Milestone™ PHARMACEUTICALS

Virtual Key Opinion Leader Event

Etripamil for the Treatment of AFib-RVR

May 22, 2023

Forward Looking Statement

The Presentation contains forward-looking statements within the meaning of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Words such as ‘‘aim,’’ ‘‘anticipate,’’ ‘‘assume,’’ ‘‘believe,’’ ‘‘contemplate,’’ ‘‘continue,’’ ‘‘could,’’ ‘‘design,’’ ‘‘due,’’ ‘‘estimate,’’ ‘‘expect,’’ ‘‘goal,’’ ‘‘intend,’’ ‘‘may,’’ ‘‘objective,’’ ‘‘plan,’’ ‘‘predict,’’ ‘‘positioned,’’ ‘‘potential,’’ ‘‘project,’’ ‘‘seek,’’ ‘‘should,’’ ‘‘target,’’ ‘‘will,’’ ‘‘would’’ (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. These forward- looking statements are based on Milestone's expectations and assumptions as of the date of this Presentation. Each of these forward-looking statements involves risks and uncertainties. Actual results may differ materially from these forward-looking statements. Forward-looking statements contained in this Presentation include statements regarding (i) the design, progress, timing, scope and results of the etripamil clinical trials in PSVT and AFib-RVR, (ii) the potential efficacy, safety and tolerability of etripamil, (iii) the potential of etripamil to deliver a clinically meaningful benefit to patients with PSVT in the home-setting environment and to empower patients to take control of their condition as well as provide value to the healthcare system, (iv) the possibility that data could fulfill the efficacy requirement for an NDA submission with the FDA for etripamil, (v) plans relating to commercializing etripamil, if approved, including the geographic areas of focus and sales strategy and (vi) the potential market size and the rate and degree of market acceptance of etripamil and any future product candidates and the implementation of Milestone's business model and strategic plans for its business, etripamil and any future product candidates. Important factors that could cause actual results to differ materially from those in the forward-looking statements include, but are not limited to, the risks inherent in biopharmaceutical product development and clinical trials, including the lengthy and uncertain regulatory approval process, uncertainties related to the timing of initiation, enrollment, completion and evaluation of clinical trials, including the RAPID and ReVeRA trials, and whether the clinical trials will validate the safety and efficacy of etripamil for PSVT, AFib-RVR, or other indications, among others, as well as risks related to pandemics and public health emergencies, including those related to COVID-19, and risks related the sufficiency of our capital resources and our ability to raise additional capital. These and other risks are set forth in Milestone's filings with the U.S. Securities and Exchange Commission, including in its annual report on Form 10-K for the year ended December 31, 2022, under the caption "Risk Factors”, as such discussion may be updated in future filings we make with the SEC. Except as required by law, Milestone assumes no obligation to update any forward- looking statements contained herein to reflect any change in expectations, even as new information becomes available.

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Etripamil is an investigational new drug, which is not approved for commercial distribution in the United States.

Participants on Today's Call

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Staff Cardiac Electrophysiologist, St. Michael's Hospital

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Joseph Oliveto
President and Chief Executive Officer

David Bharucha, MD, PhD, FACC
Chief Medical Officer

Amit Hasija
Chief Financial Officer & Executive Vice President of Corporate Development

Lorenz Muller
Chief Commercial Officer

Today's Agenda

Introduction	Joseph Oliveto	*President & CEO*
AFib-RVR Overview and Etripamil Characterization	David Bharucha, MD, PhD, FACC	*Chief Medical Officer*
Review of AFib-RVR Data Presented at HRS.2023	Paul Dorian, MD, MSC	*Professor of Medicine, Departments of Medicine and Pharmacology, University of Toronto; Staff Cardiac Electrophysiologist, St. Michael's Hospital*
Physician Perspective and Potential Etripamil Use Case	Jonathan P. Piccini, MHS, MD, FHRS	*Professor of Medicine & Population Health, Director, Cardiac Electrophysiology, Duke University & Duke Clinical Research Institute*
Etripamil Program in AFib-RVR and Next Steps	David Bharucha, MD, PhD, FACC	*Chief Medical Officer*
Closing Remarks and Q&A	Joseph Oliveto	*President & CEO*

Milestone Pharmaceuticals - Targeting Vast Unmet Need for Patient Management of Common Heart Conditions

Targeting Common Arrhythmias

- PSVT
- AFib-RVR
- High burden on patients *and* on the healthcare system

Empowering Patients to Treat Themselves

- Etripamil: novel (NCE) calcium channel blocker
- Fast-acting, well-tolerated, portable, on-demand
- Shift from Emergency Department to patient self-management

Positioned for **Success**

- Positive Phase 3 results in PSVT
- NDA submission Q3 2023
- AFib-RVR program expands market – Initial data in 2023 including from ReVeRA
- Experienced leadership driving commercialization

PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; NCE = New Chemical Entity

AFib-RVR Overview and Characterization of Etripamil

David Bharucha, MD, PhD, FACC

Chief Medical Officer

Atrial Fibrillation with Rapid Ventricular Rate (AFib-RVR) Causes Markedly Symptomatic Attacks That Disrupt Patients' Lives

Symptoms include…

- Heart palpitations
- Chest pressure or pain
- Shortness of breath
- Fatigue
- Light-headedness
- Anxiety

Many patients feel anxious and powerless

AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate

Current Treatment of Acute Attacks in the Emergency Department are Burdensome and Costly

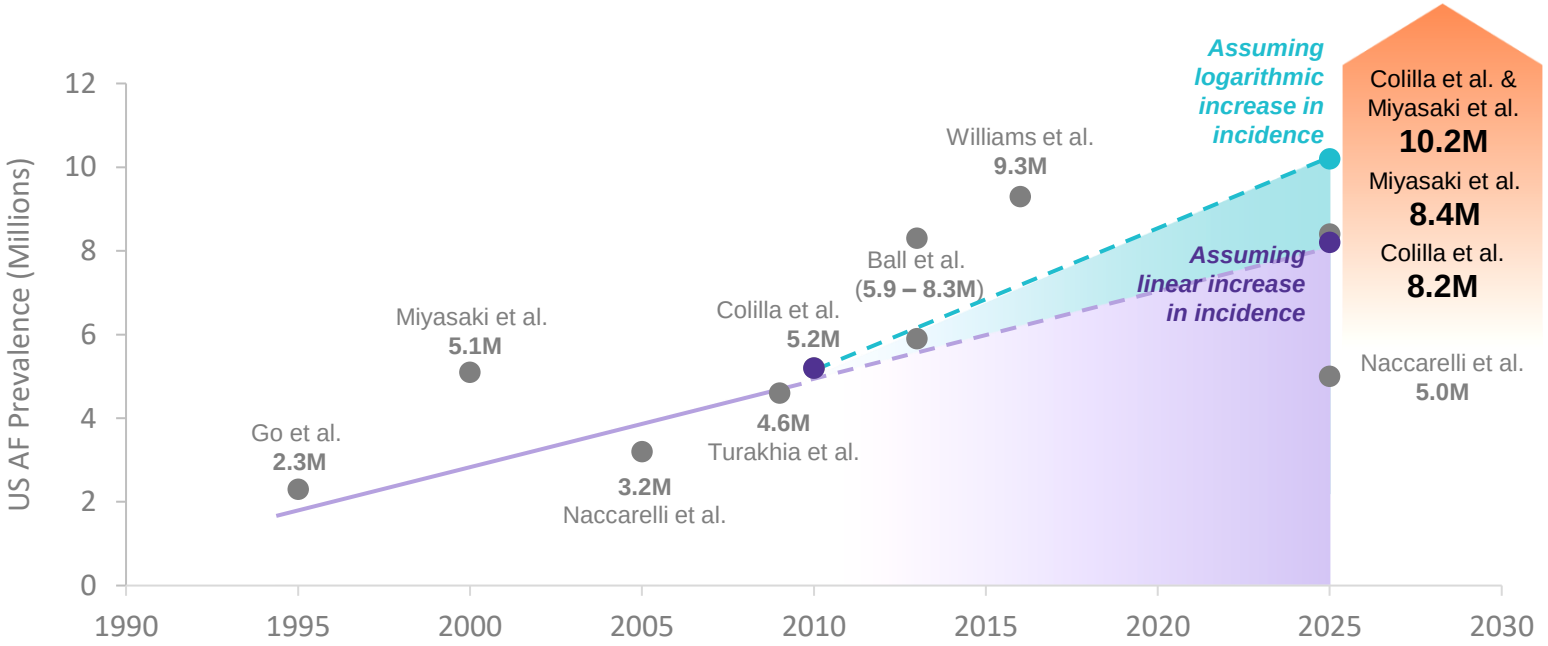
For many patients, physicians and payers:

- Time-consuming, disruptive
- Often results in a hospital admission
- Expensive use of healthcare system resources

Need for simple, fast-acting treatment, reduce trips to ED and calls to physicians

ED = Emergency Department

US Prevalence of Atrial Fibrillation Projected to be 8.2 – 10.2 million by 2025



Adapted from AHA Heart Disease and Stroke Statistics 2019 Update

Projections include US prevalence of 12M by 2030. Sources: Benjamin et al., Circulation, 2019, 139, e56-e528; Go et al., JAMA, 2001, 285(18), 2370-2375; Turakhia et al., PLOS ONE, 2018, 13(4), e0195088; Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Kornej et al. Circ. Res., 2020, 127, 4-20; Miyasaka et al., Circulation, 2006, 114, 119-125; Naccarelli et al., Am. J. Cardiol., 2009, 104(11), 1534-1539; Williams et al., Am. J. Cardiol., 2017, 120(11), 1961-1965; Ball et al., Int. J. Cardiol., 2013, 5(1), 1807-1824

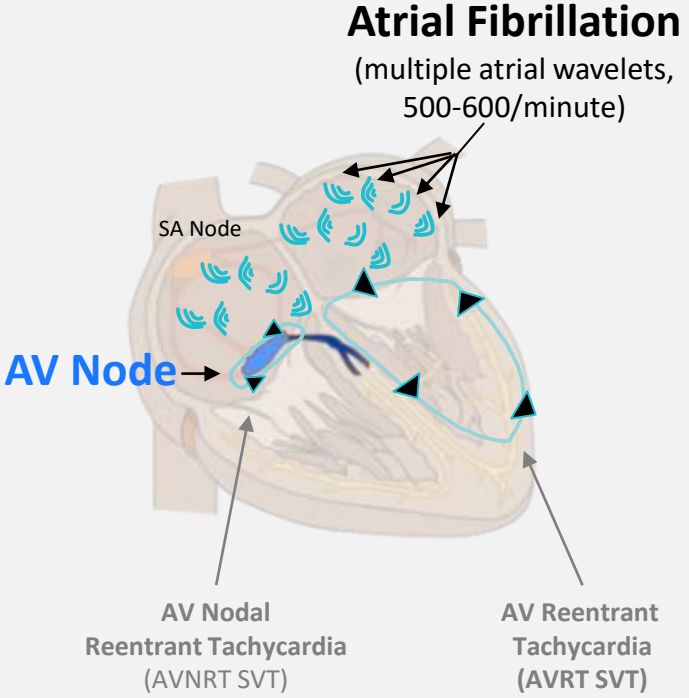
Available Care for AFib-RVR is Inadequate – Most Patients Experience Acute Events Despite Preventive Options

	Chronic / Preventive Rx	Acute Rx
AFib-RVR	• Oral Therapies for rate control (eg, CCBs, BBs) • Oral Therapies for rhythm control (eg, cardiac antiarrhythmic drugs) • Catheter ablation	• Chronic oral drugs for rate or rhythm control – do not prevent breakthrough AFib-RVR • Acutely given oral drugs (AV-nodal agents) have delayed response times, and often do not deliver effective rate control • Intravenous treatments (eg, CCBs) or electrical cardioversion require ED or hospital visits • A rapidly acting drug – self-administered without an IV, at home— could help these patients • Could be stand-alone treatment or bridge

AFib-RVR = atrial fibrillation with rapid ventricular rate; CCB = calcium channel blocker; BB = beta-blocker; ED = emergency department; DC = direct current.

ACC/AHA Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, Circulation. 2016;133

Intravenous Calcium Channel Blockers Are Proven to Control AFib-RVR



Intravenous Calcium Channel Blockers (CCBs):

- Slows & attenuates conduction signals from the atria to the ventricles over the AV Node
- In AFib-RVR, expect:
  - Acute rate control
  - Reduction in symptoms

Etripamil is an investigational, novel intranasal CCB

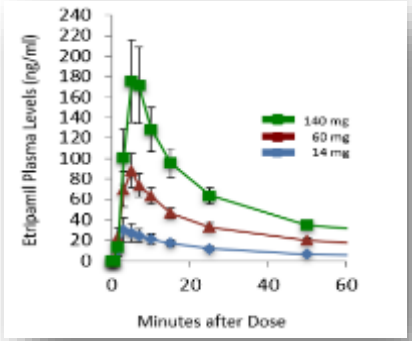
AFib-RVR = atrial fibrillation with rapid ventricular rate, CCB = calcium channel blocker

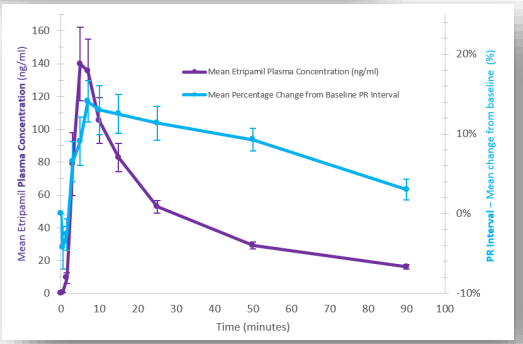
Sources: adapted from https://en.ecgpedia.org/index.php?title=Supraventricular_Rhythms, accessed 2/2021

Etripamil Nasal Spray: A Novel (NCE) CCB Designed to be Fast, Portable, and Patient-Administered

- Developed to quickly act, to prolong AV-nodal properties and to acutely impact tachycardia and rapid heart beats conducted from the atria to the ventricles
- Designed for patient self-administration where and whenever the episodes occur
- Novel, investigational, L-type, NDHP calcium channel blocker; NCE (new chemical entity) from medicinal chemistry work at Milestone*
- Formulated as intranasal spray with:
  - Rapid onset of action (T_{max} ≤ 7 min)
  - Metabolism by ubiquitous blood esterases: drug eliminated within a few hours

PK and PK/PD Plots of Intranasally Administered Etripamil





*Composition of matter and formulation patent protection until 2036. CCB=calcium channel blocker, NDHP=non-dihydropyridine, PK=pharmacokinetic, PD=pharmacodynamic, NCE=New Chemical Entity. Error bars = standard error (SE) of the mean. Sources: Stambler BS, et al., J Am Coll Cardiol. 2018; Wight D, et al. J Am Coll Cardiol. 2022 Mar, 79. Ip JE, et al. manuscript in preparation. NODE-PK-101, -103, data on file.

Review of AFib-RVR Data Presented at HRS.2023 (Heart Rhythm Society)

Paul Dorian, MD, MSC

Professor of Medicine, Departments of Medicine and Pharmacology, University of Toronto; Staff Cardiac Electrophysiologist, St. Michael's Hospital

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

NODE-303 Atrial Fibrillation Heart Rate Analysis

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Atrial Fibrillation with Rapid Ventricular Response (AF-RVR)

AF is the most common sustained arrhythmia

- An estimated 2.7 to 6.1 million people in the United States have AF with projections to reach nearly 12.1 million in 2030[1]

Prevalence of AF increasing with aging population

- Affects ~10% of the population aged 80 years and above[2]

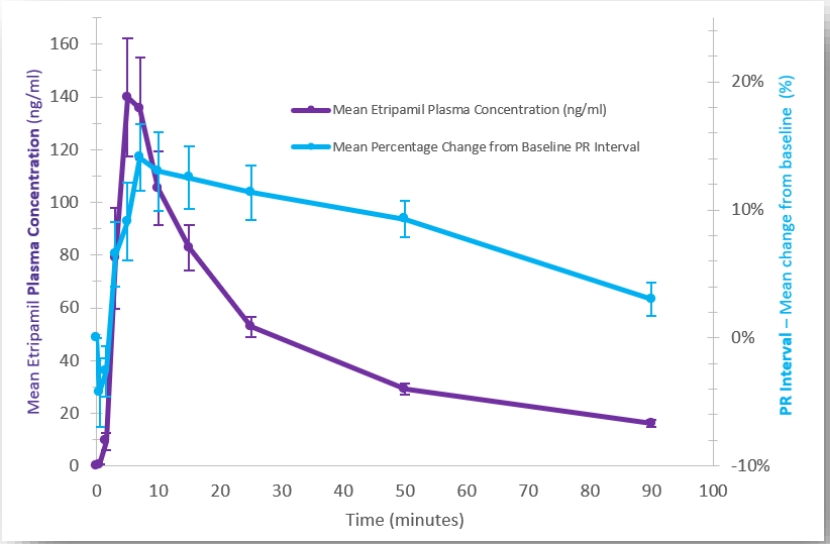
Clinical manifestations of AF are variable. Often, symptoms are due to an RVR

- Rate control in patients with AF is an important strategy to reduce symptoms, to improve quality of life, and is often needed acutely even if a rhythm control approach is planned

1. Colilla S, et al. *Am J Cardiol* 2013; 112:1142–1147; 2. Go AS, et al. *JAMA* 2001; 285:2370–2375.

Atrial Fibrillation with Rapid Ventricular Response (AF-RVR)

- Atrial fibrillation is often associated with symptoms related to a rapid ventricular response
- There are no available rapidly acting agents to slow ventricular rates, suitable for outpatient self-administration
- Etripamil is a novel (new chemical entity) calcium channel blocker formulated for intranasal administration, with rapid onset of action (T_{max} ≤ 7 min), under investigation for reentrant SVT



NODE-303: Open-Label, Phase 3 Trial of Etripamil for SVT

Trial Design

- Event-driven, multi-center, open-label, multi-exposure study to evaluate the safety of etripamil in patients with PSVT
- Patients perceived PSVT episodes as outpatients and self-administered etripamil nasal spray (70 mg)
- Continuous ECG data (patient applied) were acquired at the onset of symptoms for 1 hour

Current report: ad hoc analysis in patients with AF

Some patients in NODE-303 experienced AF rather than PSVT; these episodes were the subject of this sub-study.

- 21 of 1024 treated perceived-PSVT episodes (n = 18 patients) were actually AF-RVR rather than PSVT based on ECG data
- Start of ECG recording was used as Time=0 for assessment of ventricular rate

Limitations

- Time of drug administration was variably related to the start of ECG recording
  - Start time of the ECG recording was used as baseline for the analysis
- Patients have a history of SVT, and may not be representative of the entire AF population

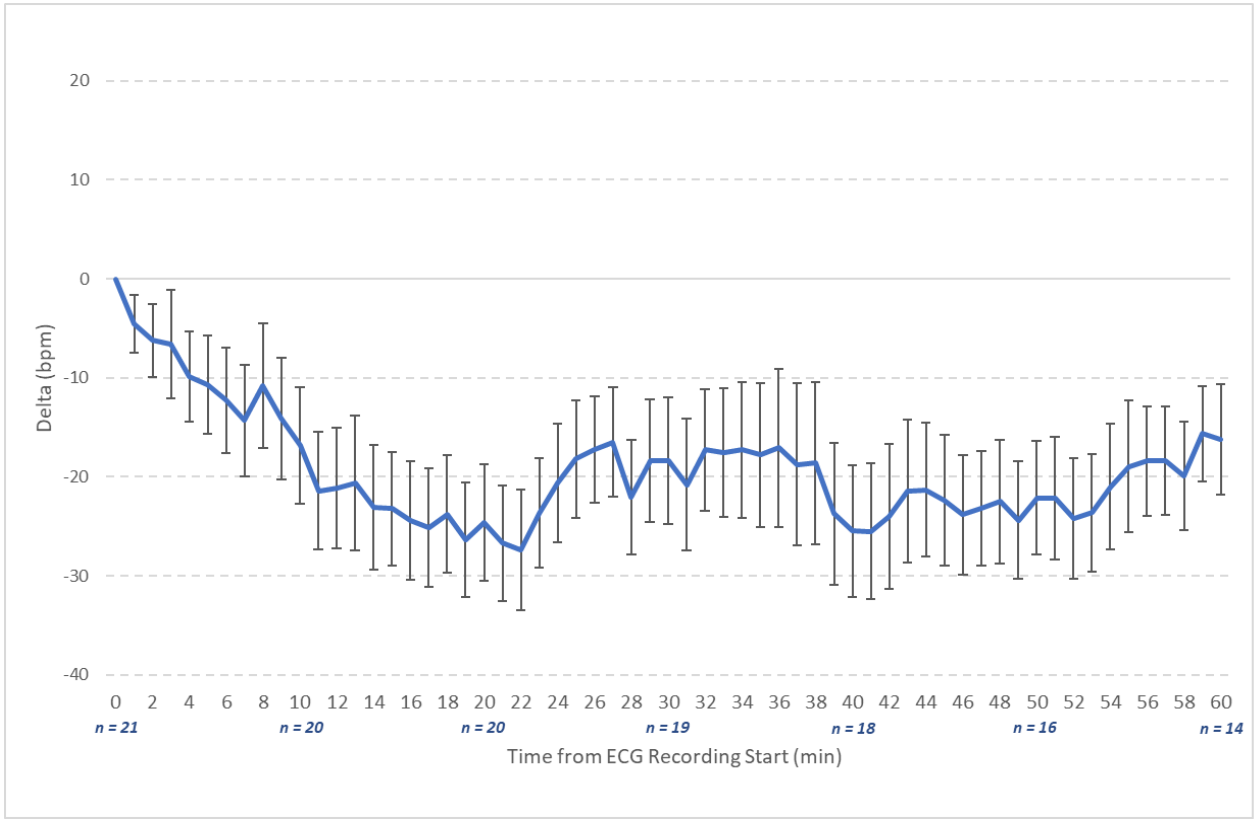
PSVT = paroxysmal supraventricular tachycardia; ECG = electrocardiogram.

Results

- Mean VR ± SEM = 129.7 ± 5.4 bpm at baseline
- Of the 21 AF episodes analyzed, 17 had a VR ≥110 bpm at baseline
  - Mean VR ± SEM =138.3 ± 4.3 bpm
- 6 episodes converted to SR over 60 min following etripamil administration,
- **Averaged reductions in VR from baseline were observed throughout the 60-min window**
- **Maximum reduction of -27.4 ± 6.1 bpm at 22 min, and -16.2 bpm ± 5.6 at 60 min**
- **Etripamil was well-tolerated and there were no serious adverse events (AEs), including in 1 patient who self-administered 2 doses (separated by ~10 min). The most common treatment-related AEs were related to the nasal administration site.**

SEM = standard error of the mean; SR = sinus rhythm; VR = ventricular rate.

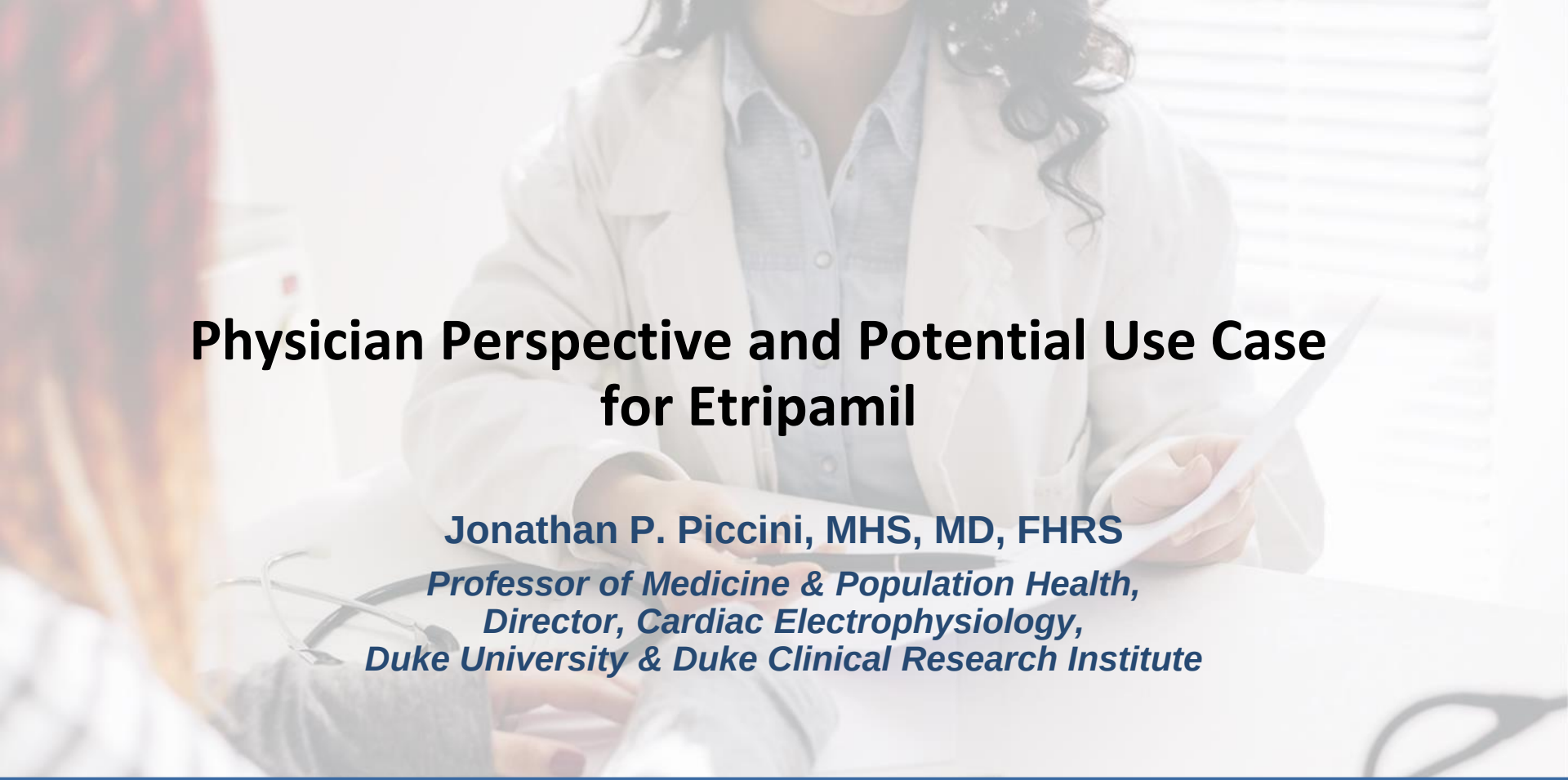
Change in Ventricular Rate from Baseline



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.

Conclusions

- In patients experiencing episodes of atrial fibrillation (AF) and a rapid ventricular response rate (RVR), self-administration of etripamil, an investigational new drug, resulted in a reduction in the ventricular rate that was sustained over 60 min
- Timing of response aligned with the known pharmacologic profile of etripamil nasal spray
- These findings warrant further study and suggest a potential role for the drug in the acute control of RVR in patients with AF



Physician Perspective and Potential Use Case for Etripamil

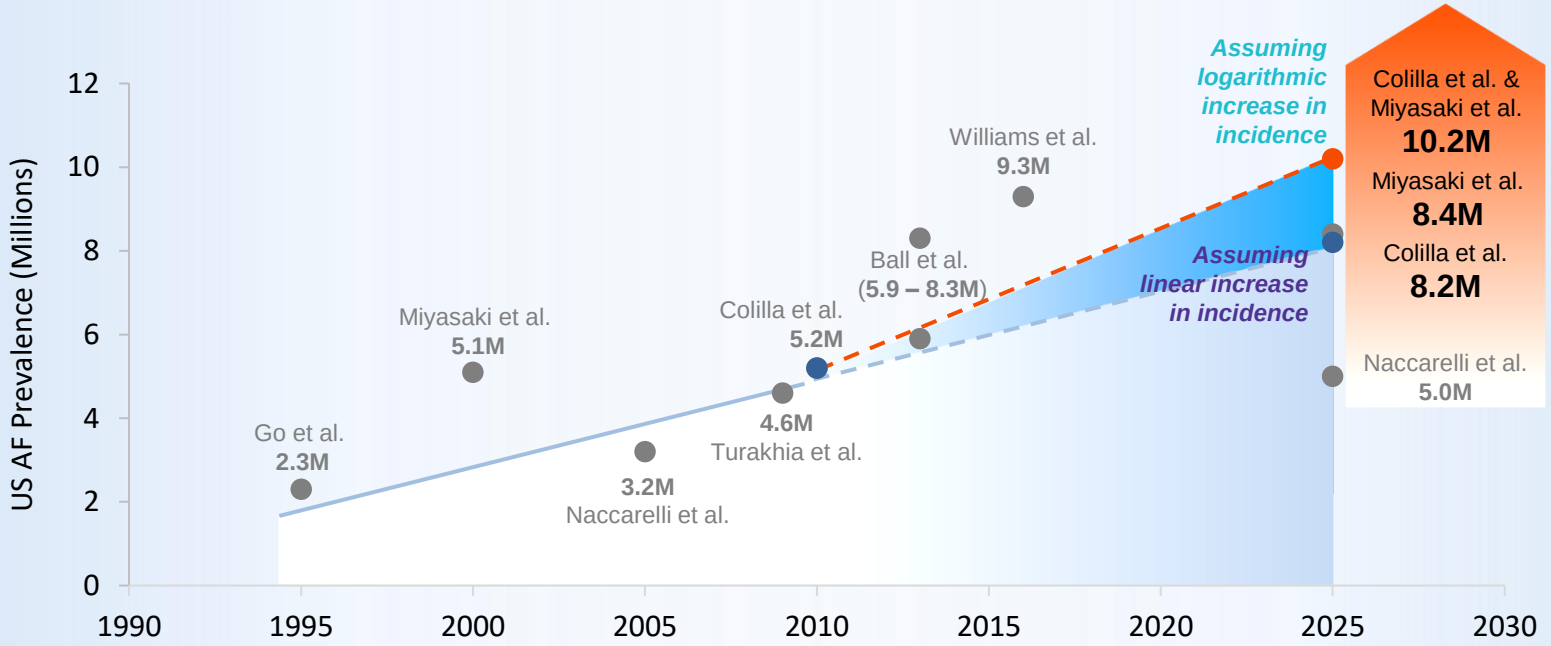
Jonathan P. Piccini, MHS, MD, FHRS

Professor of Medicine & Population Health,
Director, Cardiac Electrophysiology,
Duke University & Duke Clinical Research Institute

Currently Available Approaches / Unmet Need in AFib

1. Regardless of rate- or rhythm-control strategy, break-through episodes of AFib-RVR are frequent, symptomatic, highly burdensome, and disruptive
2. Current treatment of acute attacks in the emergency department are burdensome and costly
3. Expensive and inefficient use of healthcare system resources
4. What would be helpful, and is currently missing, is a simple, fast-acting treatment, that could:
    - be self-administered at-home
    - reduce burden of episodes, and reduce trips to ED and calls to physicians

US Prevalence of Atrial Fibrillation Projected to be 8.2 – 10.2 million by 2025



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AFib and AFib-RVR Populations in the US

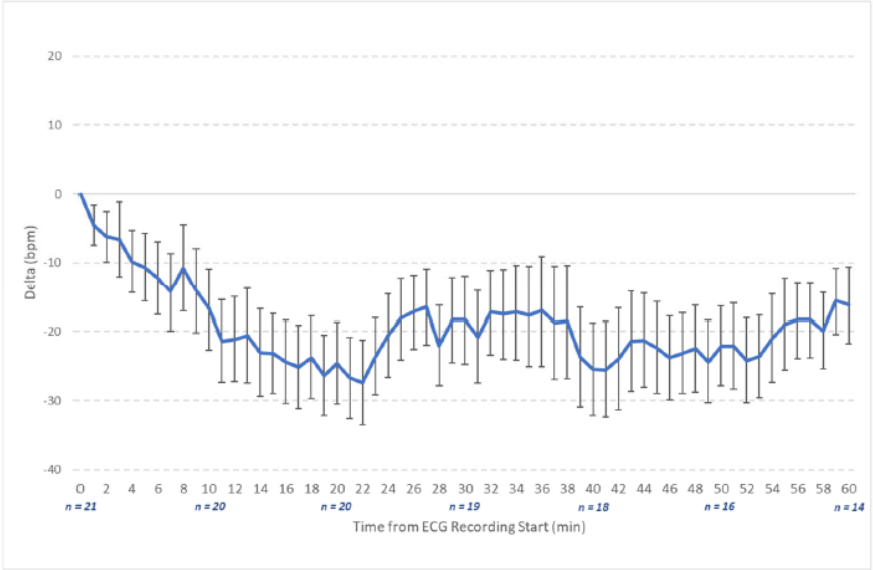
	Atrial Fibrillation
Total AFib Patients (2030)	**10 Million**[1]
Discharged ED Visits & Hospital Admissions (2016)	**785 Thousand**[2]
AFib-RVR Patient Population (2030)	**~3-4 Million**[3]

AFib-RVR = atrial fibrillation with rapid ventricular rate; ED = emergency department

Sources: **1.** Colilla et al., Am. J. Cardiol. 2013, 112(8), 1142-1147; Miyasaka et al., Circulation, 2006, 114, 119-125. American Heart Association **2**. H-CUP ED & Admissions Data, Healthcare Cost and Utilization Project (2016), accessed January 2021. **3.** Quantitative Survey conducted by Triangle Insights, May 2021, N=250 Clinical Cardiologists, Interventional Cardiologists, and Electrophysiologists.

Summary of Dorian, *et al** Data From NODE-303, and Potential Applicability to Future Study and Clinical Use

Change in Ventricular Rate from Baseline



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.

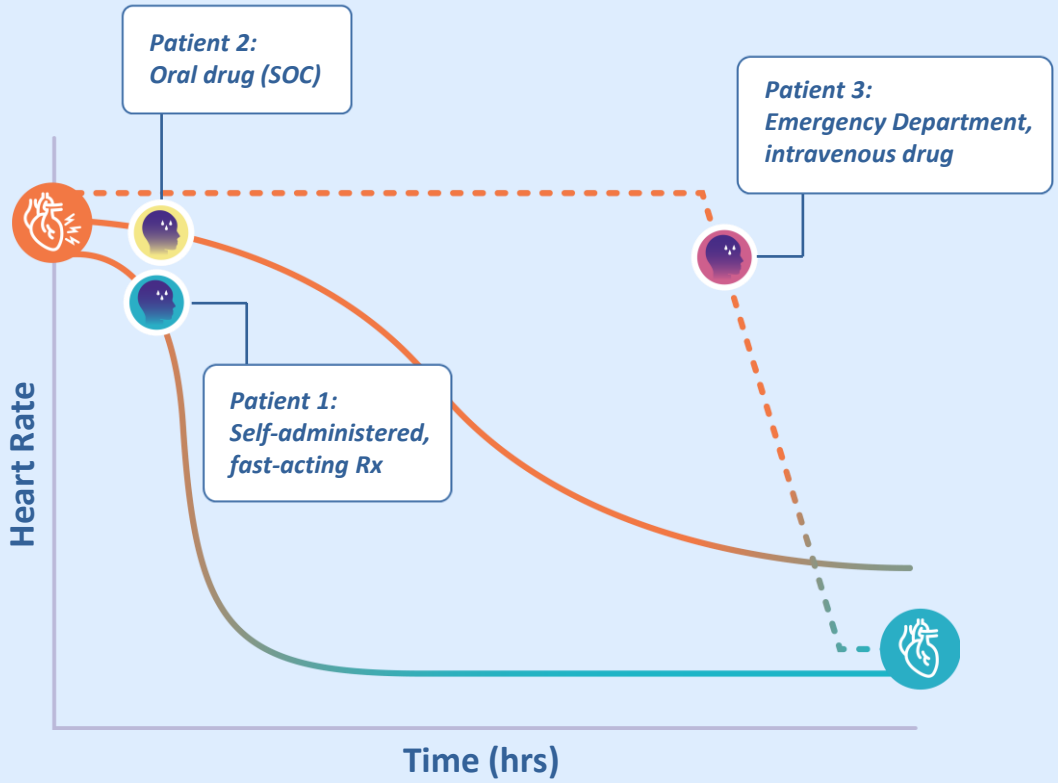
#HRS2023

*Heart Rhythm Society, May 19, 2023; Dorian, Alings, Coutu, Ip, Martinez, Piccini, Stambler, Thermil, Omodele, Shardonofsky, Plat, Bharucha, Camm.

AFib-RVR – Acute Treatment Scenarios

Acute AFib-RVR Attack

- Heart palpitations
- Chest pressure or pain
- Shortness of breath
- Fatigue
- Light-headedness
- Anxiety



Potential Use Cases of Etripamil for AFib-RVR

1. Acute, stand-alone treatment for rate control and symptom control
2. Acute treatment as a bridge to delayed effects of oral rate-control or anti-arrhythmic drug administration
3. Use peri-ablation
4. Non-invasive administration opens options for Rx without an IV line

A drug that is rapidly acting and self-administered outside of a medical setting would have characteristics that would help an unmet need.

AFib-RVR = atrial fibrillation with rapid ventricular rate, Rx = treatment, IV = intravenous

Etripamil Program in AFib-RVR: Summary and Next Steps

David Bharucha, MD, PhD, FACC

Chief Medical Officer

ReVeRA - Phase 2 Proof of Concept Trial of Etripamil in Patients Presenting to an Emergency Department with AFib-RVR

1 Patient presents to ED with episode of AFib-RVR

Inclusion:
- Atrial Fibrillation ≥ 1 hour
- Ventricular Rate (VR) ≥ 110 bpm

Select Exclusions:
- Treated with antiarrhythmic drugs
- Hemodynamically unstable
- Heart failure

2 Dosing & Assessment

1. Baseline VR ≥ 110 bpm confirmed
2. Double blind-study drug, 70 mg etripamil : placebo (1:1)
3. Monitor as in-patient for 1 hour
4. Six-hour ambulatory cardiac monitor
5. Follow-up visit, 24 hours

3 Efficacy Analysis

Primary Endpoint: Maximum reduction in VR within 60 min

Secondary Endpoints include:
- Time to max. VR reduction
- Duration of VR reductions
  - <100 bpm, ≥ 10% reduction, ≥ 20% reduction
- Patient satisfaction with treatment (PRO=TSQM-9)

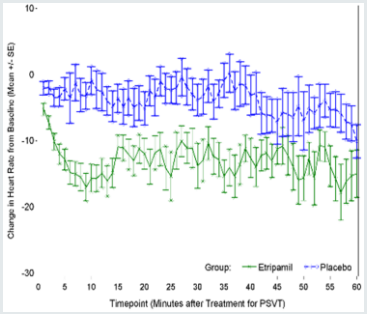
AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; TSQM-9, Treatment Satisfaction Questionnaire for Medication; ED = Emergency Department

Assessing Etripamil Ventricular Rate Reduction – How Much; How Fast; How Long

Potential Effect of Etripamil on Ventricular Rate in Patients with AFib-RVR; documented impact of drug on AV-Node

THR Reduction during AVN-Dependent SVT (NODE-301, Phase 3, event-driven, pbo-controlled trial)

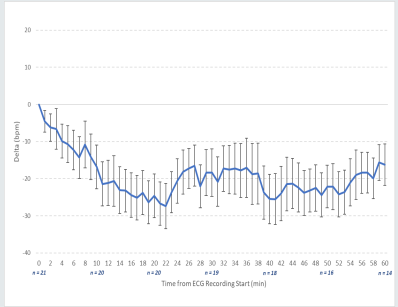
- Tachycardia Heart Rate reduction with drug, shows AV-nodal impact during SVT pre-termination.
- On-set consistent with drug's PK, and rate reduction is sustained for at least 60 min.



American Heart Association, 2021

Patients with AFib-RVR enrolled into SVT Program (NODE-303, Phase 3, open-label trial)

- Ventricular rate reduction shown in AFib-RVR after etripamil self-administration.
- Timing on-set is consistent with drug's PK, and rate reduction is sustained for at least 60 min.



Heart Rhythm Society, May 2023

Patients with AFib-RVR administered etripamil in emergency department presentation

ReVeRA, NODE-202, Phase 2 randomized, double-blinded, placebo-controlled trial. Efficacy and Safety of Intranasal Etripamil to Control Ventricular Rates in AFib/RVR

Top Line Results, 2H 2023

Utilizing Proof of Concept Data to Design Pivotal AFib-RVR Study

Summary - Etripamil for AFib-RVR Registrational Program – I

1. Based on known pharmacology of etripamil and reported data in PSVT, investigating the drug in AFib-RVR is a rational next step for this asset.
2. Recently released data, directly from patients in AFib-RVR, support the potential for utility of etripamil in this cardiac arrhythmia.
3. From HRS.2023 presentation:
    - In patients experiencing episodes of atrial fibrillation (AFib) and a rapid ventricular rate (RVR), self-administration of etripamil, an investigational new drug, resulted in a reduction in the ventricular rate that was sustained over 60 min.
    - Timing of response aligned with the known pharmacologic profile of etripamil nasal spray
    - These findings warrant further study and suggest a potential role for the drug in the acute control of RVR in patients with AFib

PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate

Summary - Etripamil for AFib-RVR Registrational Program – II

4. Opportunity to overcome limitations of currently available Rxs for AFib-RVR:
   - Current Rxs: time-consuming, potentially expensive, & inefficient use of resources
   - What would be helpful to patients and other stakeholders, and is currently missing, is a simple, fast-acting treatment that could be self-administered at-home
   - Such an Rx would provide an important opportunity to reduce the burden of episodes, trips to the ED, and calls to physicians
   - There *is* a need: One in four Americans will have AFib in their lifetime[1]
5. Phase 2 ReVeRA study is making substantial progress, with Top Line Results expected 2H 2023
6. Planning for a Phase 3, registrational program is underway
   - Out-patient, self-administration approach to be used
   - MIST R&D teams aligning with investigators and key opinion leaders on design

AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate; Rx(s) = treatment(s); ED = Emergency Department

[1] Lloyd-Jones DM. Circulation (2004) 110:1042

Q&A

Paul Dorian, MD, MSC
Professor of Medicine, Departments of Medicine and Pharmacology, University of Toronto;
Staff Cardiac Electrophysiologist, St. Michael's Hospital

Jonathan P. Piccini, MHS, MD, FHRS
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Joseph Oliveto
President and Chief Executive Officer

David Bharucha, MD, PhD, FACC
Chief Medical Officer

Amit Hasija
Chief Financial Officer & Executive Vice President of Corporate Development

Lorenz Muller
Chief Commercial Officer

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Virtual Key Opinion Leader Event

Etripamil for the Treatment of AFib-RVR

May 22, 2023

Thank you