


# BMJ Open Study protocol for a randomised, placebo-controlled, single-blind phase II study of the efficacy of morphine for dyspnoea in patients with interstitial lung disease (JORTC-PAL 15)

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## ABSTRACT

**Introduction** Dyspnoea is common in patients with interstitial lung disease (ILD) and often refractory to conventional treatment. Little is known about the efficacy of systemic morphine for dyspnoea in patients with ILD. The aim of this study is to estimate the efficacy of a single subcutaneous morphine injection for dyspnoea in patients with ILD.

**Methods and analysis** We will conduct a multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study of a single subcutaneous morphine injection for dyspnoea in patients with ILD. In patients with ILD who have dyspnoea at rest refractory to conventional treatment will be eligible for participation in this study. The morphine dose will be 2 mg. The primary endpoint is changes in dyspnoea intensity from baseline to 60 min after treatment as measured using an 11-point Numerical Rating Scale and compared between the morphine and placebo groups.

**Ethics and dissemination** Ethical approval has been obtained by the Osaka City University Certified Review Board. The results of this study will be submitted for publication in an international peer-reviewed journal and the findings will be presented at international scientific conferences.

**Trial registration number** jRCTs051190030; pre-results.

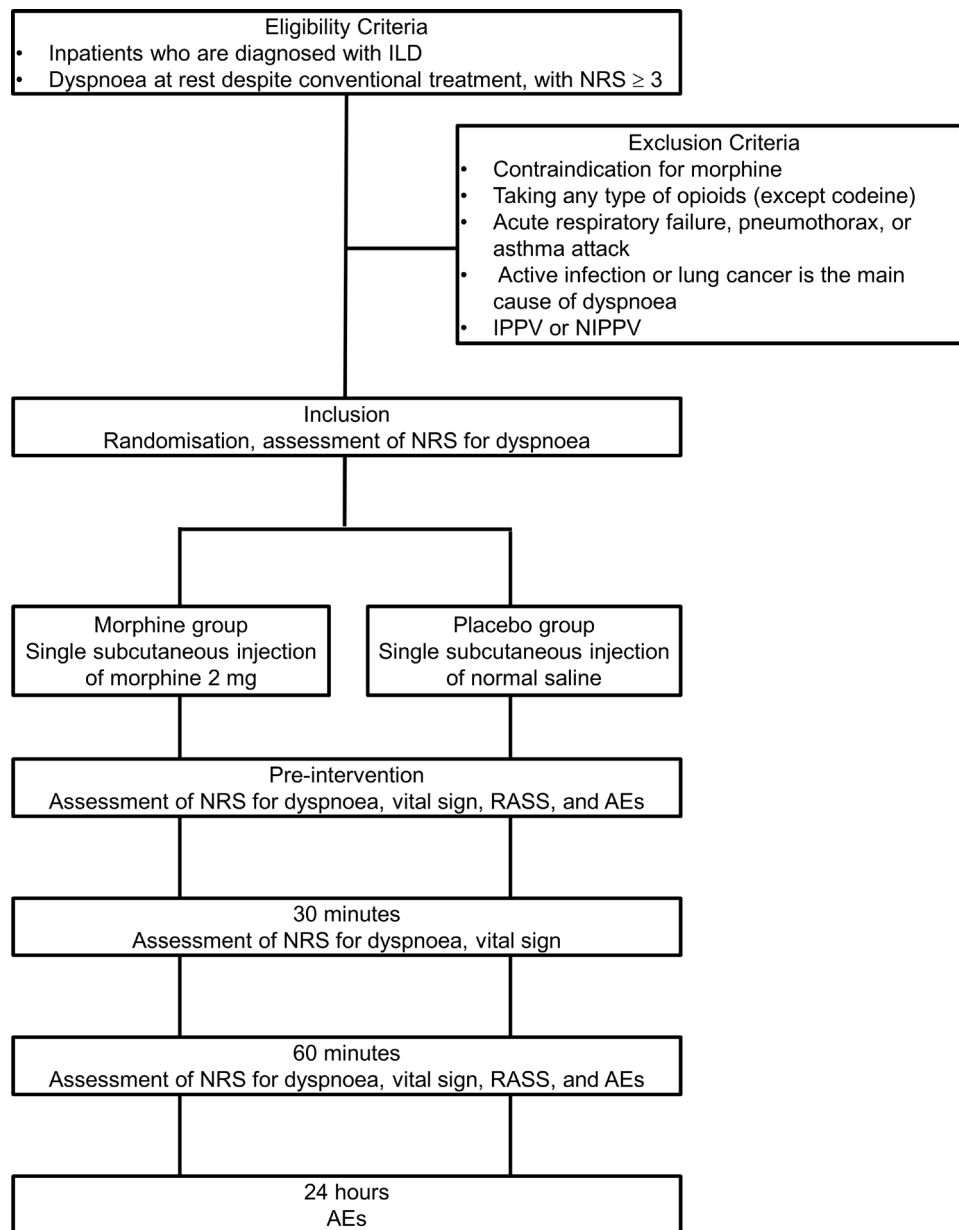
## INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of lung diseases that affect the pulmonary interstitium. They include connective tissue disease-associated ILD, drug-induced ILD, occupational and environmental ILD, sarcoidosis and idiopathic interstitial pneumonias.<sup>1</sup> A population-based registry study has shown that the prevalence of ILD was 80.9 per 100 000 in men and 67.2 per 100 000 in women.<sup>2</sup> ILD is often fatal or difficult to cure<sup>3,4</sup>; therefore, palliative care is essential for patients with ILD. However, palliative care available for patients with ILD is insufficient compared with that for patients with cancer.<sup>5,6</sup>

