Additional files for the end of trial report for the BreatheMOR-HF (Morphine for the relief of breathlessness in stable chronic heart failure) trial.

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 severely symptomatic chronic heart failure (CHF).

EudraCT number: 2014-000155-81

As large amounts of data at various time points were collected during the course of the study, additional data are reported in this document. This is in addition to that listed in the full data set.

1. Questionnaire return rates

A total of 45 participants were recruited to the BreatheMOR-HF study; 21 were allocated to the active morphine and docusate arm; and 24 to the placebo arm. Participants were followed up at the following time points: baseline, day 2, 4, and 7, week 2, 3, 4 (the primary outcome point), 8 and 12. Optional follow-ups took place at 6, 9 and 12 months after randomisation. Of the 45 participants randomised, 44 reached the primary time point of 4 weeks since one participant withdrew from the trial the day after they were randomised. There were no further withdrawals from the trial in the morphine group up to week 12. All randomised participants in the placebo group were followed up at week 4, one participant withdrew from the trial between week 4 and week 8, and a further patient between week 8 and week 12. Participant follow-up was ceased on 16th August 2017, as the trial was stopped early. Table 1 shows the questionnaire return rates at each time point.

Table 1: Return rates by treatment group and time point

Questionnaire	Morphine (n=21) Received/expected (%)	Placebo (n=24) Received/expected (%)	Total (n=45) Received/expected (%)	Total (n=45) Received/all (%)
Baseline	21/21 (100.0)	24/24 (100.0)	45/45 (100.0)	45/45 (100.0)
Day 2	20/20 (100.0)	24/24 (100.0)	44/44 (100.0)	44/45 (97.8)
Day 4	20/20 (100.0)	24/24 (100.0)	44/44 (100.0)	44/45 (97.8)
Day 7	20/20 (100.0)	24/24 (100.0)	44/44 (100.0)	44/45 (97.8)
Week 2	20/20 (100.0)	24/24 (100.0)	44/44 (100.0)	44/45 (97.8)
Week 3	20/20 (100.0)	23/24 (95.8)	43/44 (97.7)[a]	43/45 (95.6)
Week 4 (primary time point)	20/20 (100.0)	24/24 (100.0)	**44/44 (100.0)**	**44/45 (97.8)**
Week 8	20/20 (100.0)	23/23 (100.0)	43/43 (100.0)	43/45 (95.6)
Week 12	20/20 (100.0)	22/22 (100.0)	42/42 (100.0)	42/45 (93.3)
Month 6 (optional long-term follow-up)	18/20 (90.0)	15/15 (100.0)	33/35 (94.3)	33/45 (73.3)
Month 9 (optional long-term follow-up)	11/15 (73.3)	8/9 (88.9)	19/24 (79.2)	19/45 (42.2)
Month 12 (optional long-term follow-up)	5/7 (71.4)	6/7 (85.7)	11/14 (78.6)	11/45 (24.4)

[a] Week 3 missing for one participant

2. Numerical rating scale (NRS) scores

In addition to the primary outcome measure in which participants rated their average breathlessness score over the past 24 hours, participants rated the following measures on a NRS score at days 2, 4 and 7, and weeks 2, 3, 4, 8 and 12.

- *Worst* intensity of breathlessness over previous 24 hours
- Distress and unpleasantness due to breathlessness ("How unpleasant has your breathlessness been *on average* over the past 24 hours?" and "How much distress has your breathlessness caused you *on average* over the past 24 hours?")
- Pain experienced over the last 24 hours ("How much pain have you had on average over the past 24 hours")

The summary scores for these outcomes by randomised group and time point are presented in Table 2, and the adjusted means displayed graphically in Figures 1 to 5. These outcomes were analysed via 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, and a time-by-trial arm interaction were included as fixed effects with participant and site as random effect. The adjusted difference in predicted mean scores between the two groups at week 4 was extracted from the model, with a 95% confidence interval and p-value, and are presented in Table 2.

Table 2: Raw NRS summary scores for breathlessness by randomised group and time point

NRS [0 (best) – 10 (worst)] Mean (SD)	**Time point**	**Morphine (n=21)**	**Placebo (n=24)**	**Total (n=45)**	**Adjusted mean difference at week 4 (95% CI)**
How bad has your breathlessness felt on average over the past 24 hours?	Baseline	5.8 (2.0)	5.0 (1.9)	5.3 (1.9)	0.26 (-0.86-1.37) p=0.65
	Day 2	4.7 (2.1)	4.7 (1.6)	4.7 (1.8)	
	Day 4	4.4 (2.1)	4.5 (1.7)	4.5 (1.9)	
	Day 7	4.6 (2.5)	4.7 (1.7)	4.6 (2.1)	
	Week 2	4.8 (2.4)	4.7 (2.0)	4.8 (2.1)	
	Week 3	4.7 (2.4)	4.0 (2.2)	4.3 (2.3)	
	Week 4	5.3 (2.3)	4.6 (2.4)	4.9 (2.4)	
	Week 8	4.9 (2.4)	4.9 (2.1)	4.9 (2.2)	
	Week 12	4.6 (2.5)	5.0 (2.2)	4.8 (2.4)	
	Month 6	5.2 (1.4)	4.6 (2.4)	4.9 (1.9)	
	Month 9	5.4 (1.9)	4.4 (2.4)	4.9 (2.1)	
	Month 12	5.4 (1.8)	4.8 (1.5)	5.1 (1.6)	
How bad has your breathlessness felt at its worst over the past 24 hours?	Baseline	7.2 (2.4)	6.2 (1.9)	6.7 (2.2)	0.15 (-1.13-1.44) p=0.82
	Day 2	5.2 (2.1)	5.2 (2.2)	5.2 (2.1)	
	Day 4	4.5 (2.5)	5.1 (2.5)	4.8 (2.5)	
	Day 7	5.2 (2.8)	5.3 (2.3)	5.3 (2.5)	
	Week 2	5.3 (2.5)	5.1 (2.0)	5.2 (2.2)	
	Week 3	5.0 (2.3)	4.4 (2.5)	4.7 (2.4)	
	Week 4	5.9 (2.5)	5.3 (2.6)	5.6 (2.5)	
	Week 8	6.0 (2.8)	5.3 (2.5)	5.6 (2.6)	
	Week 12	5.1 (2.8)	5.5 (2.0)	5.3 (2.4)	
How unpleasant has your breathlessness been on average over the past 24 hours?	Baseline	5.6 (2.4)	4.5 (2.0)	5.0 (2.2)	-0.15 (-1.48-1.17) p=0.82
	Day 2	4.3 (2.2)	4.0 (1.8)	4.1 (2.0)	
	Day 4	4.0 (2.2)	3.8 (2.1)	3.9 (2.1)	
	Day 7	4.4 (2.8)	3.8 (2.1)	4.1 (2.5)	
	Week 2	4.3 (2.7)	4.4 (2.2)	4.4 (2.4)	
	Week 3	3.8 (2.1)	2.9 (2.2)	3.3 (2.2)	
	Week 4	4.7 (2.8)	4.3 (2.1)	4.4 (2.4)	
	Week 8	4.3 (2.6)	4.1 (2.5)	4.2 (2.6)	

