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.[6], Nikhil Hirani, M.D., Ph.D.[7], Philip L. Molyneux, M.D., Ph.D.[2], Joanna C. Porter, M.D., Ph.D.[2], Jaclyn A. Smith, M.D., Ph.D.[8], and Thomas Sciascia, M.D.[5]

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

Corresponding author: Dr Toby M. Maher, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; tobymahe@usc.edu

Twitter handle(s): @TreviThera

ABSTRACT (n=248)

BACKGROUND

There are no approved therapies for IPF-related cough. This small cross-over trial administered nalbuphine extended-release tablet (NAL ER) as a potential cough therapy.

METHODS

This randomized, double-blind, placebo-controlled, crossover trial involved two 22-day treatment periods (NAL ER→placebo; placebo→NAL ER) separated by a 2-week washout. NAL ER 27 mg once daily was titrated up to 162 mg twice daily at Day 16. Primary endpoint: 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 endpoints included change in objective 24-hour cough frequency, changes in cough frequency, cough severity, and breathlessness, per patient-reported outcomes (PROs).

RESULTS

Forty-one patients were randomized and received ≥1 dose 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 versus placebo.

CONCLUSION

In this short-term cross-over trial, NAL ER reduced cough in individuals with IPF. Larger and longer trials are needed to assess the impact on cough versus drug side-effects. (Funded by Trevi Therapeutics; ClinicalTrials.gov number, NCT04030026.)

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial pneumonia of unknown cause[1] with a median untreated survival of 2.5–3.5 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 side 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 nalbuphine could potentially provide therapeutic benefits of opioid based drugs while minimizing adverse events, 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 side-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 trial entry. An independent Data Safety Monitoring Board (DSMB) conducted unblinded monitoring of patient safety throughout the trial.

TS and TM designed the trial. All of the authors had access to the data, which was analyzed by EB. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was prepared by Thomas Sciascia with editorial assistance pre-submission, and medical writing assistance post-submission, by Juliet H.A. Bell, Excerpta Medica, funded by trial sponsor Trevi. The authors provided final approval for submission of the manuscript for publication.

PATIENT POPULATION

Eligible patients were age ≥18 years and had a multi-disciplinary 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 >8 weeks duration and daytime cough severity ≥4 on the Cough Severity Numerical Rating Scale (CS-NRS, 11-point Likert scale ranging from zero ["no cough"] to 10 ["worst possible cough"]); forced vital capacity >40% of predicted; and diffusing capacity of the lung for carbon monoxide (DL_{CO}) corrected for hemoglobin >25% of predicted within the previous 6 months. Key exclusion criteria included interstitial lung disease (ILD) known to be caused by environmental exposure, connective tissue disease or drug-related toxicity; current use of continuous oxygen therapy for >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, pages 2–3.

TRIAL DESIGN AND ASSESSMENTS

Eligible patients were randomized 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 (*qd*). This increased to 54 mg twice daily (*bid*) on Day 5, 108 mg *bid* on Day 9, and 162 mg *bid* on Day 16. Patients were to have their doses escalated only if they did not develop dose-limiting side-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, at Days 8, 15, and 21 during treatment, and a follow-up at the end of the 2-week washout period-up.

During the COVID pandemic, the protocol was amended in order to minimize potential patient risk by limiting in-person exposure (see Supplementary Appendix, page 15, for further details).

ENDPOINTS

The primary endpoint was mean change in daytime cough frequency (coughs/hour) from study baseline as assessed by a digital cough recorder at Day 22 of each treatment period (VitaloJAK™, Vitalograph Ltd); daytime was defined as the period between the time the patient reported being awake and the time the patient went to bed.[10] Secondary endpoints 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^{TM}:IPF[11]) diary of cough frequency (scored 0–4) and breathlessness (scored 0–23) from baseline at Days 9, 16, and

22 of treatment (for details of the scoring system see Supplementary Appendix, page 6); mean change in CS-NRS from baseline at Days 8, 15, and 21 and mean change in the Patient-Reported Outcomes Measurement Information System® (PROMIS®) Item Bank v1.0 Fatigue Short Form 7a scale (score 0–35) from baseline at Day 21 of treatment. Physician assessment analysis was mean change in the Clinical Global Impression of Change-Cough (CGI-C, seven-point scale ranging 1–7) from baseline at Day 21 of treatment.

