THE LANCET
Respiratory Medicine

ARTICLES | VOLUME 12, ISSUE 4, P273-280, APRIL 2024 Download Full Issue

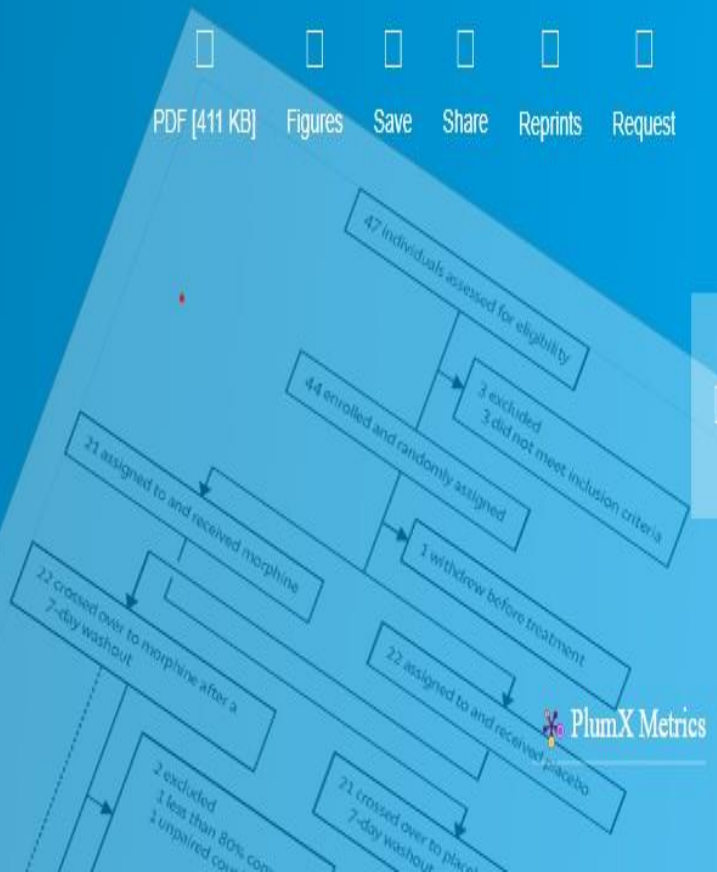
PDF [411 KB] Figures Save Share Reprints Request

Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

Zhe Wu, MD • Lisa G Spencer, MD • Winston Banya • John Westoby † • Veronica A Tudor, MD • Pilar Rivera-Ortega, MD • et al. et al. Show all authors • Show all authors • Show footnotes

Open Access • Published: January 15, 2024 • DOI: https://doi.org/10.1016/S2213-2600(23)00432-0 •

Check for updates



Introduction

Idiopathic pulmonary fibrosis (IPF) is a serious chronic (long term) disease that affects the tissue surrounding the air sacs, or alveoli, in the lungs. This condition develops when that lung tissue becomes thick and stiff for unknown reasons. (National Institutes of Health)

Most patients with IPF report cough, a distressing symptom with substantial physical, social, and psychological consequences, which is associated with rapid disease progression.
Opioids have long been advocated for the suppression of chronic cough.[5]
Morphine is thought to depress the cough reflex, acting directly on the neural pathways in the brain. Antitussive effects might occur with doses lower than those usually required for analgesia. Although morphine is frequently used as a palliative agent for dyspnea in IPF, its effect on cough has never been tested.

Purpose of This article

- Studying the use of low dose controlled-release morphine compared with placebo as an antitussive therapy in individuals with idiopathic pulmonary fibrosis.

Methods

- **Study design**

-study is a phase 2, multicentre, double-blind, placebo-controlled, crossover trial of morphine for the treatment of cough in IPF.