NRS [0 (best) – 10 (worst)] Mean (SD)	**Time point**	**Morphine (n=21)**	**Placebo (n=24)**	**Total (n=45)**	**Adjusted mean difference at week 4 (95% CI)**
	Week 12	4.3 (3.0)	4.3 (2.6)	4.3 (2.7)	
How much distress has your breathlessness caused you on average over the past 24 hours?	Baseline	5.7 (2.4)	4.1 (2.3)	4.8 (2.5)	-0.55 (-1.99-0.88) p=0.45
	Day 2	3.3 (2.5)	3.3 (2.1)	3.3 (2.2)	
	Day 4	2.7 (2.5)	3.1 (2.7)	2.9 (2.6)	
	Day 7	3.5 (3.0)	3.3 (2.3)	3.4 (2.6)	
	Week 2	3.8 (3.2)	3.1 (2.6)	3.4 (2.9)	
	Week 3	3.3 (2.7)	2.8 (2.4)	3.0 (2.5)	
	Week 4	4.2 (3.3)	3.8 (2.6)	4.0 (2.9)	
	Week 8	4.2 (3.1)	3.6 (2.6)	3.8 (2.8)	
	Week 12	3.8 (2.9)	4.0 (2.4)	3.9 (2.6)	
How much pain have you had on average over the past 24 hours?	Baseline	1.9 (3.1)	1.2 (2.1)	1.5 (2.6)	-0.05 (-1.29-1.20) p=0.94
	Day 2	1.3 (2.4)	1.3 (2.0)	1.3 (2.1)	
	Day 4	1.3 (2.5)	0.9 (1.7)	1.0 (2.1)	
	Day 7	0.8 (1.9)	0.7 (1.6)	0.8 (1.7)	
	Week 2	1.3 (2.5)	0.8 (1.4)	1.0 (2.0)	
	Week 3	0.9 (1.9)	1.0 (1.6)	0.9 (1.7)	
	Week 4	1.5 (2.8)	1.1 (1.9)	1.3 (2.3)	
	Week 8	1.8 (3.3)	1.8 (3.0)	1.8 (3.1)	
	Week 12	2.0 (3.3)	0.9 (2.0)	1.4 (2.8)	

Figure 1: Mean average breathlessness by randomised group and time point as measured on a numerical rating scale from 0 (no breathlessness) to 10 (worst imaginable breathlessness) adjusted for baseline NRS

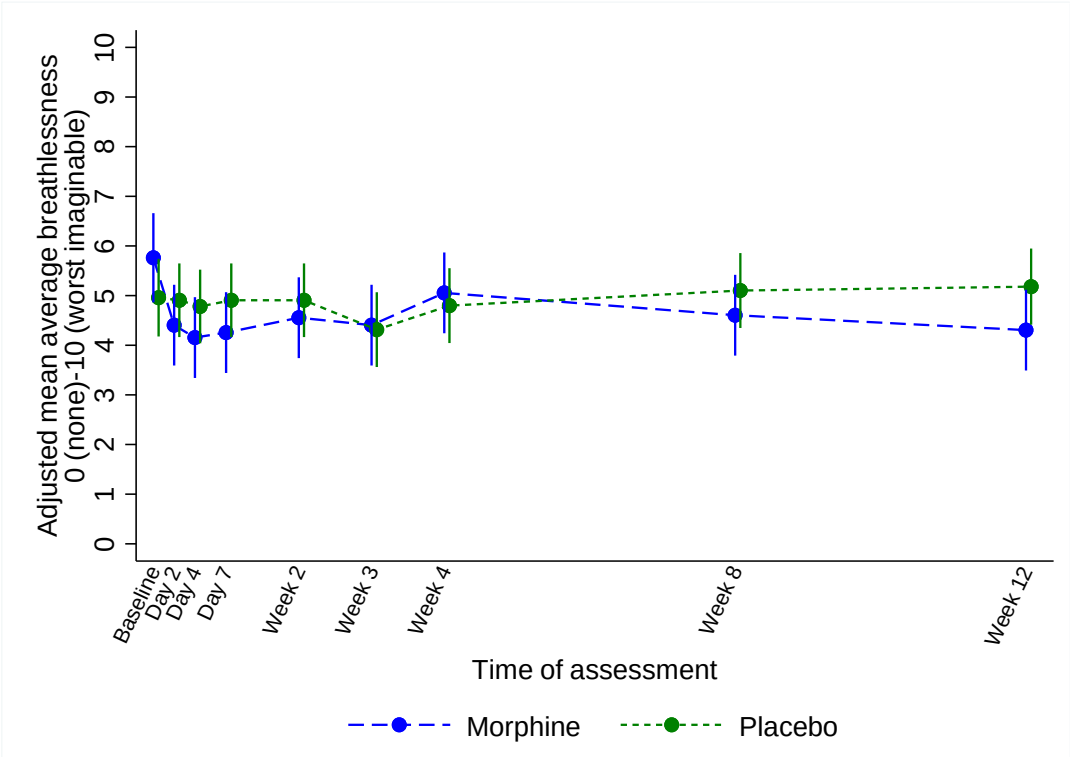


Figure 2: Mean average breathlessness at its worst by randomised group and time point as measured on a numerical rating scale from 0 (no breathlessness) to 10 (worst imaginable breathlessness) adjusted for baseline NRS

