



Clinical trial results:

A randomised, double-blind placebo controlled trial of the effectiveness of the beta-blocker bisoprolol in preventing exacerbations of chronic obstructive pulmonary disease.

Summary

EudraCT number	2017-002779-24
Trial protocol	GB
Global end of trial date	31 May 2023

Results information

Result version number	v1 (current)
This version publication date	17 August 2025
First version publication date	17 August 2025

Trial information

Trial identification

Sponsor protocol code	3.089.17
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Additional study identifiers

ISRCTN number	ISRCTN10497306
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Aberdeen
Sponsor organisation address	Research Governance, Health Sciences Building, Foresterhill, Aberdeen, United Kingdom, AB25 2ZD
Public contact	Research Governance, University of Aberdeen, +44 1224437221, researchgovernance@abdn.ac.uk
Scientific contact	Research Governance, University of Aberdeen, +44 1224437221, researchgovernance@abdn.ac.uk
Sponsor organisation name	NHS Grampian
Sponsor organisation address	Foresterhill House Annex, Foresterhill, Aberdeen, United Kingdom, AB25 2ZD
Public contact	Research Governance, NHS Grampian, researchgovernance@abdn.ac.uk
Scientific contact	Research Governance, NHS Grampian, researchgovernance@abdn.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	01 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2023
Global end of trial reached?	Yes
Global end of trial date	31 May 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine whether adding bisoprolol (maximum dose 5mg a day) to existing COPD treatment in patients who have chronic obstructive pulmonary disease will reduce the number of exacerbations (or flare ups) of the condition. If the treatment is effective, we will also assess whether it is cost effective

Protection of trial subjects:

Bisoprolol is licensed for the treatment of angina, hypertension and heart failure. In BICS used 'off label'. As per heart failure guidelines initiating dose is low and with gradual dose titration.

Main concern is that bisoprolol induced bronchospasm (worsening of lung function) - risk minimised by excluding persons with a sole diagnosis of asthma or a diagnosis of asthma before the age of 40, titrating dose of bisoprolol slowly, with maximum study dose (5mg od) less than that recommended for heart failure. Previous systematic reviews demonstrate that cardiac specific beta blockers such as bisoprolol have no significant effect on lung function, symptoms or response to beta2 agonists when administered to people with COPD.

The Chief Investigator, Clinical Trial pharmacist and Sponsor oversight committee have undertaken a review of the licensed vaccines and have confirmed that they would not expect any interaction between the COVID vaccines and the study IMP.

Adverse reactions captured, in addition to SAEs and SARs. An independent DMC reviewed accumulating unblinded safety data.

Background therapy:

Participants remained on all existing background COPD therapy

Evidence for comparator:

Clinical equipoise allowed for placebo comparator

Actual start date of recruitment	17 October 2018
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	United Kingdom: 515
Worldwide total number of subjects	515
EEA total number of subjects	0

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)	163
From 65 to 84 years	344
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Eligible participants were identified and recruited from primary and secondary care settings across the UK. All participants provided fully informed consent.

Pre-assignment

Screening details:

Participants were screened against inclusion/exclusion criteria and eligibility was confirmed by a medically qualified doctor.

Period 1

Period 1 title	Overall trial (entire period) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Bisoprolol and placebo were manufactured and packaged to be identical. Randomisation was via a computerised web-based randomisation service created and administered by the Centre for Healthcare Randomised Trials. At randomisation, participants were allocated a drug pack (and it was not possible to identify trial arm from the pack number). An emergency unblinding facility was available.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bisoprolol

Arm description:

Bisoprolol was prepared as 1.25mg tablets and packaged in bottles of 168 tablets. Participants started on one tablet per day and were titrated over a period of approximately 4-7 weeks to a maximum of four tablets per day (equivalent to 5mg bisoprolol) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.

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 prepared as 1.25mg tablets and packaged in bottles of 168 tablets. Dose titrated over approximately 4-7 weeks to 1.25mg (1 tablet once daily), 2.5mg (2 tablets once daily), 3.75mg (3 tablets once daily) or 5mg (4 tablets once daily) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.

Arm title	Placebo
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Arm description:

Placebo tablets were manufactured to be identical in appearance to 1.25mg bisoprolol tablets. Participants started on one placebo tablet per day and were titrated over a period of approximately 4-7 weeks to a maximum of four tablets per day (equivalent to 5mg bisoprolol) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.

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

Dosage and administration details:

Placebo manufactured to look identical to 1.25mg bisoprolol.

Number of subjects in period 1	Bisoprolol	Placebo
Started	259	256
Completed	259	255
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Bisoprolol
Reporting group description:	
Bisoprolol was prepared as 1.25mg tablets and packaged in bottles of 168 tablets. Participants started on one tablet per day and were titrated over a period of approximately 4-7 weeks to a maximum of four tablets per day (equivalent to 5mg bisoprolol) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets were manufactured to be identical in appearance to 1.25mg bisoprolol tablets. Participants started on one placebo tablet per day and were titrated over a period of approximately 4-7 weeks to a maximum of four tablets per day (equivalent to 5mg bisoprolol) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.	

Reporting group values	Bisoprolol	Placebo	Total
Number of subjects	259	256	515
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)	78	85	163
From 65-84 years	177	167	344
85 years and over	4	4	8
Age continuous			
Age at recruitment			
Units: years			
arithmetic mean	67.7	67.7	
standard deviation	± 8.0	± 7.7	-
Gender categorical			
Units: Subjects			
Female	125	116	241
Male	134	140	274

End points

End points reporting groups

Reporting group title	Bisoprolol
Reporting group description:	
Bisoprolol was prepared as 1.25mg tablets and packaged in bottles of 168 tablets. Participants started on one tablet per day and were titrated over a period of approximately 4-7 weeks to a maximum of four tablets per day (equivalent to 5mg bisoprolol) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets were manufactured to be identical in appearance to 1.25mg bisoprolol tablets. Participants started on one placebo tablet per day and were titrated over a period of approximately 4-7 weeks to a maximum of four tablets per day (equivalent to 5mg bisoprolol) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes.	

