Nalbuphine extended release treatment achieved rapid and sustained reduction in reported cough frequency in patients with idiopathic pulmonary fibrosis

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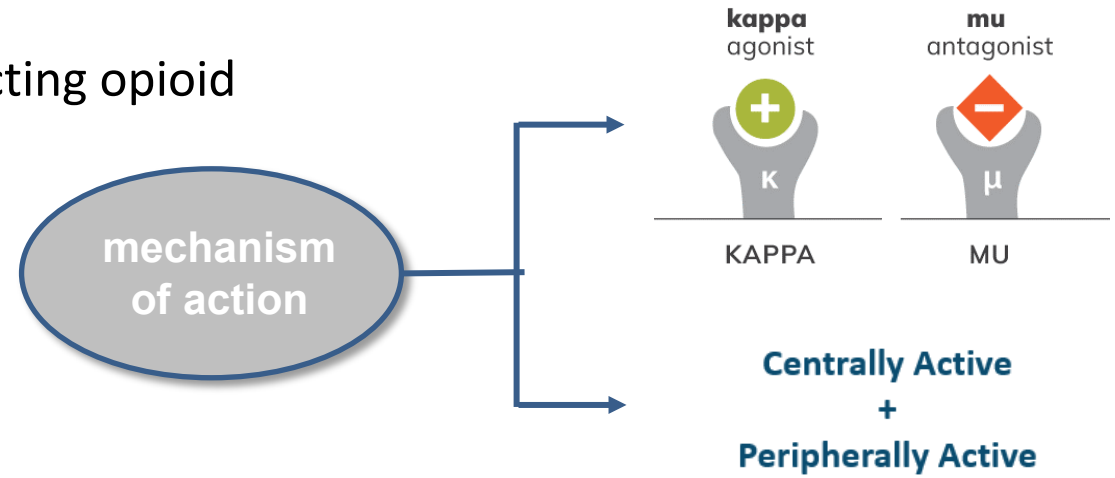
Conflicts of Interest

- TMM has, via his institution, received industry academic funding from AstraZeneca and GlaxoSmithKline R&D and has received consultancy or speaker fees from AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Fibrogen, Galapagos, Galecto, GlaxoSmithKline, IQVIA, Pliant, Roche, Trevi Therapeutics, and Veracyte.
- TS is an employee of Trevi Therapeutics and may own stock or stock options.
- EB is a consultant for Trevi Therapeutics.
- PM has, via his institution, received grand funding from AstraZeneca and has received consultancy or speaker fees from AstraZeneca, Boehringer Ingelheim, Hoffman-La Roche, and Trevi Therapeutics.
- JAS has, via her institution, received grant funding from Merck, Bellus Health and has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Trevi Therapeutics, Bellus Health, Bayer, Shionogi, Algernon, Nocion and Axalbion. Her institution, Manchester University Foundation Trust, and receives royalties from Vitalograph Ltd for the use of an algorithm to facilitate cough counting.

