Clinical trial results:
Inhaled furosemide for dyspnoea relief in advanced heart failure

Summary

EudraCT number	2015-001468-21
Trial protocol	GB
Global end of trial date	02 October 2017

Results information

Result version number	v1 (current)
This version publication date	01 April 2022
First version publication date	01 April 2022

Trial information

Trial identification

Sponsor protocol code	V1.0

Additional study identifiers

ISRCTN number	ISRCTN11011373
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Block 60, Churchill Hospital, Oxford, United Kingdom, OX137LE
Public contact	Joanna Grogono, Oxford Brookes University, 0044 1865 483257, jgrogono@brookes.ac.uk
Scientific contact	Joanna Grogono, Oxford Brookes University, 0044 1865 483257, jgrogono@brookes.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 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2017
Global end of trial reached?	Yes
Global end of trial date	02 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We want to explore whether inhaled furosemide relieves breathlessness in patients with heart failure. To address this question we first need to conduct a pilot study. This pilot study will inform a future clinical trial to test the benefit of adding inhaled furosemide to existing treatment in advanced heart failure patients.

The principle research question:
- What is the effect on inhaled furosemide on breathlessness in patients with chronic advanced heart failure?

Why ask this question?
Patients with heart failure often experience breathlessness/dyspnoea which restricts their activities. Furosemide is a prescription drug taken as a tablet or as an injection which makes kidneys produce more urine to remove fluid build-up in heart failure. Over time a third of patients will need more furosemide to get the same response from the kidneys but high level of furosemide can lead to kidney failure. If furosemide is inhaled instead this is known to stop coughing, protect the airwa

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	17 July 2015
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: 13
Worldwide total number of subjects	13
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)	2
From 65 to 84 years	9
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the heart failure clinic at John Radcliffe Hospital or those under the care of the community heart failure nurses in Oxfordshire

Pre-assignment

Screening details:

Patients were screened from heart failure clinics /community heart failure services, recruiting patients with at least NHYA class III or greater heart failure. 2 x 2 crossover study with repeated visits in the same patients - the data presented is of aggregate results of the effect of inhaled furosemide versus saline on breathlessness.

Period 1

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

Blinding implementation details:

4mls saline matched placebo or 4mls furosemide were used and the treatment unknown to the patient or investigator

Arms

Arm title	Saline

Arm description:

4mls saline

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

Dosage and administration details:

4mls of saline for inhalation

Investigational medicinal product name	Furosemide
Investigational medicinal product code	
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).

Number of subjects in period 1	Saline
Started	13
Completed	13

Period 2

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

Blinding implementation details:

As before, complete blinding of saline or furosemide solutions for inhalation, identical and patients and investigators blinded to treatment

Arms

Are arms mutually exclusive?	No
Arm title	Saline

Arm description:

Nebulised saline

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

Dosage and administration details:

4mls normal saline

Arm title	Furosemide

Arm description:

Nebulised furosemide

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

Dosage and administration details:

40mg furosemide in 4mls solution (10mg/ml)

Number of subjects in period 2	Saline	Furosemide
Started	13	13
Completed	13	13

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	75.8		
standard deviation	± 11.9	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	9	9	
NYHA class Units: Subjects			
III	13	13	
IV	0	0	
Height Units: centimetre			
arithmetic mean	169		
standard deviation	± 12	-	
Weight Units: kilogram(s)			
arithmetic mean	80		
standard deviation	± 25	-	
Heart Rate Units: beats per minute			
arithmetic mean	71		
standard deviation	± 13	-	
Systolic Blood Pressure Units: mmHg			
arithmetic mean	127		
standard deviation	± 23	-	

Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	69		
standard deviation	± 14	-	

Subject analysis sets

Subject analysis set title	Breathlessness analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All patients how had undergone the crossover study which involved either nebulised saline or nebulised furosemide given in random order, and the breathlessness responses during an excercise test. Results represent the full analysis of each patient

Reporting group values	Breathlessness analysis		
Number of subjects	13		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	75.8		
standard deviation	± 11.9		
Gender categorical			
Units: Subjects			
Female			
Male			
NYHA class			
Units: Subjects			
III			
IV			
Height			
Units: centimetre			
arithmetic mean			
standard deviation	±		
Weight			
Units: kilogram(s)			
arithmetic mean			
standard deviation	±		
Heart Rate			
Units: beats per minute			
arithmetic mean			

standard deviation	±		
Systolic Blood Pressure Units: mmHg arithmetic mean standard deviation	±		
Diastolic Blood Pressure Units: mmHg arithmetic mean standard deviation	±		

End points

End points reporting groups	
Reporting group title	Saline
Reporting group description: 4mls saline	
Reporting group title	Saline
Reporting group description: Nebulised saline	
Reporting group title	Furosemide
Reporting group description: Nebulised furosemide	
Subject analysis set title	Breathlessness analysis
Subject analysis set type	Full analysis
Subject analysis set description: All patients how had undergone the crossover study which involved either nebulised saline or nebulised furosemide given in random order, and the breathlessness responses during an excercise test. Results represent the full analysis of each patient	

Primary: VAS for breathlessness	
End point title	VAS for breathlessness
End point description:	
End point type	Primary
End point timeframe: At end of Excercise test and after nebulisation (crossover trial - summated data)	

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: millimetre(s)				
arithmetic mean (standard deviation)	3.2 (± 15.5)	-0.1 (± 12.7)		

Statistical analyses

Statistical analysis title	VAs comparison
Comparison groups	Saline v Furosemide
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.1
Method	t-test, 2-sided

Primary: Modified Borg Scale

End point title	Modified Borg Scale

End point description:

End point type	Primary

End point timeframe:

At end of Excercise test and after nebulisation (crossover trial - summated data)

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: units				
arithmetic mean (standard deviation)	0.5 (± 15.6)	2.6 (± 11.3)		

Statistical analyses

Statistical analysis title	MBS analysis
Comparison groups	Saline v Furosemide
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.1
Method	t-test, 2-sided

Primary: Dyspnoea 12

End point title	Dyspnoea 12

End point description:

End point type	Primary

End point timeframe:

At end of Excercise test and after nebulisation (crossover trial - summated data)

End point values	Saline	Furosemide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Units				
arithmetic mean (standard deviation)	-1.5 (± 10.7)	-6.1 (± 10.9)		

Statistical analyses

Statistical analysis title	D12 analysis
Comparison groups	Saline v Furosemide
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reported during acute administration of inhaled saline or furosemide and during exercise tests only

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Saline
Reporting group description: -	
Reporting group title	Furosemide

Reporting group description: -

Serious adverse events	Saline	Furosemide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (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	0 / 13 (0.00%)	2 / 13 (15.38%)	
Nervous system disorders			
Anxiety	Additional description: Short term anxiety after mist inhalation		
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: URTI after furosemide inhalation		
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	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