Oral Vernakalant for the Prevention of Atrial Fibrillation Recurrence Post-Cardioversion

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Disclosures

Steering committee work, advisory boards, symposia for Cardiome, Astellas, Merck, Sanofi

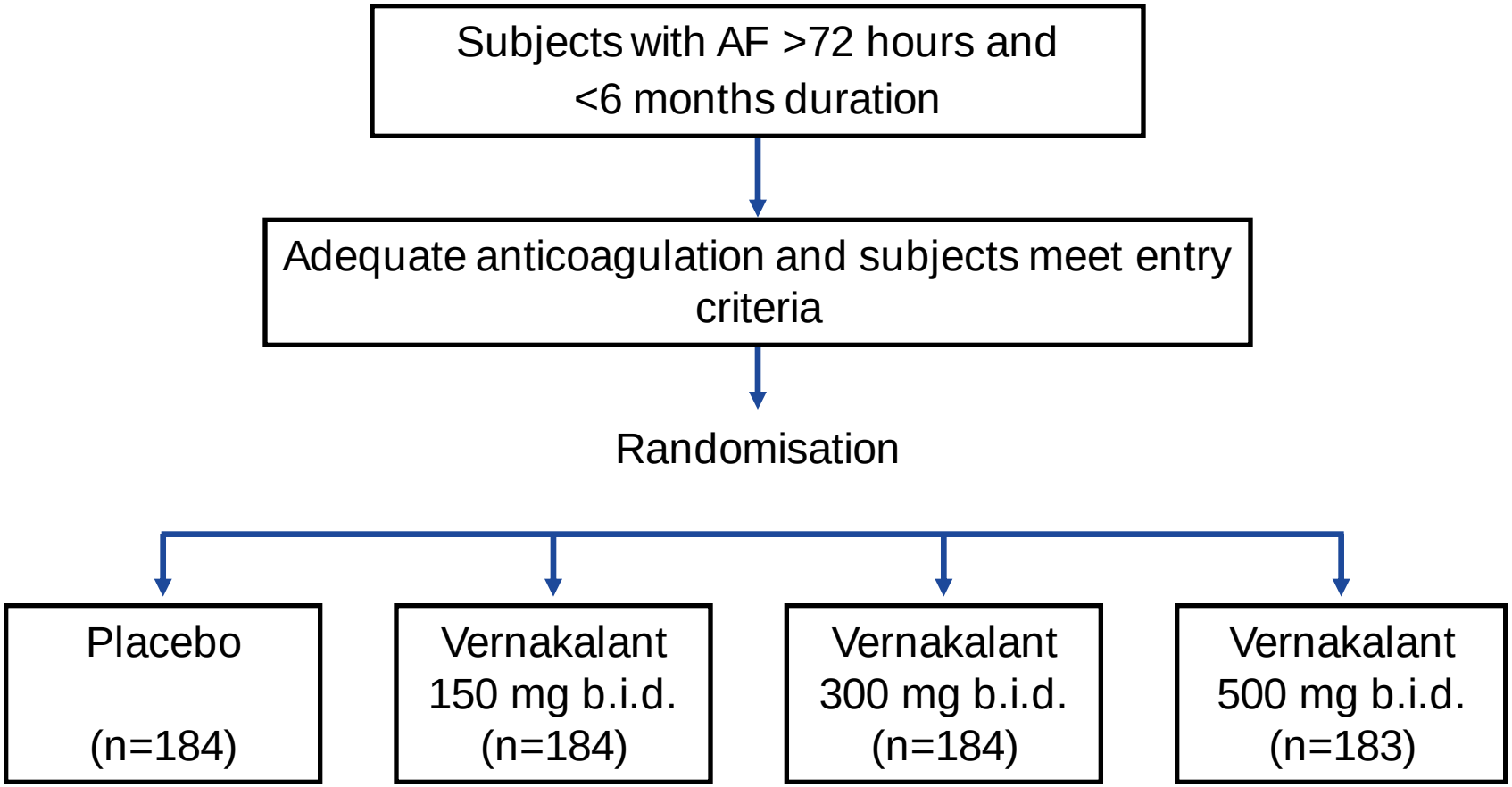
Study Objectives

To determine the most appropriate oral dose of vernakalant (VERO), a novel atrial selective antiarrhythmic drug for the prevention of AF recurrence after cardioversion.

Phase IIB Protocol Overview

- Randomised, double-blind, placebo-controlled, parallel group, multi-centre, dose-ranging study
- AF 3d - 6mo, pts stratified by background ACE-I/ARB use
- Vernakalant: 150, 300, 500 mg b.i.d.; Placebo
- 1:1:1:1 treatment allocation
- Daily TTM and diary, 12-lead ECG at scheduled visits
- Up to 90-days dosing duration
- 735 patients enrolled; involving 154 sites across 24 countries in Western & Central Europe, Russia, Australia, New Zealand, S. Africa and Singapore

Phase IIB Study Design



Key Inclusion Criteria

- Age: 18-85 years of age
- Symptomatic AF (3 days - 6 months)
- Women must be non-pregnant and non-nursing
- Adequate anticoagulation therapy (ACC/AHA/ESC practice guidelines)
- Systolic blood pressure >100 mmHg and <190 mmHg
- Body weight 45-113 kg
- Informed consent

Key Exclusion Criteria

- Long QT syndrome, previous torsades de pointes, VT, VF
- Clinically significant sustained bradycardia (<50 bpm), sick-sinus syndrome or pacemaker, 2nd or 3rd degree AV block
- QRS >0.140 sec
- Class III or IV heart failure, HF hospitalization in last 6 mo
- MI, cardiac surgery, angioplasty, acute coronary syndrome or unstable angina within past 30 days
- Significant aortic valvular stenosis (>25 mmHg), hypertrophic obstructive or restrictive cardiomyopathy, or constrictive pericarditis
- Known secondary causes of AF (e.g. hyperthyroidism)
- Received oral Class I or III antiarrhythmics within 3 days or amiodarone within 4 weeks; or Class I or III intravenous antiarrhythmics within 24 hours of randomisation

Key Demographics
(MITT Population)

	Placebo (N=160)	VERO150 (N=147)	VERO300 (N=148)	VERO500 (N=150)
Male (%)	69%	61%	72%	65%
Caucasian (%)	99%	98%	100%	99%
Age (mean (SD))	63 (10.4)	64 (9.9)	62 (11.0)	65 (10.5)
Weight (mean (SD))	86 (12.9)	86 (14.8)	86 (13.4)	85 (13.5)

Cardiovascular Medical History
(MITT Population)

	Placebo (N=160)	VERO150 (N=147)	VERO300 (N=148)	VERO500 (N=150)
Hypertension	78%	78%	78%	86%
Ischaemic heart disease	37%	30%	32%	31%
Myocardial infarction	8%	5%	9%	9%
CHF	48%	37%	33%	33%
Valvular heart disease	10%	12%	13%	13%
Diabetes	20%	14%	15%	13%

AF Characteristics
(MITT Population)

	Placebo (N=160)	VERO150 (N=147)	VERO300 (N=148)	VERO500 (N=150)
First episode	50%	50%	47%	52%
Duration of AF in years (median)	0.4	0.5	0.6	0.4
Duration of current episode in days (median)	73	66	66	67
LADD mm (mean (SD))	46 (6.2)	45 (6.5)	45 (6.3)	45 (6.0)
LADD >50 mm	21%	16%	20%	15%

Concomitant Medications
(MITT Population)

