An interim analysis of a phase 2 trial evaluating oral nalbuphine extended release for treating chronic cough in idiopathic pulmonary fibrosis

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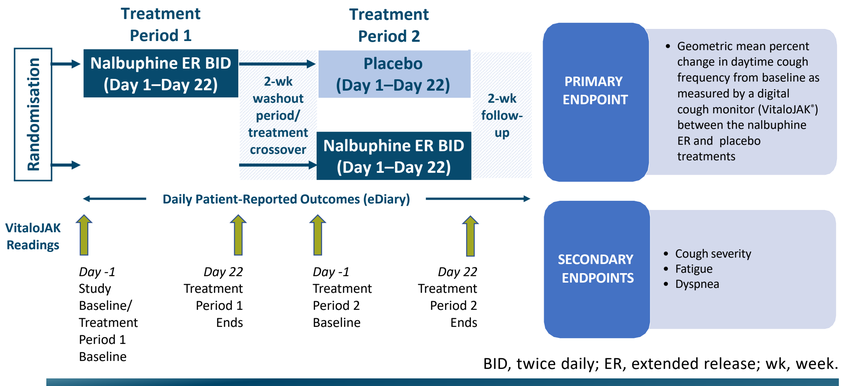
INTRODUCTION

- Cough is a major cause of morbidity in patients with idiopathic pulmonary fibrosis (IPF), which lacks effective therapies
- Dual-acting opioid agonists/antagonists are hypothesized to reduce chronic cough by pharmacologically acting on the opioid system, potentially at both peripheral and central nervous system levels
- We report an interim analysis of a phase 2 trial with nalbuphine extended release (ER) tablets, a ƙ-receptor agonist and μ-receptor antagonist

METHODS

- A randomised, double-blind, placebo-controlled, crossover trial with two 22-day treatment periods separated by a 2-week washout period was conducted (**Figure 1**)
- 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

Figure 1. Study Design



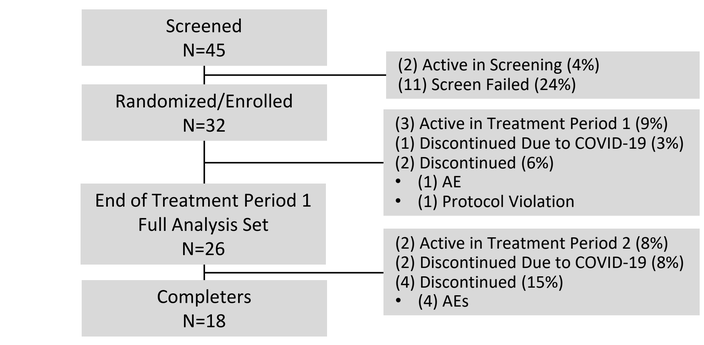
BID, twice daily; ER, extended release; wk, week.

RESULTS

Demographics

- Of 45 screened subjects, 26 comprised the 1-period full analysis set (**Figure 2**)
  - 18 subjects completed both treatment periods and were included in the completers set
- Subjects were primarily male with a mean age >70 years and a baseline mean daytime cough frequency of 31 coughs per hour (**Table 1**)

Figure 2. Patient Disposition



AE, adverse event.

Table 1. Baseline Characteristics

	Full Analysis Set (N=26)	Completers* (N=18)
Male, n (%)	22 (84.6)	14 (77.8)
Age (years), mean	72	71
Anti-fibrotic usage, n (%)	38.5	33.3
Daytime cough frequency (coughs/hour):		
Mean	31	31
Median	20.6	22.4
Min-Max	3.18 – 92.35	3.18 – 77.18

*Completers set included all subjects who completed both treatment periods.

RESULTS (CONT.)

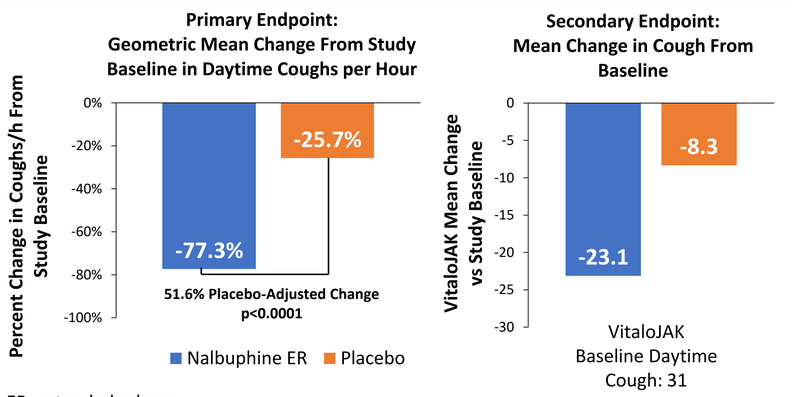
Primary Endpoint

- Statistically significant reduction in primary endpoint (100% conditional power, p<0.0001) (**Figure 3**)
- 77.3% reduction in daytime cough frequency in nalbuphine ER treatment period
- 51.6% placebo-adjusted change in daytime cough frequency for nalbuphine ER

Secondary Endpoint

- Objective daytime cough frequency measure via VitaloJAK (**Figure 3**)

Figure 3. Primary and Secondary Endpoints (N=26)