-three specialist centres for interstitial lung disease in the UK were engaged

1) the Royal Brompton Hospital
2) Aintree University Hospital NHS Foundation Trust
3) Manchester University NHS Foundation Trust

The study was approved by the London Brent Research Ethics Committee (20/LO/0368)

• Participants

- Eligible participants were aged 40–90 years, diagnosed with IPF according to the ATS/ERS/JRS/ALAT guidelines[9]

within 5 years before screening, reporting a chronic cough (duration >8 weeks), and a cough severity of 30 mm or higher on the visual analogue scale (VAS). We used a cough VAS of 30 mm or higher (using a scale ranging from 0 mm to 100 mm) on the basis of unpublished data, which suggests that, above this threshold, patients with an IPF-related cough have a significantly worse quality-of-life and higher mortality (unpublished)

	PGI-S 1-2	PGI-S 3	PGI-S 4	PGI-S 5	p values
	Mild	Moderate	Severe	Very severe	
VAS (mm)	22 (11-30)	49 (36-60)	77 (69-86)	91 (90-100)	<0.001
LCQ	16.4 (14.4-17.3)	12.0 (10.0-14.3)	8.3 (6.9-10.4)	7.0 (6.0-10.2)	<0.001

Figure 1. Cough severity visual analogue scale (VAS) and cough-specific health status Leicester Cough Questionnaire (LCQ) for different health severity states

Data presented in median (IQR)

VAS=visual analogue scale; LCQ=Leicester Cough Questionnaire and PGI-S=Patient Global Impression of Severity

inclusion criteria

- forced vital capacity (FVC) >= 45%

-an FEV_1 to FVC ratio of 0·7 or higher

-DLCO >= 30%

-The extent of fibrotic changes seen on resolution CT imaging had to be greater than the extent of emphysema

exclusion criteria

-current smokers

- an acute exacerbation of IPF within 6 months

- significant comorbidity with high coronary artery disease

-significant hepatic or renal impairment

- predicted life expectancy <6 months

- long-term oxygen therapy at rest

-history of drug or alcohol dependency

- previous intolerance to morphine

Prohibited concomitant medications =

immunosuppressive therapy or antibiotics used within 4 weeks of the screening visit, opioids used within 14 days of the screening visit, and angiotensin converting enzyme inhibitors

Randomisation and masking

-Participants were randomly assigned (1:1) to receive controlled-release morphine (5 mg twice daily orally) in period 1 followed by placebo (twice daily orally) in period 2 (sequence 1), or placebo in period 1 followed by morphine in period 2 (sequence 2) using a computer-generated schedule

-Morphine (Napp Pharmaceuticals, Cambridge, UK) was an over-encapsulated tablet and both the morphine and the matched placebo capsule were coloured Swedish orange to maintain masking.

-Patients, investigators, study nurses, and pharmacy personnel were masked to treatment allocation.

• Procedures

-screening visit : participant's medical history and concomitant medication were reviewed, and blood tests (liver and renal function) and physical examination were performed.

-Patients were randomly assigned to a sequence of two treatment periods for 14 days separated by a 7-day washout

-Participants underwent efficacy measurements 24 h before the first dose of study drug and during the last 24 h of each treatment period (on days 0, 14, 22, and 36). These included 24-h ambulatory cough monitoring, assessment of cough VAS, and patient reported outcomes. Patient reported outcomes were emailed to participants from an electronic database (Sealed Envelope EDC) with instructions to complete them within 24 h of the visit. At the end of each treatment period, the global impression of change for cough, breathlessness, and overall quality of life (better, same, or worse) were recorded. A final follow-up remote telephone call was conducted 2 weeks after administration of the last treatment

-Cough frequency was measured using the VitaloJAK cough monitor , which is a custom built ambulatory digital recording device with a lapel microphone and contact sensor applied at the sternum. The sound files were processed using validated custom-written software to remove periods of silence and non-cough sounds.[10] Cough sounds were manually counted with audio-editing software

- **Outcomes :**

1) the percentage change in frequency of daytime or awake cough (coughs per h) from baseline as centrally assessed by objective digital cough monitoring at day 14 (end of period 1) and day 36 (end of period 2).

