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The Effect of Nalbuphine Extended Release on Cough Bouts in Patients With Idiopathic Pulmonary Fibrosis From CORAL—A Phase 2b Randomized Clinical Trial

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Background

- Up to 80% of patients with idiopathic pulmonary fibrosis (IPF) experience chronic cough, for which there are no approved therapies[1]
- Oral nalbuphine extended release (NAL ER) modulates the cough reflex arc by acting as a kappa opioid receptor agonist and mu opioid receptor antagonist in both the central nervous system and the peripheral sensory nerves of the airways[2]
- In a phase 2b trial (CORAL; NCT05964335), patients with IPF treated with NAL ER demonstrated a significant reduction in 24-hour (h) objective cough frequency versus placebo[1]
- Cough events can cluster into bouts, which contribute to perceived severity of coughs and may be impactful to patients[3]

Objective

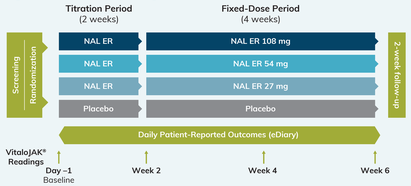
- This exploratory post hoc analysis evaluated the effect of NAL ER on 24-h cough bout frequency, number of coughs per bout, and length of bouts compared with placebo in patients with IPF from the CORAL trial

Methods

Study design

- CORAL was a randomized, double-blind, placebo-controlled, parallel-arm, phase 2b dose-ranging study to measure the efficacy and safety of 3 doses of NAL ER for management of cough in patients with IPF (**Figure 1**)
- Patients with IPF were randomized 1:1:1:1 to 1 of 4 treatment arms: placebo, NAL ER 27 mg, 54 mg, or 108 mg twice daily
- Doses were titrated during a blinded 2-week titration period, followed by a 4-week fixed-dose period, for a total of 6 weeks of treatment

Figure 1. CORAL Study Design



VitaloJAK®: Vitalograph Ltd, Buckingham, United Kingdom.

Treatment was administered twice daily.

Study participants

- CORAL included patients aged ≥18 years who had an IPF diagnosis and self-reported chronic cough lasting ≥8 weeks
- Cough Severity Numerical Rating Scale (CS-NRS [0, no cough; 10, worst possible cough]) score of ≥4 at screening and baseline
- Forced vital capacity ≥40% of predicted
- Diffusing capacity of the lungs for carbon monoxide ≥25% of predicted
- Oxygen saturation by pulse oximetry of ≥92%

Outcome measures

- In this exploratory post hoc analysis, cough bouts were analyzed from 24-h cough frequency data at Day −1 (baseline) and Week 6 (end of treatment) using a digital cough monitor (VitaloJAK®)
- Cough bouts (≥2 coughs) were generated by combining consecutive cough sounds within 2 seconds of one another and analyzed using a mixed-model repeated measures analysis
- Exploratory analyses included mean coughs per bout and bout duration (in seconds)

Results

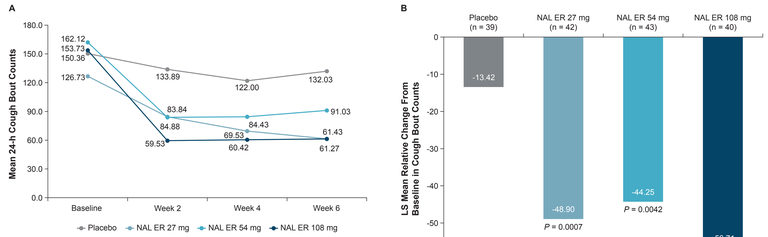
Study population

- Of the 165 patients who were randomly assigned, 164 completed the treatment phase and were included in the full analysis set
- Cough bout data were available for 162 patients at baseline and were included in this post hoc analysis

Cough bout frequency

- Treatment with NAL ER reduced mean 24-h cough bout counts over time (**Figure 2A**)
- Across all treatment arms, NAL ER significantly ($P < 0.005$) reduced cough bouts from baseline compared with placebo at Week 6 (**Figure 2B**)

Figure 2. (A) Mean 24-Hour Cough Bout Counts and (B) Relative Change From Baseline in Cough Bout Counts at Week 6



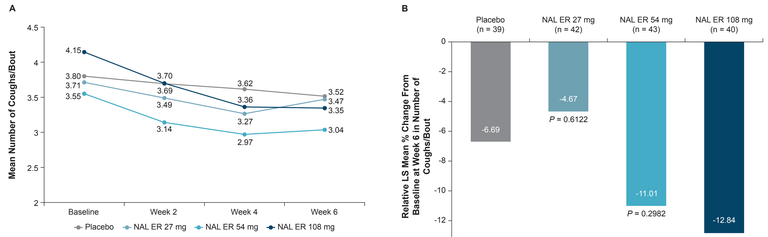
Placebo n =	39	36	37	36
NAL ER 27 mg n =	40	40	40	40
NAL ER 54 mg n =	43	38	37	34
NAL ER 108 mg n =	40	38	38	37

Cough bout is defined as a sequence of ≥2 coughs.

Number of coughs per bout

- Baseline mean coughs per bout were similar across groups: 3.8 for placebo, 3.7 for NAL ER 27 mg, 3.6 for NAL ER 54 mg, and 4.1 for NAL ER 108 mg (**Figure 3A**)
- By Week 6, treatment with NAL ER across all dose groups numerically decreased the number of coughs per bout (**Figure 3A**)
- The relative least squares (LS) mean percentage change from baseline in number of coughs per bout at Week 6 was -6.7% for placebo, -4.7% for NAL ER 27 mg, -11.0% for NAL ER 54 mg, and -12.8% for NAL ER 108 mg (**Figure 3B**)
  - There was a non-significant trend toward a greater reduction in the mean number of coughs per bout with NAL ER 54 mg and NAL ER 108 mg at Weeks 2, 4, and 6 compared with placebo

Figure 3. (A) Mean Number of Coughs per Bout and (B) Relative LS Mean Percentage Change From Baseline at Week 6 in Number of Coughs per Bout



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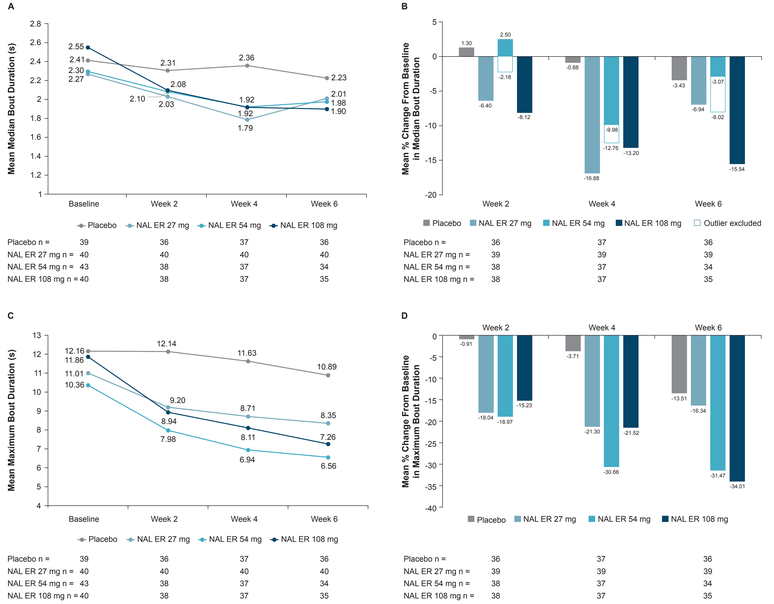
Bout length/duration

- There is a trend toward a reduction in the average median bout duration with each NAL ER dose (**Figure 4A**)
- One subject in the 54-mg group had an unusually low median bout duration of 0.831 seconds at baseline and was considered an outlier. Mean percentage change from baseline in median bout duration is shown both with and without this subject (**Figure 4B**)
- No significant difference was observed in the relative LS mean percentage change from baseline in median bout duration at Week 6 with each NAL ER dose versus placebo (NAL ER 27 mg: −8.3%, $P = 0.5527$; NAL ER 54 mg: −4.3%, $P = 0.8764$; NAL ER 108 mg: −14.55, $P = 0.2133$)
- The mean maximum bout durations at baseline were: 12.2, 11.0, 10.4, and 11.9 seconds in the placebo, NAL ER 27-mg, NAL ER 54-mg, and NAL ER 108-mg dose groups, respectively (**Figure 4C**)
- The maximum bout duration decreased by 31% and 34% from baseline to Week 6 with NAL ER 54 mg and NAL ER 108 mg, respectively (**Figure 4D**)

Figure 4. (A) Mean Median Bout Duration Over Time, (B) Mean Percentage Change From Baseline in Median Bout Duration Over Time, (C) Mean Maximum Bout Duration Over Time, and (D) Mean Percentage Change From Baseline in Maximum Bout Duration Over Time



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Placebo n =	36	37	37	36
NAL ER 27 mg n =	39	39	39	39
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NAL ER 108 mg n =	38	37	37	35

The bout duration is defined as the time interval between the first and last cough event within a bout (seconds) plus 0.326 seconds.

The median bout duration is calculated as the mean of the bout duration across all bouts within a 24-h recording.

Relative change from baseline is calculated as [(post-baseline − baseline) / baseline] * 100.

Safety

- Serious adverse events occurred in 10% of patients receiving placebo compared with 1.6% of those treated with NAL ER, and no deaths were reported[1]
- The most frequently reported adverse events with NAL ER (≥10% of patients) included nausea, vomiting, constipation, dizziness, headache, fatigue, somnolence, and dry mouth[1]

Conclusions

- Consistent with results observed for cough frequency, treatment with NAL ER at doses of 27 mg, 54 mg, and 108 mg significantly reduced the number of cough bouts compared with placebo in patients with IPF
- A trend toward decreased number of coughs per bout and median bout length was observed, with the largest impact observed on the average maximum bout duration
- While informative, these post hoc analyses are exploratory; results should be interpreted cautiously due to reduced statistical power and should be confirmed in future studies

References

1. Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.
2. Birring SS et al. *Lung*. 2025;203(1):62.
3. Lee J et al. *Chest*. 2022;162(3):603-613.

Abbreviations

CS-NRS, Cough Severity Numerical Rating Scale; h, hour; IPF, idiopathic pulmonary fibrosis; LS, least squares; NAL ER, nalbuphine extended release; SD, standard deviation.

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Disclosures

JAS has received consulting fees from Trevi Therapeutics, Inc., and holds an institutional license agreement with Vitalograph for cough detection software; royalties may be distributed to the affiliated department.

KH

DPD

TET

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JC is employed by Trevi Therapeutics, Inc., as Chief Development Officer and a Corporate Officer of the company.

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