Sample Size Re-Estimation in an Ongoing Dose-Ranging Study of Nalbuphine Extended-Release for Cough in Idiopathic Pulmonary Fibrosis: The CORAL Study

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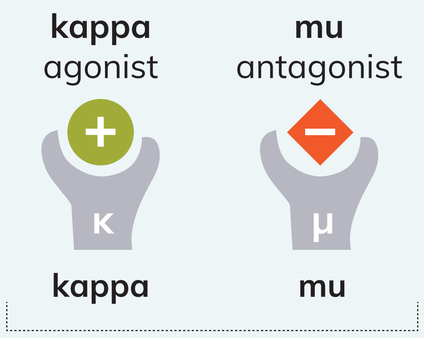
Introduction

- Idiopathic pulmonary fibrosis (IPF) is a disease that has a significant impact on quality of life.[1-2] Moreover, chronic cough in IPF may be associated with disease progression and poor health outcomes[1-3]
- Up to 84% of patients with IPF experience chronic cough, which is likely due to increased sensitivity to cough stimuli[1]
- There are no approved therapies for cough in patients with IPF[4]
- 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 (**Figure 1**)
  - NAL ER is a KOR agonist and MOR antagonist that works across the neuroinflammatory axis to rebalance hypersensitivity conditions, such as chronic cough
- In a randomized, double-blind, placebo-controlled, phase 2a crossover trial (CANAL; NCT04030026), patients with IPF treated with oral NAL ER demonstrated a 76.1% reduction in 24-hour cough frequency, compared with a 25.3% reduction in patients who received placebo[5]
- NAL ER is being evaluated in the ongoing randomized, double-blind, placebo-controlled, parallel-arm, phase 2b dose-ranging study (NCT05964335, CORAL) to measure the efficacy and safety of 3 doses of NAL ER for management of cough in patients with IPF (**Figure 2**)
- Sample size re-estimation (SSRE) is performed to ensure adequate power, account for variability, and protect study design integrity[6]

Figure 1. NAL ER Mechanism of Action in Cough



Objective

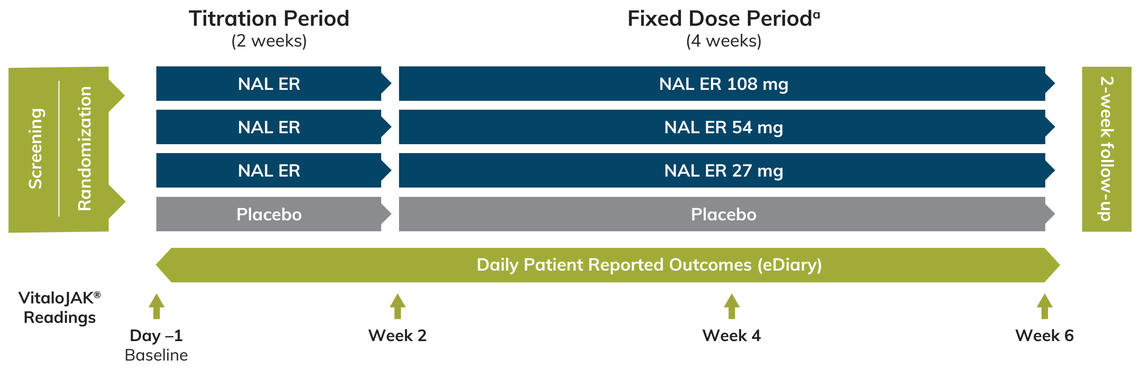
- To reaffirm predefined power assumptions using SSRE after 50% of participants completed the CORAL study

Methods

Study Design

- 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 twice daily (**Figure 2**)
- Doses will be 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 2**)

Figure 2. CORAL Study Design



VitaloJAK®; Vitalograph Ltd, Buckingham, United Kingdom.

Treatment will be administered twice daily.

[a]SSRE will be performed by an independent unblinded statistician when 50% of patients have completed the week 6 measurement, have discontinued, or have been lost to follow-up.

Study Participants

- Participants aged ≥18 years who had an IPF diagnosis and self-reported chronic cough lasting ≥8 weeks were included in this study (**Figure 3**)

Figure 3. Key Inclusion and Exclusion Criteria

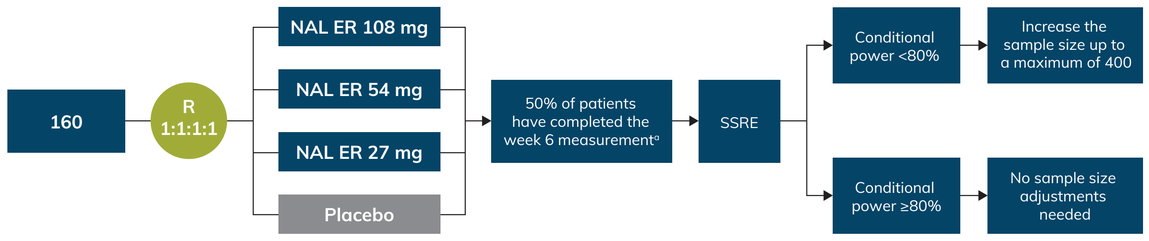
Outcome Measures

- The primary end point is 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
- The key secondary end point is the relative change from baseline at week 6 for NAL ER compared with placebo for question 2 of the Exacerbation of Chronic Pulmonary Disease Tool (EXACT), a patient-reported measure of cough frequency

Sample Size Re-Estimation

- Approximately 160 patients will be randomly assigned to a treatment cohort (40 patients per treatment arm)
- A sample size of 28 patients per arm will provide >80% power to detect a relative change from baseline of 66.1% in the NAL ER arm and 30% in the placebo arm, or a 36.1% difference between the NAL ER and the placebo arms
- To re-examine the appropriate sample size, based on predefined powering assumptions, an SSRE will be performed by an independent unblinded statistician, using the methods of Mehta and Pocock[7] after 50% of patients have completed the week 6 measurement, have discontinued, or have been lost to follow-up
- The SSRE will be used to determine the conditional power of the 108 mg dose of NAL ER compared with placebo for the primary end point to provide a recommendation regarding trial sample size
- During the SSRE, if the conditional power is <80% and within a prespecified "promising zone," the statistician will recommend increasing the sample size above 160, up to a maximum of 400 patients to provide ≥80% power (**Figure 4**)
- A sample size of 400 would provide 80% power to distinguish relative changes from baseline of 55.5% and 30% for the NAL ER and placebo arms, respectively, or a 25.5% difference between the NAL ER and the placebo arms
- If the SSRE indicates a sample size increase is necessary, the number of patients in all arms will be equally increased
- If the conditional power at the interim analysis is below a prespecified futility boundary, the statistician will provide a nonbinding recommendation to stop the study early due to futility

Figure 4. CORAL Study Size Re-Estimation Protocol



Treatment will be administered twice daily.

[a]Or after 50% of patients have discontinued, or have been lost to follow-up

Conclusions

- The SSRE will allow for an appropriately sized study to aid in evaluation of the efficacy and safety of NAL ER for patients with IPF
- This study will provide efficacy and safety data to inform determination of optimal doses for phase 3 pivotal studies of NAL ER for patients with IPF

References

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Abbreviations

CS-NSR, Cough Severity Numerical Rating Scale; IPF, idiopathic pulmonary fibrosis; KOR, κ-opioid receptor; MOR, μ-opioid receptor; NAL ER, nalbuphine extended-release; R, randomization; SSRE, sample size re-estimation.

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