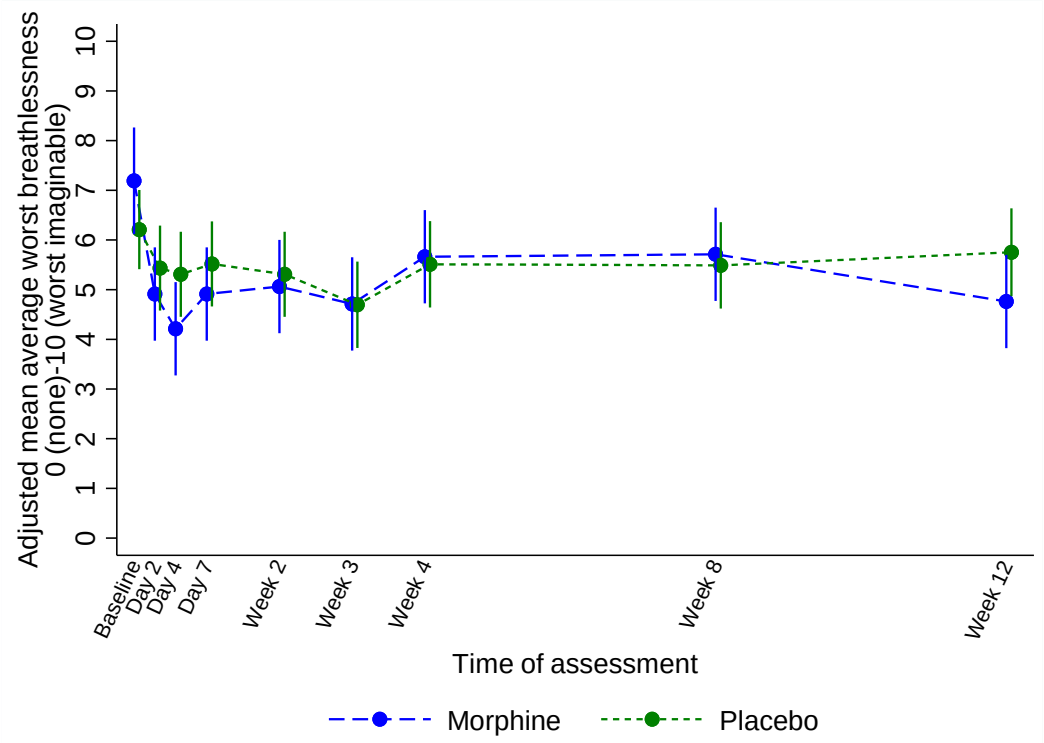


Figure 3: Mean average unpleasantness of breathlessness by randomised group and time point as measured on a numerical rating scale from 0 (not at all) to 10 (worst unpleasantness imaginable) adjusted for baseline NRS

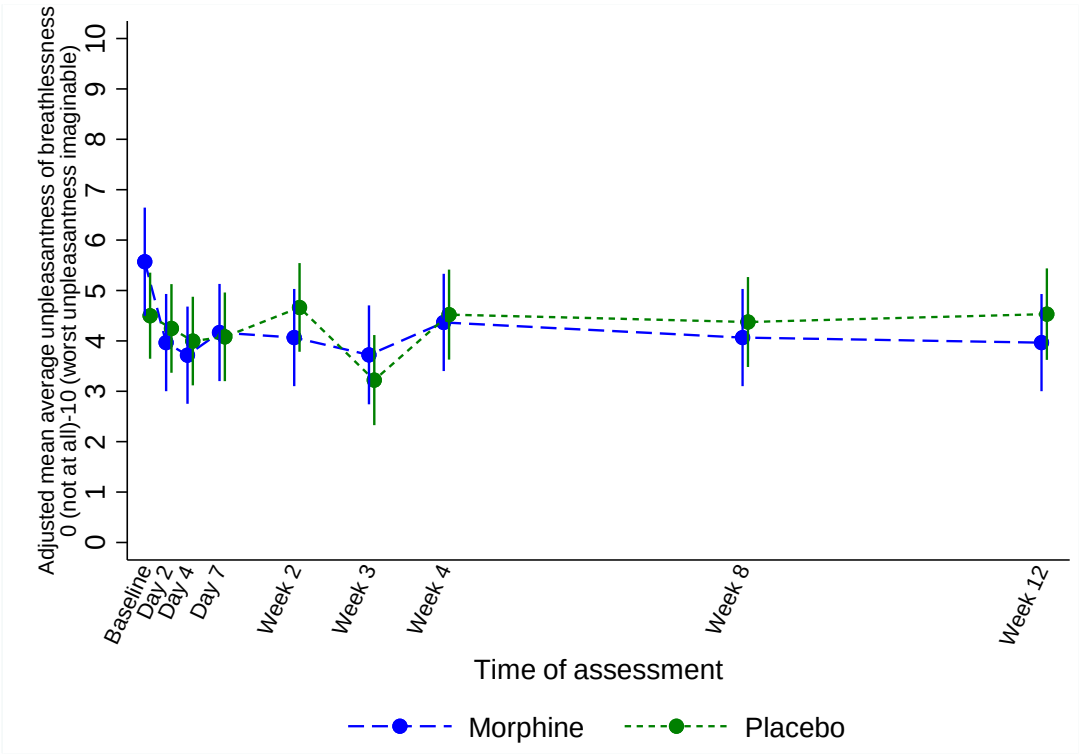


Figure 4: Mean average distress caused by breathlessness by randomised group and time point as measured on a numerical rating scale from 0 (none) to 10 (worst distress imaginable) adjusted for baseline NRS

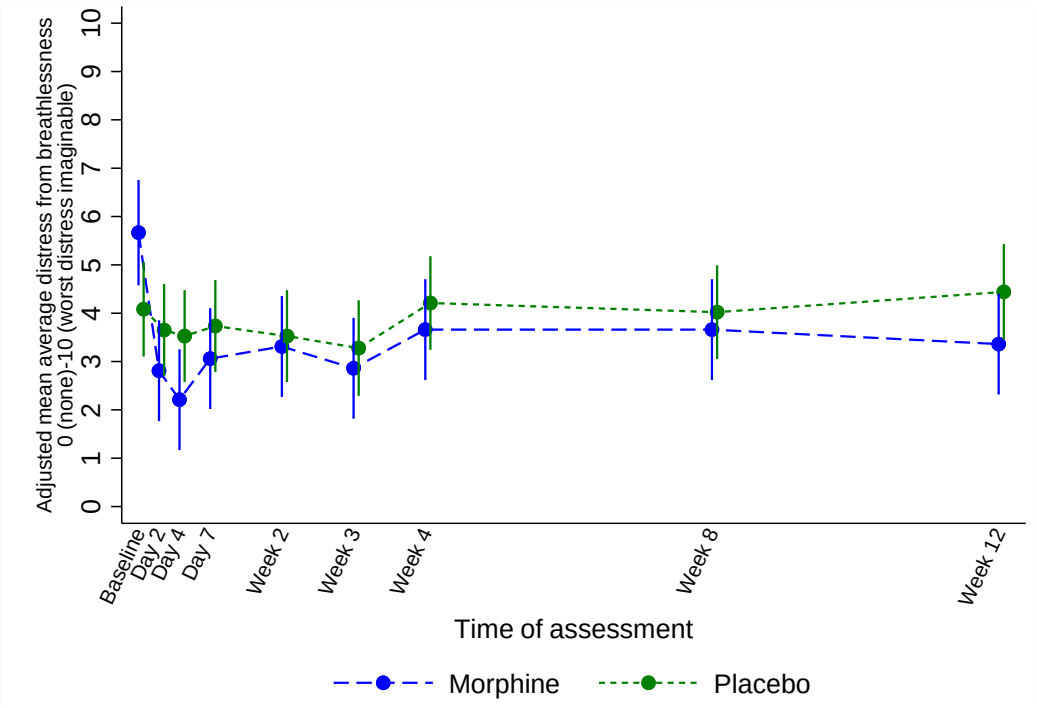
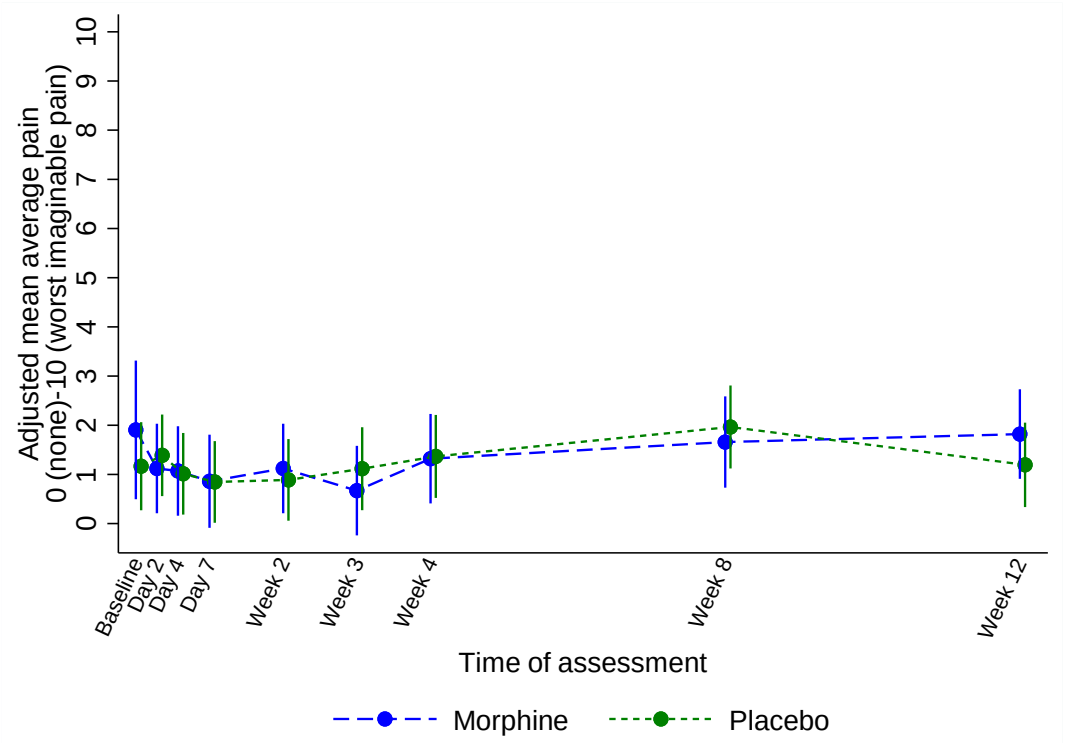


Figure 5: Mean average pain by randomised group and time point as measured on a numerical rating scale from 0 (none) to 10 (worst imaginable pain) adjusted for baseline NRS



3. Clinical assessments at week 4

Clinical assessments were undertaken, and NYHA class recorded, at baseline and at 4 weeks post-randomisation. These data from baseline are provided in the uploaded full data set, and the data from the 4 week time point are provided in Table 3.

Table 3. Clinical assessments and NYHA class at week 4 by randomised group

Characteristic	Morphine (n=21)	Placebo (n=24)	Total (n=45)
NYHA Class			
II	1 (4.8)	1 (4.2)	2 (4.4)
III	18 (85.7)	21 (87.5)	39 (86.7)
IV	1 (4.8)	0 (0.0)	1 (2.2)
Missing	1 (4.8)	2 (8.3)	3 (6.7)
Resting pulse rate (per minute) (radial)	69.5 (11.8)	72.1 (9.6)	70.9 (10.6)
Resting systolic blood pressure, mmHg	109.4 (16.4)	111.5 (19.3)	110.5 (17.8)
Resting diastolic blood pressure, mmHg	62.9 (9.0)	65.4 (12.0)	64.2 (10.6)
Resting respiratory rate (per minute)	16.6 (6.0)	15.3 (3.4)	15.9 (4.8)
Pulse Oximetry, %	96.3 (2.1)	97.0 (2.0)	96.7 (2.0)
NTproBNP[c], pg/mL	3050.7 (2909.3)	3712.1 (2715.0)	3393.6 (2775.9)

[a] Continuous data is presented as mean (SD) and categorical data as n (%);

[b] NTproBNP conducted by certain sites only

4. EQ-5D-5L, and health service use

Participants were asked about their health service use during the previous 4 weeks at baseline, and weeks 4, 8 and 12. The summary scores for these outcomes by randomised group and time point are presented in Table 4 and Table 5. No further analysis was undertaken on these data.

Table 4. EQ-5D-5L, and health service use during previous 4 weeks, at baseline and week 4 by randomised group

EQ-5D-5L, and health service use during previous 4 weeks	Morphine	Placebo	Total
Baseline	**N=21**	**N=24**	**N=45**
EQ-5D-5L index value, Mean (SD)	0.55 (0.19)	0.64 (0.15)	0.60 (0.17)
Median (min, max)	0.56 (0.04, 0.81)	0.66 (0.22, 0.81)	0.64 (0.04, 0.81)
EQ-5D-5L VAS, Mean (SD)	51.7 (18.1)	55.1 (13.7)	53.5 (15.8)
Median (min, max)	50 (5, 85)	54 (30, 90)	50 (5, 90)
Overnight stays in hospital, n (%)	0 (0.0)	2 (8.3)	2 (4.4)
Total number of nights, Mean (SD)	-	5.0 (5.7)	5.0 (5.7)
Median (min, max)		5 (1, 9)	5 (1, 9)
Outpatient appointment, n (%)	12 (57.1)	14 (58.3)	26 (57.8)
Total number of visits, Mean (SD)	1.6 (0.9)	1.6 (1.2)	1.6 (1.0)
Median (min, max)	1 (1, 3)	1 (1, 5)	1 (1, 5)
Contact with GP, n (%)	12 (57.1)	7 (29.2)	19 (42.2)
Total number of contacts, Mean (SD)	1.1 (0.3)	1.1 (0.4)	1.1 (0.3)
Median (min, max)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Number at surgery, Mean (SD)	1.0 (0.4)	1.1 (0.4)	1.1 (0.4)

