Etripamil Use in Atrial Fibrillation With Rapid Ventricular Rate

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Background

- Atrial fibrillation (AF) is the most common arrhythmic disorder and is projected to affect 12 million people in the US by 2030.[1]
- Symptoms of AF associated with a rapid ventricular rate (RVR) include fatigue, palpitations, chest pain, syncope, dizziness, dyspnea, and orthopnea.[2]
- Symptomatic AF increases the treatment burden and often requires a visit to the emergency department (ED), especially for rapid heart rate.[2]
- There is an unmet need for a self-administered therapy to control ventricular rate (VR) safely outside the healthcare setting.
- Etripamil is a novel, investigational, non-dihydropyridine L-type calcium channel blocker (CCB) rapidly metabolized by serum esterases with a rapid onset of action (T_{max} ≤7 min) formulated for intranasal administration.[3,4]
- Etripamil has shown positive results in clinical trials as a therapy for paroxysmal supraventricular tachycardia (PSVT), an arrhythmic disorder characterized by rapid heart rate with sudden onset.[3,5,6]

Objectives

- The post hoc analysis presented here describes the effect of self-administered etripamil on VR reduction in AF in two studies.
- The ReVeRA-201 study (NCT04467905) assessed the efficacy and safety of etripamil nasal spray (NS) vs placebo NS in reducing VR in patients with AF with RVR (AF-RVR).
- The NODE-303 study (NCT04072835) sought to evaluate the safety of self-administration of etripamil NS outside the clinical setting in patients with PSVT, and also enrolled patients with a history of PSVT and AF.

Methods

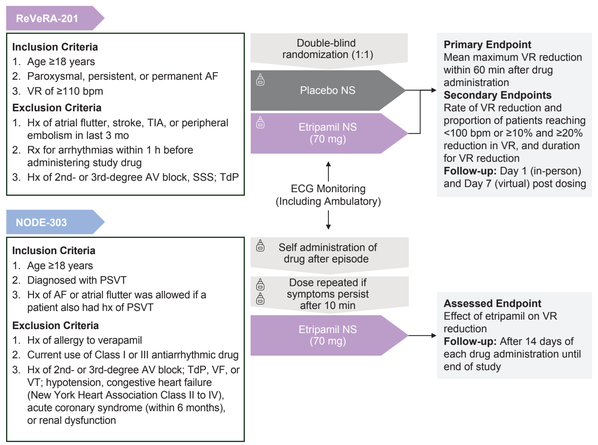
ReVeRA-201 was a randomized, double-blind, placebo-controlled, multicenter study conducted in Canada and the Netherlands (**Figure 1**).

- Etripamil NS was administered by clinical staff; one spray per nostril for a total dose of 70 mg, which was administered in patients presenting to the ED with AF and RVR (≥110 bpm).
- Cardiac monitoring in the ED occurred for at least 10 minutes prior to and for 6 hours after administration.
- Kaplan-Meier method and Wilcoxon testing for censored data were used to estimate the reduction in VR in the etripamil and placebo arms by 60 minutes and 360 minutes.
- Analysis of covariance (ANCOVA) was used to calculate the maximum reduction in VR, which was adjusted for the value of VR at baseline.

NODE-303 was a multicenter, multinational, open-label study that allowed single-dose (70 mg) etripamil **self-administration** for the resolution of up to four episodes of supraventricular tachycardia outside the supervised clinical setting (**Figure 1**).

- PSVT was documented by an ambulatory electrocardiography (ECG) cardiac monitoring system (CMS) at symptom initiation; ECG CMS was worn for at least 60 minutes after patients were dosed with etripamil NS.
- Data from patients in the NODE-303 study who experienced AF-RVR based on recorded ECG data are included, and the effect of etripamil on AF-RVR is reported here.
- Patient ECG data for AF were excluded if VR was converted to normal sinus rhythm (NSR), if there were no data or insufficient data, or if a dosing or recording error occurred.
- Difference between VR at T_0 and at 1-minute intervals was calculated for each episode up to 60 minutes post treatment. Average differences in VR from baseline were calculated at each timepoint.

Figure 1. Study Design



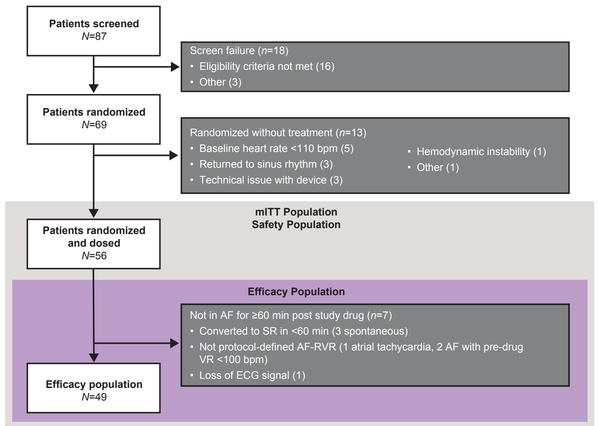
AF, atrial fibrillation; bpm, beats per minute; h, hour; Hx, history; min, minute; PSVT, paroxysmal supraventricular tachycardia; Rx, prescription; SSS, sick sinus syndrome; TdP, torsades de pointes; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

Results

ReVeRA-201

- Overall, 87 patients were screened and 69 were randomized 1:1 to receive etripamil or placebo; 13 patients did not receive treatment and 56 were administered the study drug (*n*=27, etripamil; *n*=29, placebo; **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; CMS, cardiac monitoring system; ECG, electrocardiography; min, minute; mITT, modified intention to treat; SR, sinus rhythm; VR, ventricular rate.

- Mean age (± SD) of the study population was 64.6 ± 10.47 years and 39.3% of patients were female; baseline characteristics are shown in **Table 1**.

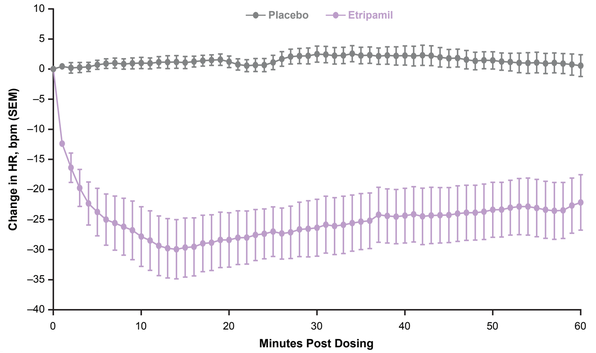
Table 1. Baseline Characteristics

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)
NODE-303	–	*N*=18[a]	–
Mean age, years	–	56.3	–
Female patients, *n* (%)	–	10 (55.5)	–
AF ECG used for analysis (NSR excluded)	–	21	–
Mean VR, bpm	–	129.7	–
SD	–	24.8	–
SEM	–	5.4	–
Median VR, bpm	–	127.0	–

[a]Patients who experienced AF-RVR as per ECG data; NODE-303 was an open-label study with no placebo group.
AF, atrial fibrillation; AF-RVR, atrial fibrillation with rapid ventricular rate; CCB, calcium channel blocker; ECG, electrocardiography; NDHP, non-dihydropyridine; NSR, normal sinus rhythm; SD, standard deviation; SEM, standard error of mean; VR, ventricular rate.

- **Primary endpoint results:** The mean maximum reduction in VR from baseline was –34.97 bpm in the etripamil arm (95% confidence interval [CI]: –45.13, –24.81) and –5.06 bpm in the placebo arm (95% CI: –7.44, –2.67; **Figure 3**); the difference in VR reduction was –29.91 bpm (95% CI: –40.31, –19.52; *P*<0.0001).

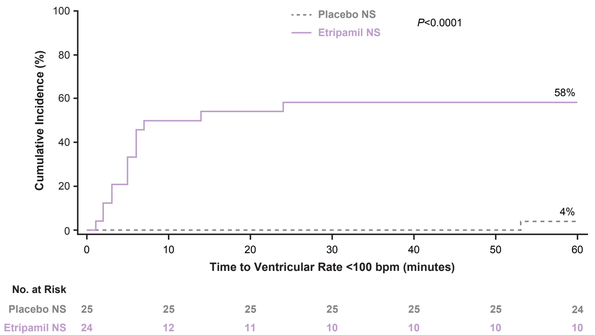
Figure 3. ReVeRA-201: Mean Change (± SEM) in VR (bpm) From Baseline to 60 Minutes



Data shown are raw and unadjusted.
bpm, beats per minute; HR, heart rate; SEM, standard error of mean; VR, ventricular rate.

- **Secondary endpoint results:** The elapsed time (adjusted change in means) from study drug administration to nadir <100 bpm in VR was significantly lower (*P*=0.0347) for the etripamil arm (20.56 minutes; 95% CI: 12.63, 28.49) than for the placebo arm (32.66 minutes; 95% CI: 24.89, 40.43).
- A 180-minute assessment of ECG data showed that the higher reduction in VR from baseline in the etripamil versus placebo arm persisted for ≥150 minutes.
- Patients achieving a VR <100 bpm within 60 minutes post drug administration were significantly higher (*P*<0.0001) in the etripamil arm (58.3%) than the placebo arm (4.0%), with the outcomes persisting for a minimum of 60 minutes.
- The median duration for maintaining a VR <100 bpm within 60 minutes after drug administration was higher for the etripamil arm (45.50 minutes [interquartile range [IQR]: 24.00, 56.00]) than the placebo arm (7.00 minutes [IQR: not approached]; **Figure 4**).

Figure 4. ReVeRA-201: Median Reduction in VR From Baseline at 60 Minutes



NS, nasal spray; VR, ventricular rate.

- A significant improvement (*P*=0.0002) in "satisfaction with symptom relief" was observed with etripamil treatment (etripamil, 4.63 ± 1.35; placebo, 3.08 ± 1.29) on the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) assessment.
- Similarly, "satisfaction with effectiveness of treatment" score was significantly (*P*<0.0001) higher for etripamil (62.69 ± 21.59) than placebo (36.67 ± 21.64) as per TSQM-9 assessment.

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NODE-303 Post hoc Analysis

- Data for VR was available for 21 episodes (*n*=18; three patients had two episodes each).
- Mean age of the study population was 56.3 years (**Table 1**).
- A VR >110 bpm at baseline was observed in 81% (17/21) of AF episodes; mean baseline VR for AF-RVR was 138.3 ± 4.3 bpm.
- At 60 minutes post etripamil administration, 33.3% (7/21) of AF episodes converted to NSR; the mean VR ± SEM was 110.2 ± 7.6 bpm (*n*=14); median VR (range) was 114 (65–161) bpm; and the mean ± SD reduction in VR from baseline was −16.2 ± 21 bpm (**Table 2**).

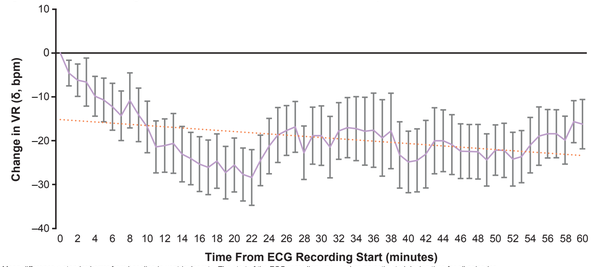
Table 2. NODE-303: Effect of Self-Administration of Etripamil on VR Over 60 Minutes

Patients with AF Episodes (*N*=18)	0 min[a]	15 min	30 min	45 min	60 min
Number of AF episodes included in analysis[b]	21	20	19	17	14
Mean VR, bpm	129.7	104.6	110.7	103.9	110.2
SD	24.8	28.7	27.6	30.0	28.5
SEM	5.4	6.4	6.3	7.3	7.6
Median VR (range), bpm	127 (79, 164)	96 (67, 152)	108 (58, 154)	98 (63, 178)	114 (65, 161)
Mean change in VR from baseline, bpm	–	−23.2	−18.4	−22.4	−16.2
SD	–	25.6	28.0	27.1	21.0
SEM	–	5.7	6.4	6.6	5.6
Median change in VR from baseline (range), bpm	–	−28.5 (−67.0, 36.0)	−22.0 (−80.0, 52.0)	−23.0 (−75.0, 33.0)	−18.0 (−43.0, 34.0)

[a]ECG data for episodes after converting to NSR were excluded. [b]Baseline.
AF, atrial fibrillation; ECG, electrocardiography; min, minute; NSR, normal sinus rhythm; SD, standard deviation; SEM, standard error of mean; VR, ventricular rate.

- Reductions in VR from baseline were sustained throughout the 60-minute observation window, and maximum average reduction in VR (28.4 ± 6.1 bpm) was observed at 22 minutes post etripamil administration (**Figure 5**).

Figure 5. NODE-303: Change in VR From Baseline Within 60 Minutes of Etripamil Self-Administration



Mean difference ± standard error from baseline in ventricular rate. The start of the ECG recording was used as an estimated dosing time for all episodes.
bpm, beats per minute; ECG, electrocardiography; VR, ventricular rate.

Safety

- For ReVeRA-201, adverse events (AEs) with ≥5% frequency of mild-moderate severity were nasal discomfort, rhinorrhea, lacrimation, throat irritation, and dizziness. No treatment-emergent serious AEs were observed in patients self-administering etripamil in the NODE-303 study (**Table 3**).
- Transient severe bradycardia and syncope were reported in one patient in the etripamil arm; this occurrence resolved without sequelae.

Table 3. Summary of AEs Across ReVeRA-201 and NODE-303 Studies

Adverse Events	ReVeRA-201		NODE-303
	Placebo (*N*=29)	Etripamil (*N*=27)	Patients With AF Episodes Administering Etripamil (*N*=18)
Patients with at least one AE related to drug, *n* (%)	0	1 (3.7)	7 (39)
Patients with severe AEs related to drug, *n* (%)	0	1 (3.7)	0 (0)

AE, adverse event; AF, atrial fibrillation.

Limitations

- Since the ReVeRA-201 study only involved AF-RVR patients who visited the ED, patients not presenting to the ED may have different characteristics and heart rates.
- Key limitations of the NODE-303 study included timing of drug administration variably related to ECG recording initiation and history of PSVT in the study population.

Conclusions

- Both ReVeRA-201 and NODE-303 studies show that etripamil 70 mg NS led to reduction in RVR from baseline, with the mean treatment effects lasting for at least 60 minutes.
- Administration of etripamil both within and outside the supervised clinical setting was safe and did not have any serious AEs.

References

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Disclosures

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