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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On behalf of all co-authors, listed on the final slide

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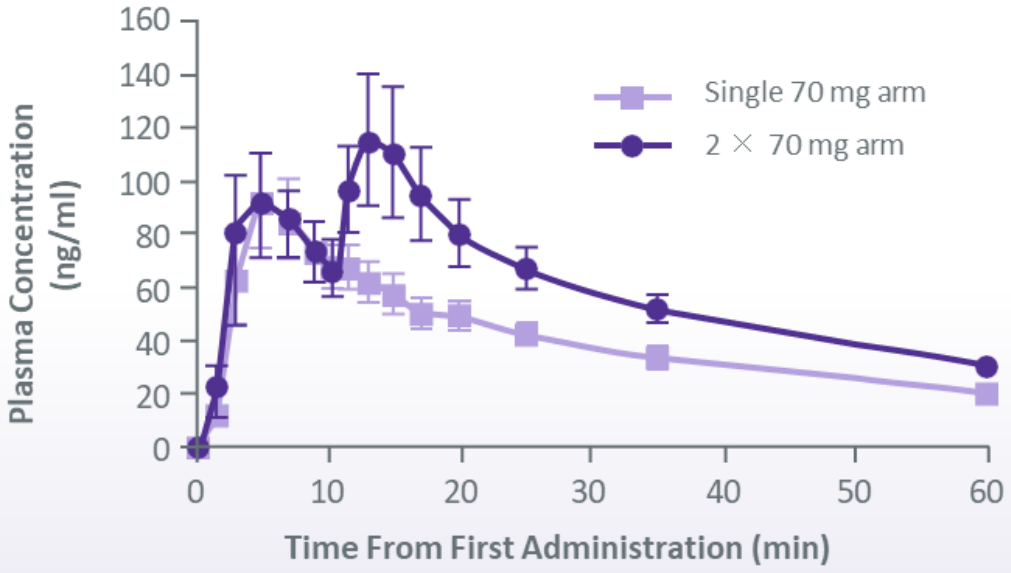
Etripamil is an investigational drug and is not approved by the FDA.

Etripamil Nasal Spray (NS)

Potential New Treatment for PSVT and AFib-RVR

- Novel, investigational, L-type calcium channel blocker
- Formulated for intranasal spray with:
  - Rapid onset of action (Tmax ≤ 7 minutes)
  - Inactivation by ubiquitous blood esterases
- Portable - developed to satisfy unmet need for self-administered therapy that is convenient & safe outside of medical setting
- Data show effectiveness in rapidly terminating AV nodal-dependent PSVT
- Potential benefit **shown to reduce ventricular rate (VR) in AFib patients**

Plasma PK, one and two sequential 70-mg doses



AFib= atrial fibrillation; AV= atrioventricular; Min= minute; PSVT= paroxysmal supraventricular tachycardia; PK = pharmacokinetic; Tmax= time to maximum concentration.

Stambler BS, et al., J Am Coll Cardiol. 2018; Wight D, et al. J Am Coll Cardiol. 2022 Mar, 79 (9_Supplement) 43; Ip JE, et al. Clin Pharmacol Drug Dev. 2024 Apr;13(4):367-379.; NODE-PK-101, -103, data on file.

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ReVeRA-201: Completed Phase 2 Study of Etripamil in AFib-RVR

Objective: To assess the safety and efficacy of intranasal etripamil vs placebo to acutely reduce VR in patients with AFib-RVR

SCREENING & TREATMENT VISIT

Study sites

23 sites in Canada and the Netherlands

Key inclusion criteria

Age ≥18 years

Paroxysmal, persistent, or permanent AFib

VR of ≥110 bpm

Key exclusion criteria

Hx of atrial flutter, stroke, TIA, or peripheral embolism in last 3 months

Rx for arrhythmias within 1 h before administering study drug[1]

Hx of conditions that could jeopardize patient safety or study outcomes

DOUBLE-BLIND STUDY RANDOMIZATION (1:1)

ETRIPAMIL NS
70 mg

PLACEBO NS

ECG monitoring (including ambulatory)

Conducted for at least 10 minutes prior to treatment and for 6 hours post-dosing

OUTCOME MEASURES

Primary endpoints

Mean maximum reduction in VR within 60 min after administering study drug

Safety assessments

Follow-up at 1 day (in-person) and 7 days (virtual) post-dosing
Safety endpoints: clinical AEs, vital signs, and ECG findings[3]

Secondary endpoints

Rapidity of VR reduction, including elapsed time from administering drug to nadir[2]

Duration and proportion of patients achieving <100 bpm, ≥10% or ≥20% reduction in VR; cardioverting to sinus rhythm, within 60 min post-dosing

TSQM-9 rating of Effectiveness & Symptom Relief

19 November 2022
FPFV

12 September 2023
Database Lock

[1]Treatments with intravenous flecainide, procainamide, digoxin, beta-blocker, or calcium channel blockers. [2]Nadir refers to the lowest 5-min moving average heart rate of <100 bpm. [3]Safety endpoints based on ECG analysis included any AV block and ventricular arrhythmia such as premature ventricular contractions and non-sustained ventricular tachycardia.

AE = adverse event; AF = atrial fibrillation; AV = atrioventricular; ECG = electrocardiogram; FPFV = first patient first visit; Hx = history; NS = nasal spray; RVR = rapid ventricular rate; Rx = treatment; SSS = sick sinus syndrome; TdP = torsade de pointes; TIA = transient ischemic attack; TSQM = Treatment Satisfaction Questionnaire for Medication patient-reported outcome; VR = ventricular rate.

Camm AJ, et al. *Circ Arrhythm Electrophysiol.* 2023 Dec, 16 (12); 639-650.

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ReVeRA-201
Etripamil Clinical Research in Atrial Fibrillation

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ReVeRA-201: Completed Phase 2 Study of Etripamil in AFib-RVR

ReVeRA–Study of Etripamil in Patients with AF-RVR

Study Population

Patients presenting to the ED with AF were screened. **87 patients** had AF-RVR with rate ≥110 bpm

69 patients were randomized, 56 received treatment

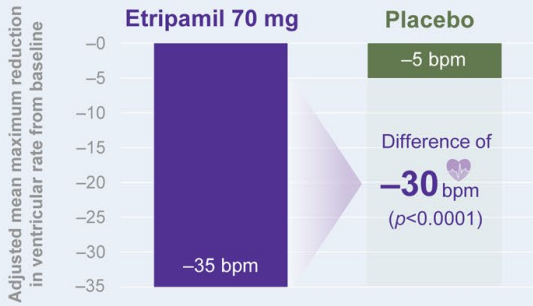
Intervention

Efficacy population* = 49

24 patients received etripamil 70 mg nasal spray

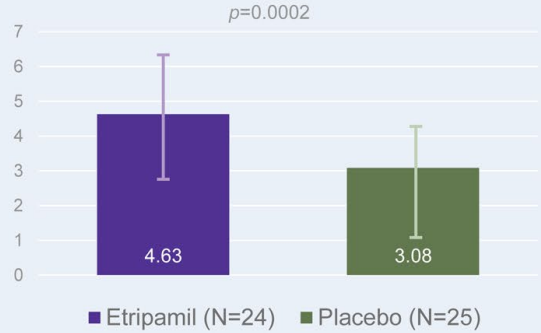
25 patients received matched placebo

Efficacy Outcomes



Median time to maximal effect of 13 min and duration of effect up to 150 min.

Relief of Symptoms



Etripamil treatment was associated with significant improvement in symptom relief and in treatment satisfaction as measured by the TSQM-9.

Baseline patient demographics

Median (IQR) age 65
(35–88) years

61% men

39% women

75% had paroxysmal atrial fibrillation

Most common adverse events

(≥5% of patients)

- Nasal discomfort
- Nasal rhinorrhea
- Lacrimation
- Throat irritation
- Dizziness

These AEs were mild or moderate in intensity

Few serious AEs occurred, 1 in the etripamil group

*Efficacy population is comprised of all randomized patients who remained in AF with adequately diagnostic ECG recordings for at least 60 min post drug