EQ-5D-5L, and health service use during previous 4 weeks	**Morphine**	**Placebo**	**Total**
Median (min, max)	1 (0, 2)	1 (1, 2)	1 (0, 2)
Number at home, Mean (SD)	0.1 (0.3)	0.0 (0.0)	0.05 (0.2)
Median (min, max)	0 (0, 1)	0 (0, 0)	0 (0, 1)
Number via telephone, Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median (min, max)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Treatment at A&E department, n (%)	0 (0.0)	3 (12.5)	3 (6.7)
Total number of visits, Mean (SD)	-	1.0 (0.0)	1.0 (0.0)
Median (min, max)		1 (1, 1)	1 (1, 1)
Contact with a nurse, n (%)	10 (47.6)	11 (45.8)	21 (46.7)
Total number of contacts, Mean (SD)	1.7 (0.9)	2.1 (1.2)	1.9 (1.1)
Median (min, max)	1 (1, 3)	2 (1, 4)	1 (1, 4)
Number at surgery, Mean (SD)	1.0 (1.1)	1.1 (1.1)	1.0 (1.1)
Median (min, max)	1 (0, 3)	1 (0, 4)	1 (0, 4)
Number at home, Mean (SD)	0.3 (0.5)	0.9 (1.2)	0.6 (1.0)
Median (min, max)	0 (0, 1)	1 (0, 4)	0 (0, 4)
Number via telephone, Mean (SD)	0.4 (1.0)	0.1 (0.3)	0.2 (0.7)
Median (min, max)	0 (0, 3)	0 (0, 1)	0 (0, 3)
Week 4	**N=20**	**N=24**	**N=44**
EQ-5D-5L index value, Mean (SD)	0.64 (0.22)	0.64 (0.17)	0.64 (0.19)
Median (min, max)	0.68 (-0.13, 0.91)	0.67 (0.16, 0.88)	0.68 (-0.13, 0.91)
EQ-5D-5L VAS, Mean (SD)	50.2 (20.7)	58.0 (17.8)	54.3 (19.4)
Median (min, max)	50 (20, 90)	60 (20, 85)	55 (20, 90)
Overnight stays in hospital, n (%)	3 (15.0)	2 (8.3)	5 (11.4)
Total number of nights, Mean (SD)	4.7 (3.5)	5.5 (6.4)	5.0 (4.1)
Median (min, max)	5 (1, 8)	6 (1, 10)	5 (1, 10)
Outpatient appointment, n (%)	6 (30.0)	4 (16.7)	10 (22.7)
Total number of visits, Mean (SD)	1.7 (0.8)	2.0 (1.4)	1.8 (1.0)
Median (min, max)	2 (1, 3)	2 (1, 4)	2 (1, 4)
Contact with GP, n (%)	13 (65.0)	10 (41.7)	23 (52.3)
Total number of contacts, Mean (SD)	1.3 (0.6)	1.1 (0.3)	1.2 (0.5)
Median (min, max)	1 (1, 3)	1 (1, 2)	1 (1, 3)
Number at surgery, Mean (SD)	0.9 (0.6)	1.0 (0.0)	1.0 (0.5)
Median (min, max)	1 (0, 2)	1 (1, 1)	1 (0, 2)
Number at home, Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median (min, max)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Number via telephone, Mean (SD)	0.4 (0.7)	0.1 (0.3)	0.3 (0.5)
Median (min, max)	0 (0, 2)	0 (0, 1)	0 (0, 2)
Treatment at A&E department, n (%)	3 (15.0)	3 (12.5)	6 (13.6)
Total number of visits, Mean (SD)	1.3 (0.6)	1.0 (0.0)	1.2 (0.4)
Median (min, max)	1 (1, 2)	1 (1, 1)	1 (1, 2)
Contact with a nurse, n (%)	7 (35.0)	10 (41.7)	17 (38.6)
Total number of contacts, Mean (SD)	2.3 (2.0)	1.8 (1.1)	2.0 (1.5)
Median (min, max)	1 (1, 6)	1 (1, 4)	1 (1, 6)
Number at surgery, Mean (SD)	1.1 (1.5)	1.3 (1.1)	1.2 (1.2)
Median (min, max)	1 (0, 4)	1 (0, 3)	1 (0, 4)
Number at home, Mean (SD)	1.1 (2.2)	0.4 (1.3)	0.7 (1.7)
Median (min, max)	0 (0, 6)	0 (0, 4)	0 (0, 6)
Number via telephone, Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Median (min, max)	0 (0, 0)	0 (0, 0)	0 (0, 0)

Table 5. EQ-5D-5L, and health service use during previous 4 weeks, at weeks 8 and 12 by randomised group

EQ-5D-5L, and health service use during previous 4 weeks	Morphine	Placebo	Total
Week 8	**N=20**	**N=23**	**N=43**
EQ-5D-5L index value, Mean (SD)	0.68 (0.20)	0.58 (0.34)	0.63 (0.29)
Median (min, max)	0.72 (0.24, 1.00)	0.66 (-0.51, 1.00)	0.68 (-0.51, 1.00)
EQ-5D-5L VAS, Mean (SD)	56.5 (20.4)	54.3 (21.0)	55.3 (20.5)
Median (min, max)	52.5 (10, 95)	60 (0, 90)	55 (0, 95)
Overnight stays in hospital, n (%)	1 (5.0)	5 (21.7)	6 (14.0)
Total number of nights, Mean (SD)	11.0 (-)	10.0 (10.3)	10.2 (9.2)
Median (min, max)	11 (11, 11)	7 (1, 26)	9 (1, 26)
Outpatient appointment, n (%)	5 (25.0)	7 (30.4)	12 (27.9)
Total number of visits, Mean (SD)	1.2 (0.4)	1.9 (1.1)	1.6 (0.9)
Median (min, max)	1 (1, 2)	2 (1, 4)	1 (1, 4)
Contact with GP, n (%)	8 (40.0)	8 (34.8)	16 (37.2)
Total number of contacts, Mean (SD)	1.8 (0.9)	1.4 (0.7)	1.6 (0.8)
Median (min, max)	1.5 (1, 3)	1 (1, 3)	1 (1, 3)
Number at surgery, Mean (SD)	1.3 (0.7)	1.3 (0.9)	1.3 (0.8)
Median (min, max)	1 (0, 2)	1 (0, 3)	1 (0, 3)
Number at home, Mean (SD)	0.0 (0.0)	0.1 (0.4)	0.1 (0.3)
Median (min, max)	0 (0, 0)	0 (0, 1)	0 (0, 1)
Number via telephone, Mean (SD)	0.5 (1.1)	0.0 (0.0)	0.3 (0.8)
Median (min, max)	0 (0, 3)	0 (0, 0)	0 (0, 3)
Treatment at A&E department, n (%)	1 (5.0)	3 (13.0)	4 (9.3)
Total number of visits, Mean (SD)	1.0 (-)	1.0 (0.0)	1.0 (0.0)
Median (min, max)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Contact with a nurse, n (%)	6 (30.0)	7 (30.4)	13 (30.2)
Total number of contacts, Mean (SD)	3.2 (1.2)	1.3 (0.5)	2.2 (1.3)
Median (min, max)	3 (2, 5)	1 (1, 2)	2 (1, 5)
Number at surgery, Mean (SD)	1.7 (0.8)	0.9 (0.7)	1.2 (0.8)
Median (min, max)	1.5 (1, 3)	1 (0, 2)	1 (0, 3)
Number at home, Mean (SD)	0.8 (1.0)	0.3 (0.5)	0.6 (0.8)
Median (min, max)	0.5 (0, 2)	0 (0, 1)	0 (0, 2)
Number via telephone, Mean (SD)	0.7 (1.0)	0.2 (0.4)	0.4 (0.8)
Median (min, max)	0 (0, 2)	0 (0, 1)	0 (0, 2)
Week 12	**N=20**	**N=22**	**N=42**
EQ-5D-5L index value, Mean (SD)	0.58 (0.21)	0.66 (0.17)	0.62 (0.19)
Median (min, max)	0.63 (0.04, 0.88)	0.67 (0.08, 0.84)	0.66 (0.04, 0.88)
EQ-5D-5L VAS, Mean (SD)	55.9 (18.6)	59.8 (15.6)	57.9 (17.0)
Median (min, max)	50 (10, 92)	60 (25, 90)	60 (10, 92)
Overnight stays in hospital, n (%)	3 (15.0)	3 (13.6)	6 (14.3)
Total number of nights, Mean (SD)	12.0 (6.1)	4.0 (3.0)	8.0 (6.1)
Median (min, max)	15 (5, 16)	4 (1, 7)	6 (1, 16)
Outpatient appointment, n (%)	12 (60.0)	6 (27.3)	18 (42.9)
Total number of visits, Mean (SD)	1.6 (1.1)	1.2 (0.4)	1.4 (0.9)
Median (min, max)	1 (1, 4)	1 (1, 2)	1 (1, 4)
Contact with GP, n (%)	14 (70.0)	6 (27.3)	20 (47.6)
Total number of contacts, Mean (SD)	1.4 (0.9)	1.7 (0.5)	1.5 (0.9)
Median (min, max)	1 (1, 4)	2 (1, 2)	1 (1, 4)
Number at surgery, Mean (SD)	1.1 (0.8)	1.5 (0.5)	1.3 (0.7)
Median (min, max)	1 (0, 3)	1.5 (1, 2)	1 (0, 3)
Number at home, Mean (SD)	0.1 (0.3)	0.0 (0.0)	0.1 (0.2)

EQ-5D-5L, and health service use during previous 4 weeks	Morphine	Placebo	Total
Median (min, max)	0 (0, 1)	0 (0, 0)	0 (0, 1)
Number via telephone, Mean (SD) Median (min, max)	0.4 (0.7) 0 (0, 2)	0.2 (0.4) 0 (0, 1)	0.3 (0.6) 0 (0, 2)
Treatment at A&E department, n (%)	4 (20.0)	4 (18.2)	8 (19.1)
Total number of visits, Mean (SD) Median (min, max)	1.0 (0.0) 1 (1, 1)	1.0 (0.0) 1 (1, 1)	1.0 (0.0) 1 (1, 1)
Contact with a nurse, n (%)	5 (25.0)	9 (40.9)	14 (33.3)
Total number of contacts, Mean (SD) Median (min, max)	1.8 (0.8) 2.0 (1, 3)	2.1 (2.3) 1.0 (1, 8)	2.0 (1.9) 1 (1, 8)
Number at surgery, Mean (SD) Median (min, max)	0.8 (0.4) 1 (0, 1)	0.8 (0.7) 1 (0, 2)	0.8 (0.6) 1 (0, 2)
Number at home, Mean (SD) Median (min, max)	0.8 (1.0) 0.5 (0, 2)	1.1 (2.6) 0 (0, 8)	1.0 (2.2) 0 (0, 8)
Number via telephone, Mean (SD) Median (min, max)	0.0 (0.0) 0 (0, 0)	0.2 (0.7) 0 (0, 2)	0.2 (0.6) 0 (0, 2)

5. Other outcomes

Other secondary outcomes are summarised in Table 6 by randomised group and time point. The median AKPS was 70 for both groups across all the time points, indicating that the population recruited were largely able to care for themselves and to carry on normal activities of daily living; this continued throughout the trial. Neither group was excessively sleepy or drowsy at baseline or week 4, and there were no between group differences in quality of life (KCCQ), or cognition (MOCA) at any time point. The randomised participants tended to walk just under 2500 steps a day at baseline. At week 4, there was a raw mean difference of 1113 steps per day favouring the placebo group but this measure had a large proportion of missing data. There was no evidence of desaturation during the 6MWT.

Table 6. Other secondary outcome scores by randomised group and time point

Australia - Modified Karnofsky Performance Status, n (%) [10 (comatose) -100 (normal)] N, Median (IQR)	**Morphine (n=21)**	**Placebo (n=24)**	**Total (n=45)**	**Mean difference at W4[a] (95% CI)**
Baseline	21, 70 (60, 80)	24, 70 (60, 70)	45, 70 (60, 70)	0.4 (-4.9, 5.7)
Week 4	20, 70 (60, 75)	22, 70 (70, 70)	42, 70 (70, 70)	
Week 12	22, 70 (60, 80)	20, 70 (60, 80)	42, 70 (60, 80)	
Cardiomyopathy Questionnaire (Kansas City) [1 (extremely limited) – 100 (not limited)] N, Mean (SD)				
Baseline	21, 36.6 (14.7)	24, 40.2 (11.9)	45, 38.5 (13.2)	-2.7 (-9.7, 4.3).
Week 4	20, 37.2 (16.0)	22, 44.1 (12.9)	42, 40.8 (14.7)	
Week 12	20, 42.2 (22.0)	22, 42.3 (17.7)	42, 42.2 (19.6)	
Epworth Sleepiness Scale [0-24; higher score = greater sleepiness] N, Mean (SD)				
Baseline	21, 9.6 (4.1)	24, 9.5 (4.8)	45, 9.6 (4.5)	1.3 (-1.7, 4.3)
Week 4	20, 10.6 (5.2)	22, 9.4 (4.3)	42, 10.0 (4.8)	
Karolinska Sleepiness Scale [1=very alert - 9=very sleepy] N, Mean (SD)				

Australia - Modified Karnofsky Performance Status, n (%) [10 (comatose) -100 (normal)] N, Median (IQR)	**Morphine (n=21)**	**Placebo (n=24)**	**Total (n=45)**	**Mean difference at W4[a] (95% CI)**
Baseline	21, 3.0 (1.5)	24, 3.3 (1.6)	45, 3.2 (1.5)	0.3 (-0.7, 1.3)
Day 2	20, 3.8 (1.7)	24, 3.4 (1.2)	44, 3.6 (1.4)	
Day 4	20, 3.8 (1.9)	24, 3.8 (1.9)	44, 3.8 (1.8)	
Day 7	20, 4.6 (2.5)	24, 3.5 (1.7)	44, 4.0 (2.2)	
Week 2	20, 3.2 (1.4)	24, 3.5 (1.9)	44, 3.4 (1.7)	
Week 3	20, 3.1 (1.4)	23, 3.2 (1.8)	43, 3.1 (1.6)	
Week 4	20, 3.3 (1.5)	23, 3.0 (1.6)	43, 3.2 (1.5)	
Montreal Cognitive Assessment [0-30 (0-16 telephone version); lower scores = greater cognitive impairment] N, Mean (SD)				
Baseline	21, 25.1 (1.9)	24, 25.4 (3.1)	45, 25.2 (2.6)	-0.6 (-2.4, 1.2)
Day 4 (telephone version)	19, 14.1 (1.3)	21, 14.3 (1.9)	40, 14.2 (1.6)	
Day 7 (telephone version)	18, 14.2 (1.1)	23, 14.7 (1.3)	41, 14.5 (1.2)	
Week 4	20, 26.2 (3.3)	21, 26.8 (2.3)	41, 26.5 (2.8)	
Six minute walk test N, Mean (SD) *Distance walked (metres)*				
Baseline	18, 177.1 (98.8)	24, 195.0 (101.5)	42, 187.3 (99.5)	-7.4 (-96.8, 82.0)
Week 4	13, 184.2 (87.7)	17, 191.5 (137.1)	30, 188.3 (116.4)	
O2 saturation at rest (%)				
Baseline	18, 97.2 (2.1)	24, 96.8 (1.7)	42, 97.0 (1.9)	-0.4 (-1.9, 1.1)
Week 4	13, 96.5 (1.7)	16, 96.9 (2.1)	29, 96.7 (1.9)	
O2 saturation at end (%)				
Baseline	18, 97.4 (1.9)	24, 97.2 (2.1)	42, 97.3 (2.0)	-0.1 (-1.4, 1.1)
Week 4	13, 97.1 (1.6)	16, 97.2 (1.7)	29, 97.1 (1.6)	
activPAL™ Average steps per day N, Mean (SD)				
Baseline	20, 2384.5 (1661.0)	22, 2402.4 (2180.8)	42, 2393.9 (1927.3)	-1113.1 (-2280.9, 54.8)
Week 4	19, 1812.9 (1425.9)	17, 2926.0 (2002.2)	36, 2338.5 (1787.7)	

[a] unadjusted except for Cardiomyopathy Questionnaire (Kansas City), which was adjusted as described for the primary NRS breathlessness outcome

6. Study drug use

All but one participant (in the Morphine group) took at least one dose of the study drug. The first doses were reported as being taken a median of 1 day after randomisation in the Morphine group (range 0 to 7), and 0.5 days in the Placebo group (range 0 to 5). Most first doses were taken in the afternoon (Morphine, n=18, 90.0%; Placebo, n=21, 87.5%).

Study drug was dispensed in three instalments; at baseline, and at the 4 and 8 week assessment time points. Each time, 56 morphine/placebo capsules were dispensed and 56 docusate/placebo capsules, one of each to be taken every morning and every night for the following four weeks. Participants were asked to return their old bottles, leaving any unused pills inside. From these data we are able to estimate how many pills were taken (Table 7). The

cases where pills were dispensed but the bottles not returned were managed in two ways, assuming: i) that all the pills in that batch were taken; and ii) that none were.

In addition to the three participants that withdrew fully from the trial (i.e. from treatment **and** follow-up), 16 participants (11 (52.4%) in the morphine group, and 5 (20.8%) in the placebo group) formally withdrew from treatment up to the 12 week assessment time point. These 16 participants agreed to continue to provide outcome data, but ceased to take the study drugs.

Table 7: Study drug use summary by randomised group

	Morphine/Placebo		**Docusate/Placebo**	
	Morphine (n=21)	**Placebo (n=24)**	**Morphine (n=21)**	**Placebo (n=24)**
Dispensed at, n (%):				
Baseline	21 (100.0)	24 (100.0)	21 (100.0)	24 (100.0)
Week 4	13 (61.9)	22 (91.7)	13 (61.9)	22 (91.7)
Week 8	9 (42.9)	17 (70.8)	9 (42.9)	17 (70.8)
Total number dispensed				
Mean (SD)	114.7 (51.6)	147.0 (36.2)	114.7 (51.6)	147.0 (36.2)
Median (min, max)	112 (56, 168)	168 (56, 168)	112 (56, 168)	168 (56, 168)
Assume NO pills unused if return pill count missing				
Total number returned				
Mean (SD)	29.8 (24.6)	17.9 (22.1)	41.8 (39.5)	32.1 (41.1)
Median (min, max)	37 (0, 91)	6 (0, 64)	39 (0, 168)	12.5 (0, 168)
Percentage taken of drugs taken that were dispensed				
Mean (SD)	59.6 (36.3)	82.6 (26.4)	52.4 (36.3)	73.2 (34.1)
Median (min, max)	67.0 (0, 100)	96.4 (5.4, 100)	44.0 (0, 100)	90.9 (0, 100)
Total used out of number intended (n=168)				
Mean (SD)	50.5 (42.0)	76.9 (31.3)	43.4 (40.4)	68.4 (36.2)
Median (min, max)	44.6 (0, 100)	96.1 (1.8, 100)	33.3 (0, 100)	86.6 (0, 100)
Assume ALL pills unused if return pill count missing				
Total number returned				
Mean (SD)	48.4 (30.6)	38.9 (42.1)	55.1 (41.0)	53.1 (51.8)
Median (min, max)	46 (0, 118)	32.5 (0, 168)	46 (0, 168)	43.5 (0, 168)
Percentage taken of drugs taken that were dispensed				
Mean (SD)	48.5 (30.1)	69.4 (32.8)	44.5 (31.4)	59.3 (38.0)
Median (min, max)	35.7 (0, 100)	79.5 (0, 100)	33.3 (0, 100)	69.3 (0, 100)
Total used out of number intended (n=168)				
Mean (SD)	39.4 (33.8)	64.4 (34.8)	35.5 (33.9)	55.9 (39.1)
Median (min, max)	33.3 (0, 100)	69.6 (0, 100)	29.8 (0, 100)	64.9 (0, 100)

7. Harms

During the course of the study, members of the research team asked participants if they had experienced any adverse events since the previous follow up. In order to reduce the burden of adverse event reporting and given the known potential clinical conditions associated with heart failure and the potential side effects of the IMP, participants were asked specifically about the following events: confusion, constipation, vomiting, nausea, memory impairment and cognitive disturbance. The research team used their clinical judgment to rate any reported event. Confusion, constipation and vomiting were scored on a scale of 0-5 inclusive or ungradable whilst nausea, memory impairment and cognitive disturbance were scored on a scale of 0-3 inclusive or ungradable. Any event scored as 2 or more, was then reported as an adverse event. If the participant experienced any other adverse event other than those listed above, then these were then recorded and an adverse event form completed.

