Effect of regular low-dose extended-release morphine on chronic breathlessness in chronic obstructive pulmonary disease: the BEAMS randomized clinical trial

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Key Points

Question: Does regular, low-dose, extended-release (ER) morphine improve worst breathlessness in people with chronic obstructive pulmonary disease (COPD) and severe chronic breathlessness?

Findings: In this randomized clinical trial of 156 participants with COPD and chronic breathlessness, treatment with ER morphine at 8 mg or 16 mg daily compared with placebo for 1 week resulted in a difference in change in the intensity of worst breathlessness on a numerical rating scale of -0.3 and -0.3, respectively. This score ranges from 0 to 10, and neither difference was statistically significant.

Meaning: Extended-release morphine compared with placebo did not significantly improve chronic breathlessness in patients with COPD.

ABSTRACT

Importance: Chronic breathlessness is common in people with chronic obstructive pulmonary disease (COPD). Regular, low-dose, extended-release (ER) morphine may relieve breathlessness, but evidence about its efficacy and dosing is needed.

Objective: To determine the effect of different doses of ER morphine on chronic breathlessness in patients with COPD after 1 week of treatment.

Design, Setting and Participants: Multicenter, randomized double-blind, placebo-controlled, clinical trial at 20 centers in Australia. 160 patients with COPD and chronic breathlessness (defined as a modified Medical Research Council score of 3 to 4) were enrolled between September 1, 2016 and November 20, 2019 and followed up through December 26, 2019.

Interventions: Patients were randomized (1:1:1) to daily, oral ER morphine 8 mg, 16 mg or placebo during week 1. At the start of weeks 2 and 3, patients were randomized (1:1) to daily ER morphine 8 mg or placebo, which was added to the prior week's dose.

Main Outcomes and Measures: The primary outcome was change of *worst breathlessness* on a numerical rating scale (0 to 10) from mean baseline (days -3 to -1) to mean at days 5 to 7 with morphine 8 mg, 16 mg and placebo. The co-primary outcome was change in daily steps (actigraphy) from baseline (day -1) to mean at days 19 to 21.

Results: Among 156 patients randomized (median age, 72 years; 48% women), 138 (88%) patients completed week 1 with ER morphine 8 mg (n=55), 16 mg (n=51), placebo (n=50); week 3: morphine 8 mg (n=39), 16 mg (n=52), 24 mg (n=40), 32 mg (n=12), placebo (n=13). Change in w*orst breathlessness* at 1 week was not significantly different between placebo and morphine 8 mg (mean difference (MD), -0.3; 95% CI, -0.9–0.4) and 16 mg (MD, -0.3; 95%, CI -1.0–0.4). Change in mean daily steps at 3 weeks was not significantly different for morphine 8 mg (MD, -1453; 95% CI -3310–405), 16 mg (MD, -1312; 95% CI -3220–596), 24 mg (MD, -692; 95% CI -2553–1170) or 32 mg (MD, -1924; 95% CI -47699–921) vs placebo.

Conclusions and Relevance: Among patients with COPD and severe chronic breathlessness, daily low-dose, ER morphine did not improve worst breathlessness at 1 week of treatment. These findings do not support the use of these doses of ER morphine to relieve breathlessness.

Trial registration: ClinicalTrials.gov NCT02720822
https://clinicaltrials.gov/ct2/show/NCT02720822

INTRODUCTION

Chronic breathlessness, defined as breathlessness at rest or with low levels of exertion that persists despite optimal treatment for the underlying conditions,[1] affects many people with chronic obstructive pulmonary disease (COPD). It often restricts activities of daily living and results in decreased physical activity and deconditioning, which further worsens breathlessness.[2] Chronic breathlessness is associated with anxiety and depression, reduced health-related quality of life (HrQoL),[3] and increased health service utilization and mortality.[4] Chronic breathlessness is often assessed using the modified Medical Research Council (mMRC) scale.[5]

Opioids may reduce symptoms in people with chronic breathlessness and severe disease.[6,7] Meta-analyses of small, short-term trials suggest beneficial effects of low-dose opioids in patients with chronic breathlessness,[8] including those with COPD.[9] However, a 1-week randomized clinical trial (RCT) demonstrated no statistically significant improvement in breathlessness with oral ER morphine, 20 mg daily vs placebo.[10] Another trial of patients with COPD and chronic breathlessness reported improved disease-specific health status with 4 weeks of low-dose sustained-release oral morphine, and *worst breathlessness* improved in participants with more severe breathlessness (mMRC score of 3 to 4).[11]

The safety of morphine for persistent breathlessness is unclear. Population-based studies of people with COPD have reported increased hospitalizations and mortality with use of morphine,[12] although these effects were not documented in patients with severe, oxygen-dependent COPD.[13] Daily use of low-dose opioids (maximal dose 20 mg morphine/day) has not been associated with serious adverse events (hospitalization or death) in RCTs.[9,10,11,14]

The Breathlessness, Exertion And Morphine Sulfate (BEAMS) trial was designed to evaluate the effect of daily oral ER morphine (8 mg, 16 mg) or placebo on *worst breathlessness* at week 1 compared to baseline. It used a blinded uptitration of morphine to evaluate change in daily steps (actigraphy) from baseline to the end of week 3.

METHODS

Trial Design and Oversight

This trial was a multicenter, placebo-controlled, phase III, double-blind, parallel-group, dose increment, randomized clinical trial of regular, low-dose oral ER morphine for patients with COPD and chronic breathlessness. The study protocol was approved by the Hunter New England Human Research Ethics Committee (HREC) (Reference No. 15/12/16/3.06). Each participating center obtained Research Governance Office approval to recruit patients to this study. Enrolled patients provided written informed consent. The trial was conducted and monitored in accordance with Good Clinical Practice.[15] The study protocol is found in Supplement 1, and has been published.[16] This study is reported in compliance with the Consolidated Standards of Reporting

Trials (CONSORT) statement.[17]All adverse event reports and the trial conduct were reviewed by an independent Data and Safety Monitoring Committee.

Patients and Study Centers

Participants were eligible for inclusion if they met the following criteria: age 18 years or older; physician diagnosis of COPD with postbronchodilator spirometry revealing an forced expiratory volume in one second (FEV_1) / forced vital capacity (FVC) < 0.7;[18] severe chronic breathlessness [1] defined as a mMRC score of 3 to 4 (corresponding to 'I stop for breath after walking about 100 yards or after a few minutes on the level' or 'I am too breathless to leave the house or I am breathless when dressing')[5] despite optimal treatment for underlying cause(s) as confirmed by a respiratory physician; *worst breathlessness* intensity ≥ 3 on a 0–10 numerical rating scale (NRS) in the prior 24 hours before study enrollment; ability to complete the assessments as determined by the study investigator; stable COPD treatment during the previous week, although 'as needed' inhaler medications were permitted.

Exclusion criteria included current use of opioids at any dose for breathlessness or use of opioids at an oral morphine equivalent dose of ≥ 8 mg per day during the previous week; previous adverse reactions to morphine; central hypoventilation syndrome, pregnancy, hepatic or kidney failure or gastrointestinal obstruction. A complete list of inclusion and exclusion criteria is in the study protocol.

The trial was coordinated by the Australian national Palliative Care Clinical Studies Collaborative (PaCCSC) and conducted at 20 oncology, palliative, or respiratory centers in Australia.[16] Participants were also recruited through Lung Foundation Australia and the Primary Health Networks. All participants were referred by their treating clinician to the principal investigator at each participating center.[16]

Randomization and Interventions

Participants were randomized 1:1:1 to daily, oral ER morphine 8 mg, 16 mg, or placebo during week 1. All randomizations were performed at baseline using computer-generated random samples tables and permuted blocks of 6. Each person was provided with a wrist actigraph unit (FitBit^R) and charger at the baseline visit. Patients were instructed to wear the actigraph unit continously. At the start of week 2 and 3, patients were randomized (1:1) to ER morphine 8 mg or placebo, which was added to the prior week's dose. . Participants could then enter an optional blinded extension treatment period of 6 months (eFigure 1). Baseline number of steps was obtained from actigraphy performed prior to study enrollment (day -1).

The trial medications, morphine sulfate pentahydrate (Kapanol) and placebo, were provided by Mayne Pharma. They were indistinguishable in appearance and were provided by the local pharmacy in a blister pack for each trial week. Participants were instructed to take 2 capsules of trial medication orally each morning throughout the study period.

Participants were also given 2 blinded tablets of laxative (docusate with sennosides for the morphine group) or placebo (for those not receiving morphine) each morning. The blister packs were collected at the end of each week. Open label laxative was also available to all participants, up to 2 tablets twice daily, as needed.

Participants were instructed to record their level of breathlessness in a diary each evening using a validated numerical rating scale (NRS)[19] which ranged from 0 (none) and 10 (worst). All participants received a battery-operated, handheld fan and an information sheet with standard breathlessness self-management strategies (ie, how to use the handheld fan, breathing control techniques, positions to reduce breathlessness and suggestions to keep active). Patients were instructed to continue all other medications and therapies in accordance with their clinicians' recommendations throughout the study period.

Blinding

All research staff, treating clinicians and participants were blinded to the treatment allocation. Unblinding could occur only after collection of the last data point for the final study participant or in an emergency situation after consultation with the principal investigator.

Outcomes

The primary outcome was change of *worst breathlessness* on a numerical rating scale ranging from 0 to 10 from mean baseline (days -3 to -1) to mean at days 5 to 7 in the ER morphine 8 mg and 16 mg vs placebo groups. The co-primary outcome was change in daily steps (actigraphy, using FitBit^{R}) from baseline (day -1) to mean at days 19 to 21 among the groups.
Secondary outcomes included change in *mean breathlessness intensity* and *overall breathlessness distress* during the previous 24 hours; Global Impression of Change (GIC) in health status;[20] Hospital Anxiety and Depression Scale (HADS);[21] Australia-modified Karnofsky Performance Scale (AKPS);[22] and HrQoL measured using the CAT; Clinical Respiratory Questionnaire Dyspnea (CRQ-D) and Mastery (CRQ-M) scores; overall wellbeing on the 0-100 mm visual analogue scale (VAS) of the instrument EuroQol Five Dimensions Five Levels (EQ-5D-5L);[23] revised Edmonton Symptom Assessment System (ESAS-r).[24] blinded participant treatment preference; end-tidal partial pressure of carbon dioxide ($ETCO_2$); respiratory rate; and peripheral oxygen saturation (SpO_2).

Treatment emergent adverse events (TEAEs) were assessed during a mid-week telephone call and at the review at the end of each week,[16] according to National Cancer Institute Common

Terminology Criteria for Adverse Events version 4 (NCI CTCAEv4).[25] TEAE was any adverse event that occurred or worsened after baseline. TEAEs with a CTCAE grade of ≥3, or otherwise reported as a serious adverse event as part of trial pharmacovigilance reporting, was categorized as a severe TEAE. Outcomes were evaluated after 1 (primary outcome) and 3 weeks.

Sample Size

We estimated that a sample of 135 patients would provide 80% power to detect a clinically important difference in the primary outcome of the minimally clinically important difference of 1.1 point on a 0-10 NRS [26] with a SD each day of 2.0 to 2.5 at week 1. Sample size calculations were based on a recent RCT.[10] Type I error rate was pre-specified as 2.5% (two-sided alpha 0.025) as the primary analysis comprised two placebo comparisons (of morphine 8mg and 16mg, respectively). Using the specified mixed linear model and variance-covariance matrix based on the mean responses from the recent RCT,[10] 45 participants per group were required after week 1.

Statistical Methods

Categorical variables are presented as number (percentage) and continuous variables are presented as median (interquartile range). Analyses were according to randomization group. The analysis set was all randomized participants who received at least one dose of study medication, both for efficacy and safety analyses.

For the NRS breathlessness and step count outcomes, treatment effects were analyzed using random effects mixed linear regression models, with the change from baseline as the dependent variable; treatment group, day, and treatment group-by-day interaction as factors; and adjustment for baseline values of age, sex, mMRC, AKPS, $ETCO_2$, SpO_2, and Charlson Comorbidity Index. An unstructured variance-covariance structure was used for NRS breathlessness. Compound symmetry and toeplitz variance-covariance structures were used for step count at the end of weeks one and three, respectively. For other secondary outcomes, treatment effects were analyzed using analysis of covariance (ANCOVA) with change from baseline to end of the week as the dependent variable, treatment group as a factor, and adjustment for the baseline value and the same covariates. The primary analysis was conducted without and with imputation for missing outcome data using multiple imputations with 100 resamples drawn. The co-primary analysis and secondary analyses were conducted using as observed data, with no imputation. Effects compared with placebo were evaluated for ER morphine 8mg and 16mg, respectively, after week one (primary analysis), and by each allocated treatment group (8mg, 16mg, 24mg, 32mg) after week three.

All estimates were reported with 95% confidence intervals (CI). Statistical significance at the end of week one was defined as two-sided p-value < 0.025 as the primary analysis compared two morphine dose levels with placebo. The co-primary outcome assessed at the end of week three used a two-sided significance level of 0.0125 as four morphine dose levels were compared with

placebo at the end of week three. A hierarchical testing procedure was used whereby if the primary outcome was not significant, the co-primary outcome would be tested but only reported as exploratory / hypothesis generating. All other statistical tests were two sided at the 5% significance level. Statistical analyses were conducted using the software package SAS Version 9.4.

RESULTS

From September 1, 2016 through December 26, 2019, 160 patients were enrolled and randomized at 20 centers. Of the randomized patients, 4 did not take any study drug (2 patients withdrew, 1 had a protocol violation and 1 had a serious adverse event) so 156 patients were included in the primary analyses (Figure 1)

The median age was 72 years; 48% were women, 121/156 (78%) had an mMRC breathlessness score of 3 and 35/156 (22%) had an mMRC score of 4. For week 1, patients were randomized into 3 groups: 55 (35%) in the morphine 8 mg/day group, 51 (33%) in the morphine 16 mg/day group, and 50 (32%) in the placebo group. Baseline characteristics were similar between treatment groups at week 1 (Table 1). The mean step count was similar between groups: 2526 [SD 2139] for morphine 8 mg/day; 2214 [SD 1801] for morphine 16 mg/day; and 2242 [SD 1708] for the placebo group (Table 2).

