Clinical trial results:
GENETIC-AF – A Genotype-Directed Comparative Effectiveness Trial of Bucindolol and Toprol-XL for Prevention of Symptomatic Atrial Fibrillation/Atrial Flutter in Patients with Heart Failure

Summary

EudraCT number	2016-000302-12
Trial protocol	HU NL PL BG
Global end of trial date	28 December 2017

Results information

Result version number	v1 (current)
This version publication date	30 April 2022
First version publication date	30 April 2022
Summary attachment (see zip file)	Bucindolol for the Maintenance of Sinus Rhythm in a Genotype-Defined HF Population Online Supplement (c. Piccini et al JACC-HF 2019 online supplement.pdf) Bucindolol for the Maintenance of Sinus Rhythm in a Genotype-Defined HF Population (b. Piccini et al JACC-HF 2019 main results.pdf)

Trial information

Trial identification

Sponsor protocol code	BUC-CLIN-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01970501
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ARCA biopharma, Inc
Sponsor organisation address	10170 Church Ranch Way, Suite 100, Westminster, United States, 80021
Public contact	Michael Bristow, ARCA biopharma, Inc, 1 7209402100, michael.bristow@arcabio.com
Scientific contact	Michael Bristow, ARCA biopharma, Inc, 1 7209402100, michael.bristow@arcabio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2017
Global end of trial reached?	Yes
Global end of trial date	28 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the effects of bucindolol and metoprolol on the recurrence of symptomatic Atrial Fibrillation (AF)/Atrial Flutter (AFL) in patients with HFREF (heart failure with reduced left ventricle ejection fraction) who have a β1389 arginine homozygous (β1389Arg/Arg) genotype.

Protection of trial subjects:

The Sponsor and Investigators followed requirements as set forth in the U.S. Code of Federal Regulations (CFR), 21CFR Parts 50, 54, 56, and 312 and the ICH E6 GCP Consolidated Guidance. Investigator responsibilities are set out in Section 4 of the E6 Guideline. Sponsor responsibilities are set out in Section 5 of the E6 ICH Guideline.
Investigators ensured the study was conducted in accordance with the principles of the ICH guidelines, or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the study patient.

Investigators had to ensure that patients' anonymity was strictly maintained and that their identities were protected from unauthorized parties. Only an identification code (i.e., not names) were recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory.

Background therapy: -

Evidence for comparator:

Metoprolol succinate (Toprol-XL, henceforth referred to as metoprolol) is a β1-AR selective β-blocker indicated for the treatment of stable, symptomatic (NYHA Class II or III) HF of ischemic or non-ischemic origin. Metoprolol has demonstrated mild efficacy for the prevention of new onset AF in a HF patient population (Nsar 2007, vanVeldhuisen 2006) and is often used off-label in this setting (Class IIa indication with a "C" level of evidence for AF prevention per ACC/AHA/ESC Joint Guidelines). In a previous study, metoprolol decreased the incidence of AF recurrence, compared to placebo, in patients with persistent AF who had recently undergone electrocardioversion to sinus rhythm (Nergardh 2007).

Actual start date of recruitment	27 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Canada: 59
Country: Number of subjects enrolled	Serbia: 21

Country: Number of subjects enrolled	United States: 127
Worldwide total number of subjects	267
EEA total number of subjects	60

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	109
From 65 to 84 years	153
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The study recruitment period began in Feb 2014 and continued through Jul 2017. Recruitment periods by country as follows:
Canada: Mar 15 - Jul 17
Hungary: Sep 16 - Jun 17
Netherlands: May 1 - Jul 17
Poland: Jan 17 - Jul 17
Serbia: May 17 - Jun 17
United States: Feb 14 - Jul 17

Pre-assignment

Screening details:

Eligible subjects were men and women, >=18 years with recent/current history of symptomatic AF and HF (LVEF < 50) indicated for ECV if AF was present, with the ADRB1 Arg389Arg genotype. 747 subjects were screened and 267 randomized. Genotype and withdrawal of consent were the primary reasons for screen failure.

Period 1

Period 1 title	Randomization (Visit 2)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Blinding will be accomplished by providing study drug (i.e., bucindolol or metoprolol tablets) in capsules that are visually indistinguishable and provided in numbered kits. Only the numbers of the kits to be administered to a given patient, and not the identity of the study drug, will be provided to sites. Investigators, site personnel, and patients will not be informed of the blinded study drug assignment at the time of study completion.

Arms

Are arms mutually exclusive?	Yes
Arm title	bucindolol

Arm description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg).

Arm type	Experimental
Investigational medicinal product name	bucindolol hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated bucindolol was provided in the following dosage strengths: 6.25 mg, 12.5, 25, 50 and 100 mg to be taken twice daily.

Arm title	Metoprolol succinate

Arm description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.

Arm type	Active comparator

Investigational medicinal product name	Metoprolol succinate
Investigational medicinal product code	
Other name	Toprol-XL, metoprolol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The comparator arm is comprised of an overencapsulated metoprolol succinate tablet and a placebo capsule. The placebo capsule is a capsule filled with micro crystalline cellulose. The metoprolol tablets range from 25mg to 200mg.

Number of subjects in period 1	bucindolol	Metoprolol succinate
Started	134	133
Completed	134	133

Period 2

Period 2 title	Drug Lead-in Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Blinding will be accomplished by providing study drug (i.e., bucindolol or metoprolol tablets) in capsules that are visually indistinguishable and provided in numbered kits. Only the numbers of the kits to be administered to a given patient, and not the identity of the study drug, will be provided to sites. Investigators, site personnel, and patients will not be informed of the blinded study drug assignment at the time of study completion.

Arms

Are arms mutually exclusive?	Yes
Arm title	bucindolol

Arm description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg).

Arm type	Experimental
Investigational medicinal product name	bucindolol hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated bucindolol was provided in the following dosage strengths: 6.25 mg, 12.5, 25, 50 and 100 mg to be taken twice daily.

Arm title	Metoprolol succinate

Arm description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.

Arm type	Active comparator
Investigational medicinal product name	Metoprolol succinate
Investigational medicinal product code	
Other name	Toprol-XL, metoprolol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The comparator arm is comprised of an overencapsulated metoprolol succinate tablet and a placebo capsule. The placebo capsule is a capsule filled with micro crystalline cellulose. The metoprolol tablets range from 25mg to 200mg.

Number of subjects in period 2	bucindolol	Metoprolol succinate
Started	134	133
Completed	132	126
Not completed	2	7
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	3
Adverse event, non-fatal	-	3
investigator or sponsor discretion	1	-

Period 3

Period 3 title	24-Week Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Blinding will be accomplished by providing study drug (i.e., bucindolol or metoprolol tablets) in capsules that are visually indistinguishable and provided in numbered kits. Only the numbers of the kits to be administered to a given patient, and not the identity of the study drug, will be provided to sites. Investigators, site personnel, and patients will not be informed of the blinded study drug assignment at the time of study completion.

Arms

Are arms mutually exclusive?	Yes

Arm title	bucindolol

Arm description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg). Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a number of participants completed this arm prior to 24 week and are noted as sponsor or investigator initiated.

Arm type	Experimental
Investigational medicinal product name	bucindolol hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated bucindolol was provided in the following dosage strengths: 6.25 mg, 12.5, 25, 50 and 100 mg to be taken twice daily.

Arm title	Metoprolol succinate

Arm description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved. Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a number of participants completed this arm prior to 24 week and are noted as sponsor or investigator initiated.

Arm type	Active comparator
Investigational medicinal product name	Metoprolol succinate
Investigational medicinal product code	
Other name	Toprol-XL, metoprolol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The comparator arm is comprised of an overencapsulated metoprolol succinate tablet and a placebo capsule. The placebo capsule is a capsule filled with micro crystalline cellulose. The metoprolol tablets range from 25mg to 200mg.

Number of subjects in period 3	bucindolol	Metoprolol succinate
Started	132	126
Completed	107	105
Not completed	25	21
Adverse event, serious fatal	1	2
Consent withdrawn by subject	5	4
Adverse event, non-fatal	2	2
investigator or sponsor discretion	16	13
medical condition	1	-

Period 4

Period 4 title	Treatment Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Blinding will be accomplished by providing study drug (i.e., bucindolol or metoprolol tablets) in capsules that are visually indistinguishable and provided in numbered kits. Only the numbers of the kits to be administered to a given patient, and not the identity of the study drug, will be provided to sites. Investigators, site personnel, and patients will not be informed of the blinded study drug assignment at the time of study completion.

