

ORIGINAL ARTICLE

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

Toby M. Maher, M.D., Ph.D.,^{1,2} Cristina Avram, M.D.,³ Enoch Bortey, Ph.D.,⁴ Simon P. Hart, M.D., Ph.D.,⁵ Nikhil Hirani, M.D., Ph.D.,⁶ Philip L. Molyneux, M.D., Ph.D.,² Joanna C. Porter, M.D., Ph.D.,² Jaclyn A. Smith, M.D., Ph.D.,⁷ and Thomas Sciascia, M.D.⁸

Abstract

BACKGROUND There are no approved therapies for cough in patients with idiopathic pulmonary fibrosis (IPF). In this small crossover trial we administered nalbuphine extended-release tablets (NAL ER) as a potential cough therapy for such patients.

METHODS This randomized, double-blind, placebo-controlled, crossover trial involved two 22-day treatment periods (NAL ER→placebo and placebo→NAL ER) separated by a 2-week washout period. NAL ER was started at a dose of 27 mg once daily and was titrated up to 162 mg twice daily at day 16. The primary end point was percent change from baseline in hourly daytime objective cough frequency as measured by an electronic cough monitor. The daytime period was defined as the patient-reported time of awakening and bedtime. Secondary end points included change in objective 24-hour cough frequency, changes in cough frequency, cough severity, and breathlessness, per patient-reported outcomes.

RESULTS A total of 41 patients were randomly assigned and received one or more doses of study medication. There was a 75.1% reduction in daytime objective cough frequency during the NAL ER treatment period versus the placebo treatment period of 22.6%, a 52.5 percentage point placebo-adjusted decrease from baseline ($P<0.001$) at day 21. There was a 76.1% (95% confidence interval, 83.1 to 69.1) decrease in the 24-hour objective cough frequency with NAL ER, versus a 25.3% (43.9 to 6.7) decrease with placebo, a 50.8 percentage point placebo-adjusted change. Nausea, fatigue, constipation, and dizziness were more common with NAL ER than with placebo.

CONCLUSIONS In this short-term crossover trial, NAL ER reduced cough in individuals with IPF. Larger and longer trials are needed to assess the impact on cough versus drug adverse effects. (Funded by Trevi Therapeutics; ClinicalTrials.gov number, [NCT04030026](https://clinicaltrials.gov/ct2/show/study/NCT04030026).)

The author affiliations are listed at the end of the article.

Dr. Maher can be contacted at tobymahe@usc.edu or at Keck School of Medicine, University of Southern California, Los Angeles, CA 90089.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial pneumonia of unknown cause¹ with a median untreated survival of 2.5 to 3.5 years from time of diagnosis.² The prevalence of chronic cough in individuals with IPF has been reported to be as high as 84% and may be an independent predictor of disease progression and time to death or lung transplant.^{3,4}

The antifibrotics pirfenidone and nintedanib are the only approved therapies for IPF; however, in randomized trials they did not show an effect on cough, breathlessness, or patient well-being.⁵⁻⁷ A small observational study did, however, report an improvement in cough with pirfenidone treatment.⁸ Opioid drugs are frequently used to manage symptoms including cough in individuals with IPF in the terminal stages of their disease. A lack of robust trial evidence and concerns regarding adverse effects frequently preclude the use of opioids in patients with early disease. Nalbuphine (NAL) belongs to the “opioid agonist-antagonists” drug class.⁹ In extended-release (ER) form, oral NAL could potentially provide therapeutic benefits of opioid-based drugs while minimizing adverse events (AEs), but NAL ER has not been subject to a test of this potential. In this report we provide a preliminary assessment of the antitussive potential and adverse-effect profile of NAL ER in individuals with IPF-related cough in a randomized, double-blind, ascending-dose, crossover trial.

Methods

TRIAL OVERSIGHT

The trial was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines and other applicable laws and regulations. Ethical approval was provided by the North West-Greater Manchester South Research Ethics Committee. All patients provided written informed consent before beginning the trial. An independent Data and Safety Monitoring Board (DSMB) conducted unblinded monitoring of patient safety throughout the trial.

T.S. and T.M.M. designed the trial. All of the authors had access to the data, which were analyzed by E.B. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol

(available with the full text of this article at evidence.nejm.org). The first draft of the manuscript was prepared by T.S. with editorial assistance presubmission and medical writing assistance postsubmission by Juliet H. A. Bell, Excerpta Medica, funded by trial sponsor Trevi Therapeutics. The authors provided final approval for submission of the manuscript for publication.