## Strengths and limitations of this study

- This is one of the few studies estimating the efficacy of systemic morphine for dyspnoea in patients with interstitial lung disease.
- This study has a rigorous design including randomisation, a placebo control group and blinding of participants.
- This is a single-blinded study.
- The observation period is short, that is, efficacy is assessed within 60 min after treatment, and monitoring for adverse events is performed for 24 hours after treatment.

Dyspnoea is the most frequent and burdensome symptom in patients with ILD,<sup>7,8</sup> and it is associated with a decreased quality of life.<sup>9–14</sup> Multiple empirical studies and systematic reviews have confirmed that morphine is effective for refractory dyspnoea in patients with chronic breathlessness predominantly caused by cancer and chronic obstructive pulmonary disease.<sup>15–18</sup> However, studies on the efficacy and safety of morphine in patients with ILD are limited. A case series of patients with end-stage idiopathic pulmonary fibrosis has reported that diamorphine is an effective treatment for dyspnoea.<sup>19</sup> A few retrospective studies have also suggested that morphine is effective in treating dyspnoea in terminally ill patients with interstitial pneumonia.<sup>20,21</sup> A randomised controlled trial found that oral morphine did not significantly reduce dyspnoea compared with placebo in patients with fibrotic ILD.<sup>22</sup> To the best of our knowledge, no published prospective study other than the one mentioned above has examined the efficacy and safety of systemic morphine for dyspnoea in patients with ILD.<sup>23–25</sup> From the phase I study we conducted to investigate the safety of systemic morphine and determine the



**Figure 1** Flow chart of the study procedures. Participants will be randomised (1:1 allocation ratio) into the morphine group or the placebo group. Assessment will be made at baseline and at 30 and 60 min, and 24 hours after treatment. AEs, adverse events; ILD, interstitial lung disease; IPPV, invasive positive pressure ventilation; NIPPV, non-invasive positive pressure ventilation; NRS, Numerical Rating Scale; RASS, Richmond Agitation Sedation Scale.

recommended dose of morphine to be used in further clinical trials, we reported that the recommended dose of single subcutaneous morphine for dyspnoea in patients with ILD is 2mg.<sup>26</sup> The aim of this study is to estimate the efficacy of a single subcutaneous morphine injection for dyspnoea in patients with ILD.

## METHODS AND ANALYSIS

### Study design

This is a multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study that will be performed to estimate the efficacy of morphine. The study design is summarised in [figure 1](#).

### Study settings and participants

Participants will be recruited from nine hospitals across Japan.

