Clinical trial results:
Evaluation of effects of chronic dose exposure to cardioselective and non-cardioselective beta blockers on measures of cardiopulmonary function in moderate to severe COPD.

Summary

EudraCT number	2011-006008-11
Trial protocol	GB
Global end of trial date	21 July 2016

Results information

Result version number	v1 (current)
This version publication date	23 July 2017
First version publication date	23 July 2017

Trial information

Trial identification

Sponsor protocol code	2012RC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01656005
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor R&D Number: 2012RC01

Notes:

Sponsors

Sponsor organisation name	University of Dundee - NHS Tayside
Sponsor organisation address	Residency Block, Level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@dundee.ac.uk
Scientific contact	Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@dundee.ac.uk

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	21 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 July 2016
Global end of trial reached?	Yes
Global end of trial date	21 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects on measures of lung and heart function of two different beta blockers - one that acts mainly on the heart and the other that acts on both the heart and lungs - after chronic dosing.

Protection of trial subjects:

This study was registered at clinicaltrials.gov under NCT01656005, and had favourable opinion from the East of Scotland Research and Ethics Committee (12/ES/0054). Patients were referred from both primary and secondary care and attended the Scottish Centre for Respiratory Research, Ninewells Hospital & Medical School, Dundee, Scotland, for their visits. Written informed consent was obtained from all participants. Participants were given a PiKO monitor device to record domiciliary FEV1 and FEV6 twice daily in a diary supplied by the department, as well as domiciliary oxygen saturation and HR monitor to be recorded twice daily. They completed a daily diary of reliever use and symptoms and these diaries were reviewed at each study visit. The beta-blocker dose was gradually uptitrated, and the participant informed that should they experience side-effects related to beta-blocker therapy, they should phone the department (during working hours) or the emergency mobile number (out of hours). An action plan would then be formulated by a qualified doctor. Participants were allowed to complete each treatment arm on their maximum tolerated dose of beta-blocker, if this was less than the maximum prescribed dose.

Background therapy:

The beta-blockers were given in combination with sequential step down inhaled therapy: starting with triple inhaler therapy as inhaled corticosteroid /long acting beta-agonist/long acting muscarinic antagonist (ICS+LABA+LAMA), then dual inhaler therapy as ICS/LABA and finally single inhaler therapy as ICS alone – to allow us to dissect out the respective interactions between beta-blockers with LAMA (i. e. ICS/LABA/LAMA vs ICS/LABA) and LABA (i.e. ICS/LABA vs ICS).

The three medications used as inhaled therapy were:
- Fostair (beclomethasone dipropionate / formoterol) (ICS/LABA)
- Spiriva (tiotropium) (LAMA)
- Clenil Modulite (beclomethasone dipropionate) (ICS)

The lengths of treatment in each treatment arm were as follows:
Weeks 1 - 4: Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 5: Fostair 100/6, 2 puffs bid via a spacer device
Week 6: Clenil Modulite 200µg, 2 puffs bid via a spacer device

Evidence for comparator:

Management guidelines clearly reinforce the use of cardioselective beta-blockers in patient with heart failure and COPD.
Despite guidelines, beta-blockers remain underused in patients with COPD who have cardiovascular disease, presumably due to concerns regarding possible broncho-constriction, even with cardioselective drugs. It remains unclear if beta-blockers might also have beneficial effects in individuals with COPD who have no history of cardiovascular disease.
We elected to perform a study comparing two commonly used selective (bisoprolol) and non-selective (carvedilol) drugs, evaluating cardiopulmonary outcomes. We aimed for realistic target doses of bisoprolol 5mg qd and carvedilol 12·5mg bid, which we identified as being the most commonly tolerated doses in real life for our elderly population

Actual start date of recruitment	18 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	18
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 45 patients screened, 25 were randomised, and 18 completed per protocol.

Pre-assignment

Screening details:

Moderate to severe stable COPD, GOLD stages 2 & 3, FEV1 30-80% predicted, FEV1/FVC <0·70, >10 pack years, O2 sats ≥92% on room air, no long term domiciliary oxygen, in sinus rhythm, no heart block on ECG. No oral corticosteroids in the past 3 months. No history of uncontrolled hypertension or heart failure (NHYA class III-IV).

Pre-assignment period milestones

Number of subjects started	45
Number of subjects completed	25

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet inclusion criteria: 18
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Screen Failed in Error: 1

Period 1

Period 1 title	Randomised Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Bisoprolol

Arm description:

Bisoprolol for 6 weeks, starting at 1.25 mg qd and uptitrating to a maximum of 5mg qd as tolerated.

Uptitration was carried out as follows:
Week 1: Bisoprolol 1.25 mg qd
Week 2: Bisoprolol 2.5 mg qd
Weeks 3-6: Bisoprolol 5.0mg qd

Bisoprolol was given in conjunction with three levels of inhaled therapy:
(a) triple: inhaled corticosteroid /long acting beta-agonist/long acting muscarinic antagonist (ICS+LABA+LAMA),
(b) dual: ICS+LABA,
(c) ICS alone.

Measurements were made at baseline on no beta-blocker, and after each inhaled step while taking beta-blocker.

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

Arm type	Experimental

Investigational medicinal product name	Bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bisoprolol was given for 6 weeks, starting at 1.25 mg qd and uptitrating to a maximum of 5mg qd as tolerated.

Bisoprolol was given in conjunction with three levels of inhaled therapy as follows:
Week 1 : Bisoprolol 1.25 mg qd + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 2: Bisoprolol 2.5 mg qd + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 3: Bisoprolol 5.0 mg qd + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 4: Bisoprolol 5.0 mg qd + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 5: Bisoprolol 5.0 mg qd + Fostair 100/6, 2 puffs bid via a spacer device
Week 6: Bisoprolol 5.0 mg qd + Clenil Modulite 200µg, 2 puffs bid via a spacer device

Arm title	Carvedilol

Arm description:

Carvedilol for 6 weeks starting at 3.125 mg bid and uptitrating to a maximum of 12·5 mg bid as tolerated.

Uptitration was carried out as follows:
Week 1: Carvedilol 3.125 mg bid
Week 2: Carvedilol 6.25 mg bid
Weeks 3-6: Carvedilol 12.5 mg bid

Carvedilol was given in conjunction with three levels of inhaled therapy:
(a) triple: inhaled corticosteroid /long acting beta-agonist/long acting muscarinic antagonist (ICS+LABA+LAMA),
(b) dual: ICS+LABA,
(c) ICS alone.

Measurements were made at baseline on no beta-blocker, and after each inhaled step while taking beta-blocker.

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

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

Dosage and administration details:

Carvedilol was given for 6 weeks, starting at 3.125 mg bid and uptitrating to a maximum of 12.5mg bid as tolerated.

Carvedilol was given in conjunction with three levels of inhaled therapy as follows:
Week 1 : Carvedilol 3.125 mg bid + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 2: Carvedilol 6.25 mg bid + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 3: Carvedilol 12.5 mg bid + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 4: Carvedilol 12.5 mg bid + Fostair 100/6, 2 puffs bid via a spacer device + Spiriva 18µg od via Handihaler
Week 5: Carvedilol 12.5 mg bid + Fostair 100/6, 2 puffs bid via a spacer device
Week 6: Carvedilol 12.5 mg bid + Clenil Modulite 200µg, 2 puffs bid via a spacer device

Number of subjects in period 1	Bisoprolol	Carvedilol
Started	25	25
Completed	18	18
Not completed	7	7
Consent withdrawn by subject	1	1
Adverse event, non-fatal	6	6

Baseline characteristics

Reporting groups[1]

Reporting group title	Randomised Treatment (overall period)

Reporting group description: -

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number enrolled is the number of subjects screened into the study (45). The number of subjects in the baseline period is the number who were then randomised into the study (25).
Of these 25 subjects, 18 completed both arms of the cross-over trial and were able to be analysed.

Reporting group values	Randomised Treatment (overall period)	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	14	14	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	5	
Male	20	20	

Subject analysis sets

Subject analysis set title	Completed Subjects
Subject analysis set type	Per protocol

Subject analysis set description:

Moderate to severe stable COPD, GOLD stages 2 & 3, FEV1 30-80% predicted, FEV1/FVC <0·70, >10 pack years, O2 sats ≥92% on room air, no long term domiciliary oxygen, in sinus rhythm, no heart block on ECG. No oral corticosteroids in the past 3 months. No history of uncontrolled hypertension or heart failure (NHYA class III-IV).

Reporting group values	Completed Subjects		
Number of subjects	18		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	9		
From 65-84 years	9		
85 years and over	0		
Gender categorical Units: Subjects			
Female	3		
Male	15		

End points

End points reporting groups

Reporting group title	Bisoprolol

Reporting group description:

Bisoprolol for 6 weeks, starting at 1.25 mg qd and uptitrating to a maximum of 5mg qd as tolerated.

Uptitration was carried out as follows:
Week 1: Bisoprolol 1.25 mg qd
Week 2: Bisoprolol 2.5 mg qd
Weeks 3-6: Bisoprolol 5.0mg qd

Bisoprolol was given in conjunction with three levels of inhaled therapy:
(a) triple: inhaled corticosteroid /long acting beta-agonist/long acting muscarinic antagonist (ICS+LABA+LAMA),
(b) dual: ICS+LABA,
(c) ICS alone.

Measurements were made at baseline on no beta-blocker, and after each inhaled step while taking beta-blocker.

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

Reporting group title	Carvedilol

Reporting group description:

Carvedilol for 6 weeks starting at 3.125 mg bid and uptitrating to a maximum of 12·5 mg bid as tolerated.

Uptitration was carried out as follows:
Week 1: Carvedilol 3.125 mg bid
Week 2: Carvedilol 6.25 mg bid
Weeks 3-6: Carvedilol 12.5 mg bid

Carvedilol was given in conjunction with three levels of inhaled therapy:
(a) triple: inhaled corticosteroid /long acting beta-agonist/long acting muscarinic antagonist (ICS+LABA+LAMA),
(b) dual: ICS+LABA,
(c) ICS alone.

Measurements were made at baseline on no beta-blocker, and after each inhaled step while taking beta-blocker.

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

Subject analysis set title	Completed Subjects
Subject analysis set type	Per protocol

Subject analysis set description:

Moderate to severe stable COPD, GOLD stages 2 & 3, FEV1 30-80% predicted, FEV1/FVC <0·70, >10 pack years, O2 sats ≥92% on room air, no long term domiciliary oxygen, in sinus rhythm, no heart block on ECG. No oral corticosteroids in the past 3 months. No history of uncontrolled hypertension or heart failure (NHYA class III-IV).

Primary: Resistance at 5Hz (R5)

End point title	Resistance at 5Hz (R5)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Primary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: kPa/L.s				
arithmetic mean (confidence interval 95%)				
baseline	0.67 (0.52 to 0.82)	0.67 (0.52 to 0.82)		
ICS/LABA/LAMA	0.58 (0.47 to 0.69)	0.61 (0.51 to 0.71)		
ICS/LABA	0.62 (0.51 to 0.73)	0.69 (0.58 to 0.8)		
ICS	0.68 (0.59 to 0.77)	0.71 (0.6 to 0.81)		

Statistical analyses

Statistical analysis title	per protocol

Statistical analysis description:

The study was powered on IOS at >80% to detect a 0·2 kPa/L.s difference in R5 with an SD of 0·23 kPa/L.s requiring a sample size of 18 completed patients per protocol using a cross-over design and alpha error of 0·05 (two-tailed). The data were checked for normality of distribution prior to analysis. Baseline values after run-in and washout were compared; having demonstrated no significant differences for treatment or sequence, the pooled baseline values were used for the purpose of subsequent c

Comparison groups	Carvedilol v Bisoprolol
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA

Secondary: FEV1

End point title	FEV1

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
baseline	1.5 (1.2 to 1.79)	1.5 (1.2 to 1.79)		
ICS/LABA/LAMA	1.53 (1.21 to 1.84)	1.47 (1.16 to 1.78)		
ICS/LABA	1.49 (1.21 to 1.84)	1.37 (1.06 to 1.68)		
ICS	1.34 (1.03 to 1.65)	1.26 (0.94 to 1.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Vital Capacity (FVC)