Primary: COPD exacerbations

End point title	COPD exacerbations
End point description:	
Participant reported COPD exacerbations treated with antibiotics and/or oral steroids, supplemented with data from medical records.	
End point type	Primary
End point timeframe:	
12 months	

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	255		
Units: number				
arithmetic mean (standard deviation)	2.03 ($\pm$ 1.91)	2.01 ($\pm$ 1.75)		

Statistical analyses

Statistical analysis title	Intention to treat - primary outcome
Statistical analysis description:	
Intention to treat analysis of primary outcome (adjusted incidence rate ratio)	
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Mixed models analysis
Parameter estimate	incidence rate ratio
Point estimate	0.973

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.13

Secondary: time to first exacerbation

End point title	time to first exacerbation
End point description: time to first exacerbation	
End point type	Secondary
End point timeframe: 12 months	

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	255		
Units: days				
median (inter-quartile range (Q1-Q3))	96 (27 to 103)	70 (27 to 160)		

Statistical analyses

Statistical analysis title	Intention to treat - time to first exacerbation
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.16

Secondary: Hospital admissions for COPD exacerbation

End point title	Hospital admissions for COPD exacerbation
End point description:	

End point type	Secondary
End point timeframe:	
12 months	

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	255		
Units: number				
arithmetic mean (standard deviation)	0.27 ($\pm$ 0.63)	0.27 ($\pm$ 0.65)		

Statistical analyses

Statistical analysis title	intention to treat - hospital admissions for COPD
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Mixed models analysis
Parameter estimate	incidence rate ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.5

Secondary: Non COPD hospital admissions

End point title	Non COPD hospital admissions
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	255		
Units: number				
arithmetic mean (standard deviation)	0.18 ($\pm$ 0.51)	0.12 ($\pm$ 0.44)		

Statistical analyses

Statistical analysis title	ITT - non-COPD hospital admissions
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Mixed models analysis
Parameter estimate	incidence rate ratio
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.45

Secondary: All cause mortality

End point title	All cause mortality
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	255		
Units: number	11	13		

Statistical analyses

Statistical analysis title	ITT - all cause mortality
Comparison groups	Bisoprolol v Placebo

Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.73

Secondary: ITT - COPD mortality

End point title	ITT - COPD mortality
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	255		
Units: number	2	9		

Statistical analyses

Statistical analysis title	ITT - COPD mortality
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.88

Secondary: ITT - dyspnoea (Transitional Dyspnoea Index)

End point title	ITT - dyspnoea (Transitional Dyspnoea Index)
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End point description:

End point type	Secondary
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End point timeframe:

12 months

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	188		
Units: score				
arithmetic mean (standard deviation)	-1.73 (± 3.66)	-1.01 (± 3.58)		

Statistical analyses

Statistical analysis title	ITT - dyspnoea
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.01

Secondary: ITT - COPD Assessment Test score (CAT)

End point title	ITT - COPD Assessment Test score (CAT)
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End point description:

End point type	Secondary
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End point timeframe:

12 months

End point values	Bisoprolol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	202		
Units: score				
arithmetic mean (standard deviation)	19.43 (± 8.86)	19.77 (± 9.4)		

Statistical analyses

Statistical analysis title	ITT - CAT
Comparison groups	Bisoprolol v Placebo
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	1.07

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

-12 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26
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Reporting groups

Reporting group title	Bisoprolol
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Reporting group description:

Participants randomised to bisoprolol

Reporting group title	Placebo
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Reporting group description:

Participants randomised to placebo

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: AEs reported by system organ class only, not possible to enter on this system. Fully reported in table 19 of Devereux et al. Bisoprolol for patients with chronic obstructive pulmonary disease at high risk of exacerbation: The BICS RCT. Health Technol Assess 2025;29(17). <https://doi.org/10.3310/TNDG8641>

Serious adverse events	Bisoprolol	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 259 (14.29%)	36 / 256 (14.06%)	
number of deaths (all causes)	11	13	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Triple negative breast cancer			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 259 (0.39%)	4 / 256 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	

Breast cancer			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endometrial cancer			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Cor pulmonale			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 259 (0.39%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	1 / 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 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 259 (1.16%)	8 / 256 (3.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 8	
Haemoptysis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			

Overdose			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 259 (0.39%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 259 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 259 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			

subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 259 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 259 (2.70%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 259 (0.39%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 259 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bisoprolol	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 259 (0.00%)	0 / 256 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2020	Addition of contingency arrangements in response to COVID-19 pandemic; ceasing face-to-face contact by moving study visits to telephone calls.
01 December 2020	Summary of the three main protocol changes to allow recruitment to restart after the COVID-19 pandemic and the justification for this: Revisions to inclusion criteria; Revisions to the titration process; Reduction in number of face-to-face study visits and associated processes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	COVID-19; suspension to recruitment to the study. Participants already recruited in the study continued to take bisoprolol/placebo and were followed up remotely (rather than in-person)	31 July 2021

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Did not meet recruitment target (loss of funding). 27% in the bisoprolol group titrated to maximum 5mg dose. 31% of ppts took <70% of expected doses; the majority of these ceased (similar proportions in both bisoprolol and placebo)

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/38762800>