Six (29%) participants in the morphine group and 14 (58%) in the placebo group reported at least one grade 1 harm at baseline; no harms graded 2 or above were reported (Table 8). Up to and including the week 4 time point, 18 (86%) participants in the morphine group and 13 (54%) in the placebo group had reported at least one harm of grade 1 or more post-randomisation, and 10 (48%) and 1 (4.2%), respectively, of grade 2 or more. Harms reported at weeks 8 and 12 are presented in Table 9.

Table 8 Harms by grade, treatment group and time point (up to week 4)

Harm symptom grade	Baseline		Day 2		Day 4		Day 7		Week 2		Week 3		Week 4	
	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo
Confusion														
0	20 (95.2)	22 (91.7)	19 (95.0)	23 (95.8)	19 (95.0)	24 (100)	19 (95.0)	22 (91.7)	18 (90.0)	22 (91.7)	20 (100)	21 (91.3)	18 (90.0)	21 (91.3)
1	1 (4.8)	2 (8.3)	1 (5.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	2 (10.0)	2 (8.3)	0 (0.0)	2 (8.7)	2 (10.0)	2 (8.7)
2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation														
0	18 (85.7)	19 (79.2)	13 (65.0)	22 (91.7)	10 (50.0)	22 (91.7)	7 (35.0)	22 (91.7)	14 (70.0)	22 (91.7)	15 (75.0)	22 (95.7)	14 (70.0)	21 (91.3)
1	3 (14.3)	5 (20.8)	7 (35.0)	2 (8.3)	7 (35.0)	2 (8.3)	9 (45.0)	2 (8.3)	6 (30.0)	2 (8.3)	4 (20.0)	1 (4.3)	6 (30.0)	2 (8.7)
2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting														
0	21 (100)	24 (100)	18 (90.0)	24 (100)	17 (85.0)	24 (100)	16 (80.0)	23 (95.8)	19 (95.0)	24 (100)	18 (90.0)	23 (100)	17 (85.0)	22 (95.7)
1	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	3 (15.0)	0 (0.0)	3 (15.0)	1 (4.2)	1 (5.0)	0 (0.0)	2 (10.0)	0 (0.0)	2 (10.0)	1 (4.3)
2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Nausea														
0	20 (95.2)	23 (95.8)	14 (70.0)	23 (95.8)	12 (60.0)	21 (87.5)	14 (70.0)	21 (87.5)	13 (65.0)	23 (95.8)	16 (80.0)	22 (95.7)	16 (80.0)	18 (78.3)
1	1 (4.8)	1 (4.2)	5 (25.0)	1 (4.2)	7 (35.0)	2 (8.3)	4 (20.0)	3 (12.5)	7 (35.0)	1 (4.2)	3 (15.0)	1 (4.3)	3 (15.0)	5 (21.7)
2+	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)	1 (4.2)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)
Memory impairment														
0	19 (90.5)	18 (75.0)	18 (94.7)	22 (91.7)	19 (95.0)	23 (95.8)	20 (100)	21 (87.5)	19 (95.0)	22 (91.7)	19 (95.0)	21 (91.3)	17 (85.0)	20 (87.0)
1	2 (9.5)	6 (25.0)	1 (5.3)	2 (8.3)	1 (5.0)	1 (4.2)	0 (0.0)	3 (12.5)	1 (5.0)	2 (8.3)	1 (5.0)	2 (8.7)	3 (15.0)	3 (13.0)
2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive disturbance														
0	19 (90.5)	23 (95.8)	20 (100)	23 (95.8)	20 (100)	24 (100)	19 (95.0)	24 (100)	18 (90.0)	23 (95.8)	19 (100)	23 (100)	18 (90.0)	22 (95.7)
1	2 (9.5)	1 (4.2)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (4.2)	0 (0.0)	0 (0.0)	2 (10.0)	1 (4.3)
2+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 9 Harms by grade, treatment group and time point (week 8 to month 12)

Harm symptom grade	Week 8		Week 12		Month 6		Month 9		Month 12	
	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo	Morphine	Placebo
Confusion										
0	16 (80.0)	21 (91.3)	17 (85.0)	19 (86.4)	15 (83.3)	14 (93.3)	11 (100.0)	7 (87.5)	5 (100.0)	6 (100.0)
1	3 (15.0)	1 (4.3)	1 (5.0)	3 (13.6)	2 (11.1)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2+	1 (5.0)	1 (4.3)	2 (10.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Constipation										
0	15 (75.0)	22 (95.7)	15 (75.0)	17 (77.3)	14 (77.8)	12 (80.0)	9 (81.8)	6 (75.0)	3 (60.0)	4 (66.7)
1	5 (25.0)	1 (4.3)	4 (20.0)	5 (22.7)	3 (16.7)	3 (20.0)	2 (18.2)	0 (0.0)	1 (20.0)	2 (33.3)
2+	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	2 (25.0)	1 (20.0)	0 (0.0)
Vomiting										
0	18 (90.0)	23 (100.0)	17 (85.0)	21 (95.5)	17 (94.4)	12 (80.0)	10 (90.9)	8 (100.0)	5 (100.0)	5 (83.3)
1	2 (10.0)	0 (0.0)	2 (10.0)	1 (4.5)	1 (5.6)	3 (20.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (16.7)
2+	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea										
0	16 (80.0)	20 (87.0)	12 (60.0)	20 (90.9)	16 (88.9)	12 (80.0)	10 (90.9)	8 (100.0)	5 (100.0)	5 (83.3)
1	3 (15.0)	1 (4.3)	5 (25.0)	1 (4.5)	2 (11.1)	3 (20.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (16.7)
2+	1 (5.0)	2 (8.7)	3 (15.0)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Memory impairment										
0	17 (85.0)	19 (82.6)	16 (80.0)	18 (85.7)	15 (83.3)	12 (85.7)	10 (90.9)	7 (87.5)	5 (100.0)	6 (100.0)
1	2 (10.0)	2 (8.7)	2 (10.0)	3 (14.3)	2 (11.1)	2 (14.3)	1 (9.1)	1 (12.5)	0 (0.0)	0 (0.0)
2+	1 (5.0)	2 (8.7)	2 (10.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive disturbance										
0	19 (95.0)	22 (95.7)	18 (90.0)	19 (86.4)	18 (100.0)	13 (86.7)	5 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2+	1 (5.0)	1 (4.3)	2 (10.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)