Efficacy of oral nalbuphine extended release for the treatment of chronic cough in idiopathic pulmonary fibrosis: data analysis of a phase 2 study

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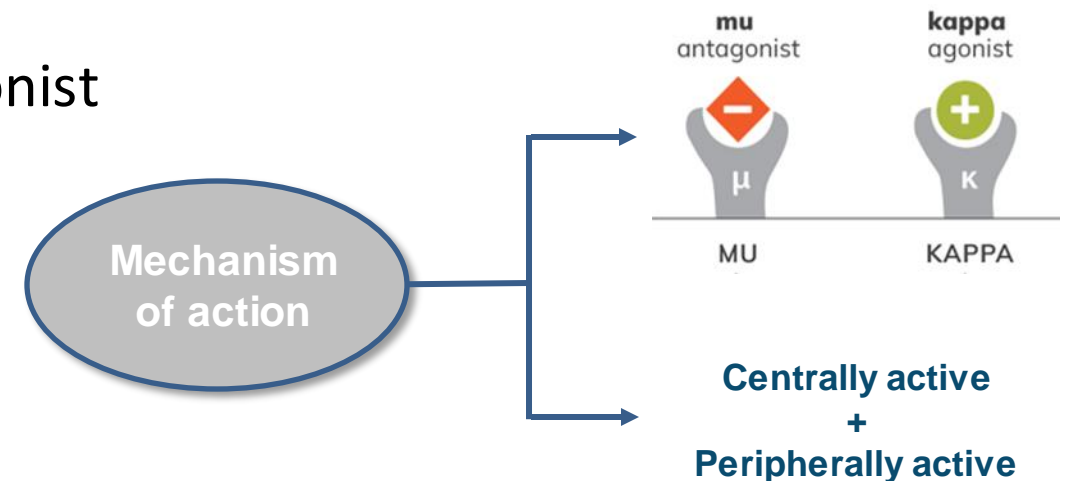
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Conflicts of interest

- PM has, via his institution, received grand funding from AstraZeneca and has received consultancy or speaker fees from AstraZeneca, Boehringer Ingelheim, Hoffman-La Roche, and Trevi Therapeutics

- EB is a consultant for Trevi Therapeutics

- TS is an employee of Trevi Therapeutics and may own stock or stock options

- TMM has, via his institution, received industry academic funding from AstraZeneca and GlaxoSmithKline R&D and has received consultancy or speaker fees from AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, FibroGen , Galápagos, Galecto Biotech, GlaxoSmithKline, IQVIA, Pliant, Roche, Trevi Therapeutics, and Veracyte

Background

- Cough is a major cause of morbidity in patients with idiopathic pulmonary fibrosis[1] and effective therapies are lacking[2]

- Dual-acting opioid agonists/antagonists are hypothesized to reduce chronic cough
  - They act pharmacologically on the opioid system, potentially at both peripheral and central nervous system levels

- We report the analysis of a phase 2 trial with nalbuphine, a dual-acting opioid agonist/antagonist, extended release tablets
  - ꝃ-receptor agonist and μ-receptor antagonist

Mechanism of action

mu antagonist

kappa agonist

μ

 κ

MU

KAPPA

**Centrally active
+
Peripherally active**

1. Lee J, et al. Chest. 2022;162:603-13.
2. van Manen MJG, Wijsenbeek MS. Curr Opin Support Palliat Care. 2019;13:143-51.

Study design
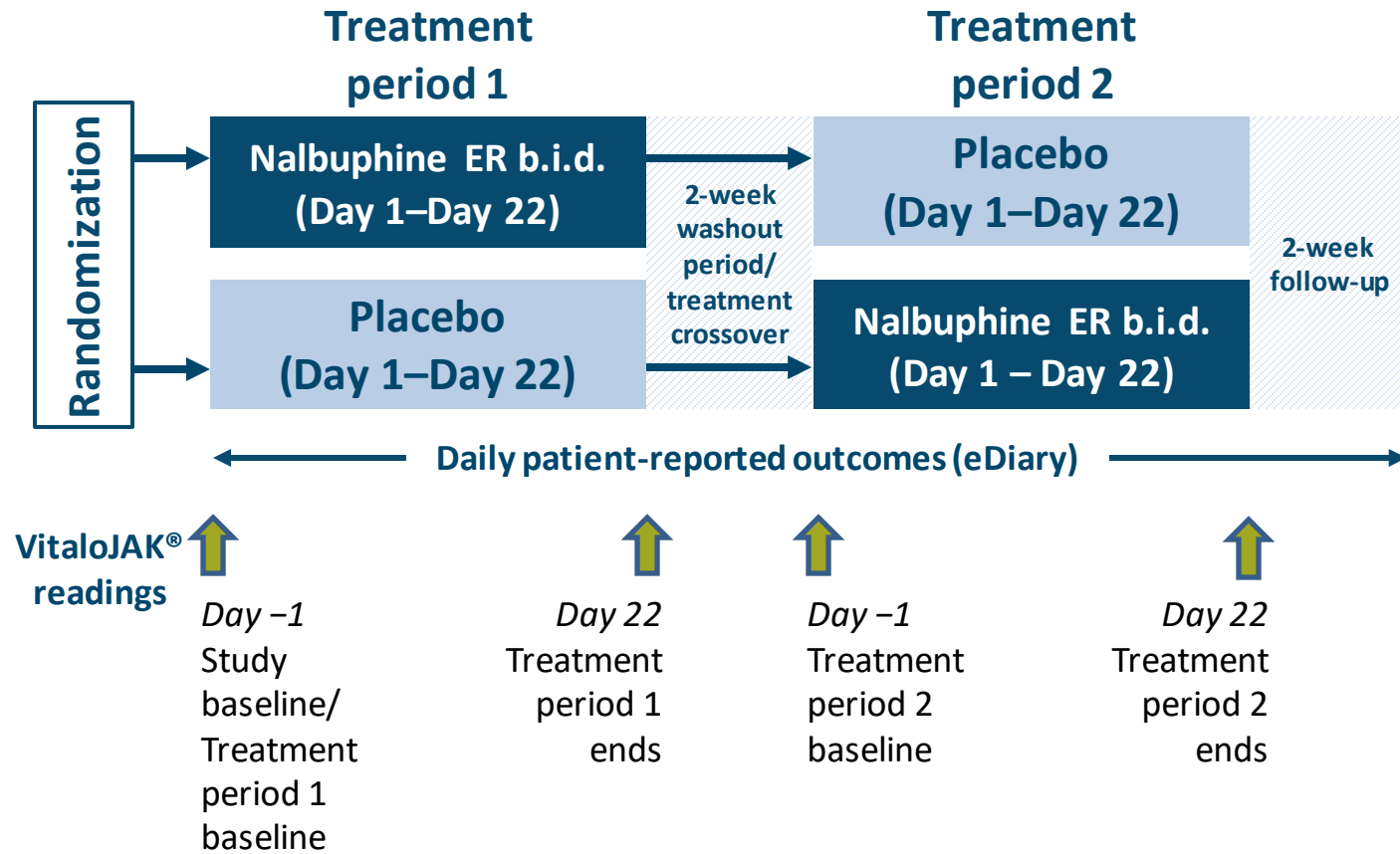
- A randomized, double-blind, placebo-controlled, crossover trial with two 22-day treatment periods separated by a 2-week washout period was conducted

- Nalbuphine ER 27 mg once daily was titrated up to 162 mg twice daily at Day 16

- Adults diagnosed with definite/probable IPF using international criteria and chronic cough for > 8 weeks were enrolled

b.i.d., twice daily; ER, extended release; IPF, idiopathic pulmonary fibrosis.

Endpoints

PRIMARY ENDPOINT
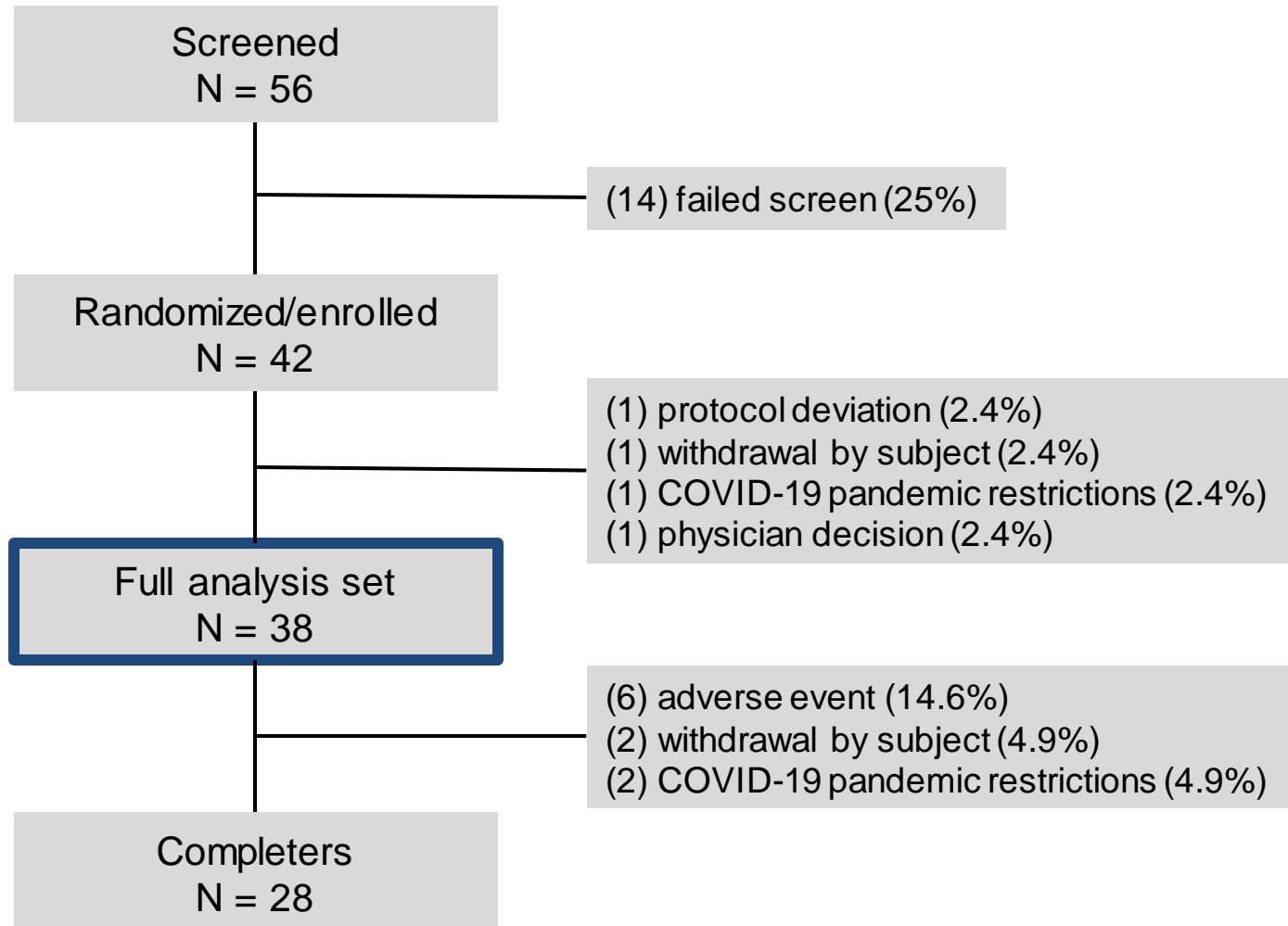
- Geometric mean percent change in daytime cough frequency from baseline as measured by a digital cough monitor (**VitaloJAK®**) between the nalbuphine ER and placebo treatments at Day 22 by treatment

SECONDARY ENDPOINTS

- Cough severity
- 24-hour cough frequency
- Concomitant anti-fibrotic therapy
- EXACT2 patient-reported outcomes

EXACT, exacerbation of chronic pulmonary disease tool.

Patient disposition

```
Screened
N = 56
   │
   ├──────── (14) failed screen (25%)
   │
Randomized/enrolled
N = 42
   │
   ├──────── (1) protocol deviation (2.4%)
   │         (1) withdrawal by subject (2.4%)
   │         (1) COVID-19 pandemic restrictions (2.4%)
   │         (1) physician decision (2.4%)
   │
Full analysis set
N = 38
   │
   ├──────── (6) adverse event (14.6%)
   │         (2) withdrawal by subject (4.9%)
   │         (2) COVID-19 pandemic restrictions (4.9%)
   │
Completers
N = 28
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- Of the 56 screened patients, **the 1-period full analysis set comprised 38 patients**
  - The completers set comprised the 28 patients who completed both treatment periods
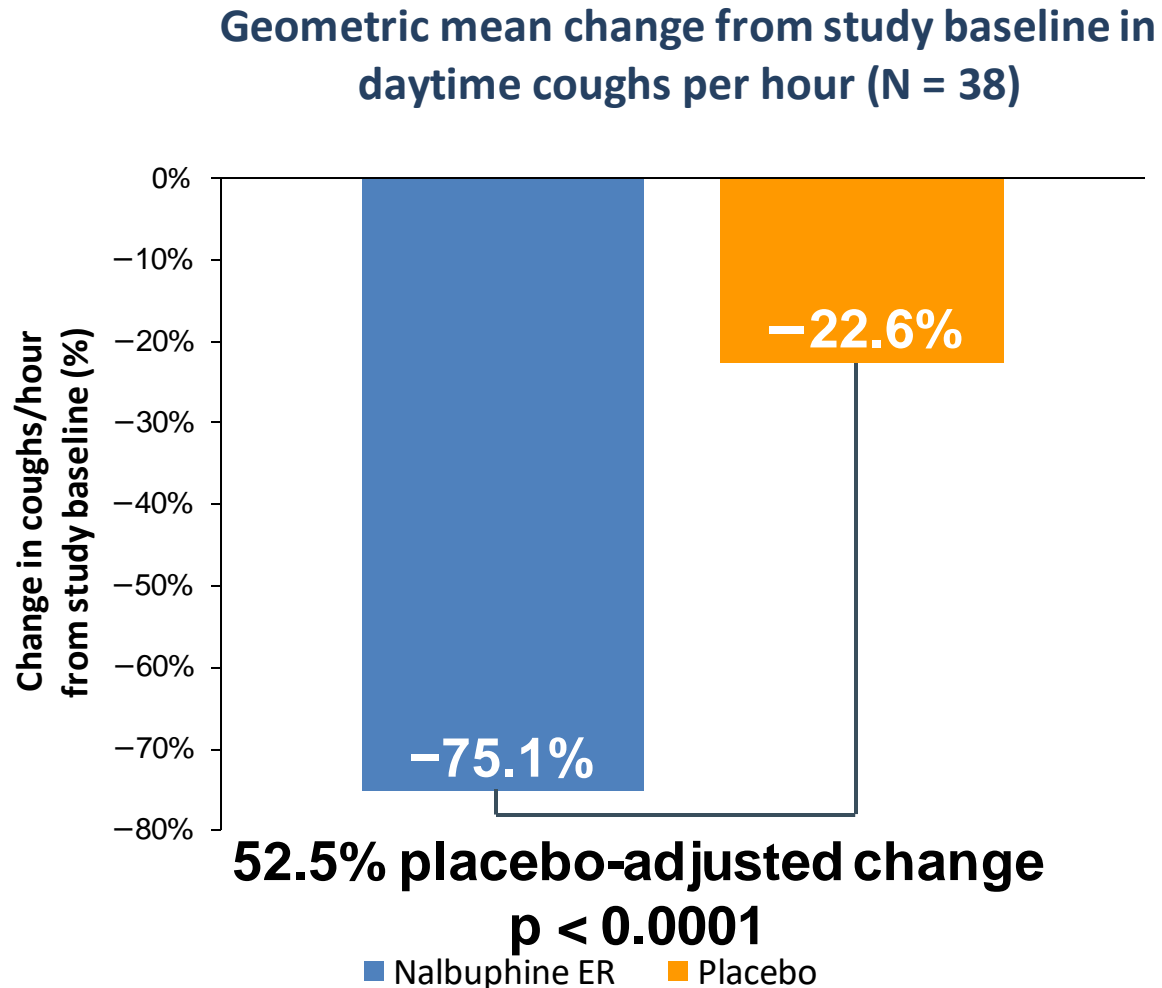
Baseline characteristics

	Full analysis set[a] (N = 38)
Male, n (%)	32 (84.2)
Mean age, years	74
Anti-fibrotic use, n (%)	18 (47.4)
Daytime cough frequency, coughs/hour	
Mean	28
Median	20
Minimum–maximum	3.18–92.35
24-hour cough frequency, coughs/hour	
Mean	21
Median	16
Minimum–maximum	3.13–66.42

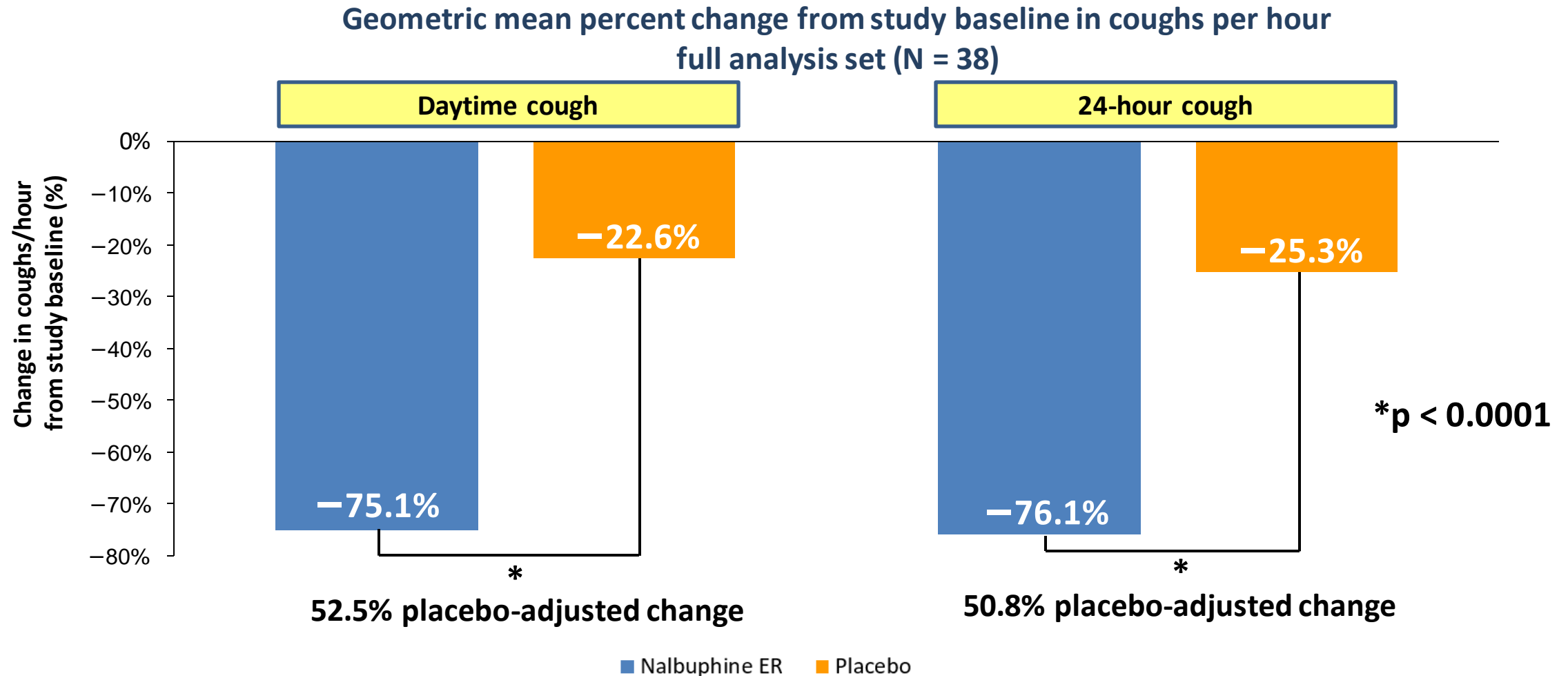[a] Patients completing ≥ 1 treatment period.

- Patients were primarily male, with a mean age of > 70 years and a baseline mean daytime cough frequency of 28 coughs per hour

The primary endpoint was achieved: a statistically significant reduction in daytime cough frequency

Geometric mean change from study baseline in daytime coughs per hour (N = 38)

Change in coughs/hour from study baseline (%)

- Nalbuphine ER: −75.1%
- Placebo: −22.6%

52.5% placebo-adjusted change
p < 0.0001

■ Nalbuphine ER   ■ Placebo

- **75.1% reduction** in daytime cough frequency at Day 22 with nalbuphine ER

- **52.5% improvement compared with placebo** in daytime cough frequency at Day 22 with nalbuphine ER
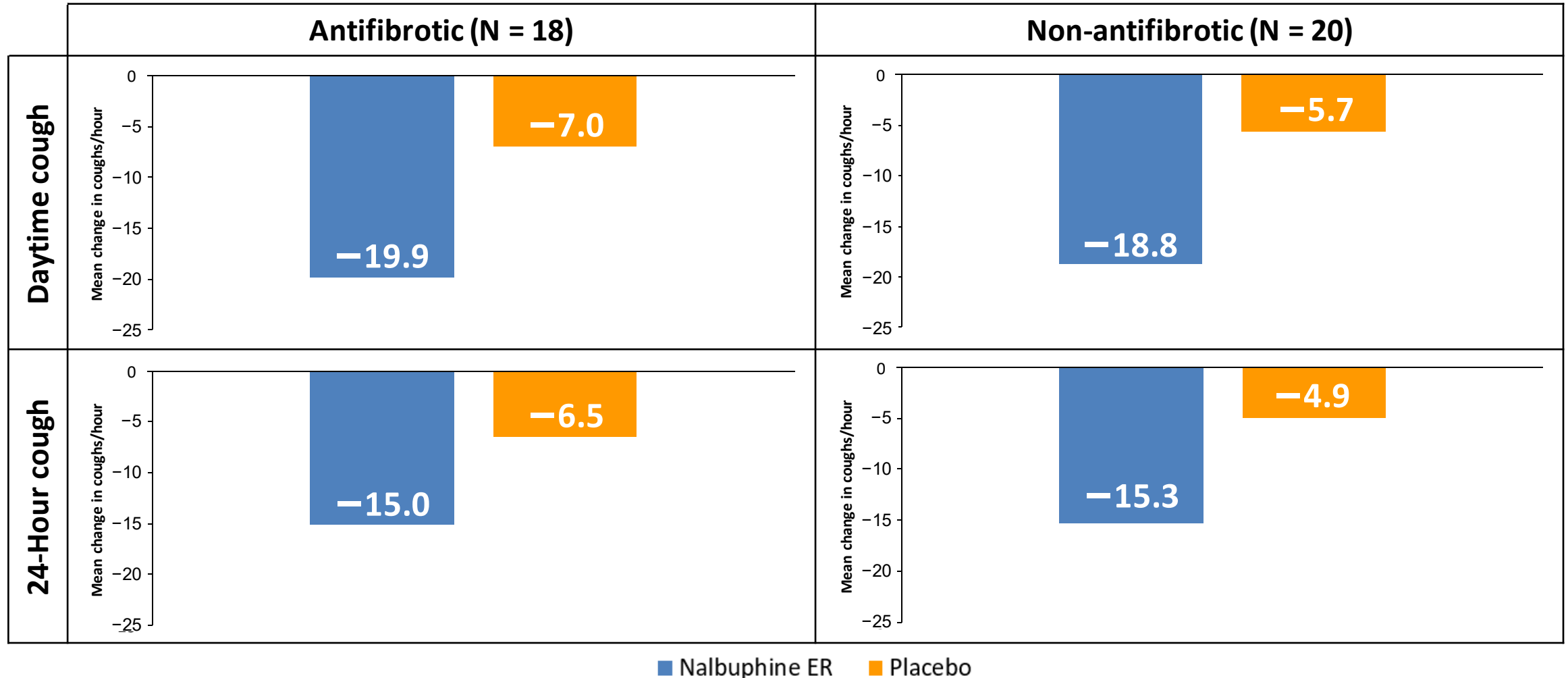
Reduction of cough frequency and placebo-adjusted change were consistent between daytime and 24-hour cough frequency

Geometric mean percent change from study baseline in coughs per hour full analysis set (N = 38)

Daytime cough

24-hour cough

Change in coughs/hour from study baseline (%)

0%
−10%
−20%
−30%
−40%
−50%
−60%
−70%
−80%

−22.6%

−25.3%

−75.1%

−76.1%

*

*

***p < 0.0001**

52.5% placebo-adjusted change

50.8% placebo-adjusted change

■ Nalbuphine ER ■ Placebo

Endpoint calculated as geometric mean percent change in daytime and 24-hour cough frequency from study baseline to Day 22.
No sequence or period effect.

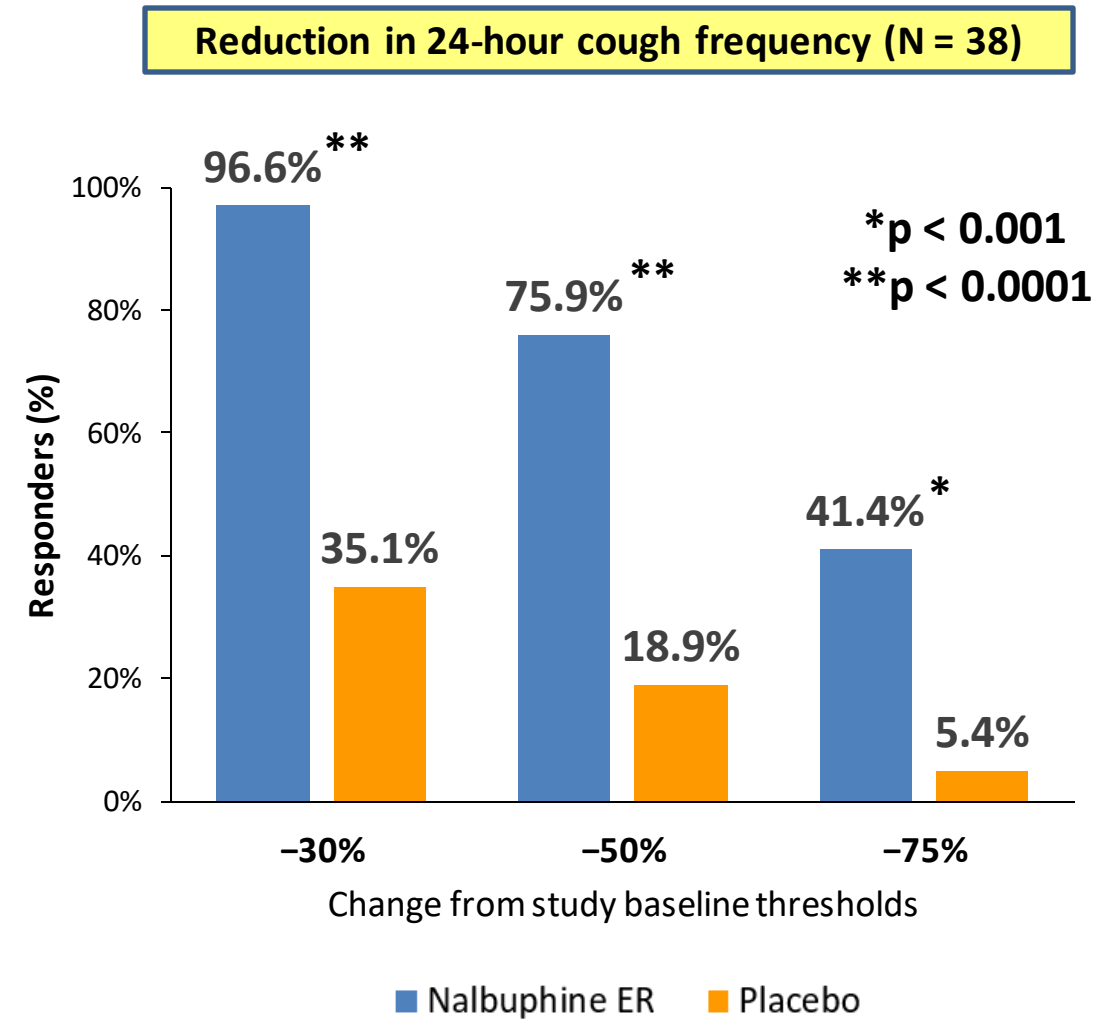# Consistent cough reduction was independent of background antifibrotic therapy

- Cough reduction was seen in patients both with and without concomitant antifibrotic medication at Day 22

	Antifibrotic (N = 18)	Non-antifibrotic (N = 20)
Daytime cough	Nalbuphine ER: −19.9; Placebo: −7.0	Nalbuphine ER: −18.8; Placebo: −5.7
24-Hour cough	Nalbuphine ER: −15.0; Placebo: −6.5	Nalbuphine ER: −15.3; Placebo: −4.9

■ Nalbuphine ER   ■ Placebo

Endpoint calculated as geometric mean percent change in daytime cough and 24-hour cough frequency from study baseline.

Supplementary responder analysis shows clear separation between nalbuphine ER and placebo at all thresholds
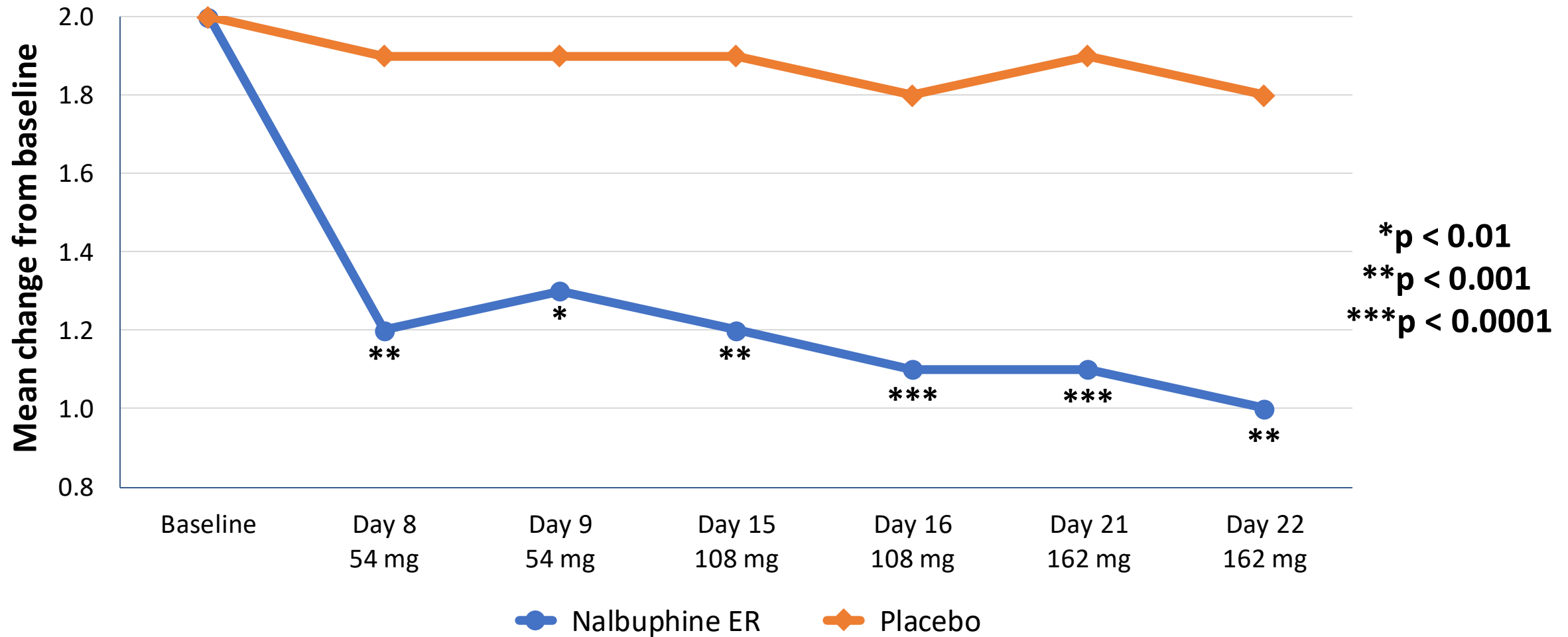
- 97% of nalbuphine ER-treated patients saw a reduction in 24-hour cough frequency at Day 22
  - A 20–30% reduction in cough frequency in patients with chronic cough is considered clinically meaningful[1]
- 76% of nalbuphine ER-treated patients saw their cough frequency reduced by half

Reduction in 24-hour cough frequency (N = 38)

*p < 0.001
**p < 0.0001

- −30%: 96.6%** (Nalbuphine ER), 35.1% (Placebo)
- −50%: 75.9%** (Nalbuphine ER), 18.9% (Placebo)
- −75%: 41.4%* (Nalbuphine ER), 5.4% (Placebo)

Responders (%)

Change from study baseline thresholds

■ Nalbuphine ER ■ Placebo

1. Nguyen AM, et al. J Allergy and Clin Immunol. 2019;143:AB169.
Endpoint calculated as geometric mean percent change in 24-hour cough frequency from study baseline.

EXACT2 patient-reported outcome supports the results seen in the objective cough monitor on the full dataset

*p < 0.01
**p < 0.001
***p < 0.0001

Y-axis: Mean change from baseline (0.8 to 2.0)

X-axis categories:
Baseline | Day 8 54 mg | Day 9 54 mg | Day 15 108 mg | Day 16 108 mg | Day 21 162 mg | Day 22 162 mg

Nalbuphine ER annotations: ** (Day 8), * (Day 9), ** (Day 15), *** (Day 16), *** (Day 21), ** (Day 22)

Legend: Nalbuphine ER, Placebo

Endpoint calculated as geometric mean percent change from study baseline.

Safety

- No deaths were reported

- 2 reported serious adverse events (i.e. pneumonia and urosepsis) were not considered to be treatment-related

  - 9 patients experienced adverse events which resulted in discontinuation (23.7%)

    - 1 patient with 4 TEAEs (agitation/anxiety/dyspnoea/suicidal ideation)

    - 8 patients with 1 TEAE each (bradycardia/headache/insomnia/lethargy/mental disorder/vertigo/vomiting)

- No new safety-related issues have arisen during the study, and the adverse event profile of the drug in the IPF population is consistent with the safety profile noted in all other past studies in which nalbuphine ER was investigated for a variety of medical conditions

TEAE, treatment-emergent adverse event.

Conclusions

Nalbuphine ER demonstrated a significant and consistent reduction in chronic cough associated with IPF in the phase 2 full analysis

- A 52.5% placebo-adjusted reduction was seen in the geometric mean percent change from study baseline for nalbuphine ER in daytime cough frequency to Day 22 of treatment (p < 0.0001)

- 41.4% of nalbuphine ER-treated subjects achieved a ≥ 75% reduction from baseline in daytime cough frequency compared with 5.4% of placebo-treated subjects

- A significant change in secondary endpoint patient-reported outcomes was seen, consistent with the reduction in daytime cough frequency

- The safety profile was consistent with previous nalbuphine ER studies in other patient populations, with no new safety signals identified