

**Clinical trial results:**
Randomised Controlled Crossover Trial of Inhaled Furosemide for
Dyspnoea Relief in Advanced Heart Failure
Summary

EudraCT number	2017-000124-95
Trial protocol	GB
Global end of trial date	02 November 2019

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information**Trial identification**

Sponsor protocol code	V1.0
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Additional study identifiers

ISRCTN number	ISRCTN14593637
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX37LE
Public contact	Hania Piotrowska, Oxford Respiratory Trials Unit, University of Oxford, 0044 01865225552, hania.piotrowska@ouh.nhs.uk
Scientific contact	Hania Piotrowska, Oxford Respiratory Trials Unit, University of Oxford, 0044 01865225552, hania.piotrowska@ouh.nhs.uk
Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX37LE
Public contact	Najib Rahman, University of Oxford,, 0044 1865225205, najib.rahman@ndm.ox.ac.uk
Scientific contact	Najib Rahman, Najib Rahman, Oxford Respiratory Trials Unit University of Oxford Churchill Hospital, 0044 1865225205, najib.rahman@ndm.ox.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	11 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2019
Global end of trial reached?	Yes
Global end of trial date	02 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We want to determine whether inhaled furosemide relieves breathlessness in patients with heart failure. This is to test the benefit of adding inhaled furosemide to existing treatment in chronic heart failure.

The principle research objective:

Determine the effect of inhaled furosemide on breathlessness in patients with chronic heart failure

Protection of trial subjects:

All recruited patients were monitored by a qualified cardiologist during the CTIMP intervention phases, and close monitoring of adverse events between interventions occurred via telephone.

Background therapy:

No specific treatments were required - but standard treatments for this patient group (advanced heart failure) were permitted according to usual clinical practice, prescribed and managed by the patient's normal clinicians and not by the study team

Evidence for comparator:

A saline mist comparator was used - there is no direct evidence that saline mist inhalation influences breathlessness in this or any other population, and is safe and well tolerated. On this basis, to avoid any placebo effect, a saline mist inhalation of identical volume (4mls) was used

Actual start date of recruitment	01 November 2017
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: 30
Worldwide total number of subjects	30
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)	0
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients recruited in Oxford, UK. Recruited from December 2017 until November 2020.

Pre-assignment

Screening details:

Patients screened from out patient cardiology clinics to confirm eligibility criteria, or those from a heart failure community • Participant is willing and able to give informed consent for participation in the trial.

- Male or Female, aged 18 years or above. (There is no upper age limit although the investigator will ensure they have the capacity

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Saline and IMP (furosemide) labelled and packaged identically, identical in appearance and allocation and treatment unknown to patient and investigator.

Arms

Arm title	Baseline
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Arm description:

Baseline characteristics of all patients

Arm type	Baseline
Investigational medicinal product name	Saline
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

4mls saline given as an inhaled medication over 15 - 20 minutes, nebulised twice per day for 1 week

Number of subjects in period 1	Baseline
Started	30
Completed	30

Period 2

Period 2 title	Visit 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Saline and IMP (furosemide) labelled and packaged identically, identical in appearance and allocation and treatment unknown to patient and investigator.

The study is a two-sequence, two-period, two-treatment crossover trial. The primary treatment effect is the one-week treatment effect of inhaled furosemide versus inhaled saline.

Arms

Are arms mutually exclusive?	No
Arm title	Saline

Arm description:

Inhaled saline for 1 week and then Air Hunger (AH) test

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

4mls saline given as an inhaled medication over 15 - 20 minutes, nebulised twice per day for 1 week

Arm title	Furosemide
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Arm description:

Furosemide 40mg in solution for nebulisation at 10mg / ml (i.e. 4mls given, identical to saline placebo in volume). Given as an inhaled medication over 15 - 20 minutes, nebulised twice per day for 1 week

Arm type	Experimental
Investigational medicinal product name	Furosemide
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Furosemide 40mg in solution for nebulisation at 10mg / ml (i.e. 4mls given, identical to saline placebo in volume). Given as an inhaled medication over 15 - 20 minutes, nebulised twice per day for 1 week

