# Responder Analysis of Nalbuphine Extended-Release in Refractory Chronic Cough: Results From the RIVER Phase 2a Trial

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## Background

- Refractory chronic cough (RCC) accounts for approximately one-third of chronic cough cases[1] and is associated with a substantial disease burden[2]
  - RCC significantly impairs physical and psychological health, with 61% of patients reporting anxiety and/or depression,[2] and has a substantial economic impact[3]
  - It remains an area of high unmet need and, currently, no therapies are approved or available in the United States
- Nalbuphine extended-release (NAL ER) acts on the cough reflex arc centrally and peripherally as a kappa agonist and a mu antagonist, targeting opioid receptors that play a key role in controlling chronic cough
- NAL ER tablets are being developed for the treatment of chronic cough in patients with idiopathic pulmonary fibrosis (IPF)[4,5] or RCC[6]

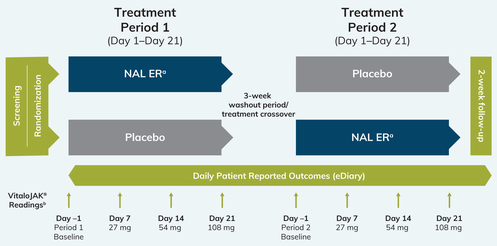
## Aim

- To evaluate responders to treatment with NAL ER, defined as patients with ≥30%, ≥50%, or ≥75% reduction in 24-hour cough frequency using an objective cough monitor, from the RIVER (NCT05962151) trial of patients with RCC

## Methods

- Study design
  - RIVER was a double-blind, randomized, placebo-controlled, 2-period crossover study in which NAL ER was initiated at 27 mg BID on Day 1 to Day 7 and titrated every 7 days (to 54 mg BID [Day 14] and then 108 mg BID [Day 21]) (**Figure 1**)
  - Patients were randomly assigned to 1 of the following 2 sequences:
    - NAL ER in treatment period 1 followed by placebo in treatment period 2
    - Placebo in treatment period 1 followed by NAL ER in treatment period 2
  - Treatment periods were separated by a 21-day washout period; the second treatment period was followed by a 14-day follow-up period
- Eligibility criteria are summarized in **Figure 2**
- Outcomes measures
  - Proportion of responders who experienced ≥30%, ≥50%, or ≥75% reduction in 24-hour cough frequency measured on days 7, 14, and 21
    - 24-Hour objective cough count was assessed using the VitaloJAK cough monitor (Vitalograph Ltd., Buckingham, United Kingdom)
  - Safety was determined by the incidence and severity of treatment-emergent adverse events (TEAEs)

### Figure 1. Study Design




[a]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.
[b]At the end of each recording session (days 7, 14, and 21), the electronic cough monitor (VitaloJAK; Vitalograph Ltd, Buckingham, United Kingdom), which was worn from 1 day before each study visit, was removed and returned to the clinical study center for data processing.

### Figure 2. Eligibility Criteria

**Key Inclusion Criteria**

- RCC diagnosis and persistent cough for ≥1 year
- Chest radiography or computed tomography (CT) of the thorax performed within the last 24 months showing no abnormalities that could significantly contribute to RCC
- A rating of ≥40 mm on the cough severity visual analog scale (CS-VAS)
- Cough frequency of 10-19 coughs/hour or ≥20 coughs/hour over 24 hours
- Forced expiratory volume in 1 second ($FEV_1$) to forced vital capacity (FVC) ratio ≥60%

**Key Exclusion Criteria**

- Upper or lower respiratory tract infection <6 weeks before enrollment
- History of smoking/vaping within the past 12 months before screening
- History of sleep apnea, bronchiectasis, chronic obstructive pulmonary disease, IPF, or uncontrolled asthma

## Results

- Of the 66 participants who were randomly assigned, 59 (89.4%) completed at least 1 treatment period and were included in the full analysis set
- Baseline characteristics of all participants are summarized in **Table 1**

### Table 1. Baseline Characteristics

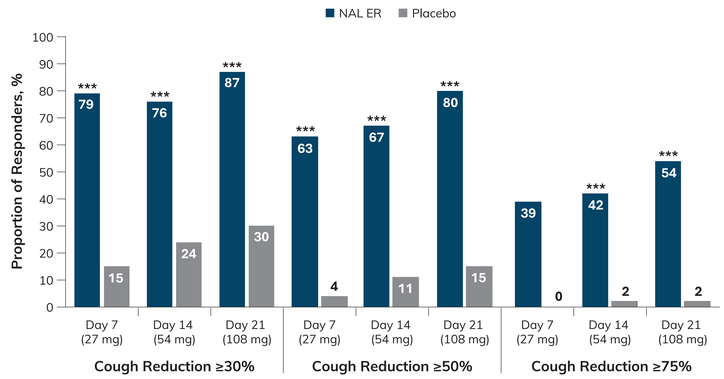
| | | Participants N = 66 |
|---|---|---|
| **Age, mean (SD), years** | | 60.2 (10.5) |
| **Sex, n (%)** | **Female** | 44 (66.7) |
| | **Male** | 22 (33.3) |
| **Race, n (%)** | **White** | 61 (92.4) |
| | **Black or African American** | 4 (6.1) |
| | **Asian** | 1 (1.5) |
| **Duration of cough, mean (SD), years** | | 12.6 (10.4) |
| **Screening 24-hour cough frequency, coughs/hour** | **Mean (SD)** | 34.7 (29.2) |
| | **Min, max** | 10.0, 165.9 |

Safety population: all patients who received ≥1 dose of study drug or placebo.

### Responder Analysis

- A significant improvement (≥30% reduction from baseline) in 24-hour cough frequency was observed on day 21 in 87% of patients treated with NAL ER 108 mg compared with those who received placebo (30%, $P < .0001$) (**Figure 3**)
- At higher response thresholds of ≥50% and ≥75% cough reduction from baseline, treatment with NAL ER resulted in significantly more responders than placebo, with a progressively increasing proportion of patients achieving a ≥75% reduction in cough frequency over time
  - The proportion of patients achieving a ≥75% reduction in cough frequency increased over time and with higher doses of NAL ER
  - Specifically, at day 21, 54% of patients achieved a ≥75% reduction in cough frequency during NAL ER 108 mg BID treatment, compared with 2% of patients during placebo treatment

### Figure 3. Proportion of Responders at Increasing Thresholds of Cough Reduction




Full analysis set: all patients who received ≥1 dose of study drug and have objective cough count data at baseline and day 21 in ≥1 treatment period.
***P < .0001; NAL ER vs placebo.

### Safety

- No serious TEAEs were reported (**Table 2**)
- TEAEs led to discontinuation in 10 patients: 9 (14.3%) who were given NAL ER treatment and 1 (1.7%) given placebo (**Table 2**)
  - TEAEs occurred in 79.4% of patients given NAL ER treatment compared with 54.2% given placebo
- TEAEs considered to be related to NAL ER were reported in 63.5% who received NAL ER compared with 23.7% who received placebo
  - Discontinuations due to TEAEs considered to be related to NAL ER occurred in 8 patients (12.7%) treated with NAL ER and 1 patient (1.7%) treated with placebo
- The most common (occurring in ≥10% of patients) TEAEs associated with NAL ER were consistent with the known class effects of opioids, with higher incidences of constipation (28.6% vs 6.8%), somnolence (25.4% vs 0%), nausea (22.2% vs 3.4%), and dizziness (19.0% vs 3.4%) compared with placebo (**Table 2**)

### Table 2. Treatment-Emergent Adverse Events

| | NAL ER n = 63 | Placebo n = 59 |
|---|---|---|
| **Any TEAE, n (%)** | 50 (79.4) | 32 (54.2) |
| Related to study drug | 40 (63.5) | 14 (23.7) |
| Serious | 0 | 0 |
| AEs leading to discontinuation | 9 (14.3) | 1 (1.7) |
| **Most frequently occurring TEAEs, n (%)** | | |
| Constipation | 18 (28.6) | 4 (6.8) |
| Nausea | 14 (22.2) | 2 (3.4) |
| Somnolence | 16 (25.4) | 0 (0) |
| Headache | 10 (15.9) | 7 (11.9) |
| Dizziness | 12 (19.0) | 2 (3.4) |
| Fatigue | 9 (14.3) | 3 (5.1) |

Safety population: all patients who received ≥1 dose of study drug or placebo.

## Conclusions

- A large proportion of patients treated with NAL ER achieved statistically significant reduction in the frequency of cough
- Statistically significant improvements were observed even at the lowest dose tested (27 mg BID) after 7 days of treatment for both the ≥30% and the ≥50% cough reduction thresholds
- NAL ER provided cough frequency reductions at the individual level, with more participants achieving clinically relevant responses compared with placebo
- These results support the potential of NAL ER as an effective treatment for RCC and warrant the further evaluation of NAL ER

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### Abbreviations

AE, adverse event; BID, twice daily; CS-VAS, cough severity visual analog scale. IPF, idiopathic pulmonary fibrosis; NAL, nalbuphine; NAL ER, nalbuphine extended release; RCC, refractory chronic cough; TEAE, treatment-emergent adverse event.

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

MG was employed by Trevi Therapeutics Inc. at the time of this study.



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