Camm AJ,et al. Circ Arrhythm Electrophysiol. 2023 Dec;16(12):639-650

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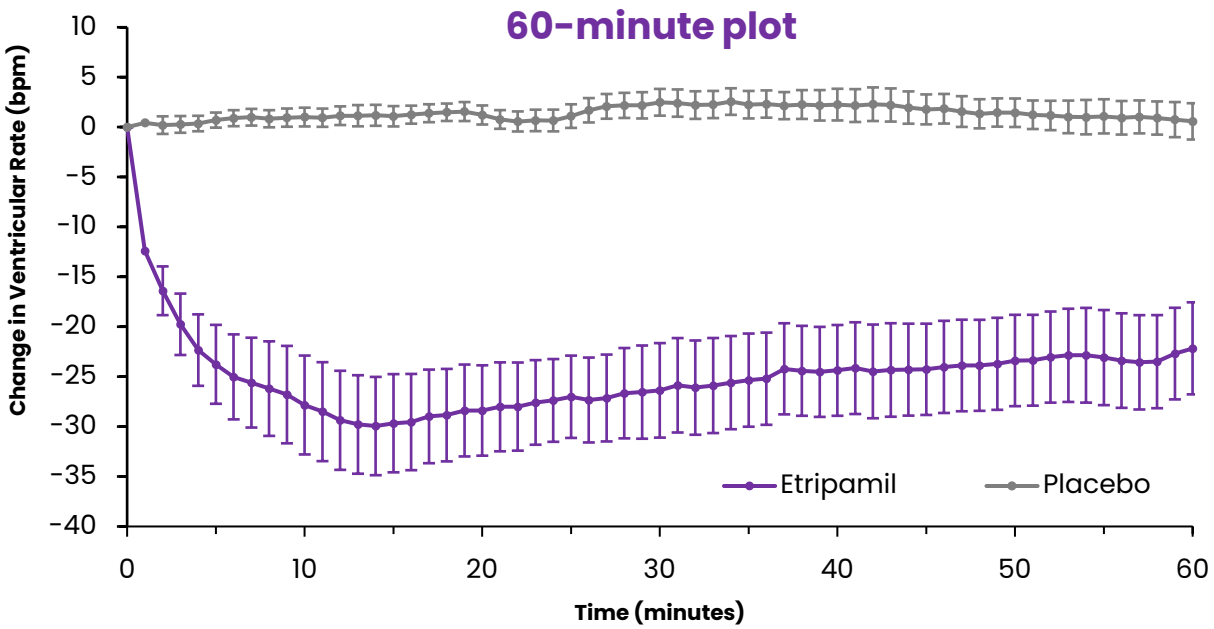

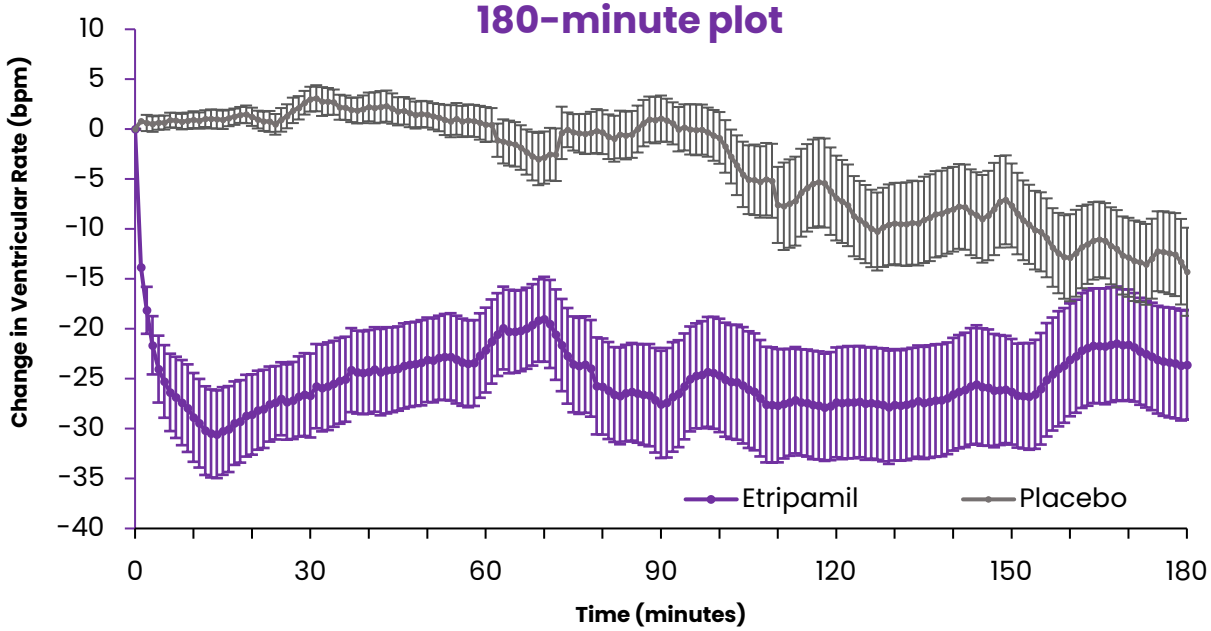

Primary Endpoint

Maximum Reduction in VR adjusting for baseline VR (bpm)	**Placebo NS**[1] N=25	**Etripamil NS, 70 mg**[1] N=24
Adjusted mean (95% CI)	-5.06 (-7.44, -2.67)	-34.97 (-45.13, -24.87)
Difference in adjusted means (95% CI)	--	**-29.91 (-40.31, -19.52)**
p-value[2]	**--**	**<0.0001**

Separation of curves, 0 →180 minutes

Difference between Areas Under the Curves ($AUC_{0 \rightarrow 180}$)	**Placebo NS**[3] N=29	**Etripamil NS**[3], **70 mg** N=27
p-value[4]		**<0.00001**

[1] Efficacy Population, per protocol, did not include pts. not in AFib at the time of dosing, or converted to SR or with significant loss in ECG signal within 60 minutes post study drug. [2] ANCOVA model, comparing maximum reductions from baseline (adjusted means) for placebo vs. etripamil. [3] Safety Population. [4] From *t* test of difference between the AUCs of plots of absolute mean heart rate over 180 min.

BPM= beats per minute; CI= confidence interval; NS=nasal spray; SEM=standard error of the mean; VR=ventricular rate.

Camm AJ,et al. Circ Arrhythm Electrophysiol. 2023 Dec;16(12):639-650

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ReVeRA-201
Etripamil Clinical Research in Atrial Fibrillation

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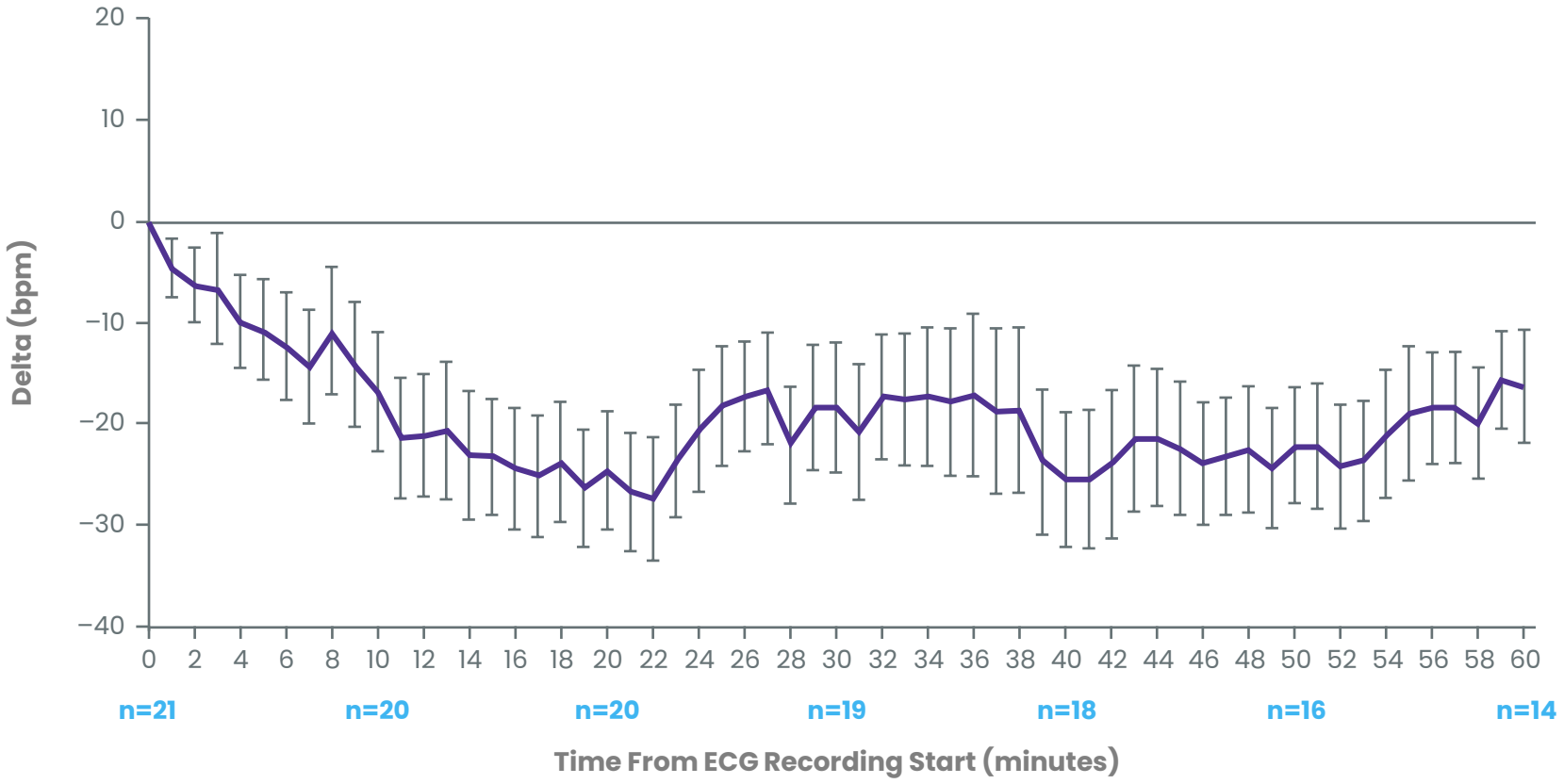
NODE-303: Post Hoc Analysis of Completed Phase 3 Study*

Etripamil Slows Ventricular Rate (VR) in Patients with Symptomatic AFib



VR Reduction in Patients with AFib

- **20 bpm** at 10 minutes
- **27 bpm** at 22 minutes
- **16 bpm** at 60 minutes

Average difference ± standard error from baseline in ventricular rate. The start of the ECG recording was used as an estimated dosing time for all episodes.
AFib-RVR = atrial fibrillation with rapid ventricular rate; BPM= beats per minute.
Dorian, et. al. Heart Rhythm Society 2023 Annual Meeting.

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NODE-303
Etripamil Clinical Research in PSVT

Etripamil is an investigational drug and is not approved by the FDA.

ReVeRA-301: Proposed Phase 3 Registration Study in AFib-RVR

Objective: Phase 3 study to assess safety & efficacy of self-administered intranasal etripamil vs. placebo to acutely reduce VR in patients with symptomatic AFib-RVR

SCREENING VISIT

Study sites

US, Canada, Netherlands

Key inclusion criteria

Age ≥18 years

Documented Hx of symptomatic episodes of AFib-RVR ≥110 bpm

Paroxysmal, persistent, or permanent AFib

Key exclusion criteria

NYHA Class III or IV

CHA_2DS_2 VASc score of >5

Hx of significant bradycardia, SSS, 2nd or 3rd degree AV block without a pacemaker

TREATMENT FOR ACUTE EPISODE ASSIGNED, INSTRUCTIONS GIVEN

Self-administer drug medically unsupervised for perceived episodes[1] of symptomatic AFib-RVR

70 mg etripamil optional repeat dose regimen

DOUBLE-BLIND STUDY RANDOMIZATION (1:1)

ETRIPAMIL NS 70 mg/70 mg

PLACEBO NS

AFib-RVR EVENT

Patient recognizes symptoms

Applies cardiac monitor (ECG or other reliable tracing)

Administers double-blind study drug

If symptoms persist for 10 minutes, administer study drug again

Contacts HCP if symptoms persist beyond 30′

OUTCOME MEASURES

Primary endpoints

Maximum reduction in VR by 30 minutes(′) after 1st dose of drug

Safety assessments

Clinical AEs, AESIs, and ECG findings

Power

Estimated study size: N≈150 total events, based on: 90% power, $P<0.05$ for key secondary

Secondary endpoints

Key secondary, PRO: improvement in patient symptoms at 30′ after 1st dose of drug

PRO: satisfaction with symptom relief at 30′, 45′

PRO: improvement in patient symptoms at 45′

Rate of VR reduction; % of patients reaching VR targets (eg, <100 bpm; reduction of ≥20 bpm); ED visits

[1]Patients may treat up to 4 episodes, re-randomized for each episode.

AESI = AE of special interest; AV = atrioventricular; AFib = atrial fibrillation; Hx = history; PSVT = paroxysmal supraventricular tachycardia; SR = sinus rhythm; VM = vagal maneuver; NS = nasal spray; NYHA = New York Heart Association; PRO = patient-reported outcome; RVR = rapid ventricular rate; SSS = sick sinus syndrome; VR = ventricular rate.

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ReVeRA-301
Etripamil Clinical Research in Atrial Fibrillation

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ReVeRA-301: Proposed Phase 3 Registration Study in AFib-RVR

Objectives

- Double-blind, randomized trial of etripamil 70 mg NS vs. placebo
- Patients self-administer drug at home for perceived episodes of symptomatic AFib-RVR
- Dose: etripamil NS 70 mg with optional repeat 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

Key Inclusion and Exclusion Criteria

Key Inclusion

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

Key Exclusion

- NYHA Class III or IV
- Hx of significant bradycardia, SSS, 2nd or 3rd degree AV Block
- CHA_2DS_2 VASc score of >5

Endpoints

- **Primary endpoint** – maximum reduction in VR at 30 minutes; etripamil vs. placebo
- **Key secondary endpoint** – 30 min PRO; improvement in patient symptoms

Objectives:

- Show $P<0.05$ for primary and key secondary endpoints in ITT population
- Show meaningful PRO-based change in target population (eg, 1-point change on 7-point scale)
- Estimated study size: N≈150-200 total events, based on[1]: 90% power, $P<0.05$

AFib-RVR = atrial fibrillation with rapid ventricular rate; AV = atrioventricular; NYHA = New York Heart Association; PRO = patient-reported outcome; NS = nasal spray; PSVT = paroxysmal supraventricular tachycardia; SSS = sick sinus syndrome.

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ReVeRA-301 Summary

- The Phase 2 ReVeRA-201 trial showed that **etripamil NS** demonstrated **substantial reduction in VR in patients with AFib-RVR** (difference between etripamil vs placebo in maximum reduction from baseline: -29.1 bpm; p <0.0001)

- In a *post hoc* analysis of the NODE-303 phase 3, open-label study, self-administered **etripamil NS** was observed to **reduce the VR in patients with symptomatic AFib**, and the effect was sustained for at least 30 to 60 minutes.

- **ReVeRA-301** (NCT06716021) 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**

ReVeRA-301
Etripamil Clinical Research in Atrial Fibrillation

Further investigation is warranted in a
Phase 3 Study with at-home, self-administration of
etripamil NS in patients with AFib-RVR

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ReVeRA-301
Etripamil Clinical Research in Atrial Fibrillation

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Thank you

James E. Ip,[1] A. John Camm,[2] Marco Alings,[3] Paul Dorian,[4] Martin Hemels,[5] Peter R. Kowey,[6] Sean D. Pokorney,[7] Denis Roy,[8] Benjamin Steinberg,[9] David B. Bharucha,[10] Jonathan P. Piccini[11]

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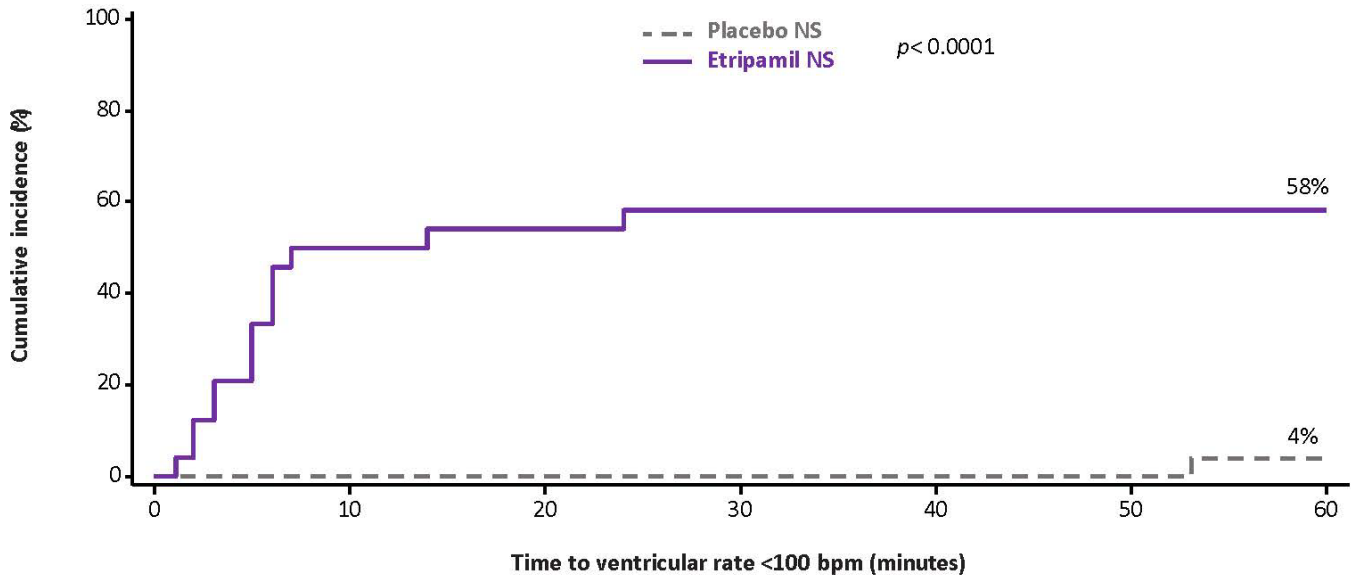
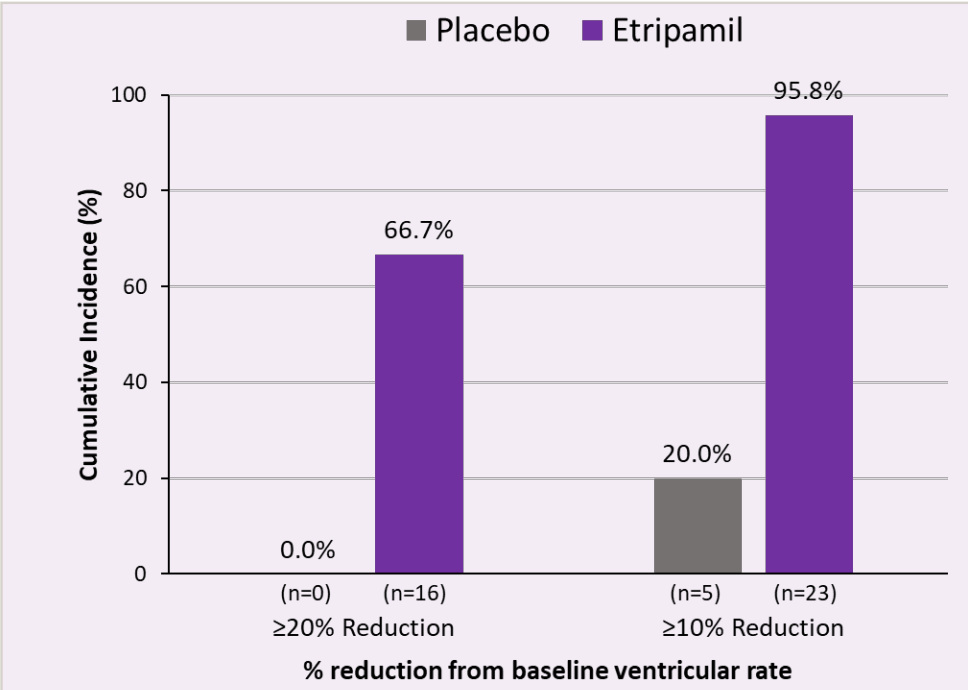
ReVeRA-201 Achievement of VR <100 bpm or a Reduction of ≥10% or ≥20% From Baseline By 60 minutes



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

Patients Achieving a VR <100 bpm	Placebo NS, n=25[1]	Etripamil NS, 70 mg, n=24[1]
n (%)	1 (4.0)	14 (58.3)
p-value[2]	--	<0.0001
Median time to achieve VR < 100 bpm	not applicable	7 min



Placebo NS (n=25[1]) vs. Etripamil NS, 70 mg (n=24[1])	
Patients Achieving a ≥10% reduction in VR from baseline, p-value[2]	<0.0001
Patients Achieving a ≥20% reduction in VR from baseline, p-value[2]	<0.0001

[1] Efficacy Population is comprised of all randomized patients receiving study drug who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. [2] By chi-square test.
Bpm = beats per minute; NS = nasal spray; VR = ventricular rate