Efficacy and Safety of Nalbuphine Extended-Release in Refractory Chronic Cough: Primary Results From the Phase 2a RIVER Trial

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Background

- Refractory chronic cough (RCC) may account 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: 61% of patients report anxiety or depression[2]
  - RCC affects daily functioning, with reported reductions in work (34%) and non-work (30%) activities[2]
  - RCC has a meaningful economic impact[1] and remains an area of high unmet need; no therapies are approved or currently available in the United States
- Nalbuphine extended-release (NAL ER) tablets are being developed for the treatment of chronic cough in patients with idiopathic pulmonary fibrosis (IPF)[3,4] or RCC[5]
- 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

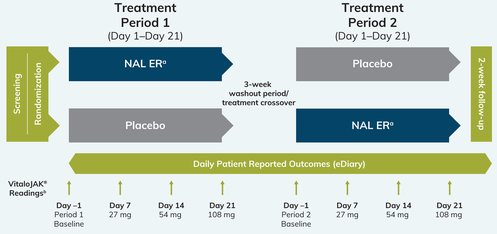
Aim

- To evaluate NAL ER for the treatment of RCC in the RIVER (NCT05962151) trial

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 with RCC were stratified into 2 subgroups based on 24-hour objective cough frequency at screening, 10-19 coughs/hour or ≥20 coughs/hour
  - 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
- 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 refractory chronic cough
  - 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 (FEV1) to forced vital capacity (FVC) ratio ≥60%
- 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

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 a day before each study visit, was removed and returned to the clinical study center for data processing.

Outcome Measures

- Primary end point
  - Relative change from baseline in 24-hour objective cough count with NAL ER compared with placebo at day 21 (108 mg BID) assessed using a cough monitor (VitaloJAK; Vitalograph Ltd, Buckingham, United Kingdom)
- Secondary end points
  - Relative change from baseline in patient-reported cough severity and frequency at days 7, 14, and 21 using the CS-VAS and the Patient-Reported Cough Frequency (PR-CF) measures
- Safety was evaluated by the incidence and severity of adverse events

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

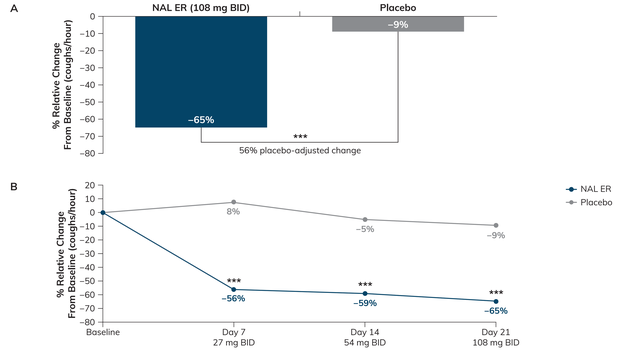
		Participants N = 66
Age, mean (SD), years		60.2 (10.5)
Sex, n (%)	Female	44 (66.7)
	Male	22 (33.3)
Race, n (%)	White	61 (92.4)
	Black or African American	4 (6.1)
	Asian	1 (1.5)
Duration of cough, mean (SD), years		12.6 (10.4)
Screening 24-hour cough frequency, coughs/hour	Mean (SD)	34.7 (29.2)
	Min, max	10.0, 165.9
Screening CS-VAS score, mean (SD)		72.2 (13.3)

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

Relative Change From Baseline in 24-Hour Cough Frequency

- NAL ER 108 mg BID and placebo reduced 24-hour cough frequency by 65% and 9% on day 21, respectively (placebo-adjusted improvement of 56%; $P < .0001$; **Figure 2A**)
- Significant reductions in 24-hour cough frequency were observed on day 7 with NAL ER 27 mg BID (mean [SD], −56.1 [30.7]; $P < .0001$) and day 14 with NAL ER 54 mg BID (mean [SD], −59.2 [33.3]; $P < .0001$; **Figure 2B**)

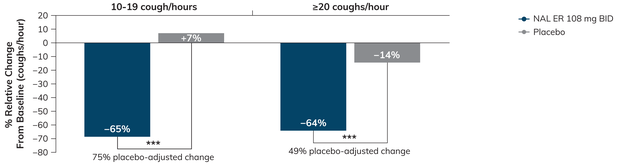
Figure 2. Relative Change From Baseline in 24-Hour Cough Frequency



*** $P < .0001$; NAL ER vs placebo.

- Reductions in 24-hour cough frequency also were observed in both cough frequency groups (**Figure 3**)

Figure 3. Relative Change From Baseline in 24-Hour Cough Frequency by Baseline Cough Frequency at Day 21

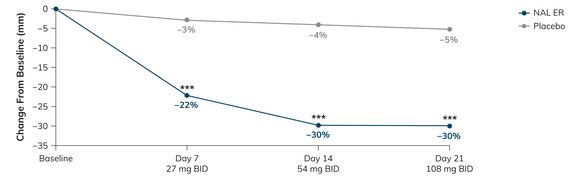


*** $P < .0001$; NAL ER vs placebo.

Patient-Reported Outcomes

- Significant improvement in cough severity per the CS-VAS was observed at day 7 with NAL ER 27 mg through day 21 with NAL ER 108 mg (**Figure 4**)