End point title	Forced Vital Capacity (FVC)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
baseline	3.4 (2.83 to 3.97)	3.4 (2.83 to 3.97)		
ICS/LABA/LAMA	3.58 (2.98 to 4.19)	3.48 (2.9 to 4.07)		
ICS/LABA	3.57 (2.94 to 4.21)	3.32 (2.74 to 3.9)		
ICS	3.17 (2.56 to 3.77)	2.97 (2.38 to 3.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relaxed vital capacity (RVC)

End point title	Relaxed vital capacity (RVC)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
baseline	3.56 (2.98 to 4.14)	3.56 (2.98 to 4.14)		
ICS/LABA/LAMA	3.73 (3.14 to 4.33)	3.67 (3.06 to 4.28)		
ICS/LABA	3.75 (3.19 to 4.31)	3.54 (2.95 to 4.12)		
ICS	3.37 (2.81 to 3.93)	3.16 (2.57 to 3.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resistance at 20Hz (R20)

End point title	Resistance at 20Hz (R20)

End point description:

Baseline refers to the completion of a 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: kPa/L.s				
arithmetic mean (confidence interval 95%)				
pre IMP baseline	0.39 (0.34 to 0.45)	0.39 (0.34 to 0.45)		

ICS/LAMA/LAMA	0.38 (0.32 to 0.44)	0.39 (0.34 to 0.44)		
ICS/LABA	0.39 (0.34 to 0.44)	0.38 (0.33 to 0.44)		
ICS	0.37 (0.34 to 0.41)	0.39 (0.33 to 0.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: AX

End point title	AX

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: kPa/L				
arithmetic mean (confidence interval 95%)				
baseline	3.01 (2.05 to 3.99)	3.01 (2.05 to 3.99)		
ICS/LABA/LAMA	2.6 (1.14 to 3.79)	2.93 (1.92 to 3.94)		
ICS/LABA	2.86 (1.8 to 3.91)	3.86 (2.75 to 4.97)		
ICS	3.89 (2.8 to 4.98)	4.3 (3.34 to 5.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: X5

End point title	X5

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: kPa/L.s				
arithmetic mean (confidence interval 95%)				
baseline	-0.29 (-0.37 to -0.21)	-0.29 (-0.37 to -0.21)		
ICS/LABA/LAMA	-0.25 (-0.34 to 0.17)	-0.28 (-0.37 to 0.2)		
ICS/LABA	-0.28 (-0.35 to 0.21)	-0.36 (-0.44 to 0.27)		
ICS	-0.35 (-0.47 to -0.23)	-0.38 (-0.46 to 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resting oxygen saturation (Sp02)

End point title	Resting oxygen saturation (Sp02)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (confidence interval 95%)				
baseline	96 (96 to 97)	96 (95 to 97)		
ICS/LABA/LAMA	96 (95 to 97)	96 (95 to 97)		
ICS/LABA	96 (93 to 96)	94 (91 to 96)		
ICS	96 (95 to 97)	96 (95 to 97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise oxygen saturation (Sp02)

End point title	Exercise oxygen saturation (Sp02)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (confidence interval 95%)				
baseline	94 (91 to 96)	94 (91 to 96)		
ICS/LABA/LAMA	93 (90 to 96)	93 (90 to 95)		
ICS/LABA	93 (90 to 95)	94 (91 to 96)		
ICS	93 (90 to 95)	93 (90 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resting heart rate (HR)

End point title	Resting heart rate (HR)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: bpm				
arithmetic mean (confidence interval 95%)				
baseline	75 (69 to 82)	75 (69 to 82)		
ICS/LABA/LAMA	62 (58 to 66)	63 (59 to 67)		
ICS/LABA	60 (56 to 64)	64 (60 to 68)		

ICS	60 (55 to 65)	63 (61 to 66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise heart rate (HR)

End point title	Exercise heart rate (HR)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: bpm				
arithmetic mean (confidence interval 95%)				
baseline	91 (83 to 98)	91 (83 to 98)		
ICS/LABA/LAMA	69 (64 to 75)	71 (67 to 74)		
ICS/LABA	67 (62 to 72)	67 (57 to 77)		
ICS	67 (62 to 73)	70 (67 to 74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resting systolic blood pressure

End point title	Resting systolic blood pressure

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
baseline	135 (129 to 142)	135 (129 to 142)		
ICS/LABA/LAMA	129 (120 to 138)	127 (119 to 135)		
ICS/LABA	127 (118 to 136)	128 (121 to 138)		
ICS	127 (119 to 134)	132 (122 to 142)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise systolic blood pressure

