Efficacy and Safety of Nalbuphine Extended-Release Tablets for the Treatment of Refractory Chronic Cough: A Phase 2 Trial in Progress

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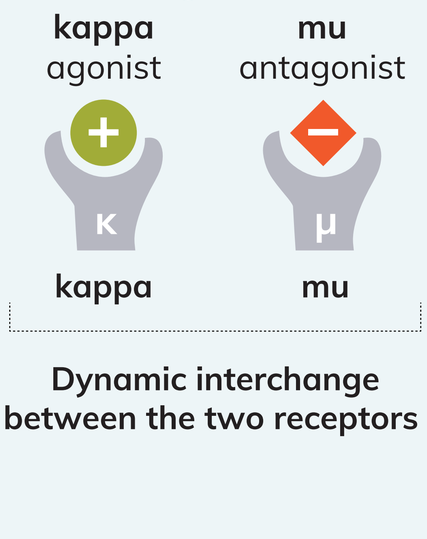
Background

- Chronic cough in adults is defined as a cough that lasts for 8 weeks or more[1]; the global prevalence of chronic cough is approximately 10%[2,3]
- Refractory chronic cough (RCC) is defined as cough that persists despite guideline-based treatment[4]
- In patients with RCC, 73% report a moderate to high frequency of daily coughs and for 72% of those patients, the coughs are uncontrolled[5]
- Most patients with RCC (87%) report that it has a severe to moderate impact on their quality of life[5]
- Nalbuphine extended-release tablets (NAL ER) act centrally in the brain and peripherally in the lungs via the κ- and μ- opioid receptors (KOR and MOR) in a novel dual-acting mechanism of action to provide an antitussive effect (**Figure 1**)
- In patients with idiopathic pulmonary fibrosis (IPF) in a phase 2a study (CANAL; NCT04030026), a 76.1% reduction in 24-hour cough frequency was seen with NAL ER, compared with a 25.3% reduction with placebo[6]
- The RIVER study (NCT05962151) is being conducted to assess the efficacy and safety of NAL ER titrated to 108 mg twice daily compared with placebo in patients with RCC

Figure 1. NAL ER Mechanism of Action in Cough



Objectives

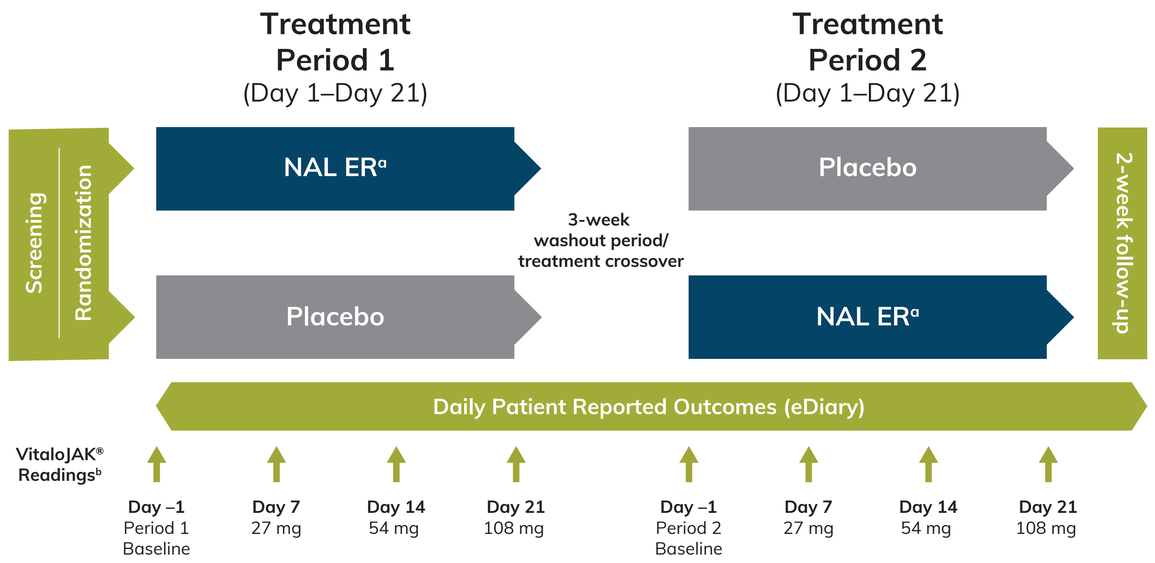
- Primary objective
  - To investigate the effect of NAL ER treatment on 24-hour cough frequency (coughs per hour) after 21 days
- Secondary objectives
  - To evaluate the safety and tolerability of NAL ER for the treatment of RCC
  - To evaluate the effect of NAL ER on cough per patient-reported and clinician-assessed outcomes measures
  - To investigate the effect of NAL ER on sleep and wake cough frequency