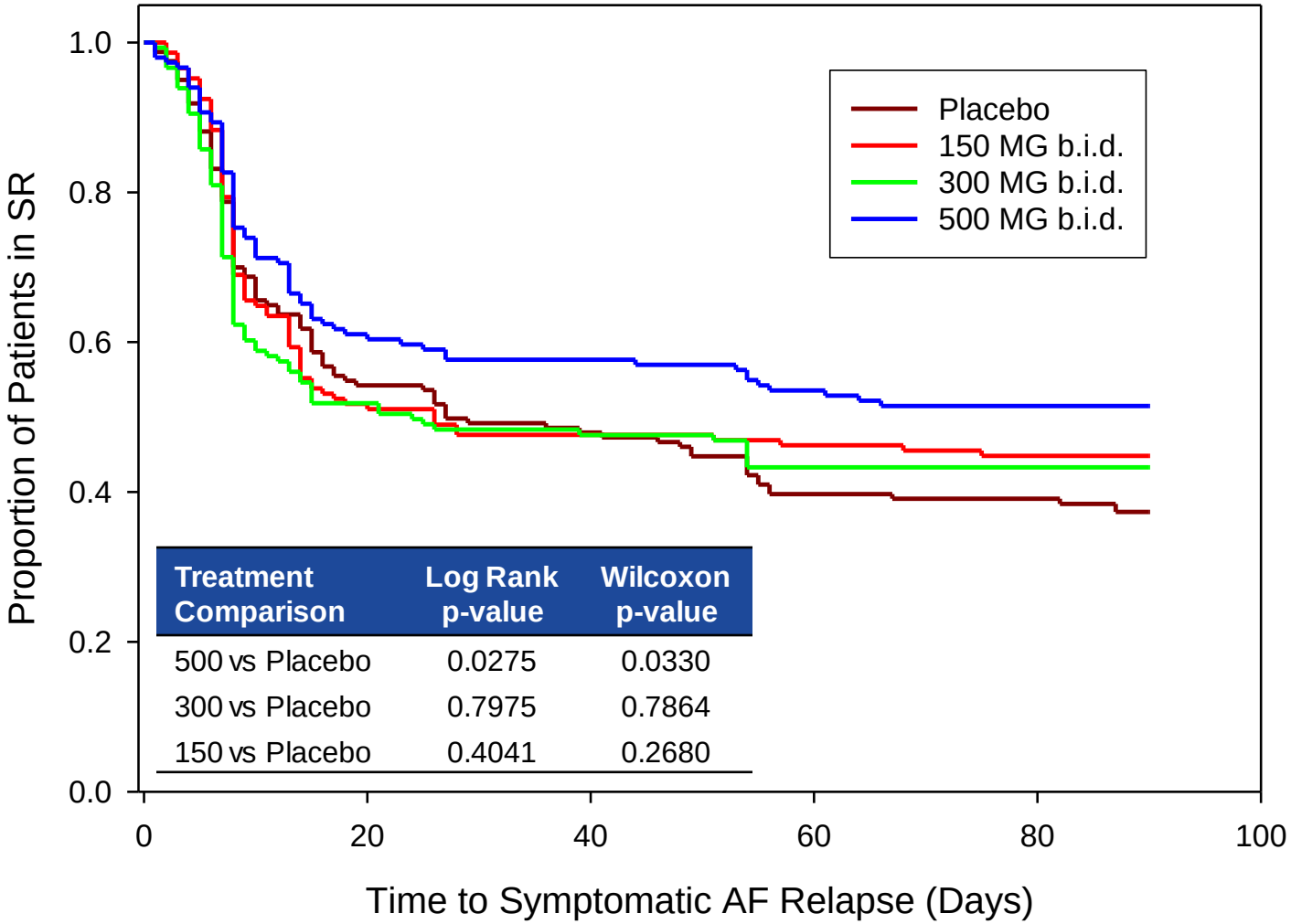
	Placebo (N=160)	VERO150 (N=147)	VERO300 (N=148)	VERO500 (N=150)
Beta blockers	83%	90%	74%	82%
ACE/ARB	69%	72%	72%	74%
Digitalis glycosides	18%	22%	16%	15%
Ca channel blockers[1]	9%	9%	13%	10%
Statins	29%	31%	31%	30%
Diuretics	48%	50%	46%	47%

N.B., Concomitant is defined as started after first dose or prior use and continuing

[1]Verapamil and Diltiazem only

Time to Symptomatic Sustained AF Recurrence

Investigators Assessment or by TTM (MITT)



Treatment Comparison	Log Rank p-value	Wilcoxon p-value
500 vs Placebo	0.0275	0.0330
300 vs Placebo	0.7975	0.7864
150 vs Placebo	0.4041	0.2680

Median time to relapse: Placebo = 29 days, VERO 500 mg b.i.d. >90 days

Key Efficacy Results

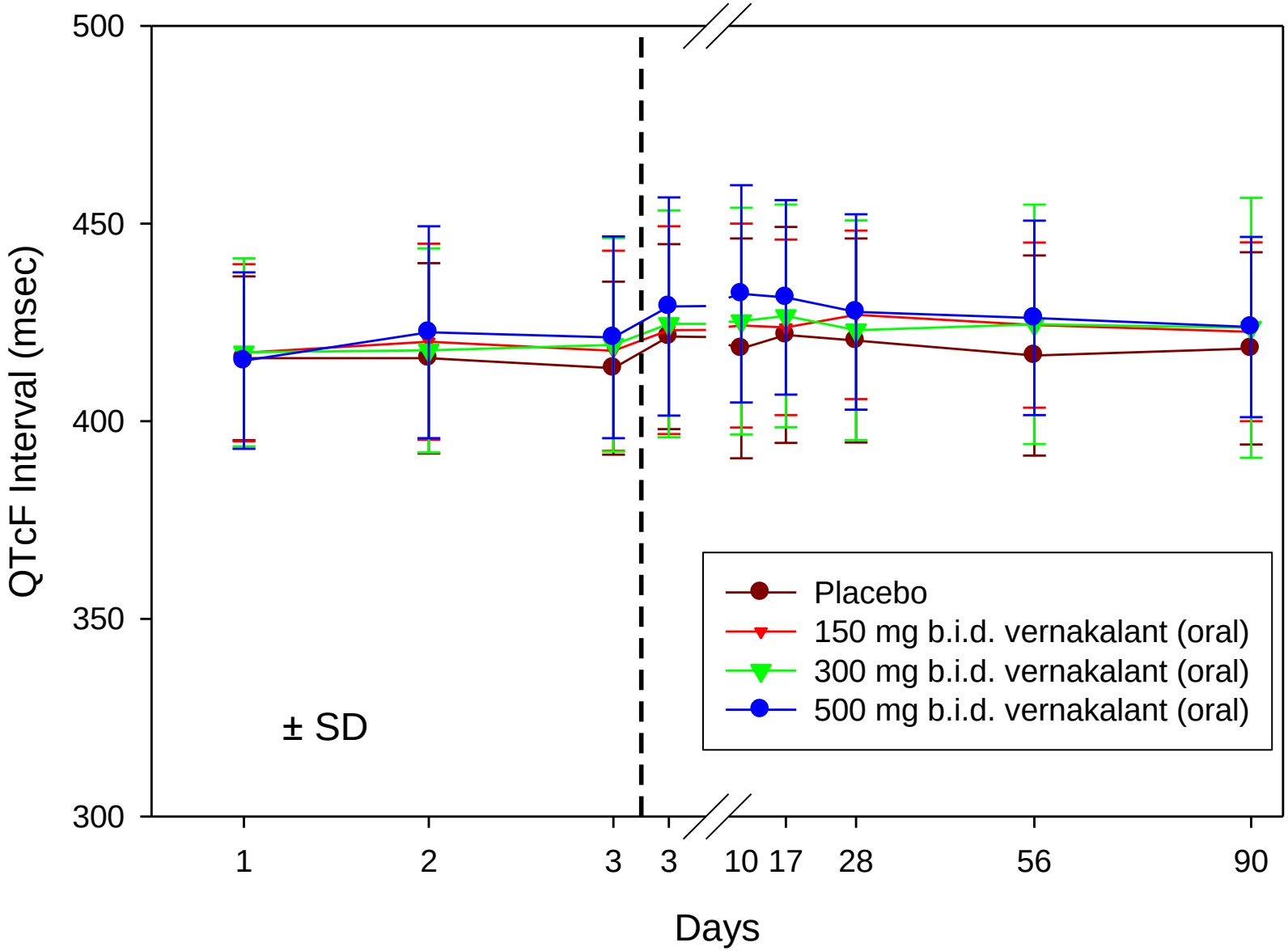
- Vernakalant PO dosed up to 500 mg b.i.d. exhibited a positive dose response
- Vernakalant PO 500 mg b.i.d. compared to placebo significantly reduced the rate of AF relapse by 27% relative to placebo (Log-Rank P-value = 0.0275)
- Vernakalant PO 500 mg b.i.d. significantly prolongs the median time to AF relapse >3 fold compared to placebo

CARDIOME PHARMA CORP.

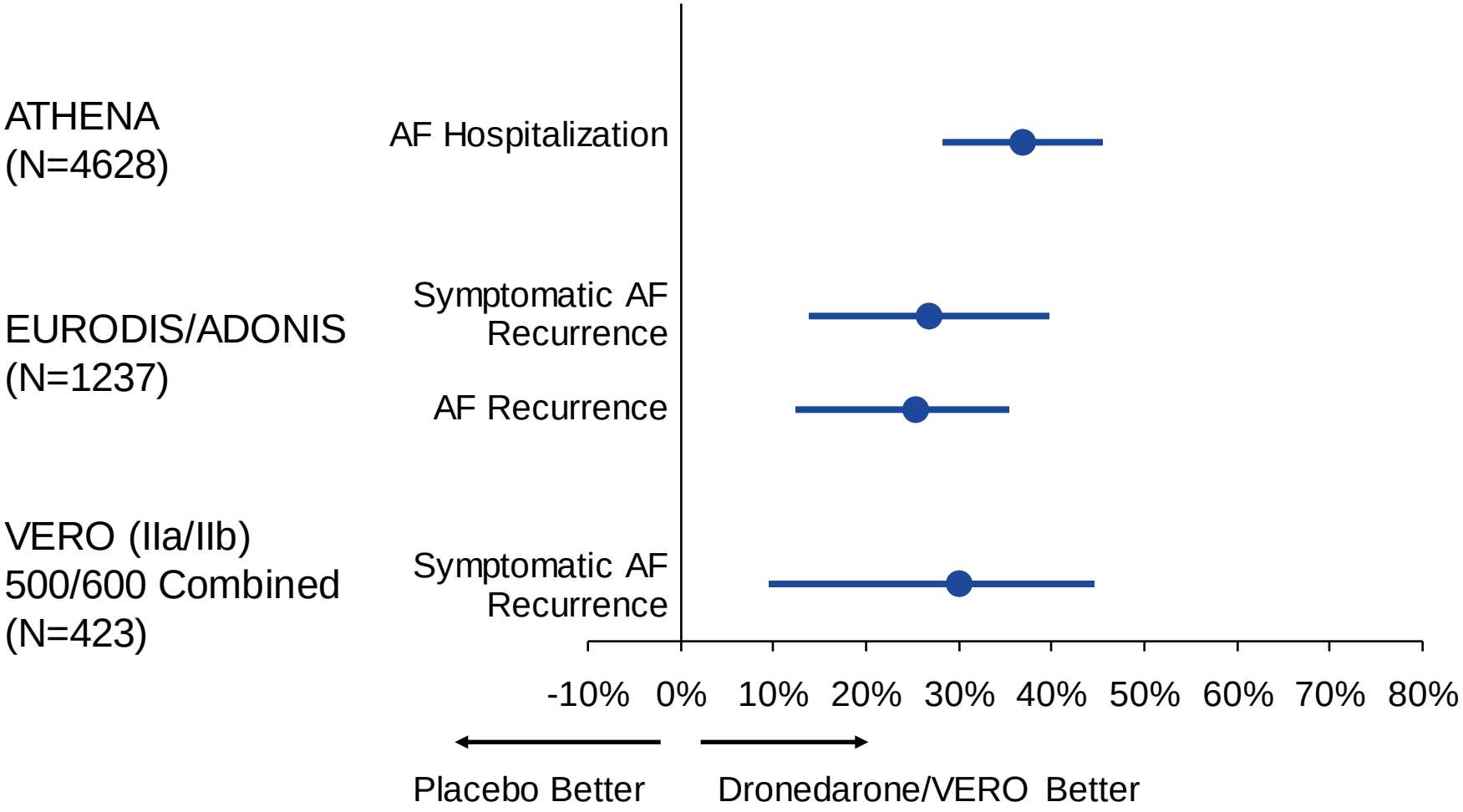
Safety Summary

	Placebo (N=184)	150 mg (N=183)	300 mg (N=183)	500 mg (N=182)
Any related AE	9 (4.9%)	16 (8.7%)	13 (7.1%)	15 (8.2%)
Any related SAE	1 (0.5%)	2 (1.1%)	1 (0.5%)	1 (0.5%)
Related AE leading to discontinuation	1 (0.5%)	4 (2.2%)	4 (2.2%)	2 (1.1%)
Deaths	2 (1.1%)	1 (0.5%)	1 (0.5%)	0