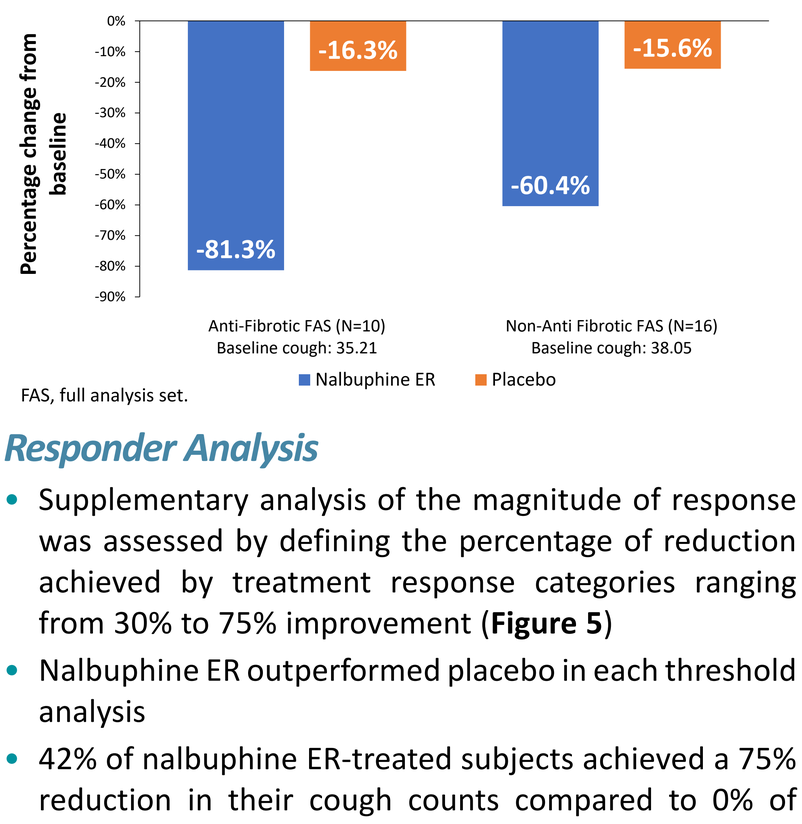


ER, extended release.
Primary endpoint calculated as geometric mean percent change in daytime cough frequency from study baseline.

Concomitant Medication

- Cough reduction was seen in patients both with and without concomitant anti-fibrotic medication (**Figure 4**)

Figure 4. Change from baseline measured by VitaloJAK in FAS (N=26)

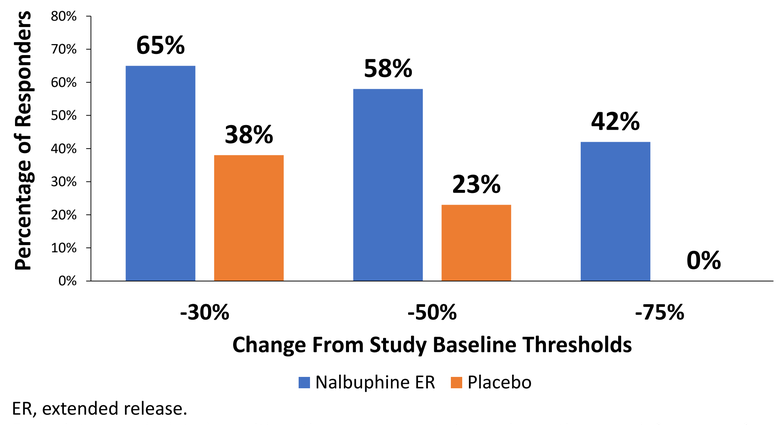


FAS, full analysis set.

Responder Analysis

- Supplementary analysis of the magnitude of response was assessed by defining the percentage of reduction achieved by treatment response categories ranging from 30% to 75% improvement (**Figure 5**)
- Nalbuphine ER outperformed placebo in each threshold analysis
- 42% of nalbuphine ER-treated subjects achieved a 75% reduction in their cough counts compared to 0% of placebo-treated patients

Figure 5. Percentage of Responders Achieving Mean Change From Study Baseline Thresholds (N=26)



ER, extended release.
Endpoint was calculated as arithmetic mean percent change in daytime cough frequency from study baseline.

- Upon study completion, statistical analyses of cough frequency as a patient-reported outcome was conducted to identify a minimally important clinical change in cough frequency

Safety

- Nalbuphine ER has been administered to >1000 subjects in previously completed clinical trials
- No safety concerns have been raised by the Data and Safety Monitoring Board overseeing the conduct of the study
- No deaths have been reported; 1 reported serious adverse event (ie, pneumonia) was not considered treatment related
- 5 adverse events have resulted in discontinuation (16%)
  - 1 anorexia, 1 depression, 1 nausea/vomiting, 1 insomnia/fatigue, 1 agitation/anxiety/dyspnea
- No new safety-related issues have arisen in the study, and the adverse event profile of the drug in the IPF population is consistent with the safety profile noted in all other past studies in which nalbuphine ER was investigated for a variety of medical conditions

CONCLUSION

- Nalbuphine ER demonstrated a highly significant and consistent reduction in chronic cough associated with IPF in an interim analysis, supporting proof of concept
- 52% placebo-adjusted reduction in the geometric mean percent change from study baseline for nalbuphine ER in daytime cough frequency to day 22 of treatment (p<0.0001)
- 42% of nalbuphine ER-treated subjects achieving a ≥75% reduction from baseline in daytime cough frequency compared to 0% of placebo-treated subjects
- Directional change in secondary endpoint patient-reported outcomes instruments, consistent with reduction in daytime cough frequency
- Safety profile consistent with prior nalbuphine ER studies in other patient populations, with no new safety signals identified

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. WF and TS are employees of Trevi Therapeutics and may own stock or stock options. EB is a consultant for Trevi Therapeutics.

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