PATIENT POPULATION

Eligible patients were age 18 years of age or older and had a multidisciplinary team-assigned diagnosis of “definite” or “probable” IPF in accordance with international guidelines current at the time of recruitment.¹ Other key inclusion criteria included a history of self-reported chronic cough of more than 8 weeks’ duration and daytime cough severity rated 4 or higher on the Cough Severity Numerical Rating Scale (CS-NRS; 11-point Likert scale ranging from 0 [“no cough”] to 10 [“worst possible cough”]); forced vital capacity greater than 40% of predicted; and diffusing capacity of the lung for carbon monoxide corrected for hemoglobin greater than 25% of predicted within the previous 6 months. Key exclusion criteria included interstitial lung disease known to be caused by environmental exposure, connective tissue disease, or drug-related toxicity; current use of continuous oxygen therapy for more than 16 hours per day; and any change in IPF-related drug treatment regimen within 8 weeks of screening. The comprehensive list of inclusion and exclusion criteria is provided in the Supplementary Appendix.

TRIAL DESIGN AND ASSESSMENTS

Eligible patients were randomly assigned at 11 sites across the United Kingdom using voice response systems or interactive Web response systems in a 1:1 ratio to receive either NAL ER in Treatment Period 1, followed by crossover to placebo in Treatment Period 2, or placebo in Treatment Period 1 followed by NAL ER in Treatment Period 2. Each treatment period was followed by a 2-week washout period. Patients on NAL ER initially received a dose of 27 mg once daily. This increased to 54 mg twice daily on day 5, 108 mg twice daily on day 9, and 162 mg twice daily on day 16. Patients were to have their doses escalated only if they did not develop dose-limiting adverse effects, in which case treatment was interrupted.

Study visits included screening to determine eligibility and then, for each treatment period, visits or phone contact at day -1 for baseline assessments and at days 8, 15, and 21

during treatment and a follow-up at the end of the 2-week washout period.

During the coronavirus disease 2019 pandemic, the protocol was amended in order to minimize potential patient risk by limiting in-person exposure (see the Supplementary Appendix for further details).

END POINTS

The primary end point was mean change in daytime cough frequency (coughs per hour) from study baseline as assessed by a digital cough recorder at day 22 of each treatment period (VitaloJAK; Vitalograph Ltd, Buckingham, United Kingdom); daytime was defined as the period between the time the patient reported being awake and the time the patient went to bed.¹⁰ Secondary end points included change from baseline in 24-hour cough at day 22 of treatment; patient-reported outcomes for mean change in the Evaluating Respiratory Symptoms (E-RS™:IPF¹¹) diary of cough frequency (scored 0 to 4) and breathlessness (scored 0 to 23) from baseline at days 9, 16, and 22 of treatment (a higher score on the scale indicates a more severe grade to the symptom; for details of the scoring system see the Supplementary Appendix); mean change in CS-NRS from baseline at days 8, 15, and 21 (a score of 0 indicates “No Cough” and a score of 10 for an assessment of “Worst Possible Cough”); and mean change in the Patient-Reported Outcomes Measurement Information System (PROMIS) Item Bank v1.0 Fatigue Short Form 7a scale (score 0 to 35; higher scores indicate more severe fatigue) from baseline at day 21 of treatment. Physician assessment analysis was mean change in the Clinical Global Impression of Change-Cough (CGI-C; 7-point scale ranging from 1 to 7; a score of 1-3 for assessments between “Very Much Improved” to “Minimally Improved,” a score of 5-7 for assessments between “Minimally Worse” to “Very Much Worse” and a score of 4 for an assessment of “No Change”) from baseline at day 21 of treatment.