Arms

Are arms mutually exclusive?	Yes
Arm title	bucindolol

Arm description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg). Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a majority of participants were not enrolled in this treatment extension period.

Arm type	Experimental
Investigational medicinal product name	bucindolol hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Over-encapsulated bucindolol was provided in the following dosage strengths: 6.25 mg, 12.5, 25, 50 and 100 mg to be taken twice daily.

Arm title	Metoprolol succinate

Arm description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved. Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a majority of participants were not enrolled in this treatment extension period.

Arm type	Active comparator
Investigational medicinal product name	Metoprolol succinate
Investigational medicinal product code	
Other name	Toprol-XL, metoprolol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The comparator arm is comprised of an overencapsulated metoprolol succinate tablet and a placebo capsule. The placebo capsule is a capsule filled with micro crystalline cellulose. The metoprolol tablets range from 25mg to 200mg.

Number of subjects in period 4[1]	bucindolol	Metoprolol succinate
Started	77	64
Completed	64	56
Not completed	13	8
Adverse event, serious fatal	5	-
Consent withdrawn by subject	3	3
Adverse event, non-fatal	3	-
Patient non-compliance	-	3
investigator or sponsor discretion	2	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: On 21 Aug 2017, the decision was made to complete the study as a Phase 2B study and not to continue into Phase 3. Participants who were scheduled to complete the Week 24 visit before 31 Dec 2017 completed all study visits through Week 24, discontinued the study at Week 24 and transitioned to commercial therapy.

Baseline characteristics

Reporting groups	
Reporting group title	bucindolol
Reporting group description:	
Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg).	
Reporting group title	Metoprolol succinate
Reporting group description:	
Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.	

Reporting group values	bucindolol	Metoprolol succinate	Total
Number of subjects	134	133	267
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	56	53	109
From 65-84 years	76	77	153
85 years and over	2	3	5
Age continuous Units: years			
arithmetic mean	65.8	65.5	
standard deviation	± 10.28	± 9.99	-
Gender categorical Units: Subjects			
Female	23	25	48
Male	111	108	219
Race Units: Subjects			
White	129	128	257
Black	2	3	5
American Indian or Alaskan Native	1	0	1
Asian	1	1	2
Native Hawaiian or Other Islander	0	1	1
Other	1	0	1
NYHA at Screen Units: Subjects			
One	40	35	75
Two	80	72	152
Three	14	26	40
Four	0	0	0

Etiology of HF Units: Subjects			
Ischemic	42	44	86
Non-Ischemic	92	89	181
LVEF (%) Strata Selection			
Left Ventricular Ejection Fraction Strata Selection			
Units: Subjects			
>35%	80	83	163
< 35%	54	50	104

End points

End points reporting groups

Reporting group title	bucindolol

Reporting group description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg).

Reporting group title	Metoprolol succinate

Reporting group description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.

Reporting group title	bucindolol

Reporting group description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg).

Reporting group title	Metoprolol succinate

Reporting group description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.

Reporting group title	bucindolol

Reporting group description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg). Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a number of participants completed this arm prior to 24 week and are noted as sponsor or investigator initiated.

Reporting group title	Metoprolol succinate

Reporting group description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved. Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a number of participants completed this arm prior to 24 week and are noted as sponsor or investigator initiated.

Reporting group title	bucindolol

Reporting group description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg). Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a majority of participants were not enrolled in this treatment extension period.

Reporting group title	Metoprolol succinate

Reporting group description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved. Sponsor requested that the last visit be between Aug-Dec 2017 and therefore a majority of participants were not enrolled in this treatment extension period.

Primary: Primary: Time to first event of symptomatic or asymptomatic atrial fibrillation/atrial flutter during 24-week follow up period.

End point title	Primary: Time to first event of symptomatic or asymptomatic atrial fibrillation/atrial flutter during 24-week follow up period.

End point description:

The primary efficacy endpoint was the time-to-first symptomatic AF/AFL during the 24-week follow-up period after establishment of stable sinus rhythm on study drug. A symptomatic AF/AFL event was defined as an AF/AFL event that was associated with a clinically relevant change in participant-reported symptoms, as determined by examination of blinded data by a Clinical Events Committee (CEC). Time-to-event was calculated as the date of the event minus the date of initiation of efficacy follow-up, with 1 day added to include both the start date and end date of the interval. For all endpoints, follow-up was censored when a participant received a cardiac transplant, was declared to be permanently lost to follow-up or withdrew consent. These analyses were two-tailed comparison of bucindolol and metoprolol, using the log-rank statistic with the exact variance calculation stratified by the randomized treatment assignment strata. These data are presented at Hazard Ratio

End point type	Primary

End point timeframe:

The primary efficacy endpoint was the time-to-first symptomatic AF/AFL during the 24-week follow-up period after establishment of stable sinus rhythm on study drug.

End point values	bucindolol	Metoprolol succinate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	126		
Units: Probability of event	69	67		

Attachments (see zip file)	Time to first symptomatic AF/AFL event/Time to event.pptx

Statistical analyses

Statistical analysis title	Time to first symptomatic AF/AFL event

Statistical analysis description:

Time-to-event is calculated as the date of the event minus the date of initiation of efficacy follow-up, with 1 added in order to include both the start date and end date of the interval. These analyses were a two-tailed comparison of bucindolol and metoprolol, using the log-rank statistic with the exact variance calculation stratified by the randomized treatment assignment strata. Time to event was statistically compared between treatment groups using a hazard ratio and was not different.

Comparison groups	bucindolol v Metoprolol succinate
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.45

Secondary: Secondary Outcome Measures

End point title	Secondary Outcome Measures

End point description:

The secondary efficacy endpoints included:

Total number of all-cause hospitalization days per participant.

End point type	Secondary

End point timeframe:

Over the course of 24 week Follow-up period after establishment of stable sinus rhythm on study drug.

End point values	bucindolol	Metoprolol succinate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	126		
Units: values				
number (not applicable)				
All cause hospitalization days	1.3	0.7		

Attachments (see zip file)	Time to first symptomatic AF/AFL event/Time to event.pptx Total hospitalizations/total hospitalizations.pptx

Statistical analyses

Statistical analysis title	Time to first symptomatic AF/AFL event

Statistical analysis description:

Event rates for the primary endpoint were similar for the bucindolol and metoprolol groups (50% and 51%, respectively), with a hazard ratio (HR) of 1.02 (95% CI: 0.72 to 1.45) for the covariate-adjusted Cox proportional hazards model.

Comparison groups	bucindolol v Metoprolol succinate
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.05 [1]
Method	Hazard Ratio

Notes:

[1] - Time-to-first symptomatic AF/AFL or ACM comparision between treatments P = 0.9053

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs were similar between treatment groups; 95 of 133 metoprolol-treated participants (71.4%) and 100 of 134 bucindolol-treated participants (74.6%) experienced at least 1 AE.

Adverse event reporting additional description:

Patients are counted once for each preferred term, once within each SOC (system organ class), and once for the overall total of patients with any adverse event.
Events with onset within 30 days of final study visit are included.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	6.1

Reporting groups

Reporting group title	bucindolol

Reporting group description:

Bucindolol taken twice daily. Starting dose of 6.25 mg, 12.5 mg, 25 mg, or 50 mg bid depending upon pre-study beta-blocker dose. Sites instructed to uptitrate to target dose of 50 mg bid (subjects < 75 kg) or 100 mg bid (subjects >= 75 kg).

Reporting group title	Metoprolol succinate

Reporting group description:

Arm 2 is comprised of metoprolol succinate taken once per day and a placebo capsule taken once per day (consistently 1 in the morning and 1 in the evening). Metoprolol succinate sarting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.

