ERS

INTERNATIONAL CONGRESS 2022

BARCELONA Spain, 4 - 6 September

AN INTERIM ANALYSIS OF A PHASE 2 TRIAL EVALUATING ORAL NALBUPHINE EXTENDED RELEASE FOR TREATING CHRONIC COUGH IN IDIOPATHIC PULMONARY FIBROSIS

Toby M. Maher, MD[1]; William Forbes, PharmD[2]; Enoch Bortey, PhD[2]*; Thomas Sciascia, MD[2]

[1]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [2]Trevi Therapeutics, New Haven, CT, USA

*Enoch Bortey is a consultant for Trevi Therapeutics.

Conflict of interest disclosure

ERS
EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

☐ I have no real or perceived conflicts of interest that relate to this presentation.

☑ I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial company
Grants/research support:	AstraZeneca; GlaxoSmithKline R&D
Honoraria or consultation fees:	AstraZeneca; Bayer; Blade Therapeutics; Boehringer Ingelheim; Bristol Myer Squibb; Fibrogen; Galapagos; Galecto; GlaxoSmithKline; IQVIA; Pliant; Roche; Trevi Therapeutics; Veracyte
Participation in a company sponsored bureau:	
Stock shareholder:	
Spouse / partner:	
Other support / potential conflict of interest:	

This event is accredited for CME credits by EBAP and speakers are required to disclose their potential conflict of interest. The intent of this disclosure is not to prevent a speaker with a conflict of interest (any significant financial relationship a speaker has with manufacturers or providers of any commercial products or services relevant to the talk) from making a presentation, but rather to provide listeners with information on which they can make their own judgments. It remains for audience members to determine whether the speaker's interests, or relationships may influence the presentation. The ERS does not view the existence of these interests or commitments as necessarily implying bias or decreasing the value of the speaker's presentation. Drug or device advertisement is forbidden.

Aims / Learning objectives

ERS
EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

1. An interim analysis of a phase 2 trial demonstrates nalbuphine extended release (ER) significantly and consistently reduces idiopathic pulmonary fibrosis-associated cough
2. There was 52% placebo-adjusted reduction in daytime cough frequency from baseline ($p<0.0001$)
3. Safety is consistent with previous nalbuphine ER trials with other patient populations

Background

ERS EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

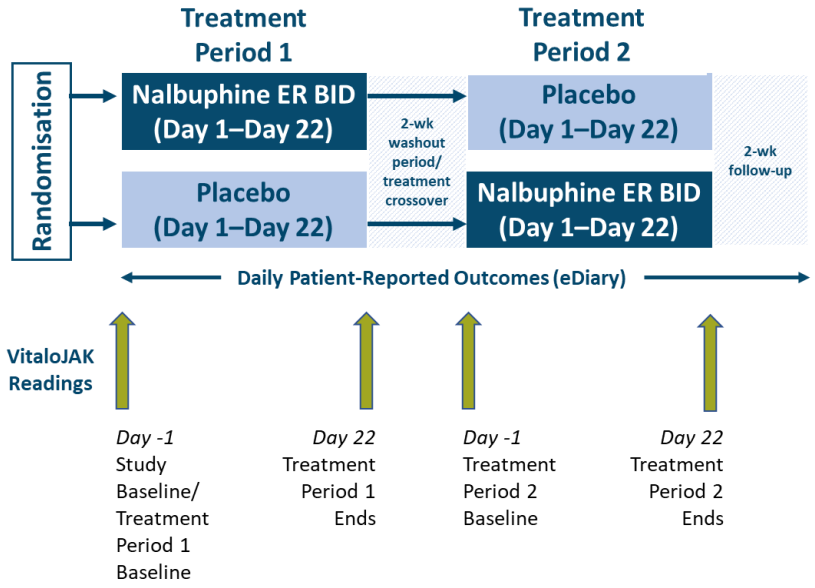
- Cough is a major cause of morbidity in patients with idiopathic pulmonary fibrosis (IPF), which lacks effective therapies
- Dual-acting opioid agonists/antagonists are hypothesized to reduce chronic cough by pharmacologically acting on the opioid system, potentially at both peripheral and central nervous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

Methods

EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

- A randomised, 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

Study Design



BID, twice daily; ER, extended release.

Primary and Secondary Endpoints

PRIMARY ENDPOINT

- Geometric mean percent change in daytime cough frequency from baseline as measured by a digital cough monitor (**VitaloJAK®**) between the nalbuphine ER and placebo treatments

SECONDARY ENDPOINTS

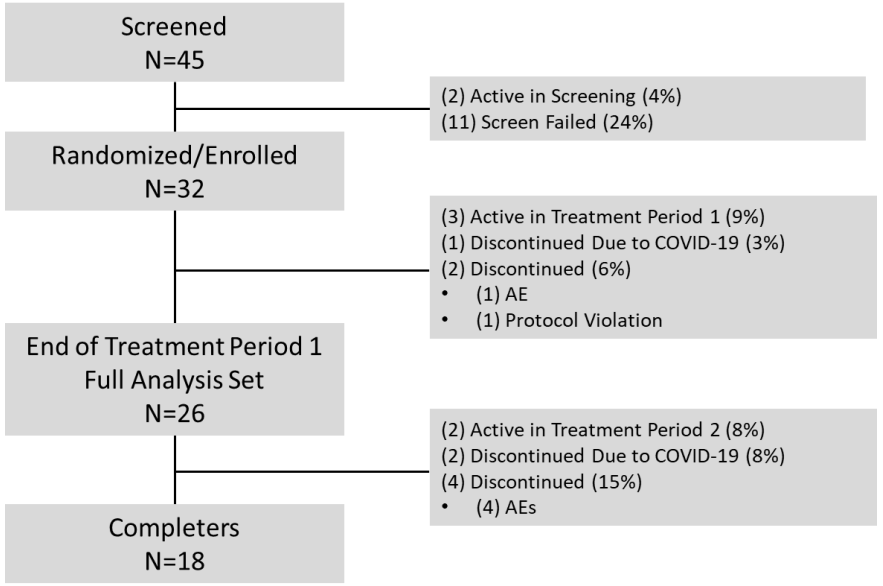
- Cough severity
- Fatigue
- Dyspnea

Results: Demographics

EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

- Of 45 screened subjects, 26 comprised the 1-period full analysis set
  - 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

Patient Disposition



AE, adverse effect.

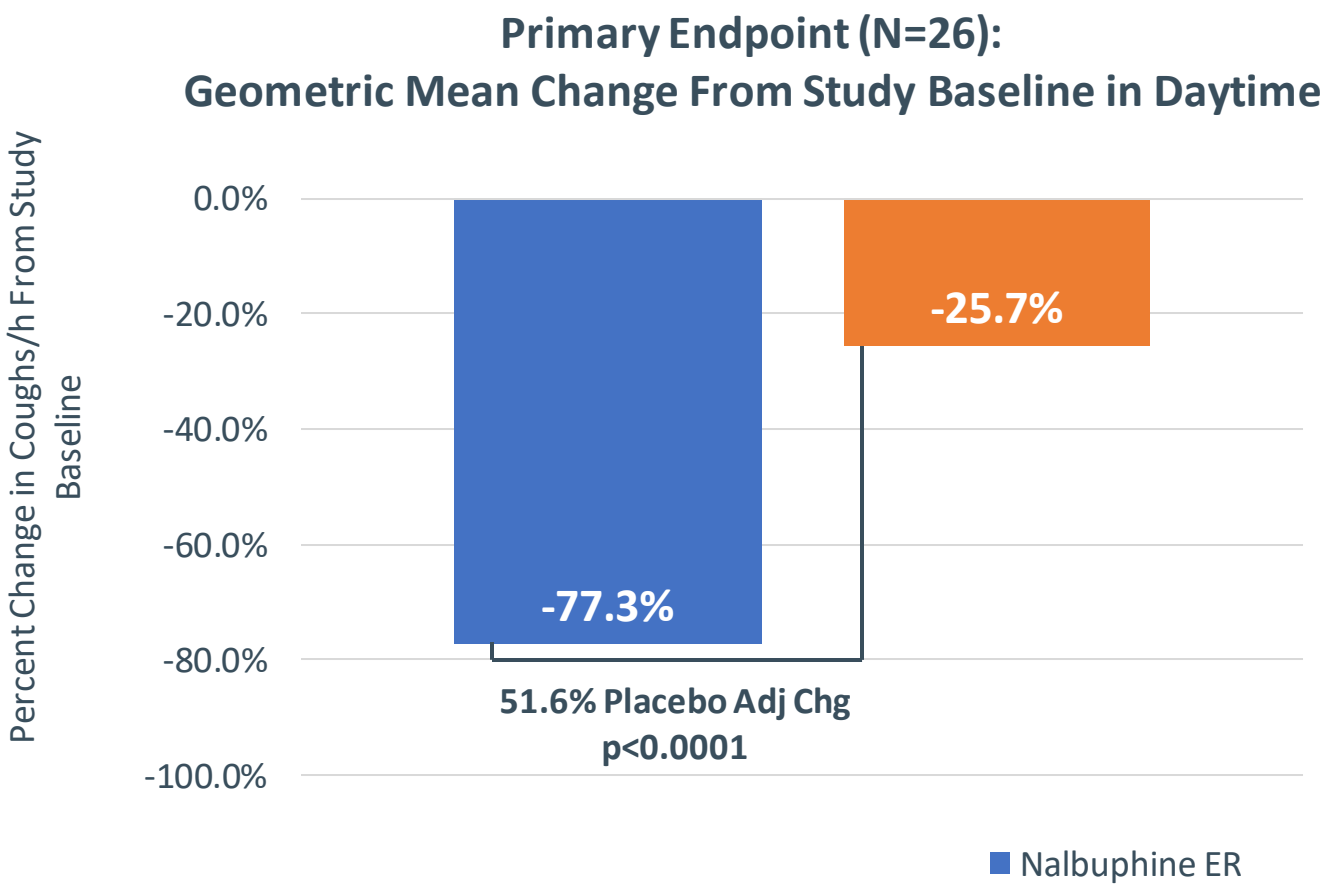
Baseline Characteristics

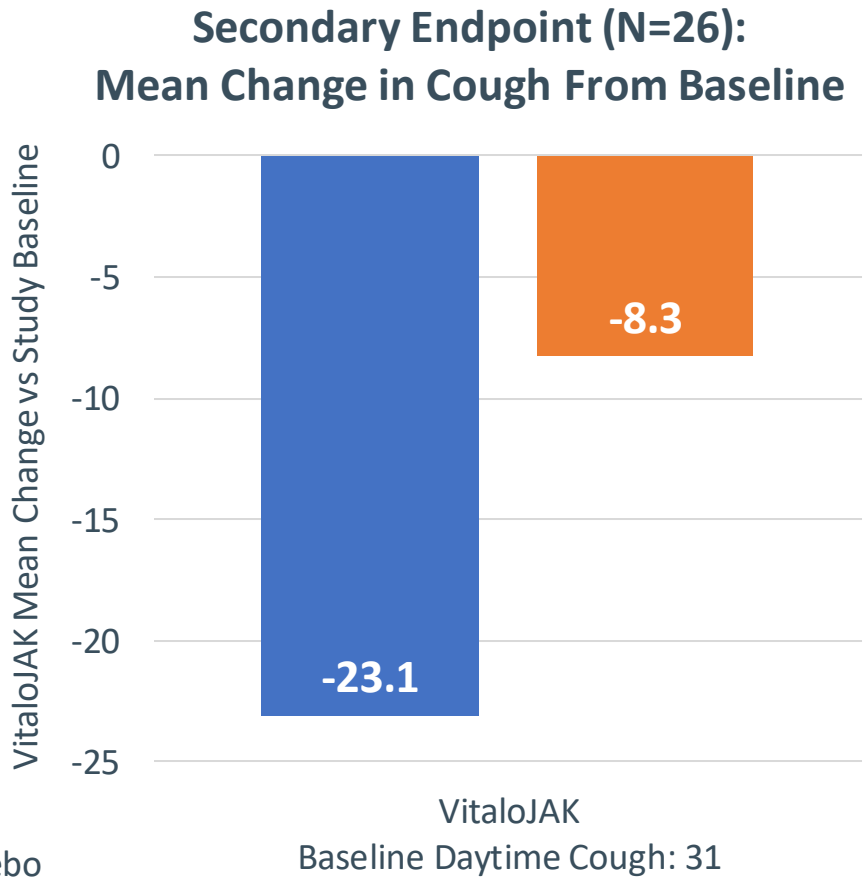
	Full Analysis Set (N=26)	Completers* (N=18)
Male, n (%)	22 (84.6)	14 (77.8)
Age (years), mean	72	71
Anti-fibrotic usage, %	38.5	33.3
Daytime cough frequency (coughs/hour):		
Mean	31	31
Median	20.6	22.4
Min-Max	3.18 – 92.35	3.18 – 77.18

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

Results: Primary and Secondary Endpoints

ERS
EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September



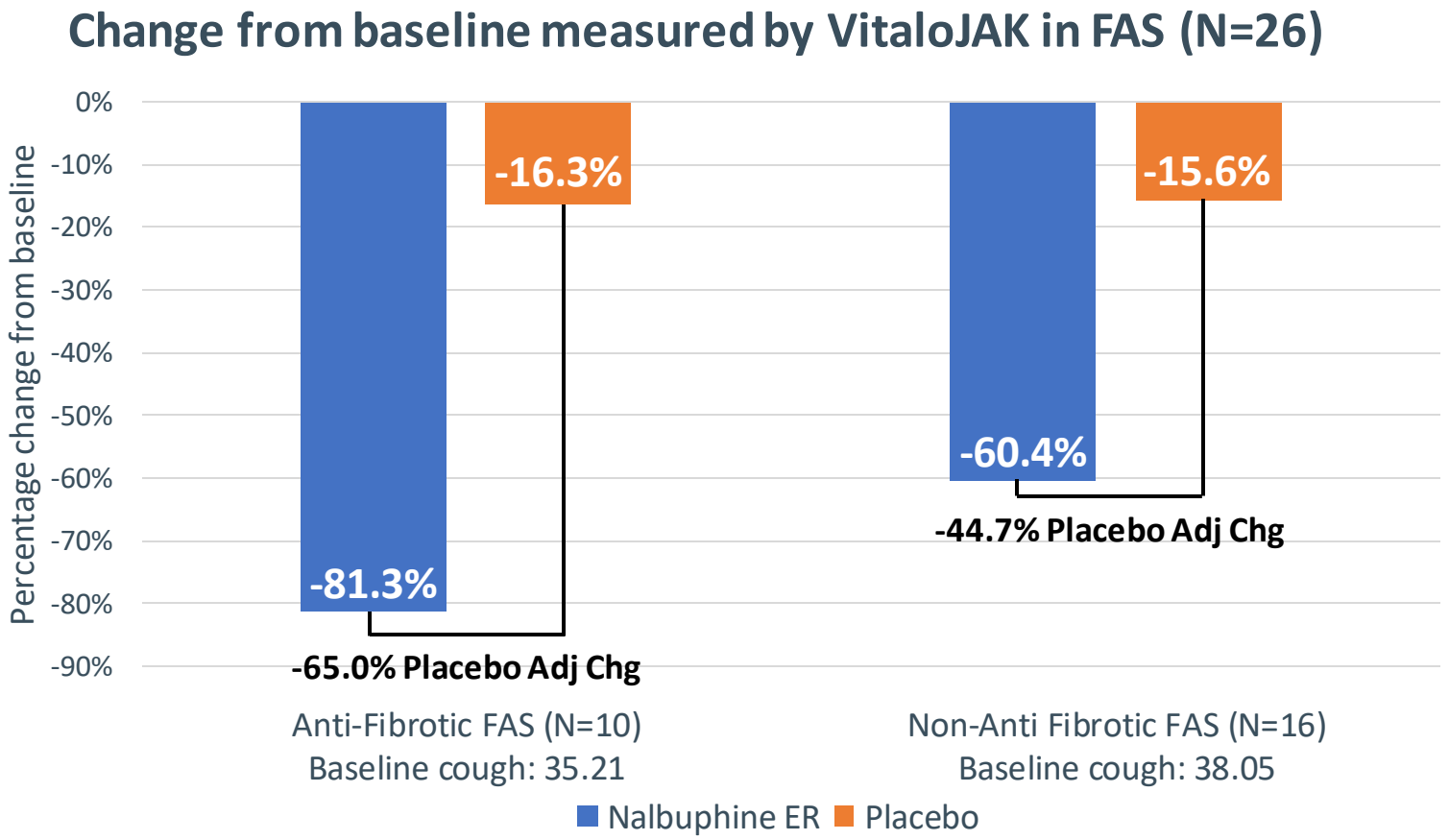


Adj Chg, adjusted change; ER, extended release.
Primary endpoint calculated as geometric mean percent change in daytime cough frequency from study baseline.

Results: Concomitant Medication

EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

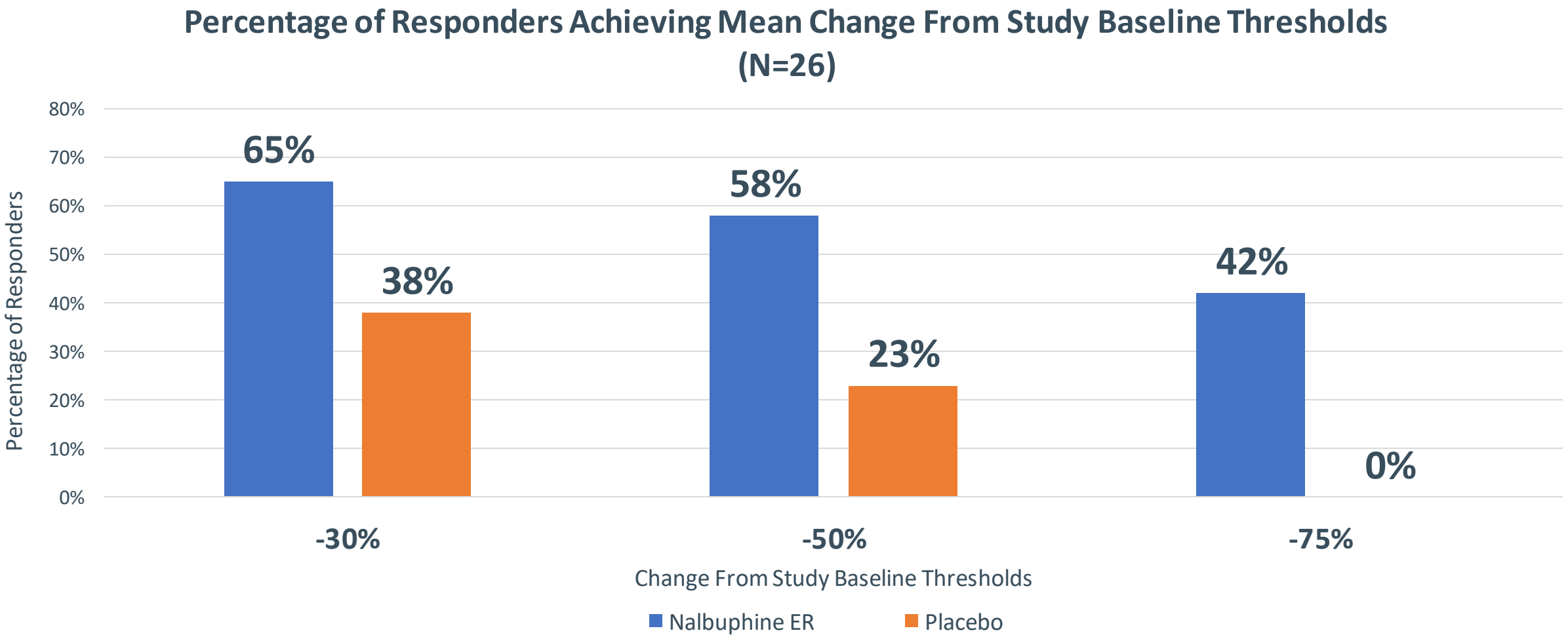
- Cough reduction was seen in patients both with and without concomitant anti-fibrotic medication



Adj, adjusted; FAS, full analysis set.

Results: Responder Analysis

EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September



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

Results: Safety

EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

- 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

Conclusions

ERS EUROPEAN RESPIRATORY SOCIETY
INTERNATIONAL CONGRESS 2022
BARCELONA Spain, 4 - 6 September

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

List of references

Bacci ED, O'Quinn S, Leidy NK, Murray L, Vernon M. Evaluation of a respiratory symptom diary for clinical studies of idiopathic pulmonary fibrosis. *Respir Med*. 2018 Jan;134:130-138. doi: 10.1016/j.rmed.2017.11.011.