2) change from baseline in patient reported outcomes , and change from baseline in global impression of change in overall quality of life, cough, and breathlessness.

Results :

-Between Dec 17, 2020, and March 21, 2023, 47 individuals were assessed for eligibility, and 44 were randomly assigned, of whom one withdrew consent before treatment. Of the 43 participants, 21 were randomly allocated to receive morphine in period 1 and then placebo in period 2, and 22 received placebo in period 1 and then morphine in period 2; figure 1). 43 participants completed morphine treatment. In the placebo group, before completion of treatment, one patient was excluded due to withdrawal of consent and one patient died. 41 participants completed placebo. The cough recording failed for two patients (ie, poor sound quality) at one time point, and two patients were found to have had less than 80% treatment compliance during a treatment period. These patients were all included in the ITT analysis but excluded from the per-protocol analysis. All 43 participants were included in the analysis for the primary outcome.

-Mean age : 71 year

-44 participants → 31 male (70%)

-44 participants → 13 female (30%)

-Mean FVC = 2·7 L

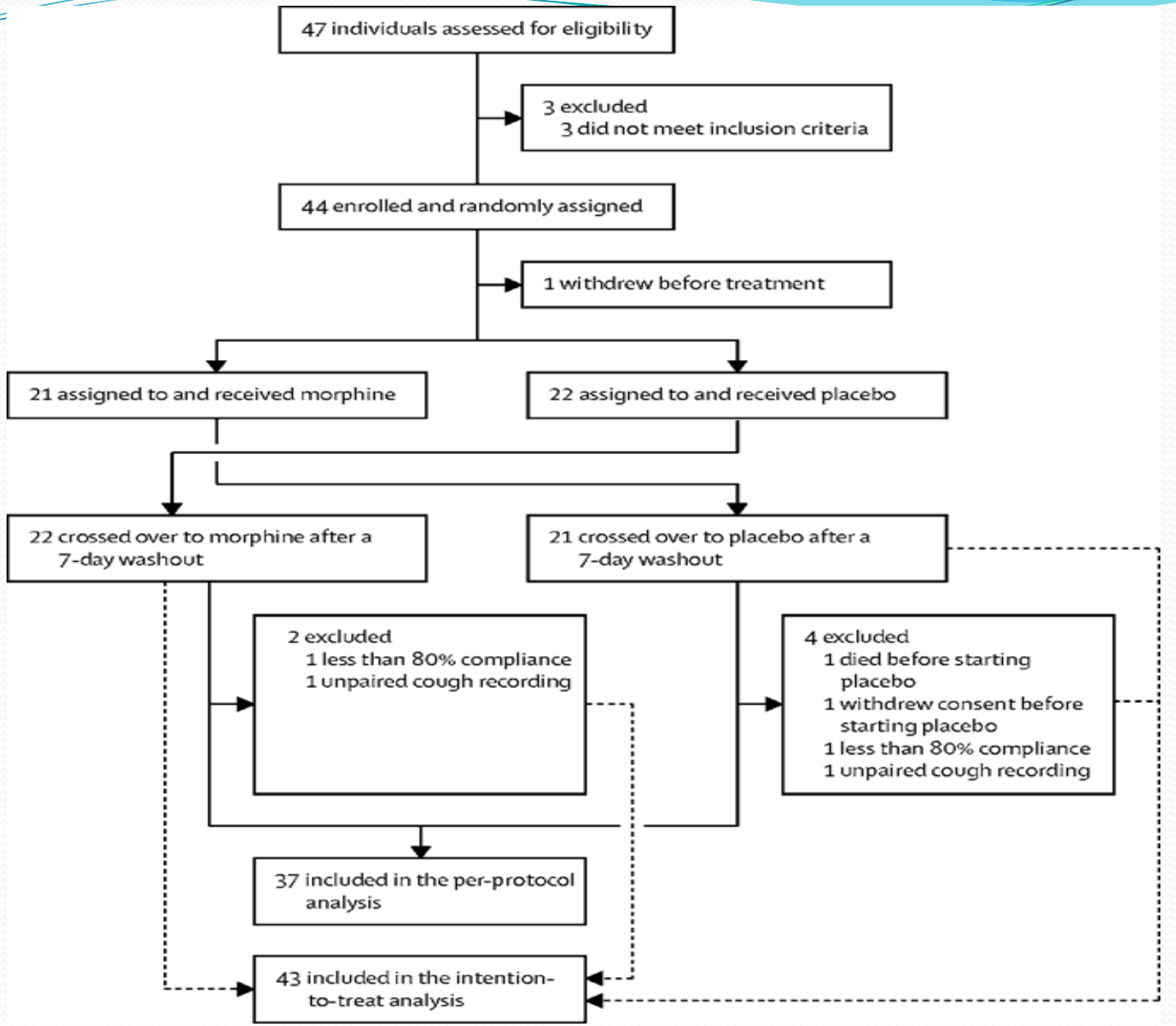
-Mean predicted FVC =82% (17·3)

