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 Study (STOP-AP)

Study drug:	Memantine Hydrochloride Tablets
Indications:	Frequent Symptomatic Premature Atrial Contractions
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Document Revision History and Amendment Summary		
Version Number	**Effective Date**	**Revision Summary**
1.0	2025-02-14	Statistical Analysis Plan, Version 1.0 — Final
2.0	2025-07-17	**1.** Removal of the planned interim analysis. An interim analysis for sample- size re- estimation had been prespecified after 128 participants completed the 6- week follow- up. At the planned interim time point, however, enrollment had already reached nearly 256 participants—the trial's final target sample size. The Trial Steering Committee reviewed enrollment progress and unanimously resolved to cancel the prespecified interim analysis before unblinding. The trial remained fully blinded throughout, thereby preserving data integrity. **2.** Addition of secondary endpoints: a) The cumulative incidence of new-onset atrial fibrillation (AF) from baseline to Week 8: The proportion of participants who experience their first episode of AF lasting ⩾30 seconds during any of the 4th, 6th, or 8th-week follow-up windows, with each participant counted only once, even if they have multiple occurrences across different follow-up windows. b) Efficacy analysis (e.g., ≥50% reduction) for premature atrial contractions (PACs) or non- sustained atrial tachycardia (NSAT), based on the proportion of responders. **3.** Introduction of a subgroup analysis stratified by left- atrial diameter.

		4. Revision of the secondary endpoint description from "incidence of new-onset sustained atrial tachycardia (SAT), AF, or atrial flutter (AFL) during consecutive 72-hour electrocardiogram (ECG) recordings at Weeks 4, 6, and 8" to "proportion of participants with new-onset SAT, AF, or AFL during consecutive 72-hour ECG recordings at Weeks 4, 6, and 8." **5.** Implementation of multiplicity-control procedures and inferential testing for the key secondary endpoints. Pre-specifying and reporting an appropriate multiplicity-control strategy preserves the family-wise type I error rate and reinforces statistical rigor. A hierarchical fixed-sequence testing procedure focuses on the most clinically relevant questions, thereby strengthening the confirmatory value and credibility of the conclusions without compromising participant safety or rights. These amendments do not affect participant rights, safety information, or the trial data structure and were finalized before unblinding.

Catalogs

1. Trial Overview

This Statistical Analysis Plan (SAP) specifies the statistical methods and data-handling procedures for the trial entitled "Efficacy and Safety of Memantine in the treatment of Frequent Symptomatic Atrial Premature beats: a multicenter randomized double-blind placebo- controlled study (STOP-AP)".

The present SAP is based on Clinical Trial Protocol Version 2.3, dated 29 June 2025.

1.1 Study Objectives

1.1.1 Primary Objective

To evaluate the efficacy of memantine in treating frequent symptomatic 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 PACs at Week 6.

1.2.2 Secondary Endpoints

a) The change from baseline in the 24-hour mean number and burden of PACs at Weeks 4, 6, and 8;

b) The change from baseline in the 24-hour mean episode count and burden of NSAT at Weeks 4, 6, and 8;

c) The change from baseline in the 24-hour mean episode count of SAT, AF, and AFL at Weeks 4, 6, and 8;

d) The proportion of participants with new-onset SAT, AF, or AFL lasting ≥30 seconds during a consecutive 72-hour monitoring period at Weeks 4, 6, and 8. This endpoint will be calculated based on the first occurrence of SAT, AF, or AFL during the respective 72-hour monitoring windows;

e) The cumulative incidence of new-onset AF from baseline to Week 8: The proportion of participants who experience their first episode of AF lasting ≥30 seconds during any of the 4th, 6th, or 8th-week follow-up windows, with each participant counted only once, even if they have multiple occurrences across different follow-up windows；

f) The change from baseline in the SF-36 quality of life score at Week 6;

g) Efficacy analysis of PACs or NSAT, based on the proportion of responders.

1.2.3 Safety Endpoints

The incidence of adverse events (including psychiatric symptoms, seizures, bradycardia and new-onset heart failure, etc.), serious adverse events, laboratory test abnormalities, and abnormal ECG findings.

1.3 Study Design

1.3.1 Overall Design

This investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial will enroll 256 adults (18–80 years of age) 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; ≤ 14 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 ECG monitoring.

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

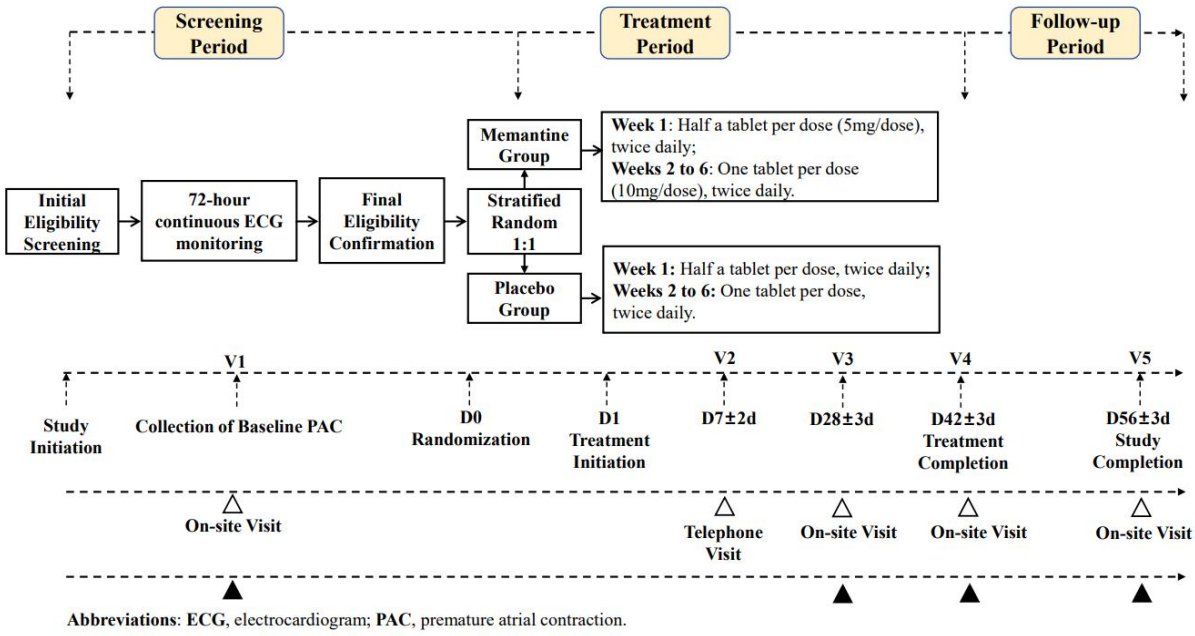

Figure 1 Study Design Flowchart

The treatment phase will last 42 to 45 days. Seventy- two- hour ambulatory ECG will be initiated on study days 25−28 for Visit 3 (V3), days 39−42 for Visit 4 (V4), and days 53−56 for Visit 5 (V5). For V4, monitoring must begin 72 hours before the final scheduled dose; thus, if dosing concludes on day 42, monitoring must start on day 39. Conversely, if monitoring is initiated on day 42, study medication must continue through day 45. All other assessments scheduled for V3 – V5 must be completed between placement and removal of the 72- hour ECG device.

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 α = 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 randomly assigned (intention-to-treat principle).
- **Per Protocol Set (PPS)** — Includes 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 Multiplicity Adjustment

If the primary endpoint is statistically significant (two-sided $P < 0.05$), key secondary endpoints will be evaluated with a fixed-sequence testing procedure to control the family-wise type I error rate. Each endpoint will be tested at a two-sided α of 0.05, and testing will proceed down the hierarchy only while significance is maintained.

Testing hierarchy

a) Week 6 responder rate for PACs (≥50% reduction).

b) Change from baseline to Week 6 in NSAT burden.

c) Cumulative incidence of new-onset AF from baseline to Week 8.

d) Incidence of new-onset AF at Week 4.

e) Incidence of new-onset AF at Week 6.

f) Incidence of new-onset AF at Week 8.

If any endpoint fails to achieve significance, formal hypothesis testing will stop, and all remaining secondary endpoints will be summarized descriptively.

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.

- 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.

a) 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.

b) Month missing only

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

c) 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.

Imputation of Adverse-Event (AE) End Dates

• For incomplete end dates, impute the last calendar day of the reported month; if both month and day are missing, impute 31 December of the reported year.

• Participants who die: If the imputed end date falls after the date of death, replace it with the death date.

• Participants alive at study completion or data cutoff: If the imputed end date exceeds the last known contact date or the data-cutoff date, replace it with the earlier of those two dates.

Imputation Rules for Start and End Dates of Prior and Concomitant Medications and Non-Drug Therapies

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.

Consistency Checks

• If the imputed end date exceeds the participant's date of death, replace it with the date of death.

• If the participant is alive at study completion or data cut-off and the imputed end date exceeds either the last known contact date or the data-cut-off date, replace it with the earlier of those two dates.

3.2.2 Imputation of Missing AE Attributes

A conservative "worst-case" strategy will be applied whenever essential AE fields are missing:

• Causality missing → the AE will be coded as treatment-related.

• Severity missing → the AE will be assigned the maximum applicable CTCAE grade.

• Outcome missing and no end date recorded → the outcome will be imputed as not recovered/not resolved.

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), BMI will be calculated as baseline weight (kg) divided by the square of baseline height (m) 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.

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 Diagnoses

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 History

Within the FAS, all medical history present before or at baseline will be summarized descriptively by treatment group. Medical history 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 concurrent medical history will be provided.

• Prior medical history — Medical history that occurred before the first study dose (i.e., the end date of medical history the first-dose date).

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

4.1.6 Prior and Concomitant Drug Therapies

Within the FAS, prior and concomitant medications will be summarized descriptively by treatment group. Prior and concomitant drug therapies 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 drug therapies will be provided.

Prior drug therapies — any drug therapies that occurred before the first study dose (i.e., the stop date precedes the first-dose date).

Concomitant drug therapies — any drug therapies 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-Drug Therapies

Within the FAS, all non-drug interventions administered before or during the trial will be summarized descriptively by treatment group. Each intervention will be coded with the MedDRA and tabulated by SOC and PT. SOCs and PTs will be ranked in descending

order of overall frequency, with alphabetical ordering applied to ties. A participant-level listing of every prior and concomitant non-drug therapy will also be provided.

- **Prior Non-Drug Therapy:** an non-drug intervention completed before the first administration of study drug (i.e., the stop date precedes the first-dose date).
- **Concomitant Non-Drug Therapy:** an non-drug intervention that either (i) is initiated on or after the first-dose date or (ii) is initiated before the first-dose date and continues on or after that date.

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

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-baseline value) ÷ Baseline value × 100%

4.2.1 Primary Efficacy Analysis

The primary end point—the percent change from baseline in the 24-hour mean PAC count at Week 6—will be evaluated with an analysis-of-covariance (ANCOVA) model. Treatment group will be included as a fixed effect, and age and baseline 24-hour mean PAC count will be included as covariates. The between-group effect will be reported as the least-squares mean difference with its two-sided 95% confidence interval (CI) and p value.

Least-squares mean percentage reductions in the 24-hour mean PAC count will be plotted for each scheduled visit to depict response trajectories in both treatment 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 Endpoint Analysis

All secondary efficacy end points will be evaluated in the FAS. Missing data for secondary end points will not be imputed.

• **Continuous Endpoints** At each scheduled visit, analyses will be based exclusively on observed values (observed-cases approach); participants lacking data at a given visit will be omitted from that visit's analysis.

• **Categorical Endpoints** Participants with missing data will be classified as non-responders—that is, as not having met the specified end point.

a) The change from baseline in the 24-hour mean number and burden of PACs at Weeks

4, 6, and 8；

b) The change from baseline in the 24-hour mean episode count and burden of NSAT at Weeks 4, 6, and 8;

c) The change from baseline in the 24-hour mean episode count of SAT, AF, and AFL at Weeks 4, 6, and 8;

d) The proportion of participants with new-onset SAT, AF, or AFL lasting ≥ 30 seconds during a continuous 72-hour monitoring period at Weeks 4, 6, and 8. This endpoint will be calculated based on the first occurrence of SAT, AF, or AFL during the respective 72-hour monitoring windows;

e) The cumulative incidence of new-onset AF from baseline to Week 8: The proportion of participants who experience their first episode of AF lasting ≥ 30 seconds during any of the 4th, 6th, or 8th-week follow-up windows, with each participant counted only once, even if they have multiple occurrences across different follow-up windows；

f) The change from baseline in the SF-36 quality of life score at Week 6;

g) The responder rate for PACs or NSAT will be calculated at Weeks 4, 6, and 8 and compared between the memantine and placebo groups. A PAC responder is defined as a participant whose 24-hour mean PAC count is reduced by ≥ 50% from baseline after treatment, and an NSAT responder is defined as a participant whose 24-hour mean NSAT burden is reduced by ≥ 50% from baseline after treatment.

• For categorical end points, counts and proportions will be summarized by treatment group. Two-sided 95% CIs for incidence, cumulative incidence, or response rate will be calculated with the Clopper – Pearson method. The absolute risk reduction (ARR = incidence in the memantine group − incidence in the placebo group) will be reported, and between-group differences will be tested with a stratified Cochran – Mantel – Haenszel χ^2 test that uses the randomization strata—age (≥ 65 vs. < 65 yr) and baseline PAC count (≥ 5000 vs. < 5000 beats/24 h)—as stratification factors. The relative risk (RR = incidence in the memantine group ÷ incidence in the placebo group) and its 95% CI, together with the number needed to treat (NNT = 1/|ARR|), will also be presented.

• For continuous end points—including the change from baseline at weeks 4, 6, and 8 in the 24-hour mean PAC count and burden; the episode count and burden of NSAT; the

episode count of SAT, AF, and AFL; and the change from baseline to week 6 in the total SF-36 score—an ANCOVA will be fitted. The model will include treatment group as a fixed effect and age and the baseline value of the respective end point as covariates. For each end point, the least-squares mean difference between groups, its two-sided 95% CI, and the corresponding p value will be reported.

4.2.3 Subgroup Analysis

Subgroup analyses of the primary end point will be conducted using an ANCOVA model. Treatment group will be included as a fixed effect, with age and baseline 24-hour mean PAC count as covariates. If a covariate is also used as a subgroup factor, it will be excluded from the analysis model. The difference between groups will be reported as the point estimate, along with its 95% CI and p value.

Subgroups (not limited to) will include:

- Sex (male, female)
- Baseline 24-hour mean PAC count (≥ 5000 beats/24h, <5000 beats/24h)
- Age (≥ 65 years, <65 years)
- Left atrial diameter (≥ 40 mm, <40 mm)

The interaction between treatment group and subgroup factors will be assessed to evaluate whether the treatment effect varies across subgroups. The subgroup analysis is exploratory, and p values will not be adjusted for multiple comparisons; therefore, the results should not be used for inferential purposes.

Forest plots will be generated to present the results of the subgroup analyses.

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

4.3.2 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

TEAE will be summarized in the safety population. For each treatment group, the number and percentage of participants with at least one TEAE will be reported, along with the corresponding figures for the following categories:

All TEAEs

Treatment-related TEAEs. Drug relatedness is defined as *possibly related*, *probably related*, or *definitely related*; TEAEs with missing relatedness will be classified as treatment-related.

• TEAEs of moderate or greater severity

Treatment-related TEAEs of moderate or greater severity

• Serious adverse events (SAEs)

Treatment-related SAEs

• SAEs of moderate or greater severity

Treatment-related SAEs of moderate or greater severity

• TEAEs resulting in death

Treatment-related TEAEs resulting in death

• TEAEs leading to permanent discontinuation of the study drug

Treatment-related TEAEs leading to permanent discontinuation

• TEAEs leading to withdrawal from the trial

Treatment-related TEAEs leading to withdrawal

4.3.2.2 Safety Analysis of TEAEs by SOC and PT

For each treatment group, the number and percentage of participants with at least one event will be tabulated by MedDRA SOC and, within each SOC, by PT for the following categories:

TEAE category	Subcategory (Treatment-related)
All TEAEs	Treatment-related TEAEs
TEAEs of ≥ moderate severity	Treatment-related TEAEs of ≥ moderate severity
Serious adverse events (SAEs)	Treatment-related SAEs
TEAEs leading to death	Treatment-related TEAEs leading to death
TEAEs leading to permanent discontinuation of study drug	Treatment-related TEAEs leading to permanent discontinuation
TEAEs leading to withdrawal from the trial	Treatment-related TEAEs leading to withdrawal

Counting Rules

•For “all TEAEs” and for drug-related TEAEs, additional summaries will cross-classify events by SOC, PT, and maximum CTCAE grade.

• If a participant reports multiple events within the same SOC or PT, the participant is counted once at the highest CTCAE grade observed for that SOC or PT.

Sorting Conventions

• SOCs are ordered in descending frequency of affected participants; ties are broken alphabetically.

• Within each SOC, PTs are ordered in descending frequency; alphabetical ordering resolves any ties.

When appropriate, the incidence of TEAEs will be compared between treatment groups by calculating the relative risk and its two-sided 95% CI.

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

None.

6. Deviations from the planned analysis in the protocol

None.