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Nalbuphine Extended Release Reduces Cough Bouts in Patients With Refractory Chronic Cough in the Phase 2a RIVER Trial

Jacky Smith,[1] Kim Holt,[1] Denis P. Drennan,[2] Terence E. Taylor,[2] James Cassella[3]

[1]The University of Manchester, Manchester, United Kingdom; [2]Vitalograph, Ennis, Ireland; [3]Trevi Therapeutics, New Haven, CT, USA

Background

- Refractory chronic cough (RCC) is associated with a substantial disease burden and significantly impacts patients' quality of life[1-3]
- There are currently no approved therapies for RCC in the United States, highlighting a significant unmet medical need[4]
- 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[5]
- In the phase 2a RIVER trial (NCT05962151), NAL ER treatment demonstrated a significant reduction in 24-hour objective cough frequency versus placebo in patients with RCC using a digital cough monitor (VitaloJAK® [Vitalograph Ltd; Buckingham, United Kingdom])[6]
- Cough events can occur in clusters, or bouts, which may be impactful to patients[7]

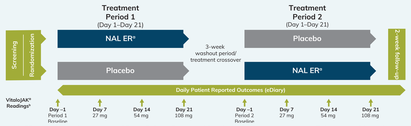
Objective

- This exploratory *post hoc* analysis evaluated the effect of NAL ER on 24-hour cough bout frequency, number of coughs per bout, and bout duration compared with placebo in patients with RCC in the RIVER trial

Methods

- Study design
  - This was a double-blind, placebo-controlled, 2-period crossover study that stratified patients with RCC into 2 subgroups based on 24-hour cough frequency at screening (10-19 coughs/hour and ≥20 coughs/hour) (**Figure 1**)
  - Patients were randomly assigned to one of two 21-day treatment sequences: NAL ER to placebo, or placebo to NAL ER, with a 21-day washout period in between
  - NAL ER was initiated at 27 mg once daily on Days 1-2, increased to 27 mg twice daily (BID) through Day 7, then titrated every 7 days (54 mg and 108 mg, both BID)

Figure 1. RIVER Study Design



NAL ER was titrated starting at 27 mg BID on Day 1, with subsequent increases every 7 days to achieve the dose shown for each respective visit day.

At the end of each recording session (Days 7, 14, and 21), the electronic cough monitor (VitaloJAK), which was worn starting a day before each study visit, was removed and returned to the clinical study center for data processing.

- Study participants
  - Adults aged ≥18 years with a diagnosis of RCC, defined as cough persisting despite treatment or without identifiable cause[8]
  - Cough duration ≥1 year
  - Normal chest imaging (X-ray or computed tomography [CT]) within the past 24 months
  - Cough severity visual analog scale (CS-VAS) score ≥40 mm
  - 24-hour cough frequency ≥10 coughs/hour (stratified as 10-19 and ≥20 coughs/hour)
  - Forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC) ≥60%
- Outcome measures
  - In this exploratory *post hoc* analysis, cough bouts were analyzed from 24-hour cough frequency data 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 with a mixed model repeated measures analysis
  - Exploratory analyses included mean and median coughs per bout and median bout duration (in seconds)

Results

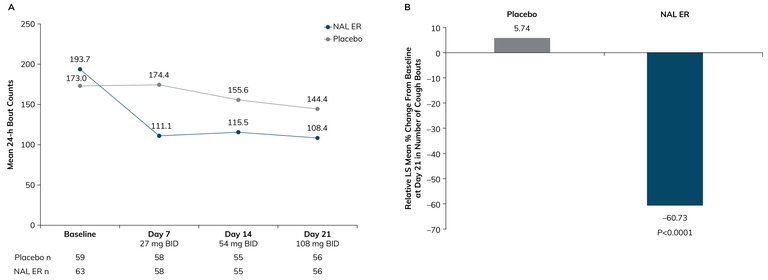
Study Population

- A total of 59 patients received placebo and 63 patients received NAL ER

Cough Bout Counts

- Treatment with NAL ER reduced mean 24-hour cough bout counts over time versus a minimal change seen with placebo (**Figure 2A**)
- There was a numerically greater reduction in cough bout counts with NAL ER compared with placebo across all time points
- Treatment with NAL ER resulted in a significant (*P*<0.0001) reduction in the number of cough bouts from baseline compared with placebo at Day 21 (**Figure 2B**)
  - Similar improvements in relative percent change from baseline with NAL ER compared with placebo were seen at Day 7 (27 mg BID; mean = 6.8 vs –56.5, placebo vs NAL ER) and Day 14 (54 mg BID; mean = –2.7 vs –56.7, placebo vs NAL ER)

Figure 2. (A) Mean 24-Hour Cough Bouts Over Time and (B) Relative LS Mean Percent Change in 24-Hour Cough Bouts From Baseline at Day 21 in Patients With RCC Treated With NAL ER vs Placebo

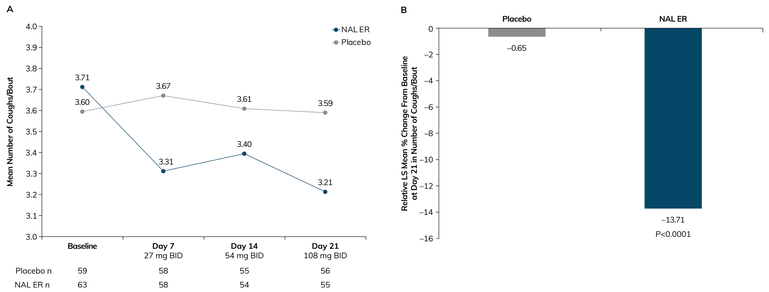


Cough bout is defined as a sequence of 2 or more coughs.