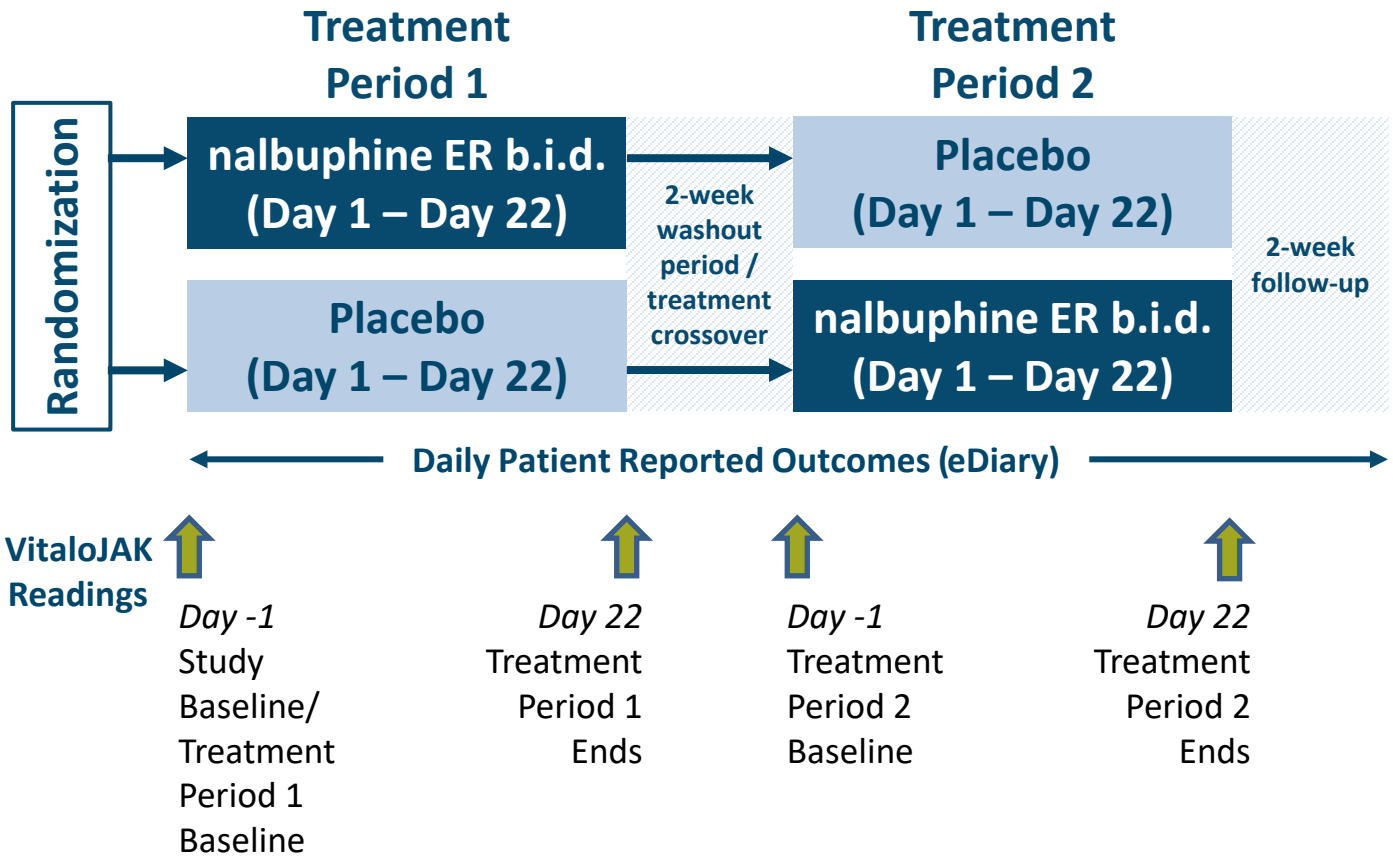
Background

- Cough is a major cause of morbidity in patients with idiopathic pulmonary fibrosis (IPF)[1], which lacks effective therapies[2]
- In IPF, cough can impact health outcomes, such as being pro-fibrotic and increasing risk of respiratory hospitalizations, mortality, and transplant requirement[3]
  - Chronic cough may contribute to enhanced activation of profibrotic mechanisms and disease worsening in IPF
- Dual-acting opioid agonists/antagonists are hypothesised to reduce chronic cough
  - Act pharmacologically on the opioid system, potentially on the central and peripheral nervous systems
- Nalbuphine extended release (ER) tablets are dual-acting opioid agonists/antagonists
  - Agonist: κ-receptor
  - Antagonist: μ-receptor



1. Lee J, et al. Chest 2022:S0012-3692(22)00545-1, 2. van Manen MJG, Wijsenbeek MS. Curr Opin Support Palliat Care. 2019;13(3):143-151, 3. van Manen MJ, et al. Eur Respir Rev. 2016 Sep;25(141):278-86.

