Clinical trial results:
A parallel group, double-blind, randomised placebo-controlled trial comparing the efficacy and cost-effectiveness of 20mg daily oral modified release morphine (MRM) versus placebo on the intensity of dyspnoea in patients with stable symptomatic chronic heart failure (CHF).

Summary

EudraCT number	2014-000155-81
Trial protocol	GB
Global end of trial date	24 August 2017

Results information

Result version number	v2 (current)
This version publication date	29 November 2018
First version publication date	31 August 2018
Version creation reason	• New data added to full data set Additional adverse event included for one participant.
Summary attachment (see zip file)	Additional summary attachment (Additional summary attachment_v3_14.08.2018_clean.pdf)

Trial information

Trial identification

Sponsor protocol code	R1730

Additional study identifiers

ISRCTN number	ISRCTN41349358
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hull and East Yorkshire Hospitals NHS Trust
Sponsor organisation address	R&D Department, Office 13, 2nd Floor Daisy Building, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire, United Kingdom, HU16 5JQ
Public contact	Prof Miriam Johnson, The University of Hull, +44 1482 463482, miriam.johnson@hyms.ac.uk
Scientific contact	Prof Miriam Johnson, The University of Hull, +44 1482 463482, miriam.johnson@hyms.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	24 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2017
Global end of trial reached?	Yes
Global end of trial date	24 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Our primary objective was to determine whether medium-term morphine therapy is superior to placebo for the relief of chronic breathlessness in people with stable heart failure and symptomatic despite maximally tolerated medical therapy.

Protection of trial subjects:

Participants were telephoned by the research nurse to check toxicity and adverse events in the first week of the study. This included a call within 24 hours of the participant's first study dose, midweek, and at the end of the week. Safety data were reviewed at IDMC meetings held on 26 July 2016, 26 Jan 2017, 24 July 2017 and 1 Dec 2017. No safety issues were noted from any meeting. A telephone call was made to patients after they stopped taking study drug to check for potential withdrawal symptoms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2016
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: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	8
From 65 to 84 years	35
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Thirteen sites in the UK were opened to recruitment between 10 Dec 2015 and 18 April 2017. Seven sites recruited at least one participant. The first participant was randomised on 14 Jan 2016 and the last on 15 May 2017. Recruitment was closed early, on 24 May 2017.

Pre-assignment

Screening details:

386 patients were screened for participation between December 2015 and May 2017 across the 13 sites (median 27 per site, range 0 to 55), of which 175 (45%) were ineligible, 165 (43%) declined, one (0.3%) was eligible and consenting but the trial closed to recruitment before they could be randomised, and 45 (12%) were randomised

Period 1

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

Blinding implementation details:

Modified release morphine (MRM) capsules (the Investigational Medicinal Product) and placebo IMP capsules were over-encapsulated, so as to be identical in appearance to maintain blinding. As constipation is a common side-effect of morphine, an overencapsulated laxative (docusate) capsule (the Non-Investigational Medicinal Product), or identical overencapsulated placebo NIMP capsule, was given to the IMP or comparator groups respectively, to prevent unblinding due to development of constipation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Morphine

Arm description:

Subjects received 10mg twice daily oral modified release morphine (IMP) and 100mg twice daily oral docusate (NIMP).

Arm type	Experimental
Investigational medicinal product name	Modified release morphine (MRM)
Investigational medicinal product code	ATC code: N02A A01
Other name	MST® CONTINUS®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects took one 10mg capsule oral MRM plus one 100mg capsule oral docusate on waking in the morning, and one 10mg capsule MRM plus one 100mg capsule docusate on going to bed at night for 12 weeks.

Arm title	Placebo

Arm description:

Subjects received twice daily oral placebo IMP and twice daily oral placebo NIMP.

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

Dosage and administration details:

twice daily placebo capsule.

Number of subjects in period 1	Morphine	Placebo
Started	21	24
Reached primary time point of 4 weeks	20	24
Completed	20	22
Not completed	1	2
Consent withdrawn by subject	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Morphine
Reporting group description:	
Subjects received 10mg twice daily oral modified release morphine (IMP) and 100mg twice daily oral docusate (NIMP).	
Reporting group title	Placebo
Reporting group description:	
Subjects received twice daily oral placebo IMP and twice daily oral placebo NIMP.	

