SUPPLEMENTAL MATERIAL

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Trial Networks

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Methods I. Inclusion and Exclusion Criteria

Inclusion Criteria:

A patient will be eligible for study participation if they meet all of the following criteria:

1. Aged 18 years and over
2. Has provided written informed consent
3. Patients with episodes of paroxysmal, persistent or permanent AF, presenting with AF and a ventricular rate ≥110 bpm measured over 1 minute
4. Patients should receive appropriate antithrombotic therapy as per the applicable guidelines for AF management (e.g. Canadian Cardiovascular Society (CCS) / European Society of Cardiology (ESC) guidelines).
    a. Etripamil (a calcium channel blocker) is intended for acute rate control only. If rhythm control is desired (outside of the present protocol), anticoagulation as per guidelines may start after the administration of study drug.

Exclusion criteria:

A patient will be excluded from the study if they meet any of the following criteria:

1. Has evidence of atrial flutter (ECG) at presentation
2. Has a history of stroke, transient ischemic attack or peripheral embolism within the last 3 months
3. Has received by IV route any of the following within one hour before study drug administration: flecainide, procainamide, digoxin, beta-blocker, or calcium channel blocker
4. Has signs and symptoms of severe congestive heart failure at presentation (e.g. tachypnea, oxygen desaturation <90% unless due to known pulmonary disease, pulmonary rales, sign of peripheral hypoperfusion)
5. Hemodynamic instability, with systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg
6. Known uncorrected severe aortic or mitral stenosis

7. Hypertrophic cardiomyopathy with outflow tract obstruction
8. Has a history of second- or third-degree atrioventricular block
9. Regular rhythm suggesting a complete AV block
10. Has a history or evidence of torsades de pointes, sick sinus syndrome, or Brugada syndrome
11. Evidence of Acute Coronary Syndrome within the last 12 months except if patient was successfully revascularized
12. Positive pregnancy test result at screening, and females of childbearing potential who do not agree to use adequate method of contraception for the duration of the study.
13. Has evidence of any clinically significant acute or chronic condition of the nasal cavity (e.g., rhinitis or deviated septum) which could interfere with administration of the study drug in either or both nasal cavities
14. Has a history of sensitivity to verapamil
15. Has previously participated in a clinical study for etripamil
16. Has a history of sensitivity to any components of the investigational product
17. Signs of alcohol or drug intoxication at the time of presentation which, in the opinion of the Investigator, would impact the validity of study results
18. Is currently participating in another drug or device study, or has received an investigational drug or device within 30 days of screening
19. Has evidence of clinically significant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, neurologic, oncologic, pulmonary, psychiatric, or renal disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of study results

Methods II. Treatment Satisfaction Questionnaire for Medication (TSQM-9)

After study drug administration, patients will be asked to complete the TSQM-9 (Appendix C). The TSQM-9 is a 9 question, validated, indication agnostic patient reported outcome. It includes 3 items measuring treatment effectiveness, 3 items measuring treatment convenience, and 3 items measuring global satisfaction with treatment. The domain scores range from 0 to 100 with higher scores representing higher satisfaction with the treatment. The formula for calculating each domain score is shown below:

Effectiveness:

([(Question 1 + Question 2 + Question 3) − 3] divided by 18) × 100

If one item is missing: ([(Sum(the two completed items) – 2] divided by 12) * 100

Convenience:

([(Question 4 + Question 5 + Question 6) − 3] divided by 18) × 100

If one item is missing: ([(Sum(the two completed items) – 2] divided by 12) * 100

Global satisfaction:

([(Question 7 + Question 8 + Question 9) − 3] divided by 14) × 100

If either Item 7 or 8 is missing ([(Sum(the two completed items)) – 2] divided by 10) * 100

If Item 9 is missing ([(Sum(Item7 and Item8)) – 2] divided by 8) * 100

TREATMENT SATISFACTION QUESTIONNIARE FOR MEDICATION (TSQM-9)

TSQM-9 Abbreviated Treatment Satisfaction Questionnaire for Medication Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to treat your condition?