Serious adverse events	bucindolol	Metoprolol succinate	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 134 (24.63%)	26 / 133 (19.55%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events	6	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm- unspecified			
subjects affected / exposed	1 / 134 (0.75%)	3 / 133 (2.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Motor vehicle accident			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			

Hypotension			
subjects affected / exposed	2 / 134 (1.49%)	2 / 133 (1.50%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure aggravated			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 134 (2.24%)	3 / 133 (2.26%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Acute myocardial infarction			
subjects affected / exposed	2 / 134 (1.49%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	2 / 134 (1.49%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	2 / 134 (1.49%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleed			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 134 (1.49%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 134 (1.49%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	3 / 134 (2.24%)	2 / 133 (1.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 134 (2.24%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Product issues			
Lead dislodgement			
subjects affected / exposed	1 / 134 (0.75%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	bucindolol	Metoprolol succinate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 134 (50.00%)	69 / 133 (51.88%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 134 (9.70%)	10 / 133 (7.52%)	
occurrences (all)	13	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 134 (3.73%)	7 / 133 (5.26%)	
occurrences (all)	5	7	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 134 (3.73%)	4 / 133 (3.01%)	
occurrences (all)	5	4	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 134 (0.75%)	4 / 133 (3.01%)	
occurrences (all)	1	4	
Anxiety			
subjects affected / exposed	1 / 134 (0.75%)	3 / 133 (2.26%)	
occurrences (all)	1	3	
Confusion			
subjects affected / exposed	0 / 134 (0.00%)	2 / 133 (1.50%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	0 / 134 (0.00%)	3 / 133 (2.26%)	
occurrences (all)	0	3	
Investigations			
Creatinine increased			
subjects affected / exposed	3 / 134 (2.24%)	2 / 133 (1.50%)	
occurrences (all)	3	2	
Glomerular filtration rate			
subjects affected / exposed	3 / 134 (2.24%)	0 / 133 (0.00%)	
occurrences (all)	3	0	
Weight			
subjects affected / exposed	0 / 134 (0.00%)	2 / 133 (1.50%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Leg injury			
subjects affected / exposed	2 / 134 (1.49%)	4 / 133 (3.01%)	
occurrences (all)	2	4	
Fall			
subjects affected / exposed	2 / 134 (1.49%)	2 / 133 (1.50%)	
occurrences (all)	2	2	
Wound			

subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	6 / 134 (4.48%)	9 / 133 (6.77%)	
occurrences (all)	6	9	
Bradycardia			
subjects affected / exposed	5 / 134 (3.73%)	8 / 133 (6.02%)	
occurrences (all)	5	8	
Sinus bradycardia			
subjects affected / exposed	0 / 134 (0.00%)	7 / 133 (5.26%)	
occurrences (all)	0	7	
Cardiac failure			
subjects affected / exposed	6 / 134 (4.48%)	5 / 133 (3.76%)	
occurrences (all)	6	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 134 (2.99%)	5 / 133 (3.76%)	
occurrences (all)	4	5	
Headache			
subjects affected / exposed	6 / 134 (4.48%)	5 / 133 (3.76%)	
occurrences (all)	6	5	
Syncope			
subjects affected / exposed	3 / 134 (2.24%)	2 / 133 (1.50%)	
occurrences (all)	3	2	
Eye disorders			
Allergic conjunctivitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Blurry vision			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Double vision			

subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 134 (5.97%)	2 / 133 (1.50%)	
occurrences (all)	8	2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 134 (2.99%)	2 / 133 (1.50%)	
occurrences (all)	4	2	
Acute renal failure			
subjects affected / exposed	3 / 134 (2.24%)	2 / 133 (1.50%)	
occurrences (all)	3	2	
Urinary retention			
subjects affected / exposed	2 / 134 (1.49%)	1 / 133 (0.75%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 134 (5.22%)	3 / 133 (2.26%)	
occurrences (all)	7	3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 134 (5.22%)	6 / 133 (4.51%)	
occurrences (all)	7	6	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 134 (0.75%)	2 / 133 (1.50%)	
occurrences (all)	1	2	
Gout			
subjects affected / exposed	2 / 134 (1.49%)	4 / 133 (3.01%)	
occurrences (all)	2	4	
Hyperglycemia			