Reporting group values	Morphine	Placebo	Total
Number of subjects	21	24	45
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)	1	7	8
From 65-84 years	19	16	35
85 years and over	1	1	2
Age continuous			
Units: years			
arithmetic mean	74.4	70.1	
standard deviation	± 6	± 14	-
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	18	20	38
Ethnicity			
Units: Subjects			
White	21	24	45
New York Heart Association (NYHA) Class			
Class I – no symptoms; Class II – breathless and/or fatigue on moderate exertion; Class III – breathless and/or fatigue on mild exertion; Class IV – breathless and/or fatigue at rest			
Units: Subjects			
III	20	24	44
IV	1	0	1
modified MRC Breathlessness Scale			
0=Not troubled by breathlessness except on strenuous exercise, 1=Short of breath when hurrying or walking up a slight hill, 2=Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace, 3=Stops for breath after about 100m or after a few minutes on the level, 4=Too breathless to leave the house, or breathless when dressing or undressing			
Units: Subjects			

score=0	0	0	0
score=1	0	0	0
score=2	7	3	10
score=3	11	21	32
score=4	3	0	3
estimated Glomerular Filtration Rate (eGFR)			
Units: ml/min			
arithmetic mean	53.0	62.2	
standard deviation	± 18.2	± 21.4	-
Resting pulse rate (radial)			
Units: Pulse rate per minute			
arithmetic mean	77.0	77.0	
standard deviation	± 24.0	± 11.2	-
Resting diastolic blood pressure			
Units: mmHg			
arithmetic mean	69.4	68.0	
standard deviation	± 12.3	± 11.6	-
Resting respiratory rate			
Units: per minute			
arithmetic mean	17.9	15.6	
standard deviation	± 6.8	± 4.4	-
Pulse Oximetry %			
Units: percentage			
arithmetic mean	97.1	96.7	
standard deviation	± 2.1	± 1.6	-
Charlson Co-morbidity Index			
A scoring system whereby a score is assigned to each of 18 medical conditions, plus a score for patient's age, to provide a total score for the patient.			
Units: Score between 0 and 46			
arithmetic mean	6.7	6.2	
standard deviation	± 1.4	± 2.3	-
NT-proBNP			
NT-proBNP (N-Terminal pro-Brain Natriuretic Peptide) was only measured at certain sites (Morphine arm: N=20; Placebo arm: N=22). If not available BNP was measured instead.			
Units: pg/mL			
arithmetic mean	3666.7	3926.4	
standard deviation	± 2459.1	± 3729.3	-
Australia-modified Karnofsky Performance Status (AKPS)			
AKPS score, between 0 and 100, in increments of 10, based on ability to perform activities of daily living. Hgher scores imply better function; 100 signifies normal physical activities.			
Units: Score from 0 to 100			
median	70	70	
inter-quartile range (Q1-Q3)	60 to 80	60 to 70	-
Kansas City Cardiomyopathy Questionnaire-short form (KCCQ-SF)			
12-item, self-administered instrument quantifying physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. Higher scores indicate better functioning, fewer symptoms, and better disease-specific quality of life.			
Units: Score between 0 and 100			
arithmetic mean	36.6	40.2	
standard deviation	± 14.7	± 11.9	-
Epworth Sleepiness Scale			

Screening tool for sleep-disordered breathing. Specifically distinguishes reports of daytime dozing behaviour from fatigue and drowsiness/sleepiness. Higher scores indicate excessive sleepiness (11-12 mild; 13-16 moderate; >16 severe).			
Units: Score between 0 to 24			
arithmetic mean	9.6	9.5	
standard deviation	± 4.1	± 4.8	-
Karolinska Sleepiness Scale			
9-point Likert scale of the patient's level of drowsiness (1=very alert to 9=very sleepy)			
Units: Score 1 to 9			
arithmetic mean	3.0	3.3	
standard deviation	± 1.5	± 1.6	-
Montreal Cognitive Assessment			
30-item questionnaire assessing cognitive function. Scores between 0 and 30; ≥ 26 implies no cognitive impairment; lower scores indicate greater cognitive impairment.			
Units: Score between 0 and 30			
arithmetic mean	25.1	25.4	
standard deviation	± 1.9	± 3.1	-
Six minute walk test			
Recorded distance walked in metres. Morphine N=18; Placebo: N=24.			
Units: Distance walked in metres			
arithmetic mean	177.1	195.0	
standard deviation	± 98.8	± 101.5	-
Six minute walk test			
Oxygen saturation at rest. Morphine N=18; Placebo: N=24.			
Units: Percentage			
arithmetic mean	97.2	96.8	
standard deviation	± 2.1	± 1.7	-
Six minute walk test			
Oxygen saturation post-test. Morphine N=18; Placebo: N=24.			
Units: Percentage			
arithmetic mean	97.4	97.2	
standard deviation	± 1.9	± 2.1	-
activPAL™ Average steps per day			
Physical activity monitor, activPAL™ , worn for 7 days at baseline prior to randomisation. Average daily step count documented. Morphine: N=20; Placebo: N=22.			
Units: Steps per day			
arithmetic mean	2384.5	2402.4	
standard deviation	± 1661.0	± 2180.8	-
Average breathlessness intensity score over the past 24 hours			
Average numerical rating scale (NRS) breathlessness intensity score over the past 24 hours, measured from 0 to 10 where 0 indicates no breathlessness and 10 indicates worst imaginable breathlessness, at Baseline.			
Units: NRS from 0 to 10			
arithmetic mean	5.8	5.0	
standard deviation	± 2.0	± 1.9	-
Average worst breathlessness score over the past 24 hours			
Average numerical rating scale (NRS) for worst breathlessness score over the past 24 hours, measured from 0 to 10 where 0 indicates no breathlessness and 10 indicates worst imaginable breathlessness, at Baseline.			
Units: NRS from 0 to 10			
arithmetic mean	7.2	6.2	
standard deviation	± 2.4	± 1.9	-

Average unpleasantness of breathlessness over the past 24 hours			
Average numerical rating scale (NRS) for how unpleasant breathlessness has been over the past 24 hours, measured from 0 to 10 where 0 indicates not unpleasant at all and 10 indicates worst unpleasantness imaginable, at Baseline.			
Units: NRS from 0 to 10			
arithmetic mean	5.6	4.5	
standard deviation	± 2.4	± 2.0	-
Average distress breathlessness has caused over the past 24 hours			
Average numerical rating scale (NRS) for how much distress breathlessness has caused over the past 24 hours, measured from 0 to 10 where 0 indicates no distress and 10 indicates worst distress imaginable, at Baseline.			
Units: NRS from 0 to 10			
arithmetic mean	5.7	4.1	
standard deviation	± 2.4	± 2.3	-
Average pain experienced over the past 24 hours			
Average numerical rating scale (NRS) for pain experienced over the past 24 hours, measured from 0 to 10 where 0 indicates no pain and 10 indicates worst pain imaginable, at Baseline.			
Units: NRS from 0 to 10			
arithmetic mean	1.9	1.2	
standard deviation	± 3.1	± 2.1	-
Resting systolic blood pressure			
Units: mmHG			
arithmetic mean	119.8	116.1	
standard deviation	± 24.2	± 14.5	-
BNP			
If NT-proBNP measurement was not available, then BNP was measured (Morphine arm: N=1; Placebo arm: N=2)			
Units: pg/ml			
arithmetic mean	528	844	
standard deviation	± 0	± 526.1	-

End points

End points reporting groups

Reporting group title	Morphine
Reporting group description:	
Subjects received 10mg twice daily oral modified release morphine (IMP) and 100mg twice daily oral docusate (NIMP).	
Reporting group title	Placebo
Reporting group description:	
Subjects received twice daily oral placebo IMP and twice daily oral placebo NIMP.	

