Table S1 Comparison of the original study population (before July 2014) and the final study population (after July 2014) for key clinical and demographic characteristics

		Intention-to-treat – whole population. Baseline characteristics		**Intention-to-treat – mMRC 3 *or* 4. Screening characteristics**	
		Morphine n=145	**Placebo n=139**	**Morphine n=88**	**Placebo n=79**
Age	Mean (SD)	74.0 (9.6)	74.5 (9.1)	75.0 (9.2)	74.0 (9.6)
	Min, max	44.8, 94.1	44.3, 89.4	46.0, 94.1	44.3, 88.8
Gender n (%)	Female	52 (35.9)	52 (37.4)	30 (34.1)	30 (38.0)
Performance status (AKPS)	Mean (SD)	60.8 (11.5)	61.5 (9.5)	60.5 (10.2)	62.0 (9.8)
	Min, max	3, 90	40, 80	40, 80	40, 80
BMI (kg/m^2)	Mean (SD)	25.2 (7.6)	25.9 (7.0)	24.9 (6.8)	26.1 (7.3)
	Min, max	13.0, 66.1	12.3, 47.8	13.0, 48.8	12.3, 47.8
mMRC breathlessness score n (%)	1	18 (14.1)	12 (10.3)		
	2	22 (17.2)	25 (21.6)		
	3	33 (25.8)	33 (28.4)	33 (37.5)	33 (41.8%)
	4	55 (43.0)	46 (39.7)	55 (62.5)	46 (58.2)
Charlson Co-morbidity Index	Mean (SD)	3.3 (2.46)	3.2 (2.5)	2.9 (2.2)	3.4 (2.4)
	Min, max	0, 12	1, 13	0, 12	1, 11
Pulse oximetry SpO_2	Mean (SD)	92.60 (4.17)	92.96 (4.46)	92.8 (3.9)	93.3 (3.6)
	Min, max	77.0, 99.0	72.0, 99.0	80.0, 99.0	79.0, 99.0
End-tidal CO_2	Mean (SD)	27.41 (8.29)	25.53 (6.98)	27.3 (8.7)	23.9 (6.8)
	Min, max	8.5, 53.1	9.9, 45.0	8.5, 53.1	9.9, 42.9
Primary cause for breathlessness n (%)	COPD	82 (56.6)	82 (59.0)	52 (59.1)	47 (59.5)
	Cancer	26 (17.9)	22 (15.8)	13 (14.8)	12 (15.2)
	Cardiac failure	2 (1.4)	2 (1.4)	0 (0.0)	2 (2.5)
	Mixed	18 (12.4)	19 (13.7)	11 (12.5)	10 (12.7)
	Other	17 (11.7)	14 (10.1)	12 (13.6)	8 (10.1)
Oxygen use	Yes n (%)	87 (60.0)	75 (54.0)	56 (63.6)	43 (54.4)
Smoking status n (%)	Never smoked	24 (16.6)	26 (18.7)	16 (18.2)	11 (13.9)
	Ex-smoker	104 (71.7)	95 (68.3)	60 (68.2)	59 (74.7)
	Current smoker	17 (11.7)	16 (11.5)	12 (13.6)	7 (8.9)
	Missing	0 (0.0)	2 (1.4)	0 (0.0)	2 (2.5)

COPD – chronic obstructive pulmonary disease; AKPS – Australia-modified Karnofsky Performance Status

Table S2 Comparison of treatment emergent adverse events (TEAEs) between the whole study population and the original study population (up until July 2014)

		Safety analysis - whole population		Safety analysis - mMRC 3 or 4 at screening	
		Morphine n=142 n (%)	**Placebo n=137 n (%)**	**Morphine n=88 n (%)**	**Placebo n=79 n (%)**
Subjects with at least one special interest treatment emergent adverse event (TEAE)		129 (90·8)	130 (94·9)	78 (89.7)	73 (92.4)
Respiratory	**Any**	**61 (43·0)**	**71 (51·8)**	**36 (41.4)**	**38 (48.1)**
	Bronchospasm	56 (39·4)	65 (47·4)	36 (41.4)	38 (48.1)
	Wheezing	3 (2·1)	4 (2·9)	1 (1.1)	2 (2.5)
Gastrointestinal	**Any**	**108 (76·1)**	**94 (68·6)**	**69 (79.3)**	**55 (69.6)**
	Pain or discomfort	10 (7·0)	5 (3·6)	10 (11.4)	5 (6.4)
	Constipation*	79 (55·6)	59 (43·1)	54 (62.1)	36 (45.6)
	Dry mouth	36 (25·4)	40 (29·2)	23 (26.4)	20 (25.3)
	Nausea	6 (4·2)	4 (2·9)	3 (5·9)	1 (1.3)
	Vomiting	53 (37·3)	32 (23·4)	29 (33.3)	22 (27.8)
Cardiac	**Any**	**23 (16·2)**	**13 (9·5)**	**19 (21.8)**	**10 (12.7)**
	Arrhythmia	22 (15·5)	13 (9·5)	18 (20.7)	10 (12.7)
	Bradycardia	2 (1·4)	0 (0·0)	2 (2.3)	0 (0·0)
	Tachycardia	1 (0·7)	0 (0·0)	1 (1.1)	0 (0·0)
Vascular	**Any**	**20 (14·1)**	**23 (16·8)**	**13 (14.9)**	**13 (16.5)**
	Flushing	7 (4·9)	10 (7·3)	4 (4.6)	5 (6.3)
	Hypertension	13 (9·2)	16 (11·7)	9 (10.3)	9 (11.4)
Renal / urinary tract	**Any**	**14 (9.9)**	**7 (5.1)**	**10 (11.5)**	**3 (3.8)**
	Urinary retention	14 (9.9)	7 (5.1)	10 (11.5)	3 (3.8)
Nervous system	**Any**	**105 (73·9)**	**95 (69·3)**	**63 (72.4)**	**57 (72.2)**
	Dizziness	37 (26·1)	35 (25·5)	23 (26.4)	21 (26.6)
	Headache	29 (20·4)	27 (19·7)	19 (21.8)	12 (15.2)
	Somnolence	85 (59·9)	70 (51·1)	49 (56.3)	41 (51.9)
	Tremor	26 (18·3%)	20 (14·6)	17 (19.5)	11 (13.9)
Psychiatric	**Any**	**56 (39·4)**	**53 (38·7)**	**35 (40.2)**	**27 (34.2)**
	Agitation	37 (26·1)	38 (27·7)	19 (21.8)	18 (22.8)
	Delirium	12 (8·5)	10 (7·3)	11 (12.6)	5 (6.3)
	Mood altered	21 (14·8)	21 (15·3)	15 (17.2)	11 (13.9)
Skin	**Any**	**23 (16·2)**	**16 (11·7)**	**17 (19.5)**	**10 (12.7)**
	Urticaria	23 (16·2)	15 (10·9)	17 (19.5)	10 (12.7)

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Table S3 Comparison of breathlessness scores (mean) days 5-7 of a randomised controlled trial of regular, low dose, sustained release morphine and placebo on a 0-100mm visual analogue scale (VAS).

		Morphine n=116*		Placebo n=119*	
		Value	Change from baseline	Value	Change from baseline
		Mean (standard deviation (SD))			
Breathlessness scores	*Now (intensity)*	34.5 (21.8)	-5.7 (18.8)	36.4 (22.0)	-7.4 (20.5)
	Average (intensity)	36.6 (20.0)	-5.5 (16.8)	39.6 (19.1)	-3.4 (19.1)
	Best (intensity)	25.9 (19.1)	-2.1 (18.4)	28.4 (20.5)	-0/9 (19.6)
	Worst (intensity)	48.7 (25.9)	-9.6 (24.3)	54.6 (22.3)	-5.9 (23.3
	Unpleasantness now (affective)	33.7 (22.6)	-2.6 (18.3)	36.5 (23.0)	-1.2 (20.7)

* the differences account for withdrawal before the final day of the study

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Table S4 – Detailed reasons for screening failure. 1141 patients with reasons for not proceeding including general reasons and those that related directly to specific eligibility criteria.

General Reasons	Frequency	Percentage
Deceased	27	2.4%
Declined / not interested / did not return contact from research team	224	19.6%
Trial burden	7	0.6%
Too unwell / unstable / terminal phase / deteriorating / unable to swallow tablets / poor prognosis	193	16.9%
Potential participant has issues with opioids	3	0.3%
Consent pending (Interested / awaiting review)	79	6.9%
Problem with location (e.g. Nursing home, Hostel, Hospital, hospice)	16	1.4%
Family issues	6	0.5%
Other	52	4.6%
Not applicable	13	1.1%
Total	620	54.3%

***Not* Meeting Inclusion Criteria**	**Frequency**	**Percentage**
Refractory breathlessness where the underlying cause of the breathlessness had been maximally treated	7	0.6%
Breathlessness of a level 2 or higher on the modified MRC breathlessness scale	49	4.3%
On stable medications over the prior week except routine 'as needed' medications	36	3.2%
Prognosis was at least 2 months in the opinion of the treating clinician	15	1.3%
English-speaking and able to read study questionnaires	28	2.5%
Total	135	11.8%

Meeting Exclusion Criteria	Frequency	Percentage
On regular opioid medications, including codeine preparations at or above the dose being studied in the previous 7 days	316	27.7%
Anaemia for which transfusion was not indicated within one month of baseline evaluation	18	1.6%
Severely restricted performance status with Australian Karnofsky Performance score of <40 at baseline	18	1.6%
Uncontrolled nausea, vomiting and/or gastrointestinal obstruction	4	0.4%
Renal dysfunction with creatinine clearance calculated as less than 25 mls/minute	26	2.3%
Medical history of severe hepatic impairment ...	7	0.6%
Documented previous respiratory failure induced by an opiate medication	13	1.1%
Unable to give informed consent or complete diary entries	34	3.0%
Intolerant to morphine	37	3.2%

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Total	473	41.5%

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