Safety was assessed on the basis of AEs, clinical laboratory measurements, central cardiac core laboratory-read electrocardiograms (ECGs), vital signs, spirometry, and physical examinations. AEs were assessed using the five-category Common Terminology Criteria for AEs (CTCAE) v4.03 grading system. Patients completed the Subjective Opiate Withdrawal Scale (SOWS)¹² on a daily basis via an electronic diary for 14 days following the last dose of the investigational product at the end of each treatment period. The scoring criteria for SOWS is 1 to 10 for mild, 11 to 20 for

moderate, and 21 or greater for severe withdrawal¹³ (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Sample size calculations are provided in the Supplementary Appendix. The primary analysis utilized the natural log scale of the daytime objective cough frequency data. The data were analyzed using a mixed-model repeated-measures analysis. Two-sided P values were calculated from the placebo-adjusted change estimates for both the primary and secondary analyses; sample size and power considerations were based on NAL ER tablet treatment compared with placebo tablets at the 5% significance level (two-sided). The difference between NAL ER at the 162-mg dose and placebo was estimated using a model with sequence, period, and treatment as fixed effects; the log-transformed study baseline cough frequency was used as a covariate and the change from baseline in log-transformed scale (i.e., log-transformed daytime cough frequency at day 21 – log-transformed baseline) was used as the dependent variable. The model variance-covariance matrix was compound symmetry. No imputation for dropouts or missing data was performed for assessments not completed at study visits. In case no cough was registered during daytime, one cough was imputed for derivation of daytime cough frequency in order to allow for log transformation.

In the presentation of results, log-scale fitted mean treatment group differences at day 21 together with associated 95% confidence intervals (CIs) were back-transformed to fitted ratios of geometric mean and were interpreted as the difference of NAL ER versus placebo in daytime cough-rate reduction from baseline.

Descriptive statistics were provided for continuous data in terms of the number of patients with nonmissing values, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise stated. Categorical data were summarized in terms of the number of patients providing data at the relevant time point, frequency counts, and percentages. The denominator for the proportion was based on the number of patients who provided nonmissing responses to the categorical variable. No multiplicity adjustments for the secondary and exploratory end points were defined. Therefore, only point estimates and 95% CIs are provided. The CIs have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

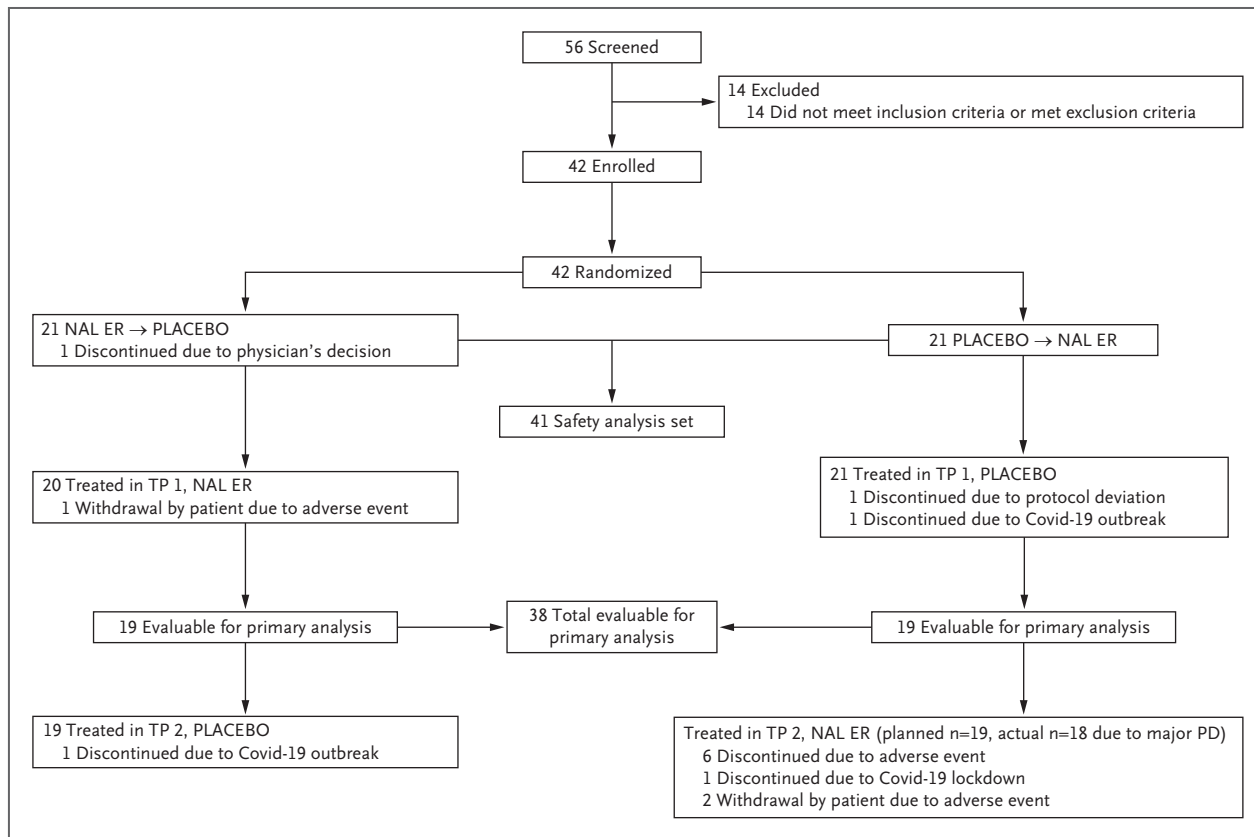


Figure 1. Patient Disposition.