The number of patients who completed 3 weeks of treatment was 21 for morphine 8 mg/day, 27 for morphine 16 mg/day, 22 for morphine 24 mg/day, 8 for morphine 32 mg/day, and 7 for placebo.

Primary Outcome

The primary outcome change in *worst breathlessness* intensity after 1 week was not significantly different for morphine 8 mg (mean difference -0.3; 95% CI -0.9–0.4) and 16 mg (mean difference, -0.3; 95% CI -1.0–0.4) compared with placebo (Table 2; Figure 2). There was no significant treatment effect when accounting for missing data using multiple imputation for morphine 8mg/day (mean difference -0.20; [95% CI] -0.86 to 0.46) or for morphine 16 mg/day (-0.30; -0.98 to 0.38) compared with placebo. Overall, 10/156 (6%) of data was missing in the primary outcome analysis: 3/50 (6%) in the placebo group, 1/55 (2%) in morphine 8 mg/day group and 6/51 (12%) in the morphine 16 mg/day group. The primary outcome was not significantly different in participants with mMRC 3 or 4 (eFigure 2), or when analyzed *per protocol*: (-0.20 [-0.86 to 0.46] for morphine 8 mg/day; -0.30 [-0.98 to 0.38] for morphine 16 mg/day, *v*s. placebo).

Co-primary Outcome

There were no significant differences in the co-primary outcome of change in mean daily steps after 3 weeks compared to placebo, for morphine 8 mg/day (mean difference, -1453; 95% CI -3310–405), 16 mg/day (mean difference, -1312; 95% CI -3220–596), 24 mg/day (mean difference, -692; 95% CI -2553–1170) or 32 mg/day (mean difference, -1924; 95% CI -47699–921) (Figure 2)

Secondary Outcomes

All secondary outcomes were not significantly different between treatment groups after week 1 (Table 2; eTable 2–3), including mean daily steps (eFigure 3), mean breathlessness intensity and overall distress (eFigure 4).

Based on capsule count at the end of the study periods, adherence to the allocated treatment was very high and similar among the groups. Mean adherence at week 1 was 97-100% (eTable 4), at week 2 was 95%-100% (eTable 5) and at week 3 was 93%-100% (eTable 6).

Treatment-emergent adverse events during week 1 occurred in 24/50 (48%) in the placebo group, 35/55 (64%) in the morphine 8 mg/day group and 40/51 (78%) in the 16 mg/day group (eTables 7 and 8). The TEAEs were common morphine-related side effects, and included constipation, fatigue, dizziness, nausea, and vomiting. However, these TEAEs did not appear to be associated with study drug adherence (eTable 4–6). TEAEs during weeks 2 and 3 are shown in eTables 9 and 10. During week 1, the number of patients who discontinued treatment due to unacceptable AEs was 0 (0%) in the placebo group, 2 in the morphine 8 mg/day group and 5 in the 16 mg/day group (Figure 1). During week 2, study discontinuation due to AE occurred in 1 patient in the morphine 8 mg/day group, 3 in morphine 16 mg/day, 2 in morphine 24 mg/day and 1 in the placebo group (Figure 1). During week 3, study discontinuation due to AE occurred in 1 patient in morphine 8 mg/day, 1 in morphine 16 mg/day, 4 in morphine 24 mg/day, 0 in morphine 32 mg/day and 0 in the placebo group.

Throughout the trial, serious TEAEs (which included hospitalization or death) occurred in 46/139 (33%; 85 episodes) patients who received any morphine, compared to 2/17 (12% participants; 2 episodes) in those who received only placebo. Serious TEAEs (Table 3) included increased breathlessness, infections, morphine-related side effects, and 2 events of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria for respiratory failure (both in the morphine group).

DISCUSSION

This randomized clinical trial of patients with COPD and severe chronic breathlessness daily ER morphine did not significantly improve the primary outcome of *worst breathlessness* intensity at 1 week. There was also no significant improvement in the co-primary outcome of mean daily steps using actigraphy or in any of the secondary outcomes, including symptoms, function, or HrQoL. The lack of efficacy was consistent across severities of breathlessness (mMRC 3 and 4).

This trial tested the efficacy and adverse event profile of several different up-titrated doses of ER morphine across clinically relevant doses (8, 16, 24 and 32 mg/day) over 3 weeks in patients with COPD and severe chronic breathlessness. To our knowledge, this study is the first to measure physical function using actigraphy concurrently with blinded uptitration of morphine in an adequately powered trial. These doses of ER morphine were not associated with a decreased total step count compared to placebo. The unchanged total step count does not support the hypothesis that the lack of efficacy on breathlessness was due to participants increasing their physical activity (thereby masking a true symptom improvement).[10,27]

The study findings may not be applicable to patients with very advanced COPD and breathlessness who are in palliative care or near the end of life, at which time opioids may be useful treatment options to provide relief of severe dyspnea.[4,28] Further research is needed to determine if specific groups of patients with COPD are more likely to experience a reduction in breathlessness with morphine, if some may benefit from higher doses of morphine, and to clarify the role of short-acting opioids for severe episodes of breathlessness.

Strengths of this study include its multicenter, double-blind, parallel-group randomized design, and blinded up-titration in each stage against placebo. Blinded administration of laxative (or placebo) improved blinding; participants were not allowed to take ‘as needed’ morphine during the trial, and clinically relevant efficacy and safety outcomes were assessed using validated instruments.[29]

Limitations

This study has several limitations. First, the number of participants in each group decreased over the 3-week period, and only 42% of patients completed treatment at week 3. However, the trial was adequately powered for the primary outcome and recruited the target number of patients. Second, breathlessness was measured in daily life and not during standardized exercise testing. Third, ER morphine can be administered every 12 to 24 hours so it is possible that the 24-hour dosing interval used in this study may have provided a suboptimal dose of morphine.

Conclusions

Among patients with severe COPD and chronic breathlessness, daily use of low-dose, ER morphine did not improve worst breathlessness after 1 week of treatment. These findings do not support the use of these doses of ER morphine to relieve breathlessness.

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Conflicts of Interest: ME, DF, BF report no conflicts of interest. DCC has received an unrestricted research grant from Mundipharma, is an unpaid member of an advisory board for Helsinn Pharmaceuticals and has consulted for and received intellectual property payments from Mayne Pharma. MJJ has received consulting payments from Mayne Pharma. SL is employed by McCloud Consulting Group and received consulting fees for her work on this study. Outside the submitted work, DJE had a Collaborative Research Centre (CRC) Consortium Grant between the Australian Government, Academia and Industry (Industry partner: Oventus Medical) and research grants from Takeda, Bayer, Invicta Medical, and Apnimed and served as a consultant for Bayer, Apnimed, Takeda and on advisory boards for Eisai, Invicta Medical and Apnimed. MRA has received payment to facilitate a workshop on the multidisciplinary care of older people with lung cancer from Astra Zeneca.