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

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

5. How easy or difficult is it to plan when you will use the medication each time? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

6. How convenient or inconvenient is it to take the medication as instructed? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

7. Overall, how confident are you that taking this medication is a good thing for you? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

8. How certain are you that the good things about your medication outweigh the bad things? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

9. Taking all things into account, how satisfied or dissatisfied are you with this medication? □1 Extremely Dissatisfied □2 Very Dissatisfied □3 Dissatisfied □4 Somewhat Satisfied □5 Satisfied □6 Very Satisfied □7 Extremely Satisfied

Methods III. Efficacy Endpoints

Primary efficacy variable:

- Maximum reduction in ventricular rate, measured on Holter monitoring, within 60 minutes from drug administration

Secondary efficacy variables:

- Elapsed time from drug administration to nadir (lowest average heart rate) in the 60 minutes post drug administration
- Percentage of patients achieving ventricular rate of <100 bpm in the 60 minutes post drug administration
- Elapsed time from drug administration to ventricular rate <100 bpm
- Duration of ventricular rate <100 bpm in the 60 minutes post drug administration
- Percentage of patients with 10% reduction from baseline ventricular rate in the 60 minutes post drug administration
- Elapsed time from drug administration to 10% reduction from baseline ventricular rate
- Duration of 10% reduction from baseline ventricular rate in the 60 minutes post drug administration
- Percentage of patients with 20% reduction from baseline ventricular rate in the 60 minutes post drug administration
- Elapsed time from drug administration to 20% reduction from baseline ventricular rate
- Duration of 20% reduction from baseline ventricular rate in the 60 minutes post drug administration
- Percentage of patients cardioverting into sinus rhythm in the 60 minutes post drug administration
- Elapsed time from drug administration to cardioversion into sinus rhythm

- Area under the curve (AUC) of heart rate over the 60 minutes and the 360 minutes post drug administration; 180 minutes post administration performed as additional analysis
- Patient satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Safety Variables:

- Safety variables will include clinical adverse events (AEs), vital signs, and findings from electrocardiographic analysis (ventricular arrhythmia such as premature ventricular contractions, non-sustained ventricular tachycardia, any AV block)

Supplemental Table I. Proportion of patients achieving > 20 bpm reduction from baseline VR over time

Patients achieving > 20 bpm reduction from baseline VR	Efficacy Population* (N=49)					mITT Population† (N=56)				
	Placebo		Etripamil		p-value‡	Placebo		Etripamil		p-value‡
	No. at risk	n (%)	No. at risk	n (%)		No. at risk	n (%)	No. at risk	n (%)	
30 min	25	0 (0.0)	24	15 (62.5)	<0.0001	28	0 (0.0%)	27	18 (66.7)	<0.0001
60 min	25	0 (0.0)	24	13 (54.2)	<0.0001	26	0 (0.0%)	26	15 (57.7)	<0.0001
90 min	25	2 (8.0)	24	13 (54.2)	0.0005	25	2 (8.0)	26	13 (50.0)	0.0029
180 min	25	8 (32.0)	24	12 (50.0)	0.2	25	8 (32.0)	26	13 (50.0)	0.1917
360 min	--	--	--	--	--	--	--	--	--	--

* The Efficacy Population is comprised of all randomized patients receiving study drug who remained in atrial fibrillation with adequately diagnostic ECG CMS recordings for at least 60 min post drug.

† The mITT Population is comprised of all randomized patients who received the study drug and who had a post-drug ECG CMS recording

‡ By chi-square test

ECG CMS data at 360 min, which was at or just after termination of the recording, contained technical artifact, precluding analysis.

ECG CMS = electrocardiographic cardiac monitoring system

Supplemental Table II. Efficacy data (unadjusted for baseline HR) in Efficacy and mITT Populations

	Efficacy Population*		mITT Population†	
Assessment	**Placebo NS** N=25	**Etripamil NS, 70 mg** N=24	**Placebo NS** N=29	**Etripamil NS, 70 mg** N=27
Baseline Ventricular Rate (bpm)‡				
Mean ± SD	135.54 ± 13.93	130.33 ± 15.28	134.12 ± 16.00	128.40 ± 15.79
Median (IQR)	135.40 (125.00, 140.20)	126.90 (122.40, 141.60)	135.20 (125.00, 140.20)	125.40 (118.00, 139.00)
Nadir (bpm)§				
Mean ± SD	130.66 ± 16.37	95.18 ± 23.68	129.24.66 ± 18.49	92.84 ± 23.39
Median (IQR)	132.20 (121.20, 137.80)	96.00 (77.30, 109.50)	132.20 (117.00, 137.80)	94.20 (71.20, 107.80)
Maximum Reduction from Baseline to Nadir (bpm)				
Mean ± SD	-4.88 ± 5.73	-35.16 ± 23.63	-4.88 ± 5.86	-35.56 ± 22.29
Median (IQR)	-3.80 (-7.60, -1.80)	-28.10 (-46.80, -19.20)	-3.80 (-7.60, -1.80)	-31.40 (-45.00, -19.40)
Elapsed Time (minutes) from Drug Administration to Nadir				
Mean ± SD	32.96 ± 20.07	20.25 ± 17.84	30.90 ± 20.09	18.85 ± 17.35
Patients Achieving a Ventricular Rate <100 bpm				
n (%)	1 (4.0)	14 (58.3)	3 (10.3)	17 (63.0)
p-value‖	-	<0.0001	-	<0.0001
Duration of Ventricular Rate <100 bpm (minutes)				
Mean ± SD	7.00 ± na	40.93 ± 18.07	11.00 ± 12.49	42.06 ± 17.62
Median (IQR)	7.00 (7.00, 7.00)	45.50 (24.00, 56.00)	7.00 (1.00, 25.00)	47.00 (27.00, 57.00)

* The 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

† The mITT Population is comprised of all randomized patients who received the study drug and who had a post-drug ECG CMS recording

‡ Baseline ventricular rate = the average heart rate over the five min immediately prior to drug administration

§ Nadir = the lowest 5-minute moving average heart rate recorded in the 60 min post drug administration

|| Wilcoxon test for censored data

NS= nasal spray, bpm = beats per minute, SD = standard deviation, IQR = interquartile range

Supplemental Table III. Secondary Analyses Performed on the Efficacy Population, Sensitivity Analyses Performed on the mITT Population

	Efficacy Population*		**mITT Population†**	
	Placebo NS N=25	**Etripamil NS, 70 mg,** N=24	**Placebo NS** N=29	**Etripamil NS, 70 mg,** N=27
Patients with 10% Reduction from Baseline VR				
n (%)	5 (20.0)	23 (95.8)	6 (20.7)	26 (96.3)
p-value§	--	<0.0001	--	<0.0001
Patients with 20% Reduction from Baseline VR				
n (%)	0 (0)	16 (66.7)	1 (3.4)	19 (70.4)
p-value§	--	<0.0001		<0.0001
Duration of 10% Reduction from Baseline VR (minutes)				
Median (IQR)	5.00 (2.00, 6.00)	49.00 (30.00, 57.00)	3.50 (2.00, 6.00)	50.00 (30.00, 58.00)
Mean (95% CI)‡	5.04 (-3.55, 13.63)	43.25 (34.82, 51.69)	4.49 (-1.95, 10.94)	43.89 (36.35, 51.42)
Difference of Means	--	38.21 (27.01, 49.42)	--	39.40 (30.13, 48.66)
p-value	--	<0.0001	--	<0.0001
Duration of 20% Reduction from Baseline VR (minutes)				
Median (IQR)	na	48.00 (14.50, 57.50)	1.00 (1.00, 1.00)	47.00 (15.00, 58.00)
Mean ± SD‖	na	35.44 ± 23.26	1.00 ± na	36.32 ± 21.95
Difference of Means	--	na	--	35.18 (-13.29, 83.65)
Patients cardioverting to sinus rhythm in the 60 minutes post drug administration				
n (%)	--	--	2 (6.9)	1 (3.7)

Difference between AUCs of VR over 60 min (AUC_{0-60})				
p-value#		<0.0001		<0.0001
Difference between AUCs of VR over 180 min (AUC_{0-180})				
p-value**		<0.00001		<0.00001
Difference between AUCs of VR over 360 min (AUC_{0-360})				
p-value#	--	0.0015	--	<0.0003

* The 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.

† The mITT Population is comprised of all randomized patients who received the study drug and who had a post-drug ECG CMS recording

‡ Using ANCOVA model, adjusting for baseline ventricular rate

§ By chi-square test

|| Unadjusted means reported, as ANCOVA model not suitable given distribution of cases placebo vs etripamil arms

From ANCOVA model for area under the curve (AUC) adjusting for baseline ventricular rate

** From *t* test of difference between the areas under the curves (AUC) of plots of absolute mean heart rate.

NS = nasal spray, VR = ventricular rate, CI = confidence interval, IQR = interquartile range, SD = Standard deviation.

Supplemental Table IV. Sensitivity analysis of differing durations of ventricular rate moving-average

	Duration of Time-Window of Moving Average of VR Used for Measurements				
Mean Maximum Reduction from Baseline* to Nadir† (bpm)	**1 min**	**2 min**	**3 min**	**5 min§**	**10 min**
Adjusted Mean (95% CI), Placebo-arm	-8.23 (-10.24, -6.23)	-6.79 (-8.99, -4.59)	-6.12 (-8.51, -3.73)	-5.06 (-7.44, -2.67)	-3.90 (-6.31, -1.50)
Adjusted Mean (95% CI), Etripamil-arm	-39.27 (-49.77, -28.78)	-37.02 (-47.33, -26.72)	-35.95 (-46.21, -25.68)	-34.97 (-45.13, -24.81)	-33.39 (-43.40, -23.39)
Difference of Means (95% CI)	-31.04 (-41.70, -20.39)	-30.23 (-40.73, -19.74)	-29.83 (-40.32, -19.33)	-29.91 (-40.31, -19.52)	-29.49 (-39.73, -19.24)
p-value‡	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* Baseline ventricular rate = the average heart rate over the five min immediately prior to drug administration

† Nadir = the lowest moving average heart rate recorded in the 60 min post drug administration

‡ From ANCOVA model, comparing maximum reductions from baseline (means) for placebo vs. etripamil.

§ Primary analysis used 5-min moving average

VR = ventricular rate, CI = confidence interval, bpm = beats per minute

Supplemental Table V. Summary of patient satisfaction with treatment measured by Treatment Satisfaction Questionnaire for Medication (TSQM-9) sensitivity analysis (Efficacy and mITT Populations)

		Efficacy Population*			**mITT Population†**		
Domains		**Placebo** (N=25)	**Etripamil** (N=24)	**p-value‡**	**Placebo** (N=29)	**Etripamil** (N=27)	**p-value‡**
Effectiveness§	Mean (SD)	36.67 (21.64)	62.96 (21.59)	p<0.0001	36.97 (24.50)	65.43 (21.86)	p<0.0001
	Median (IQR)	33.33 (22.22, 55.56)	66.67 (50.00, 77.78)		33.33 (22.22, 55.56)	66.67 (50.00, 83.33)	
Relief of Symptoms Question‖	Mean (SD)	3.08 (1.29)	4.63 (1.35)	p=0.0002	3.10 (1.47)	4.78 (1.37)	p<0.0001
	Median (IQR)	3.00 (2.00, 4.00)	5.00 (4.00, 5.50)		3.00 (2.00, 4.00)	5.00 (4.00, 6.00)	
Global Satisfaction§	Mean (SD)	37.14 (25.42)	53.87 (21.17)	p=0.0161	36.45 (25.78)	52.65 (22.51)	p=0.0157
	Median (IQR)	42.86 (14.29, 57.14)	57.14 (42.86, 71.43)		42.86 (14.29, 57.14)	57.14 (42.86, 71.43)	
Convenience§	Mean (SD)	72.00 (16.08)	65.28 (12.50)	p=0.1100	71.26 (16.93)	63.37 (14.39)	p=0.667
	Median (IQR)	72.22 (61.11, 83.33)	66.67 (55.56, 72.22)		72.22 (61.11, 83.33)	66.67 (50.00, 72.22)	

***** The 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. Data reported in Table 3 and also shown here for comparison.

† The mITT Population is comprised of all randomized patients who received the study drug and who had a post-drug ECG CMS recording.

‡ p-value was obtained by *t* test.

§ Domain Score measured “satisfaction of effectiveness of treatment” on a 0-100 scale.

|| TSQM-9, Question 2 measured “satisfaction on relief of symptoms” using a 7-point anchored scale.

SD = standard deviation

Supplemental Table VI. Medications Started After Study Drug Administration

	Placebo* N=29	**Etripamil* N=27**	**Total* N=56**
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%)

* Safety Population is comprised of all randomized patients who received study drug

Patients were counted more than once if multiple classes of medications were administered.

AAD = antiarrhythmic drug (included Type IC and III drugs), BB = beta blocker, IV = intravenous, NDHP CCB = non-dihydropyridine calcium channel blocker.

Supplemental Table VII. Summary of Treatment-Emergent Serious Adverse Events

Patients, N (%)	**Placebo* (N= 29)**	**Etripamil* (N=27)**
Patients with at least one TESAE†	2 (6.9%)	1 (3.7%)
Patients with at least one severe TESAE	0 (0.0%)	1 (3.7%)
Patients with at least one TESAE leading to study discontinuation	0 (0.0%)	0 (0.0%)
Patients with at least one TESAE related to study drug	0 (0.0%)	1 (3.7%)
Death	0 (0.0%)	0 (0.0%)

* Safety Population is comprised of all randomized patients who received study drug

† Treatment-Emergent Serious Adverse Events (TESAEs) are serious adverse events (SAEs) with onset date/time within 24 hours after study drug administration. In case of a missing AE onset time, the AE is considered treatment-emergent if onset date is equal to study drug administration date or the next.

Supplemental Table VIII. Summary of treatment-emergent serious adverse events (TESAEs) by preferred term, system organ class, severity and relation to study drug

Patients, n (%)	**Placebo* (N= 29)**			**Etripamil* (N=27)**		
Patients with at least one TESAE†	2 (6.9%)‡			1 (3.7%)		
TESAEs by preferred term	**n (%)**	**Severity**	**Relation to Study Drug**	**n (%)**	**Severity**	**Relation to Study Drug**
Cardiac Disorders	2 (6.9%)	Moderate	Not Related	1 (3.7%)	Severe	Related
Atrial fibrillation	1 (3.4%)	Moderate	Not Related	0 (0.0%)	-	-
Bradyarrhythmia	0 (0.0%)	-	-	1 (3.7%)	Severe	Related
Intracardiac thrombus	1 (3.4%)	Moderate	Not Related	0 (0.0%)	-	-
Myocardial ischemia	1 (3.4%)	Moderate	Not Related	0 (0.0%)	-	-
Nervous System Disorders	0 (0.0%)	-	-	1 (3.7%)	Severe	Related
Syncope (vasovagal)	0 (0.0%)	-	-	1 (3.7%)	Severe	Related
Vascular Disorders	1 (3.4%)	Moderate	Not Related	0 (0.0%)	-	-
Peripheral artery occlusion	1 (3.4%)	Moderate	Not Related	0 (0.0%)	-	-

* Safety Population is comprised of all randomized patients who received the study drug

† Treatment-Emergent Serious Adverse Events (TESAEs) are serious adverse events (SAEs) with onset date/time within 24 hours after study drug administration. In case of a missing AE onset time, the AE is considered treatment-emergent if onset date is equal to study drug administration date or the next.

‡ One placebo patient had TESAEs of intracardiac thrombus and peripheral artery occlusion; another placebo patient had TESAEs of atrial fibrillation and myocardial ischemia.

Subjects reporting multiple TESAEs within a given system organ class/preferred term were counted only once within the category.

MedDRA terms used in table.