Safety was assessed based on adverse events (AEs), clinical laboratory measurements, central cardiac core laboratory-read electrocardiograms (ECGs), vital signs, spirometry, and physical examinations. AEs were assessed using the 5-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 eDiary for 14 days following the last dose of the investigational product at the end of each treatment period. The scoring criteria for SOWS is 1–20 for mild, 11–20 for moderate, and >21 for severe withdrawal[13] (see Supplementary Appendix, page 7).

STATISTICAL ANALYSIS

Sample size calculations are provided in the Supplementary Appendix, page 15. 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 (MMRM). 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 to placebo tablets at the 5% significance level (2-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 vs. placebo in daytime cough-rate reduction from baseline.

Descriptive statistics were provided for continuous data in terms of the number of patients with non-missing 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 non-missing responses to the categorical variable. No multiplicity adjustments for the secondary and exploratory endpoints were defined. Therefore, only point estimates and 95% confidence intervals are provided. The confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

RESULTS

PATIENTS

From October 2019 through February 2022, 56 patients were screened, and 14 patients failed screening (most commonly due to unwillingness to comply with study requirements and restrictions [n=3] and diffusing capacity of the lung for carbon monoxide corrected for hemoglobin > 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

randomized but not treated, and treatment was discontinued prematurely in 13 patients (31.0%) (Fig. 1).

The majority of patients were male (84.2%) with a mean age of 74; 47.4% were on background anti-fibrotic therapies and 73.7% were on 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.

PRIMARY ENDPOINT

NAL ER-treated patients had a 75.1% reduction (95% confidence interval [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 (equivalent to a test of carry-over effect) yielded an estimate of −0.017 and 95% CI is −0.59 to 0.55. Since the 95% CI includes the null value, we conclude there was no evidence of a carry-over effect between treatment periods.

Supplemental primary efficacy analyses were also performed using responder analyses for patients reaching pre-determined reduction thresholds for NAL-ER versus placebo (Supplementary Appendix, Fig. S1). Furthermore, efficacy analyses of 24-hour cough counts for patients with and without concomitant anti-fibrotic therapy are provided in Supplementary Appendix, Fig. 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 NAL ER-treated patients 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 ENDPOINTS

Further secondary endpoints are shown in Figure 3. The E-RS^{TM}: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), while Mean (SD) CS-NRS scores at Day 21 were 3.9 (2.28) and 6.0 (1.74), respectively (Fig. 3b). Furthermore, The E-RSTM: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 on study drug had an improvement in their cough, compared with 19% for placebo (Fig. S3). Finally, PROMIS® Fatigue Short Form 7a data for both treatment arms are provided in Supplementary Appendix, Fig. S4.

SAFETY DATA

There were no deaths and two serious AEs (SAEs) reported during the trial: one case of pneumonia in a patient during the placebo period of the crossover; this patient had never received NAL ER. There was one case of urosepsis reported 2 weeks after a 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 9 patients on NAL ER (Table 2): 6 patients discontinued on Day 5 (40.5 mg mean dose at time of discontinuation) or earlier, and 3 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 (CNS) AEs were more common in the NAL ER dosing periods. Of the AE/,s, 95% were of grade 1–2 in severity, and 51% of these AEs had clinically resolved after 7 days. Twelve Grade 3 AEs were reported by 4 patients (8 events during the NAL ER period and 4 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, while 7.5% reported fatigue, 5.0 % constipation, and 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 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 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 study drug discontinuation.

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 side-

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 anti-fibrotics.[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 abuse.

In this 3-week study there was no clinical evidence of withdrawal symptoms, with self-reported scores by the patients 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 drug abuse, 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 a trial of low dose morphine in chronic cough which 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 COVID 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 wash-out period.