Methods

Study Design

- RIVER is a double-blind, randomized, placebo-controlled, 2-period crossover study (**Figure 2**)
- It is expected that ~60 patients with RCC will be enrolled in a 1:1 ratio stratified by subgroups of 24-hour cough frequency of 10-19 coughs/hour and ≥20 coughs/hour based on screening cough monitor results
- Eligible patients will be 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 will be 21 days separated by a 21-day washout period and followed by a 14-day follow-up period
- Expected completion in 2nd half of 2024

Figure 2. RIVER Study Design



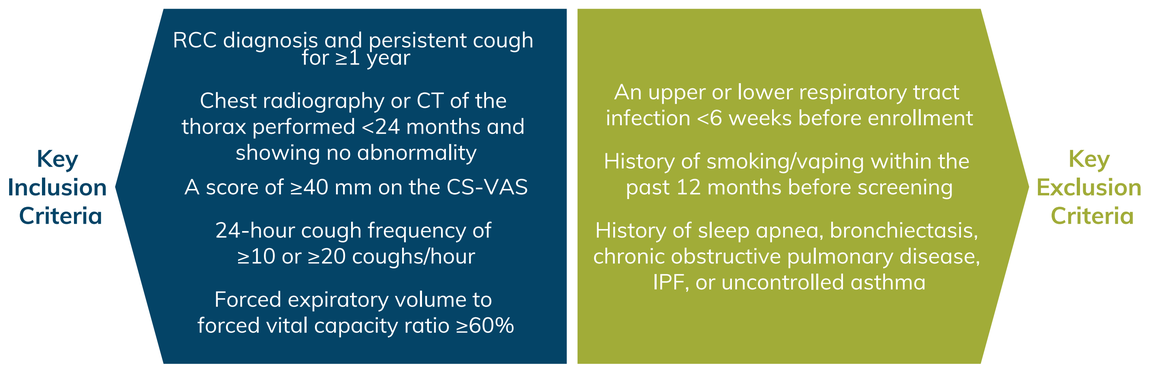
Patients are randomly assigned 1:1 in subgroups of 24-hour cough frequency of 10-19 coughs/hour (moderate-frequency coughers) and ≥20 coughs/hour (high-frequency coughers).

[a]NAL ER will be titrated according to a dosing scheme 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 prior to each study visit, will be removed and returned to the clinical study center to process the data recorded.

Study Participants

- Key eligibility criteria are summarized in **Figure 3**

Figure 3. Key Inclusion and Exclusion Criteria



Outcome Measures

- Relative change from baseline in 24-hour cough frequency at days 7 and 14
- Proportion of responders with ≥30%, ≥50%, or ≥75% reduction in 24-hour cough frequency at days 7, 14, and 21
- Relative change from baseline in wake and sleep cough frequency at days 7,14, and 21, Cough Severity Visual Analogue Scale (CS-VAS) score, Leicester Cough Questionnaire response, Patient-Reported Cough Frequency score, Patient Global Impression of Severity and Change for Cough score, and Clinicians Global Impression of Severity and Change for Cough score
- Incidence and severity of treatment-emergent adverse events (TEAEs)

Key Benefits of the RIVER Trial

- The crossover trial design uses self-control comparisons in which participants act as their own control, enhancing assessment effectiveness and minimizing variability through direct comparison of effects
- Inclusion of participants across the range of baseline cough frequencies provides a patient population expected to be generalizable to the clinical RCC population
- Patient- and clinician-reported assessments provide comprehensive outcome measures

Conclusion

- Results of this study will provide information on the efficacy and safety of NAL ER for patients with RCC

References

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Abbreviations

CT, computed tomography; CS-VAS, Cough Severity Visual Analogue Scale; IPF, idiopathic pulmonary fibrosis; NAL ER, nalbuphine extended-release; RCC, refractory chronic cough.

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Disclosures

JAS has received consultancy fees from Trevi Therapeutics and Vitalograph Ltd. Manchester University NHS Foundation Trust receives royalties from Vitalograph Ltd.

DC is employed by Trevi Therapeutics.

KFC has received payments for participation on advisory board meetings for GSK, AZ, Novartis, Roche, Merck, Trevi, Rickett-Beckinson, Nocion, and Shionogi on asthma, COPD, and chronic cough. He is also the recipient of a research grant paid to his institution by Merck to study the effect of adenosine triphosphate in chronic cough.

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