A Phase 2b Trial (CORAL) of Nalbuphine Extended-Release Tablets in Patients With Idiopathic Pulmonary Fibrosis Experiencing Chronic Cough: Primary and Subgroup Analyses

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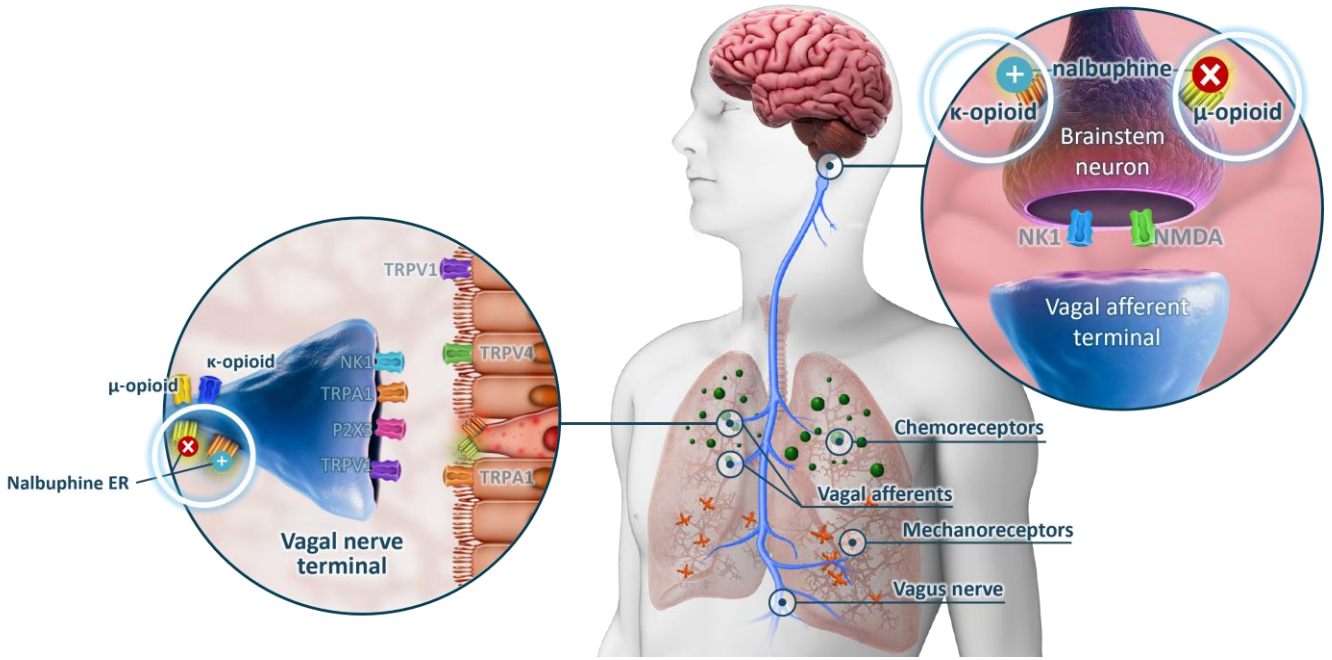
Presented at the American Thoracic Society International Conference; May 15-20, 2026; Orlando, FL

Disclosures

- Institutional grant funding from AstraZeneca, GSK, Asthma & Lung UK, and Action for Pulmonary Fibrosis
- Consulting fees from Boehringer Ingelheim, AstraZeneca, Caluna, Continum, GlaxoSmithKline, Gossamer Bio, Puretech, Qureight, Redx, IQVIA, Roche, Vicore, and Trevi Therapeutics
- Speaker fees from Boehringer Ingelheim and GSK
- Advisory board participation for United Therapeutics
- Stock options in Qureight

Background
Chronic Cough in Patients With IPF

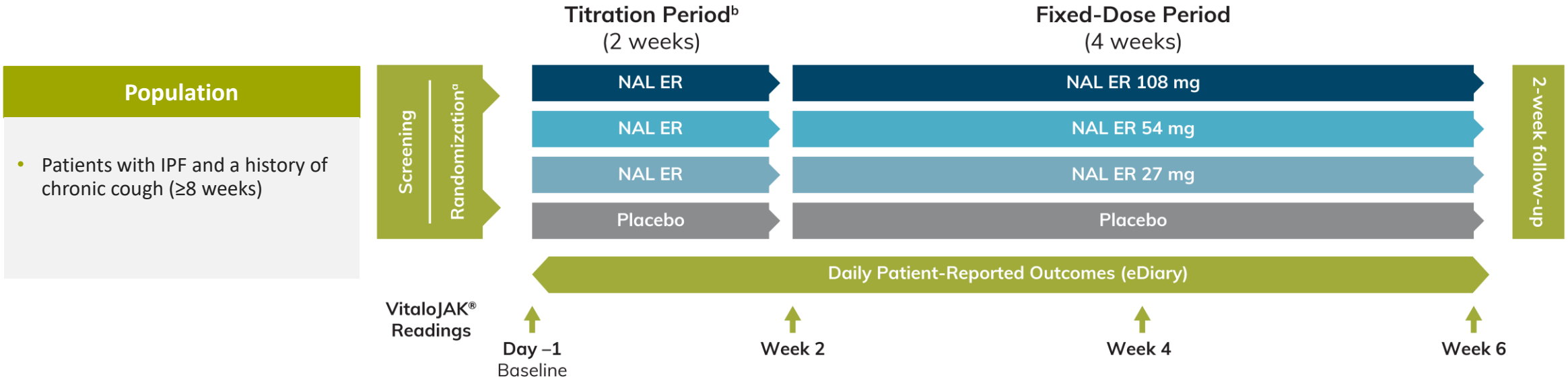
- Chronic cough affects up to 80% of patients with IPF and is associated with disease progression, reduced quality of life, and poor health outcomes[1-3]
- There are currently no approved therapies targeting chronic cough in patients with IPF in the US[1]
- Oral nalbuphine extended-release (NAL ER) tablets modulate the cough reflex arc by acting as a kappa opioid receptor agonist and mu opioid receptor antagonist in both the central nervous system and the peripheral sensory nerves of the airways[1]
- The phase 2b CORAL trial (NCT05964335) evaluated the efficacy and safety of NAL ER for chronic cough in patients with IPF[1]



IPF, idiopathic pulmonary fibrosis; NAL ER, nalbuphine extended release.

1. Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059; 2. Birring SS et al. *Lung*. 2025;203(1):62; 3. Lee J et al. *Chest*. 2022;162(3):603-613.

Methods
CORAL Phase 2b Study Design



Primary Efficacy Endpoint (mITT population)

- Relative change from baseline in 24-hour cough frequency versus placebo at Week 6 (using objective cough monitoring)

Post Hoc Subgroup Analyses

Subgroup analyses by antifibrotic use and baseline cough severity were performed to better understand treatment effects

Repeat primary endpoint mixed model for repeated measures within subgroups:

- Background antifibrotic use (yes/no)
- Baseline cough counts ≤10 vs >10 coughs/hour

[a]Patients were randomized 1:1:1:1, stratified by antifibrotic use and sex.
[b]Blinded titration period consisted of: Day 1-2, 27 mg QD; Day 3-7, 27 mg BID; Day 8-14, 54 mg BID (54 mg BID and 108 mg BID dose groups only).
VitaloJAK®; Vitalograph Ltd, Buckingham, United Kingdom.
Treatment was administered twice daily.
BID, twice daily; IPF, idiopathic pulmonary fibrosis; mITT, modified intent-to-treat; NAL ER, nalbuphine extended release; QD, once daily.
Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.

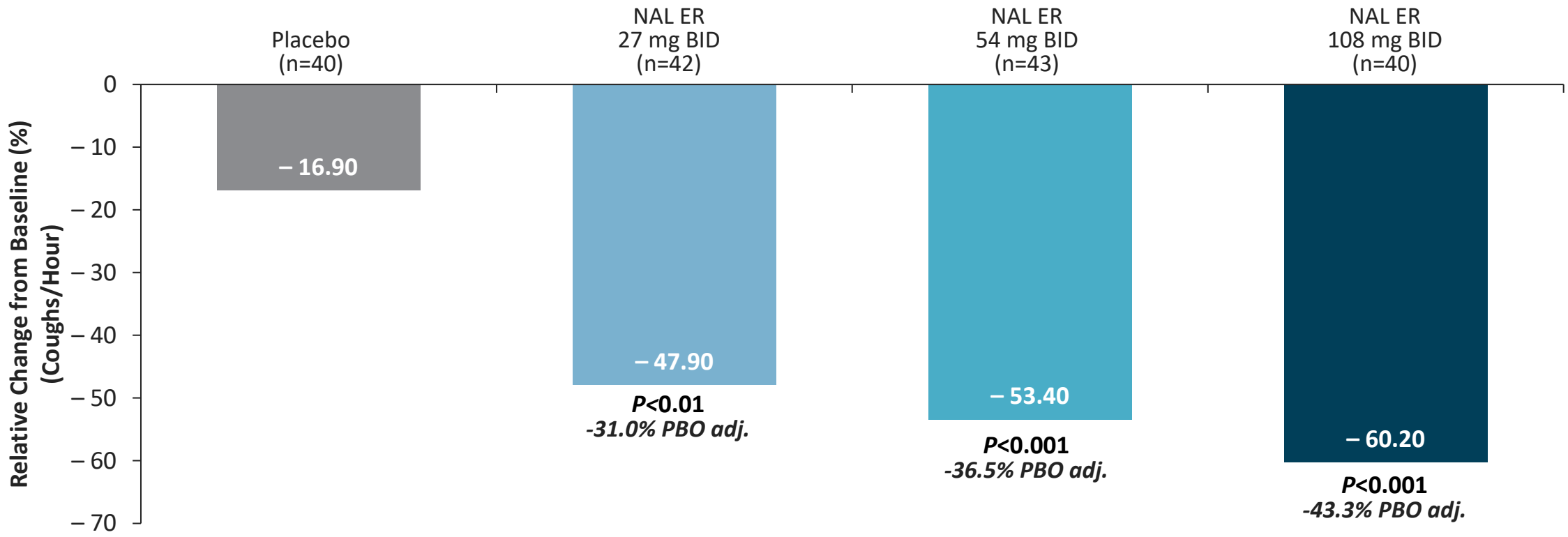
Results
Patient Demographics and Baseline Characteristics