Covid-19 denotes coronavirus disease 2019; NAL ER, nalbuphine extended-release tablets; PD, protocol deviation; and TP, treatment period.

Results

PATIENTS

From October 2019 through February 2022, 56 patients were screened and 14 patients failed screening (most commonly because of unwillingness to comply with study requirements and restrictions [n=3] and diffusing capacity of the lung for carbon monoxide corrected for hemoglobin less than 25% predicted of normal within the past 6 months [n=3]). A total of 42 patients were assigned to receive either NAL ER→placebo or placebo→NAL ER. One patient was randomly assigned but not treated, and treatment was discontinued prematurely in 13 patients (31.0%) (Fig. 1).

The majority of patients were male (84.2%) and their mean age was 74 years; 47.4% were receiving background antifibrotic therapies and 68.3% were taking proton pump

inhibitors (Table 1). Demographic characteristics by initial treatment regimen are provided in Table S1 and indicate older, mostly White male patients in this small trial population; the representativeness of this population is shown in Table S2.

PRIMARY END POINT

NAL ER-treated patients had a 75.1% reduction (95% CI, –82.7 to –67.6) in the geometric mean percent change compared with a 22.6% reduction (95% CI, –42.5 to –2.7) during the placebo treatment period at day 22; this represents a 52.5 percentage point placebo-adjusted change for treatment with NAL ER ($P<0.001$) (Fig. 2). An analysis by assigned treatment and treatment period showed a geometric mean ratio of 0.33 (95% CI, 0.18 to 0.62) between NAL ER and placebo for NAL ER→placebo patients and a geometric mean ratio of 0.26 (95% CI, 0.11 to 0.62) for patients who received the placebo→NAL ER sequence (Table S2). Furthermore, analysis of sequence effect

Table 1. Baseline Characteristics.	
No. of patients	38
Mean age — yr	74
Male — no. (%)	32 (84.2)
Antifibrotic usage — no. (%)	18 (47.4)
Proton pump inhibitors — no. (%)*	28 (68.3)
Daytime cough frequency (coughs/hour)	
Mean	28.0
Median	20.0
Minimum–maximum	3.2–92.4
24-hour cough frequency (coughs/hour)	
Mean	21.2
Median	16.0
Minimum–maximum	3.1–66.4

* These data are collected from the safety analysis set (n=41). All other data are from the full analysis set (patients completed one or more treatment periods).

(equivalent to a test of carryover effect) yielded a point estimate of -0.017 , with 95% CIs of -0.59 to 0.55 . Because the 95% CI includes the null value, we conclude there was no evidence of a carryover effect between treatment periods.

Supplemental primary efficacy analyses were also performed using responder analyses for patients reaching predetermined reduction thresholds for NAL ER versus placebo (Fig. S1). Efficacy analyses of 24-hour cough

counts for patients with and without concomitant antifibrotic therapy are provided in Figure S2.

PRESPECIFIED SECONDARY EFFICACY ANALYSES

Twenty-four-hour objective cough data (geometric mean percent change) showed a 76.1% improvement (95% CI, -83.1 to -69.1) for patients during the NAL ER treatment period compared with a 25.3% (95% CI, -43.9 to -6.7) improvement in patients during the placebo treatment period; this was a 50.8 percentage point placebo-adjusted change (Fig. 2).

SECONDARY END POINTS

Further secondary end points are shown in Figure 3. The E-RS:IPF diary cough subscale showed a mean (SD) score of 1.6 (0.85) with NAL ER compared with 2.3 (0.77) with placebo at day 22 (Fig. 3A), and mean (SD) CS-NRS scores at day 21 were 3.9 (2.28) and 6.0 (1.74), respectively (Fig. 3B). Furthermore, The E-RS:IPF diary breathlessness subscale analysis showed a mean (SD) score of 6.6 (3.83) with NAL ER compared with 6.9 (3.82) with placebo (Fig. 3C).

Using the CGI-C the principal investigators indicated that at day 21, 62% of the patients receiving the study drug had an improvement in their cough, compared with 19% for placebo (Fig. S3). PROMIS Fatigue Short

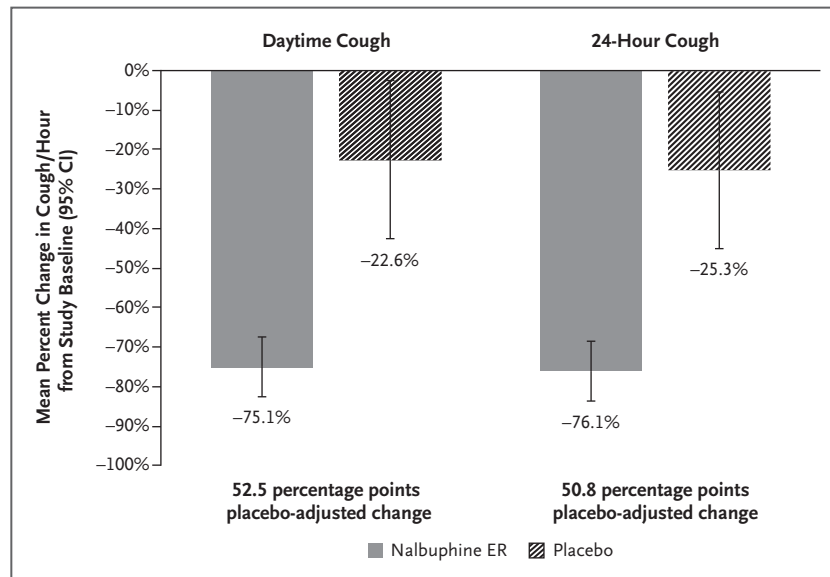


Figure 2. Geometric Mean Percent Change from Study Baseline in Coughs per Hour (n=38).

Daytime was defined as the period between the time the patient reported being awake and the time the patient went to bed. CI denotes confidence interval; and ER, extended release.

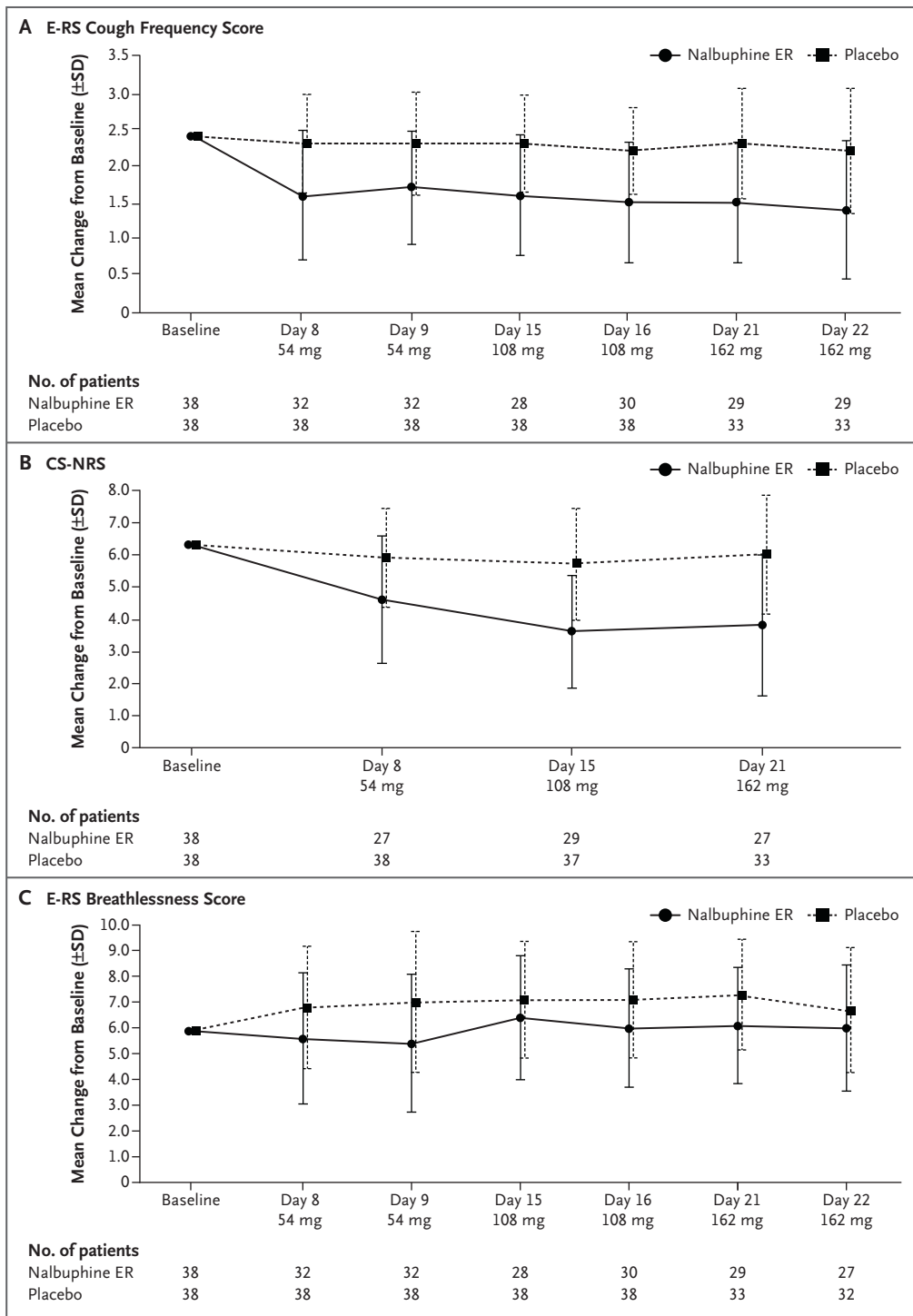


Figure 3. Mean Change from Study Baseline for Patient-Reported Outcomes.

E-RS cough frequency (Panel A) is scored 0 to 4; CS-NRS (Panel B) is scored 0 to 10; E-RS breathlessness (Panel C) is scored 0 to 23. CS-NRS denotes Cough Severity Numerical Rating Scale; E-RS, Evaluating Respiratory Symptoms; for all three panels a decrease in score represents a clinical improvement; ER, extended release; and SD, standard deviation.

Table 2. Adverse Events.			
Adverse Events	NAL ER* Twice Daily (n=38) — no. (%)	Placebo (n=40) — no. (%)	Total (n=41) — no. (%)
Patients with treatment-emergent adverse events leading to investigational product discontinuation			
Vomiting	2 (5.3)	0	2 (4.9)
Agitation	1 (2.6)	0	1 (2.4)
Anxiety	1 (2.6)	0	1 (2.4)
Bradycardia	1 (2.6)	0	1 (2.4)
Dyspnea	1 (2.6)	0	1 (2.4)
Headache	1 (2.6)	0	1 (2.4)
Insomnia	1 (2.6)	0	1 (2.4)
Lethargy	1 (2.6)	0	1 (2.4)
Mental disorder	1 (2.6)	0	1 (2.4)
Suicidal ideation	1 (2.6)	0	1 (2.4)
Vertigo	1 (2.6)	0	1 (2.4)
Treatment-emergent adverse events with 10% or greater frequency			
Nausea	16 (42.1)	0 (0)	16 (39.0)
Fatigue	12 (31.6)	3 (7.5)	15 (36.6)
Constipation	11 (28.9)	2 (5.0)	13 (31.7)
Dizziness	10 (26.3)	0 (0)	10 (24.4)
Somnolence	9 (23.7)	1 (2.5)	9 (22.0)
Vomiting	7 (18.4)	5 (12.5)	10 (24.4)
Dyspnea	6 (15.8)	2 (5.0)	8 (19.5)
Dry mouth	5 (13.2)	1 (2.5)	5 (12.2)
Headache	5 (13.2)	5 (12.5)	10 (24.4)
Anxiety	5 (13.2)	0 (0)	5 (12.2)
Decreased appetite	4 (10.5)	3 (7.5)	7 (17.1)
Depression	4 (10.5)	0 (0)	4 (9.8)

* NAL ER denotes nalbuphine extended-release tablets.

Form 7a data for both treatment groups are provided in Figure S4.

SAFETY DATA

There were no deaths, and two serious AEs were reported during the trial. One patient had pneumonia during the placebo period of the crossover; this patient had never received NAL ER. One case of urosepsis was reported 2 weeks after the patient's final NAL ER dose. A common clinical finding with opioids can be tolerability during drug initiation.^{14,15} In this forced-titration study design, AEs leading to discontinuation occurred in nine patients on NAL ER (Table 2): Six patients were discontinued on day 5 (40.5-mg mean dose at time of discontinuation) or earlier and three patients on day 14 (108.0 mg) or earlier. No patients discontinued study medication for an AE after completing dose titration. There were no significant safety-related concerns raised by the DSMB during the course of the study.

Gastrointestinal and central nervous system AEs were more common in the NAL ER dosing periods. Of the AEs, 95% were of grade 1 or 2 in severity, and 51% of these AEs had clinically resolved after 7 days. Twelve grade-3 AEs were reported by four patients (eight events during the NAL ER period and four events during the placebo period). The most frequently reported AEs during the NAL ER treatment period were nausea (42.1%), fatigue (31.6%), constipation (28.9%), and dizziness (26.3%); in the placebo period, no patients reported nausea, whereas 7.5% reported fatigue and 5.0% reported constipation. None reported dizziness (Table 2).

There were no significant changes in vital signs, pulse oximetry, spirometry readings, or clinical laboratory values. Two patients developed ECG abnormalities (one patient with a known past history of atrial fibrillation developed atrial fibrillation and another patient withdrew from the study secondary to sinus bradycardia).

SOWS data were evaluated for 36 patients after the NAL ER treatment period and for 38 patients after the placebo treatment period. The mean SOWS total raw scores in the NAL ER treatment group were 4.71 versus 2.41 in the placebo treatment group ($P=0.0029$). No patients received treatment for an AE related to discontinuation of the study drug.

Discussion

Our short-term crossover trial demonstrated a statistically significant reduction in IPF-related cough; cough was monitored using a dedicated monitor to provide an objective measure of daytime cough frequency. These data therefore provide equipoise for a larger and longer trial of NAL ER for the treatment of chronic cough in patients with IPF in which the longer-term adverse effects and habituation associated with chronic opioid use can be reliably judged against its clinical benefits.

IPF-related cough is clinically reported to be refractory to conventional antitussive therapy and currently available antifibrotics.^{8,16} Although opioids are traditionally considered effective antitussive agents, there has not been a well-designed controlled clinical trial investigating any opioid-class drug for IPF-related chronic cough. Although positive results have been reported from small trials of low-dose morphine in refractory and unexplained chronic cough,^{17,18} the main barrier to adoption of opioid treatment is concern about physical dependence and misuse.

In this 3-week study there was no clinical evidence of withdrawal symptoms, and scores self-reported by the patients were consistent with the clinical assessment that there were no AEs suggestive of drug withdrawal. However, longer treatment periods will be required to better assess any risk for inducing the development of physical dependence, determining any potential for developing a substance use disorder, and establishing a titration scheme for drug initiation. Nausea, fatigue, constipation, and dizziness were reported in more than 25% of NAL ER patients, which should be balanced with the observed efficacy results. These safety results are similar to those of a trial of low-dose morphine in chronic cough that reported constipation and drowsiness in 40% and 25% of patients, respectively.¹⁷

There were limitations to this trial. A proportion of patients discontinued treatment (31.0%), mainly due to the coronavirus disease 2019 pandemic ($n=3$) and AEs ($n=9$),

which led to a smaller sample size. Future trials should have longer duration, a larger sample size, and a parallel-group design to avoid the need for a washout period.

In conclusion, treatment with NAL ER for 3 weeks resulted in a rapid and marked reduction in recorded daytime cough among patients with IPF-related cough. Although our trial was not designed to statistically test other outcomes, the data are encouraging enough to merit further assessment in longer and larger clinical studies. Such trials permit weighing the long-term effects on cough against the adverse effects and loss of efficacy due to habituation associated with chronic opiate use.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

The study was funded by Trevi Therapeutics.

Author Affiliations

- ¹ Keck School of Medicine, University of Southern California, Los Angeles
- ² National Heart and Lung Institute, Imperial College London, London
- ³ Northwest Interstitial Lung Disease Unit, Manchester University NHS Foundation Trust, Manchester, United Kingdom
- ⁴ Pharmaceutical Development Strategies, LLC, Chapel Hill, NC
- ⁵ University of Hull, Hull, United Kingdom
- ⁶ Centre for Inflammation Research, University of Edinburgh, Edinburgh
- ⁷ Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, Manchester, United Kingdom
- ⁸ Trevi Therapeutics, New Haven, CT

References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical guideline. *Am J Respir Crit Care Med* 2018;198:e44-e68. DOI: [10.1164/rccm.201807-1255ST](https://doi.org/10.1164/rccm.201807-1255ST).
2. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431-440. DOI: [10.1164/rccm.201006-0894CI](https://doi.org/10.1164/rccm.201006-0894CI).
3. Ryerson CJ, Abbritti M, Ley B, Elicker BM, Jones KD, Collard HR. Cough predicts prognosis in idiopathic pulmonary fibrosis. *Respirology* 2011;16:969-975. DOI: [10.1111/j.1440-1843.2011.01996.x](https://doi.org/10.1111/j.1440-1843.2011.01996.x).
4. Lee J, White E, Freiheit E, et al. Cough-specific quality of life predicts disease progression among patients with interstitial lung disease: data from the pulmonary fibrosis foundation patient registry. *Chest* 2022;162:603-613. DOI: [10.1016/j.chest.2022.03.025](https://doi.org/10.1016/j.chest.2022.03.025).
5. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071-2082. DOI: [10.1056/NEJMoa1402584](https://doi.org/10.1056/NEJMoa1402584).

6. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083-2092. DOI: [10.1056/NEJMoa1402582](https://doi.org/10.1056/NEJMoa1402582).
7. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J* 2016;47:243-253. DOI: [10.1183/13993003.00026-2015](https://doi.org/10.1183/13993003.00026-2015).
8. van Manen MJG, Birring SS, Vancheri C, et al. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2017;50:1701157. DOI: [10.1183/13993003.01157-2017](https://doi.org/10.1183/13993003.01157-2017).
9. Yaksh T, Wallace M. Opioids, analgesia, and pain management. In: Brunton, L, Chabner, B, Knollman, B, eds. *Goodman & Gilman's pharmacological basis of therapeutics*. 12th ed. Columbus, OH: McGraw Hill, 2011:481-527.
10. Smith JA, Holt K, Dockry R, et al. Performance of a digital signal processing algorithm for the accurate quantification of cough frequency. *Eur Respir J* 2021;58:2004271. DOI: [10.1183/13993003.04271-2020](https://doi.org/10.1183/13993003.04271-2020).
11. Bacci ED, O'Quinn S, Leidy NK, Murray L, Vernon M. Evaluation of a respiratory symptom diary for clinical studies of idiopathic pulmonary fibrosis. *Respir Med* 2018;134:130-138. DOI: [10.1016/j.rmed.2017.11.011](https://doi.org/10.1016/j.rmed.2017.11.011).
12. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987;13:293-308. DOI: [10.3109/00952998709001515](https://doi.org/10.3109/00952998709001515).
13. Queensland alcohol and drug withdrawal clinical practice guidelines. Queensland Health. August 2012 (https://adis.health.qld.gov.au/sites/default/files/resource/file/qh_detox_guide.pdf).
14. Petrone D, Kamin M, Olson W. Slowing the titration rate of tramadol HCl reduces the incidence of discontinuation due to nausea and/or vomiting: a double-blind randomized trial. *J Clin Pharm Ther* 1999;24:115-123. DOI: [10.1046/j.1365-2710.1999.00203.x](https://doi.org/10.1046/j.1365-2710.1999.00203.x).
15. Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. *Pharmacotherapy* 1999;19:88-93. DOI: [10.1592/phco.19.1.88.30515](https://doi.org/10.1592/phco.19.1.88.30515).
16. van Manen MJG, Geelhoed JJ, Tak NC, Wijsenbeek MS. Optimizing quality of life in patients with idiopathic pulmonary fibrosis. *Ther Adv Respir Dis* 2017;11:157-169. DOI: [10.1177/1753465816686743](https://doi.org/10.1177/1753465816686743).
17. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. *Am J Respir Crit Care Med* 2007;175:312-315. DOI: [10.1164/rccm.200607-892OC](https://doi.org/10.1164/rccm.200607-892OC).
18. Al-Sheklly B, Mitchell J, Issa B, et al. S35 Randomised control trial quantifying the efficacy of low dose morphine in a responder group of patients with refractory chronic cough. *Thorax* 2017;72(Suppl 3): A24-A25. DOI: [10.1136/thoraxjnl-2017-210983.41](https://doi.org/10.1136/thoraxjnl-2017-210983.41).