subjects affected / exposed occurrences (all)	0 / 134 (0.00%) 0	2 / 133 (1.50%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2014	Amendment 1 changes: -AF Burden substudy has been modified. -The requirement for a third rhythm assessment 7-9 days after the initial AF event for the classification of paroxysmal/persistent AF has been removed. -The AFSQ previously required at the time of the ECG/TTM assessment for the determination of paroxysmal/persistent AF was removed. -Clarification has been provided on the use of concomitant and prohibited medications allowed during the study. -Text has been added to clarify that a trough blood sample for the Population PK substudy only needs to be collected at Visit 3 for patients who spontaneously convert to SR. -Two additional genes have been included in the required genetic analysis to explore the potential for polymorphisms in these genes to alter the effectiveness of bucindolol. -The management of patient visits during the Drug Lead-In Period has been modified to emphasize that unscheduled visits should be used to manage study drug titration prior to ECV at Visit 3. -The estimate for the number of investigational sites participating in the Phase 3 portion of the trial has been updated. -The stratification criterion for randomization, “type of Medtronic device (Reveal/Non-Reveal/No Device)”, has been clarified. -The protocol has been updated to emphasize that vital status (i.e., alive/dead) will be assessed periodically during the study, including for patients who withdraw from the study who consent to periodic telephone contact. -inclusion/exclusion criteria updated. -endpoints have been modified. -up-titration schedule has been modified -optional substudies and schedule of assessments have been modified or clarified.

29 April 2015	Expansion of the participant population to include participants in SR at randomization with a recent episode of symptomatic AF Randomization stratum added to ensure balance between the 2 treatment arms for participants in SR at randomization and participants in AF at randomization Stable SR definition for primary endpoint adjusted to reflect new population Additional language added to the protocol to clarify when ECV should be performed Modified requirements for early ECV (i.e., earlier than 3 weeks after randomization) have to ensure that participants are receiving therapeutic doses of study drug prior to ECV Additional information provided regarding the timing of study drug dosing on the day of randomization and on the requirement for titration of study drug dose to protocol-specified targets Study drug transition algorithm updated to include guidance for immediate release metoprolol, controlled release carvedilol, and bisoprolol LVIDD requirement for participants with LVEF between 0.40 and 0.50 deleted Study entry criterion that defines the exclusion period for previous AF ablation modified Malignancy exclusion criteria clarified Several inclusion and exclusion criteria modified to be effective at the randomization visit instead of at the screening visit Modified timing of clinical visits during the 24-week follow-up period to occur every 4 weeks, altheranaing with at-home TTM Modified timing of required second ECG to at least 10 minutes after the first ECG recording if AF/AFL is observed on the first assessment from 1 hour Streamlined AF symptom questionnaire and device interrogation administration for greater consistency Collections schedule for several clinical laboratory tests modified to limit the number of separate phlebotomy procedures Participation in the population pharmacokinetic analysis made mandatory Sample size justification updated to reference the EURIDIS/ADONIS dronedarone AF studies

09 April 2016	Primary efficacy endpoint definition of stable SR changed to SR on rhythm assessments at least 1 hour apart at Week 0 or 1 hour after ECV. Supportive secondary efficacy endpoint analysis has been added for hospitalizations: the subset of HF-related hospitalization Updated statistical methodology for several tertiary/exploratory efficacy endpoints and AF burden definition in the device substudy Interim analyses: Phase 2B interim analysis details relocated to DSMB charter. new Phase 3 interim analysis added to assess the absence of futility and whether an expansion of the total sample size is warranted Updated description of study drug packaging Updated study drug titration schedule table to provide guidance for the transition from the β-blocker nebivolol to blinded study drug Concomitant administration of 2 anti-arrhythmic drugs (i.e., flecainide and propafenone) is no longer permitted due to the potential for CYP2D6-mediated drug interactions with study drug Sample size for Phase 2B changed from 200 to 250 participants Inclusion and exclusion criteria updated: upper age limit of 85 years added; minimum weight requirement changed from screening to randomization visit; qualifying LVEF assessment anytime during previous 12 months; window for qualifying AF episode enlarged from 120 to 180 days before screening; modifications to criteria of timing of ECV, clinical euvolemia, informed consent, β-blocker contraindications, lab value retesting; new exclusion criteria added for left ventricular assist devices, symptomatic bradycardia, and pulmonary hypertension. Concomitant medication criteria modified to only exclude frequent use of short acting nitroglycerine for the treatment of acute angina; prophylactic use of sustained release nitroglycerine for the prevention of angina is not exclusionary The maximum time period between the screening visit and the randomization visit has been increased from 4 to 8 weeks to allow additional time

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29754666

http://www.ncbi.nlm.nih.gov/pubmed/31042551