The inclusion criteria are as follows: hospitalised patients who (1) are  $\geq 20$  years of age; (2) have been diagnosed with ILD by two respiratory physicians and one respiratory radiologist; (3) have dyspnoea at rest with Numerical Rating Scale (NRS)  $\geq 3$  despite conventional treatment; (4) have an expected survival of 1 month or longer; (5) are capable of communication and do not have cognitive impairments; (6) have blood oxygen saturation levels ( $\text{SpO}_2$ )  $\geq 90\%$  (supplemental oxygen was allowed) and partial pressure of carbon dioxide ( $\text{PaCO}_2$ )  $\leq 50$  Torr; (7)

have normal liver and renal function (aspartate aminotransferase (AST)  $\leq 100$  IU/L, alanine aminotransferase (ALT)  $\leq 100$  IU/L, total bilirubin (T-Bil)  $\leq 2.0$  mg/dL and creatinine  $\leq 2.0$  mg/dL) and (8) have an ejection fraction of  $\geq 50\%$  as confirmed on ECG.

ILDs in this study include idiopathic pulmonary fibrosis, idiopathic non-specific interstitial pneumonia (NSIP), unclassifiable idiopathic interstitial pneumonia, collagen vascular disease-related interstitial pneumonia, chronic hypersensitivity pneumonia and pneumoconiosis. Idiopathic pulmonary fibrosis is diagnosed according to the criteria in the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society statement.<sup>27</sup> NSIP and unclassifiable idiopathic interstitial pneumonia are diagnosed according to the criteria in the official American Thoracic Society/European Respiratory Society statement.<sup>28</sup>

The exclusion criteria are as follows: (1) patients with contraindications to morphine including allergy to morphine, (2) patients using opioids (if the patient is receiving any dose of codeine, that was discontinued 12 hours prior to the study treatment), (3) patients with acute respiratory failure, pneumothorax or asthma attack, (4) patients with dyspnoea predominantly due to an active infection or lung cancer, (5) patients using invasive or non-invasive positive pressure ventilation, (6) patients with a current or history of drug abuse or (7) patients who are pregnant.

We do not exclude patients who use codeine because codeine is frequently used for cough in patients with ILD. We exclude other weak opioids such as tramadol.

## Recruitment, randomisation, masking and follow-up

### Recruitment

Potentially eligible patients will be screened by site investigators. Patients who fit the inclusion criteria will be invited to participate in the study.

### Randomisation

During enrolment and after providing a written informed consent, patients will be randomly allocated to the intervention (morphine) or control (placebo) groups by a web-based central randomisation system using minimisation methods and a computer-generated randomisation schedule with a 1:1 allocation ratio. In performing this allocation, we will minimise the following adjustment factors to avoid a large bias: (1) current dyspnoea intensity as measured using the NRS ( $\leq 6$ ,  $\geq 7$ ), (2) codeine use (yes, no) and (3) study site.

### Masking

Patients will be blinded to the administration of morphine or placebo. The intervention will only be unblinded 60 min after treatment, if patients in the placebo group do not experience dyspnoea relief and wish to receive morphine. Clinicians and medical staff will be unblinded because the process of disposing

opioids in Japan is very complex. However, the clinicians or medical staff who will check the self-administered questionnaire for current dyspnoea intensity (primary endpoint) will be blinded.

### Data management, central monitoring and audit

Evaluation will be performed at five timepoints: enrolment, baseline, 30, 60 min and 24 hours after treatment. The timing and details of the assessments are shown in table 1. The investigators at each study site will maintain records of each patient as source data, which include signed informed consent forms, medical records, laboratory data and other records or notes. All data will be collected by the Japanese Organisation for Research and Treatment of Cancer (JORTC) data centre. The JORTC data centre will oversee the intrastudy data sharing process. Clinical data entry, data management and central monitoring will be performed using the VIEDOC 4 (PCG Solutions, Sweden) electric data capture system. An interim analysis will not be performed. Auditing will not be done in this study.

### Treatment Interventions

Single subcutaneous injection of morphine 2 mg or placebo (normal saline 0.2 mL) will be performed. Injection will be performed by an unblinded physician. Patients in the placebo group who do not experience dyspnoea relief and who wish to receive morphine after the assessment performed 60 min after injection will be administered 2 mg of morphine. Following previous studies,<sup>19 29</sup> we decided to use subcutaneous injection, not oral preparations, for practical reasons, such as the feasibility of a placebo (normal saline) in future clinical trials, and simple logistics at the study site.



### Cotreatments

Uniformity in oxygen flow rate and oxygen delivery device use will be maintained except in cases of unacceptable hypoxia. In addition, hypotensive drugs, diuretics, hypnotics, anxiolytics and antipsychotics will not be administered until 1 hour after treatment. Codeine use will be permitted until 12 hours before treatment. The use of inhaled bronchodilators and pulmonary rehabilitation will be restricted for 1 hour before and after treatment.

### Data collection

Blood pressure, heart rate, respiratory rate, SpO<sub>2</sub> and oxygen requirement will be recorded at baseline and at 30 and 60 min after morphine administration. Furthermore, sedation (assessed using the Richmond Agitation Sedation Scale (RASS)),<sup>30 31</sup> vomiting frequency (events/60 min) and the common terminology criteria for adverse events (CTCAE) will be assessed at baseline and 60 min after drug administration. In addition, the CTCAE of all patients will be recorded for 24 hours following drug administration.

**Table 1** Study procedure and time point for evaluation

Time point	Inclusion	Baseline	30 min	60 min	24 hours
Consent, randomisation	✓				
Modified MRC scale	✓				
ECOG PS	✓				
Medicines history	✓				
Smoking history	✓				
Weight	✓				
AST, ALT, T-Bil, Cre	✓				
PaCO <sub>2</sub>	✓				
Ejection fraction	✓				
NRS for current dyspnoea	✓	✓	✓	✓	
Vital signs		✓	✓	✓	
Oxygen		✓	✓	✓	
RASS		✓		✓	
Number of vomiting					
Adverse events					

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; ECOG PS, European Cooperative Oncology Group Performance Status; MRC, Medical Research Council; NRS, Numerical Rating Scale; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; RASS, Richmond Agitation Sedation Scale; T-Bil, total bilirubin.

## Measures

### Demographics and clinical characteristics

Participants' sex, age, body weight, type of ILD, concomitant drug use (corticosteroids, immunosuppressants, anti-fibrotic agents, bronchodilators, pulmonary vasodilators, anxiolytics and codeine), the modified Medical Research Council Dyspnoea Scale,<sup>32</sup> the European Cooperative Oncology Group Performance Status, ejection fraction on ECG, PaCO<sub>2</sub>, SpO<sub>2</sub>, oxygen flow rate, oxygen delivery devices, AST, ALT, T-Bil, creatinine and current dyspnoea intensity at rest in the NRS will be assessed before enrolment.

### Numerical Rating Scale

Current dyspnoea intensity will be assessed using an 11-point Likert-type NRS from 0 (no dyspnoea) to 10 (worst possible dyspnoea).<sup>33</sup>

### Richmond Agitation Sedation Scale

Agitation and sedation will be assessed using the RASS. The RASS is a validated 10-point scale that ranges from -5 (unarousable) to +4 (combative).<sup>30 31</sup>

### Common terminology criteria for adverse events

The worst grade of an adverse event (AE) during the preceding period will be assessed using the CTCAE V.5.0, Japanese Clinical Oncology Group version. Three AEs including somnolence, nausea and delirium will

be investigated because they occur at a relatively high frequency. Other AEs may also be assessed.

## Study endpoints

### Primary endpoint

The primary endpoint is the changes in dyspnoea intensity at rest from baseline to 60 min after treatment as measured using the NRS and compared between the morphine and placebo groups.

### Secondary endpoints

The secondary endpoints include the following: (1) changes in dyspnoea intensity at rest from baseline to 30 min after treatment as measured using the NRS between the morphine and placebo groups; (2) percentage of patients with NRS  $\geq 1$  improvement in dyspnoea intensity at rest from baseline to 60 min after treatment and compared between the morphine and placebo groups; (3) respiratory rate; (4) blood pressure; (5) SpO<sub>2</sub>; (6) heart rate; (7) the frequency of vomiting; (8) RASS and (9) AEs from baseline to 24 hours after treatment.

## Safety

Investigators will record all AEs in electronic data capture systems. All AEs will be followed up throughout the course. All severe AEs will be reported to the certified review board (CRB) and investigators at all sites and discussed.

## Statistical considerations

### Statistical analysis

Comparison of the primary endpoint of changes in NRS score for dyspnoea from baseline to 60 min after treatment between the morphine and placebo groups will be conducted using the two-sided Student's t-test or Wilcoxon rank-sum test, as appropriate, at a significance level of 5% according to the intention-to-treat principle. Point estimates and 95% CIs for the difference between two group means will be calculated.