QTcF Interval



Relative Reduction in AF Endpoints from ATHENA, EURODIS/ADONIS, and VERO



Conclusions

- Vernakalant PO 500 mg b.i.d. was effective at maintaining sinus rhythm
  - 51.5% of patients were in sinus rhythm at 90 days (H.R. = 0.735, p= 0.0275 vs placebo)
  - Time to AF relapse delayed 3 fold: >90 vs 29 days on placebo
- Vernakalant PO 150/300/500 mg b.i.d. was well tolerated
- No ventricular pro-arrhythmia observed
- No deaths related to study drug

Back-ups

Adverse Reactions Comparison (vs. Multaq Label)

	Placebo (N=2875)	Dronedarone 400 mg twice daily (N=3282)	Placebo (N=257)	VERO ≤1200 ng/mL (N=617)	VERO ≥1200 ng/mL (N=77)
Gastrointestinal					
Diarrhea	6%	9%	0.4%	2.3%	3.9%
Nausea	3%	5%	0.4%	1.5%	1.3%
Abdominal pain	3%	4%	0.4%	0.8%	1.3%
Vomiting	1%	2%	0.8%	0.8%	1.3%
Dyspeptic signs and symptoms	1%	2%	0	0.8%	1.3%
General					
Asthenic conditions	5%	7%	1.2%	2.3%	2.6%
Cardiac					
Bradycardia	1%	3%	2.7%	3.2%	9.1%
Skin and subcutaneous tissue					
Including rashes (generalized, macular, maculo-papular, erythematous), pruritis, eczema, dermatitis, dermatitis allergic	3%	5%	1.2%	2.6%	6.5%

Benefit of Vernakalant 500 mg b.i.d Consistently Maintained across Subgroups

- The treatment benefit of Vernakalant PO 500 mg b.i.d. is consistent across subgroups:
  - CHF Hx
  - Hypertension Hx
  - Ischaemic heart disease Hx
  - Atrial fibrillation Hx
  - AF duration
  - Age
  - Gender
  - Concomitant ACE/ARB use
  - Concomitant beta blocker use

CARDIOME PHARMA CORP.

Time to Symptomatic Sustained AF Recurrence
Investigators Assessment or TTM (MITT)

1) KM Estimates of the Probability of Maintaining Sinus Rhythm

Time Point	Placebo (N=160)	VERO 150 (N=147)	VERO 300 (N=148)	VERO 500 (N=150)
30 Days	50%	48%	48%	58%
60 Days	40%	46%	43%	54%
90 Days	38%	45%	43%	51%
Median (days)	**29**	**26**	**24**	**>90**

2) Results of Statistical Inference

Treatment Comparison	Log Rank p-value	Wilcoxon p-value	Hazard Ratio (95% CI)
500 vs placebo	**0.0275**	**0.0330**	**0.74 (0.54, 0.997)**
300 vs placebo	0.7975	0.7864	0.97 (0.74, 1.34)
150 vs placebo	0.4041	0.2680	0.90 (0.67, 1.22)