Access to Data and Data Analysis: DCC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contributions: ME, SL, MJJ, DJE, BF, KJC, MRA and DCC contributed to the trial design. SL wrote the statistical analysis plan based on the analyses specified in the protocol, and conducted the statistical analysis. ME wrote the first draft; and all authors participated in interpreting the results, revised the draft for intellectual content and approved the final version to be published.

Data Sharing Statement: See Supplement 5.

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463 **TABLES**

464 **Table 1.** Baseline patient characteristics, week 1.

	Baseline value[c]		
Characteristic[a,b]	**Morphine 8mg/day**	**Morphine 16mg/day**	**Placebo**
N	55	51	50
Age	73 (67, 78)	73 (67, 78)	72 (66, 76)
Male	28 (51%)	25 (49%)	28 (46%)
Female	27 (49%)	26 (51%)	22 (44%)
Body mass index	26.1 (22.4, 31.2)	27.0 (23.0, 31.6)	25.9 (21.7, 30.5)
Smoking Status			
Ex-smoker	43 (78%)	43 (84%)	38 (76%)
Current smoker	10 (18%)	6 (12%)	12 (24%)
Never smoked	2 (4%)	2 (4%)	0 (0%)
Living arrangements			
Private residence	53 (96%)	51	47 (94%)
Residential aged care facility	1 (2%)	0 (0%)	3 (6%)
Inpatient palliative care unit	1 (2%)	0 (0%)	0 (0%)
Had caregiver	33/49 (67%)	38/46 (83%)	32/48 (67%)
mMRC breathlessness scale [d]			
3	49 (89%)	38 (75%)	34 (68%)
4	6 (11%)	13 (25%)	16 (32%)
Charlson comorbidity index [e]			
0	22 (40%)	19 (37%)	23 (46%)
1-2	23 (42%)	23 (45%)	17 (34%)
≥ 3	10 (18%)	9 (18%)	10 (20%)
Other Causes of Breathlessness			
Subjects with at least one other cause of breathlessness	28 (51%)	24 (47%)	21 (42%)

Heart failure	12 (22%)	12 (24%)	5 (10%)
Asthma	6 (11%)	5 (10%)	7 (14%)
Restrictive lung disease	4 (7%)	2 (4%)	3 (6%)
Thromboembolic cause	3 (6%)	2 (4%)	2 (4%)
Bronchiectasis	2 (4%)	1 (2%)	1 (2%)
Lung cancer or metastasis	1 (2%)	1 (2%)	2 (4%)
Lung infection or inflammation	1 (2%)	0 (0%)	2 (4%)
Other	10 (18%)	8 (16%)	12 (24%)
Supplemental oxygen therapy			
No	28 (51%)	29/50 (56%)	33 (66%)
Yes, continuous use	16 (29%)	10/50 (20%)	9 (18%)
Usual flow rate (L/min)	2 (2, 2)	2 (1.5, 2.5)	2 (1.5, 2)
Yes, only on exertion	3 (5%)	7/50 (14%)	3 (6%)
Yes, only when needed	8 (15%)	4/50 (8%)	5 (10%)

Abbreviations: mMRC, modified Medical Research Council;

[a] Data are presented as median (quantile one, quantile three) or frequency (%).

[b] Baseline characteristics by randomized treatment group for week 3 is shown in supplemental eTable 1.

[c] Baseline values were defined as the mean for the three days before the day of first study drug administration except for step count, where baseline was the full 24 hours (midnight to midnight) of the day before randomization. No data were imputed for baseline summary statistics.

[d] mMRC is an ordinal scale between 0 and 4 (worst) of the self-rated impact of exertional breathlessness on physical function, with a score of 3 corresponding to 'I stop for breath after walking about 100 yards or after a few minutes on the level' or 'I am too breathless to leave the house or I am breathless when dressing').

[e] A weighted score based on the presence of 19 comorbidities. Scores range from 0 to 37, with higher scores indicating worse comorbidity.

[f] Other causes of breathlessness included anemia, anxiety, arrhythmia, deconditioning, ischemic heart disease, overweight, pulmonary fibrosis, pulmonary hypertension and valvular disease.

Table 2. Primary, secondary, and other outcomes at one week

	Morphine 8mg/day			Morphine 16mg/day			Placebo			Adjusted between-group change[a]	
	Mean (SD)			Mean (SD)			Mean (SD)				
Outcome[b]	**Baseline (day -3 to -1)[c]**	**Week 1 (day 5 to 7)[d]**	**Unadjusted within-group change**	**Baseline (day -3 to -1)[c]**	**Week 1 (day 5-7)[d]**	**Unadjusted within-group change**	**Baseline (day -3 to -1)[c]**	**Week 1 (day 5-7)[d]**	**Unadjusted within-group change**	**Morphine 8mg/day *vs.* placebo, mean (95% CI)**	**Morphine 16mg/day *vs.* placebo, mean (95% CI)**
Primary outcome											
Worst breathlessness intensity[e]	5.9 (1.5)	5.1 (2.1)	-0.8 (1.7)	6.5 (1.7)	5.6 (2.1)	-1.0 (1.7)	6.2 (1.4)	5.4 (2.2)	-0.7 (1.7)	-0.3 (-0.9, 0.4)	-0.3 (-1.0, 0.4)
Secondary outcomes											
Daily steps[f]	2526 (2139)	2392 (1867)	84 (1003)	2214 (1801)	1938 (1388)	-399 (956)	2242 (1708)	2430 (2246)	99 (1329)	39 (-501, 579)	-388 (-1053, 277)
Symptoms											
Mean breathlessness intensity[e]	4.6 (1.5)	4.0 (1.9)	-0.6 (1.4)	5.1 (1.7)	4.6 (2.3)	-0.5 (1.7)	5.0 (1.6)	4.4 (2.2)	-0.6 (1.5)	-0.1 (-0.7, 0.5)	0.0 (-0.6, 0.7)
Overall	4.1 (2.4)	3.0	-1.0 (2.2)	4.8 (2.4)	3.5	-1.3 (2.3)	4.0 (2.5)	3.2	-0.7 (1.5)	-0.4 (-1.1,	-0.4 (-1.2,

breathlessness distress[e]		(2.5)			(2.5)			(2.7)		0.4)	0.4)
HADS anxiety[g]	6.8 (3.9)	5.5 (3.5)	-1.2 (3.0)	6.4 (3.7)	5.6 (3.2)	-0.5 (2.8)	5.7 (3.7)	5.6 (3.9)	0.1 (3.2)	-0.4 (-1.5, 0.8)	0.1 (-1.1, 1.2)
HADS depression[g]	6.3 (3.2)	5.3 (2.8)	-0.7 (1.7)	7.0 (4.0)	6.3 (3.9)	-0.8 (2.6)	6.2 (3.4)	6.2 (3.2)	0.3 (2.2)	-0.8 (-1.7, 0.1)	-0.8 (-1.7, 0.1)
Function											
Australia-modified Karnofsky Performance Scale [h]	66.0 (8.9)	66.7 (9.44)	-0.0 (1.8)	64.7 (8.6)	65.0 (8.9)	0.2 (5.8)	64.6 (8.9)	64.2 (8.7)	-0.4 (4.1)	1.4 (-0.9, 3.7)	0.9 (-1.4, 3.3)
Health-related quality of life											
COPD Assessment Test [i]	21.5 (6.5)	18.7 (6.1)	-3.1 (5.6)	22.9 (5.5)	19.7 (6.1)	-3.2 (4.7)	23.8 (6.3)	20.9 (5.4)	-2.9 (4.6)	-0.8 (-2.7, 1.0)	-0.6 (-2.5, 1.2)
Clinical Respiratory Questionnaire -Dyspnea[j]	3.5 (0.9)	3.8 (1.1)	0.3 (1.1)	3.2 (1.4)	3.7 (1.3)	0.4 (1.4)	3.4 (1.3)	3.6 (1.3)	0.2 (1.3)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.6)
Clinical Respiratory Questionnaire -Mastery[j]	4.0 (1.0)	4.2 (0.7)	0.1 (0.8)	4.2 (0.9)	4.2 (0.7)	0.0 (0.9)	3.9 (0.8)	4.0 (0.8)	0.1 (1.1)	0.2 (-0.1, 0.5)	0.1 (-0.2, 0.4)
EQ5D-5L, 0-100mm VAS[k]	63.0 (18.0)	64.5 (17.7)	2.3 (18.8)	57.9 (19.9)	61.2 (20.8)	3.5 (18.8)	59.1 (20.0)	64.1 (18.7)	3.8 (18.5)	-0.7 (-7.3, 6.0)	-1.8 (-8.7, 5.1)

Physiological parameters											
$ETCO_2$ (mmHg)	27.2 (8.2)	27.7 (8.0)	0.6 (9.8)	28.0 (8.3)	28.4 (7.4)	0.1 (6.6)	27.6 (11.6)	26.4 (7.9)	-1.6 (12.1)	2.0 (-1.0, 5.0)	2.0 (-1.2, 5.1)
SpO_2 (%)	92.7 (3.8)	91.5 (3.5)	-1.3 (3.3)	90.9 (12.3)	90.9 (2.8)	0.1 (12.7)	93.2 (3.7)	90.9 (13.8)	-2.2 (13.5)	1.5 (-2.0, 4.9)	0.7 (-2.9, 4.2)
Respiratory rate (min^{-1})	22.3 (10.8)	21.5 (10.8)	-1.1 (13.3)	19.8 (4.9)	19.6 (4.5)	-0.2 (4.3)	21.2 (4.5)	21.4 (4.3)	0.2 (4.2)	-0.7 (-3.6, 2.1)	-1.6 (-4.5, 1.4)
Other outcomes											
Edmonton Symptom Assessment Scale, revised version [e]											
Pain	1.3 (2.0)	1.3 (2.2)	-0.0 (1.8)	1.8 (2.4)	1.2 (2.0)	-0.3 (2.1)	2.0 (2.4)	1.4 (1.9)	-0.5 (1.8)	0.2 (-0.5, 0.8)	0.0 (-0.7, 0.7)
Tiredness	2.7 (2.0)	2.3 (2.2)	-0.3 (2.5)	3.5 (2.6)	3.5 (2.7)	0.2 (2.6)	3.7 (2.7)	3.1 (2.6)	-0.5 (2.8)	-0.4 (-1.3, 0.6)	0.5 (-0.5, 1.4)
Nausea	0.4 (1.4)	0.3 (0.7)	-0.2 (1.6)	0.3 (0.9)	0.4 (1.6)	0.2 (1.6)	0.5 (1.7)	0.3 (1.0)	-0.3 (1.6)	-0.1 (-0.6, 0.4)	0.2 (-0.3, 0.6)
Depression	1.1 (1.8)	0.7 (1.2)	-0.3 (1.6)	1.6 (2.4)	1.3 (2.5)	-0.2 (2.7)	1.3 (2.5)	1.3 (2.4)	0.0 (2.7)	-0.4 (-1.2, 0.4)	0.0 (-0.8, 0.8)
Anxiety	1.2 (2.0)	1.0 (1.6)	-0.2 (1.4)	1.6 (2.3)	1.5 (2.5)	0.0 (2.3)	1.6 (2.6)	1.4 (2.3)	-0.0 (2.8)	-0.3 (-1.0, 0.5)	0.0 (-0.7, 0.8)
Drowsiness	1.4 (1.9)	1.6	0.4 (1.8)	2.3 (2.6)	3.2	1.0 (2.7)	2.7 (2.6)	1.9	-0.8 (2.5)	0.5 (-0.4,	1.6 (0.7,

		(2.1)			(2.7)			(2.3)		1.3)	2.4)
Lack of appetite	1.7 (2.4)	1.6 (2.4)	-0.0 (2.1)	1.4 (2.6)	1.5 (2.7)	0.4 (2.4)	2.1 (3.0)	1.4 (2.3)	-0.8 (2.6)	0.2 (-0.6, 1.0)	0.5 (-0.4, 1.3)
Breathlessness	3.9 (2.8)	3.3 (2.5)	-0.6 (2.4)	4.3 (3.3)	4.0 (3.1)	-0.2 (2.9)	5.2 (2.9)	4.4 (2.6)	-0.2 (2.9)	-0.5 (-1.4, 0.5)	0.1 (-0.9, 1.1)
Wellbeing	3.2 (1.9)	3.1 (2.2)	0.0 (2.0)	4.1 (2.4)	3.8 (2.4)	-0.4 (2.0)	3.8 (2.3)	3.7 (2.1)	-0.0 (2.9)	-0.2 (-1.0, 0.6)	-0.2 (-1.0, 0.7)

Abbreviations: EQ5D-5L, EuroQol Five Dimensions Five Levels; $ETCO_2$, end-tidal partial pressure of carbon dioxide; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council breathlessness scale; NRS, numerical rating scale; SpO_2, peripheral saturation of oxygen.

[a] Between-group difference in the change from baseline after one week with morphine vs. placebo. A negative value is interpreted as a decrease in the outcome with morphine as compared with placebo. For the breathlessness and step count outcomes, treatment effects were analyzed using random effects mixed linear regression models, with the change from baseline as the dependent variable; treatment group, day, and treatment group-by-day interaction as factors; and adjustment for baseline values of age, sex, mMRC, AKPS, $ETCO_2$, SpO_2, and Charlson Comorbidity Index. An unstructured variance-covariance structure was used for NRS breathlessness and compound symmetry variance-covariance structure for daily steps. For other secondary outcomes, treatment effects were analysed using analysis of covariance (ANCOVA) with change from baseline to end of the week as the dependent variable, treatment group as a factor, and adjustment for the baseline value and the same covariates.

[b] Additional categorical outcomes after one week are shown in eTable 2. Outcomes after three weeks are shown in eTable 3.

[c] baseline values were defined as the mean for the three days before the day of first study drug administration except for step count, where baseline was the full 24 hours (midnight to midnight) of the day before randomization.

[d] values at the end of the week were defined as the mean of the last three days of the week, to try to ensure measurement on the allocated treatment at steady state.

[e] symptom(s) measured on a numerical rating scale between 0 (none) and 10 (worst or most intense)

[f] daily steps measured using actigraphy (FitBit^R) for 24 hours at baseline and the mean of three 24 hour days at the end of week one.

[g] measure of anxiety or depression, with scores ranging between 0 and 21 (worst)

[h] measure of overall functional status assigned by staff based on observations of a participant's ability to perform common

tasks relating to activity, work and self-care. Scored between 100 (normal) and 10 (comatose or barely rousable).

[i] measure of health-related quality of life (HrQoL), with scores ranging between 0 and 40 (worst)

[j] measure of HrQoL, with scores ranging between 1 (worst) to 7 (best)

[k] measure of the self-rated perceived overall well-being on a 100mm visual analogue scale between 0 (worst) to 100 (best)

Table 3. Serious treatment-emergent adverse events, hospitalizations, and deaths, with onset during weeks 1 to 3

Serious TEAE [a]	Morphine 8 mg/day (N=43) Subjects (%)	Morphine 16 mg/day (N=54) Subjects (%)	Morphine 24 mg/day (N=33) Subjects (%)	Morphine 32 mg/day (N=9) Subjects (%)	Placebo (N=17) Subjects (%)
Patients with at least one serious TEAE	8 (19%)	10 (19%)	2 (6%)	0 (0%)	1 (6%)
Hospitalization	7 (16%)	8 (15%)	3 (9%)	0 (0%)	1 (6%)
Death	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: TEAE, treatment-emergent adverse event.

[a] Patients are grouped by the highest dose treatment they received during the study.

FIGURE LEGENDS

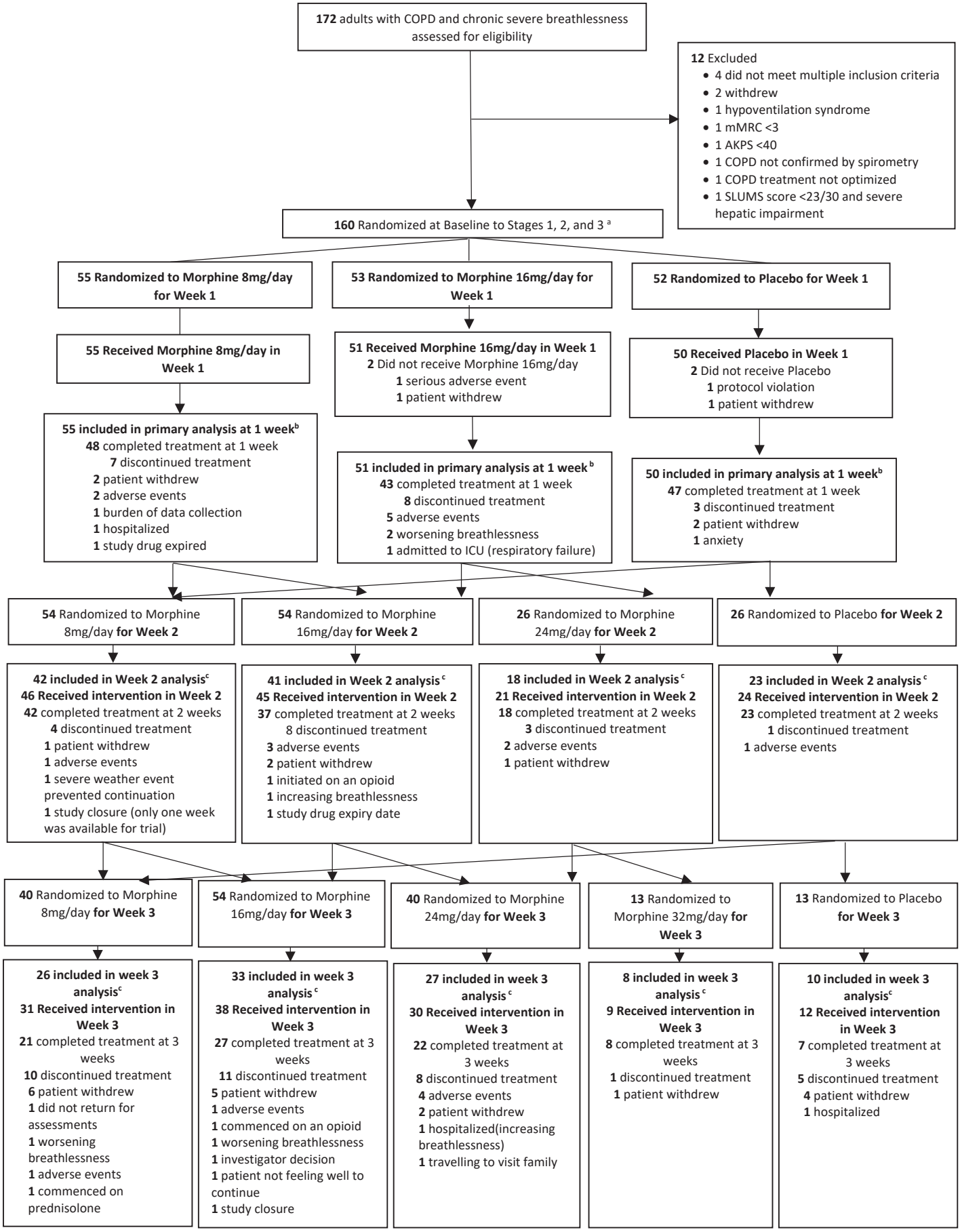
Figure 1. Participant flow diagram.

