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The Effect of Nalbuphine Extended-Release Tablets on Breathlessness in Patients With Idiopathic Pulmonary Fibrosis Experiencing Chronic Cough from the Phase 2b CORAL Trial

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Background

- Breathlessness, along with cough and fatigue, greatly impacts daily life in patients with idiopathic pulmonary fibrosis (IPF)[1,2]
- Although no pharmacologic therapies effectively relieve dyspnea in these patients, management may include supplemental oxygen, pulmonary rehabilitation, and supportive care[3]
- 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 peripheral sensory nerves of the airways and the central nervous system[4]
- In the phase 2b CORAL trial (NCT05964335), NAL ER (27 mg, 54 mg, and 108 mg twice daily [BID]) significantly reduced objectively measured cough at Week 6 by 47.9%, 53.4%, and 60.2%, respectively, versus placebo (16.9%) in patients with IPF[4]

Objective

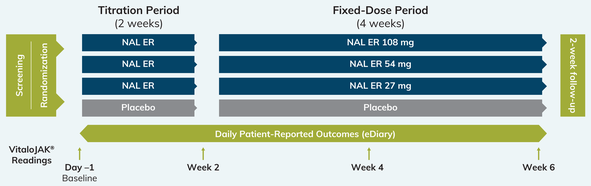
To evaluate the change in breathlessness in patients treated with NAL ER in the CORAL trial

Methods

Study design[4]

- 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**)
- Eligible participants were randomly assigned (1:1:1:1) to 1 of 4 treatment arms: placebo or NAL ER 27 mg, 54 mg, or 108 mg BID
- 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 participants aged ≥18 years who had an IPF diagnosis and self-reported chronic cough lasting ≥8 weeks[4]

Outcome measures

- The primary endpoint was the relative change from baseline in 24-hour cough frequency at Week 6 for NAL ER compared with placebo, measured using objective digital cough monitoring[4]
- A secondary objective was the change from baseline in the Evaluating Respiratory Symptoms in IPF (E-RS:IPF)™ breathlessness subdomain score at Week 6 for NAL ER versus placebo[4,5]
  - The E-RS:IPF is a daily diary used to assess respiratory symptom severity
  - Its 5-item breathlessness subdomain serves as an exploratory measure for evaluating treatment effects on breathlessness, with higher scores indicating greater symptom severity
  - Items evaluated include breathlessness when walking, breathlessness when washing or dressing, breathlessness when doing chores, overall breathlessness on the worst day, and general shortness of breath
- A correlation analysis was conducted between the E-RS:IPF breathlessness subdomain and the E-RS:IPF cough subdomain, the Patient Global Impression of Severity (PGI-S) scale, and the quality-of-life instrument Leicester Cough Questionnaire (LCQ)
  - The E-RS:IPF cough subdomain is a patient-reported measure assessing cough frequency[5]
  - The PGI-S is a self-reported, single-item scale that captures patients' overall perception of disease severity at a given timepoint[6]
  - The LCQ is a validated quality-of-life instrument assessing the physical, psychological, and social impact of cough, with higher scores indicating better health status[7]

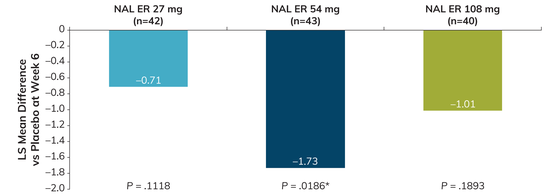
Results

- A total of 165 patients were randomized[4]
  - Median age was 71 years and 71.5% of patients were male
  - Mean (SD) baseline cough count was 28.3 (27.4) coughs/hour, and 77% of patients were receiving background antifibrotic medication

Change From Baseline in Breathlessness Scores

- Among patients with chronic cough, mean baseline E-RS:IPF breathlessness scores were 8.04 (placebo), 7.49 (27 mg BID), 9.20 (54 mg BID), and 7.56 (108 mg BID)
- At Week 6, NAL ER 54 mg demonstrated a statistically significant placebo-adjusted improvement in E-RS:IPF breathlessness score (LS mean difference: –1.73 vs placebo; *P* = .0186) (**Figure 2**)

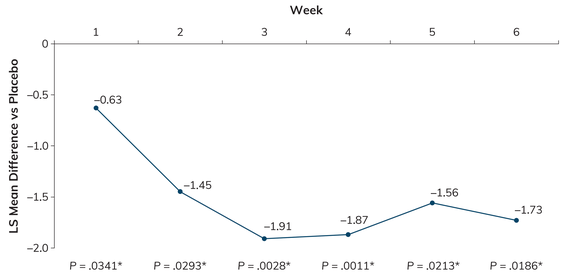
Figure 2. Placebo-Adjusted Change From Baseline in E-RS:IPF Breathlessness Score at Week 6



Negative values indicate improvement (reduction) in breathlessness score. *P* values are based on Wilcoxon rank sum test.
*P < .05 was considered statistically significant.

- Placebo-adjusted improvements in E-RS:IPF breathlessness scores were statistically significant starting at Week 1 with NAL ER 54 mg (**Figure 3**). Other doses were not significantly different from placebo

Figure 3. Placebo-Adjusted Change From Baseline in E-RS:IPF Breathlessness Score Through Week 6 With NAL ER 54 mg



Negative values indicate improvement (reduction) in breathlessness score.
P values are based on Wilcoxon rank sum test.
*P < .05 was considered statistically significant.

Correlation Analyses

- At Week 6, change from baseline in E-RS:IPF breathlessness scores was significantly correlated with patient-reported cough severity (PGI-S), cough frequency (E-RS:IPF cough subdomain), and quality of life (LCQ Total and Physical scores) in the overall pooled population (placebo and all NAL ER dose groups; *P* < .0001 for all) (**Table 1**)
- A significant (*P* < .01) correlation at Week 6 between change from baseline in E-RS:IPF breathlessness scores and PGI-S, cough frequency (E-RS:IPF cough subdomain), and quality of life (LCQ Total and Physical scores) was also seen in the NAL ER 54-mg and pooled NAL ER 54-/108-mg dose groups (**Table 1**)

Table 1. Correlations of Change From Baseline in E-RS:IPF Breathlessness at Week 6

Treatment	Breathlessness/PGI-S	Breathlessness/E-RS:IPF Cough Subdomain	Breathlessness/LCQ Total Score	Breathlessness/LCQ Physical Score
Overall	r=.4791 *P*<0.0001 n=98	r=.5710 *P*<0.0001 n=143	r=-.5024 *P*<0.0001 n=102	r=.5530 *P*<0.0001 n=102
NAL ER 54 mg	r=.5629 *P*<0.0042 n=24	r=.6046 *P*<0.0001 n=35	r=-.6048 *P*<0.0011 n=26	r=-.5721 *P*<0.0023 n=26
NAL ER 108 mg	r=.3975 *P*<0.0603 n=23	r=.5158 *P*<0.0013 n=36	r=-.4789 *P*<0.0154 n=25	r=-.5329 *P*<0.0061 n=25
NAL ER 54/108 mg	r=.4656 *P*<0.0007 n=49	r=.6289 *P*<0.0001 n=69	r=-.4877 *P*<0.0002 n=52	r=-.5674 *P*<0.0001 n=52

Results in form of Pearson's *r* (*P* value) and number of patients. Positive *r* indicates direct association; negative *r* indicates inverse association.
P value from two-sided Pearson correlation test.

- At Weeks 2, 4, and 6, change from baseline in E-RS:IPF breathlessness showed significant (*P* ≤ .0001) positive correlations with patient-reported cough severity (PGI-S) in the overall pooled population (**Table 2**)
- Statistically significant (*P* < .05) associations were observed in the NAL ER 54 mg and pooled NAL ER 54-mg/108-mg dose groups starting at Week 2 and extending to Week 6

Table 2. Correlation of Change From Baseline in E-RS:IPF Breathlessness With PGI-S at Weeks 2, 4, and 6

Treatment	Week 2	Week 4	Week 6
Overall	r=.3546 *P*<0.0001 n=112	r=.4465 *P*<0.0001 n=129	r=.4791 *P*<0.0001 n=98
NAL ER 54 mg	r=.4371 *P*<0.0200 n=28	r=.5489 *P*<0.0008 n=34	r=.5629 *P*<0.0042 n=24
NAL ER 108 mg	r=.0462 *P*<0.8192 n=27	r=.2687 *P*<0.1438 n=31	r=.3975 *P*<0.0603 n=23
NAL ER 54/108 mg	r=.4469 *P*<0.0004 n=59	r=.5380 *P*<0.0001 n=64	r=.4656 *P*<0.0007 n=49

Results in form of Pearson's *r* (*P*-value) and number of patients. Positive *r* indicates direct association; negative *r* indicates inverse association.
P value from two-sided Pearson correlation test.

- In the overall pooled population, change from baseline in E-RS:IPF breathlessness was significantly positively correlated with the E-RS:IPF cough subdomain at all time points (Weeks 1-6; *P* < .0001 for all) (**Table 3**)
- The significant positive correlation was also seen within each individual dose group and placebo (data not shown; all *P* < .01)

Table 3. Overall Correlation of Change From Baseline in E-RS:IPF Breathlessness With E-RS:IPF Cough Subdomain (Weeks 1-6)

Overall population	Week 1 (n=148)	Week 2 (n=150)	Week 3 (n=148)	Week 4 (n=147)	Week 5 (n=145)	Week 6 (n=143)
Pearson's *r* (*P* value)	.5244 (<.0001)	.6053 (<.0001)	.5930 (<.0001)	.6038 (<.0001)	.5943 (<.0001)	.5710 (<.0001)

Overall values represent correlations pooled across all randomized treatment arms (placebo and all NAL ER dose groups).

Safety

- Safety findings were generally consistent with the known safety profile of NAL ER from previous trials[4]
- Common adverse events (AEs) experienced included nausea, vomiting, constipation, dizziness, headache, fatigue, somnolence, and dry mouth[4]
- Serious AEs (all non-fatal) were reported for 4 patients (10.0%) in the placebo group and for 2 patients (1.6%) in the NAL ER group[4]

Conclusions

- This initial exploratory analysis shows that treatment with NAL ER 54 mg significantly reduced breathlessness measured by the E-RS:IPF at Week 6 in patients with IPF and chronic cough
- Reductions in breathlessness were generally correlated with lower patient-perceived cough frequency and severity measured by the E-RS:IPF cough subdomain and PGI-S scale, and better quality of life measured by the LCQ
- Additional future analyses will further define the effect of NAL ER on breathlessness

References

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Abbreviations

AE, adverse event; BID, twice daily; E-RS:IPF, Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis; IPF, idiopathic pulmonary fibrosis; LCQ, Leicester Cough Questionnaire; LS, least squares; NAL ER, nalbuphine extended release; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

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Disclosures

DAM is a consultant for Trevi Therapeutics and Viatris; participates in advisory boards for AstraZeneca, Theravance, Verona, and Viatris; receives royalties from Johns Hopkins University Press for authoring a book entitled, "COPD: Answers to Your Most Pressing Questions about COPD" (2022), and Pharma companies for use of the baseline and transition dyspnea indexes in clinical trials.

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

TS is employed by Trevi Therapeutics Inc. as Chief Scientific Officer and a Corporate Officer of the company and owns stock and stock options with Trevi Therapeutics Inc. TS is listed as an inventor on issued and pending patents related to the use of nalbuphine (a kappa agonist–mu antagonist opioid) in chronic cough.

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