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)

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Version number: Version 2.1

Version Date: June 28, 2024

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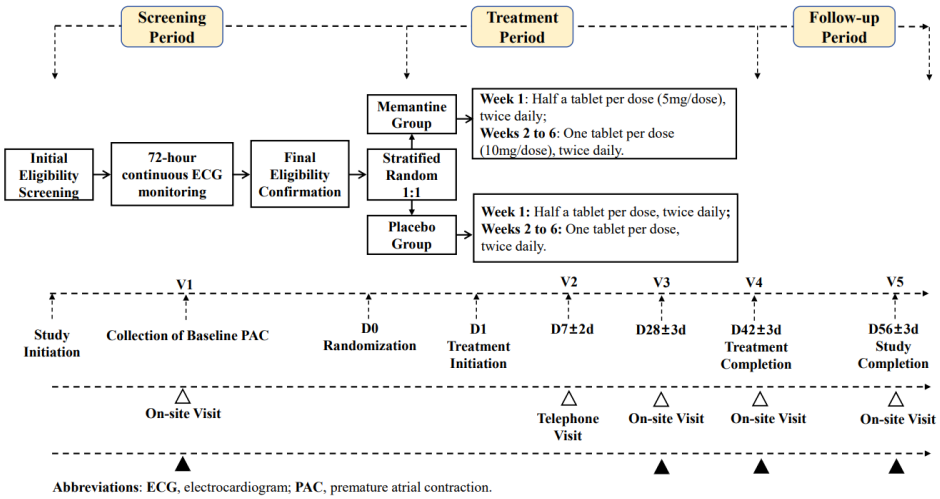
Abstract of the Research Program

Title	Efficacy and safety of memantine in the treatment of frequent symptomatic atrial premature beats: a multicenter, randomized, double-blind, placebo-controlled, adaptive-design study
Objective	MAIN OBJECTIVE: To evaluate the effectiveness of memantine in the treatment of frequent symptomatic atrial premature beats. SECONDARY OBJECTIVE: To evaluate the safety of memantine in the treatment of frequent symptomatic atrial premature beats.
Principal Investigator and Lead Institution	Yi-Han Chen, Shanghai East Hospital, Tongji University.
Sample Size	A total of 256 patients with frequent symptomatic atrial premature beats are to be recruited, with the sample size potentially adjusted based on interim analysis results.
Inclusion Criteria	**(1) Age**: 18 to 80 years, inclusive. **(2) Symptomatic premature atrial contractions (PACs)**: Documented at screening as ≥ 1,000 PACs during a 24-hour ambulatory electrocardiogram (ECG) recording. **(3) Informed consent**: Ability and willingness to understand and comply with all study procedures and to sign the written informed-consent form before any protocol-specific activities are performed.
Exclusion criteria	**(1) Atrial or ventricular arrhythmias** Atrial fibrillation, atrial flutter, or persistent atrial tachycardia documented by 12-lead ECG within 6 months before screening or detected on the baseline 72-hour patch-type ambulatory ECG. Ventricular tachycardia (excluding brief nocturnal runs) or ventricular fibrillation. **(2) Recent cerebrovascular or cardiac events** Ischemic or hemorrhagic stroke, or transient ischemic attack, within 6 months before screening. Cardiac surgery, myocardial infarction, percutaneous coronary intervention, or cardiac radiofrequency ablation within 6 months before screening. **(3) Severe left-sided cardiac dysfunction** Left-ventricular ejection fraction ≤ 40 %. New York Heart Association class III or IV heart failure. **(4) Clinically significant conduction disease** Sick-sinus syndrome without a permanent pacemaker. Second-degree type II or higher atrioventricular block, or bifascicular block.

	Diagnosed systemic or metabolic condition that could lead to severe bradycardia or conduction abnormalities, such as cardiac sarcoidosis or untreated severe hypothyroidism. **(5) Recent antiarrhythmic therapy** Amiodarone within 4 weeks before screening. Any other antiarrhythmic agent—including herbal preparations with antiarrhythmic properties—within 2 week before screening. **(6) Other serious cardiac conditions** Unstable angina, severe congenital heart disease (except patent foramen ovale), prior prosthetic heart-valve replacement, acute myocarditis or endocarditis, rheumatic valvular disease, hypertrophic cardiomyopathy, congenital long QT syndrome, congenital short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia. **(7) Limited life expectancy** Any comorbid condition with an anticipated survival of < 1 year. **(8) Hepatic impairment** Active hepatitis or clinically significant liver dysfunction (ALT or AST > 3 × ULN, or total bilirubin > 3 × ULN). **(9) Renal impairment** Estimated glomerular filtration rate < 40 mL · min^{-1} · 1.73 m^{-2} (CKD-EPI formula). **(10) Concurrent investigational therapy** Use of any investigational drug or device within 1 month—or five elimination half-lives, whichever is longer—before screening. **(11) Pregnancy or lactation** Pregnant or breastfeeding women, or a positive serum pregnancy test before randomization. **(12) Metabolic, surgical, or pulmonary instability** The presence of atrial premature beats due to potential reversible causes, such as hyperthyroidism, cardiovascular surgery, electrolyte imbalances, etc. APBs decrease and symptoms significantly improve after the removal of triggers (e.g., alcohol abuse, acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with respiratory failure, or unresolved infections). **(13) Neurologic or psychiatric disorders** History of epilepsy, seizures, or psychiatric illness that could interfere with study participation. **(14) Drug hypersensitivity** Known allergy to memantine hydrochloride or any excipient of the study drug. **(15) Current memantine therapy**

	Ongoing treatment with memantine for moderate-to-severe Alzheimer's disease. **(16) Other contraindications** Any condition that, in the investigator's judgment, makes the participant unsuitable for enrollment in the study.
Research Design	This study is a multicenter, randomized, double-blind, parallel-group, placebo-controlled superiority trial.
Efficacy Endpoints	**Primary Efficacy Endpoint:** The percentage change from baseline in the 24-hour mean number of premature atrial contractions (PACs) at Week 6. **Secondary Efficacy Endpoints:** (1) The change from baseline in the 24-hour mean number and burden of PACs at Weeks 4, 6, and 8; (2) The change from baseline in the 24-hour mean number and burden of non-sustained atrial tachycardia (NSAT) at Weeks 4, 6, and 8; (3) The change from baseline in the number of episodes of sustained atrial tachycardia, atrial fibrillation, and atrial flutter over a 24-hour period at Weeks 4, 6, and 8. (4) The change from baseline in the SF-36 quality of life score at Week 6.
Safety Endpoints	The incidence of adverse events (including psychiatric symptoms, seizures, bradycardia, new-onset heart failure, etc.), serious adverse events, laboratory test abnormalities, and abnormal electrocardiogram findings.
Study Overview	This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled superiority trial aimed at enrolling 256 patients aged 18 to 80 years with frequent symptomatic PACs. Eligible patients, following initial screening, will undergo 72-hour continuous ambulatory ECG monitoring to establish baseline PAC counts. Based on the monitoring data, eligibility will be confirmed. Qualified participants will then be randomly assigned in a 1:1 ratio on Day 0 to either the memantine group or the placebo group. A total of 256 participants will be enrolled, with 128 in each group. Stratification factors will include age (≥65 years vs. <65 years) and baseline PAC count (≥5000 per 24 hours vs. <5000 per 24 hours). The study is comprised of a screening period (≤ 7 days), a treatment period (Day 42 ± 3 days), and a follow-up period (Day 56 ± 3 days). The study design is presented in the figure below.



Notes:

a) The drug administration period for this study spans from Day 42 to Day 45. The 72-hour ambulatory ECG monitoring at visits V3, V4, and V5 is scheduled to begin on Day 25 to Day 28 for V3, Day 39 to Day 42 for V4, and Day 53 to Day 56 for V5. For the V4 visit, the ECG monitoring must commence 3 days prior to the end of the administration period. For example, if drug administration concludes on Day 42, the 72-hour ambulatory ECG monitoring must begin on Day 39. Should the monitoring occur on Day 42, drug administration must continue until Day 45.

(2) Other procedures during the V3 to V5 visits should be conducted after completing the 3-day Holter monitoring.

The memantine group: participants will receive memantine according to the following regimen:

Week 1: ½ tablet per dose (5 mg per dose), twice daily, to be taken at the same time each morning and evening (with a recommended dosing interval of 12 hours ± 2 hours).

Weeks 2 to 6: 1 tablet per dose (10 mg per dose), twice daily, to be taken at the same time each morning and evening (with a recommended dosing interval of 12 hours± 2 hours).

The placebo group: participants will receive placebo tablets according to the following regimen:

Week 1: ½ tablet per dose, twice daily, to be taken at the same time each morning and evening (with a recommended dosing interval of 12 hours ± 2 hours).

Weeks 2 to 6: 1 tablet per dose, twice daily, to be taken at the same time each morning and evening (with a recommended dosing interval of 12 hours ± 2 hours).

