

**Milestone**  
PHARMACEUTICALS

# Etripamil Nasal Spray: Data for Acute Rate Control in AFib-RVR\*

\*Atrial Fibrillation with a Rapid Ventricular Rate

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STANFORD BIODESIGN ARRHYTHMIA TECHNOLOGIES MEETING  
BOSTON, MA  
MAY 15, 2024

ETRIPAMIL NASAL SPRAY IS AN INVESTIGATIONAL DRUG





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## POTENTIAL CONFLICTS:

*David Bharucha is an officer, employee, & stockholder of Milestone*

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## Acute Outpatient Arrhythmia Treatment



### Therapeutic Targets (current)

- ✓ Paroxysmal supraventricular tachycardia (PSVT), acute rx
- ✓ Atrial fibrillation with a rapid ventricular rate (AFib-RVR), acute rx



### Novel Approaches

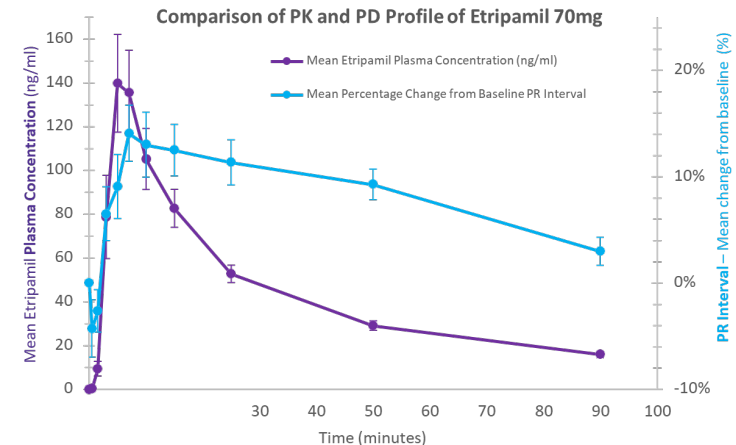
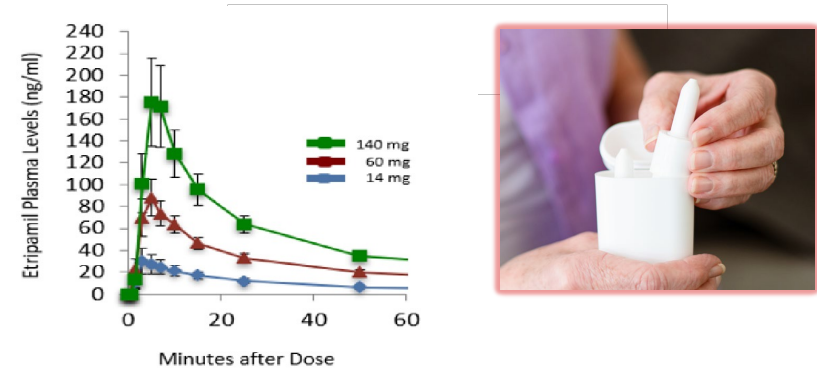
- ✓ Shift from Emergency Department care to patient self-management
- ✓ Etripamil: novel calcium channel blocker (IP protection until 2036)
- ✓ **With intranasal administration, achieve pharmacologic profile customarily observed with intravenous bolus rx**

PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; NDA = New Drug Application

# Etripamil Pharmacology: Potential Treatment for AFib with RVR



- Novel, investigational, L-type NDHP  $\text{Ca}^{+2}$  channel blocker
- Formulated for intranasal spray with:
  - Rapid onset of action ( $T_{\text{max}} \leq 7 \text{ min}$ )
  - Inhibits slow inward Ca channels & prolongs AVN ERP
  - Inactivated by serum esterases
  - Clinical data indicate an acute effect on AVN refractoriness and conduction
- Unmet need for self-administered therapy that is portable & safe outside healthcare setting



Stambler, et al., *J Am Coll Cardiol.* 2018.

