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

Toby M. Maher[1]; Cristina Avram[2]; Enoch Bortey[3]; Simon P. Hart[4]; Nikhil Hirani[5]; Philip L. Molyneaux[6]; Joanna C. Porter[7]; Thomas Sciascia[3]

[1]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [2]Northwest Interstitial Lung Disease Unit, Manchester, UK; [3]Trevi Therapeutics, New Haven, CT, USA; [4]University of Hull, Hull, UK; [5]Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK; [6]National Heart & Lung Institute, Imperial College London, London, UK; [7]University College London, London, UK

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

OBJECTIVE

- 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

METHODS

- 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 **(Figure 1)**
- Adults diagnosed with definite/probable IPF using international criteria and chronic cough for > 8 weeks were enrolled
- Of the 56 screened patients, 38 comprised the 1-period full analysis set
- The **completers analysis set** was comprised of the 28 patients who completed both treatment periods
- The primary endpoint was the 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 included 24-hour cough frequency, patient reported outcomes, and Clinical Global Impression of Change-Cough

Figure 1. Study design.

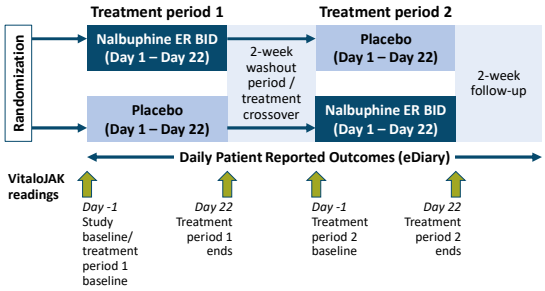


Table. Baseline characteristics.

	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.

Figure 2. Geometric mean change from study baseline in daytime and 24-hour coughs per hour at Day 22 (N = 28).

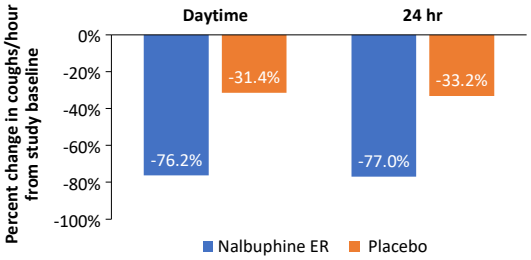
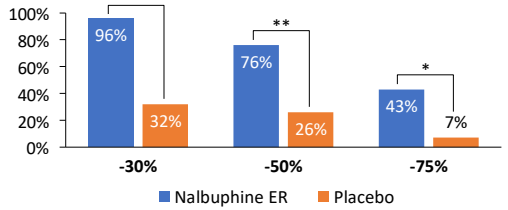
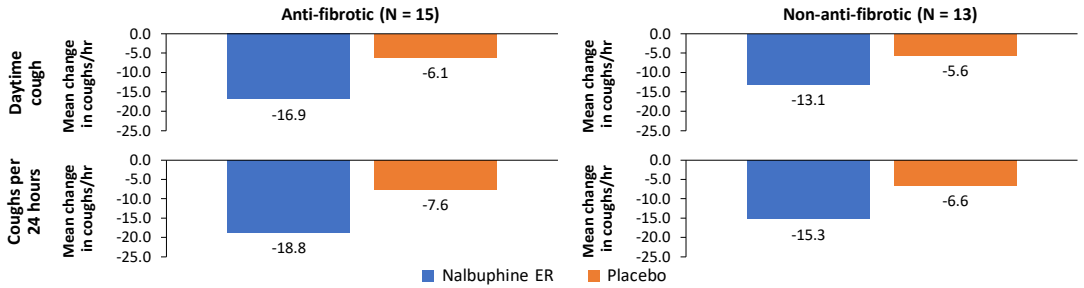


Figure 4. Responder analysis showing change from study baseline thresholds for clinically meaningful reduction in 24-hour cough frequency at Day 22.



*p < 0.01; **p < 0.0001.

Figure 3. Reduction in daytime and 24-hour cough frequency with and without concomitant anti-fibrotic medication at Day 22.



RESULTS

- Patients were primarily male with a mean age of > 70 years and a baseline mean daytime cough frequency of 28 coughs per hour **(Table)**
- 76.2% reduction in daytime cough frequency at Day 22 with nalbuphine ER (75.1% in full analysis set) **(Figure 2)**
- 77.0% reduction in 24-hour cough frequency (76.1% in full analysis set) **(Figure 2)**
- Cough reduction was seen in patients both with and without concomitant anti-fibrotic medication at Day 22 **(Figure 3)**
- 96% of nalbuphine ER patients saw a reduction in 24-hour cough frequency at Day 22 (97% in full analysis set) **(Figure 4)**
- 75% of nalbuphine ER patients saw their cough frequency reduced by half (76% in full analysis set)
- 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
- 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
- Safety profile consistent with prior nalbuphine ER studies in other patient populations, with no new safety signals identified

References: 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. **Acknowledgments and funding sources**: This presentation was prepared by the authors with medical-writing assistance from Excerpta Medica, funded by Trevi therapeutics.
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