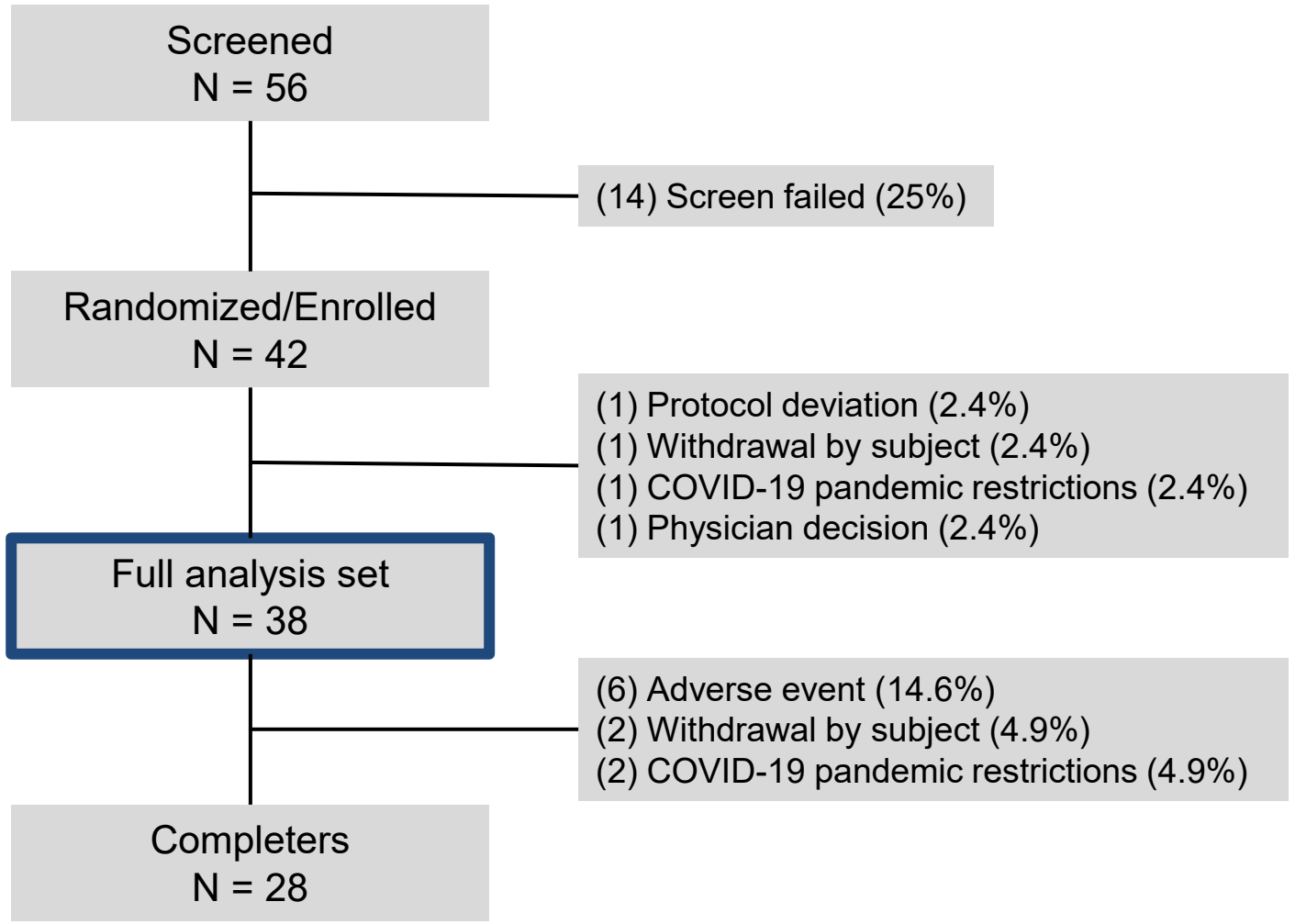
CANAL Study Design



- A randomized, double-blind, placebo-controlled, crossover trial with two 22-day treatment periods separated by a 2-week washout period was conducted
- Nalbuphine ER 27 mg once daily was titrated up to 162 mg twice daily at Day 16
- Adults diagnosed with definite/probable IPF using international criteria and chronic cough for > 8 weeks were enrolled

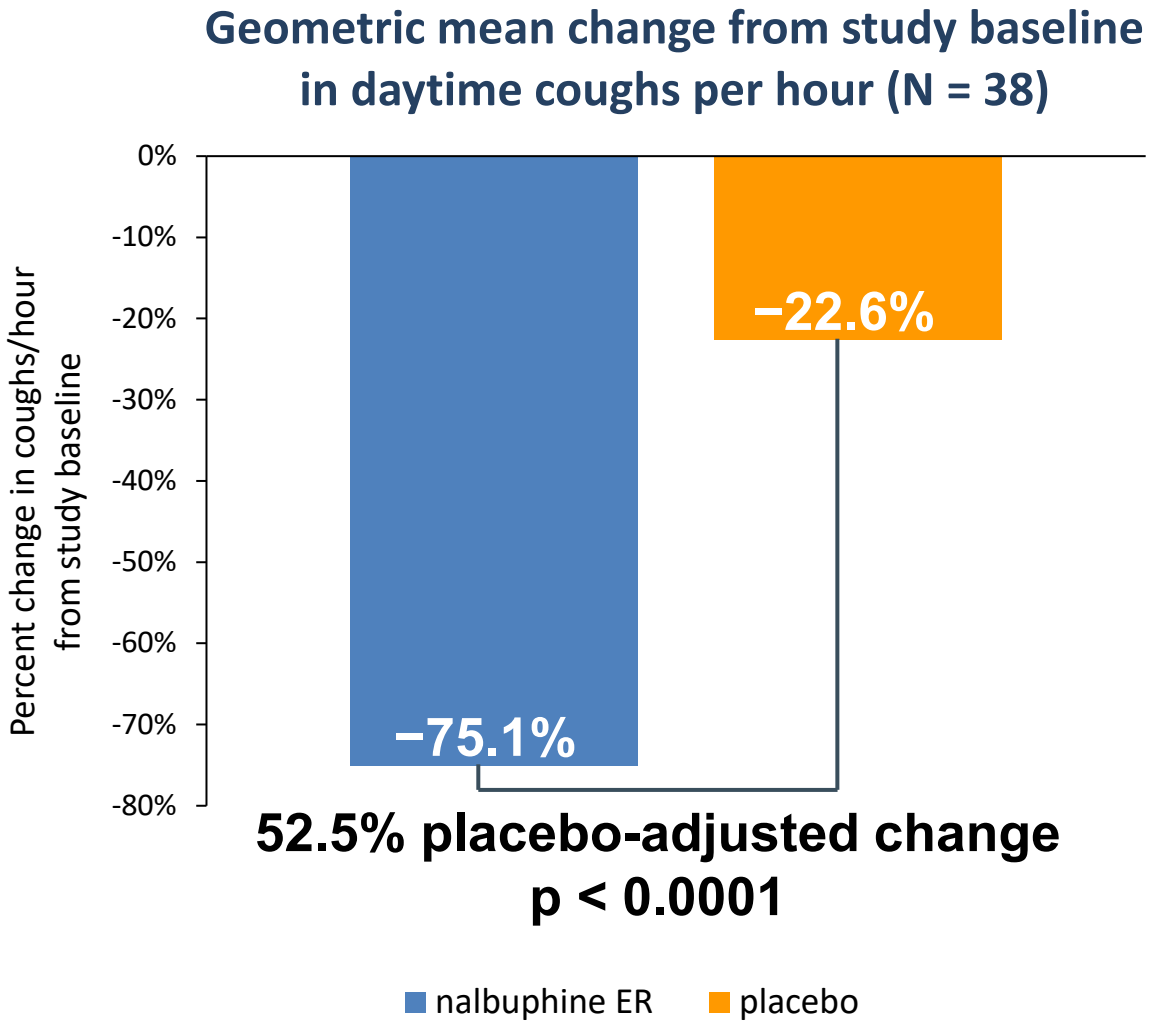
b.i.d., twice daily; ER, extended release; IPF, idiopathic pulmonary fibrosis.

Patient Disposition



- Of the 56 screened patients, **38 comprised the 1-period full analysis set**
  - The completers set was comprised of the 28 patients who completed both treatment periods

CANAL primary endpoint



- **75.1% reduction** in daytime cough frequency at Day 22 with nalbuphine ER (nalbuphine ER, n = 29; placebo n = 37), measured using an objective digital cough monitor
- **52.5% change compared to placebo** in daytime cough frequency at Day 22 with nalbuphine ER

Primary endpoint calculated as geometric mean percent change in daytime cough frequency from study baseline.
ER, extended release.

