Clinical trial results:
Proof of concept study to assess the differential effects of chronic beta-blockade (celiprolol versus bisoprolol) on cardiopulmonary outcomes at rest and during exercise in chronic obstructive pulmonary disease.

Summary

EudraCT number	2015-000207-13
Trial protocol	GB
Global end of trial date	30 April 2019

Results information

Result version number	v1 (current)
This version publication date	25 June 2021
First version publication date	25 June 2021

Trial information

Trial identification

Sponsor protocol code	2012RC22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02380053
WHO universal trial number (UTN)	-

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	General Enquiries, Scottish Centre for Respiratory Research, +44 1382 383902, scrr@dundee.ac.uk
Scientific contact	General Enquiries, Scottish Centre for Respiratory Research, +44 1382 383902, scrr@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	30 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2019
Global end of trial reached?	Yes
Global end of trial date	30 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the relative effects on heart and lung (airway) responses at rest and during exercise following beta-blocker treatment with bisoprolol versus celiprolol in COPD patients.

Protection of trial subjects:

The Sponsor carried out a study risk assessment before issuing approval. The study was approved by the East of Scotland Research Ethics Service (EoSRES) (Ref: 15/ES/0102) and full informed consent was obtained from all participants. Participants were checked against all inclusion and exclusion criteria and were only included if their COPD was stable; those with a low blood pressure or heart rate were not included. A medically-qualified person confirmed the participant's suitability to receive the study drug according to the study protocol. Participants were given a paper diary card, PiKO device and pulse oximeter for daily a-home monitoring of their lung function, heart rate and oxygen saturation.
The beta-blockers (IMP) were given by slowly escalating the dose during each treatment period. Initial beta-blocker dosing started at a low dose and was titrated up halfway through each treatment period. Participants were contacted when they were due to increase their beta-blocker dose and the following items assessed: symptoms attributable to beta-blocker therapy, FEV1, and heart rate. If these were satisfactory, participants progressed to the higher beta-blocker dose for the remainder of the treatment period. Participants were contacted again within 1 week of increasing their dose to repeat the checks. Participants intolerant of higher beta-blockers doses returned to their previous maximum tolerated dose for the remainder of the treatment period. Participants unable to tolerate the minimum beta-blocker dose were withdrawn.
Participants were given an instruction leaflet with information on how to measure their lung function, heart rate and oxygen saturation, how to complete their diary cards, potential side effects of study drugs, and how to record adverse events and concomitant medications. Participants were given an out-of-hours mobile number carried by medical staff for advice if they encountered any adverse effects.

Background therapy:

Subjects remained on their usual COPD medications. The IMP was given in addition to their standard treatments.

Evidence for comparator:

Beta-blockers are underused in COPD despite evidence for reducing mortality from cardiovascular comorbidities. Beta-blockers are pharmacologically heterogeneous and the study was designed to assess the clinical consequences of different beta-blockers in COPD.

Bisoprolol (BIS) is a beta-1 selective antagonist that may cause bronchoconstriction due to dose related beta-2 blockade.

Celiprolol (CEL) is a beta-1 selective antagonist which also exhibits partial beta-2 agonist activity.

The study assessed the relative effects of both BIS and CEL in COPD patients to establish whether the proposed benefits on survival with beta-blockers in COPD are reflected in improved cardiovascular and respiratory response to exercise and exercise tolerance.

Actual start date of recruitment	07 June 2016
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	5
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject recruitment began 7 June 2016 and the study completed on 30 April 2019. Of the 20 patients screened, 14 were randomised and 11 completed per protocol and were included in the final analysis.

Pre-assignment

Screening details:

Males and females, 40-80 years, stable COPD (GOLD stage 2/3), post-SABA FEV1 30-80% predicted and FEV1/FVC ratio <70%, no exacerbation in the last month, no hospitalisation for exacerbation in the last 3 months, ≥ 10 pack-years; O2 sats ≥ 92% on room air, sinus rhythm on ECG, average resting systolic BP ≥ 110 mmHg, average resting HR ≥ 55 bpm.

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	14[1]

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Elective Intervention Scheduled: 1
Reason: Number of subjects	Did Not meet Inclusion Criteria: 4

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: 14 subjects completed run-in and attended a baseline visit.
This is a cross-over study where subjects participate in both arms during the course of the study.
Bisoprolol arm - 11 patients received at least 1 dose and are counted as participants in this arm.
Celiprolol arm - 13 subjects received at least 1 dose and are counted as participants in this arm.
11 subjects completed both arms of this cross-over trial and were able to be analysed.

Period 1

Period 1 title	Overall Trial (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 (BIS)

Arm description: -

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 2.5 mg OD for 2 weeks, followed by 5 mg OD for 2 weeks.

Arm title	Celiprolol (CEL)

Arm description: -

Arm type	Experimental

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

Dosage and administration details:

Celiprolol 200 mg OD for 2 weeks, followed by 400 mg OD for 2 weeks.

Number of subjects in period 1	Bisoprolol (BIS)	Celiprolol (CEL)
Started	11	13
Completed	11	11
Not completed	0	2
IMP Not Tolerated	-	2

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall Trial
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 (20). The number of subjects in the baseline period is the number who were randomised into the study (14). Of these 14 subjects, 11 completed both arms of the cross-over trial and were able to be analysed.

Reporting group values	Overall Trial	Total	
Number of subjects	14	14	
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)	5	5	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	69.64		
standard deviation	± 7.14	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	9	9	

End points

End points reporting groups

Reporting group title	Bisoprolol (BIS)
Reporting group description: -	
Reporting group title	Celiprolol (CEL)
Reporting group description: -	
Subject analysis set title	Completed Subjects
Subject analysis set type	Per protocol
Subject analysis set description:	
11 subjects who completed both arms of the study per protocol	

Primary: Inspiratory Capacity

End point title	Inspiratory Capacity
End point description:	
End point type	Primary
End point timeframe:	
Inspiratory Capacity was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks.	

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres				
arithmetic mean (confidence interval 95%)	2.05 (1.72 to 2.38)	1.77 (1.42 to 2.12)		

Statistical analyses

Statistical analysis title	Inspiratory Capacity
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	ANOVA

Primary: DH, dynamic hyperinflation; at exercise isotime 4min

End point title	DH, dynamic hyperinflation; at exercise isotime 4min
End point description:	
End point type	Primary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres				
arithmetic mean (confidence interval 95%)	-0.42 (-0.61 to -0.23)	-0.67 (-1.12 to -0.23)		

Statistical analyses

Statistical analysis title	Dynamic Hyperinflation
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	ANOVA

Secondary: Borg Score (Breathing)

End point title	Borg Score (Breathing)

End point description:

End point type	Secondary

End point timeframe:

Borg Score (Breathing) was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: units				
geometric mean (confidence interval 95%)	6.3 (4.8 to 8.1)	6.6 (5.2 to 8.2)		

Statistical analyses

Statistical analysis title	Borg Breathlessness
Statistical analysis description: Peak Borg score breathlessness*	
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	ANOVA

Secondary: Heart Rate recovery over 3 min n=10	
End point title	Heart Rate recovery over 3 min n=10
End point description:	
End point type	Secondary
End point timeframe: Heart Rate was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks.	

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: beats/min				
arithmetic mean (confidence interval 95%)	6.7 (5.3 to 8.0)	4.6 (3.5 to 5.7)		

Statistical analyses

Statistical analysis title	Heart rate recovery
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	ANOVA

Secondary: Cardiac Output Peak heart rate	
End point title	Cardiac Output Peak heart rate
End point description:	
End point type	Secondary

End point timeframe:

Cardiac Output was measured at baseline (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: L/min				
arithmetic mean (confidence interval 95%)	102 (96 to 109)	104 (99 to 108)		

Statistical analyses

Statistical analysis title	Heart rate
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Secondary: Peak VO2, oxygen uptake

End point title	Peak VO2, oxygen uptake

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: litres				
arithmetic mean (confidence interval 95%)	1.21 (1.00 to 1.42)	1.24 (1.02 to 1.45)		

Statistical analyses

Statistical analysis title	Oxygen uptake
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	ANOVA

Secondary: Peak VE, minute ventilation

End point title	Peak VE, minute ventilation

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres/minute				
arithmetic mean (confidence interval 95%)	48.2 (41.0 to 55.4)	48.3 (41.0 to 55.6)		

Statistical analyses

Statistical analysis title	Minute ventilation
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	ANOVA

Secondary: Peak RR, respiratory rate

End point title	Peak RR, respiratory rate

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Breaths/min				
arithmetic mean (confidence interval 95%)	34 (30 to 38)	31 (28 to 34)		