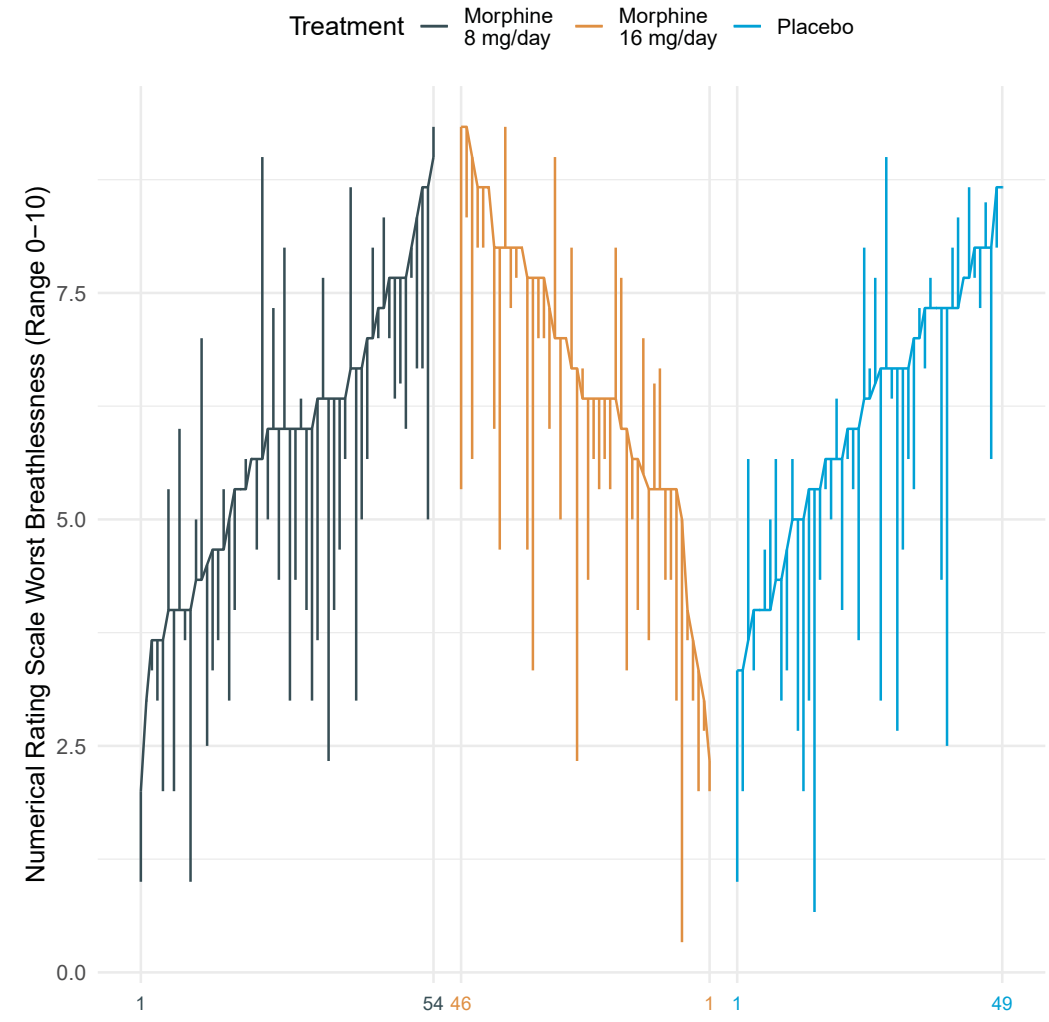
[a] Randomization was by blocks of 6 to ensure relatively even allocation to each treatment group at each site. Randomization for the 3 stages occurred at baseline: for week one in a 1:1:1 ratio to either oral ER morphine 8 mg/day, 16 mg/day, or placebo. For weeks 2 and 3, each participant was further randomized (1:1) to ER morphine 8 mg or placebo.

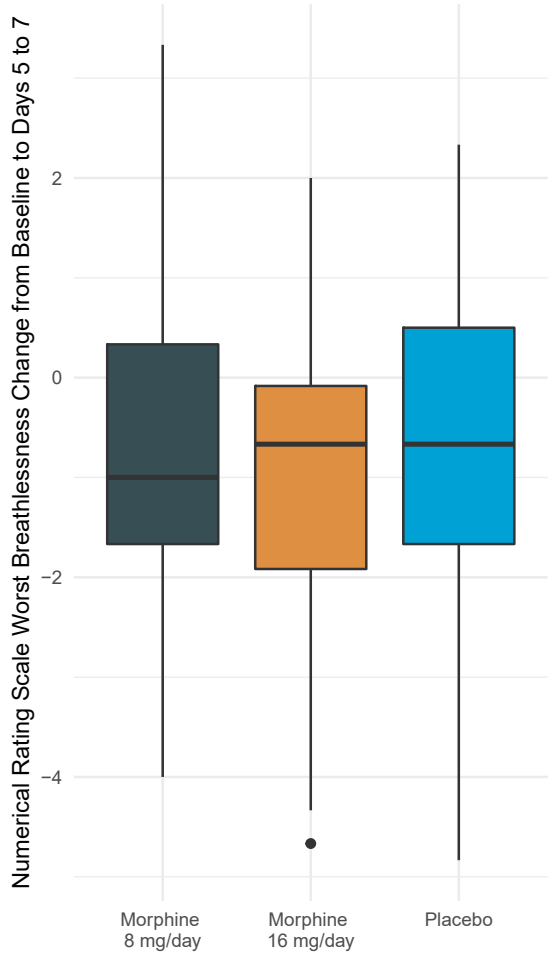
[b] With missing data imputed using multiple imputation with 100 samples redrawn.

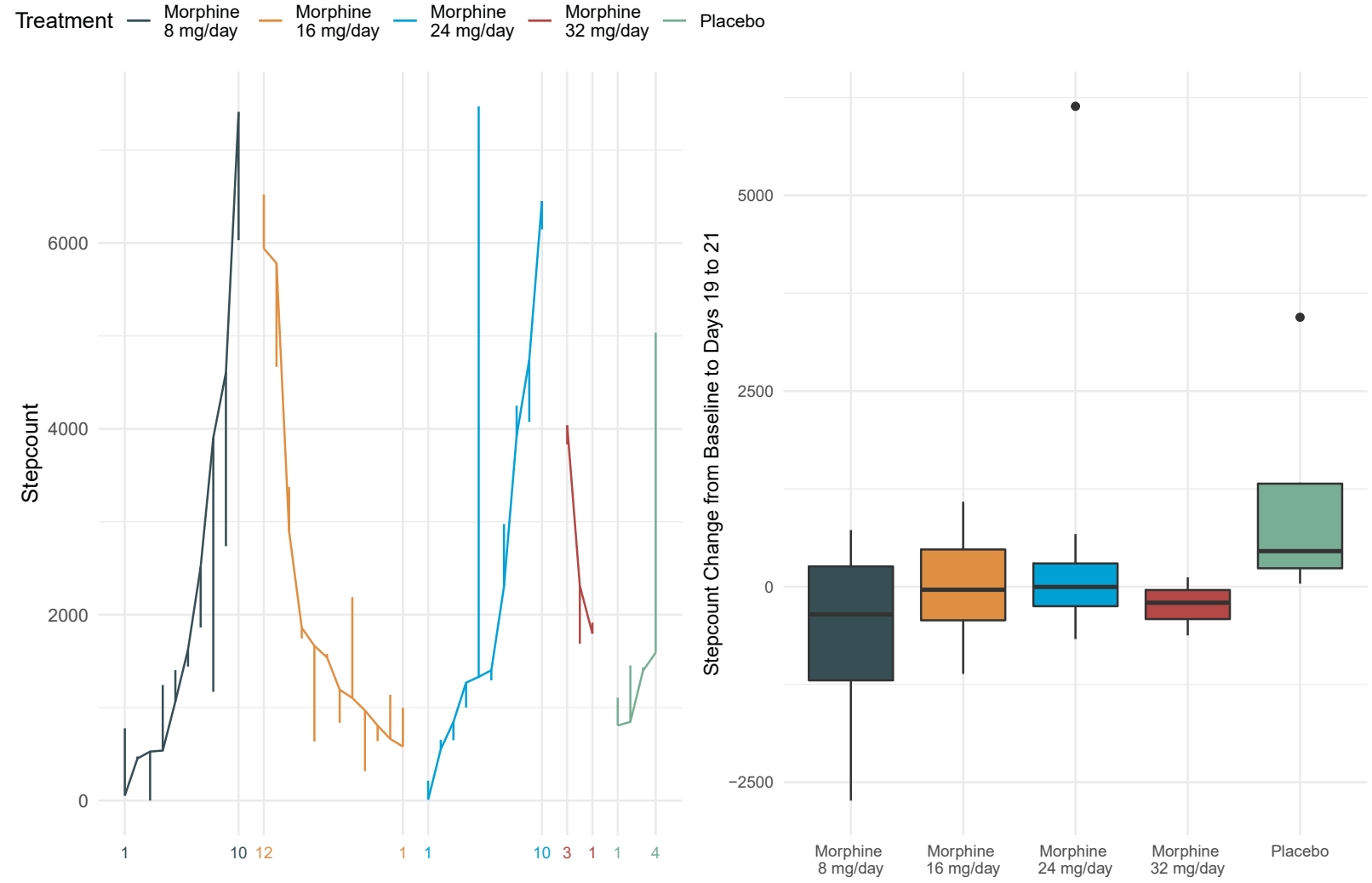
[c] For change from baseline in worst breathlessness. Only patients with non-missing data were analyzed.

