Concomitant Antiarrhythmic Use Among Patients Who Received Etripamil for Atrial Fibrillation With Rapid Ventricular Rate

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Background

- Patients with symptomatic atrial fibrillation with rapid ventricular rate (AF-RVR) often present to the emergency department (ED) requiring intravenous (IV) medications for prompt management of the RVR.[1,2]
- Patients have limited options for self-administered therapies outside the healthcare setting that provide rapid and early treatment; acute administration of oral therapies such as β-blockers (BBs) or L-type calcium channel blockers (CCBs) for AF-RVR do not show immediate effect due to delayed onset of action.[3]
- Etripamil nasal spray (NS) is a novel, investigational, self-administered, non-dihydropyridine (NDHP) L-type CCB that prolongs atrioventricular-nodal refractoriness and conduction velocity.[4]
- Etripamil NS has a rapid onset of action, reaching maximum concentration within 7 minutes when administered at a dose of 70 mg. Clinical trials report that etripamil has a consistent safety profile and demonstrated efficacy in managing acute paroxysmal supraventricular tachycardia episodes.[5,6]

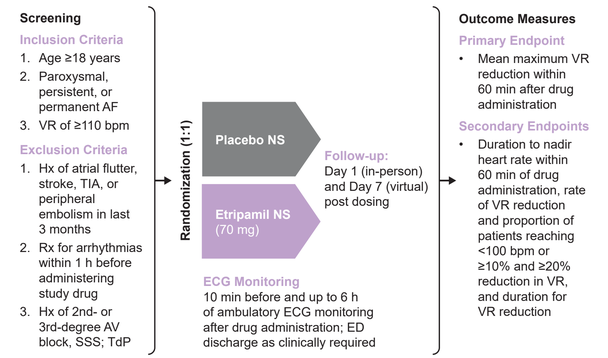
Objectives

- The primary objective of the ReVeRA-201 study (NCT04467905) was to assess the efficacy and safety of etripamil NS in reducing RVR and its symptoms in patients presenting to the ED with symptomatic AF-RVR.
- Here, we present a post hoc analysis on the effect of etripamil on concomitant antiarrhythmic medication use in patients with AF-RVR.

Methods

- ReVeRA-201 was a phase 2, randomized, double-blind, placebo-controlled study conducted across multiple sites in Canada and the Netherlands between November 2020 to September 2023 (study design shown in **Figure 1**).

Figure 1. Study Design



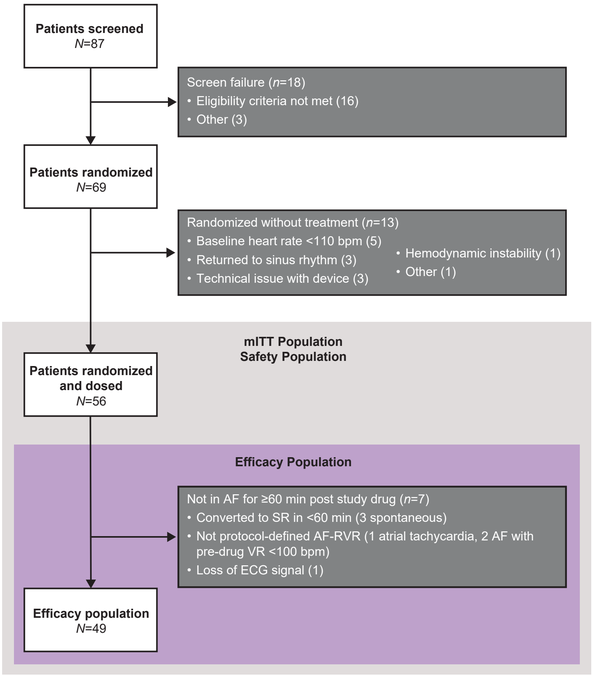
AF, atrial fibrillation; AV, atrioventricular; bpm, beats per minute; ECG, electrocardiography; h, hour; Hx, history; min, minute; NS, nasal spray; Rx, prescription; SSS, sick sinus syndrome; TdP, torsades de pointes; TIA, transient ischemic attack; VR, ventricular rate.

- Etripamil or placebo was administered intranasally by clinical staff at the study site, with one spray in each nostril for a total dose of 70 mg.
- Patients were monitored by electrocardiography 10 minutes before study drug administration and until 6 hours post dosing.
- Baseline use of concomitant drugs such as antiarrhythmic drugs (AADs), NDHP CCBs, BBs, digoxin, and oral anticoagulants (OACs) was documented and included drugs initiated at least one day before study drug administration.
- The use of concomitant medications was assessed by comparing baseline use with that during the 24 hours after study drug administration. Descriptive statistics were used for this study, and percentage of patients using an AAD at baseline and after treatment are reported.

Results

- Overall, 87 patients were screened and 56 were randomized 1:1 to receive etripamil (*n*=27) or placebo (*n*=29) (**Figure 2**).

Figure 2. Patient Disposition



Safety population: All randomized patients receiving either etripamil or placebo.
mITT population: All randomized patients receiving study drug and with a post-treatment ECG CMS recording.
Efficacy population: All patients in the mITT population who remained in AF with adequately diagnostic ECG recordings for at least 60 minutes post etripamil administration.
n=1 patient had two reasons for screen failure.
AF, atrial fibrillation; AF-RVR, atrial fibrillation with rapid ventricular rate; bpm, beats per minute; CMS, cardiac monitoring system; ECG, electrocardiography; mITT, modified intention to treat; SR, sinus rhythm; VR, ventricular rate.

- Mean (standard deviation [SD]) age of the population was 64.6 (10.47) years and 39.3% (22/56) of patients were female (**Table 1**).
- Most patients had paroxysmal AF (75.0% [42/56]) with a mean ± SD baseline systolic blood pressure of 127.71 ± 18.52 mmHg (**Table 1**).
- Baseline use of concomitant AADs was comparable across the placebo and etripamil arms (**Table 1**).

Results

- **Primary endpoint:** Results for the primary endpoint show significant adjusted mean maximum reduction (95% confidence interval [CI]) in VR (etripamil, −34.97 [−45.13, −24.81] bpm; placebo, −5.06 [−7.44, −2.67] bpm, with a difference amounting to −29.91 [−40.31, −19.52] bpm; *P*<0.0001).

Table 1. Baseline Characteristics

Characteristics	Placebo	Etripamil	Total
ReVeRA-201	*n*=29	*n*=27	*N*=56
Age, years			
Mean ± SD	64.59 ± 10.53	64.63 ± 10.61	64.6 ± 10.47
Median (range)	66.00 (35.00, 83.00)	64.00 (45.00, 88.00)	65.00 (35.00, 88.00)
Sex, female, *n* (%)	11 (37.9)	11 (40.7)	22 (39.3)
Site location, *n* (%)			
Canada	14 (48.3)	12 (44.4)	26 (46.4)
The Netherlands	15 (51.7)	15 (55.6)	30 (53.6)
Baseline systolic blood pressure, mmHg			
Mean ± SD (median)	125.59 ± 17.34 (124.00)	130.00 ± 19.78 (126.00)	127.71 ± 18.52 (124.50)
AF diagnosis classification, *n* (%)			
Paroxysmal	22 (75.9)	20 (74.1)	42 (75.0)
Persistent	5 (17.2)	5 (18.5)	10 (17.9)
Permanent	2 (6.9)	2 (7.4)	4 (7.1)
Concomitant medications, *n* (%)			
Any β-blocker	10 (34.5)	13 (44.8)	23 (41.1)
Any NDHP CCB	3 (10.3)	4 (14.8)	7 (12.5)
Any β-blocker or CCB	13 (44.8)	15 (55.6)	28 (50.0)
Any Class IC or III antiarrhythmic	5 (17.2)	8 (29.6)	13 (23.2)
Oral anticoagulant	16 (55.1)	16 (59.3)	32 (57.1)

AF, atrial fibrillation; CCB, calcium channel blocker; NDHP, non-dihydropyridine; SD, standard deviation.

Use of Concomitant Medications After Drug Administration

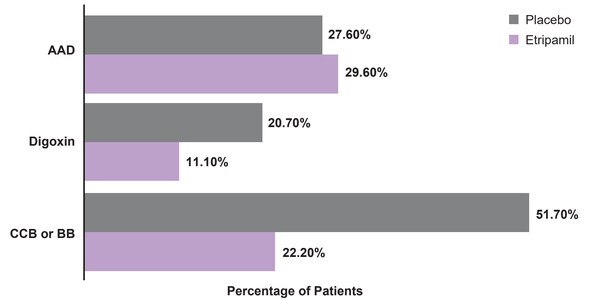
- Across both etripamil and placebo arms, patients did not receive any additional medications within the first 60 minutes after study drug administration (**Table 2**).
- More patients received oral NDHP CCBs or BBs (33.9%) and oral AADs (23.2%) than intravenous (IV) NDHP CCBs or BBs (3.6%) and IV AADs (5.4%) within the 24 hours after study drug administration.
- Within the 24 hours (>60 minutes window), 37.5% (21/56) of patients received a CCB or BB, 16.1% (9/56) received digoxin, and 28.6% (16/56) received an AAD in the overall population.
- The number of patients receiving a CCB or BB and digoxin was higher in the placebo arm than the etripamil arm, while administration of Class IC and III AADs was similar between both arms (**Figure 3**).

Table 2. Administration of Concomitant Medications After Study Drug Administration in the Safety Population[a]

Concomitant Medications, *n* (%)	Placebo[b] (*n*=29)	Etripamil[b] (*n*=27)	Total[b] (*N*=56)
CCB or BB, ≤24 h	15 (51.7)	6 (22.2)	21 (37.5)
IV NDHP CCB or IV BB, ≤60 min	0	0	0
IV NDHP CCB or IV BB, >60 min and ≤24 h	2 (6.9)	0	2 (3.6)
Oral NDHP CCB or oral BB, ≤60 min	0	0	0
Oral NDHP CCB or oral BB, >60 min and ≤24 h	13 (44.8)	6 (22.2)	19 (33.9)
IV or oral digoxin, ≤24 h	6 (20.7)	3 (11.1)	9 (16.1)
AAD, ≤24 h	8 (27.6)	8 (29.6)	16 (28.6)
IV AAD, ≤60 min	0	0	0
IV AAD, >60 min and ≤24 h	2 (6.9)	1 (3.7)	3 (5.4)
Oral AAD, ≤60 min	0	0	0
Oral AAD, >60 min and ≤24 h	6 (20.7)	7 (25.9)	13 (23.2)

[a]Safety population involves all patients who received the study drug. [b]Data for concomitant medication use is not mutually exclusive, multiple drugs may have been administered to a single patient.
AAD, antiarrhythmic drug (including Class IC and III drugs); BB, β-blocker; CCB, calcium channel blocker; h, hour; IV, intravenous; min, minute; NDHP, non-dihydropyridine.

Figure 3. Proportion of Patients Administered Concomitant Medications Within 24 Hours Following Study Treatment



AAD, antiarrhythmic drug; BB, β-blocker; CCB, calcium channel blocker.

Safety

- Most common adverse events (AEs) of ≥5% frequency included nasal discomfort, nasal burning, rhinorrhea, and dizziness, which were mild to moderate in severity.
- Frequency of serious treatment-emergent AEs (TEAEs) was 3.7% (1/27) in the etripamil arm and 6.9% (2/29) in the placebo arm. Serious TEAEs of transient severe bradycardia in the etripamil arm resolved without sequelae. One case in the etripamil arm of transient severe bradycardia and syncope (resolved without sequelae).
- Use of oral anticoagulants was not associated with an increase in epistaxis in the patient population.

Conclusions

- Administration of etripamil NS in patients with symptomatic AF-RVR was associated with less frequent use of rate control medications (NDHP CCBs or BBs and digoxin) in the 24 hours following etripamil treatment when compared with patients receiving placebo nasal spray.
- Data from the ReVeRA-201 study show that for patients with symptomatic AF-RVR, etripamil NS is a potential treatment to provide prompt rate control and should be investigated as a self-administered therapy outside the healthcare setting.

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