Ip, et al., *AHA.* 2021

Wight, et al. *J Am Coll Cardiol.* 2022

Stambler, et al. *Circ Arrhythm Electrophysiol.* 2022

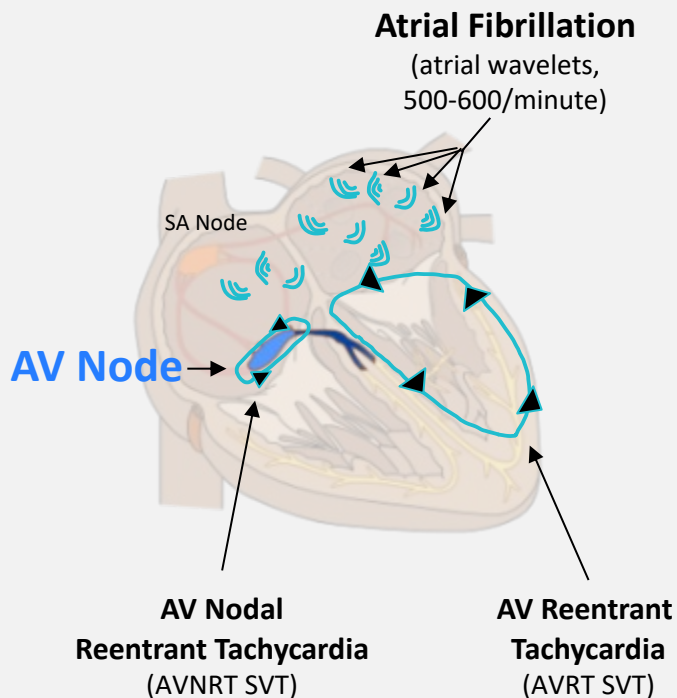
NDHP=non-dihydropyridine, AVN=AV nodal, ERP=effective refractory period

Dorian, *HRS.* 2023

Stambler-Ip et al, *ACC.* 2024

Ip, et al. *Clin Pharmacol Drug Dev.* 2024

# Known Role of NDHP Calcium Channel Blockers To Alter AV-Nodal Conduction, Impacting Select Tachyarrhythmias



## For NDHP Calcium Channel Blockers, expect:

- Prolongation of AVN refractoriness & slowed conduction velocity through the AVN
- In AVN-dependent SVT, expect (and shown for etripamil, intranasal)<sup>1,2</sup>:
  - Slowing of tachycardia rate during SVT
  - Termination of SVT & conversion to SR
- In AFib-RVR, expect:
  - Acute rate control<sup>3</sup>

Etripamil (intranasal) is an investigational, novel NDHP CCB

NDHP = non-dihydropyridine; AVN = AV node; SVT = supraventricular tachycardia; AFib-RVR = atrial fibrillation and rapid ventricular rate