Primary: Average breathlessness intensity score over the past 24 hours

End point title	Average breathlessness intensity score over the past 24 hours
End point description:	
The primary outcome measure was the average numerical rating scale (NRS) breathlessness intensity score over the past 24 hours, measured from 0 to 10 where 0 indicates no breathlessness and 10 indicates worst imaginable breathlessness, at 4 weeks.	
End point type	Primary
End point timeframe:	
Measured at 4 weeks post-randomisation	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: numerical rating scale measured 0 to 10				
arithmetic mean (standard deviation)	5.3 (± 2.3)	4.6 (± 2.4)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
NRS at W4 was compared among patients randomly allocated to MRM/placebo. This result was extracted from a covariance pattern linear mixed model in which NRS at each timepoint was nested within patients. NRS at baseline, trial arm, each follow-up timepoint, a time-by-trial arm interaction were included as fixed effects with participant and site as random effect. An exchangeable covariance structure for the repeated measurements was used; this provided the smallest Akaike's information criterion.	
Comparison groups	Placebo v Morphine

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Mixed-effect linear regression
Parameter estimate	Mean difference (net)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	1.37

Secondary: Average worst breathlessness score over the past 24 hours

End point title	Average worst breathlessness score over the past 24 hours

End point description:

Average numerical rating scale (NRS) for worst breathlessness score over the past 24 hours, measured from 0 to 10 where 0 indicates no breathlessness and 10 indicates worst imaginable breathlessness, at 4 weeks.

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: NRS measured from 0 to 10				
arithmetic mean (standard deviation)	5.9 (± 2.5)	5.3 (± 2.6)		

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

A covariance pattern linear mixed model in which NRS at each time point (D2, D4, D7, W2, W3, W4, W8, W12) was nested within patients. NRS at baseline, trial arm, each time point of follow-up, a time-by-trial arm interaction were included as fixed effects with participant and site as random effect.

Comparison groups	Morphine v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	Mixed-effect linear regression
Parameter estimate	Mean difference (net)
Point estimate	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	1.44

Secondary: Average unpleasantness of breathlessness over the past 24 hours

End point title	Average unpleasantness of breathlessness over the past 24 hours

End point description:

Average numerical rating scale (NRS) for how unpleasant breathlessness has been over the past 24 hours, measured from 0 to 10 where 0 indicates not unpleasant at all and 10 indicates worst unpleasantness imaginable, at 4 weeks.

End point type	Secondary

End point timeframe:

Measured at 4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: numerical rating scale from 0 to 10				
arithmetic mean (standard deviation)	4.7 (± 2.8)	4.3 (± 2.1)		

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

A covariance pattern linear mixed model in which NRS at each time point (D2, D4, D7, W2, W3, W4, W8, W12) was nested within patients. NRS at baseline, trial arm, each time point of follow-up, a time-by-trial arm interaction were included as fixed effects with participant and site as random effect.

Comparison groups	Placebo v Morphine
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	Mixed-effect linear regression
Parameter estimate	Mean difference (net)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	1.17

Secondary: Average distress breathlessness has caused over the past 24 hours

End point title	Average distress breathlessness has caused over the past 24 hours

End point description:

Average numerical rating scale (NRS) for how much distress breathlessness has caused over the past 24 hours, measured from 0 to 10 where 0 indicates no distress and 10 indicates worst distress imaginable, at 4 weeks.

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: numerical rating scale from 0 to 10				
arithmetic mean (standard deviation)	4.2 (± 3.3)	3.8 (± 2.6)		

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

A covariance pattern linear mixed model in which NRS at each time point (D2, D4, D7, W2, W3, W4, W8, W12) was nested within patients. NRS at baseline, trial arm, each time point of follow-up, a time-by-trial arm interaction were included as fixed effects with participant and site as random effect.

Comparison groups	Morphine v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Mixed-effect linear regression
Parameter estimate	Mean difference (net)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	0.88

Secondary: Average pain experienced over the past 24 hours

End point title	Average pain experienced over the past 24 hours

End point description:

Average numerical rating scale (NRS) for pain experienced over the past 24 hours, measured from 0 to 10 where 0 indicates no pain and 10 indicates worst pain imaginable, at 4 weeks.

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: numerical rating scale from 0 to 10				
arithmetic mean (standard deviation)	1.5 (± 2.8)	1.1 (± 1.9)		

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

A covariance pattern linear mixed model in which NRS at each time point (D2, D4, D7, W2, W3, W4, W8, W12) was nested within patients. NRS at baseline, trial arm, each time point of follow-up, a time-by-trial arm interaction were included as fixed effects with participant and site as random effect.

