#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

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DISCLOSURES

Marco Alings

Honoraria/speaking/consulting fee: Sanofi, Milestone Pharmaceuticals

AJ Camm

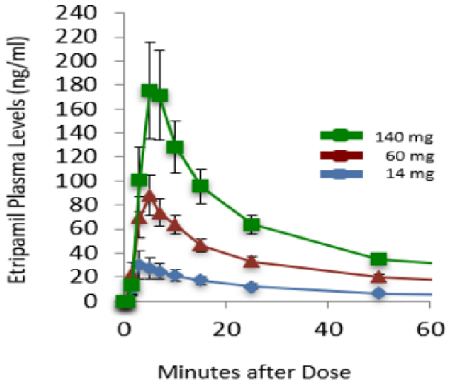
Honoraria/speaking/consulting fee: Abbott, Acesion, Anthos Therapeutics, ARCA Biopharma, Bayer Healthcare Pharmaceuticals, Biotronik, Boston Scientific, Bristol Myers Squibb, Daiichi, InCarda Therapeutics, Medtronic, Milestone Pharmaceuticals, Pfizer, Sanofi

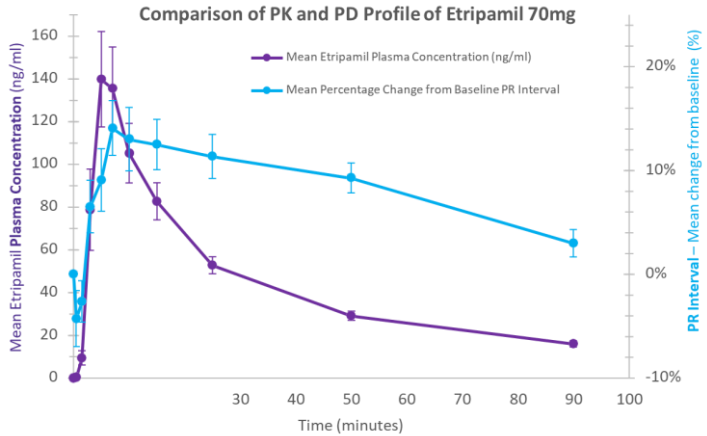
The ReVeRA Trial was funded by Milestone Pharmaceuticals (Charlotte, NC; Montreal, QC)

Trial Networks: The trial was conducted and coordinated by Montreal Health Innovations Coordinating Centre, Montreal QC, and by the WCN Network (Werkgroep Cardiologische Centra Nederland) for Netherlands sites.

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]

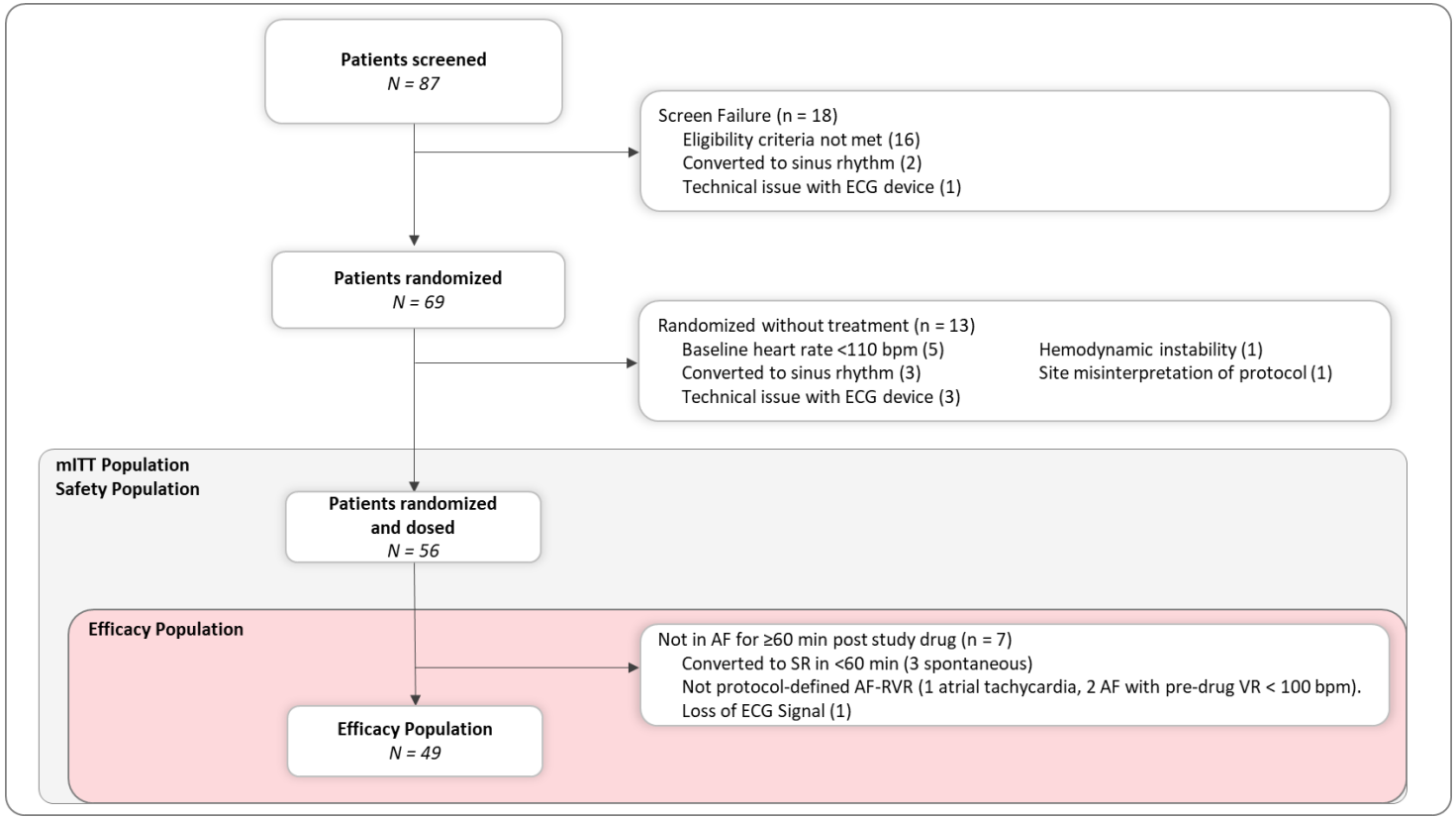
Timeline

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

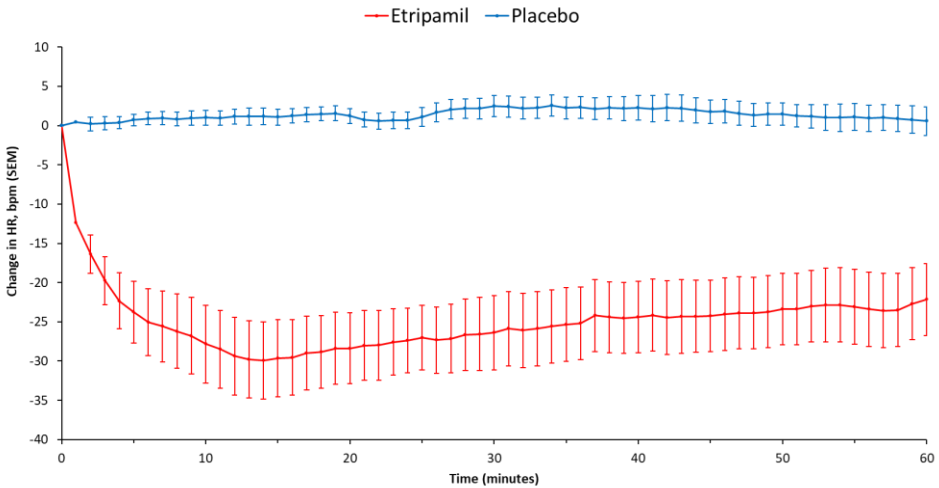
	Placebo NS[1] N=25	**Etripamil NS, 70 mg**[1] N=24
Baseline Ventricular Rate (bpm)[2]		
Mean ± SD	135.54 ± 13.93	130.33 ± 15.28
Median (IQR)	135.40 (125.00, 140.20)	126.90 (122.40, 141.60)
Nadir (bpm)[3]		
Mean ± SD	130.66 ± 16.37	95.18 ± 23.68
Median (IQR)	132.20 (121.20, 137.80)	96.00 (77.30, 109.50)
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

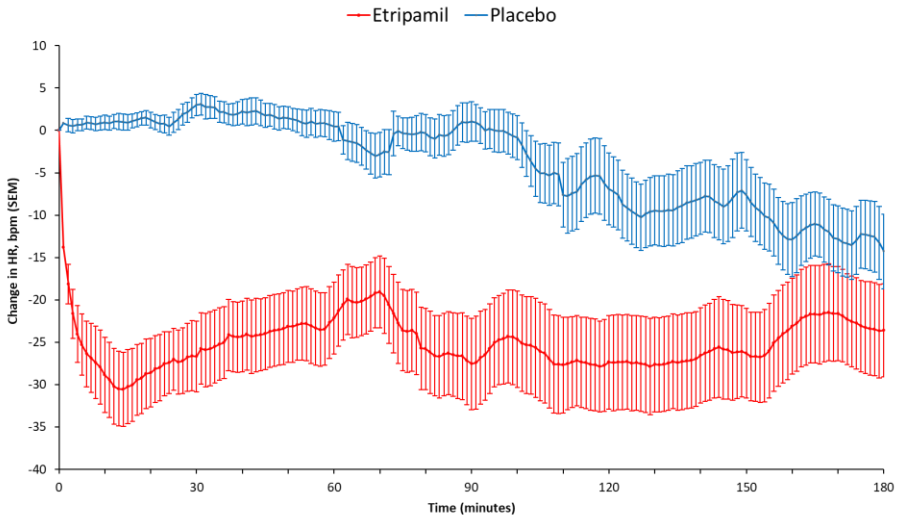
VR = ventricular rate; IQR = interquartile range, expressed as Q1, Q3; SD = standard deviation; CI = confidence interval

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.

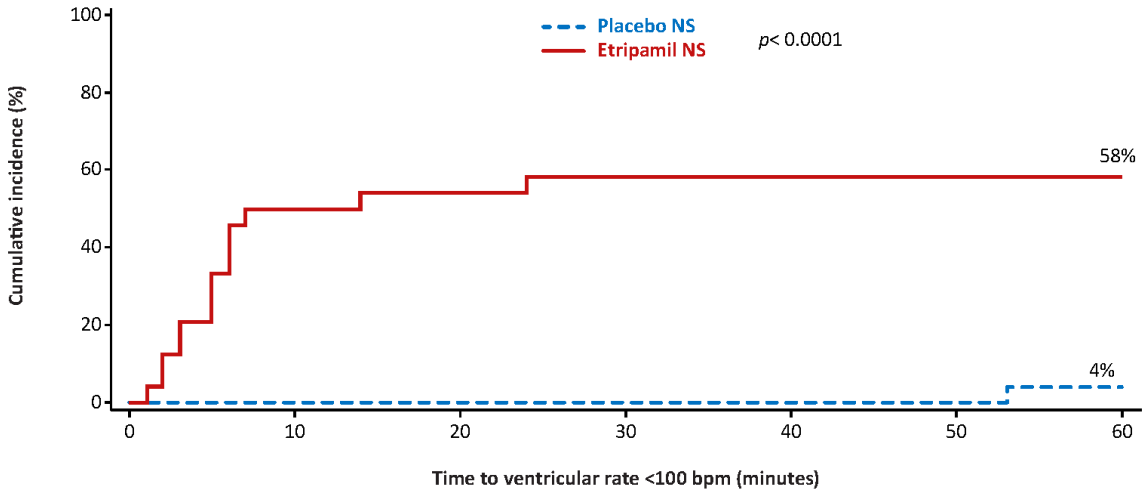
SECONDARY ANALYSES

	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

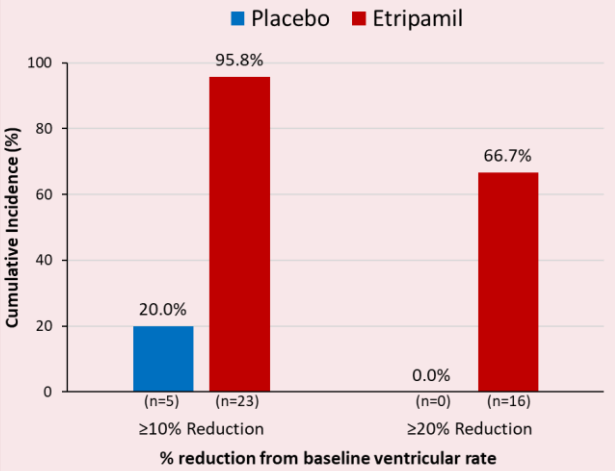
Consistent results observed in sensitivity analyses performed in mITT population.[6]

[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

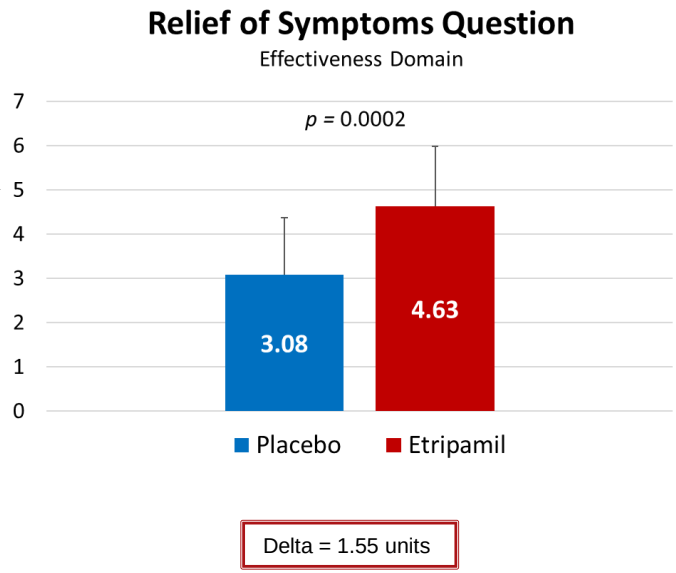
REVERA TSQM-9 PRO[1] ASSESSMENT AND RESULTS

- 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



[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.

ACKNOWLEDGEMENTS

Canada Sites

Amir Abdel-Wahab, Halifax, NS

Fabian Alejandro Azzari, Rimouski, QC

Miguel Barrero, Trois-Rivières, QC

Gilbert Gosselin, Montréal, QC

Isabelle Greiss, Montréal, QC

Hugue Jeanmart, Montréal, QC

Sebastian-Xavier Joncas, Québec, QC

Yaariv Khaykin, Newmarket, ON

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Anne Morisset, Granby, QC

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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)

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American Heart Association.

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

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THANK YOU!