Figure 4. Patient-Reported Cough Severity



***$P < .0001$; NAL ER vs placebo.

- Cough frequency measured using PR-CF decreased over the 21-day treatment period, assessed by the question, "Over the past 24 hours, how often did you cough?"
  - Patients treated with NAL ER had a significant reduction in mean cough frequency scores from day 7 (27 mg BID) through day 21 (108 mg BID)
  - During the placebo treatment period, patients reported minimal change from baseline

Safety

- There were no serious treatment-emergent adverse events (TEAEs; **Table 2**)
- TEAEs led to discontinuation in 10 patients: 9 (14.3%) during treatment with NAL ER and 1 (1.7%) after being given placebo (**Table 2**)
  - TEAEs occurred in 79.4% of patients during NAL ER treatment and in 54.2% after being given placebo
  - Study drug–related TEAEs were reported in 63.5% of participants who received NAL ER and in 23.7% who received placebo
- The most common TEAEs during NAL ER treatment 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 those that occurred during placebo treatment (**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
AE 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

- NAL ER significantly reduced 24-hour objective cough frequency over a broad range of baseline cough frequencies, reinforcing its potential as a promising therapeutic agent for patients with RCC
- Reductions in objective cough frequency with NAL ER compared with placebo were evident as early as day 7 (at the lowest dose of NAL ER)
- Improvement in patient-reported cough severity and frequency was consistent with objective cough monitoring data
- These findings support the continued development of NAL ER for patients with RCC

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Abbreviations

AE, adverse event; BID, twice daily; CS-VAS, cough severity visual analog scale; CT, computed tomography; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; NAL ER, nalbuphine extended-release; RCC, refractory chronic cough; TEAE, treatment-emergent adverse event.

Acknowledgments

This study was sponsored by Trevi Therapeutics (New Haven, CT, USA). Medical writing and editorial assistance under the guidance of authors was provided by ApotheCom, San Francisco, CA, USA, and was funded by Trevi Therapeutics Inc., New Haven, CT, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (*Ann Intern Med*. 2022; 10.7326/M22-1460).

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.

KRC has received grants from AstraZeneca, Boehringer Ingelheim, Bellus, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Regeneron, Sanofi, Takeda, Vertex, consulting fees from AstraZeneca, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Sanofi, Takeda. He has a leadership or fiduciary role in Alpha-1 Canada, Canadian Thoracic Society, Alpha-1 Foundation, and AlphaNet Canada.

IS is supported by the Canada Research Chair program, reports grants to McMaster University from Merck, MITACS, GSK, Bellus, Trevi Therapeutics Inc., Bayer, Genentech; personal speaker fees from Merck, GSK, AstraZeneca, Sanofi-Regeneron, Vitalograph; consulting fees from Merck, GSK, Bellus, Sanofi-Regeneron, Trevi Therapeutics Inc., Methapharm outside the submitted work.

EM has received consulting fees from Boehringer Ingelheim, GSK, Valeo, and Sanofi, as well as speaker fees from Boehringer Ingelheim, AstraZeneca, GSK, Pfizer, and Pliant.

SMP has received consulting fees from Merck, Menlo Therapeutics, and Trevi Therapeutics Inc.

LM has received grants from Merck, Bellus Health, Shionogi, Bayer, Chiesi, and GSK; consulting fees from Merck, Chiesi, Nocion, Genentech, AstraZeneca, Bellus Health, Shionogi, GSK, Trevi Therapeutics Inc., and Reckitt Benckiser; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Chiesi, Bellus Health, GSK, Merck, NeRRe Therapeutics, Nocion, Trevi Therapeutics Inc., Shionogi Inc., Reckitt Benckiser, and Boehringer Ingelheim; and holds a leadership role as co-chair of the ERS NeuroCOUGH Clinical Research Collaboration.

AM has received consulting fees from Bayer, Bellus Health Inc., Merck & Co, NeRRe Therapeutics, Shionogi Inc., and Trevi Therapeutics, Inc.; lecture fees from Boehringer Ingelheim, Merck & Co and Chiesi Farmaceutici; and grant support from Bayer, Bellus Health Inc., Merck & Co, Nocion Therapeutics, Philips Pharma Group, NeRRe Therapeutics, Shionogi Inc., and Trevi Therapeutics Inc.

PM has received grants from MSD and consultancy fees from GSK and Trevi Therapeutics Inc.

SSB has received consulting fees from Bellus Health Inc., Merck & Co, Genentech, NeRRe Therapeutics, Nocion Therapeutics, and Trevi Therapeutics Inc.; lecture fees from AstraZeneca; and grant support from Merck & Co.

AT has received grants from Chiesi, Vertex, Takeda, NIHR ARC & PSRC, CSL Behring and Grifols Biotherapeutics, has participated in advisory board for Beam, and is funded by the NIHR Midlands Patient Safety Research Collaboration and Applied Research Collaborative West Midlands.

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.

Presented at the European Respiratory Society (ERS) Congress; September 27-October 1, 2025; Amsterdam, Netherlands