Number of Coughs per Bout

- Baseline mean number of coughs per bout was 3.6 with placebo versus 3.7 with NAL ER
- Treatment with NAL ER reduced mean number of coughs per bout compared with placebo across all time points (**Figure 3A**)
- There was a significantly (*P*<0.0001) greater reduction in the number of coughs per bout with NAL ER versus placebo at Day 21 (**Figure 3B**)

Figure 3. (A) Mean Number of Coughs per Bout and (B) Relative LS Mean Percent Change in Number of Coughs per Bout From Baseline at Day 21 in Patients With RCC Treated With NAL ER vs Placebo

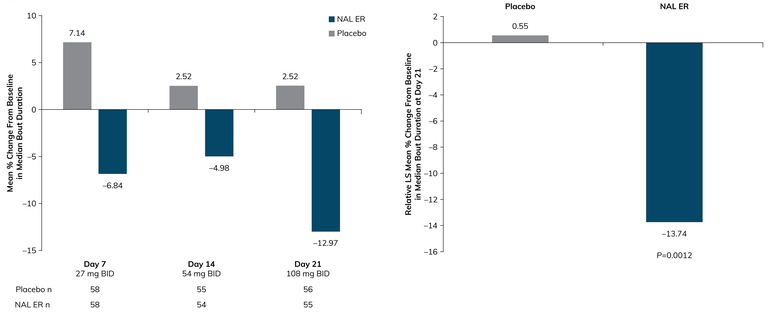


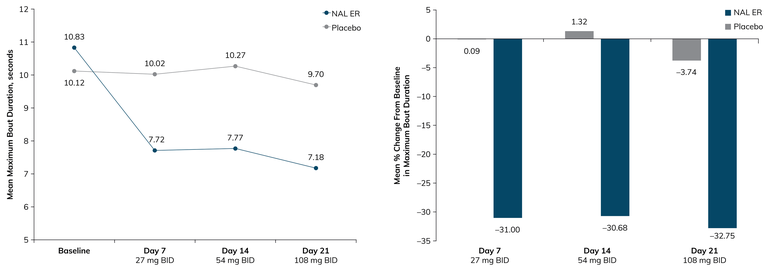
The mean coughs per bout is calculated as the mean of the number of coughs in a bout across all bouts within a 24-hour recording.

Bout Duration

- The baseline mean (SD) median bout duration was 1.77 seconds (1.10 seconds) with placebo versus 1.86 seconds (0.96 seconds) with NAL ER
- Treatment with NAL ER reduced the average median bout duration compared with placebo across all time points (**Figure 4A**)
  - There was a significantly (*P*=0.0012) greater reduction in bout duration with NAL ER at Day 21 compared with placebo (**Figure 4B**)
- Mean maximum bout duration decreased with NAL ER over time, with greater reductions from baseline versus placebo at all time points (**Figures 4C, D**)

Figure 4. (A) Mean Percent Change From Baseline in Median Bout Duration at Days 7, 14, and 21, (B) Relative LS Mean Percent Change in Median Bout Duration From Baseline at Day 21, (C) Mean Maximum Bout Duration at Baseline and Over Time and (D) Mean Percent Change in Maximum Bout Duration From Baseline at Days 7, 14, and 21 in Patients With RCC Treated With NAL ER vs Placebo





The bout duration is defined as the time interval between the first and last cough event within a bout plus 0.326 seconds.
The median bout duration is calculated as the median of the bout duration across all bouts within a 24-hour recording.
The maximum bout duration is calculated as the maximum of the bout duration across all bouts within a 24-hour recording.

Safety

- Safety findings were generally consistent with the known safety profile of NAL ER from previous trials[6]
  - Common adverse events (AEs) experienced included constipation, nausea, somnolence, headache, dizziness, and fatigue, and there were no treatment-emergent serious AEs[6]

Conclusions

- Consistent with results observed for cough frequency, NAL ER significantly reduced the number of cough bouts, coughs per bout, and bout duration compared with placebo in patients with RCC
- 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

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Abbreviations

AE, adverse event; BID, twice daily; CS-VAS, cough severity visual analog scale; CT, computed tomography; FEV_1/FVC, forced expiratory volume in 1 second/forced vital capacity; LS, least squares; NAL ER, nalbuphine extended release; RCC, refractory chronic cough.

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Disclosures

JS 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 and **TET** have no conflicts of interest to declare.

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

Please see Poster #11854 for an exploratory *post hoc* analysis of the effect of NAL ER on cough bouts compared with placebo in patients with idiopathic pulmonary fibrosis in the CORAL trial.

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