End point title	Exercise systolic blood pressure

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
baseline	151 (137 to 166)	151 (137 to 166)		
ICS/LABA/LAMA	151 (135 to 167)	152 (137 to 166)		
ICS/LABA	149 (132 to 164)	145 (133 to 157)		
ICS	145 (133 to 157)	151 (138 to 163)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resting diastolic blood pressure

End point title	Resting diastolic blood pressure

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
baseline	80 (76 to 84)	80 (76 to 84)		
ICS/LABA/LAMA	77 (71 to 83)	75 (70 to 79)		
ICS/LABA	72 (67 to 77)	76 (70 to 81)		
ICS	73 (68 to 78)	78 (72 to 83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exercise diastolic blood pressure

End point title	Exercise diastolic blood pressure

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: mmHg				
arithmetic mean (confidence interval 95%)				
baseline	86 (82 to 91)	86 (82 to 91)		
ICS/LABA/LAMA	83 (76 to 89)	86 (81 to 91)		
ICS/LABA	81 (75 to 87)	81 (75 to 87)		
ICS	83 (77 to 89)	87 (82 to 91)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6 minute walk distance

End point title	6 minute walk distance

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: meter				
arithmetic mean (confidence interval 95%)				
baseline	495 (449 to 542)	495 (449 to 542)		
ICS/LABA/LAMA	470 (420 to 520)	489 (449 to 542)		
ICS/LABA	486 (435 to 536)	484 (422 to 567)		
ICS	469 (422 to 515)	474 (416 to 532)		

Statistical analyses

No statistical analyses for this end point

Secondary: St George's Respiratory Questionnaire (SGRQ)

End point title	St George's Respiratory Questionnaire (SGRQ)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: units				
arithmetic mean (confidence interval 95%)				
baseline	33 (24 to 42)	33 (24 to 42)		
ICS/LABA/LAMA	34 (24 to 44)	36 (27 to 45)		
ICS/LABA	33 (24 to 42)	34 (25 to 43)		
ICS	36 (28 to 44)	36 (26 to 45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Dyspnoea Index (BDI) & Transition Dyspnoea Index (TDI)

End point title	Baseline Dyspnoea Index (BDI) & Transition Dyspnoea Index (TDI)

End point description:

Baseline is after 2 week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA). LAMA= long acting muscarinic receptor antagonist.

End point type	Secondary

End point timeframe:

2 weeks

End point values	Bisoprolol	Carvedilol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: units				
arithmetic mean (confidence interval 95%)				
baseline	6.7 (5.5 to 7.8)	6.7 (5.5 to 7.8)		
ICS/LABA/LAMA	0.83 (-0.24 to 1.69)	0.22 (-0.82 to 1.27)		
ICS/LAMA	-0.33 (-1.31 to 0.65)	0.22 (-0.69 to 1.13)		
ICS	-1.1 (-2.01 to 0.21)	-0.83 (-1.92 to 0.25)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs were recorded from the time a participant consented to join the study until their last study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Completed Subjects

Reporting group description: -

Serious adverse events	Completed Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Completed Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)		
Vascular disorders			
Poor circulation in fingers			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Surgical and medical procedures			
Dental Procedures (Crown)			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	4		
Headache			

subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 8		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 3 / 18 (16.67%) 3		
Gastrointestinal disorders Upset stomach subjects affected / exposed occurrences (all)	 2 / 18 (11.11%) 2		
Respiratory, thoracic and mediastinal disorders Hoarse voice subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all) Phlegm subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1 5 / 18 (27.78%) 8 3 / 18 (16.67%) 3 1 / 18 (5.56%) 4 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1		
Psychiatric disorders Panic attack			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Painful Lower Limb (foot/leg)			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Chest pain (muscular)			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Strained Back Muscle			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Joint Pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	5		
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	7 / 18 (38.89%)		
occurrences (all)	8		
Chest infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2015	REC Amendment - Amendment to notify REC of the use of a patient register as a source for recruiting participants.
10 December 2015	REC Amendment - Amendment to seek prospective approval of patient-facing documents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported