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ORIGINAL ARTICLE

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

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Efficacy of Oral Nalbuphine Extended Release in Patients With Idiopathic Pulmonary Fibrosis Related Chronic Cough: a Phase 2 Study

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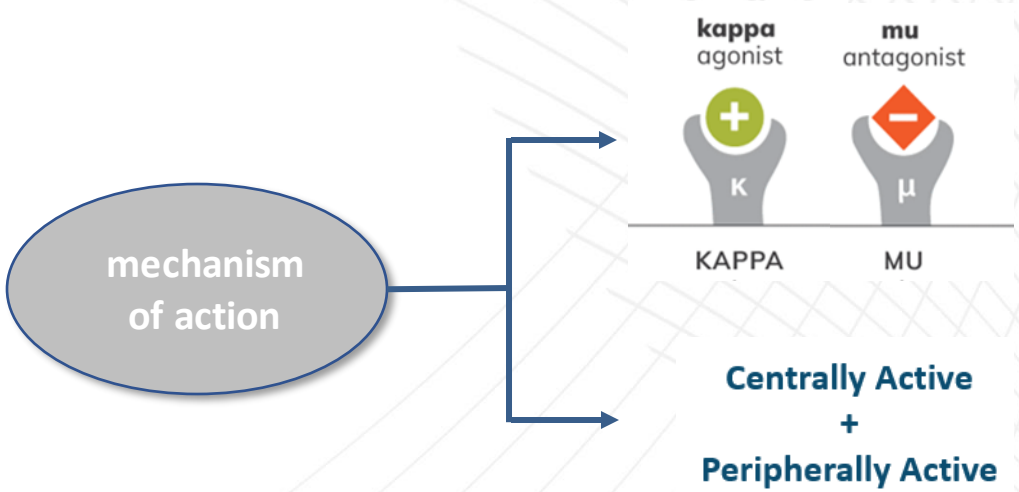
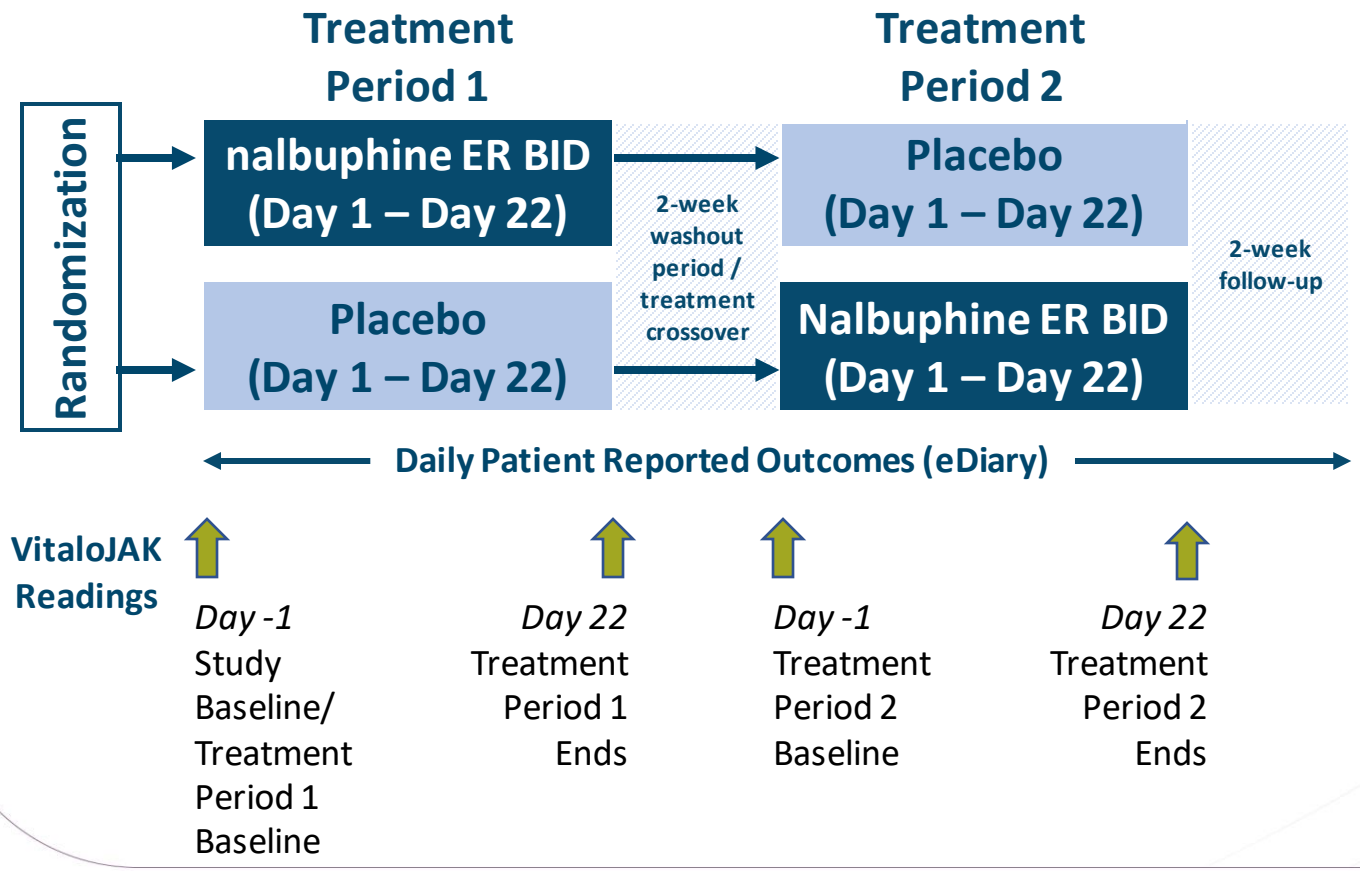
Background

- Cough is a major cause of morbidity in patients with idiopathic pulmonary fibrosis (IPF)[1], which lacks effective therapies[2]
- Dual-acting opioid agonists/antagonists are hypothesised to reduce chronic cough via the opioid receptors
  - May influence both the central and peripheral nervous system receptors
- We report the analysis of a phase 2 trial with nalbuphine extended release (ER) tablets, a dual-acting opioid agonist/antagonist
  - κ-receptor agonist and μ-receptor antagonist



1. Lee J, et al. Chest 2022:S0012-3692(22)00545-1, 2. van Manen MJG, Wijsenbeek MS. Curr Opin Support Palliat Care. 2019;13(3):143-151.

Study design



- Randomised, double-blind, placebo-controlled, crossover trial with two 22-day treatment periods separated by a 2-week washout period. 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

Endpoints

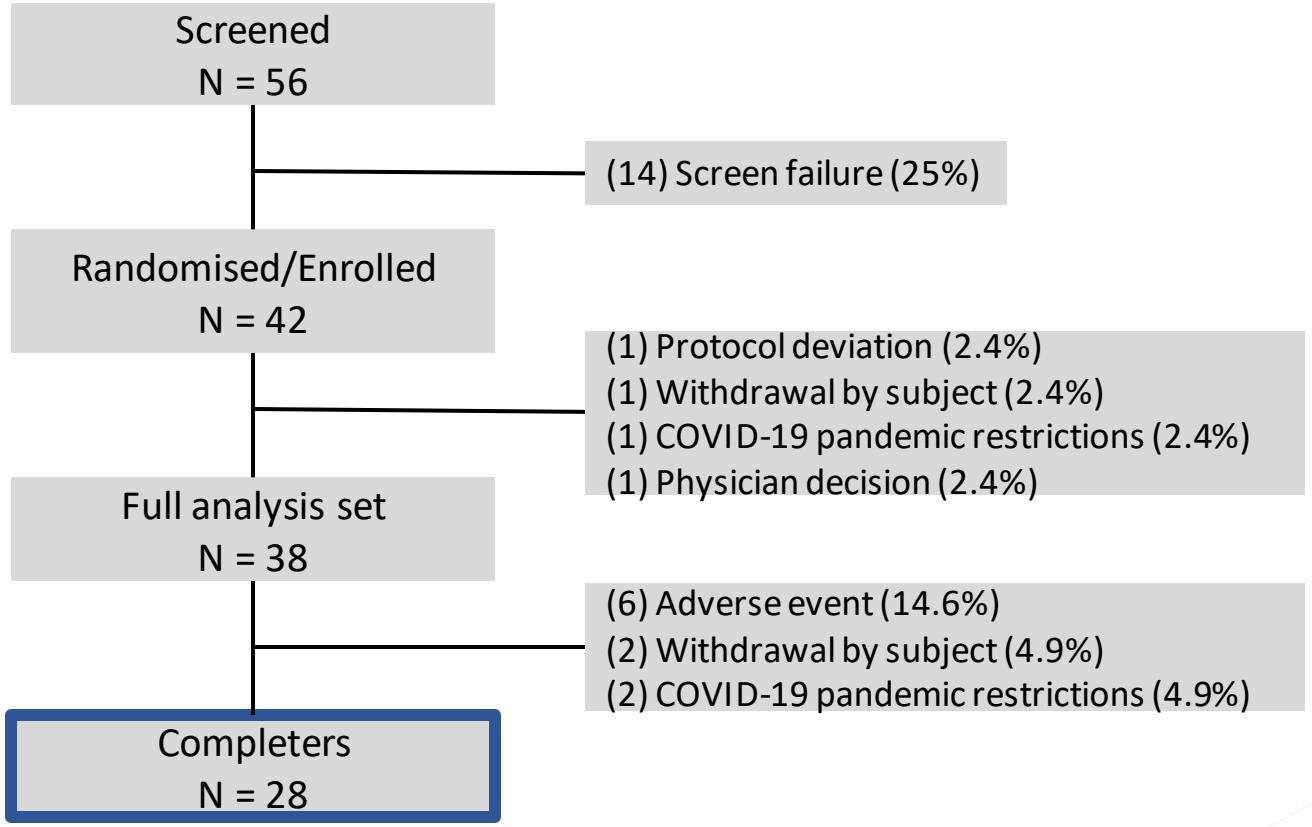
PRIMARY ENDPOINT

- 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

SECONDARY ENDPOINTS

- 24-hour cough frequency at Day 22
- Evaluating Respiratory Symptoms (E-RS™:IPF)
  - Cough frequency and breathlessness at Days 9, 16, and 22
- Cough Severity Numerical Rating Scale (CS-NRS) at Days 8, 15, and 21
- Patient-Reported Outcomes Measurement Information System® 21 (PROMIS®)
  - Fatigue Short Form 7a scale at Day 21
- Clinical Global Impression of Change-Cough (CGI-C) at Day 21

Patient disposition – completer analysis set



- Of the 56 screened patients, 38 comprised the 1-period full analysis set
- The **completers set** was comprised of the 28 patients who completed both treatment periods

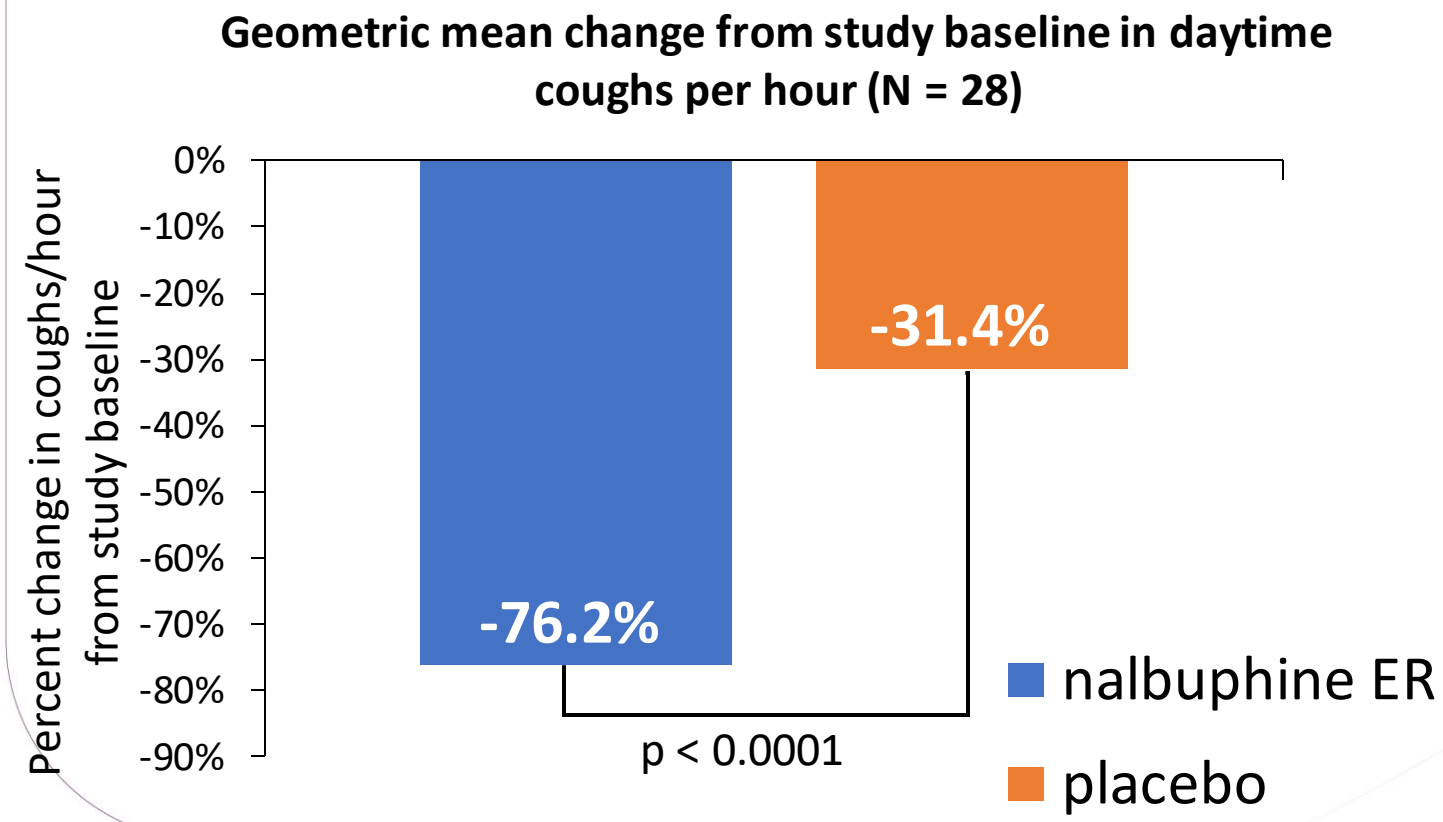
Baseline Characteristics

	Completer Analysis Set* (N = 28)
Male, n (%)	23 (82.1)
Age (years), mean	74
Anti-fibrotic usage, n (%)	15 (53.6)
Daytime cough frequency (coughs/hour):	
Mean	28
Median	20
Min-max	3.18 – 92.35
24-hour cough frequency (coughs/hour):	
Mean	21
Median	16
Min-max	3.13 – 66.42

*Subjects completing both treatment periods

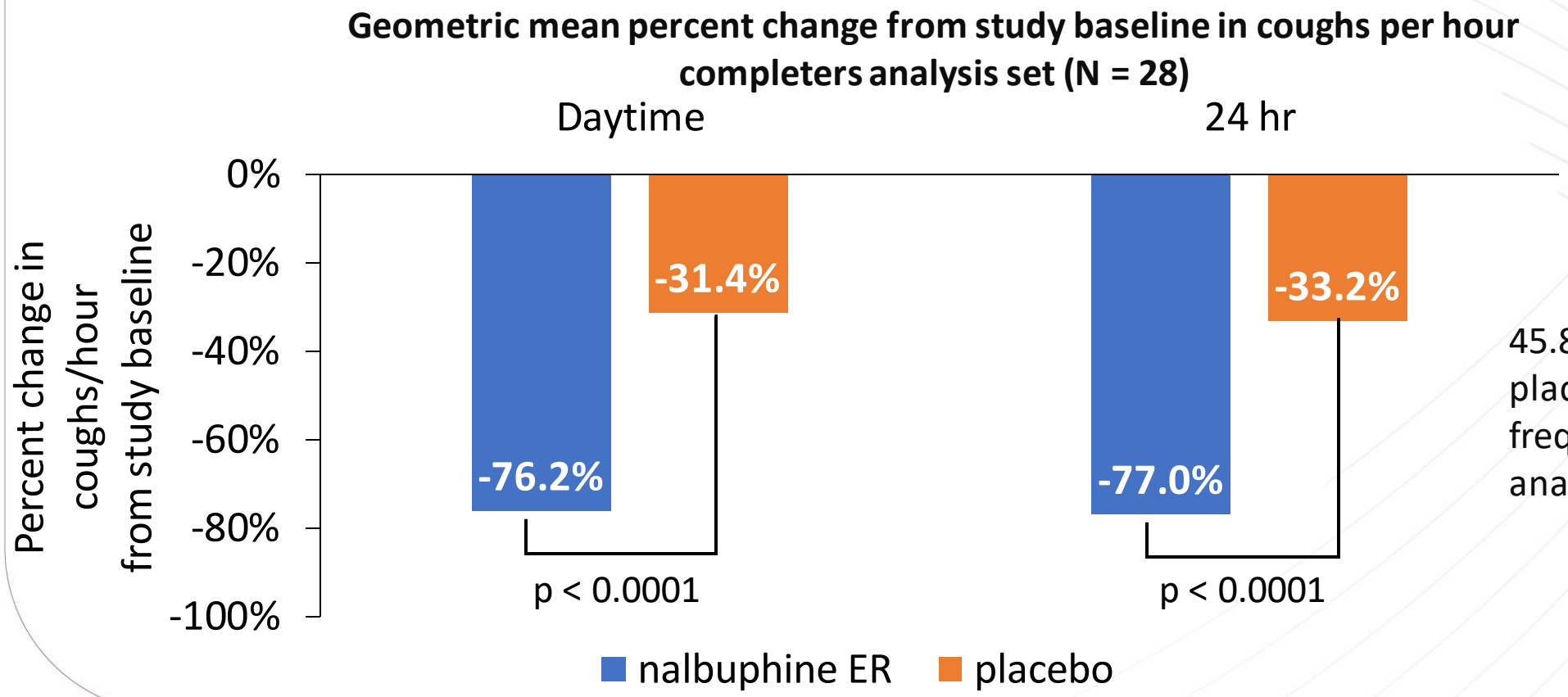
- Patients were primarily male with a mean age of > 70 years and a baseline mean daytime cough frequency of 28 coughs per hour

Primary Endpoint Achieved Statistically Significant Reduction in Daytime Cough Frequency



- **76.2% reduction** in daytime cough frequency at Day 22 with nalbuphine ER (nalbuphine ER, n = 28; placebo n = 28)
- **45.8% change compared to placebo** in daytime cough frequency at Day 22 with nalbuphine ER
  - Similar to full analysis set: 52.5% change compared to placebo

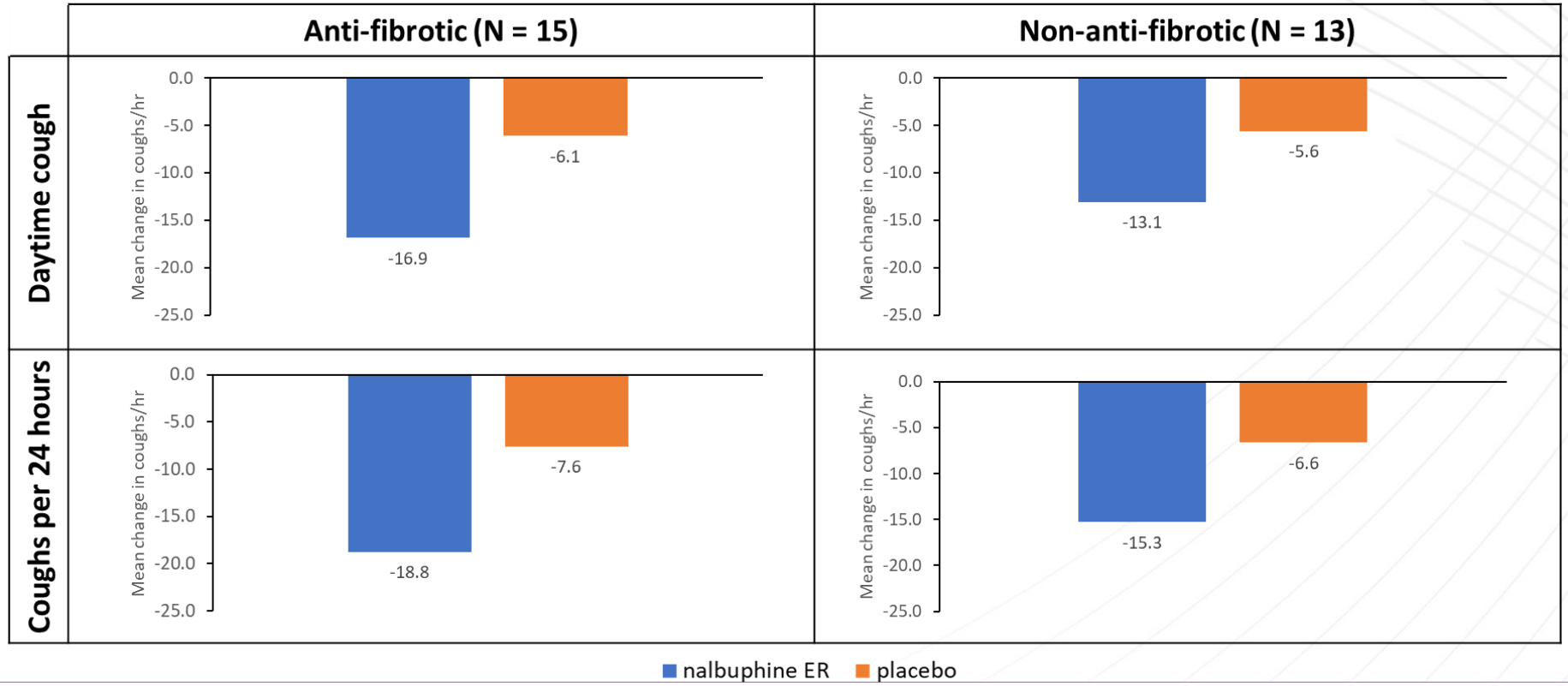
Reduction of Cough Frequency and Placebo-Adjusted Change Were Consistent Between Daytime and 24-Hour Cough Frequency



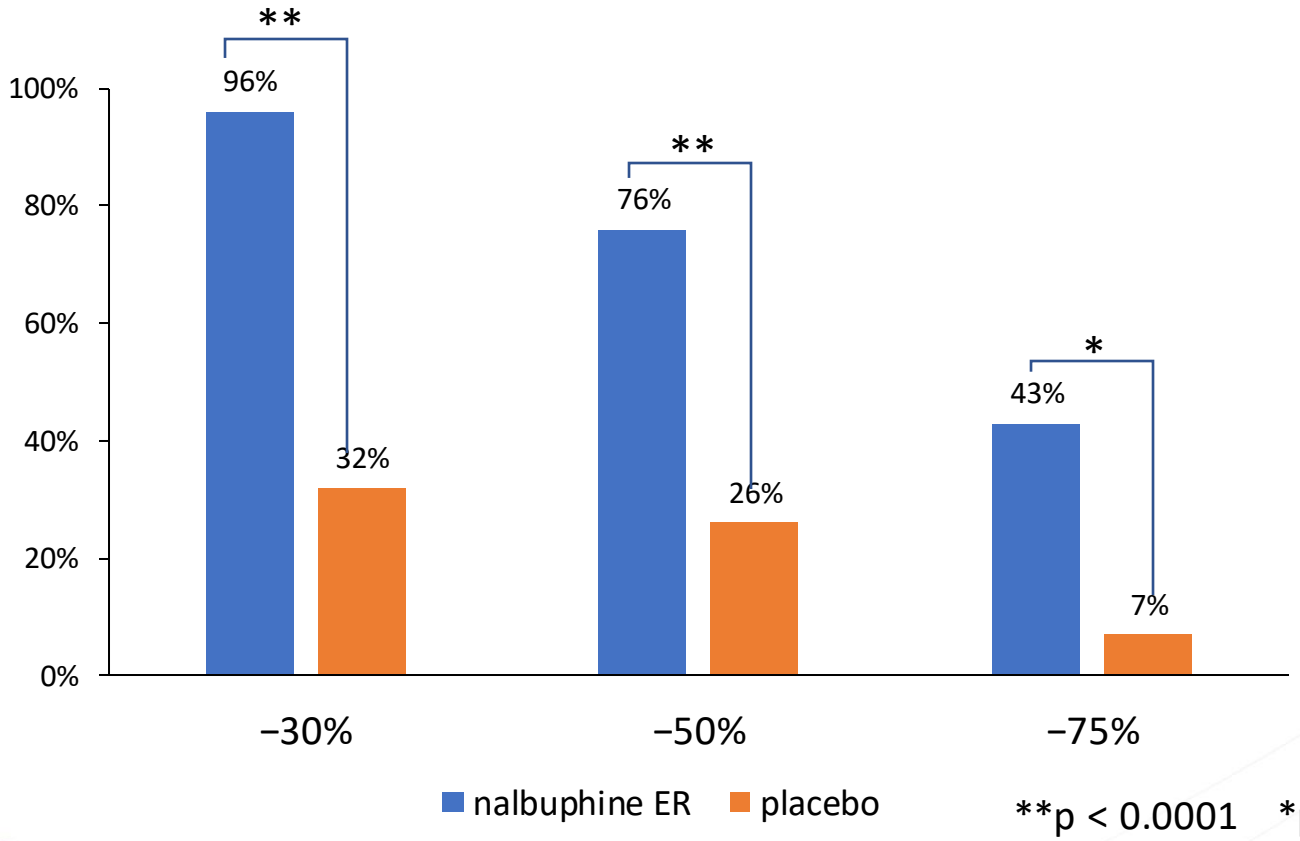
45.8% change compared to placebo for 24-hour cough frequency (50.8% in full analysis set)

Magnitude of Efficacy was Consistent Independent of Background Anti-Fibrotic Therapy

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



Post-Hoc Responder Analysis Shows Clear Separation Between Nalbuphine ER vs Placebo at All Thresholds (N = 28)



**p < 0.0001 *p < 0.01

- 96% of nalbuphine ER patients saw a reduction in 24-hour cough frequency at Day 22 (97% in full analysis set)
- 75% of nalbuphine ER patients saw their cough frequency reduced by half (76% in full analysis set)

1. Lee J, et al. Chest 2022:S0012-3692(22)00545-1

Safety

- No deaths reported
- 2 reported serious adverse events (lung infection, urosepsis) were not considered treatment-related
- 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

Conclusions

- Nalbuphine ER demonstrated a significant reduction in chronic cough associated with IPF in the phase 2 completers analysis set (N = 28)
- 46% placebo-adjusted reduction in the geometric mean percent change from study baseline for nalbuphine ER in daytime cough frequency to Day 22 of treatment ($p < 0.0001$)
- 43% of nalbuphine ER-treated subjects achieving a ≥ 75% reduction from baseline in daytime cough frequency compared to 7% of placebo-treated subjects
- Data consistent between full analysis set and completer analysis set
- Safety profile consistent with prior nalbuphine ER studies in other patient populations, with no new safety signals identified