Duration of administration

<table>
<tr><td></td><td>The duration of drug administration in this study will be from Day 42 to Day 45.</td></tr>
<tr><td>Prohibited Medications</td><td>The following medications are prohibited throughout the study period:
a) NMDA antagonists, including amantadine, ketamine, dextromethorphan, and others.
b) Levodopa, dopamine receptor agonists, anticholinergic agents, and barbiturates.
c) Antiarrhythmic drugs
d) Antispasmodic agents, including dantrolene, baclofen, and others.
e) Other medications that, in the investigator’s judgment, may interfere with the efficacy or safety assessments.</td></tr>
<tr><td>Calculation of Sample size</td><td>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.
Interim Analysis
This study plans to conduct a non-blinded sample size re-estimation after approximately 128 participants (50%) have completed the primary endpoint assessment. The table below presents the superiority boundaries for the primary endpoint:
<table>
<tr><th>Analysis</th><th>Event Information Fraction</th><th>α = 0.025</th></tr>
<tr><td>Interim Analysis</td><td>50% (approximately 128 subjects)</td><td>Superiority Boundary: z = 2.963</td></tr>
<tr><td>Final Analysis</td><td>100% (256 subjects)</td><td>Superiority Boundary: z = 1.969</td></tr>
</table>
Note: The superiority boundaries are calculated using the Lan-Demets approximation of the O’Brien-Fleming boundaries with a spending function. These boundaries will be adjusted based on the actual number of participants observed.
In addition to early termination for efficacy, if the conditional power derived from the actual observed results of both groups falls between 40% and 90% at the time of the interim analysis, a sample size adjustment will be made.
The interim analysis will be conducted by an independent analysis team, and the results will be reviewed by an independent Data Monitoring Committee (IDMC),</td></tr>
</table>

	which will provide recommendations. The specific decision rules are outlined in Section 7.3.8.
Statistical Analysis	**General Principle** For continuous data, statistical descriptions will include the number of cases, mean, standard deviation, median, minimum, and maximum. For categorical data, statistical descriptions will include the number and percentage of cases. Percentages will be calculated using the number of participants in the corresponding group as the denominator, unless otherwise specified. **Efficacy Analysis** The difference between the two groups for the primary endpoint will be assessed by calculating the mean difference in the percentage reduction of 24-hour mean PACs at Week 6 between the memantine and placebo groups, along with its 95% confidence interval (CI). Descriptive statistics will be applied to the secondary efficacy endpoints. **Safety Analysis** All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), categorized by System Organ Class (SOC) and Preferred Term (PT). The number and incidence rate of adverse events (AEs), serious adverse events (SAEs), and AEs leading to death will be summarized. AEs, SAEs, and those resulting in death will also be summarized by SOC and PT, with the corresponding number of cases and incidence rates reported.

1. Background

The incidence of PACs increases with age [1,2]. Previously, PACs were considered benign arrhythmias with minimal clinical significance. However, recent studies have shown that frequent PACs may indicate subclinical cardiovascular disease. After adjusting for multiple variables, patients with frequent PACs have a 2- to 4-fold increased risk of developing AF, a 2- to nearly 3-fold increased risk of first stroke, a 39% to 100% increased risk of all-cause mortality, and a 74% increased risk of coronary artery disease [3].

The association between frequent PACs and AF, stroke, and mortality may be mediated by three distinct mechanisms: First, frequent PACs are more likely to progress to subclinical AF, which in turn increases the risk of stroke and death. Second, PACs are associated with traditional cardiovascular risk factors. Third, frequent PACs may indicate atrial cardiomyopathy, a condition characterized by electrophysiological abnormalities and a hypercoagulable state, which may still lead to thrombus formation in sinus rhythm, thus increasing stroke risk [1-2,4]. The growing recognition of the potential risks associated with frequent PACs has prompted clinicians to reconsider their clinical significance, suggesting that they should no longer be regarded as a benign condition.

The European Heart Rhythm Association (EHRA) consensus on the management of asymptomatic arrhythmias recommends monitoring rhythm, addressing cardiovascular risk factors, and assessing for structural heart disease in patients with frequent PACs. For patients with >500 PACs/24 hours or any continuous episode of more than 20 PACs, especially if brief episodes of AF are observed, individualized anticoagulation therapy should be considered [5]. However, due to the lack of clinical evidence supporting antiarrhythmic drug treatment for PACs, the consensus does not recommend pharmacological therapy. Limited evidence from previous studies suggests that for patients with persistent symptomatic PACs, after minimizing potential triggers (e.g., smoking, caffeine, alcohol, stress), β-blockers may be used to reduce PAC frequency and associated symptoms, provided there are no contraindications. However, the effectiveness of β-blockers is uncertain and varies among patients. A cohort study

investigating the use of low-dose β-blockers to improve the long-term prognosis of PAC patients found that, after propensity score matching, mortality was significantly lower in the treated group in the high-load subgroup (≥100 PACs/day) over a mean follow-up of approximately three years, although the incidence of new-onset stroke and AF was similar between groups [6]. Class IA, IC, and III antiarrhythmic drugs have been shown to reduce the frequency of symptomatic PACs and suppress arrhythmias such as AF, AFL, and atrioventricular reentrant tachycardia [7-9]. However, these drugs have not been subjected to controlled studies, and their use must be carefully weighed against the potential risk of pro-arrhythmia. Furthermore, digoxin, calcium channel blockers, and class IB antiarrhythmic drugs have not shown clear benefits in patients with symptomatic PACs. Therefore, there is an urgent need to develop novel drugs for the treatment of PACs and conduct prospective studies on antiarrhythmic therapies.

The glutamate neurotransmitter system is a crucial signaling pathway that regulates the excitability and conduction of neurons. Similarly, myocardial cells, as excitable cells, also exhibit excitability and conduction properties. Yi-Han Chen's team first discovered that rat atrial myocardial cells have an intrinsic, rich glutamatergic neurotransmitter system, which regulates myocardial cell excitability and conduction by controlling ionotropic glutamate receptors (iGluRs). Under resting potential, activation of glutamate receptors in rat atrial muscle cells induces transient inward currents, facilitating the generation of action potentials, thus increasing cell excitability and conduction. Importantly, specific glutamate receptor inhibitors block this effect. Furthermore, a similar glutamatergic system with electrophysiological regulatory functions has been identified in human atrial myocardial cells [10,11].

Memantine (Mem) is a voltage-dependent, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that inhibits the activity of ionotropic glutamate receptors (iGluRs) [12]. It is used as a first-line treatment for moderate to severe Alzheimer's disease, with a good safety profile and patient tolerance [13]. Notably, preclinical studies conducted by Yi-Han Chen’s team have shown that memantine effectively reduces the incidence of AF induced by three different pathophysiological conditions (stretch-induced, cholinergic, and ischemic AF) in isolated rat hearts in a concentration-

dependent manner. In in vivo experiments, memantine effectively prevented and terminated AF induced by three different pathophysiological conditions (aortic constriction, acetylcholine, and hypoxia) in rats. The primary mechanism of action is that memantine blocks glutamate currents in atrial myocardial cells, reducing calcium leakage, and effectively reducing trigger activity, delayed afterdepolarization, and ectopic beats, thereby reducing AF triggers and effectively preventing AF. Additionally, memantine significantly decreased the number of reentrant circuits in the atrial myocardium, thus effectively terminating AF. Furthermore, memantine was shown to reduce the incidence of AF-like abnormal electrophysiological events and delayed afterdepolarization in human-induced pluripotent stem cell-derived atrial myocardial cells (iPSC ACMs), suggesting that this drug may also exert electrophysiological regulatory effects on human myocardial cells. Previous animal and clinical studies have demonstrated that memantine has a favorable safety profile, reducing the occurrence of reperfusion arrhythmias and slowing heart rate without prolonging the QT interval [15-17], thus not increasing the risk of torsades de pointes. Based on these findings, we hypothesize that memantine may be an ideal treatment for rapid atrial arrhythmias. The repurposing of an existing drug significantly shortens the drug development timeline and reduces research costs. Therefore, this study aims to explore the efficacy and safety of memantine in patients with frequent PACs.

2. Study Objectives and Endpoints

2.1 Objectives

Primary Objective — To evaluate the efficacy of memantine in treating frequent symptomatic PACs.

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

2.2 Endpoints

2.2.1 Efficacy Endpoints

Primary Efficacy Endpoint: The percentage change from baseline in the 24-hour mean number of PACs at Week 6.

Secondary Efficacy Endpoints:

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

2) The change from baseline in the 24-hour mean number and burden of non-sustained atrial tachycardia (AT) at Weeks 4, 6, and 8;

3) The change from baseline in the number of episodes of sustained atrial tachycardia, atrial fibrillation, and atrial flutter over a 24-hour period at Weeks 4, 6, and 8.

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

2.2.2 Safety Endpoints

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

3. Study Design

3.1 Overall Design

This investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled two-stage adaptive-design 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; ≤ 7 days before randomization) — Baseline clinical assessments and 72-hour ambulatory ECG monitoring.

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

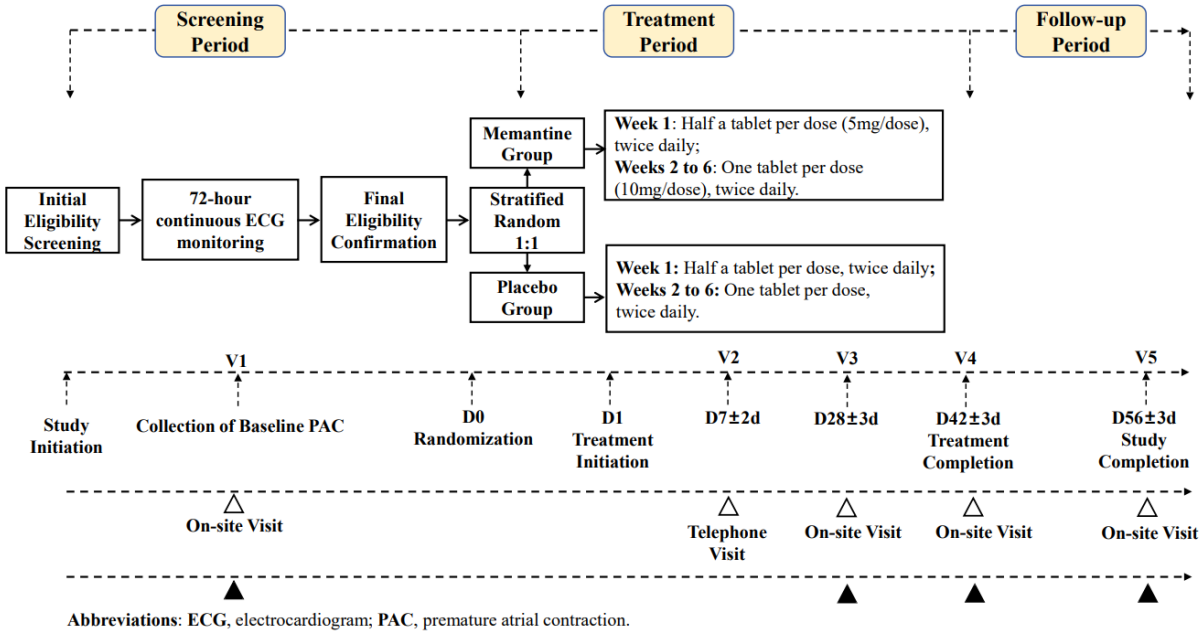


Figure 1 Study Design Flowchart

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.

Other procedures during the V3 to V5 visits should be performed after completing 72 hours (3 days) of continuous Holter monitoring.

3.2 Study Centers

The trial will be conducted at approximately 20 hospitals across China; the number of participating sites may be adjusted on the basis of operational considerations.

3.3 Randomization and Blinding

3.3.1 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 statistical team which 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.

3.3.2 Blinding

This is a double-blind trial: investigators, participants, and site personnel—including monitors, data managers, and statisticians—will remain unaware of treatment allocation until the prespecified unblinding conditions are met. Placebo tablets are identical to active tablets in appearance, odor, weight, packaging, and dosing schedule but contain no active memantine. Blinding will be maintained from generation of the randomization code through drug dispensing, data collection, monitoring, data management, and statistical analysis.

3.3.3 Emergency Unblinding

Unblinding is permitted only when a participant experiences a medical emergency in which knowledge of the assigned treatment is indispensable for appropriate management. If emergency unblinding is not required to manage the event, the blind must be maintained.

- The investigator must document the date, time, reason, and personnel involved in the unblinding and notify the study monitor without delay.

- A safety report must be submitted to the institutional ethics committee as soon as possible.
- The participant must discontinue study medication but will remain in the study for continued follow-up; the reason for treatment discontinuation must be recorded in the case-report form.
- At study close-out, the frequency, reasons, extent, and timing of all emergency unblinding will be summarized and evaluated for their potential impact on efficacy and safety analyses.

In the event of an unexpected SAE, individual unblinding will be performed according to the same procedure to determine whether the SAE constitutes a suspected unexpected serious adverse reaction (SUSAR). All other study personnel will remain blinded, and the participant will not be considered lost to follow-up.

3.3.4 Interim Analysis Unblinding

Interim analysis unblinding: At the pre-specified time point for interim analysis, following database lock, population stratification, and finalization of the statistical analysis plan, unblinding will occur. Group assignment information will be disclosed only to the Data Monitoring Committee and its independent statistical team for analysis and reporting.

3.3.5 Final Unblinding

After the database lock, confirmation of analysis populations, and finalization of the statistical analysis plan, the study statistician will submit a written request for final unblinding. The request must be countersigned by the principal investigator and the statistician. Upon receipt of the signed approval, the randomization manager will release the treatment codes.

4. Study Population

4.1 Inclusion Criteria

(1) Age: 18 to 80 years, inclusive.

(2) Symptomatic PACs: Documented at screening as $\geqslant$ 1,000 PACs during a 24-hour ambulatory ECG recording.

(3) Informed consent: Ability and willingness to understand and comply with all study procedures and to sign the written informed-consent form before any protocol-specific activities are performed.

4.2 Exclusion Criteria

(1) Atrial or ventricular arrhythmias

Atrial fibrillation, atrial flutter, or persistent atrial tachycardia documented by 12-lead ECG within 6 months before screening or detected on the baseline 72-hour patch-type ambulatory ECG.

Ventricular tachycardia (excluding brief nocturnal runs) or ventricular fibrillation.

(2) Recent cerebrovascular or cardiac events

Ischemic or hemorrhagic stroke, or transient ischemic attack, within 6 months before screening.

Cardiac surgery, myocardial infarction, percutaneous coronary intervention, or cardiac radiofrequency ablation within 6 months before screening.

(3) Severe left-sided cardiac dysfunction

Left-ventricular ejection fraction ≤ 40 %.

New York Heart Association class III or IV heart failure.

(4) Clinically significant conduction disease

Sick-sinus syndrome without a permanent pacemaker.

Second-degree type II or higher atrioventricular block, or bifascicular block.

Diagnosed systemic or metabolic condition that could lead to severe bradycardia or conduction abnormalities, such as cardiac sarcoidosis or untreated severe hypothyroidism.

(5) Recent antiarrhythmic therapy

Amiodarone within 4 weeks before screening.

Any other antiarrhythmic agent—including herbal preparations with antiarrhythmic properties—within 2 week before screening.

(6) Other serious cardiac conditions

Unstable angina, severe congenital heart disease (except patent foramen ovale), prior prosthetic heart-valve replacement, acute myocarditis or endocarditis, rheumatic

valvular disease, hypertrophic cardiomyopathy, congenital long QT syndrome, congenital short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia..

(7) Limited life expectancy

Any comorbid condition with an anticipated survival of < 1 year.

(8) Hepatic impairment

Active hepatitis or clinically significant liver dysfunction (ALT or AST > 3 × ULN, or total bilirubin > 3 × ULN).

(9) Renal impairment

Estimated glomerular filtration rate < 40 mL · min^{-1} · 1.73 m^{-2} (CKD-EPI formula).

(10) Concurrent investigational therapy

Use of any investigational drug or device within 1 month—or five elimination half-lives, whichever is longer—before screening.

(11) Pregnancy or lactation

Pregnant or breastfeeding women, or a positive serum pregnancy test before randomization.

(12) Metabolic, surgical, or pulmonary instability

The presence of atrial premature beats due to potential reversible causes, such as hyperthyroidism, cardiovascular surgery, electrolyte imbalances, etc. APBs decrease and symptoms significantly improve after the removal of triggers (e.g., alcohol abuse, acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with respiratory failure, or unresolved infections).

(13) Neurologic or psychiatric disorders

History of epilepsy, seizures, or psychiatric illness that could interfere with study participation.

(14) Drug hypersensitivity

Known allergy to memantine hydrochloride or any excipient of the study drug.

(15) Current memantine therapy

Ongoing treatment with memantine for moderate-to-severe Alzheimer’s disease.

(16) Other contraindications

Any condition that, in the investigator's judgment, makes the participant unsuitable for enrollment in the study.

4.3 Withdrawal Criteria

4.3.1 Participant-Initiated Withdrawal

Participants have the right to withdraw from the study at any time, as outlined in the informed consent form. This includes situations where a participant withdraws consent, discontinues the study medication or related assessments, or is lost to follow-up (which is also considered a withdrawal or dropout). The reasons for withdrawal should be documented whenever possible. Participants may choose to withdraw for various reasons, including but not limited to lack of efficacy, adverse events, or for no specific reason.

4.3.2 Investigator-Initiated Withdrawal

If a participant who has been enrolled in the study experiences any of the following conditions during the study, the investigator will decide whether the participant should be withdrawn from the study:

(1) The investigator determines, from an ethical standpoint, that it is necessary to withdraw the participant.

(2) The participant demonstrates poor adherence (e.g., failing to follow the study protocol for medication use or missing more than half of scheduled follow-up visits).

(3) The participant is unable to tolerate symptoms related to atrial premature beats.

(4) The participant experiences allergic reactions, neuropsychiatric symptoms, or other serious adverse events, and the investigator deems withdrawal necessary.

(5) The participant experiences an emergency requiring treatment that is not part of the study protocol.

In the event of withdrawal due to the reasons mentioned above, the study assessments or telephone follow-ups will continue.

4.4 Procedures for Early Withdrawal

For participants who withdraw early from the study, if the participant is unwilling to continue participating but agrees to follow-up for safety monitoring, relevant exit visits

should be conducted. Every effort should be made to collect pertinent information, including the withdrawal date, reason for withdrawal, and any other relevant details.

(1) If a participant voluntarily requests to withdraw from the study, the reason for discontinuing the study medication should be inquired about, along with any adverse events that may have occurred. If adverse events are reported, the investigator should identify and document the adverse event data, record it in the CRF, and conduct follow-up on the adverse event.

(2) Every effort should be made to capture all available data from participants who discontinue, with special attention to potential endpoint events. Complete loss to follow-up threatens data integrity and should be avoided whenever possible.

(3) Participants who discontinue the study should continue to be followed at scheduled visit time points whenever possible, and data should be collected in accordance with the study protocol. If a participant declines in-person visits and assessments but agrees to modified follow-up by telephone, telephone follow-up should be conducted until the end of the study. If the participant declines all forms of follow-up, he or she will be formally withdrawn from the study, and this should be documented in the electronic case report form (eCRF).

(4) Study medication must be retrieved from all participants who discontinue the study, and proper documentation of the return must be maintained.

5. Investigational Products

5.1 Product Characteristics

Table 1 Investigational Product Information

Parameter	Memantine Hydrochloride (Active)	Placebo
Dosage form	Film-coated tablet	Film-coated tablet
Strength	10 mg per tablet	Not applicable
Route of administration	Oral	Oral

Parameter	Memantine Hydrochloride (Active)	Placebo
Storage conditions	Sealed container, 10–30 °C	Sealed container, 10–30 °C
Shelf life	48 months	48 months
Manufacturer	Lundbeck A/S, (Denmark)	Qilu Pharmaceutical Co., Ltd., (China)

The placebo tablets are indistinguishable from the active tablets in appearance, weight, taste, packaging, and dosing schedule but contain no memantine hydrochloride.

5.2 Dosing Regimen

Beginning on Day 1, participants in both the memantine and placebo groups will receive one-half tablet (5 mg) twice daily for 7 days. From Week 2 onward, the dose will be increased to one tablet (10 mg) twice daily and continued through the end of Week 6. The complete dosing schedule is summarized in Table 1.

Participants assigned to either memantine or matching placebo will follow a two-step, twice-daily schedule:

Table2 Dosing Regimen

Study Week	Dose per administration	Total daily dose	Administration details*
Week 1	½ tablet (5 mg)	10 mg	Orally, at consistent morning and evening times (recommended interval, 12 h ± 2 h)
Weeks 2 – 6	1 tablet (10 mg)	20 mg	Orally, at consistent morning and evening times (recommended interval, 12 h ± 2 h)

* Each active tablet contains 10 mg memantine. Placebo tablets are identical in appearance, weight, packaging, and schedule but contain no active ingredient. The planned treatment duration is 42–45 days.

5.3 Supply, Packaging and Labeling of Investigational Product

Sufficient quantities of investigational product will be supplied to each study site for the full duration of the trial. All products will be packaged and labelled in compliance with applicable regulatory requirements.

The memantine and matching placebo will be packaged identically. Each outer carton will display the statement **"For Clinical Trial Use Only"** together with the product name, kit number, batch number, expiration date, storage conditions, and sponsor name.

Cartons and labels will be identical except for the unique kit number assigned to each package.

5.4 Investigational Product Accountability

Designated pharmacy personnel at each study site are responsible for the receipt, storage, dispensing, and reconciliation of all investigational product (IP). Complete, contemporaneous documentation must be maintained throughout the trial.

Table 3 Study Drug Handling and Accountability

Process	Requirements
Receipt	Upon delivery, the site pharmacist (or authorized designee) verifies the shipment against the packing list, completes and signs the drug-receipt form, and documents the date of receipt.
Storage	IP must be stored in a locked, access-controlled cabinet under the temperature conditions specified on the label (10 – 30 °C). Storage and handling procedures must comply with all applicable regulations.
Dispensing	IP is dispensed according to each participant's randomization number and corresponding kit number, as assigned by the IRT system.
Reconciliation	For every kit, the following details must be entered promptly and indelibly in the drug-accountability log: date dispensed, quantity issued, kit number, participant randomization number, return of empty packaging, and quantity of unused tablets returned or destroyed.
Inspection	All IP accountability records are subject to review by study monitors, auditors, and regulatory inspectors.

Any discrepancies must be documented, investigated, and resolved in accordance with the sponsor's standard operating procedures.

5.5 Return and Destruction of Investigational Product

At study close-out, all unused, partially used, and empty investigational-product containers—together with their original packaging—must be returned to the sponsor for authorized destruction. Each shipment shall be accompanied by a fully completed, dated, and signed Drug-Accountability/Return Form.

The outer shipping carton must be clearly labelled with the protocol number, study-site identifier, and the statement **"Clinical Trial Material – Return for Destruction."**

5.6 Concomitant Medications

From the signing of informed consent until the final study visit, any pharmacotherapy given for comorbid conditions or to treat adverse events must be documented in full. Required details include the medication name, indication, dose, dosing frequency, start and stop dates/times, and route of administration.

5.7 Prohibited Medications

The following medications are prohibited throughout the study period:

(1) NMDA antagonists, including amantadine, ketamine, dextromethorphan, and others.

(2) Levodopa, dopamine receptor agonists, anticholinergic agents, and barbiturates.

(3) Antiarrhythmic drugs.

(4) Antispasmodic agents, including dantrolene, baclofen, and others.

(5) Other medications that, in the investigator's judgment, may interfere with the efficacy or safety assessments.

6. Study Procedures and Visit Schedule

The trial is divided into three phases: a screening period (Visit 1, V1), a treatment period (Visits 2– 4, V2–V4), and a follow-up visit (Visit 5, V5). Participants will attend all visits as outlined in the protocol. Any AE occurring during the study will be followed until the event resolves, stabilities, or the participant is lost to follow-up.

An overview of scheduled activities is provided in the study-flow diagram, and detailed requirements for each assessment are listed in Table 2. For participant safety, the investigator may increase the frequency of scheduled assessments or add unscheduled assessments not specified in the flow diagram whenever clinically warranted (e.g., in response to an AE).

6.1 Study Flow Diagram

	Screening period [1] (≤ 7d)	**treatment period**			**follow-up period**	**early withdrawal Visits [2]**	**Symptom initiation additional visit**
manipulate	**V1**	**V2**	**V3**	**V4**	**V5**		
		D7±2d	D28±3d	D42±3d	D56±3d	Day of exit +7d	
Signed informed consent	☑						
Symptom assessment [3]	☑	☑	☑	☑	☑	☑	☑
Inclusion/exclusion criteria	☑						
Demographic information	☑						
Basic information [4]	☑						
Prior and co-morbidities, smoking and drinking, history of allergies[5]	☑						
History of prior non-drug treatment, prior drug therapies [6]	☑						
Vital signs [7]	☑	☑	☑	☑	☑	☑	☑
NYHA Cardiac Function Classification	☑			☑		☑	

Cardiac ultrasound	☑			☑		☑	
Hematology tests [8]	☑			☑		☑	
Urine PH	☑			☑		☑	
Blood or urine HCG[9]	☑				☑	☑	
12-lead ECG	☑		☑	☑	☑	☑	
3-day cardiac patch monitoring [10]	☑		☑	☑	☑	☑	
Randomization	☑(D0)						
Issuance and collection of diary cards	☑(Issuance only)		☑	☑	☑	☑(Collection)	
Return of experimental drugs					☑	☑(If applicable)	
Adjustment of medication		☑	☑	☑			
AEs and co-medication	☑	☑	☑	☑	☑	☑	☑
SF-36 Health Questionnaire Scores	☑			☑		☑	

Table 4 Study Flow Diagram

Notes:

1. The screening period examination of this study can accept the relevant examination results of our center within 1 month prior to the informed date (acceptable at the judgment of the investigator, otherwise the relevant examination is required).

2. If a subject withdraws from the study after completing the end - of - treatment visit (V4), for the relevant examinations related to early withdrawal (excluding the 3 - day ECG patch monitoring), if the time interval from the V4 visit is ≤ 7 days or the investigator determines that repetition is unnecessary, these examinations do not need to be repeated. However, the reason for not conducting

the examinations should be described in the original case report. Pregnancy tests should be carried out as required. If a subject withdraws before V4, regardless of whether the V3 visit has been completed, all relevant procedures for early withdrawal must be performed.

3. Symptom assessment: the assessment includes the nature of the PACs symptoms, the frequency and duration of the episodes, and whether the nature of the symptoms has changed.

Nature of symptoms: Palpitations, a fluttering or pounding sensation in the heart, a sense of the heart skipping beats, fatigue, weakness, shortness of breath, discomfort in the chest or precordial area, dizziness, etc.

Frequency of episodes: daily, weekly, monthly, etc;

Duration: minutes, hours, sustained;

Symptom scores:

Score 0: No symptoms;

Score 1: Mild symptoms, occasional palpitations that do not affect daily life;

Score 2: Moderate symptoms, frequent palpitations, mildly interfering with daily life;

Score 3: Severe symptoms with persistent palpitations that significantly interfere with daily life;

4. Basic information including height, weight, waist circumference, education level, etc;

5. Past medical history: hemorrhagic/ischemic stroke, transient ischemic attack, myocardial infarction, history of epilepsy or seizures, and psychiatric disorders;

6. History of prior medications: medication use within 4 weeks prior to screening; history of non-drug therapy (including surgery): history of non- drug therapy within 6 months prior to screening; collection of a full history of prior cardiac-related surgery;

7. Vital signs include temperature, blood pressure, pulse, and respiration;

8, Including routine blood, liver function (alanine aminotransferase, glutamic aminotransferase, gamma glutamyl transpeptidase, total bilirubin, direct bilirubin, indirect bilirubin), thyroid function (fT3, fT4, TSH), renal function (creatinine, urea nitrogen or urea, glomerular filtration rate), electrolytes (blood sodium, potassium, magnesium, calcium), blood lipids (total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol ester), fasting blood glucose, glycated hemoglobin, NT-pro BNP or BNP.

9. Female subjects of childbearing age should undergo blood or urine HCG test to exclude pregnancy.

10. The duration of drug administration in this study was 42-45 days, and the start time of 3-day (72h) ECG recorder monitoring for V3~V5 visits was D25~D28 for V3, D39~D42 for V4, and D53~D56 for V5, respectively. ECG monitoring for the V4 visit should be started 3 days prior to the end of the drug administration, and the 3 consecutive days (72h) of ECG recorder monitoring should be performed at D39, if the administration of drug was ended at D42. recorder monitoring needs to be performed at D39. If 3 consecutive days (72h) of ECG monitoring is performed at D42, the drug must be administered until D45; other operations for V3~V5 visits are performed after completing the 3-day ECG recorder monitoring.

Table 5 Specific requirements for each inspection item

Inspection item	**Requirements and observables**
vital signs	Temperature, blood pressure, pulse, respiration.
12-lead ECG	Heart rate, P-R interval, QRS wave duration, Q-Tc interval (calculated by Bazett's formula), presence of AFL, presence of AF, presence of atrioventricular block
Blood or urine pregnancy	Blood/urine human chorionic gonadotropin, fertile women only. For infertile women, please note the reason, e.g. menopause ≥ 1 year, hysterectomy, sterilization, etc.
Laboratory tests	➢ Routine blood count: white blood cell count, neutrophil ratio and count, lymphocyte ratio and count, red blood cell count, hemoglobin amount, red blood cell pressure volume, platelet count ➢ Liver function: alanine aminotransferase, glutamine aminotransferase, gamma glutamyl transpeptidase, total bilirubin, direct bilirubin, indirect bilirubin. ➢ Thyroid function: fT3, fT4, TSH; ➢ Renal function: creatinine, urea nitrogen or urea, glomerular filtration rate; ➢ Electrolytes: blood sodium, blood potassium, blood magnesium, blood calcium ➢ Lipids: total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol esters ➢ Fasting glucose, glycosylated hemoglobin, NT-pro BNP or BNP ➢ Urine PH
Ambulatory electrocardiograph monitoring	➢ 24-hour average number and load of PACs, 24-hour average number and load of bouts of NSAT, 24-hour average episodes count of NSAT, SAT, AF, AFL ➢ Monitoring start time and end time, monitoring duration
Cardiac ultrasound	➢ Left atrial internal diameter (mm), septal thickness (mm), left ventricular end-systolic internal diameter (mm), left ventricular end-diastolic internal diameter (mm), left ventricular ejection fraction (LVEF %)

Inspection item	Requirements and observables
NYHA Cardiac Function Classification	➢ Class I, II, III, IV

6.2 Study Procedure

6.2.1 Screening Period (Visit 1)

Informed consent. Written informed consent must be obtained before any study-specific procedure performed.

Medical interview and data collection.

Demographics: age, sex, height, weight, waist circumference, race/ethnicity, and highest educational level.

Medical history: past and current illnesses (within 6 months before screening), allergy history, smoking and alcohol use, prior non-drug cardiac interventions (e.g., percutaneous coronary intervention, coronary-artery bypass grafting, catheter ablation), participation in clinical trials, concomitant medications, and prior surgeries.

Physical examination.

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

NYHA functional class.

Laboratory and diagnostic tests.

Complete blood count.

Urine pH.

Serum or urine human chorionic-gonadotropin (hCG) test, as appropriate.

Standard 12-lead ECG.

Health-related quality-of-life assessment using the SF-36 questionnaire.

Baseline ambulatory ECG.

Candidates who meet the above criteria undergo 72-hour continuous patch-based ECG monitoring to quantify PACs and confirm eligibility. Randomization is based on these data.

Randomization and study materials.

Eligible participants are randomized, then provided with study medications and diaries.

Ambulatory ECG data points.

The 72-hour recording captures:

24-hour mean PAC count and burden.

24-hour mean number and burden of NSAT episodes.

Episodes of SAT, AF, and AFL.

Incidence of new-onset SAT, AF, or AFL during any 72-hour recording window.

Any AE identified during screening is followed until it resolves, stabilizes, or the participant is lost to follow-up.

6.2.2 Treatment Phase

Day 1 (D1) marks the initiation of study drug administration. Participants will self-administer the investigational product per the dosing regimen described in Section 6.2 and will attend all protocol-specified visits.

The treatment phase consists of three scheduled visits:

- **Visit 2 (Day 7 ± 2 days; telephone)** — Evaluate treatment adherence, review AEs, and document concomitant medications.
- **Visit 3 (Day 28 ± 3 days; on-site)** — Conduct a clinical assessment and initiate 72-hour continuous patch-based ambulatory ECG monitoring.
- **Visit 4 (Day 42 ± 3 days; on-site; end of treatment)** — Perform a clinical assessment and repeat 72-hour ambulatory ECG monitoring.

All procedures will be conducted in strict accordance with the protocol to ensure consistent safety and efficacy assessments.

6.2.3 Follow-up Phase

A single post-treatment follow-up visit will be conducted on Day 56 ± 3 days. All evaluations will be performed in accordance with the study-flow schedule.

7. Statistical Analysis

7.1 Sample-Size Determination

In our preliminary exploratory single-arm study, memantine produced a 75.4 % mean reduction in 24-hour PAC burden. Considering the robustness of results from the small-sample trial and potential sampling error, the present trial conservatively assumes a 50 % reduction in the memantine group and a 30 % reduction in the placebo group, with a common standard deviation of 35 %. Factoring in a 15 % dropout rate, a one-sided α level of 0.025, and a 1:1 randomization ratio, a sample-size calculation performed with

EAST software (version 6.5) indicates that 256 participants (128 per group) will provide >95 % statistical power to detect the prespecified between-group difference.

7.2 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.

7.3 Analysis Plan

7.3.1 Statistical Hypothesis

The primary efficacy endpoint is the percentage change from baseline to Week 6 in the 24-hour mean count of PACs.

- **Null hypothesis (H_0):** The mean percentage reduction in the memantine group is ≤ the mean percentage reduction in the placebo group.
- **Alternative hypothesis (H_1):** The mean percentage reduction in the memantine group is > the mean percentage reduction in the placebo group.

These hypotheses will be tested at a two-sided α of 0.05.

A one-sided p-value of less than 0.025 indicates that the null hypothesis can be rejected, suggesting that the treatment group is superior to the placebo group.

7.3.2 General principles

- **Continuous variables** will be summarized by the number of observations (n), mean, standard deviation, median, minimum, and maximum values.

- **Categorical variables** will be summarized by the number of observations (n) and corresponding percentage. Unless otherwise specified, all percentages will use the relevant analysis-population denominator.

Comprehensive statistical methods are detailed in the Statistical Analysis Plan (SAP), which will be finalized before database lock. This protocol provides only an overview of the planned analyses; in the event of any discrepancy, the SAP will take precedence.

7.3.3 Study Disposition and Participant Flow

The number and percentage of participants who were screened, experienced screen failure, were randomized, received at least one dose of study medication, and completed the trial will be summarized. Principal reasons for treatment discontinuation and/or study withdrawal will be tabulated according to the categories recorded in the electronic case-report form (eCRF). Final counts for each analysis population will also be provided.

7.3.4 Demographics and Baseline Characteristics

Demographic and baseline variables will be summarized descriptively for each treatment group. Key parameters will include (but are not limited to) age, sex, race/ethnicity, body-mass index, relevant medical history, and previous therapies. All summaries will be performed on the FAS.

7.3.5 Medication Adherence

(1) Study-drug exposure and adherence will be described for each treatment group using descriptive statistics.

(2) Concomitant medications will be tabulated and analyzed as appropriate.

7.3.6 Efficacy Analyses

All efficacy evaluations will be conducted on the FAS.

- **Primary endpoint** — The between-group difference in the percentage change from baseline to Week 6 in 24-hour premature atrial contraction (PAC) burden will be estimated, and the mean difference will be presented with its two-sided 95 % confidence interval.
- **Secondary endpoints**—Descriptive statistics will be applied to the secondary efficacy endpoints.

7.3.7 Safety Analysis

7.3.7.1 Adverse-Event Analyses

All AEs will be coded using the MedDRA and classified by SOC and PT. The analysis will focus on treatment-emergent adverse events (TEAEs)—events that first occur or worsen after the initial dose of study drug. Unless otherwise specified, AE denotes TEAEs throughout this section.

- Overall incidence — For each treatment group, the number of participants (n) and proportion (%) with any TEAE, SAE, or AE leading to death will be summarized.
- Incidence by SOC and PT — TEAEs, SAEs, and fatal events will also be tabulated by SOC and PT, with counts and percentages reported for each group.

7.3.7.2 Other Safety Assessments

Additional safety parameters—such as clinical laboratory results, vital signs, and 12-lead ECG findings—will be summarized descriptively.

7.3.8 Mid-term Analysis

This study plans to conduct a sample size re-estimation in an unblinded manner after approximately 128 participants (50%) have completed the primary endpoint evaluation. The table below presents the superiority boundaries for the primary endpoint.

Table 6 Interim analysis

Analysis	Event Information Ratio	α = 0.025
Interim Analysis	50% (approximately 128 subjects)	Superiority Boundary: z = 2.963
Final Analysis	100% (256 subjects)	Superiority Boundary: z = 1.969

Note: The superiority boundaries were calculated using the Lan-Demets approximation of the O'Brien-Fleming boundaries with a spending function. These boundaries 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 results of the two groups falls between 40% and 90% at the time of the interim analysis, a sample size adjustment will be made.

The interim analysis will be conducted by an independent analysis team, with the results

reviewed by an independent Data Monitoring Committee (IDMC), which will provide corresponding recommendations. The decision rules are shown in the figure below:

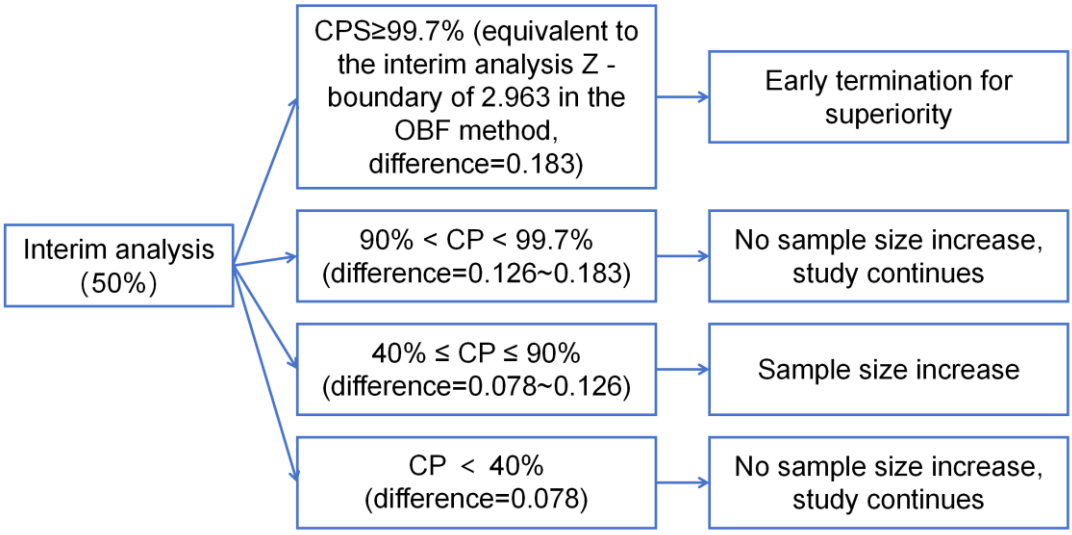


Figure 2 Interim analysis for sample size re-estimation

Note: Conditional power (CP) is calculated based on the efficacy observed at the time of the interim analysis. The calculation of the difference is based on a standard deviation of 0.35; different standard deviations will yield different values for the difference.

7.3.9 Multiplicity Adjustment

The Lan-Demets spending function with the O' Brien-Fleming approximation, in combination with the CHW method, will be used to strictly control the one-sided Type I error rate at $\alpha = 0.025$.

7.3.10 Handling of Missing Data

In the event that data on the number of premature beats at Week 6 is missing, LOCF will be applied. If required, sensitivity analyses will be provided in the SAP.

Missing values for other secondary and safety endpoints will not be imputed.

8. Safety Evaluation

8.1 Definitions

8.1.1 AEs

An AE is any untoward medical occurrence in a participant who has received the investigational product. Manifestations may include clinical signs or symptoms, new

illnesses, or clinically significant laboratory abnormalities, irrespective of an established causal relationship with the study drug.

Because pre-dose safety information provides essential context for interpreting on-treatment findings, AE recording begins at the signing of the informed-consent form. These data establish the participant's baseline status and assist in determining whether subsequent events are study related.

TEAE is an AE that first appears—or an existing event that worsens in severity—after the initial dose of study medication. Unless otherwise noted, the term *AE* in this protocol refers to TEAEs.

8.1.2 Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence that, after administration of the investigational product, satisfies one or more of the following criteria:

(1) Results in death

Death is an outcome and should not be used as the event term.

If the death is sudden and the cause is initially unclear, report the event as "sudden unexplained death." Continue follow-up until the cause is established; once confirmed, update the SAE term to reflect the specific cause of death.

(5) **Is life- threatening**

The participant was, at the time of the event, at immediate risk of death; events that could have become life-threatening if they had progressed are not included.

(3) Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalization (or extension of an existing stay) is not classified as an SAE if it meets any of the following conditions:

Inpatient stay < 12 hours.

Admission planned before the first study dose (e.g., elective surgery or a protocol-mandated procedure).

Admission unrelated to an AE (e.g., social or respite care).

Elective admission for treatment of a pre-existing condition that has not worsened relative to baseline.

Note: Any SAE that otherwise meets serious criteria and occurs during such a hospital stay must still be reported.

(4) Results in persistent or significant disability/incapacity

A substantial disruption in a participant's ability to conduct normal daily activities.

(5) Results in a congenital anomaly or birth defect

(6) Other medically important events

Events that may not immediately result in death, be life-threatening, or require hospitalization but, in the investigator's judgment, could jeopardise the participant or require medical or surgical intervention to prevent one of the outcomes listed above. Examples include emergency treatment for severe bronchospasm, seizures managed outside the hospital, clinically significant cachexia, or the development of drug dependence or addiction.

8.2 AE Assessment

All AEs will be assessed and documented by the investigator according to the categories outlined below.

8.2.1 Seriousness

Each AE will be evaluated for seriousness in accordance with the protocol definition of a SAE.

8.2.2 Severity Grading

AEs will be classified as *mild, moderate,* or *severe*:

- Mild events are transient or easily tolerated, do not interfere with daily activities, and require no treatment or only minimal intervention.
- Moderate events interfere to some extent with daily activities, may partially impair normal function, and generally warrant medical intervention.
- Severe events prevent normal daily activities, entail marked functional impairment, and require systemic therapy or other intensive treatment; they may be life-threatening or disabling.

Severity describes the intensity of an event and is distinct from its *seriousness*; the two attributes are assessed independently.

8.2.3 Causality

The investigator is responsible for assessing the causality between each AE recorded in the eCRF and the investigational product. This evaluation will be based on all available information at the time of completing the eCRF and is a clinical judgement.

The causality will be classified into one of five categories based on the plausibility of a relationship between the AE and the investigational product: *related, very likely related, possibly related, possibly unrelated,* and *unrelated*. Events classified as *related, very likely related,* or *possibly related* will be considered to have a potential or cannot be excluded as related to the study treatment, and will be classified as *related*. Events categorized as *possibly unrelated* or *unrelated* will be classified as *unrelated*.

When assessing the causal relationship between an AE and the study treatment, the following factors should be considered:

Related: There is a reasonable temporal relationship; the event aligns with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; the event is positively dechallenged; no other reasonable explanation exists for the event; and the event is positively rechallenged.

Very Likely Related: There is a reasonable temporal relationship; the event aligns with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; the event is positively dechallenged; no other reasonable explanation exists for the event; and there is no evidence of positive rechallenge.

Possibly Related: There is a reasonable temporal relationship; there is no evidence of positive rechallenge; and the event falls into one of the following categories:

(1) The event is consistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; the event is positively dechallenged, but other plausible explanations exist.
(2) The event is consistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; there is no evidence of positive dechallenge, and no other plausible explanations exist.

(3) The event is not consistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; the event is positively dechallenged, and no other plausible explanations exist.

(4) The event is not consistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; the event is positively dechallenged, but other plausible explanations exist.

(5) The event is not consistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; there is no evidence of positive dechallenge, and no other plausible explanations exist.

Possibly Unrelated: There is a reasonable temporal relationship; no evidence of positive dechallenge or positive rechallenge; and the event falls into one of the following categories:

(1) The event is inconsistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product, and other reasonable explanations exist.

(2) The event is consistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product, but other more plausible explanations exist.

Unrelated: From a medical perspective, there is no reasonable temporal relationship; the event is inconsistent with the known pharmacological mechanism, characteristics, or known adverse effects of the investigational product; there is no evidence of positive dechallenge or positive rechallenge; and other reasonable explanations exist.

8.2.4 Measures taken with Regard to Study Treatment

Any actions taken regarding the study treatment following an AE should be recorded according to the following classification criteria:

No Change

Permanent Discontinuation

Not Applicable

Unknown

8.2.5 Measures Taken for Adverse Events

During the study, any specific treatments administered for AEs will be recorded according to the following categories:

- **None**
- **Pharmacological treatment**
- **Other therapeutic interventions**

8.2.6 Outcome

The outcome of each AE will be recorded using the following categories:

- **Recovered/Resolved**
- **Improved**
- **Recovered/Resolved with sequelae**
- **No Improvement**
- **Death**
- **Unknown**

8.3 AE Reporting

All clinically significant abnormalities occurring from the time the participant signs the informed consent form through to the final visit (or withdrawal visit) must be fully documented in the participant's eCRF. This includes abnormalities observed by the investigator, reported by the participant, or identified through clinical symptoms, laboratory abnormalities, or other clinically relevant findings. Abnormalities that occur during the screening period up until the administration of the study drug should be recorded as part of the participant’s medical history. Abnormalities occurring after the administration of the study drug, up to the final visit, will be recorded as AEs. If a clinically significant abnormality is present at baseline and does not worsen during the study, it should not be recorded as an AE.

The investigator is responsible for the ongoing monitoring of all AEs until they resolve, return to baseline, stabilize, or no further information can be obtained. The outcome of each AE should be documented in the participant's source records.

After the AE reporting period, only SAEs that are suspected to be related to the study treatment should be reported, and these should be followed up accordingly.

AEs should be recorded using appropriate medical terminology, with a preference for a definitive medical diagnosis. If a definitive diagnosis is not available, symptoms or signs should be used. Once a definitive diagnosis is made, the AE record should be updated to reflect the diagnosis in place of the symptoms or signs. Each AE should be documented as a single event; a diagnosis, sign, or symptom must be recorded as an individual AE. Terms such as hospitalization, surgery, and death are not considered AEs by themselves, but the underlying cause leading to these outcomes should be documented as an AE.

The investigator is responsible for grading the severity of all AEs according to the predefined categories. Additionally, the investigator should assess the seriousness and causality of each event. For SAEs, the SAE-specific fields in the eCRF must be completed.

For each AE, the following details should be recorded: the date of onset and resolution, severity, causal relationship with the study drug, possible alternative explanations (e.g., comorbidities or concomitant medications), actions taken with regard to the study treatment, any treatment administered for the AE, and the final outcome.

In cases of death, the cause of death should be recorded as the AE term. The term "death" should not be used as the AE term itself. The cause of death should be documented as the AE outcome. If the cause of death is initially unknown, it should be reported as "cause of death unknown" and monitored until the cause is determined. Once the cause of death is clarified, the SAE term should be updated to reflect the specific cause of death.

The investigator must independently assess all SAEs, evaluating their expectedness, severity, and the causal relationship with the investigational product.

8.4 Observation and Management of Special Adverse Events

(1) In clinical trials, investigators must closely monitor participants for any AEs or SAEs that occur following the administration of the investigational product, to ensure prompt identification and management.

(2) For participants experiencing common adverse reactions associated with the investigational product, the investigator must immediately report the event to the Principal Investigator (PI). Based on the severity of the event, the investigator will determine the necessary diagnostic and therapeutic measures, and decide whether discontinuation of the trial is required. All AEs must be followed up, with detailed records of the actions taken and outcomes. Follow-up should continue until the event is resolved or the participant's condition stabilizes. If laboratory abnormalities occur, monitoring should continue until the values return to normal. The method of follow-up (e.g., inpatient, outpatient, home visit, telephone, or written communication) should be chosen based on the severity of the AE.

(3) For serious adverse events, the investigator should immediately provide emergency treatment according to standard operating procedures (SOP) and document the actions taken. A consultation with the relevant medical specialists should be requested. In urgent situations, the participant should be transferred to the ICU with medical staff accompaniment. The PI at the study site must be notified immediately, and the sponsor should be informed without delay.

(4) After any serious adverse event in a clinical trial, the investigator is required to report the SAE to the sponsor and the ethics committee immediately, and no later than 24 hours after becoming aware of the event. Relevant reports and information will be compiled in the investigator’s file and updated as necessary.

In the case of death, the investigator must provide the sponsor and the ethics committee with all necessary documentation, such as the autopsy report and final medical report.

The investigator must continue to follow up on all SAEs. Any new information obtained after the initial report should be submitted in a follow-up SAE report, which should be submitted in the same format and within the same timeframe as the initial report.

(5) If an SAE is determined to be related to the study, any medical or living expenses incurred, as well as compensation for damages, will be covered by clinical trial insurance purchased by the sponsor, in accordance with applicable regulations.

(6) Management of Potential Adverse Events in This Study

1) Psychiatric Symptoms:

Symptoms such as delirium, hallucinations, anxiety, depression, and agitation may arise after randomization. If any of these symptoms occur during the study, a consultation with a specialist should be conducted. If necessary, further evaluations, including electroencephalogram (EEG), self-assessment symptom questionnaires (e.g., SCL-90), and cranial MRI, should be performed. For mild symptoms, the study medication may be withheld for observation; for moderate to severe symptoms, hospitalization for specialist care is required. Regardless of symptom severity, all participants will complete the SCL-90 questionnaire at the end of the treatment period. If any abnormalities are detected, further EEG, cranial MRI, and appropriate medical interventions should be carried out.

2) Seizures:

If a participant, with no prior history of epilepsy, experiences a seizure after study initiation, and EEG confirms the event, other potential causes unrelated to the study drug, such as trauma, stroke, or intracranial hemorrhage, must be excluded. If the event is deemed related to the investigational treatment, a neurologist's consultation is required. For mild cases, the study medication should be discontinued, and the participant monitored, with a follow-up EEG after one month. For moderate to severe cases, the study drug should be discontinued, and the participant should be hospitalized for further evaluation and treatment. Post-discharge, the participant should undergo close follow-up.

3) New or Worsening Heart Failure:

If a participant develops new symptoms or signs of heart failure, or if pre-existing symptoms worsen, and they meet the criteria outlined in the table below, the investigator must promptly document these symptoms and assess the possibility of new or worsening heart failure. NT-pro BNP or BNP levels should be measured, and chest X-ray or lung ultrasound and echocardiography should be performed. If NT-pro BNP ≥ 300 ng/L or BNP ≥ 100 ng/L, with X-ray or lung ultrasound indicating pulmonary congestion, and echocardiography showing cardiac structural or functional abnormalities, the event should be classified as new or worsening heart failure. The cause of heart failure should be investigated: if related to the underlying disease, continue treatment; if related to memantine, for mild heart failure, discontinue the medication and prescribe anti-heart failure medications in an outpatient setting; for moderate to severe heart failure, hospitalization is required.

Table 7 Clinical manifestations of acute heart failure

Left Heart Failure Symptoms	**Left Heart Failure Signs**
exertional dyspnea	Wet rales in the lungs
Nocturnal paroxysmal dyspnea	Widened apical beat range
Resting dyspnea or sit-up breathing	Pathologic 3rd heart sound (gallop rhythm)
Coughing at night or lying down	
Decreased exercise tolerance	
Right Heart Failure Symptoms	**Right Heart Failure Signs**
Loss of appetite (poor appetite), abdominal bloating, nausea	Elevated jugular venous pressure (engorged or raging external jugular veins)
	Positive hepatic jugular venous reflux sign
	Peripheral edema (lower extremities or low hanging body parts)
	Pleural effusion, abdominal effusion and other plasma cavities

4) Bradycardia:

If a participant's daytime or ambulatory ECG shows an average heart rate of <50 bpm,

or even <40 bpm, with or without symptoms such as dizziness, fatigue, weakness, poor concentration, syncope, chest tightness, palpitations, or shortness of breath, the following management steps should be taken:

If the heart rate is <50 bpm, discontinue the study drug and monitor.

If the heart rate is 40–50 bpm and associated with symptoms, hospitalization and management are required.

If asymptomatic, discontinue the drug and closely monitor, with daily reporting of heart rate and symptoms.

If the heart rate is <40 bpm, hospitalization is required for further management.

9. Ethical Principles and Requirements for Clinical Research

This clinical study will be conducted in accordance with the Declaration of Helsinki as adopted by the World Medical Association, as well as the Ethical Review Procedures for Biomedical Research Involving Human Participants issued by the National Health and Family Planning Commission of the People's Republic of China, and other relevant regulations. The study will adhere to principles related to informed consent, privacy protection, compensation and reimbursement for participation, risk management, protection of vulnerable populations, and compensation for research-related harm.

Prior to the initiation of the study, approval must be obtained from the Ethics Committee of Shanghai East Hospital. Before enrolling in the study, each participant will be thoroughly informed by the investigator about the study’s objectives, procedures, and potential risks. Written informed consent will be obtained from the participant and/or their legal representative. Participants will be informed that their participation in the study is entirely voluntary, and they have the right to refuse participation or withdraw from the study at any point without facing discrimination or retaliation. Their medical treatment and rights will not be affected by their decision to participate or withdraw.

The informed consent document will be retained as part of the clinical study records and will be available for review. The privacy and confidentiality of participant data will be rigorously protected throughout the study.

9.1 Ethical Standards

The investigator will ensure that this study is conducted in full compliance with Chinese legal requirements and internationally recognized principles for the protection of study participants.

Prior to the implementation of the study, the protocol must be reviewed and approved in writing by the hospital's Ethics Committee. The following documents must be provided to the Ethics Committee: the study protocol, any protocol amendments, the informed consent form, and other relevant documents such as recruitment advertisements. This clinical trial must adhere to the Declaration of Helsinki and applicable regulatory requirements. The study can only commence once approval has been granted by the Ethics Committee.

No changes to the study protocol may be made without the investigator’s consent. The investigator may modify the protocol only if necessary to eliminate immediate or direct harm to participants. Any such modifications must be made prior to approval by the Ethics Committee/Institutional Review Board (IRB). All modifications or deviations, along with their justifications, should be promptly submitted to the Ethics Committee/IRB for review. The investigator must provide explanations and document any protocol deviations.

During the course of the clinical trial, any amendments to the protocol must be submitted to the Ethics Committee for review. If necessary, other study documents should be updated accordingly and submitted for review and/or approval by the Ethics Committee. The investigators are responsible for submitting interim reports to the ethics committee as required, and must notify the ethics committee when the study has been completed.

9.2 Ethics Committee

The study protocol, informed consent form, recruitment materials, and all participant-related documents will be submitted to the Ethics Committee for review and approval. Participants may only be enrolled after the protocol and informed consent form have been approved. Any amendments to the protocol must be reviewed and approved by the Ethics Committee before implementation. Similarly, any revisions to the informed

consent form must also receive approval from the Ethics Committee. The Ethics Committee will determine whether participants who have already signed a previous version of the informed consent form need to sign the updated version.

9.3 Informed Consent

The informed consent form includes all elements required by applicable regulations and adheres to the ethical principles set forth in the Declaration of Helsinki. It provides a comprehensive description of the investigational product and study procedures, along with a clear explanation of the associated risks. Written informed consent must be obtained from the participant prior to the initiation of any study-related procedures.

The informed consent form also outlines that the participant's personal information will remain confidential, but that access to the participant’s data may be granted to the hospital, its authorized personnel, and regulatory authorities for monitoring and compliance purposes.

9.3.1 Informed Consent Process and Documentation

The informed consent process begins prior to a participant’s decision to join the clinical study and continues throughout the study. The risks and potential benefits of participation will be thoroughly explained to the participant. The participant will be asked to read and review the informed consent form, which has been approved by the Ethics Committee. The investigator will provide an explanation of the clinical study and address any questions the participant may have. Participants may only begin their participation after signing the informed consent form. Throughout the study, participants have the right to withdraw their consent at any time. Two copies of the informed consent form will be made: one for the participant and one for the study site.

9.3.2 Confidentiality of Participant Information

The confidentiality of participant information will be strictly maintained by the investigator, study staff, and their supervisors. This confidentiality extends not only to clinical data but also to biological samples and genetic testing results. All study documents, data, and information generated will be treated as confidential.

Without breaching confidentiality or violating applicable regulations, monitors, the Ethics Committee, and regulatory authorities may access the participant's original medical records to verify the study's conduct and data integrity.

Participant contact information will be securely stored at the study site and will be used solely for purposes related to the study. After the study is completed, all records will be securely archived for the duration required by the study site and regulatory guidelines.

10. Data Management and Quality Control

10.1 Data Management

This study will utilize an electronic data capture (EDC) system for data collection and management. The system has been thoroughly validated to ensure proper audit trail tracking and effective management of user accounts and permissions. System administrators will create user accounts for various roles, including Data Managers (DM), Investigators, Clinical Research Associates (CRA), and Clinical Research Coordinators (CRC), and assign appropriate access levels. The creation, modification, and deactivation of accounts will be strictly controlled.

Data management personnel will design the case report forms (CRFs) based on the study protocol, following CDISC standards. The CRFs will be used to develop data entry guidelines and validation rules. Database designers will configure the electronic case report forms (eCRFs) in the EDC system, implementing data validation checks. Data management personnel will conduct database testing, and the system will only be launched once it passes these tests. Before using the EDC system, all users must undergo sufficient training and be provided with the appropriate login credentials.

The investigator is responsible for collecting participant data in accordance with regulatory requirements and the study protocol. The investigator or CRC must enter the data into the EDC system following the eCRF completion guidelines, ensuring accuracy, completeness, and compliance with the protocol within the specified time frame. Once the data is saved, it may still be edited in the EDC system. The EDC system will automatically perform logical checks, and if the data meet the validation criteria, any discrepancies or queries will be triggered for review. The investigator or CRC will

review the data against the original source documents, address any queries, and either correct or confirm the data, providing necessary explanations. Data management personnel will review all modifications or responses to queries and may issue additional queries as needed, until all issues are resolved or clarified.

The CRA will ensure that all data entered into the EDC system are accurate and consistent with the source data (source documents). Data management personnel will manually review data to ensure integrity, consistency, and accuracy. Medical coders will review clinical data requiring coding, while medical personnel will perform necessary medical reviews of the clinical data. During source data verification and data review, these four roles may raise manual queries in the EDC system. The investigator or CRC will respond to these queries in the system, modifying data when necessary. If queries remain unresolved, reviewers may raise the queries again until all issues are addressed or clarified. All data modifications and query responses will be stored in the EDC system's audit trail.

Once all queries are resolved and data review confirms accuracy, the principal investigator will electronically sign all eCRFs in the EDC system, confirming the authenticity of the data. If any data are updated after signing, the updated eCRFs must be re-signed by the investigator.

After data cleaning is completed, a data review meeting will be held, attended by the principal investigator, medical personnel, statistical analysts, data management personnel, and project managers. The team will review the data, discuss and resolve any data issues, finalize the definition and classification of analysis populations, and approve the data management team to lock the database.

Once the database is locked, no further modifications should be made. If data errors are identified after database locking, the project team (including medical personnel, statistical analysts, data management staff, project managers, etc.) must assess the potential impact of these errors on the safety and efficacy analyses. A discussion will be held to determine how to handle these errors. Data errors will be documented in the statistical analysis report and clinical study report. If it is determined that modifications are needed after database locking, the project team members must sign the relevant

documents to unlock the database for data modification. After the data are modified and cleaned, the data management team will lock the database again. The final data will be exported by the data management team and provided to the statistical team for analysis. Upon completion of the study, the data management team will prepare a data management report and ensure the archiving of both paper and electronic documents. All data will be securely stored and backed up, and the EDC system will be deactivated (taken offline) by the EDC system administrator.

Unless local regulations or institutional policies require a longer retention period, the investigator must ensure that study-related records and documents (including signed informed consent forms) are retained for a minimum of 10 years following study completion. No records may be destroyed during the retention period without written approval from the sponsor. Records may not be transferred to other locations or to third parties without written notification from the principal investigator.

Before submission, all eCRFs must be electronically signed by the investigator. Any obvious errors or omissions in the data or forms must be clarified by directly contacting the medical center responsible for the data source for verification.

10.2 Monitoring

The study will be monitored in accordance with applicable Chinese regulations and standard operating procedures. Throughout the study, the sponsor or designated personnel will monitor the conduct of the study sites to ensure the following:

- Data are accurate, complete, and reliable.
- The safety and rights of participants are protected.
- The study is conducted in compliance with the most recent version of the approved protocol, including the administration of the investigational treatment as per the protocol.
- The study adheres to all other study agreements and regulatory requirements.

Before data are entered into the eCRF, source documentation must be available. The monitor will verify whether the data entered into the eCRF is complete, in compliance with the protocol, and consistent with regulatory requirements. The monitor will

compare the eCRF data with the original source data. All source documents must be maintained by the study site and must be available for review.

11. Study Management

11.1 Quality Control and Quality Assurance

Qualifications of Research Institutions: Clinical research institutions must be accredited and authorized to conduct pharmaceutical clinical trials.

Qualifications of Researchers: Researchers must undergo appropriate training and perform their tasks under the supervision of qualified professionals.

Laboratory Quality Control Measures: Laboratories must comply with relevant regulations and establish SOPs for experimental observation metrics and quality control procedures.

Clinical Research Quality Control Measures:

(1) Prior to the commencement of the clinical trial, all researchers and study-related personnel at the research institutions must receive training on the study protocol.

(2) All necessary equipment for the study must be fully operational, meet the required testing conditions, and be free from malfunctions. The equipment must undergo a preliminary testing phase to confirm its functionality.

(3) Investigational products must be handled by designated personnel and stored according to the conditions outlined in the study protocol. Any remaining investigational products should be stored separately, with a detailed log of the remaining quantities, and returned to the sponsor upon completion of the study.

11.2 Document Retention

In compliance with relevant regulations, both the researchers and the medical institutions they are affiliated with must ensure that they have adequate facilities and conditions for storing essential clinical trial documents. The storage conditions must prevent direct exposure to light, be waterproof, and provide an environment conducive to the long-term preservation of documents. Additionally, document management policies and SOPs must be established.

Retained documents must be easily identifiable, accessible, retrievable, and properly organized. Any documents generated during the clinical trial that are not listed in the essential document management directory for each phase of the trial must also be included in the researchers' and institutions' essential document archives.

12. Responsibilities of All Parties and Other Relevant Provisions

12.1 Responsibilities of the Lead Study Institution

(1) Design and develop the clinical study protocol and execute the clinical study protocol contract.

(2) Provide relevant training to clinical research sites prior to the commencement of the study.

(3) Prepare, compile, and maintain clinical data and documentation.

(4) Develop, collect, and maintain relevant documents, including the clinical protocol, medical records, ethics committee approvals, adverse event reports, statistical analysis and raw data, and the final clinical report.

(5) Ensure the documentation and reporting of adverse events to the appropriate regulatory authorities, and collaborate with clinical research sites to conduct study reviews.

(6) Verify that research sites enroll participants in accordance with the established study protocol and procedures.

(7) Monitor the enrollment progress at each research site.

(8) Oversee the quality of data collection and reporting at each research site.

(9) Collaborate with clinical research sites to evaluate the potential termination of the study when necessary.

12.2 Responsibilities of Clinical Research Sites (Study Centers)

(1) Investigators must thoroughly review and comprehend the study protocol and adhere strictly to its guidelines.

(2) Complete the clinical study within the prescribed timeline, in accordance with the established “Clinical Study Protocol,” including conducting in-person or telephone follow-up visits at the designated time points.

(3) Submit the clinical study protocol to the relevant ethics committee for review, obtain feedback and suggestions, and communicate the results to the investigators.

(4) Investigators must be fully familiar with the nature, mechanism of action, efficacy, and safety profile of the investigational drug.

(5) Clinical studies must be conducted in medical institutions with adequate medical facilities, laboratory equipment, and appropriate staffing. The institution must be equipped to handle emergencies to ensure participant safety, and laboratory results must be accurate and reliable.

(6) Investigators must obtain approval from the medical institution or relevant governing body to ensure sufficient time and resources to conduct the study within the specified timelines.

(7) Investigators must ensure that participants are well-informed about the investigational drug and have sufficient time to consider participation in the study before providing written informed consent.

(8) AEs occurring during the study must be accurately documented. Investigators must promptly notify the lead study institution and ethics committee of any SAEs within 24 hours of discovery and implement appropriate therapeutic measures. Investigators must swiftly assess any SAEs and take necessary actions to safeguard participant safety and rights.

(9) Investigators must ensure that all clinical data, including medical records (such as photos and videos) and eCRFs, are recorded truthfully, accurately, completely, in a timely manner, and in compliance with legal and regulatory requirements.

(10) Investigators must cooperate with monitoring and auditing activities conducted by the lead study institution to ensure the quality and integrity of the clinical study.

(11) Investigators must ensure that the study does not conflict with or interfere with other concurrent clinical trials.

(12) In the event of an emergency, the protection of participant welfare must take precedence. Investigators must assess whether it is necessary to deviate from the clinical study protocol, which should not be considered a protocol violation, but must be clearly explained and documented in the final report.

(13) Any modifications to the clinical study protocol that may impact participant safety or the scientific validity of the study must be communicated to the ethics committee, with approval from the implementing institution, along with the rationale for the changes.

(14) In the event of unforeseen circumstances or increased risks, investigators must promptly inform participants or their primary healthcare providers and may discontinue the study if necessary.

(15) Investigators are primarily responsible for ensuring the accuracy, clarity, and reliability of all study-related documents.

(16) Investigators must maintain confidentiality regarding all aspects of the investigational drug and related clinical processes and documentation.

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