Comparison groups	Morphine v Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	Mixed-effect linear regression
Parameter estimate	Mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	1.2

Secondary: Australia-modified Karnofsky Performance Status (AKPS)

End point title	Australia-modified Karnofsky Performance Status (AKPS)

End point description:

Australia-modified Karnofsky Performance Status score, between 0 and 100, in increments of 10, based on ability to perform activities of daily living. Hgher scores imply better function; 100 signifies normal physical activities

End point type	Secondary

End point timeframe:

week 4 post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: score, between 0 and 100				
median (inter-quartile range (Q1-Q3))	70 (60 to 75)	70 (70 to 70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kansas City Cardiomyopathy Questionnaire-short form (KCCQ-SF)

End point title	Kansas City Cardiomyopathy Questionnaire-short form (KCCQ-SF)

End point description:

Kansas City Cardiomyopathy Questionnaire-short form score from 0 to 100, where a higher score indicates better disease-specific quality of life, at week 4

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: score from 0 to 100				
arithmetic mean (standard deviation)	37.2 (± 16.0)	44.1 (± 12.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Epworth Sleepiness Scale

End point title	Epworth Sleepiness Scale

End point description:

Epworth Sleepiness Scale score from 0 to 24, where a higher score indicates excessive sleepiness, at week 4

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: score from 0 to 24				
arithmetic mean (standard deviation)	10.6 (± 5.2)	9.4 (± 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Karolinska Sleepiness Scale

End point title	Karolinska Sleepiness Scale

End point description:

Karolinska Sleepiness Scale score from 1 to 9, where a higher score indicates excessive sleepiness, at week 4

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: score from 1 to 9				
arithmetic mean (standard deviation)	3.3 (± 1.5)	3.0 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global impression of change

End point title	Global impression of change

End point description:

The Global Impression of Change question related to the patients' breathing; it asked whether there had been any overall change in breathing since taking the trial medicine that week.

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: Patients				
About the same	13	9		
Better - almost the same, hardly any better at all	0	0		
Better - a little better	3	4		
Better - somewhat better	1	2		
Better - moderately better	0	2		
Better - a good deal better	2	2		
Better - a great deal better	0	1		
Better - a very great deal better	0	0		
Worse - almost the same, hardly any worse at all	0	0		
Worse - a little worse	0	0		
Worse - somewhat worse	0	1		
Worse - moderately worse	0	0		
Worse - a good deal worse	1	0		
Worse - a great deal worse	0	0		
Worse - a very great deal worse	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Montreal Cognitive Assessment

End point title	Montreal Cognitive Assessment

End point description:

30-item questionnaire assessing cognitive function. Scores between 0 and 30. Lower scores indicates greater cognitive impairment.

End point type	Secondary

End point timeframe:

4 weeks post-randomisation

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: Score from 0 to 30				
arithmetic mean (standard deviation)	26.2 (± 3.3)	26.8 (± 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Six minute walk test - distance walked (m)

End point title	Six minute walk test - distance walked (m)
End point description: Distance walked (m)	
End point type	Secondary
End point timeframe: 4 weeks post-randomisation	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: Distance walked in metres				
arithmetic mean (standard deviation)	184.2 (± 87.7)	191.5 (± 137.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Six minute walk test - Oxygen saturation at rest (%)

End point title	Six minute walk test - Oxygen saturation at rest (%)
End point description: Oxygen saturation at rest (%)	
End point type	Secondary
End point timeframe: 4 weeks post-randomisation	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: Oxygen saturation %				
arithmetic mean (standard deviation)	96.5 (± 1.7)	96.9 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Six minute walk test - Oxygen saturation at end (%)

End point title	Six minute walk test - Oxygen saturation at end (%)
End point description:	
Oxygen saturation at end of 6MWT (%)	
End point type	Secondary
End point timeframe:	
4 weeks post-randomisation	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: Oxygen saturation %				
arithmetic mean (standard deviation)	97.1 (± 1.6)	97.2 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: activPAL™ Average number of steps per day

End point title	activPAL™ Average number of steps per day
End point description:	
Physical activity monitor, activPAL™ , worn for 7 days prior to week 4. Average daily step count documented.	
End point type	Secondary
End point timeframe:	
4 weeks post-randomisation	

End point values	Morphine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Steps per day				
arithmetic mean (standard deviation)	1812.9 (± 1425.9)	2926.0 (± 2002.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event (AE) reporting period began as soon as patients were consented to the trial and ended one month after the patient's final study assessment (week 12) .

Adverse event reporting additional description:

Participants' health status was checked at each study assessment and the local investigator recorded all directly observed AEs and all AEs reported by participants. AEs were recorded in a trial AE form and in patients' medical notes. AEs reported as possibly, probably or definitely related to morphine are listed here as related to treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Morphine

Reporting group description:

Subjects received 10mg twice daily oral modified release morphine (IMP) and 100mg twice daily oral docusate (NIMP). One participant withdrew from the study immediately after randomisation and did not receive any study medication. Therefore they have been removed from the denominator for this group.

Reporting group title	Placebo

Reporting group description:

Subjects received twice daily oral placebo IMP and twice daily oral placebo NIMP.

Serious adverse events	Morphine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)	10 / 24 (41.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Surgical and medical procedures			
Pacemaker update	Additional description: Admission to hospital for pacemaker update		
subjects affected / exposed	1 / 20 (5.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			

subjects affected / exposed	1 / 20 (5.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal reaction			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Skin infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 20 (5.00%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (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: 0 %

Non-serious adverse events	Morphine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)	12 / 24 (50.00%)	
Investigations			
Chronic kidney disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 20 (5.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Alcohol intoxication			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Cardiac disorders			
Unconfirmed presyncope			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Heart failure			
subjects affected / exposed	1 / 20 (5.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Ventricular tachycardia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Cognitive disturbance			
subjects affected / exposed	3 / 20 (15.00%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Memory impairment			
subjects affected / exposed	1 / 20 (5.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Social circumstances			
Respite care			
subjects affected / exposed	0 / 20 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 20 (25.00%)	1 / 24 (4.17%)	
occurrences (all)	6	1	
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Anorexia			

subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	4 / 20 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 20 (5.00%)	4 / 24 (16.67%)	
occurrences (all)	1	4	
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Skin infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 20 (5.00%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2014	During the CTA approval process, MHRA requested a change to the emergency unblinding procedure as part of their review. This Substantial Amendment (SA1) to the protocol was submitted to the NHS National Research Ethics Service (NRES) Research Ethics Committee (REC).
18 February 2015	Substantial Amendment 2; submitted to REC only: A new patient information sheet regarding the law on driving after certain drugs; a new "as-needed" opioids patient diary; amendments to two new GP letters regarding patients in the study; removal of the "within 3 months" time-limit for the echocardiogram for eligibility; removal of the Day 1 assessments.
13 April 2015	Substantial Amendment 3; submitted to REC only: Patient Information Sheet and consent form amended to indicate anonymised data may be held on 3rd party database, that capsules contact gelatin and text regarding driving amended; a new patient information created - List of morphine side-effects; addition of 2 study sites.
06 July 2015	Substantial Amendment 4; submitted to REC only: Addition of a Study Experience survey for all participants and a Study Experience telephone interview in a sample of participants
15 July 2015	Substantial Amendment 5; submitted to REC only: Addition of 4 new NHS sites.
02 February 2016	Substantial Amendment 6; submitted to REC only: Minor amendment to Patient Information Sheet and patient invitation letter templates; both made more flexible to allow sites to enter number of clinic visits needed by participants.
29 March 2016	Substantial Amendment 7; submitted to both MHRA and REC: For sites where pharmacy are unable to emergency unblind, the CI or her deputy will do it via an online system. Approved by REC 29/02/16; approved by MHRA 29/03/16.
13 September 2016	Substantial Amendment 9; submitted to REC only: addition of 2 new NHS study sites.
22 December 2016	Substantial Amendment 10; submitted to REC only: Study site Christmas hamper incentive.
28 July 2017	Substantial Amendment 8, submitted to REC only: addition of 3 new NHS study sites.

Notes:

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.

The major limitation of this study was the early termination due to poor recruitment and subsequent lack of power. Thus these data can only be interpreted as preliminary.

Notes: