Milestone PHARMACEUTICALS

Investor and Analyst Webcast

ReVeRA Phase 2 Results

November 13, 2023

Forward Looking Statement

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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

A. John Camm, MD
British Heart Foundation Emeritus Professor of Clinical Cardiology, The Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London

Sean Pokorney, MD, MBA
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Joseph Oliveto
President and Chief Executive Officer

David Bharucha, MD, PhD
Chief Medical Officer

Amit Hasija
Chief Financial Officer

Lorenz Muller
Chief Commercial Officer

Today's Agenda

Introduction	Joseph Oliveto	*President & CEO*
ReVeRA Data Review	A. John Camm, MD	*Lead Author, ReVeRA Study* *St. George's University of London*
Physicians' Perspective and Potential Etripamil Use Case	Sean Pokorney, MD, MBA A. John Camm, MD	*Duke University School of Medicine* *St. George's University of London*
Etripamil Program in AFib-RVR and Next Steps	David Bharucha, MD, PhD	*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 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 Oct 2023
- AFib-RVR program expands market
  - ➢ Phase 2 data Q4 2023
- Experienced leadership driving commercialization

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

Review of ReVeRA Data Presented at AHA Scientific Sessions 2023

A. John Camm, MD

British Heart Foundation Emeritus Professor of Clinical Cardiology, The Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK

#AHA23

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

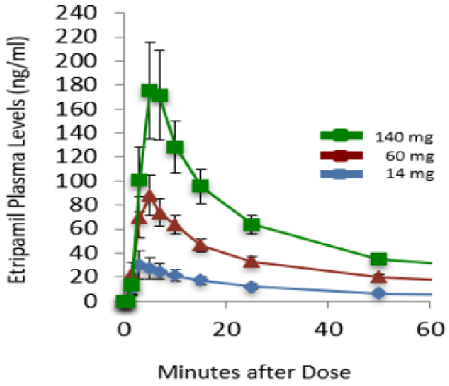
A. John Camm[1], Jonathan Piccini[2], Marco Alings[3], Paul Dorian[4], Gilbert Gosselin[5], James Ip[6], Peter Kowey[7], Blandine Mondesert[8], Fransisco J Prins[9], Jean-Francois Roux[10], Bruce S. Stambler[11], Martijn van Eck[12], Nadea Al Windy[13], Nathalie Thermil[14], Silvia Shardonofsky[14], David Bharucha[15], Denis Roy[16] *on behalf of the ReVeRA investigators*

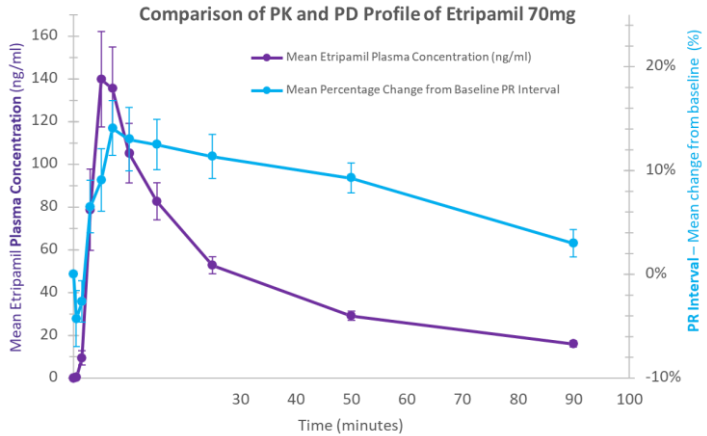
[1]The Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK; [2]Duke University Medical Center and Duke Clinical Research Institute, Durham, NC; [3]Department of Cardiology, Amphie Hospital, Breda, The Netherlands; [4]The Division of Cardiology, Unity Health Toronto, Toronto, Canada; [5]Department of Medicine, Montreal Heart Institute, Montreal, Québec, Canada; [6]Division of Cardiology, Department of Medicine, Weill Cornell Medicine, New York Presbyterian Hospital, New York, USA; [7]Cardiology Division and Lankenau Institute for Medical Research, Lankenau Medical Center, Wynnewood, PA, USA; [8]Electrophysiology Service, Montreal Heart Institute, Université de Montréal, Montreal, Canada; [9]Cardiologist at Elkerliek, Rotterdam, Netherlands; [10]Centre Hospitalier de Universite de Sherbrooke, Sherbrooke, Québec, Canada; [11]Piedmont Heart Institute, Atlanta, GA, USA; [12]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [13]Gelre Ziekenhuizen, Zutphen, The Netherlands; [14]Milestone Pharmaceuticals, Montreal, Canada; [15]Milestone Pharmaceuticals, Charlotte, NC, USA; [16]Department of Medicine, University of Montreal, Montreal, Canada

American Heart Association.

ETRIPAMIL: POTENTIAL TREATMENT FOR AF WITH RVR

- Novel, investigational, L-type calcium channel blocker[1,2]
- Formulated for intranasal spray with:
  - Rapid onset of action (T_{max} ≤ 7 min)[3]
  - Short-lasting plasma exposure: inactivated by blood esterases[4]
- Developed to satisfy unmet need for self-administered therapy that is portable & well-tolerated outside healthcare setting[3,4]
- Developed to rapidly control ventricular rate in patients with symptomatic AF[5]





N=24; Error bars indicate standard error

1. Stambler BS, *et al.*, *J Am Coll Cardiol*. 2018. 2. Ip, J, *et al.,* in *Heart Rhythm 2022*. 3. Wight D, *et al. J Am Coll Cardiol.* 2022. 4. NODE-PK-102, NODE-PK-103, data on file. 5. Dorian et al, *HRS* 2023 and NODE-303, data on file

RVR = rapid ventricular rate; PD = pharmacodynamic; PK = pharmacokinetic; SE = standard error; T_{max} = time to maximum concentration.

REVERA STUDY DESIGN

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

Screening & Treatment Visit

Study sites
- 23 sites (Canada, Netherlands)

Key inclusion criteria
- Age ≥18 years
- Paroxysmal, persistent, or permanent AF
- 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 study drug[1]
- Hx 2nd or 3rd degree AV block; SSS; TdP

DOUBLE-BLIND DRUG RANDOMIZATION (1:1)

- **PLACEBO NS**
- **ETRIPAMIL NS** 70 mg

ECG monitoring (including ambulatory)
- Conducted for at least 10 minutes prior to treatment and for 6 hours post-dosing

Outcome measures

Primary endpoint
- Mean maximum reduction in VR within 60 min after administering study drug; sized to detect a 20-bpm reduction (placebo corrected)

Key Secondary endpoints
- Rapidity of VR reduction, including elapsed time from administering drug to nadir VR[2]
- Duration & proportion of patients achieving <100 bpm, or ≥10% or ≥20% reduction in VR
- TSQM-9 rating of Effectiveness & Symptom-Relief

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

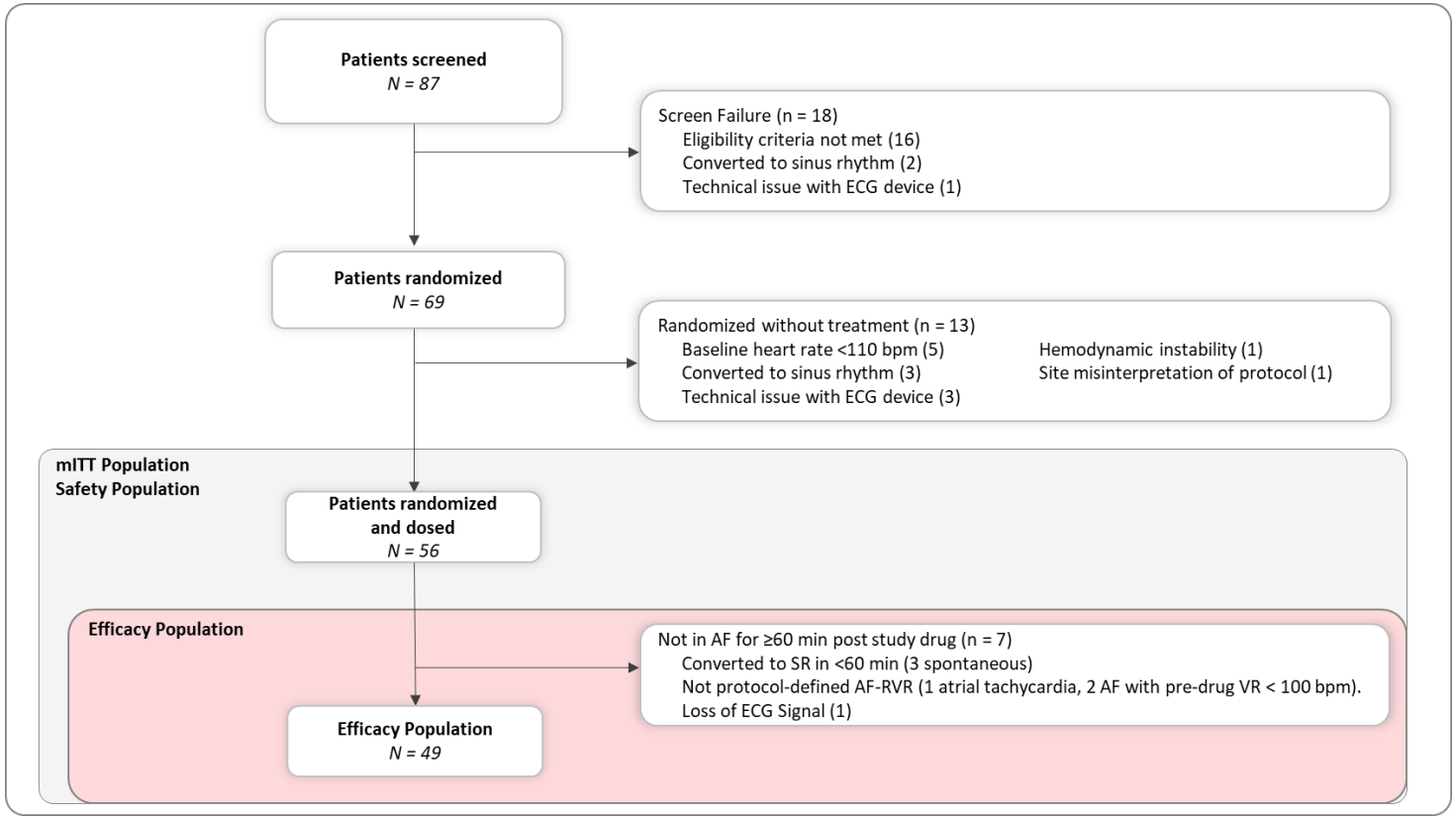
Timeline

19 November 2020
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. AE = adverse event; AF-RVR = atrial fibrillation with rapid ventricular rate; FPFV = first patient first visit; NS = nasal spray; SSS = sick sinus syndrome; TdP = torsade de pointes; TSQM-9 = Treatment Satisfaction Questionnaire for Medication patient reported outcome tool; VR = ventricular rate.

REVERA PATIENT DISPOSITION



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 randomized patients who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. One patient had 2 reasons for screen failure. AF-RVR = atrial fibrillation with rapid ventricular rate; CMS = cardiac monitoring system; mITT = modified intention to treat; SR = sinus rhythm; VR = ventricular rate.

DEMOGRAPHICS & BASELINE CHARACTERISTICS (SAFETY POPULATION)

	Placebo (N=29)	Etripamil (N=27)	Overall (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			
Canada	14 (48.3%)	12 (44.4%)	26 (46.4%)
The Netherlands	15 (51.7%)	15 (55.6%)	30 (53.6%)
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%)
Persistent	5 (17.2%)	5 (18.5%)	10 (18%)
Permanent	2 (6.9%)	2 (7.4%)	4 (7%)
Concomitant Medications			
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 BB or NDHP CCB	13 (44.8%)	15 (55.6%)	28 (50%)
Any Class IC or Class III antiarrhythmic	5 (17.2%)	8 (29.6%)	13 (23.2%)
Anticoagulant, oral	16 (55.1%)	16 (59.3%)	32 (57.1%)

Safety Population = all randomized patients receiving study drug.
BB= beta blocker; NDHP = nondihydropyridine; SD = standard deviation; CCB = calcium channel blocker.

EFFICACY RESULTS - PRIMARY ANALYSIS

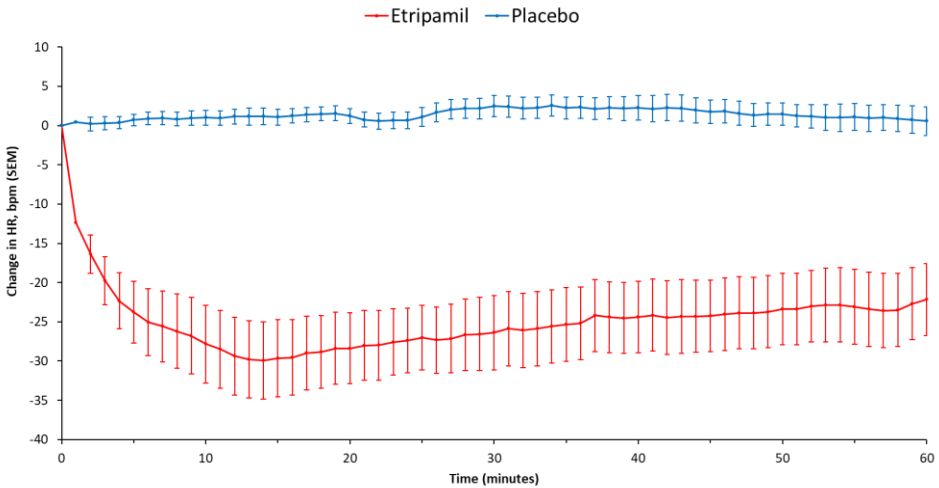
	Placebo NS[1] N=25	**Etripamil NS, 70 mg[1]** N=24
Baseline Ventricular Rate (bpm)[2]		
Mean ± SD	135.54 ± 13.93	130.33 ± 15.28
Median (IQR)	135.40 (125.00, 140.20)	126.90 (122.40, 141.60)
Nadir (bpm)[3]		
Mean ± SD	130.66 ± 16.37	95.18 ± 23.68
Median (IQR)	132.20 (121.20, 137.80)	96.00 (77.30, 109.50)
Maximum Mean Reduction From Adjusted Baseline To Nadir (bpm)		
Adjusted mean (95% CI)	-5.06 (-7.44, -2.67)	**-34.97 (-45.13, -24.81)**
Difference of Means (95% CI)	**--**	**-29.91 (-40.31, -19.52)**
p-value[4]	**--**	**<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] Baseline ventricular rate = the average heart rate over the 5 min immediately prior to drug administration. [3] Nadir = the lowest 5-minute moving average heart rate recorded in the 60 min. post drug administration. [4] From ANCOVA model, comparing maximum reductions from baseline (means) for placebo vs. etripamil

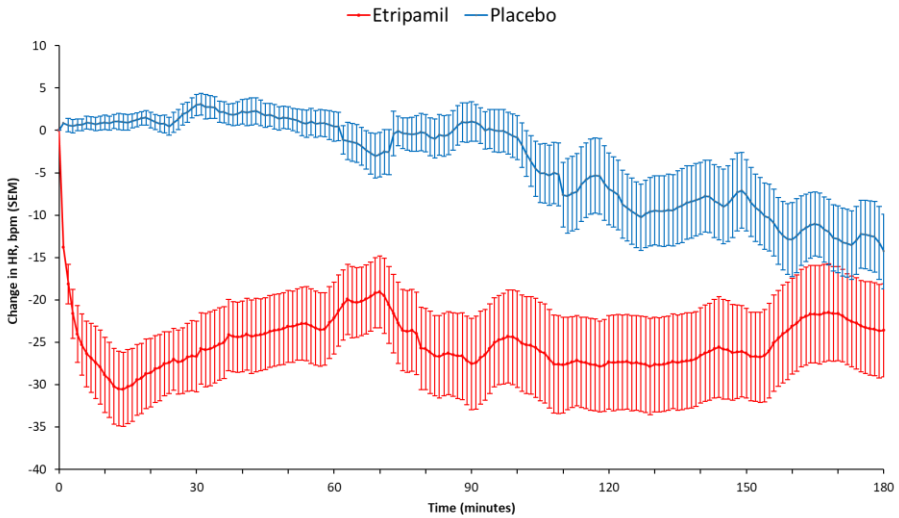
VR = ventricular rate; IQR = interquartile range, expressed as Q1, Q3; SD = standard deviation; CI = confidence interval

EFFICACY ENDPOINTS – MEAN VR CHANGE FROM BASELINE

60 min plot



180 min plot



Primary Endpoint (Efficacy Population)		
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 (mITT Population)		
Difference between Areas under the curves over 180 min ($AUC_{0 \rightarrow 180}$)	**Placebo NS[3]** N=29	**Etripamil NS[3], 70 mg** N=27
p-value[4]		**<0.00001**

[1] Efficacy Population. [2] From ANCOVA model, comparing maximum reductions from baseline (adjusted means) for placebo vs. etripamil. [3] modifed intention to treat (mITT) Population. [4] From *t* test of difference between the areas under the curves (AUC) of plots of absolute mean heart rate. SEM = standard error of the mean; bpm = beats per minute; NS=nasal spray; VR = ventricular rate.

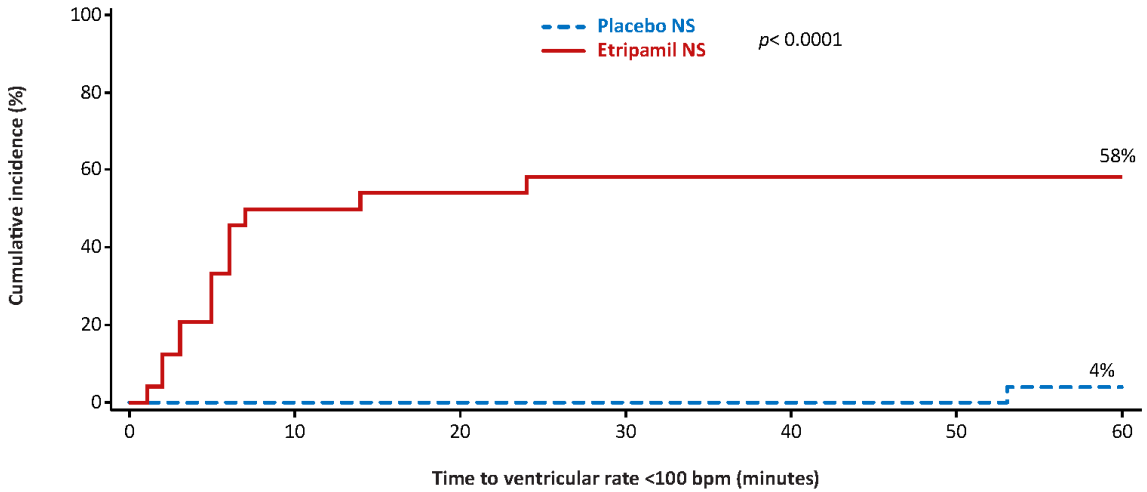
SECONDARY ANALYSES

	Placebo NS[1] n=25	Etripamil NS[1] 70 mg n=24
Elapsed Time (Minutes) from Drug Administration to Nadir[2]		
Median (IQR)	**31.00 (18.00, 51.00)**	**13.00 (8.50, 28.50)**
Adjusted mean (95% CI)	32.66 (24.89, 40.43)	20.56 (12.63, 28.49)
Difference of Means	--	-12.10 (-23.29, -0.91)
p-value[3]	--	0.0347
Patients Achieving a Ventricular Rate <100 bpm		
n (%)	1 (4.0)	14 (58.3)
p-value[4]	--	<0.0001
Duration of Ventricular Rate <100 bpm (minutes)		
Median (IQR)	7.00 (na)	45.50 (24.00, 56.00)
Minimum, Maximum	7.00, 7.00	1.00, 59.00
Adjusted mean (95% CI)[5]	5.96 (-14.30, -26.21)	42.95 (34.71, 51.19)
Difference of Means[5]	--	-36.99 (14.88, 59.11)
p-value[3,5]	--	0.0026

Consistent results observed in sensitivity analyses performed in mITT population.[6]

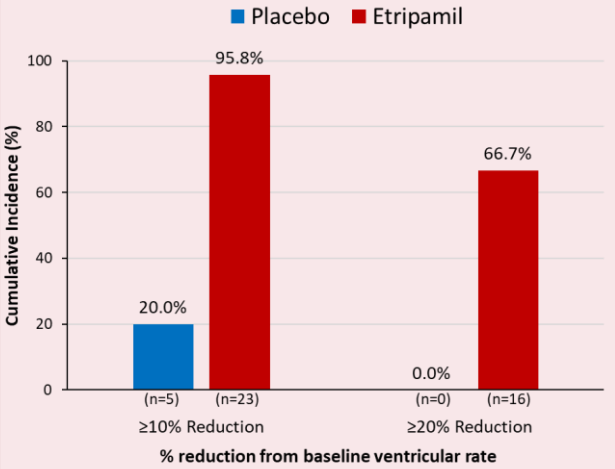
[1] Efficacy Population is comprised of all randomized patients receiving study drug who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. [2] Nadir = the lowest 5-minute moving average heart rate recorded in the 60 min post drug administration. [3] From ANCOVA model, comparing maximum reductions from baseline (means) for placebo vs. etripamil. [4] Chi-square test for percent of patients achieving ventricular rate <100 bpm in the 60 min post drug. [5] Calculated from mITT population as meaningful calculation could not be performed from the 1 patient in the placebo arm with a VR < 100 bpm. [6] mITT Population is all randomized patients receiving study drug and with a post-drug ECG CMS recording. NS = nasal spray; IQR = interquartile range, expressed as Q1, Q3; CI = confidence interval; CMS = cardiac monitoring system; mITT = modified intention to treat.

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

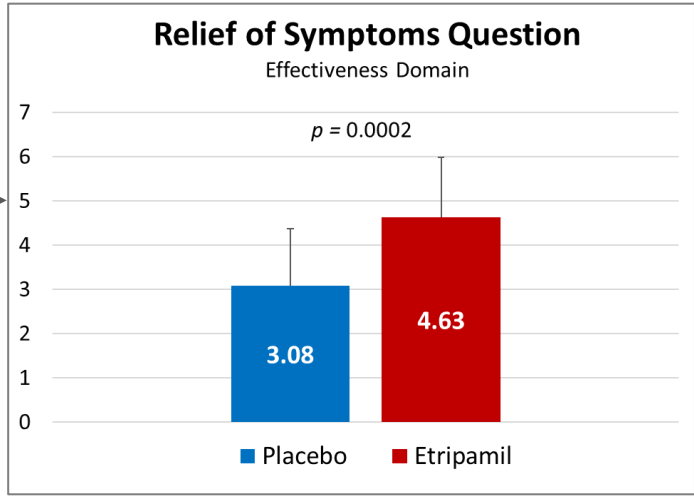
ReVeRA TSQM-9 PRO[1] Assessment and Results

- Three TSQM-9 Domains: Effectiveness, Global Satisfaction, & Convenience
- Three questions per domain, each answered on 7-point anchored scale

1	2	3	4	5	6	7
Extremely Dissatisfied	Very Dissatisfied	Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied	Extremely Satisfied

- Each domain score is calculated from three question scores
  - Domain score is on a 0 to 100-point scale
  - Domain score of 50/100 corresponds to a 4/7 = “Somewhat Satisfied”

Domains	Placebo[2] n=25	Etripamil[2] n=24	p-value[3]
Effectiveness, mean (SD)	**36.67 (21.64)**	**62.69 (21.59)**	**p<0.0001**
Global Satisfaction, mean (SD)	37.14 (25.42)	53.87 (21.17)	p=0.0161
Convenience, mean (SD)	72.00 (16.08)	65.28 (12.50)	p=0.1100



Delta = 1.55 units

[1] Treatment Satisfaction Questionnaire for Medication-9, a validated Patient-Reported Outcome tool. [2] Efficacy Population is all randomized patients receiving study drug who remained in atrial fibrillation with adequately diagnostic ECG recordings for at least 60 min post drug. [3] From *t* test. SD = standard deviation

TREATMENT-EMERGENT ADVERSE EVENTS

Most common TEAEs ≥ 5%, Patients with ≥ 1 TEAEs (Safety population)	Placebo NS[1] (n= 29)	Etripamil NS[1] (n=27)
Respiratory, Thoracic, and Mediastinal disorders		
Epistaxis	--	2 (7.4%)
Nasal Congestion	1 (3.4%)	2 (7.4%)
Nasal Discomfort	11 (37.9%)	16 (59.3%)
Oropharyngeal Pain	--	2 (7.4%)
Rhinorrhea	1 (3.4%)	9 (33.3%)
Throat Irritation	--	5 (18.5%)
Infections and Infestations		
Nasopharyngitis	--	2 (7.4%)
Eye Disorders		
Increased Lacrimation	5 (17.2%)	8 (29.6%)
Nervous System Disorders		
Dizziness	3 (10.3%)	3 (11.1%)
Headache	--	3 (11.1%)
Paresthesia	2 (6.9%)	1 (3.7%)
Cardiac Disorders		
Bradyarrhythmia	--	2 (7.4%)
Intracardiac Thrombus	2 (6.9%)	--

Two placebo-arm patients experienced 4 treatment-emergent serious adverse events (TESAEs); 1 etripamil patient experienced 2 TESAEs (transient severe bradycardia and syncope, assessed as due to hyper-vagotonia, classified as related to study drug, occurred in a patient with a history of vagal events, and fully resolved with placing the patient supine and without sequelae). TESAEs were SAEs occurring within 24 hours of drug administration.

[1]Safety endpoints based on ECG analysis included any AV block and ventricular arrhythmia such as premature ventricular contractions and non-sustained ventricular tachycardia.
TEAE = treatment emergent adverse event; NS = nasal spray; SAE= Serious adverse events

ReVeRA Phase 2 Study: Summary and Conclusions

- **The ReVeRA trial showed that etripamil NS demonstrated substantial reduction in VR in patients with AF-RVR (difference between etripamil vs. placebo in maximum reduction from baseline: -29.91 bpm; p < 0.0001)**
  - **Median time to maximum reduction of 13 min, and duration of effect for at least 150 min**
  - **Median duration of maintaining a VR <100 bpm was 45.5 min in the first 60 min following drug in the etripamil arm**
- **Majority of common AEs were localized to the drug-administration site, and a low incidence of serious adverse events**
- **Etripamil treatment was associated with significant improvement in symptom relief and in treatment satisfaction as measured by the TSQM-9**
- **Results indicate a potential role of etripamil nasal spray 70 mg to reduce VR in patients with symptomatic AF-RVR**
- **Future investigation is warranted with at-home, self-administration of etripamil NS in patients with AF-RVR**

AF-RVR = atrial fibrillation with rapid ventricular rate; VR = ventricular rate; bpm = beats per minute; AEs = adverse events; TSQM-9 = Treatment Satisfaction Questionnaire for Medication patient reported outcome tool.

#AHA23

Simultaneous Publication:
The ReVeRA Study is published on-line,
Circulation: Arrhythmia and Electrophysiology
https://www.ahajournals.org/doi/10.1161/CIRCEP.123.012567

A 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)

A. John Camm, Jonathan Piccini, Marco Alings, Paul Dorian, Gilbert Gosselin, James Ip, Peter Kowey, Blandine Mondesert, Fransisco J Prins, Jean-Francois Roux, Bruce S. Stambler, Martijn van Eck, Nadea Al Windy, Nathalie Thermil, Silvia Shardonofsky, David Bharucha, Denis Roy on behalf of the ReVeRA investigators

American Heart Association.

Physicians' Perspective and Potential Use Case for Etripamil

A. John Camm, MD
British Heart Foundation Emeritus Professor of Clinical Cardiology, The Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London

Sean Pokorney, MD, MBA
Director of the Arrhythmia Core Laboratory, Duke Clinical Research Institute, Assistant Professor of Medicine, Duke University School of Medicine

Etripamil Program in AFib-RVR: Summary and Next Steps

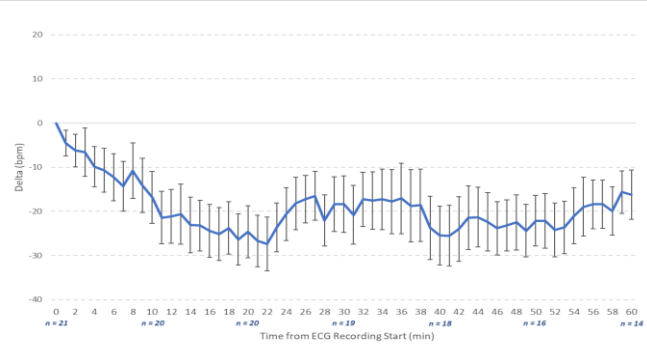
David Bharucha, MD, PhD

Chief Medical Officer

Observed Impact of Etripamil on AV-Nodal Conduction Including in AFib-RVR

Ventricular rate reduction in patients with AFib-RVR with etripamil in at-home setting (NODE-303, Phase 3, open-label SVT trial)

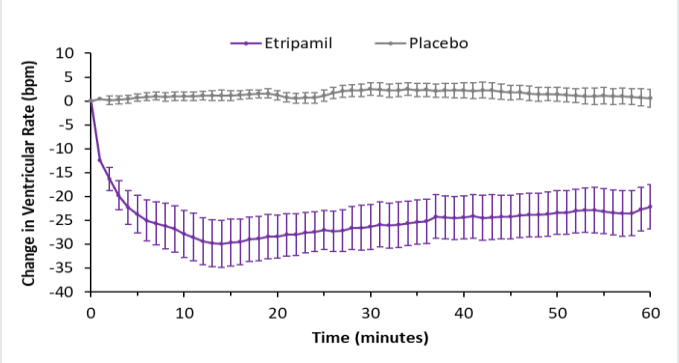
- Ventricular rate reduction shown in AFib-RVR after etripamil self-administration
- Rapid on-set of effect consistent with drug's PK, and rate reduction is sustained for at least 60 min



Heart Rhythm Society, 2023

Ventricular rate reduction in patients with AFib-RVR with etripamil In emergency department setting (ReVeRA, Phase 2, placebo-control trial)

- Rapid onset of effect consistent with drug's PK, and rate reduction is sustained for approx. 150 min after single dose
- Significant relief of symptoms by PRO, and less use of additional IV or PO medication



American Heart Association, 2023

AVN=AV node, THR=tachycardia heart rate, PK=pharmacokinetics, AFib-RVR=atrial fibrillation with rapid ventricular response, PRO=patient reported outcome

FDA Pre-IND Guidance for Path to Approval in AFib-RVR[1]

- Single study with self-administered etripamil in at-home setting, to gain a labelled indication via supplemental NDA (sNDA)
- Can utilize the safety database from PSVT
- Primary Endpoint - Reduction in Ventricular Rate (VR); etripamil vs. placebo
- Key secondary endpoint must be based on benefit on symptoms, via patient reported outcome (PRO)
  - $p < 0.05$ to gain approval, assessed in ITT population (all patients self-administering study drug)
  - Key recommendation: use of anchored 7-point scale; FDA gave latitude on specific PRO
  - FDA expectation of 1-unit improvement in Target population (verified AFib-RVR)

1. We have held Pre-IND Meeting with Cardio-Renal Division of FDA. We expect additional discussion with FDA regarding the proposed design of our Phase 3 pivotal trial, including whether the proposed trial will support registration of etripamil for the treatment of AFib-RVR. AFib-RVR = atrial fibrillation with rapid VR. VR = ventricular rate

Proposed Phase 3 Registrational Study in AFib-RVR

- Key Inclusion Criterion: history of symptomatic episodes of AFib-RVR
- Patients self-administer drug at-home for perceived episodes of AFib-RVR
- Dose: etripamil NS 70 mg (same as proposed indication in PSVT); repeat-dose regimen
- Primary endpoint = maximum reduction in VR, same as ReVeRA; etripamil vs placebo
- Key Secondary endpoint = symptom relief, via PRO
- Objectives:
  - Show $p < 0.05$ for Primary and Key Secondary endpoints in ITT population; no alpha-spend
  - 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, $p < 0.05$
- Timing
  - FDA Confirmation of Ph3 Protocol: 1Q 2024
  - Study Start: Mid 2024
  - Top-Line Data: Mid 2026

[1] Sizing assumptions also include PRO delta of 1.2 points, standard deviation = 1.6, Target/ITT population ratio of 0.70. AFib-RVR = atrial fibrillation with rapid ventricular rate; ITT = intention to treat; PSVT = paroxysmal supraventricular tachycardia; TSQM = Treatment Satisfaction Questionnaire for Medication PRO; PRO = patient reported outcome

Thank you and Q&A

A. John Camm, MD
British Heart Foundation Emeritus Professor of Clinical Cardiology, The Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London

Sean Pokorney, MD, MBA
Director of the Arrhythmia Core Laboratory, Duke Clinical Research Institute, Assistant Professor of Medicine, Duke University School of Medicine

Joseph Oliveto
President and Chief Executive Officer

David Bharucha, MD, PhD
Chief Medical Officer

Amit Hasija
Chief Financial Officer

Lorenz Muller
Chief Commercial Officer

Milestone PHARMACEUTICALS

Investor and Analyst Webcast

ReVeRA Phase 2 Results

November 13, 2023

Thank you

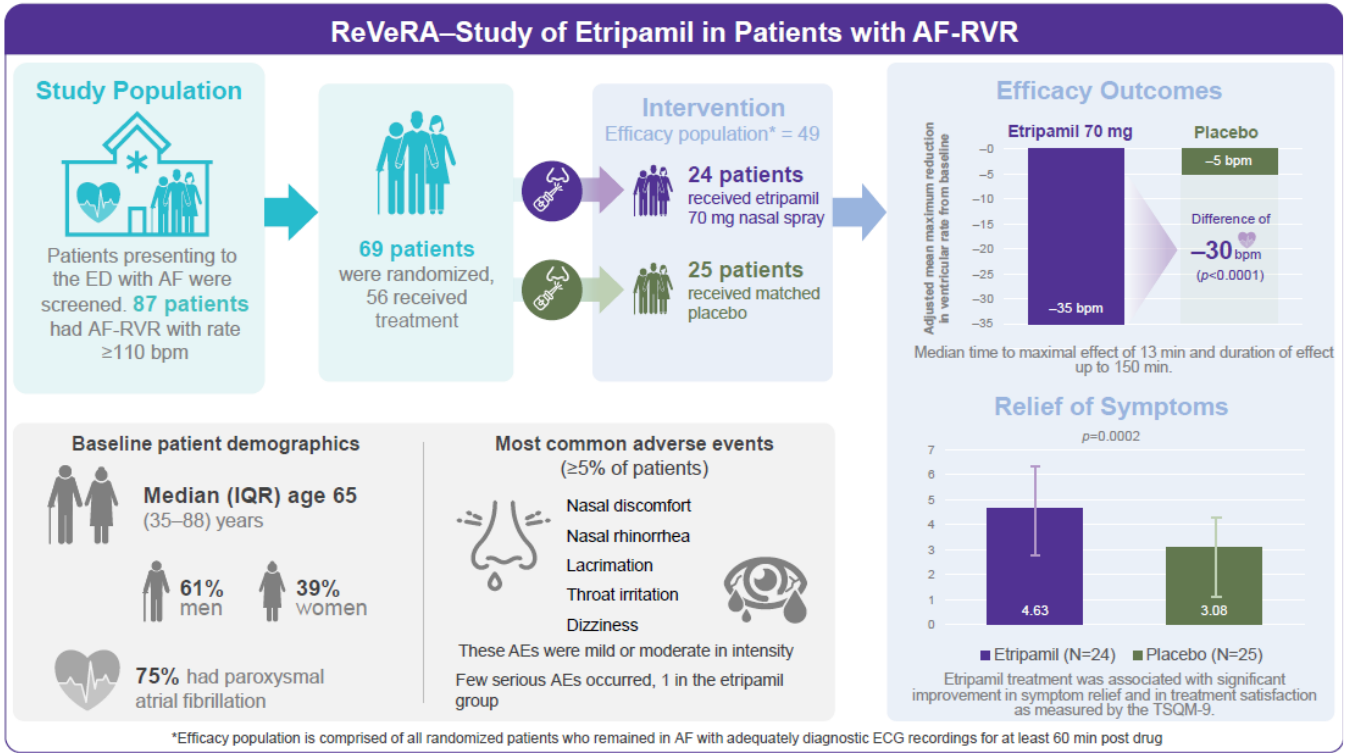
Appendix

ReVeRA - Medications Started After Study Drug Administration

	Placebo N=29[1]	Etripamil N=27[1]	Total N=56[1]
Medications and time-interval given after study drug administration, n (%)			
CCB or BB, ≤24 h	**15 (51.7%)**	**6 (22.2%)**	**21 (37.5%)**
IV NDHP CCB or IV BB, ≤60 min	0	0	0
IV NDHP CCB or IV BB, >60 min and ≤24 h	2 (6.9%)	0	2 (3.6%)
Oral NDHP CCB or Oral BB, ≤60 min	0	0	0
Oral NDHP CCB or Oral BB, >60 min and ≤24 h	13 (44.8%)	6 (22.2%)	19 (33.9%)
Digoxin, IV or PO, ≤24 h	**6 (20.7%)**	**3 (11.1%)**	**9 (16.1%)**
AAD, ≤24 h	**8 (27.6%)**	**8 (29.6%)**	**16 (28.6%)**
IV AAD, ≤60 min	0	0	0
IV AAD, >60 min and ≤24 h	2 (6.9%)	1 (3.7%)	3 (5.4%)
Oral AAD, ≤60 min	0	0	0
Oral AAD, >60 min and ≤24 h	6 (20.7%)	7 (25.9%)	13 (23.2%)

[1] Safety Population. AAD = antiarrhythmic drug (included Type I and III drugs), BB= beta blocker, NDHP CCB = non-dihydropyridine calcium channel blocker. Patients were counted more than once if multiple classes of medications were administered.

Summary of Camm, *et al** Data From ReVeRA, and Potential Applicability to Future Study and Clinical Use

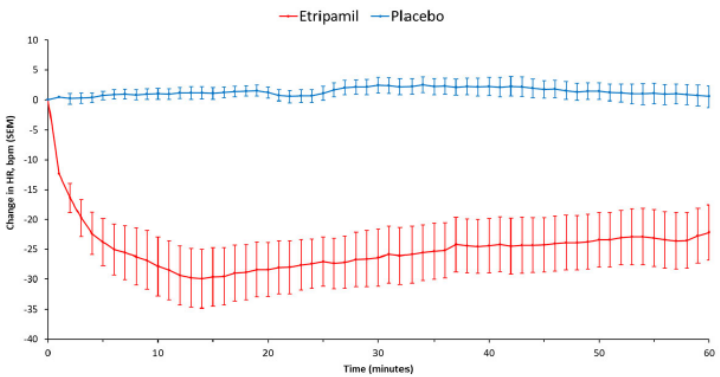


* American Heart Association, Featured Science, November 11, 2023,
Simultaneous publication: Circulation: Arrhythmia & Electrophysiology,
Camm, Piccini, Alings, Dorian, Gosselin, Ip, Kowey, Prins, Roux, Stambler, van Eck, Al Windy, Thermil, Shardonofsky, Bharucha, Roy.

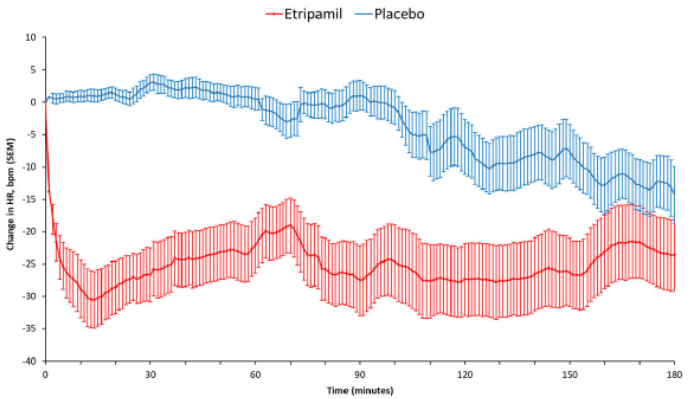
Summary of Camm, *et al** Data From ReVeRA, and Potential Applicability to Future Study and Clinical Use

EFFICACY ENDPOINTS – MEAN VR CHANGE FROM BASELINE

60 min plot



180 min plot

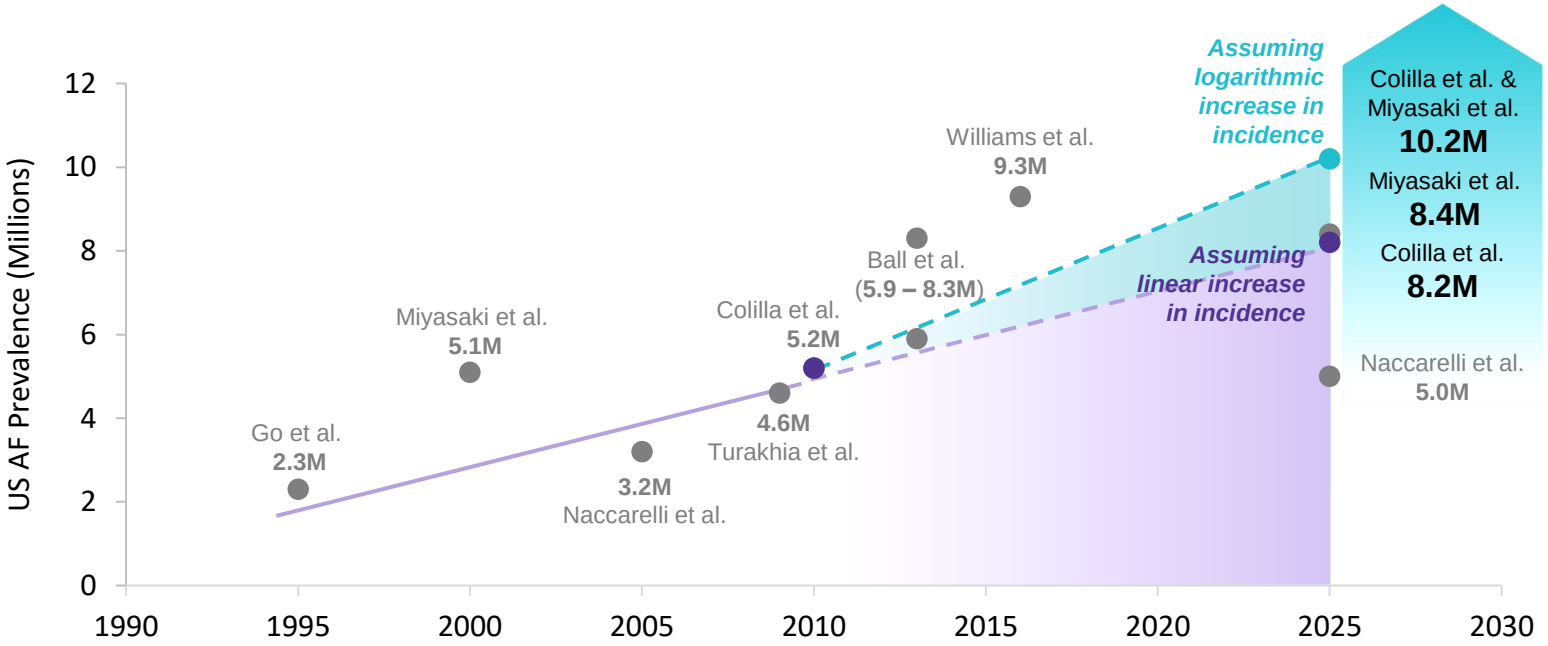


Primary Endpoint (Efficacy Population)		
Maximum Reduction in VR adjusting for baseline VR (bpm)	**Placebo NS[1] N=25**	**Etripamil NS, 70 mg[1] N=24**
Adjusted mean (95% CI)	-5.06 (-7.44, -2.67)	-34.97 (-45.13, -24.87)
Difference in adjusted means (95% CI)	--	-29.91 (-40.31, -19.52)
p-value[2]	**--**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

Separation of curves (mITT Population)		
Difference between Areas under the curves over 180 min (AUC_{0-180})	**Placebo NS[3] N=29**	**Etripamil NS[3], 70 mg N=27**
p-value[4]		**<0.00001**

*American Heart Association, Featured Science, November 11, 2023.
Simultaneous publication: Circulation: Arrhythmia & Electrophysiology.
Camm, Piccini, Alings, Dorian, Gosselin, Ip, Kowey, Prins, Roux, Stambler, van Eck, Al Windy, Thermil, Shardonofsky, Bharucha, Roy.

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

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.

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 (“precursor”) to the delayed effects of oral rate-control or anti-arrhythmic drug administration
3. Use peri-ablation
4. Non-invasive administration opens options for potential Rx without an IV line in emergency-department or ambulance setting

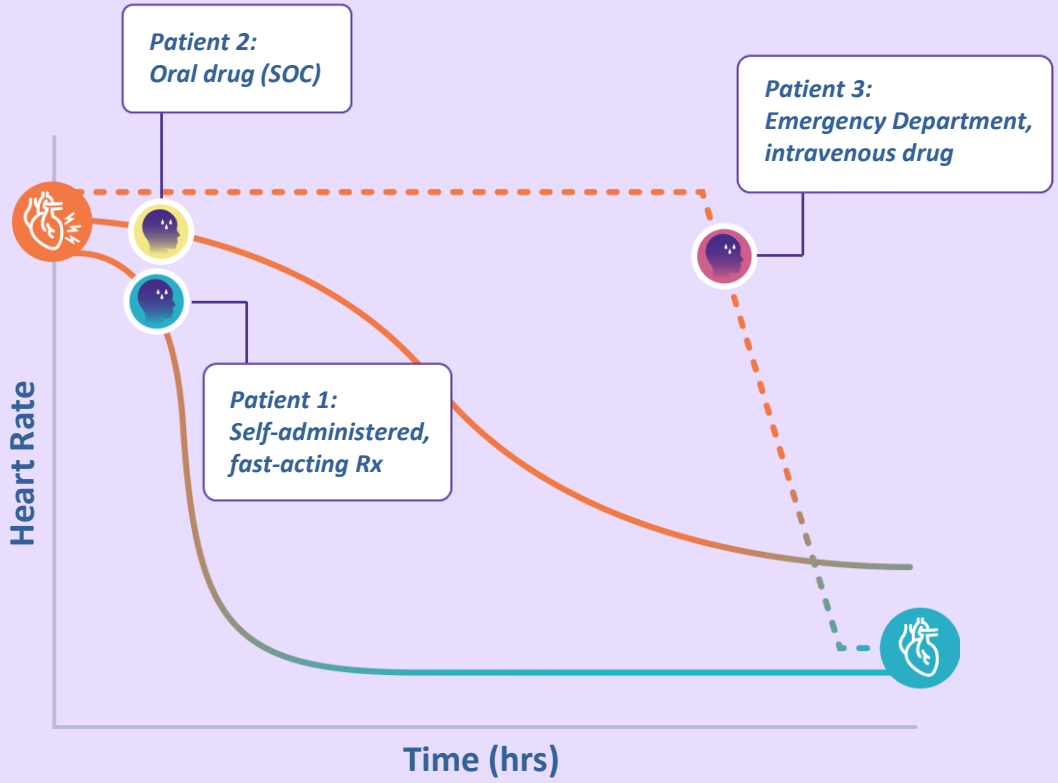
A drug that is rapidly acting and self-administered outside of a medical setting would have characteristics that would help an unmet need.

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

AFib-RVR – Acute Treatment Scenarios

Acute AFib-RVR Attack

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

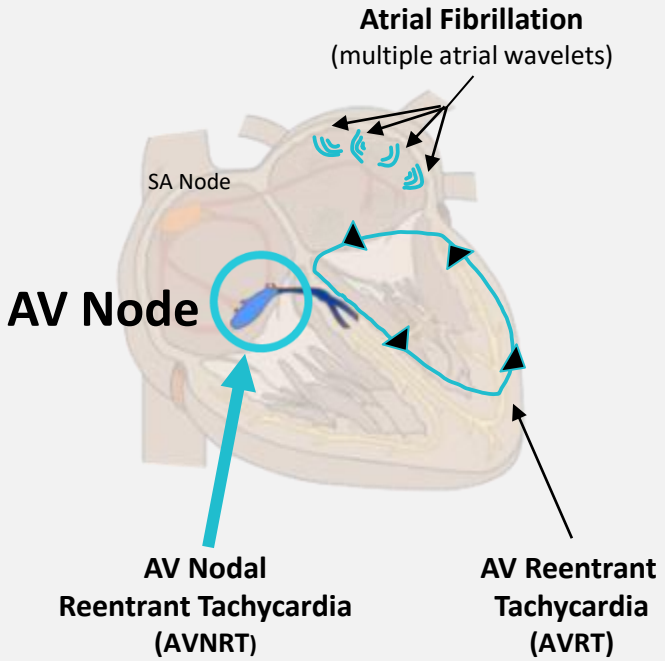


Intravenous Calcium Channel Blockers Are Proven Effective for PSVT and AFib-RVR

Intravenous Calcium Channel Blockers (CCB)

- Slows conduction signal from the atria to the ventricles over the AV Node
- PSVT: breaks the circuit, returning heart to normal rhythm
- AFib-RVR: slows heart rate and reduces symptoms while remaining in Atrial Fibrillation

Etripamil Nasal Spray is an investigational novel CCB

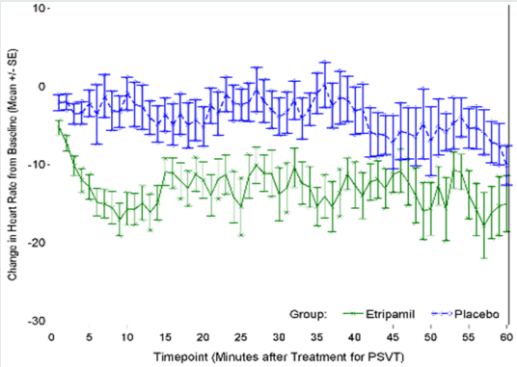


PSVT = Paroxysmal Supraventricular Tachycardia; AFib-RVR = Atrial Fibrillation with Rapid Ventricular Rate
Sources: adapted from https://en.ecgpedia.org/index.php?title=Supraventricular_Rhythms, accessed 2/2021

Observed Impact of Etripamil on AV-Nodal Conduction Including in AFib-RVR

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

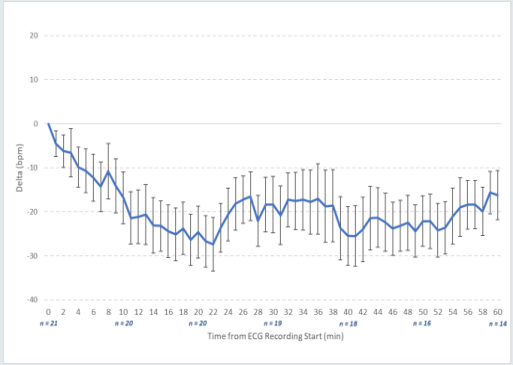
- Tachycardia Heart Rate reduction with drug shows AV-nodal impact during SVT, pre-termination.
- Rapid on-set consistent with drug's PK, and rate reduction is sustained for at least 60 min.



American Heart Association, 2021

Ventricular rate reduction in AFib-RVR patients (NODE-303, Phase 3, open-label SVT trial)

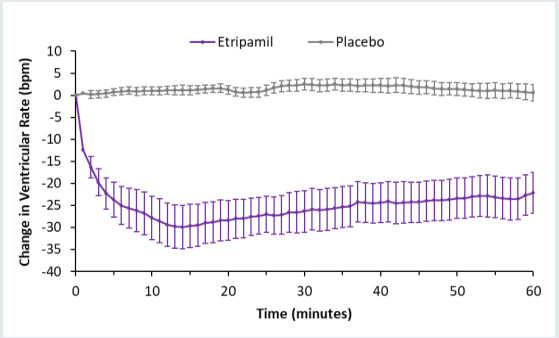
- Ventricular rate reduction shown in AFib-RVR after etripamil self-administration.
- Rapid on-set of effect consistent with drug's PK, and rate reduction is sustained for at least 60 min.



Heart Rhythm Society, 2023

Ventricular rate reduction in AFib-RVR with etripamil in emergency department presentation (ReVeRA, Phase 2, placebo-control trial)

- Rapid on-set of effect consistent with drug's PK, and rate reduction is sustained for approx. 150 min after single dose
- Significant relief of symptoms by PRO, and less use of additional IV or PO medication



American Heart Association, 2023

AVN=AV node, THR=tachycardia heart rate, PK=pharmacokinetics, AFib-RVR=atrial fibrillation with rapid ventricular response, PRO=patient reported outcome