Statistical analyses

Statistical analysis title	Respiratory rate
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	ANOVA

Secondary: Peak O2 Sats*, oxygen saturations

End point title	Peak O2 Sats*, oxygen saturations

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percent				
median (inter-quartile range (Q1-Q3))	97 (90 to 98)	97 (91 to 99)		

Statistical analyses

Statistical analysis title	Oxygen saturations
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	ANOVA

Secondary: BR, breathing reserve at peak exercise

End point title	BR, breathing reserve at peak exercise

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percent				
arithmetic mean (confidence interval 95%)	1.1 (-7.8 to 10.0)	-3.5 (-14.3 to 7.2)		

Statistical analyses

Statistical analysis title	Breathing reserve
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	ANOVA

Secondary: Total exercise time (min)

End point title	Total exercise time (min)

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Minutes				
arithmetic mean (confidence interval 95%)	6.5 (4.5 to 8.5)	7.2 (5.4 to 8.9)		

Statistical analyses

Statistical analysis title	Total exercise time
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	ANOVA

Secondary: Peak Borg score leg discomfort*

End point title	Peak Borg score leg discomfort*

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units				
geometric mean (confidence interval 95%)	17 (15.8 to 18.3)	17.4 (16.1 to 18.8)		

Statistical analyses

Statistical analysis title	Borg Leg Discomfort
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANOVA

Secondary: FEV1 , forced expiratory volume in 1 second

End point title	FEV1 , forced expiratory volume in 1 second

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percentage of predicted				
arithmetic mean (confidence interval 95%)	52 (45 to 59)	52 (45 to 59)		

Statistical analyses

Statistical analysis title	FEV1
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	ANOVA

Secondary: FVC, forced vital capacity

End point title	FVC, forced vital capacity

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percentage of predicted				
arithmetic mean (confidence interval 95%)	102 (87 to 117)	100 (88 to 112)		

Statistical analyses

Statistical analysis title	FVC
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	ANOVA

Secondary: Relaxed vital capacity

End point title	Relaxed vital capacity

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percentage of predicted				
arithmetic mean (confidence interval 95%)	108 (93 to 124)	109 (96 to 121)		

Statistical analyses

Statistical analysis title	Relaxed VC
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	ANOVA

Secondary: Residual Volume/Total Lung Capacity ratio

End point title	Residual Volume/Total Lung Capacity ratio

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percent				
arithmetic mean (confidence interval 95%)	47.7 (43.3 to 52.0)	49.6 (44.8 to 54.3)		

Statistical analyses

Statistical analysis title	RV/TLC ratio
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	ANOVA

Secondary: R5*, resistance at 5 Hertz

End point title	R5*, resistance at 5 Hertz

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percent				
geometric mean (confidence interval 95%)	144 (124 to 167)	163 (149 to 179)		

Statistical analyses

Statistical analysis title	R5
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	ANOVA

Secondary: Ax*, reactance at 5 Hertz

End point title	Ax*, reactance at 5 Hertz

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Kilopascals/Litre				
geometric mean (confidence interval 95%)	1.98 (1.24 to 2.73)	2.44 (1.74 to 3.13)		

Statistical analyses

Statistical analysis title	Ax
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANOVA

Secondary: Oxygen pulse

End point title	Oxygen pulse

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: millilitres per beat				
arithmetic mean (confidence interval 95%)	11.7 (9.8 to 13.5)	11.6 (10.0 to 13.3)		

Statistical analyses

Statistical analysis title	Oxygen pulse
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Secondary: Peak mean arterial blood pressure

End point title	Peak mean arterial blood pressure

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: millimetres of mercury				
arithmetic mean (confidence interval 95%)	106 (91 to 120)	106 (93 to 120)		

Statistical analyses

Statistical analysis title	Mean arterial blood pressure
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	ANOVA

Secondary: Cardiac Outcomes Non-Invasive Cardiac Output Monitor -peak cardiac output

End point title	Cardiac Outcomes Non-Invasive Cardiac Output Monitor -peak cardiac output

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres/minute				
arithmetic mean (confidence interval 95%)	11.2 (9.7 to 12.8)	10.4 (9.4 to 11.4)		

Statistical analyses

Statistical analysis title	Cardiac output
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	ANOVA

Secondary: Cardiac Outcomes Non-Invasive Cardiac Output Monitor - Peak Stroke Volume, n=10

End point title	Cardiac Outcomes Non-Invasive Cardiac Output Monitor - Peak Stroke Volume, n=10