Comparison of the secondary endpoint of changes in NRS score for dyspnoea from baseline to 30 min after treatment between the morphine and placebo groups will be evaluated similarly to the primary endpoint. Comparison of the rates of patients who experienced improvement in the NRS of  $\geq 1$  from baseline to 30 or 60 min after treatment will be evaluated using the  $\chi^2$  test or Fisher's exact test. Point estimates and 95% CIs for the difference between two mean values will be calculated. A full statistical analysis plan (including the handling of missing values) will be written prior to the data evaluation. We will report AEs separately for patients who receive placebo alone and for those who receive placebo followed by morphine.

### Sample size calculation

The aim of this study is to estimate the efficacy of morphine for dyspnoea in patients with ILDs and gain the data to calculate the sample size for future phase III study. Therefore, we set the sample size as all patients whom we will be able to enrol during the 3-year scheduled period. We plan to recruit 50 patients (25 patients in each group).

### Patient and public involvement

Patients and the public will not be involved in this study. However, the CRB included a representative of a patient group as a member to assess our protocol.

## ETHICS AND DISSEMINATION

### Ethics

All patients will be required to provide a written informed consent. The study will be conducted in accordance with the Declaration of Helsinki and the Clinical Trials Act. The protocol was approved by the Osaka City University CRB (approved number: OCU0006). This trial has been registered at the Japan Registry of Clinical Trials (jRCT) as jRCTs051190030. This study protocol adheres to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013. Modifications in the study protocol will be communicated to the CRB as well as the independent data monitoring committee of the JORTC.

### Dissemination

The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at national and international

conferences. Authorship will be ascribed in accordance with the International Committee of Medical Journal Editors guidelines.

## DISCUSSION

This study protocol describes multicentre, prospective, randomised, placebo-controlled, single-blinded phase II study of morphine against dyspnoea in patients with ILDs. In this phase II study, we expect to obtain data to estimate the efficacy of a single subcutaneous injection of morphine for dyspnoea in patients with ILD and be able to use the data to calculate the sample size for the phase III study.

Recently, Kronborg-White *et al*<sup>22</sup> found in a randomised controlled trial that oral morphine did not significantly reduce dyspnoea compared with placebo in patients with fibrotic ILD. Despite similarities between their trial and our study, there are some differences. First, their trial included outpatients with Medical Research Council scores of  $\geq 3$ , while our study included inpatients with dyspnoea at rest in NRS  $\geq 3$ . Therefore, the patients in our study would be at a more terminal stage of their illness than the patients in their study. Second, the primary endpoint of their study was dyspnoea during the past week, whereas we plan to assess current dyspnoea at rest. Furthermore, trial conducted by Kronborg-White *et al* was small and their study was a single-centre study. Therefore, the efficacy of morphine for dyspnoea in patients with ILD should be evaluated in other studies such as ours.

The strengths of this study are as follows: first, this is one of the few studies to assess the efficacy of morphine for dyspnoea in patients with ILD. Second, this study is a randomised placebo-controlled study; therefore, we can compare the efficacy of morphine with placebo even though this is phase II study.

Several issues related to the content of the trial require discussion. First, this is a single-blinded trial. Clinicians and medical staff, except those who check the self-administered sheet, will be unblinded. If clinicians and medical staff are blinded, other unblinded clinicians or medical staff will be needed to dispose of the treatment drug, that is, morphine or normal saline. To minimise the burden on the clinicians and medical staff at each site, we decided that the clinicians and medical staff would be unblinded. However, the primary endpoint will be assessed using a self-administered sheet and checked by blinded clinicians or medical staff. Thus, the effect of unblinded clinicians or staff will be minimised. Second, the observation period in our study is short, that is, efficacy is assessed within 60 min after treatment and monitoring for AEs is performed for 24 hours after treatment. This is because we assume the patients with ILD in this study to be vulnerable, and longer study periods may result in decreased feasibility; treatments other than morphine could be changed and supplemental oxygen could be provided. Finally, we will not exclude patients who use codeine because many patients with ILD use

codeine for cough. However, codeine will be discontinued for 12 hours prior to the study intervention to minimise its effect on dyspnoea.

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**Contributors** YM: lead author of the study protocol and principal investigator. YM, TM, SO, KA, TY and SI: participated in the design of the study. SO and TY: designed the statistical analysis plan. All authors contributed to writing and revising the manuscript critically, and all gave their final approval of the version to be published.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

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