A Multicenter, Placebo-Controlled, Phase 3 Study of Etripamil in Patients with Atrial Fibrillation and Rapid Ventricular Rate: ReVeRA-301 Trial Design

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Introduction

- Atrial fibrillation (AF) is the most common sustained arrhythmia and affects over 37 million worldwide.[1]
- AF can be associated with rapid ventricular rates (RVRs) that require rate control to alleviate symptoms.[2]
- Oral medications can have a delayed and ineffective response, prompting patients to seek emergency care for intravenous medications or cardioversion.[3,4]
- There are currently no self-administered, fast-acting treatments available for patients with AF with RVR (AF-RVR).
- Etripamil nasal spray (NS) is a self-administered, fast-acting, non-dihydropyridine calcium channel blocker in development to treat paroxysmal supraventricular tachycardia and AF-RVR.[5]
- Phase 2 data suggest etripamil NS can reduce the rate of AF-RVR and improve patient satisfaction.[5]

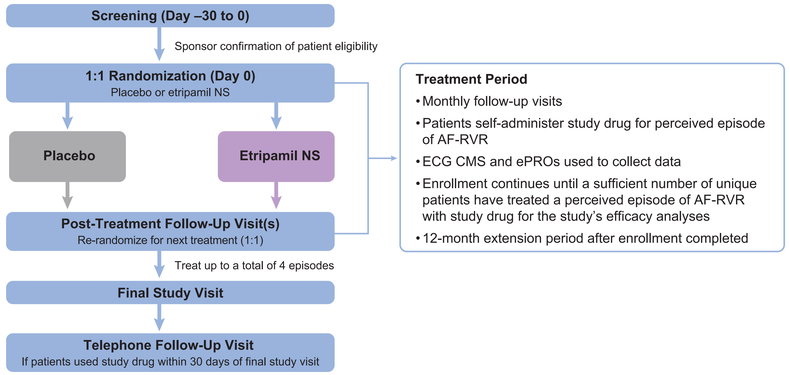
Objectives

- The primary objective of this study is to demonstrate the efficacy of etripamil NS over placebo in patients with AF.
- The secondary objectives of this study are to demonstrate the safety of etripamil NS when used in an at-home setting in patients with AF and to further characterize the clinical benefit of etripamil NS in patients with AF.

Methods

- ReVeRA-301 (NCT06716021)[6]* is a Phase 3, randomized, event-driven, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of etripamil NS 70 mg, which will be self-administered for an episode of AF-RVR outside the healthcare setting.
- The study will be conducted at approximately 150 sites in North America and Europe.
- Roughly 750 patients with a history of AF-RVR will be randomized to treat a target of at least 150 patients.
- Patients will be randomized 1:1 to receive placebo or etripamil NS 70 mg (**Figure 1**).
- Eligible patients are adults (≥18 years of age) with a history of repeated (≥2 in past 12 months), prolonged (≥20 minutes), and symptomatic AF-RVR episodes **(Figure 2**).
- Patients must be receiving appropriate anticoagulation therapy per their national/local guidelines.
- Key exclusion criteria include primary diagnosis of atrial flutter/tachycardia; history of New York Heart Association (NYHA) Class III or IV heart failure during the past 3 months; and history of second- or third-degree atrioventricular (AV) block or sinus bradycardia (<40 beats per minute [bpm]) without a pacemaker (**Figure 2**).
- Patients experiencing symptoms of perceived AF-RVR will affix an electrocardiography (ECG) monitoring device.
- After confirming ventricular rate (VR) of ≥110 bpm, etripamil NS 70 mg or placebo will be self-administered, and if symptoms persist after 10 minutes, a second dose of study drug can be self-administered (**Figure 2**).
- Patients will then complete questions from an electronic patient-reported outcomes (ePROs) questionnaire at prespecified times after administering the study drug (**Figure 2**).
- Patients may treat up to four episodes with randomized study drug each time (**Figure 1**).
- After administering the study drug, patients will return to the study site for a post-treatment follow-up visit (**Figure 1**).

Figure 1. Study Design



AF-RVR, atrial fibrillation with rapid ventricular rate; CMS, cardiac monitoring system; ECG, electrocardiography; ePRO, electronic patient-reported outcome; NS, nasal spray.

Figure 2. Overview of ReVeRA-301

1 Objectives

- Double-blind, randomized trial of etripamil NS 70 mg vs placebo
- Patients self-administer drug without direct medical supervision for perceived episodes of symptomatic AF-RVR
- Dose: etripamil NS 70 mg with optional repeat dose of 70 mg in 10 min if symptoms persist (same as proposed indication in PSVT)
- Patients may treat up to 4 episodes, re-randomized for each episode

2 Key Inclusion and Exclusion Criteria

Key Inclusion

- Age ≥18 years
- Documented history of symptomatic episodes of AF-RVR ≥110 bpm
- Paroxysmal, persistent, or permanent AF

Key Exclusion

- NYHA Class III or IV heart failure
- History of SSS, second or third degree AV block, or bradycardia (<40 bpm) without a pacemaker
- CHA_2DS_2-VASc score >5

3 Endpoints

- Primary endpoint – maximum reduction in VR at 30 min; etripamil NS vs placebo
- Key secondary endpoint – 30 min ePRO; improvement in symptoms
- Objectives
  - Show $P<0.05$ for primary and key secondary endpoints in ITT population
  - Show meaningful ePRO-based change in target population (eg, 1-point change on 7-point scale)
- Estimated study size: N≈150–200 total events based on 90% power and $P<0.05$

AF-RVR, atrial fibrillation with rapid ventricular rate; AV, atrioventricular; bpm, beats per minute; ePRO, electronic patient-reported outcome; ITT, intention to treat; NS, nasal spray; NYHA, New York Heart Association; PSVT, paroxysmal supraventricular tachycardia; SSS, sick sinus syndrome; VR, ventricular rate.

Results

- **The primary efficacy endpoint,** measured from ECG recordings, will be the maximum VR reduction within 30 minutes from first drug administration (**Figure 2**).
  - Maximum VR reduction will be calculated as the change between baseline value and nadir.
  - For patients treating multiple episodes during the study, the first episode which meets criteria for inclusion in the primary analysis will be utilized.
- **The key secondary endpoint** will be improvement in symptoms as measured by ePROs collected at 30 minutes after first study drug administration using a seven-unit anchored Likert scale (**Figure 2**).
- **Other secondary endpoints** (**Figure 2**):
  - Patient satisfaction with treatment.
  - Conversion of AF to sinus rhythm.
  - Medical interventions including the use of rescue medications, emergency department visits, and/or contact with a healthcare provider.
- **Safety assessments** will include:
  - Clinical adverse events.
  - Clinical examinations and vital signs.
  - ECG CMS recordings.
- **Statistical analysis:**
  - Primary efficacy analysis will be performed in the intention-to-treat (ITT) population and will compare the VR reduction in placebo versus etripamil-treated patients using an analysis of covariance (ANCOVA).
  - Key secondary analysis will be performed on the ITT population for improvement in patient symptoms from the ePROs; mean scores will be analyzed via ANCOVA.
- **Interim analysis:**
  - A blinded interim analysis will occur at approximately N=100 unique patients treating a perceived episode of AF-RVR with study drug.
  - Study sample size may be adjusted to maintain a 90% power to detect at least a one-unit difference on the key secondary endpoint in the target population.

Conclusions

- The efficacy and safety of etripamil NS is being evaluated in patients with AF-RVR as a potential treatment that can be self-administered outside the healthcare setting.

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Conflict of Interests/Disclosures

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