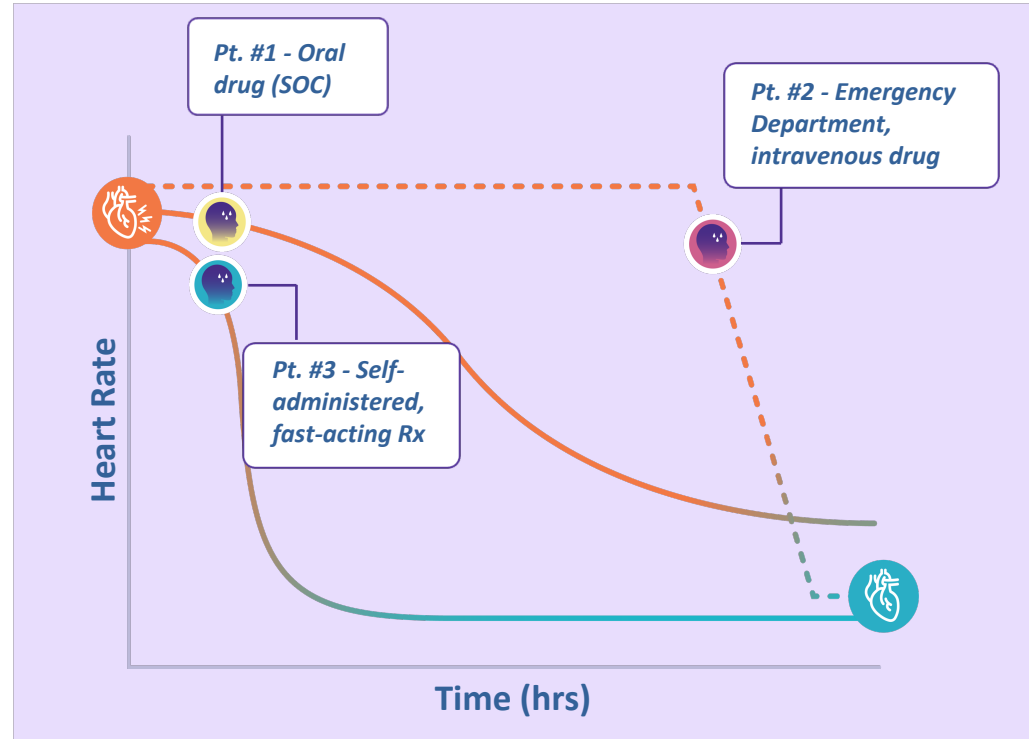
Source: adapted from <https://en.ecgpedia.org>, accessed 2/2021. 1. Ip JE et al, *AHA*.2021. 2. Stambler BS et al, *Lancet* (2023). 3. Camm AJ et al, *Circ Arrhythm Electrophysiol.* (2023).

# Unmet Need & Rationale for Etripamil in AF-RVR



Hypothetical course of 3 patients, each starting with AFib and a rapid ventricular rate

- Patient #1: oral AVN-acting drug
- Patient #2: intravenous AVN-acting drug
- Patient #3: self-administered, fast-acting, AVN-acting drug