Figure 2. Change in A) worst breathlessness intensity at days 5-7, and B) mean daily step count at days 19-21, measured using Actigraphy. The parallel line plots displays the individual results at baseline and follow-up (days 5-7 breathlessness and days 19-21 for mean step count) for each patient. The baseline results are plotted, with the follow-up result connected by a vertical line. Patients are ordered from left to right in increasing baseline values for morphine 8mg/day and placebo, and morphine 24 mg/day, and decreasing baseline values for morphine 16 mg/day and morphine 32 mg/day. The boxes represent the interquartile range (quartile 1 to quartile 3) for the change from baseline to follow-up, with the horizontal black line in the middle representing the median. The whiskers represent the smallest and largest values within 1.5 times the interquartile range of the first and third quartile respectively. The dots represent points outside the range.


172 adults with COPD and chronic severe breathlessness assessed for eligibility
12 Excluded
• 4 did not meet multiple inclusion criteria
• 2 withdrew
• 1 hypoventilation syndrome
• 1 mMRC <3
• 1 AKPS <40
• 1 COPD not confirmed by spirometry
• 1 COPD treatment not optimized
• 1 SLUMS score <23/30 and severe hepatic impairment
160 Randomized at Baseline to Stages 1, 2, and 3 [a]
55 Randomized to Morphine 8mg/day for Week 1
53 Randomized to Morphine 16mg/day for Week 1
52 Randomized to Placebo for Week 1
55 Received Morphine 8mg/day in Week 1
51 Received Morphine 16mg/day in Week 1
2 Did not receive Morphine 16mg/day
1 serious adverse event
1 patient withdrew
50 Received Placebo in Week 1
2 Did not receive Placebo
1 protocol violation
1 patient withdrew
55 included in primary analysis at 1 week [b]
48 completed treatment at 1 week
7 discontinued treatment
2 patient withdrew
2 adverse events
1 burden of data collection
1 hospitalized
1 study drug expired
51 included in primary analysis at 1 week [b]
43 completed treatment at 1 week
8 discontinued treatment
5 adverse events
2 worsening breathlessness
1 admitted to ICU (respiratory failure)
50 included in primary analysis at 1 week [b]
47 completed treatment at 1 week
3 discontinued treatment
2 patient withdrew
1 anxiety
54 Randomized to Morphine 8mg/day **for Week 2**
54 Randomized to Morphine 16mg/day **for Week 2**
26 Randomized to Morphine 24mg/day **for Week 2**
26 Randomized to Placebo **for Week 2**
42 included in Week 2 analysis [c]
46 Received intervention in Week 2
42 completed treatment at 2 weeks
4 discontinued treatment
1 patient withdrew
1 adverse events
1 severe weather event prevented continuation
1 study closure (only one week was available for trial)
41 included in Week 2 analysis [c]
45 Received intervention in Week 2
37 completed treatment at 2 weeks
8 discontinued treatment
3 adverse events
2 patient withdrew
1 initiated on an opioid
1 increasing breathlessness
1 study drug expiry date
18 included in Week 2 analysis [c]
21 Received intervention in Week 2
18 completed treatment at 2 weeks
3 discontinued treatment
2 adverse events
1 patient withdrew
23 included in Week 2 analysis [c]
24 Received intervention in Week 2
23 completed treatment at 2 weeks
1 discontinued treatment
1 adverse events
40 Randomized to Morphine 8mg/day **for Week 3**
54 Randomized to Morphine 16mg/day **for Week 3**
40 Randomized to Morphine 24mg/day **for Week 3**
13 Randomized to Morphine 32mg/day **for Week 3**
13 Randomized to Placebo **for Week 3**
26 included in week 3 analysis [c]
31 Received intervention in Week 3
21 completed treatment at 3 weeks
10 discontinued treatment
6 patient withdrew
1 did not return for assessments
1 worsening breathlessness
1 adverse events
1 commenced on prednisolone
33 included in week 3 analysis [c]
38 Received intervention in Week 3
27 completed treatment at 3 weeks
11 discontinued treatment
5 patient withdrew
1 adverse events
1 commenced on an opioid
1 worsening breathlessness
1 investigator decision
1 patient not feeling well to continue
1 study closure
27 included in week 3 analysis [c]
30 Received intervention in Week 3
22 completed treatment at 3 weeks
8 discontinued treatment
4 adverse events
2 patient withdrew
1 hospitalized(increasing breathlessness)
1 travelling to visit family
8 included in week 3 analysis [c]
9 Received intervention in Week 3
8 completed treatment at 3 weeks
1 discontinued treatment
1 patient withdrew
10 included in week 3 analysis [c]
12 Received intervention in Week 3
7 completed treatment at 3 weeks
5 discontinued treatment
4 patient withdrew
1 hospitalized


Treatment
Morphine 8 mg/day
Morphine 16 mg/day
Placebo
Numerical Rating Scale Worst Breathlessness (Range 0–10)
0.0
2.5
5.0
7.5
1
54
46
1
1
49


Numerical Rating Scale Worst Breathlessness Change from Baseline to Days 5 to 7
2
0
−2
−4
Morphine 8 mg/day
Morphine 16 mg/day
Placebo


Treatment
Morphine 8 mg/day
Morphine 16 mg/day
Morphine 24 mg/day
Morphine 32 mg/day
Placebo
Stepcount
6000
4000
2000
0
1
10
12
1
1
10
3
1
1
4
Stepcount Change from Baseline to Days 19 to 21
5000
2500
0
−2500
Morphine 8 mg/day
Morphine 16 mg/day
Morphine 24 mg/day
Morphine 32 mg/day
Placebo