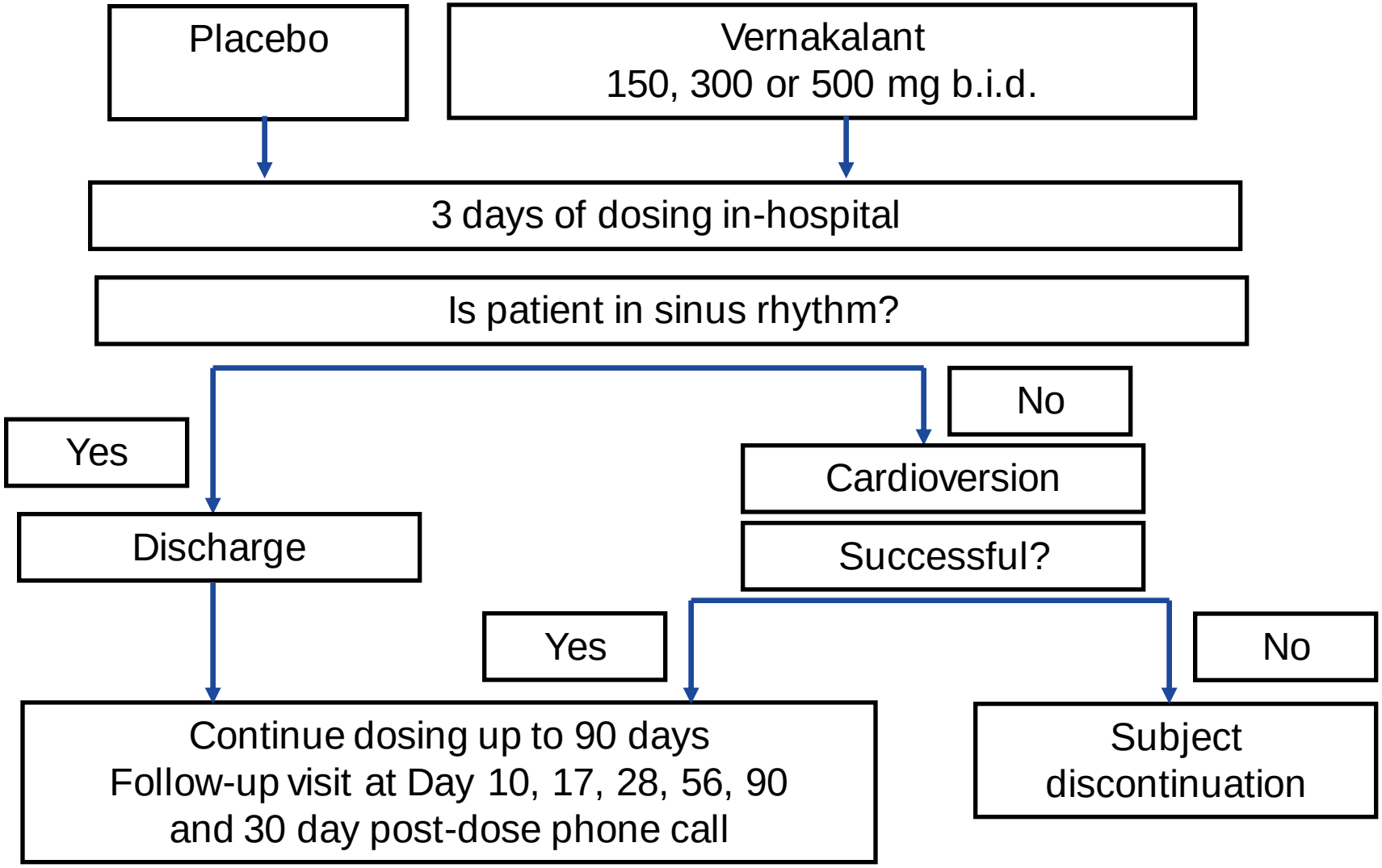
Phase IIB Deaths – Placebo

- 70 yr old male – placebo
  - Cause of death – ischaemic stroke
  - Day 85 admitted to hospital with ischaemic stroke
  - Died following day
  - Not related to study drug
- 58 yr old male – placebo
  - Acute myocardial infarction 6 weeks before randomization
  - Cause of death – myocardial infarction with cardiac arrest day 1
  - Anoxic brain damage and died in hospital nine days later
  - Not related to study drug

Phase IIB Deaths – Vernakalant

- 70 yr old female – vernakalant 150 mg b.i.d.
  - Cause of death – cervical cancer
  - Day 60 admitted to hospital for investigation of abdominal pain
  - Diagnosed with cervical cancer – inoperable
  - Died in hospital – day 79 – no autopsy
  - Not related to study drug
- 59 yr old female – vernakalant 300 mg b.i.d.
  - Cause of death – post-op pulmonary embolism/pneumonia
  - Not related to study drug

Phase IIB Study Design



Patient Disposition

	Placebo	VERO150	VERO300	VERO500	Total
Randomised	184	184	184	183	735
Dosed (safety pop)	184	183	183	182	732
MITT[1] (efficacy pop)	160	147	148	150	605