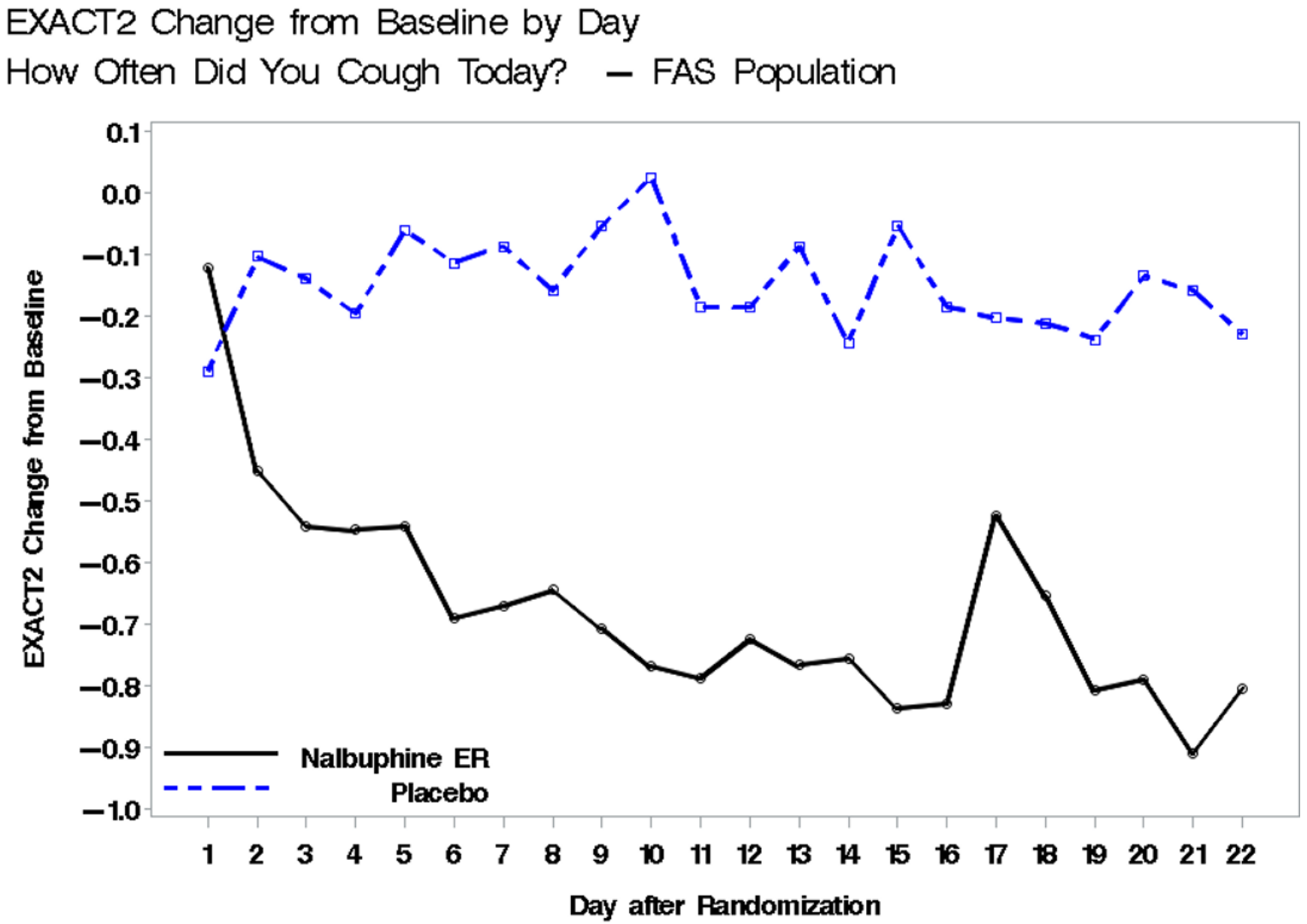
Objective

- To report the CANAL secondary endpoint: The time to onset of effect and day-to-day time course of NAL-ER treatment versus placebo, using the Evaluating Respiratory Symptoms-IPF (E-RS^{TM}:IPF) cough subscale.

Methods - EXACT2

- The Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) is a patient reported, 14-item questionnaire[1]
- This is used in the Evaluating Respiratory Symptoms: idiopathic pulmonary fibrosis (E-RS™:IPF) diary
  - Question 2 (EXACT2) asks how often the patient coughed today
    - Daily cough frequency was categorized as not at all, rarely, occasionally, frequently, or almost constantly, based on a score range of 0–4

EXACT2 Patient-Reported Outcome (PRO) Supports the Primary Endpoint



- Overall reduction in the PRO daily cough frequency of nalbuphine ER treated patients compared with placebo over 22 days was –0.53 ($p < 0.0001$).
- Effect was evident from Day 3, with a net improvement of –0.40 ($p = 0.0145$).
    - Improvements were sustained: the net improvement on Day 22 was –0.58 ($p = 0.0026$).

ER, extended release; EXACT, Exacerbation of chronic pulmonary disease tool; PRO, patient-reported outcome

Conclusions

- This is the first trial to show a reduction in cough frequency for IPF patients.
- The patient-reported improvement in daily cough frequency (E-RS^{TM}:IPF diary) was consistent with improvements observed with the objective digital cough monitor.
  - Early separation of treatment arms in the PRO cough subscale suggests a rapid onset of NAL-ER from Day 3 versus placebo.
  - The reduction in cough with NAL-ER was consistent and sustained over the 22-day treatment period compared with placebo.
  - Data suggest the EXACT2 questionnaire can capture responses to cough treatments, which has not been reported previously to our knowledge.

ER, extended release; IPF, idiopathic pulmonary fibrosis; PRO, patient-reported outcome

1. van Manen MJ, et al. Eur Respir Rev. 2016 Sep;25(141):278-86.