

Milestone
PHARMACEUTICALS

Intranasal Etripamil for the Potential Acute Treatment of Supraventricular Tachycardia and Atrial Fibrillation with Rapid Ventricular Rate

DAVID BHARUCHA, MD, PHD, FACC,
CHIEF MEDICAL OFFICER, MILESTONE

STANFORD BIODESIGN NEW ARRHYTHMIA TECHNOLOGIES RETREAT,
NEW ORLEANS, LA
MAY 18, 2023

ETRIPAMIL IS AN INVESTIGATIONAL DRUG. PRESENTED MATERIAL IS NOT PROMOTIONAL.



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POTENTIAL CONFLICTS:

David Bharucha is an officer, employee & stock-holder of Milestone



Mid-/Late-Stage Development and Pre-Commercial Cardiovascular Company



Targeting Large Areas of Unmet Need

- ✓ PSVT, acute Rx
- ✓ AFib-RVR, acute Rx
- ✓ Additional pipeline opportunities - cardiac



Paradigm-Changing Approach

- ✓ Shift from Emergency Department care to patient self-management
- ✓ Etripamil: novel calcium channel blocker
- ✓ With intranasal administration, achieve pharmacologic profile customarily observed with intravenous Rx

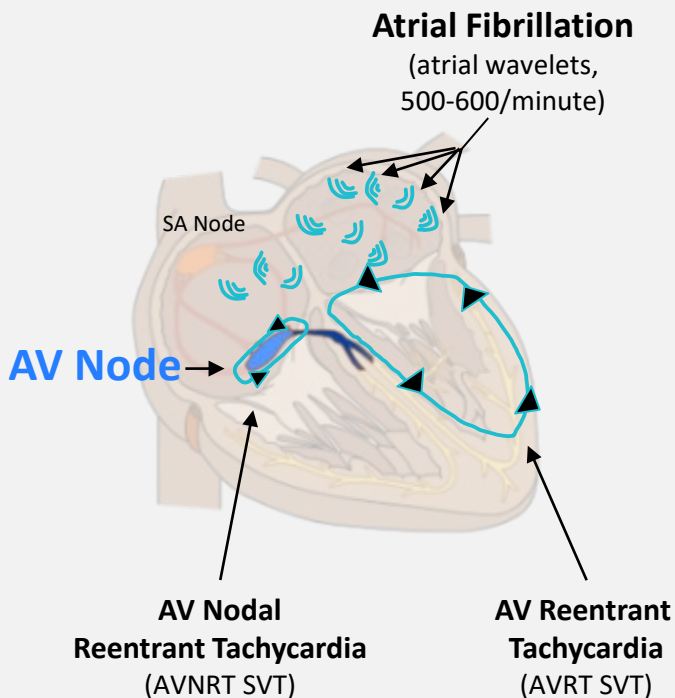


Positioning for Future Success

- ✓ PSVT: pivotal RAPID Phase 3 efficacy met primary endpoint with high-degree of efficacy and favorable safety
- ✓ PSVT: NDA submission on-track for Q3-2023
- ✓ AFib-RVR Program: Reporting data in 2023, and planning for Phase 3

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

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



Intravenous NDHP Calcium Channel Blockers

- Prolong AVN refractoriness & slow velocity of signals conducted through the AVN
- In AVN-dependent SVT, expect:
 - Slowing of tachycardia rate during SVT
 - Termination of SVT & conversion
- In AFib-RVR, expect:
 - Acute rate control

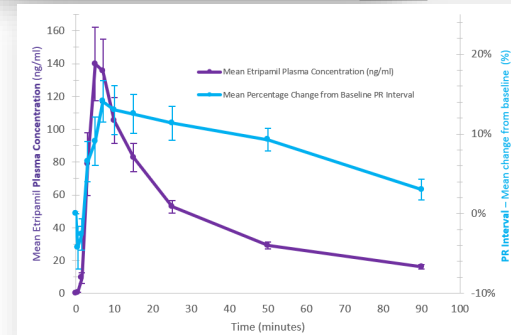
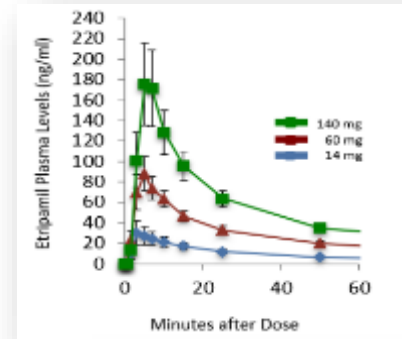
Etripamil (intranasal) is an investigational, novel NDHP CCB

NDHP = non-dihydropyridine; AVN = AV node; SVT = supraventricular tachycardia; AFib-RVR = atrial fibrillation with rapid ventricular rate
Source: adapted from https://en.ecgpedia.org/index.php?title=Supraventricular_Rhythms, accessed 2/2021

Etripamil: Investigational, Potential New Treatment for Select Tachycardias

- New Chemical Entity (NCE), investigational, NDHP L-type calcium channel blocker, from medicinal chemistry work at Milestone
- Formulated for intranasal delivery:
 - Rapid onset of action ($T_{max} \leq 7$ min)
 - Inactivation by ubiquitous blood esterases
- Effective at rapidly altering AV-nodal EP properties, delivered as nasal spray
- Portable - developed to satisfy unmet need for self-administered therapy that is convenient & safe outside of medical setting

PK and PK/PD Plots of
Intranasally Administered Etripamil

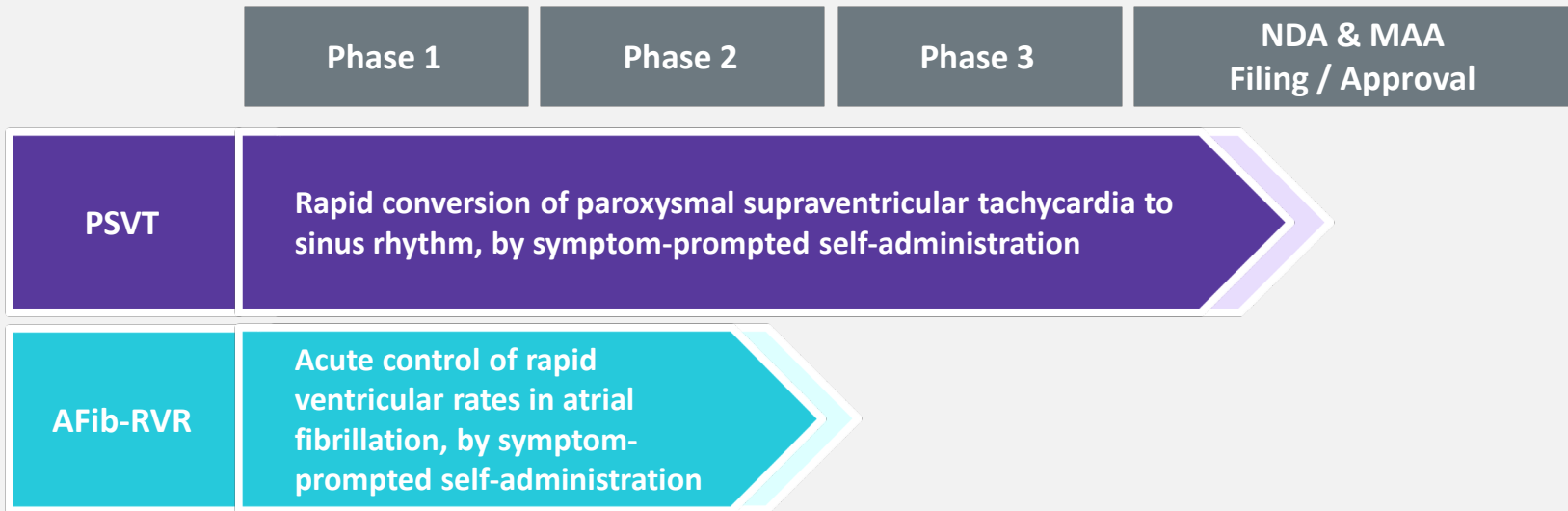


NDHP = non-dihydropyridine, EP = electrophysiologic, PK = pharmacokinetic, PD = pharmacodynamic. Error bars = standard error (SE). Sources: Stambler BS, et al., J Am Coll Cardiol. 2018; Wight D, et al. J Am Coll Cardiol. 2022; Ip JE, et al. manuscript in preparation; NODE-PK-101, data on file.

Clinical Pipeline Advancement



Etripamil, intranasally self-administered, being investigated for 'at-home' use, outside a medical setting



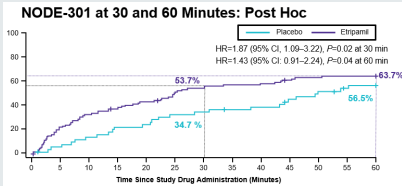
PSVT = paroxysmal supraventricular tachycardia; AFib-RVR = atrial fibrillation with rapid ventricular rate, NDA = New Drug Application [FDA], MAA = Marketing Authorization Application [EMA]

Impact of Etripamil (70 mg, intranasal) on AVN during SVT and in AFib-RVR

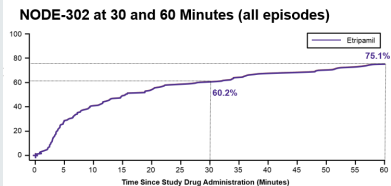


Conversion of AVN-Dependent SVT to SR (Ph3, event-driven trials, pbo-control* & open-label)**

***At 30 min.: Hazard Ratio: 1.87, $p < 0.02$**



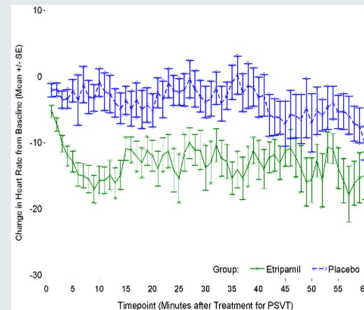
****Conversion event curve, open-label**



ACC 2021 / HRS 2022

Tachycardia-Rate Reduction during AVN-Dependent SVT (Ph3, event-driven trial, pbo-controlled)

Tachycardia Heart Rate reduction with drug, compared with pbo, shows AVN impact during SVT pre-termination. Timing consistent with drug's PK



AHA 2021

Patients with AFib-RVR enrolled into SVT Program

Effect of Etripamil Nasal Spray on Ventricular Rate in Patients Experiencing Symptomatic Atrial Fibrillation

Patients with AFib-RVR, administered etripamil in emergency-department presentation

ReVeRA, NODE-202, randomized, double-blinded, placebo-controlled trial. Efficacy and Safety of Intranasal Etripamil to Control Ventricular Rates in AFib-RVR

**HRS,
May 19, 2023[‡]**

**Top Line Results,
2H 2023**

[‡]Moderated Poster Session MP-453091, PO-456094, Friday May 19, 2023, 3:00-3:05 pm CDT; Dorian, Alings, Coutu, Ip, Martinez, Piccini, Stambler, Thernil, Omodele, Shardonofsky, Plat, Bharucha, Camm.



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Thank you

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