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: millilitres/beat				
arithmetic mean (confidence interval 95%)	122 (102 to 142)	105 (96 to 113)		

Statistical analyses

Statistical analysis title	Stroke volume
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANOVA

Secondary: Domiciliary Outcomes - Oxygen saturations (AM)

End point title	Domiciliary Outcomes - Oxygen saturations (AM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percent				
arithmetic mean (confidence interval 95%)	95 (94 to 96)	95 (94 to 96)		

Statistical analyses

Statistical analysis title	Oxygen saturations
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	ANOVA

Secondary: Domiciliary Outcomes -oxygen saturations (PM)

End point title	Domiciliary Outcomes -oxygen saturations (PM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Percent				
arithmetic mean (confidence interval 95%)	94 (93 to 96)	95 (94 to 96)		

Statistical analyses

Statistical analysis title	Oxygen saturations
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	ANOVA

Secondary: Domiciliary Outcomes - Heart rate (AM)

End point title	Domiciliary Outcomes - Heart rate (AM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Beats per minute				
arithmetic mean (confidence interval 95%)	67 (62 to 72)	73 (68 to 77)		

Statistical analyses

Statistical analysis title	Heart rate
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Secondary: Domiciliary Outcomes - Heart rate (PM)

End point title	Domiciliary Outcomes - Heart rate (PM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Beats per minute				
arithmetic mean (confidence interval 95%)	67 (63 to 70)	74 (70 to 79)		

Statistical analyses

Statistical analysis title	Heart rate
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (AM)

End point title	Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (AM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres				
arithmetic mean (confidence interval 95%)	1.24 (0.99 to 1.49)	1.22 (0.95 to 1.49)		

Statistical analyses

Statistical analysis title	FEV1
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	ANOVA

Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (PM)

End point title	Domiciliary Outcomes - FEV1 , forced expiratory volume in 1 second (PM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres				
arithmetic mean (confidence interval 95%)	1.21 (0.96 to 1.46)	1.22 (0.92 to 1.52)		

Statistical analyses

Statistical analysis title	FEV1
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANOVA

Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (AM)

End point title	Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (AM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres				
arithmetic mean (confidence interval 95%)	2.41 (2.01 to 2.81)	2.41 (1.96 to 2.86)		

Statistical analyses

Statistical analysis title	FEV6
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	ANOVA

Secondary: Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (PM)

End point title	Domiciliary Outcomes - FEV1 , forced expiratory volume in 6 second (PM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Mean of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Litres				
arithmetic mean (confidence interval 95%)	2.35 (1.89 to 2.80)	2.38 (1.91 to 2.85)		

Statistical analyses

Statistical analysis title	FEV6
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANOVA

Secondary: Domiciliary Outcomes - Symptoms (AM)**	
End point title	Domiciliary Outcomes - Symptoms** (AM)
End point description:	
End point type	Secondary
End point timeframe:	
Continuous diurnal measurement throughout the study. Median of last 3 days of each period.	

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units (0-3)				
median (inter-quartile range (Q1-Q3))	0 (0 to 1)	0 (0 to 1)		

Statistical analyses

Statistical analysis title	Daily symptoms
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Friedman’s two-way analysis of variance

Secondary: Domiciliary Outcomes - Symptoms (PM)**	
End point title	Domiciliary Outcomes - Symptoms** (PM)
End point description:	
End point type	Secondary
End point timeframe:	
Continuous diurnal measurement throughout the study. Median of last 3 days of each period.	

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units (0-3)				
median (inter-quartile range (Q1-Q3))	1 (0 to 1)	1 (0 to 1)		

Statistical analyses

Statistical analysis title	Daily symptoms
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	Friedman’s two-way analysis of variance

Secondary: Domiciliary Outcomes - Reliever use (AM)**

End point title	Domiciliary Outcomes - Reliever use** (AM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Median of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Number of puffs	0	0		

Statistical analyses

Statistical analysis title	Daily reliever use
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Friedman’s two-way analysis of variance

Secondary: Domiciliary Outcomes - Reliever use** (PM)

End point title	Domiciliary Outcomes - Reliever use** (PM)

End point description:

End point type	Secondary

End point timeframe:

Continuous diurnal measurement throughout the study. Median of last 3 days of each period.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Number of puffs	0	0		

Statistical analyses

Statistical analysis title	Daily reliever use
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	Friedman’s two-way analysis of variance

Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) GRQ Symptoms

End point title	Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) GRQ Symptoms

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units				
arithmetic mean (confidence interval 95%)	45 (24 to 47)	45 (30 to 60)		

Statistical analyses

Statistical analysis title	SGRQ Symptoms
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	ANOVA

Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) SGRQ Activity

End point title	Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ) SGRQ Activity

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units				
arithmetic mean (confidence interval 95%)	60 (47 to 72)	60 (47 to 73)		

Statistical analyses

Statistical analysis title	SGRQ Activity
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	ANOVA

Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Impacts

End point title	Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Impacts

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units				
arithmetic mean (confidence interval 95%)	25 (17 to 33)	25 (16 to 33)		

Statistical analyses

Statistical analysis title	SGRQ Impacts
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	ANOVA

Secondary: Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Total score

End point title	Quality of Life Outcome - St Georges Respiratory Questionnaire (SGRQ)SGRQ Total score

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units				
arithmetic mean (confidence interval 95%)	39 (30 to 49)	37 (29 to 45)		

Statistical analyses

Statistical analysis title	SGRQ Total score
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	ANOVA

Secondary: Biomarker (Venous Blood) Outcomes NT-pro-BNP*, N-terminal pro-B-type natriuretic peptide

End point title	Biomarker (Venous Blood) Outcomes NT-pro-BNP*, N-terminal pro-B-type natriuretic peptide

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: picomoles/Litre				
arithmetic mean (confidence interval 95%)	6.3 (3.2 to 11.6)	3.97 (1.55 to 8.69)		

Statistical analyses

Statistical analysis title	NT-pro-BNP
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANOVA

Secondary: Biomarker (Venous Blood) Outcomes Galectin-3

End point title	Biomarker (Venous Blood) Outcomes Galectin-3

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: nanograms/Litre				
arithmetic mean (confidence interval 95%)	8.0 (6.3 to 9.7)	8.5 (7.0 to 10.0)		

Statistical analyses

Statistical analysis title	Galectin-3
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	ANOVA

Secondary: Beta-2 Adrenceptor activity Creatinine kinase, n=10

End point title	Beta-2 Adrenceptor activity Creatinine kinase, n=10

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units/Litre				
arithmetic mean (confidence interval 95%)	112 (78 to 147)	131 (91 to 171)		

Statistical analyses

Statistical analysis title	Creatinine kinase
Comparison groups	Celiprolol (CEL) v Bisoprolol (BIS)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	ANOVA

Secondary: Beta-2 Adrenceptor activity - Total Cholesterol

End point title	Beta-2 Adrenceptor activity - Total Cholesterol

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: millimoles/litre				
arithmetic mean (confidence interval 95%)	4.8 (4.2 to 5.4)	4.7 (4.2 to 5.2)		

Statistical analyses

Statistical analysis title	Total Cholesterol
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	ANOVA

Secondary: Beta-2 Adrenceptor activity - Cholestrol/High Density Lipoprotein ratio

End point title	Beta-2 Adrenceptor activity - Cholestrol/High Density Lipoprotein ratio

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: no units				
arithmetic mean (confidence interval 95%)	3.2 (2.8 to 3.6)	3.0 (2.6 to 3.3)		

Statistical analyses

Statistical analysis title	Chol/HDL ratio
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANOVA

Secondary: Beta-2 Adrenceptor activity - Potassium

End point title	Beta-2 Adrenceptor activity - Potassium

End point description:

End point type	Secondary

End point timeframe:

Measured at baselines (pre-beta blocker) and post-beta blocker at 4 weeks.

End point values	Bisoprolol (BIS)	Celiprolol (CEL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: millimoles/litre				
arithmetic mean (confidence interval 95%)	4.5 (4.3 to 4.6)	4.4 (4.2 to 4.6)		

Statistical analyses

Statistical analysis title	Potassium
Comparison groups	Bisoprolol (BIS) v Celiprolol (CEL)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were recorded from the time a participant consented to join the study until the last study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Received IMP

Reporting group description: -

Serious adverse events	Received IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (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	Received IMP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all)	5 / 13 (38.46%) 7 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Gait disturbance subjects affected / exposed occurrences (all)	 4 / 13 (30.77%) 4 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Gastrointestinal disorders Gastroenteritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Irritable bowel syndrome subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Sputum increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Catarrh			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Productive cough			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Swelling in Left Hallux subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported