Efficacy and Safety of Etripamil Nasal Spray for the Acute Reduction of Rapid Ventricular Rate in Patients With Atrial Fibrillation: Phase 2 ReVeRA-201

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Background

- Etripamil is a novel, investigational, L-type calcium channel blocker[1,2] that is formulated as an intranasal spray, which has the following attributes:
  - Rapid onset of action (T_{max} ≤7 min).[3]
  - Short-lasting: inactivated by blood esterases.[4]
- Etripamil was developed to satisfy the unmet need for self-administered therapy that is portable and safe outside the healthcare setting.[3,4]
- Previous studies have demonstrated that etripamil is effective at rapidly controlling ventricular rate (VR) in patients with symptomatic atrial fibrillation (AF).[5]

Objective

The ReVeRA-201 trial (NCT04467905) assessed the efficacy and safety of intranasal etripamil versus placebo to acutely reduce VR in patients with AF with rapid ventricular rate (RVR).

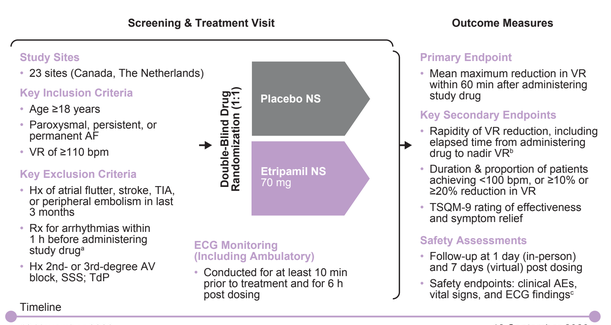
Methods

- The ReVeRA phase 2 study design is shown in **Figure 1**.
  - The study drug was administered by clinical site staff, one spray in each nostril of participants with each spray equating to half of the relevant dose.
  - ECG monitoring in the emergency department occurred for at least 10 minutes prior to treatment and for 6 hours post dosing.
- The key primary endpoint assessed the mean maximum reduction in VR within 60 minutes after study drug administration.
- Key secondary endpoints included:
  - Rapidity of VR reduction, including elapsed time from administering drug to nadir.[2]
  - Duration and proportion of patients achieving <100 bpm, or ≥10% or ≥20% reduction in VR.
  - TSQM-9 rating of effectiveness and symptom relief.

Statistical Methods

- The reduction in VR in the etripamil and placebo arms by 60 minutes and 360 minutes was evaluated using the Kaplan-Meier method and a Wilcoxon test for censored data.
- The maximum reduction in VR was calculated using an ANCOVA test and was adjusted for the value of VR at baseline.
- The percentage of patients who achieved a VR <100 bpm or a 10% to 20% reduction from baseline VR was assessed using a chi-square test.
- Statistical analyses were conducted using SAS (version 9.4).

Figure 1. ReVeRA Phase 2 Study Design



Patients were excluded if they had signs and symptoms of severe congestive heart failure; were hemodynamically unstable (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg). Patients were excluded if they had a history of cardiovascular, endocrinal, gastrointestinal, hematologic, hepatic, immunologic, neurologic, oncologic, pulmonary, psychiatric, renal, or any other disease; second- or third-degree AV block; sick sinus syndrome; torsades de pointes; or Brugada syndrome. Safety endpoints included any AV block and ventricular arrhythmia such as premature ventricular contractions and non-sustained ventricular tachycardia, based on ECG findings.

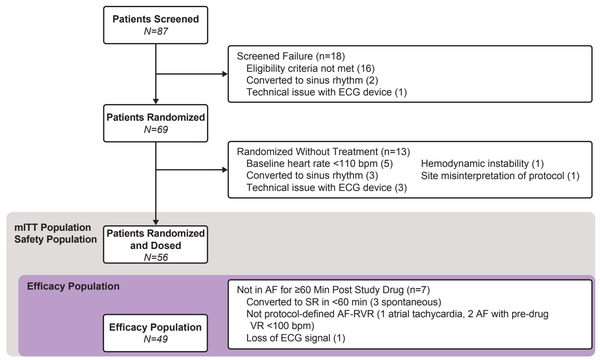
[a]Treatments with intravenous flecainide, procainamide, digoxin, beta-blocker, or calcium channel blockers. [b]Nadir refers to the lowest 5-minute moving average heart rate of <100 bpm. [c]Safety endpoints based on ECG analysis included any AV block and ventricular arrhythmia such as premature ventricular contractions.

AE, adverse event; AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiography; FPFV, first patient first visit; Hx, medical history; NS, nasal spray; Rx, treatment; SSS, sick sinus syndrome; TdP, torsade depointes; TIA, transient ischemic attack; TSQM-9, Treatment Satisfaction Questionnaire for Medication patient-reported outcome tool; VR, ventricular rate.

Results

- Of the 87 patients screened, 69 patients were randomized 1:1 to receive either etripamil or placebo; 56 participants received the study drug (etripamil n=27; placebo n=29; **Figure 2**).
- Few differences in the use of oral beta-blockers and antiarrhythmic drugs were observed between etripamil and placebo groups.
- **Table 1** shows the baseline characteristics were comparable among participants in the etripamil and placebo arms.
- In the overall study population, participants had a mean age of 64.6 years ± 10.5, and 39.3% of participants were female; the baseline systolic blood pressure was 130.00 ± 19.78 mmHg in the etripamil arm and 125.59 ± 17.34 mmHg in the placebo arm (**Table 1**).
- Patients diagnosed with paroxysmal, persistent, or permanent AF were included in both study arms (**Table 1**).

Figure 2. Patient Disposition[a]



[a]The safety population is all randomized patients receiving study drug. The mITT population is all randomized patients receiving study drug and who had a post-drug ECG CMS recording. The efficacy population is all mITT patients who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. One patient had two reasons for screen failure. AF, atrial fibrillation; AF-RVR, atrial fibrillation with rapid ventricular rate; CMS, cardiac monitoring system; ECG, electrocardiography; mITT, modified intention to treat; SR, sinus rhythm; VR, ventricular rate.

Table 1. Demographics and Baseline Characteristics in the mITT and Safety Population

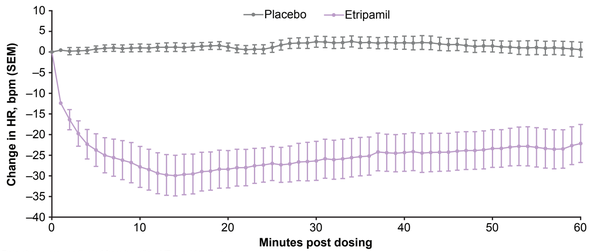
Characteristics	Placebo n=29	Etripamil n=27	Total N=56
Age, years			
Mean (SD)	64.59 ± 10.53	64.63 ± 10.61	64.6 ± 10.47
Median (range)	66.00 (35.00, 83.00)	64.00 (45.00, 88.00)	65 (35.00, 88.00)
Sex, female, n (%)	11 (37.9)	11 (40.7)	22 (39.3)
Site location, n (%)			
Canada	14 (48.3)	12 (44.4)	26 (46.0)
The Netherlands	15 (51.7)	15 (55.6)	30 (54.0)
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 (18.0)
Permanent	2 (6.9)	2 (7.4)	4 (7.0)
Concomitant medications, n (%)			
Any beta-blocker	10 (34.5)	13 (44.8)	23 (41.1)
Any NDHP CCB	3 (10.3)	4 (14.8)	7 (12.5)
Any beta-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)
Anticoagulant, oral	16 (55.1)	16 (59.3)	32 (57.1)

AF, atrial fibrillation; CCB, calcium channel blocker; mITT, modified intention to treat; NDHP, non-dihydropyridine; SD, standard deviation.

Key Primary Endpoint Results

- Mean maximum reduction from baseline in VR 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. Mean Change (± Standard Error of Mean) in Ventricular Rate (bpm) From Baseline to 60 Minutes



Data shown are unadjusted from baseline. VR, ventricular rate.

Key Secondary Endpoint Results

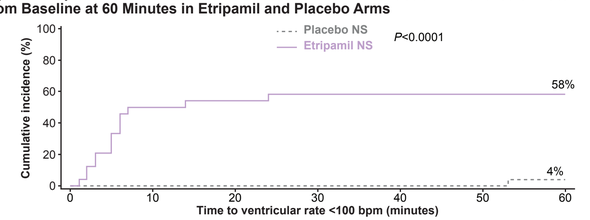
- The adjusted change in means for elapsed time from drug administration to nadir <100 bpm in VR was 20.56 min (95% CI: 12.63, 28.49) for the etripamil arm versus 32.66 min (95% CI: 24.89, 40.43) for the placebo arm (*P*=0.0347).
- The higher reduction in VR from baseline in the etripamil versus placebo arms, shown in 180 min collection of ECG data, persisted for ≥150 min.
- The proportion of patients achieving a VR of <100 bpm during the first 60 min post drug administration was higher for patients receiving etripamil (58.3%) than for those receiving placebo (4.0%; *P*<0.0001), and these outcomes persisted for at least 60 min.
- The median duration of maintaining a VR <100 bpm during the first 60 min post drug was 45.50 min (IQR: 24.00, 56.00) in the etripamil arm versus 7.00 min (IQR: not approached) in the placebo arm (**Figure 4**).
- The etripamil arm showed significant improvement in "satisfaction on relief of symptoms" and "satisfaction of effectiveness of treatment" versus those on placebo (**Table 2**).
  - More symptom relief was reported by participants in the etripamil arm (4.63 ± 1.35) than in the placebo arm (3.08 ± 1.29; *P*=0.0002).
  - For the effectiveness domain of the TSQM-9, the mean ± SD was 62.69 ± 21.59 for patients who received etripamil versus 36.67 ± 21.64 for those who received placebo (*P*<0.0001).

Table 2. Summary of Patient Satisfaction with Treatment Measured by Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Domains		Placebo[a] (N=25)	Etripamil[a] (N=24)	*P* value[b]
Effectiveness[c]	Mean (SD)	36.67 (21.64)	62.96 (21.59)	*P*<0.0001
Relief of symptoms question[d]	Mean (SD)	3.08 (1.29)	4.63 (1.35)	*P*=0.0002
Global satisfaction[c]	Mean (SD)	37.14 (25.42)	53.87 (21.17)	*P*=0.0161
Convenience[c]	Mean (SD)	72.00 (16.08)	65.28 (12.50)	*P*=0.1100

[a]Efficacy population is comprised of all mITT patients (randomized patients receiving study drug) who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 minutes post drug.
[b]From t test.
[c]Each domain score is calculated from 3-question score.
[d]Each question answered on a 7-point anchored scale.
ECG, electrocardiography; IQR, interquartile range; mITT, modified intention to treat; SD, standard deviation.

Figure 4. Kaplan-Meier Curves Demonstrate the Median Reduction in Ventricular Rate From Baseline at 60 Minutes in Etripamil and Placebo Arms



No. at risk							
Placebo NS	25	25	25	25	25	25	24
Etripamil NS	24	12	11	10	10	10	10

NS, nasal spray.

Safety Outcomes

- In the safety population (N=56), the most common (≥5%) AEs were nasal discomfort, rhinorrhea, lacrimation, throat irritation, and dizziness, which were mild or moderate in intensity.
- Treatment-emergent serious adverse events (TESAEs) occurred in 1 patient (3.7%, 1/27) in the etripamil arm and 2 patients (6.9%, 2/29) in the placebo arm (**Table 3**).
- The 1 TESAE in the etripamil arm (transient severe bradycardia and syncope, assessed as due to hypervagotonia) occurred in a patient with a history of vagal events, and fully resolved with placing the patient supine and without sequelae.

Table 3. Summary of Treatment-Emergent Serious Adverse Events

Patients, n (%)	Placebo[a] (N=29)	Etripamil[a] (N=27)
Patients with at least one TESAE[b]	2 (6.9)	1 (3.7)
Patients with at least one severe TESAE	0 (0.0)	1 (3.7)
Patients with at least one TESAE leading to study discontinuation	0 (0.0)	0 (0.0)
Patients with at least one TESAE related to study drug	0 (0.0)	1 (3.7)

[a]Safety population refers to all randomized subjects who received the study drug.
[b]Treatment-emergent serious adverse events (TESAEs) are serious adverse events (SAEs) with onset date/time within 24 hours after study drug administration. In case of a missing AE onset time, the AE is considered treatment-emergent if onset date is equal to study drug administration date or the next day.

Limitations

- The characteristics and heart rates of AF may be different in patients who do not present to an emergency department.
- Patients presenting to a hospital setting received the treatment; future investigation of self-administered treatment in an at-home setting is needed.
- A single dose of intranasal etripamil was administered; safety and efficacy of a repeat-dose regimen can be evaluated in future studies.

Conclusions

- Compared to placebo, etripamil 70 mg significantly reduced RVR from baseline, which resulted in a duration of effect for at least 60 min.
- Etripamil nasal spray 70 mg is a potential treatment to reduce RVR in patients with symptomatic AF-RVR, and these data support further investigation of etripamil 70 mg as a self-administered treatment outside the healthcare setting.

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