-Mean predicted DLCO was 48%

-19 (43%) had gastroesophageal reflux disease, 13 (30%) used proton pump inhibitors, and 26 (59%) were on ant fibrotic therapy.

-2 withdrew from the study : one died before starting placebo , one withdrew constent

- treatment adherence : 98% in the morphine group and 98% in the placebo group.


47 individuals assessed for eligibility
3 excluded
3 did not meet inclusion criteria
44 enrolled and randomly assigned
1 withdrew before treatment
21 assigned to and received morphine
22 assigned to and received placebo
22 crossed over to morphine after a 7-day washout
21 crossed over to placebo after a 7-day washout
2 excluded
1 less than 80% compliance
1 unpaired cough recording
4 excluded
1 died before starting placebo
1 withdrew consent before starting placebo
1 less than 80% compliance
1 unpaired cough recording
37 included in the per-protocol analysis
43 included in the intention-to-treat analysis

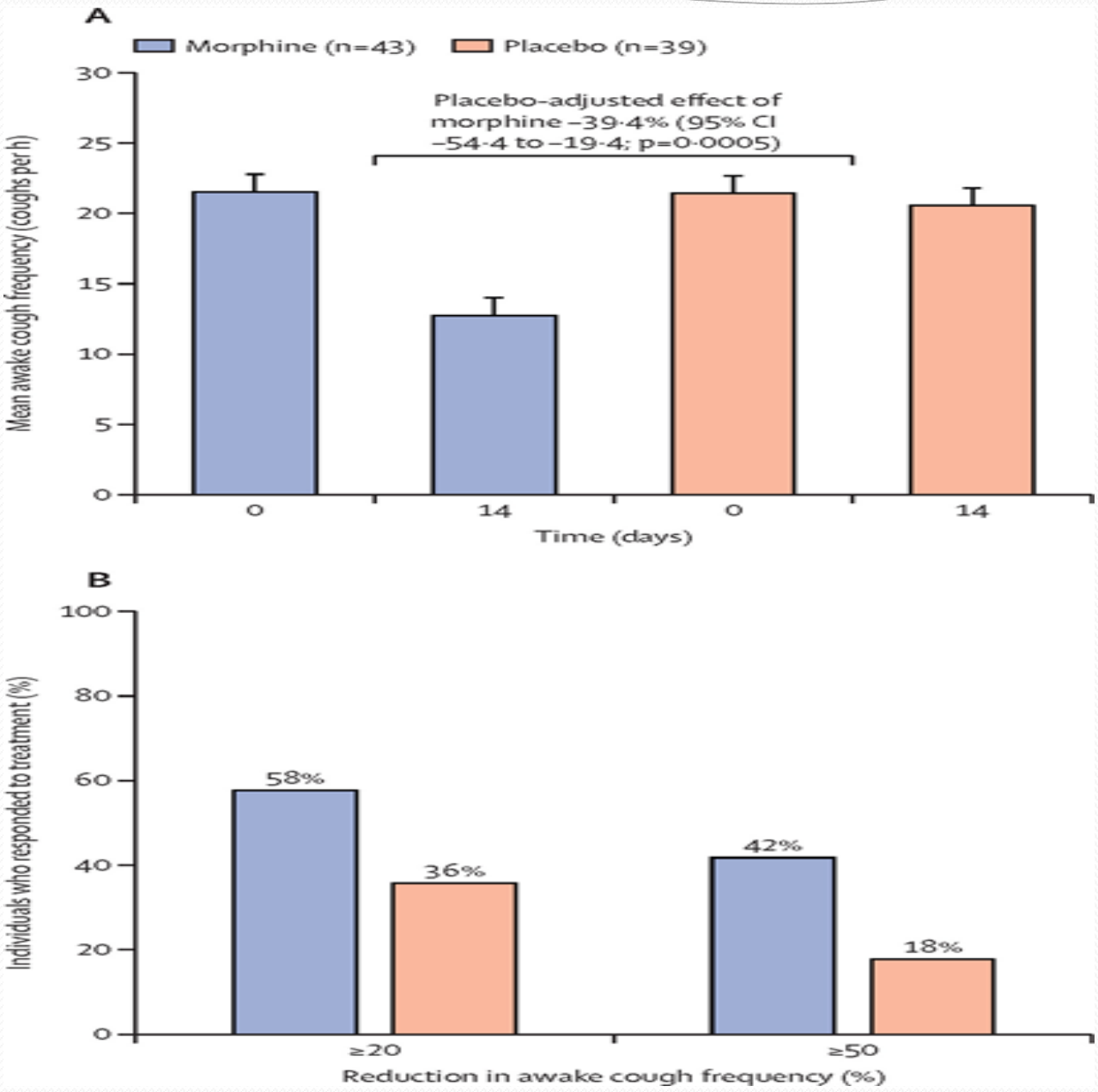
- **Results :**

-In the analysis for the primary outcome, controlled-release morphine treatment reduced daytime cough frequency by 39·4% compared with placebo (figure 2A).

-Mean daytime cough frequency changed from 21·6 coughs per h at the baseline to 12·8 coughs per h on day 14 with morphine treatment, and from 21·5 coughs per h at the baseline to 20·6 (1·2) coughs per h at day 14 in the placebo group

-In the per-protocol analysis, treatment with morphine reduced daytime cough frequency by 40·3% (−55·9 to −18·9; p=0·0009) compared with placebo (table 2).

-Treatment with controlled-release morphine improved all cough-related patient-reported outcomes: cough VAS reduced by 16·1 mm and Leicester Cough Questionnaire increased by 1·8 points from baseline.


A
Morphine (n=43)
Placebo (n=39)
Placebo-adjusted effect of morphine −39·4% (95% CI −54·4 to −19·4; p=0·0005)
Mean awake cough frequency (coughs per h)
30
25
20
15
10
5
0
0
14
0
14
Time (days)
B
Individuals who responded to treatment (%)
100
80
60
40
20
0
58%
36%
42%
18%
≥20
≥50
Reduction in awake cough frequency (%)

-Scores reduced for L-IPF impacts (−5·2 points) and L-IPF overall symptoms (−5·2 points) with morphine, with improvement in the cough domain (−10·8 points) . These effects remained significant when adjusting for placebo (table 2). A period effect was observed in the L-IPF Symptoms cough domain, with patients in period 2 reporting higher scores, indicating worse cough (7·5 points).

-Morphine had no effect on breathlessness (as measured by Dyspnea-12 and L-IPF Symptoms dyspnea domain), anxiety or depression scores (Hospital and Depression Scale), King's Brief Interstitial Lung Disease questionnaire, or L-IPF Symptoms energy domain. With respect to global impression of change, morphine treatment led to an improvement in cough in over half of participants (24 [56%] of 43) and overall quality of life in a third (14 [32%] of 43).

-In the cough responder analysis, morphine reduced awake cough frequency by 20% or more in 25 (58%) of 43 participants and by 50% or more in 18 (42%) of 43 participants .

- In the placebo group, awake cough frequency reduced by 20% or more in 14 (36%) of 39participants and by 50% or more in seven (18%) of 39 participants.

-Adverse events were observed in 17 (40%) of 43 participants in the controlled-release morphine treatment group and six (14%) of 42 participants in the placebo group (table 3).

-The most common side-effects with morphine were constipation (nine [21%] of 43 participants) and nausea (six [14%] of 43 participants). Initiation of laxatives was not required during treatment with morphine.

-One participant developed nausea (moderate) and hypersomnia (severe) with morphine treatment and discontinued treatment, having taken half of the prescribed regimen.

- Only one severe adverse event occurred (lung infection resulting in death during placebo treatment), which was attributed to underlying IPF disease trajectory.

Discussion :

-This multicentre study shows that low-dose controlled-release morphine is effective in reducing awake cough frequency and improving quality of life in participants with significant IPF-related cough. Morphine reduced daytime cough frequency by at least 20% and improved the global impression of change in cough in more than half of patients. The improvements seen in patient reported outcomes were robustly mirrored across multiple tools. Treatment was generally well tolerated by most participants.

-There is a large unmet need for treatments that improve quality of life in individuals with IPF and address highly prevalent and frequently disabling symptoms like cough. A recent study assessing the longitudinal effects of cough burden on quality of life in IPF highlighted the stability of this symptom over time.[13]

-Insufficient clarity about the pathogenic mechanisms driving cough in IPF has limited the therapeutic options available to patients and clinicians. Individuals with IPF have been shown to have a more sensitive cough reflex than healthy volunteers.

Use of opioids in patients with chronic respiratory disease is often curbed due to concerns about side-effects and the potential for addiction and abuse. In a recent trial, extended release nalbuphine, a dual acting κ-opioid agonist or μ-opioid antagonist, reduced awake cough frequency in individuals with IPF by 51·6%.

However, almost a quarter of participants discontinued treatment during nalbuphine treatment due to side-effects. Further studies are required to establish a dose that preserves clinical benefit with optimal tolerability

By contrast, in our trial only one participant discontinued low-dose controlled-release morphine treatment and a lower proportion of participants developed side-effects than participants in the nalbuphine study.

And Finally :

Treatment with low dose controlled-release morphine significantly improved objective and subjective cough measures in patients with IPF-associated cough. Given the negative effects of cough in individuals with IPF, these findings merit its short-term use in clinical practice. Longer term studies should be the focus of future research.


شكرا
рахмат
danke
謝謝
ngiyabonga
teşekkür ederim
Баярлалаа
спасибо
faafetai lava
mersi
kia ora
barka
welalin
tack
spas
dank je
misaotra
paldies
grazzi
mahalo
tapadh leat
vinaka
спасибі
blagodaram
matondo
thank you
gracias
kiitos
dankie
nanni
nandri
dhanyavad
köszönöm
mauruuru
hvala
bedankt
bayarlalaa
grăçie
enkosi
akun
dankon
ačiū
djiere dieuf
tau
mochchakkeram
хвала
asante
manana
obrigada
tenki
murakoze
chokrane
mamnun
дякую
dziękuję
chnorakaloutioun
gratias ago
gràcies
sulpáy
go raibh maith agat
sobodi
děkuji
sagolun
sukriya
kop khun krap
taiku
obrigado
mèsi
ありがとう
tanemirt
grazie
arigatô
takk
dakujem
trugarez
didi madloba
najis tuke
rahmat
terima kasih
kam sah hamnida
rahmet
diolch
dhanyavadagalu
shukriya
merce
мерси
তোমাকে ধন্যবাদ
감사합니다
xièxie
merci
ευχαριστώ