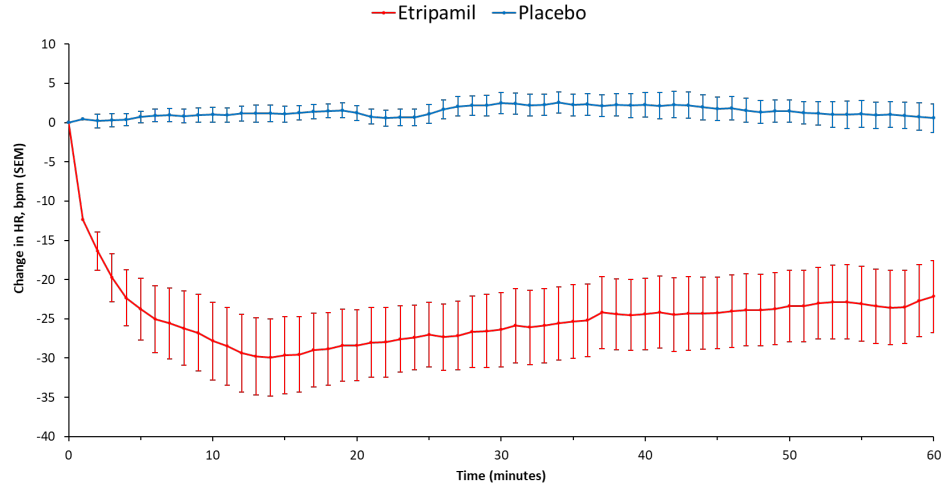


AVN = AV node, AFib-RVR = atrial fibrillation with rapid ventricular rate

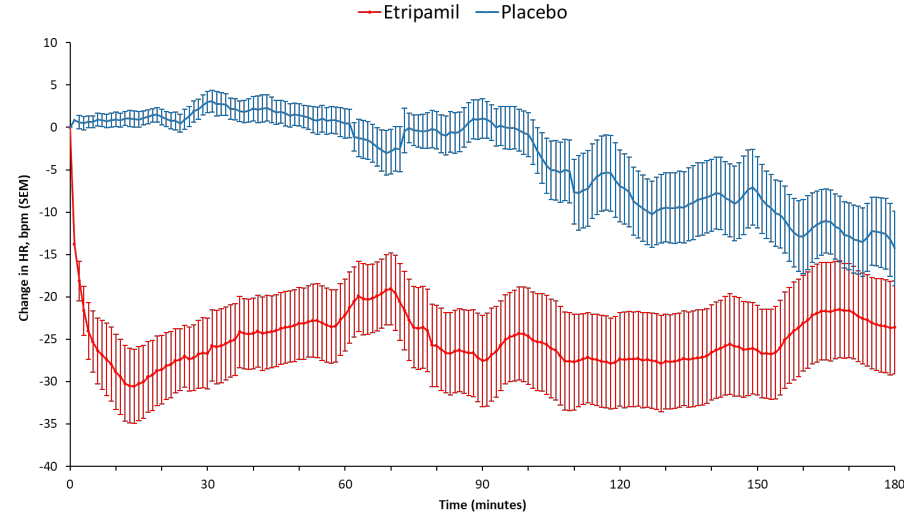
# ReVeRA – Etipamil v. Pbo, Patients Presenting to an Emergency Department with AFib-RVR ; Randomized, Double-Blinded



60 min plot



180 min plot



## Primary Endpoint

Maximum Reduction in VR adjusting for baseline VR (bpm)	Placebo NS <sup>1</sup> N=25	Etipamil NS, 70 mg <sup>1</sup> N=24
Adjusted mean (95% CI)	-5.06 (-7.44, -2.67)	-34.97 (-45.13, -24.87)
Difference in adjusted means (95% CI)	--	<b>-29.91 (-40.31, -19.52)</b>
p-value <sup>2</sup>	--	<b>&lt;0.0001</b>

## Separation of curves, 0 → 180 minutes

Difference between Areas Under the Curves (AUC <sub>0→180</sub> )	Placebo NS <sup>3</sup> N=29	Etipamil NS <sup>3</sup> , 70 mg N=27
p-value <sup>4</sup>	--	<b>&lt;0.00001</b>

<sup>1</sup> Efficacy Population, per protocol, did not include pts. not in AF at the time of dosing, or converted to SR or with significant loss in ECG signal within 60 minutes post study drug.. <sup>2</sup> ANCOVA model, comparing maximum reductions from baseline (adjusted means) for placebo vs. etipamil. <sup>3</sup> Safety Population. <sup>4</sup> From t test of difference between the AUCs of plots of absolute mean heart rate over 180 min. SEM=standard error of the mean; NS=nasal spray; VR=ventricular rate.

Sources: Camm AJ et al. *Circ Arrhythm Electrophysiol.* (2023); AHA Scientific Sessions (Nov. 2023)





- **In patients presenting to an emergency department with AF-RVR, etripamil (intranasal) was quickly and significantly effective in reducing RVR**
  - Maximal reduction from baseline in first 60 min.: -34.97 bpm (placebo-corrected: -29.91 bpm;  $p < 0.0001$ )
  - Median time to maximum reduction of 13 min & duration of effect >150 min
  - Median duration of maintaining a VR <100 bpm was 45.5 min in the first 60 min after drug
- **Further data:**
  - Majority of AEs were localized to the drug-administration site & low incidence of serious AEs
  - Significant symptom relief & satisfaction as measured by the TSQM-9 PRO
  - Approx. 2-fold greater use of AVN-acting drugs in 1st 24-hours in placebo arm
- **Potential role of etripamil nasal spray, 70 mg, to acutely reduce VR in patients with symptomatic AF-RVR**
- **Phase 3 trial with at-home, self-administration of etripamil: in-planning & in-discussion with regulators**

Camm AJ, et al. Multicenter, Phase 2, Randomized Controlled Study of the Efficacy and Safety of Etripamil Nasal Spray for the Acute Reduction of Rapid Ventricular Rate in Patients with Symptomatic Atrial Fibrillation (ReVeRA-201). *Circ Arrhythm Electrophysiol.* 2023; 16(12):639-650





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***Thank you!***

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American Heart Association, Featured Science Session (11 Nov 2023, Philadelphia, PA)  
Online published 11 Nov 2023; print Dec 2023

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