[1]Received study medication and discharged in SR on Day 3

CHF Characteristics
(MITT Population)

	Placebo (N=160)	VERO150 (N=147)	VERO300 (N=148)	VERO500 (N=150)
CHF (%)	48%	37%	33%	33%
NYHA class				
Class I	13%	8%	9%	9%
Class II	35%	29%	24%	24%
CHF duration				
<6 Months	27%	23%	17%	16%
6-12 Months	4%	5%	3%	4%
>12 Months	18%	10%	13%	13%
LVEF % (mean (SD))	54 (9.8)	55 (9.8)	55 (10.0)	55 (9.2)
LVEF ≤40%	11%	10%	10%	7%

SAEs Related to Study Drug

Placebo (N=184)	150 mg (N=183)	300 mg (N=183)	500 mg (N=182)
1(0.5%)	2 (1.1%)	1(0.5%)	1(0.5%)
Ventricular tachycardia	Angina	Atrial flutter	Sinus pause
	Conduction disorder		

Cardiac Adverse Events Continued[1]

	Placebo (N=184)	150 mg (N=183)	300 mg (N=183)	500 mg (N=182)
Angina pectoris	0	2 (1.1%)	0	0
Cardiac failure	0	0	0	2 (1.1%)
Myocardial infarction	1 (0.5%)	0	0	1 (0.5%)
Ventricular tachycardia	1 (0.5%)	0	0	1 (0.5%)
Cardiac amyloidosis	0	1 (0.5%)	0	0
Nodal rhythm	0	0	1 (0.5%)	0
Sinus pause	0	0	0	1 (0.5%)
Sinus tachycardia	0	1 (0.5%)	0	0
Wandering pacemaker	0	1 (0.5%)	0	0
Torsades de pointes	0	0	0	0

[1]Excludes AF, AFL and SVT as these were considered endpoints

CARDIOME PHARMA CORP.

Nervous System Adverse Events

	Placebo (N=184)	150 mg (N=183)	300 mg (N=183)	500 mg (N=182)
Stroke	1 (0.5%)	1 (0.5%)	2 (1.1%)	0
Disturbance in attention	0	0	0	1 (0.5%)
Dizziness	4 (2.2%)	4 (2.2%)	4 (2.2%)	5 (2.7%)
Dysgeusia	1 (0.5%)	0	0	1 (0.5%)
Headache	6 (3.3%)	7 (3.8%)	1 (1.1%)	7 (3.8%)
Hypoesthesia	1 (0.5%)	0	0	0
Hypoglycemic coma	0	1 (0.5%)	0	0
Transient ischaemic attack	1 (0.5%)	1 (0.5%)	0	0
Tremors	0	0	0	0

Vascular Adverse Events

	Placebo (N=184)	150 mg (N=183)	300 mg (N=183)	500 mg (N=182)
Flushing	0)	1 (0.5%)	1 (0.5%)	0
Hypertension	5 (2.7%)	4 (2.2%)	6 (3.3%)	6 (3.3%)
Hypotension	3 (1.6%)	1 (0.5%)	1 (0.5%)	0
Labile hypertension	0	0	0	1 (0.5%)
Orthostatic hypotension	1 (0.5%)	0	0	0
Phlebitis superficial	1 (0.5%)	0	0	0

Cardiac Adverse Events[1]

	Placebo (N=184)	150 mg (N=183)	300 mg (N=183)	500 mg (N=182)
Bradycardia/sinus bradycardia	6 (3.3%)	5 (2.7%)	4 (2.2%)	12 (6.6%)
Palpitations	3 (1.6%)	3 (1.6%)	2 (1.1%)	6 (3.3%)
First degree AV block	4 (2.2%)	2 (1.1%)	2 (1.1%)	2 (1.1%)
Supraventricular extrasystoles	1 (0.5%)	5 (2.7%)	1 (0.5%)	2 (1.1%)
Ventricular extrasystoles	0	3 (1.6%)	0	2 (1.1%)
Conduction disorder	0	1 (0.5%)	1 (0.5%)	1 (0.5%)

[1]Excludes AF, AFL and SVT as these were considered endpoints

Systolic Blood Pressure