Number of subjects in period 2	Saline	Furosemide
Started	30	30
Completed	25	25
Not completed	5	5
Lost to follow-up	5	5

Baseline characteristics

Reporting groups

Reporting group title	Baseline
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Reporting group description:

Baseline characteristics for all recruited patients

Reporting group values	Baseline	Total	
Number of subjects	30	30	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	70.6		
standard deviation	± 17.2	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	27	27	
Ethnicity			
Ethnicity			
Units: Subjects			
White	30	30	
Other	0	0	
Smoking status			
Smoking status at recruitment			
Units: Subjects			
Current Smoker	2	2	
Ex-smoker	14	14	
Never Smoker	14	14	
MRC Dyspnoea Score			
Categorised in to class 2, 3, 4 and 5			
Units: Subjects			
Class 2	13	13	
Class 3	7	7	
Class 4	7	7	
Class 5	3	3	
NYHA classification			
New York Heart Association Classification of Heart Failure at baseline			
Units: score			
arithmetic mean	2.6		
standard deviation	± 0.6	-	
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	114.8		
standard deviation	± 28.6	-	
Diastolic Blood Pressure			

Units: mmHg arithmetic mean standard deviation	62.7 ± 15.0	-	
Heart rate Units: Beats per minute arithmetic mean standard deviation	66.7 ± 17.5	-	
Height Units: cm arithmetic mean standard deviation	172.4 ± 8.6	-	
Weight Units: kg arithmetic mean standard deviation	90.1 ± 24.6	-	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description:	
Baseline characteristics of all patients	
Reporting group title	Saline
Reporting group description:	
Inhaled saline for 1 week and then Air Hunger (AH) test	
Reporting group title	Furosemide
Reporting group description:	
Furosemide 40mg in solution for nebulisation at 10mg / ml (i.e. 4mls given, identical to saline placebo in volume). Given as an inhaled medication over 15 - 20 minutes, nebulised twice per day for 1 week	

Primary: Chronic Air Hunger Test - 100mm Visual Analogue Score (Primary)

End point title	Chronic Air Hunger Test - 100mm Visual Analogue Score (Primary)
End point description:	
On Air Hunger (AH) test days, up to two 10 minute practice AH tests will be conducted to establish familiarity with the breathing circuit and consistency in use of VAS. Participants will undergo the first AH test before inhaling the mist (see Appendix A). This will be followed by a further test of induced AH test after the mist inhalation. The AH test involves one ramp (gradual increasing level of ETCO ₂ to maximal level of breathlessness tolerated and two 4 min periods of raising inspired CO ₂ ; one period (the 'test' period) with a level of inspired CO ₂ that produced 50% AH on the VAS during practice sessions; the other period (the 'masking' period) with a level of inspired CO ₂ that will be varied to ensure that subjects experience similar levels of AH even if sensitivity changes. Participants will rate their AH on a 10 cm VAS scale labelled 'none' (no sensation) at one end, and 'extreme' (an intolerable level) at the other end, every 15 seconds.	
End point type	Primary
End point timeframe:	
Post 1 week of inhaled saline / furosemide and compared between crossover periods	

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[1]	25 ^[2]		
Units: millimetre(s)				
arithmetic mean (standard deviation)	0.9 (± 25.0)	0.2 (± 21.5)		

Notes:

[1] - AH test results not available in 5 patients

[2] - AH test results not available in 5 patients

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description:	
Statistical comparison of dyspnoea relief (100mm visual analogue score) comparing 1 week saline to 1 week furosemide	
Comparison groups	Furosemide v Saline

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 ^[3]
Method	Mixed models analysis

Notes:

[3] - No evidence of significant difference

Secondary: Acute Air Hunger Test - 100mm Visual Analogue Score (Secondary)

End point title	Acute Air Hunger Test - 100mm Visual Analogue Score (Secondary)
End point description:	As before for AH test
End point type	Secondary
End point timeframe:	Acute effects of inhaled saline or furosemide on visits with AH test conducted immediately after inhalation

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[4]	25 ^[5]		
Units: millimetre(s)				
arithmetic mean (standard deviation)	-0.3 (± 23.7)	-0.6 (± 22.7)		

Notes:

[4] - 5 patients did not complete AH test

[5] - 5 patients did not complete AH test

Statistical analyses

Statistical analysis title	Comparison of AH test for acute inhalation
Comparison groups	Furosemide v Saline
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 ^[6]
Method	Mixed models analysis

Notes:

[6] - No evidence of significant difference between groups

Secondary: D12

End point title	D12
End point description:	Dyspnoea 12 measurement of breathlessness during Air Hunger Test
End point type	Secondary
End point timeframe:	During Air Hunger Test

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[7]	25 ^[8]		
Units: units				
arithmetic mean (standard deviation)	-7.8 (\pm 18.2)	-6.2 (\pm 17.0)		

Notes:

[7] - 5 patients did not complete AH test

[8] - 5 patients did not complete AH test

Statistical analyses

Statistical analysis title	D12 comparison during AH test
Comparison groups	Furosemide v Saline
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Mixed models analysis

Secondary: Serum BNP post 1 week inhalation

End point title	Serum BNP post 1 week inhalation
End point description:	
End point type	Secondary
End point timeframe:	
Blood measurements post 1 week of inhalation of saline or furosemide	

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 ^[9]	20 ^[10]		
Units: ng/L				
arithmetic mean (standard deviation)	13.7 (\pm 35.4)	-6.4 (\pm 27.0)		

Notes:

[9] - Blood not collected in 10 patients

[10] - Blood not collected in 10 patients

Statistical analyses

Statistical analysis title	BNP comparison post 1 week inhalation
Comparison groups	Furosemide v Saline

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 ^[11]
Method	t-test, 2-sided

Notes:

[11] - Borderline evidence of clinically non significant reduction in BNP after inhaled furosemide compared with saline

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reported during entire study period (3 weeks which encompasses initial inhalation week, 1 week washout and then 2nd inhalation week, total 3 weeks)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Saline
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Reporting group description: -

Reporting group title	Furosemide
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Reporting group description: -

Serious adverse events	Saline	Furosemide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Saline	Furosemide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)	15 / 30 (50.00%)	
Cardiac disorders			
Hypotension	Additional description: Transient hypotension in one patient post inhaled furosemide		
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Oedema	Additional description: Peripheral oedema seen in one patient post inhaled saline		
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cardiac failure	Additional description: Worsening in known cardiac failure status in 2 patients post inhaled saline		
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			

Confusional state	Additional description: Confusion transiently in 2 patients post inhaled furosemide.		
	subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)
	occurrences (all)	0	2
Sleep deficit	Additional description: Sleep disturbance in one patient post inhaled furosemide		
	subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
	occurrences (all)	0	1
Gastrointestinal disorders			
Dysgeusia	Additional description: Short term altered / metallic test after inhalation of both saline (1) and furosemide (3)		
	subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)
	occurrences (all)	1	3
Appetite disorder	Additional description: Loss of appetite in 1 patient post inhaled saline and 1 furosemide		
	subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)
	occurrences (all)	1	1
Reflux gastritis	Additional description: Gastroesophageal reflux disease in one patient post inhaled furosemide		
	subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
	occurrences (all)	0	1
Dry mouth	Additional description: Dry mouth seen in two patients post inhaled furosemide		
	subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)
	occurrences (all)	0	2
Respiratory, thoracic and mediastinal disorders			
Diarrhoea	Additional description: Short term diarrhoea after furosemide inhalation		
	subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
	occurrences (all)	0	1
Hyperventilation	Additional description: Hyperventilation seen short term after inhaled saline (3) and furosemide (1)		
	subjects affected / exposed	3 / 30 (10.00%)	1 / 30 (3.33%)
	occurrences (all)	3	1
Dyspnoea	Additional description: In one patient on inhaled saline		
	subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)
	occurrences (all)	1	0
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash in one patient post inhaled furosemide		
	subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)
	occurrences (all)	0	1
Renal and urinary disorders			

urinary frequency subjects affected / exposed occurrences (all)	Additional description: Increased frequency in 1 furosemide patient		
	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	
Infections and infestations viral illness subjects affected / exposed occurrences (all)	Additional description: Possible viral illness post saline treatment in one patient		
	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	

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

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

Aimed for recruitment not achieved.

Notes: