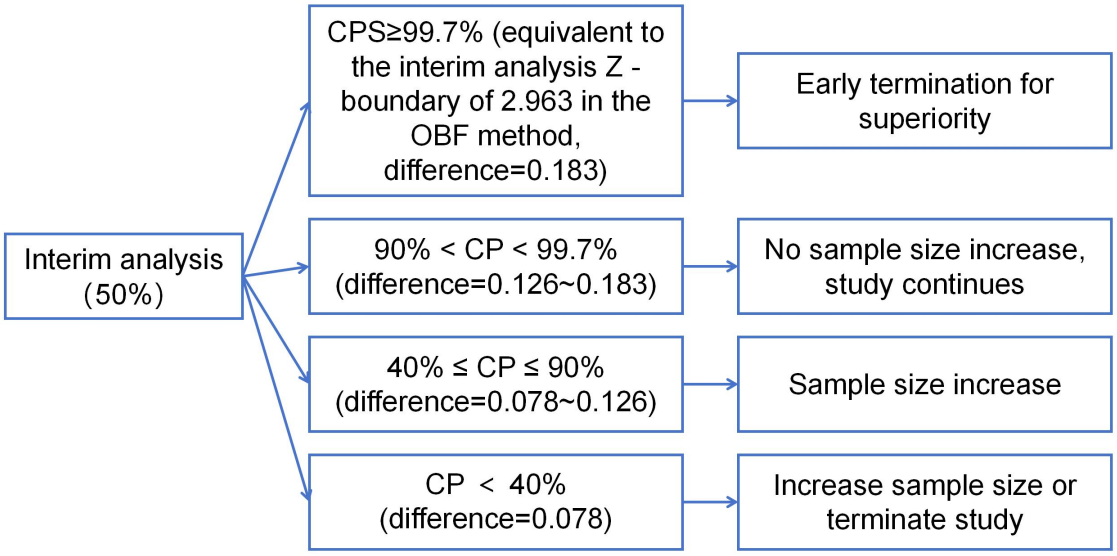
An unblinded sample size reassessment is planned for this study after approximately 128 (50%) of the subjects have completed the primary endpoint assessment. The following table shows the superiority boundaries for the primary endpoint:

Analyze	Event Information Fraction	α = 0.025
Interim analysis	50% (about 128 cases)	Superiority margin: z = 2.963
Final analysis	100% (256 cases)	Superiority margin: z = 1.969

Note: These boundaries are calculated using the Lan-Demets spending function, which approximates the O'Brien-Fleming boundaries, and will be adjusted based on the actual number of participants observed.

In addition to early termination for efficacy, if the conditional power based on the actual observed data from both groups at the time of the interim analysis falls between 40% and 90%, an adjustment to the sample size will be implemented.

The interim analysis will be conducted by an independent statistical team, and the results will be reviewed by an independent Data Monitoring Committee (IDMC), which will provide corresponding recommendations. The decision rules are illustrated in the figure below：



Note: Conditional power (CP) is calculated based on the treatment effect actually observed at the interim analysis. The difference used in the calculation is based on an assumed standard deviation of 0.35; different standard deviations would yield different values for the difference.

6. Deviations from the Planned Analyses in the Protocol

No deviations from the analyses planned in the protocol are made in this Statistical Analysis Plan.