In conclusion, treatment with NAL ER for 3 weeks resulted in a rapid and marked reduction in recorded daytime cough among patients suffering from 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 side-effects and loss of efficacy due to habituation associated with chronic opiate use.

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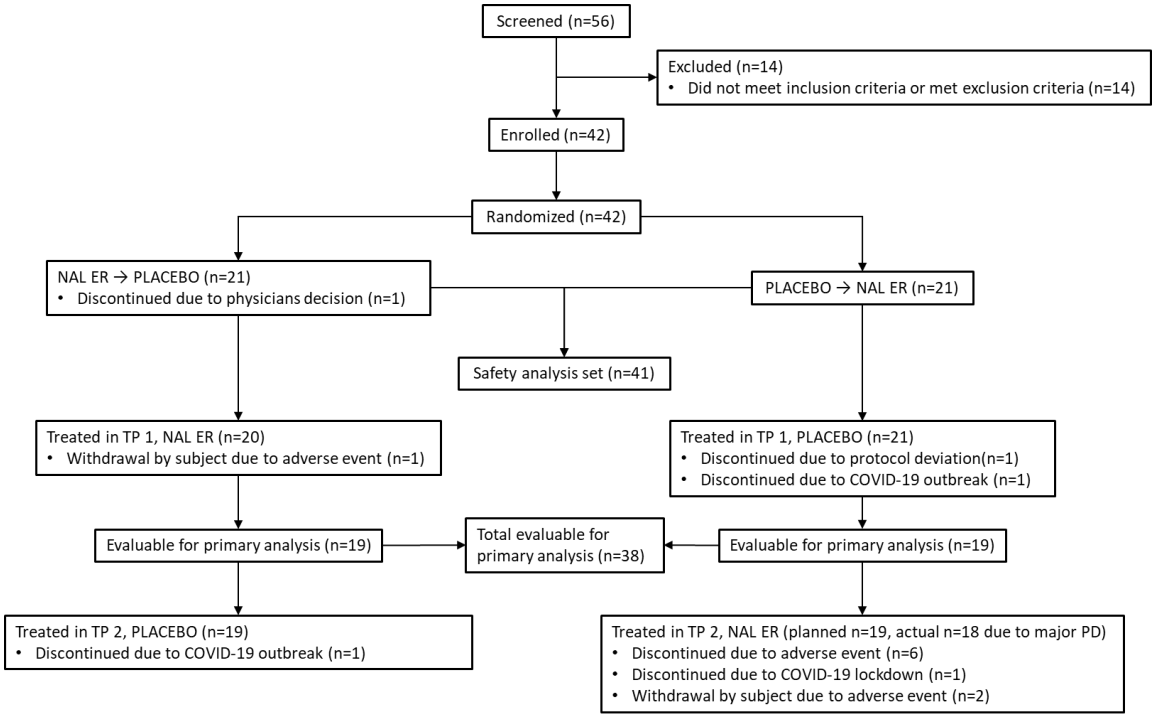


Figure 1: Patient Disposition.

NAL ER denotes NAL ER, nalbuphine extended-release, PD denotes protocol deviation and TP denotes treatment period.

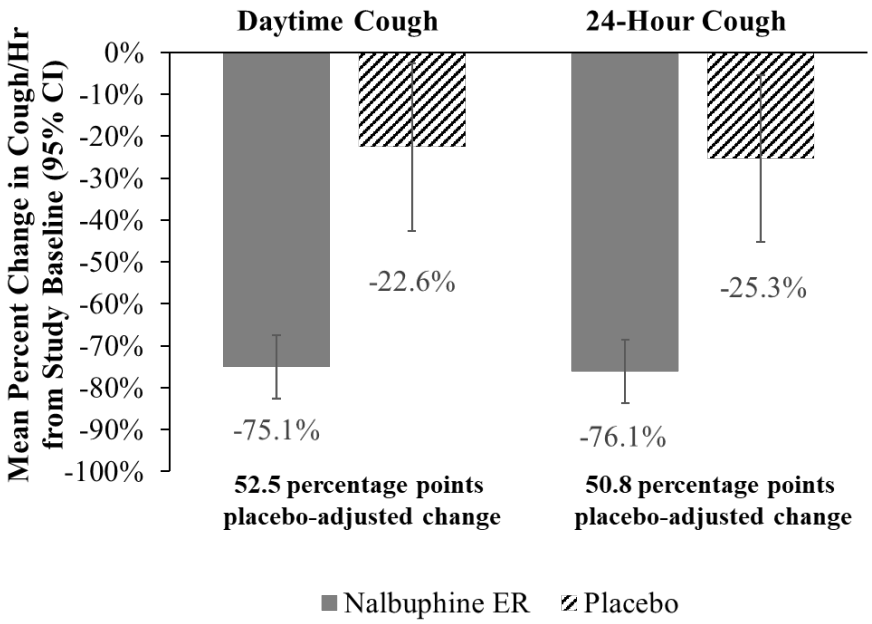


Figure 2: Geometric Mean Percent Change from Study Baseline in Coughs per Hour.

(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 denotes extended release.

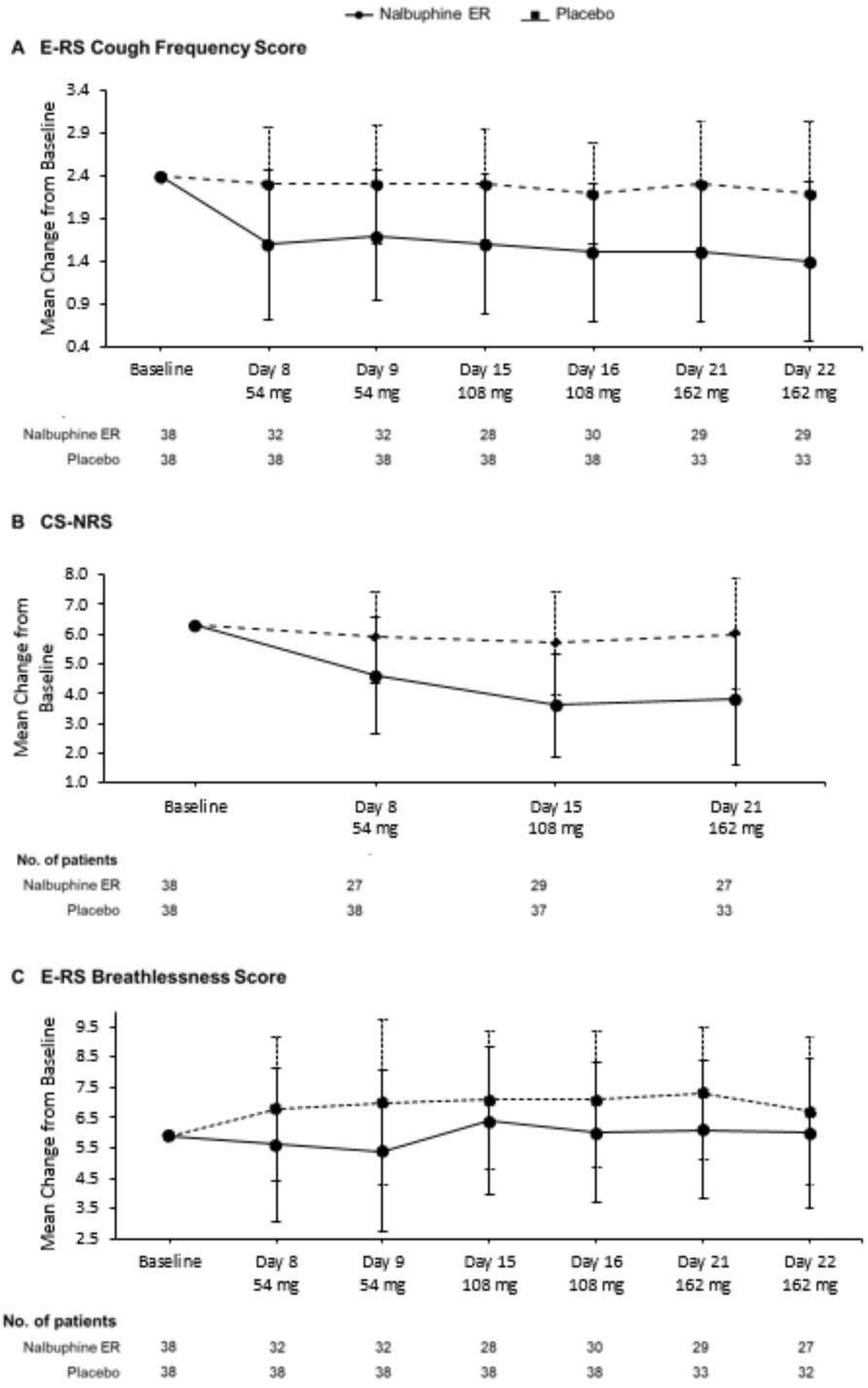
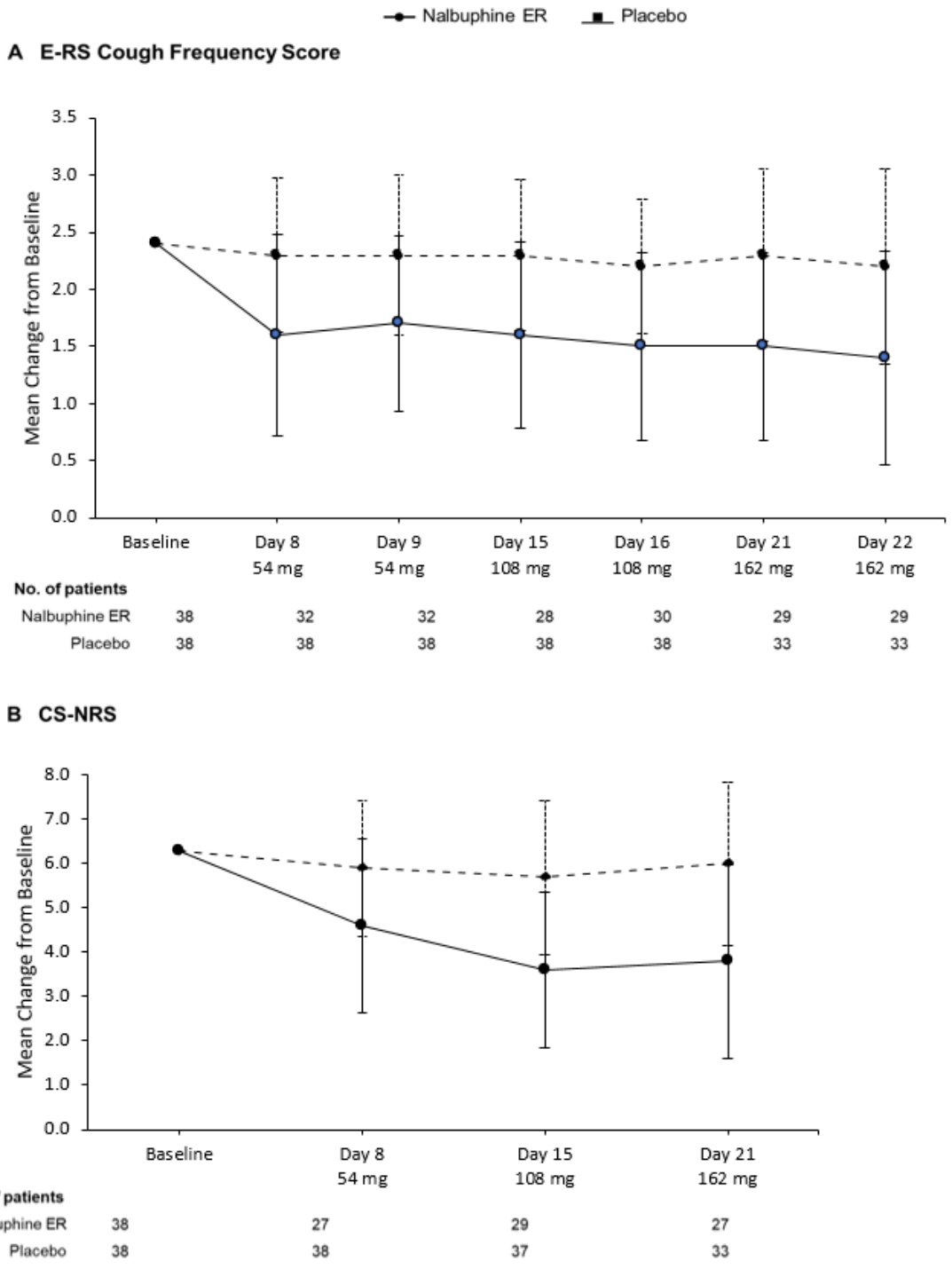


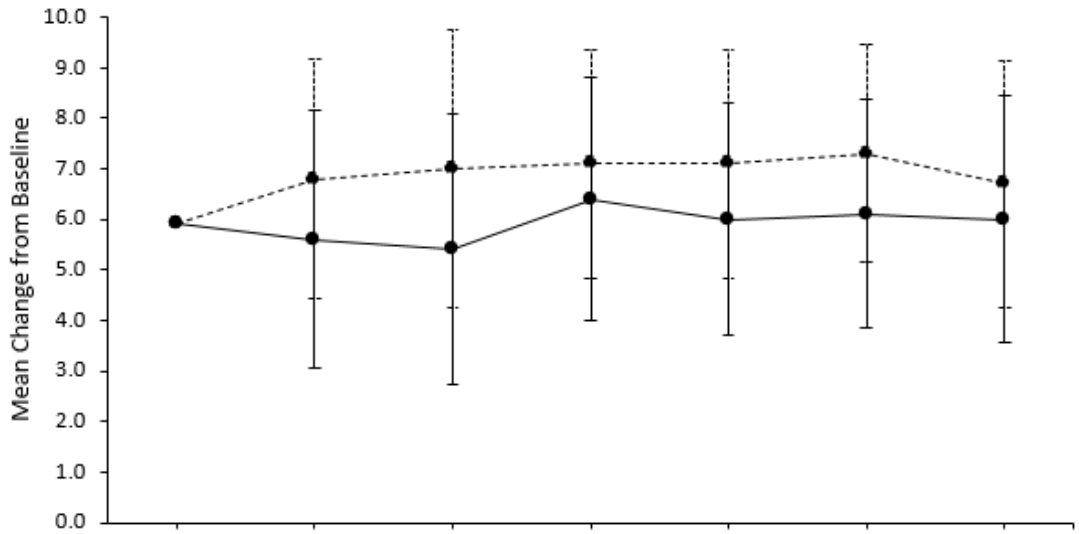
Figure 3: Mean Change from Study Baseline for Patient-Reported Outcomes.

E-RS cough is scored 0-4; CS-NRS is scored 0–10; E-RS breathlessness is scored 0–23.

CS-NRS denotes Cough Severity Numerical Rating Scale, E-RS denotes Evaluating Respiratory Symptoms, and ER denotes extended release.



C E-RS Breathlessness Score



No. of patients							
Nalbuphine ER	38	32	32	28	30	29	27
Placebo	38	38	38	38	38	33	32

1

2

Table 1: Baseline Characteristics.

Patients — no.	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 ≥1 treatment period).

Table 2: Adverse Events.

	NAL ER *bid* N = 38 no. (%)	Placebo N = 40 no. (%)	Total N = 41 no. (%)
Patients with treatment-emergent adverse events leading 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% 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)

1 *bid* denotes twice a day and NAL ER denotes nalbuphine extended release.