	NAL ER 27 mg (n=42)	NAL ER 54 mg (n=43)	NAL ER 108 mg (n=40)	Placebo (n=40)
Age, mean (SD), y	69.1 (7.0)	68.5 (7.3)	71.9 (7.0)	71.2 (7.7)
Sex				
Male, n (%)	29 (69.0)	31 (72.1)	29 (72.5)	29 (72.5)
Female, n (%)	13 (31.0)	12 (27.9)	11 (27.5)	11 (27.5)
Forced vital capacity, mean (SD), L	2.6 (0.9)	2.5 (0.7)	2.7 (0.9)	2.4 (0.9)
DCLO, mean (SD), % predicted	52.6 (14.8)	49.0 (12.3)	56.6 (21.4)	49.6 (16.2)
Cough duration, mean (SD), y	3.0 (2.8)	4.1 (5.2)	5.4 (10.8)	4.4 (4.8)
Cough count, mean (SD)	24.6 (19.2)	28.0 (29.6)	31.5 (29.3)	29.4 (30.9)
Concomitant antifibrotics, n (%)	31 (73.8)	34 (79.1)	31 (77.5)	31 (77.5)

Safety Population: All patients who have received at least one dose of NAL ER or placebo.
DLCO, diffusing capacity of the lungs for carbon monoxide; NAL ER, nalbuphine extended release; SD, standard deviation; y, years.
Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.

Results
Primary Endpoint: Objective 24-Hour Cough Count

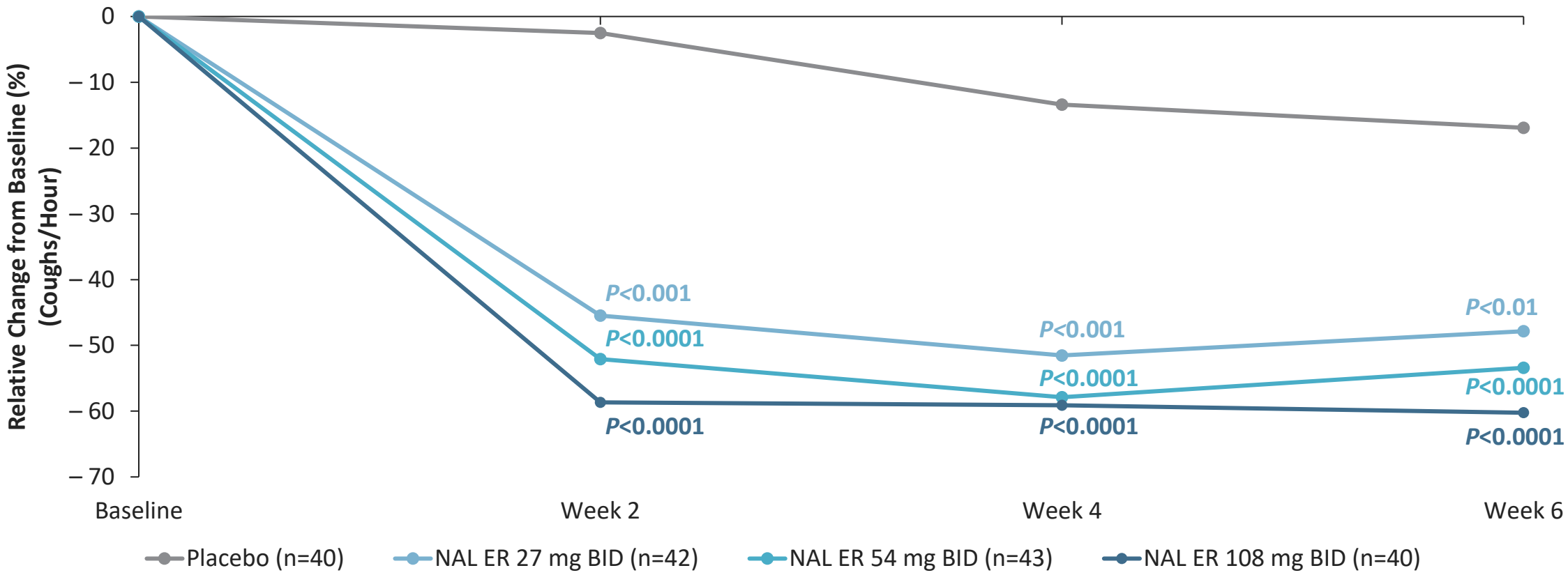
A significant difference in the relative change from baseline was observed across all dose groups at Week 6



Primary efficacy analysis conducted on log-transformed cough frequency data in the mITT population.
BID, twice daily; mITT, modified intent-to-treat; NAL ER, nalbuphine extended release; PBO, placebo.
Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.

Results
Objective 24-Hour Cough Count by Study Week

Rapid reduction in cough frequency was observed by Week 2 and was sustained through end of treatment

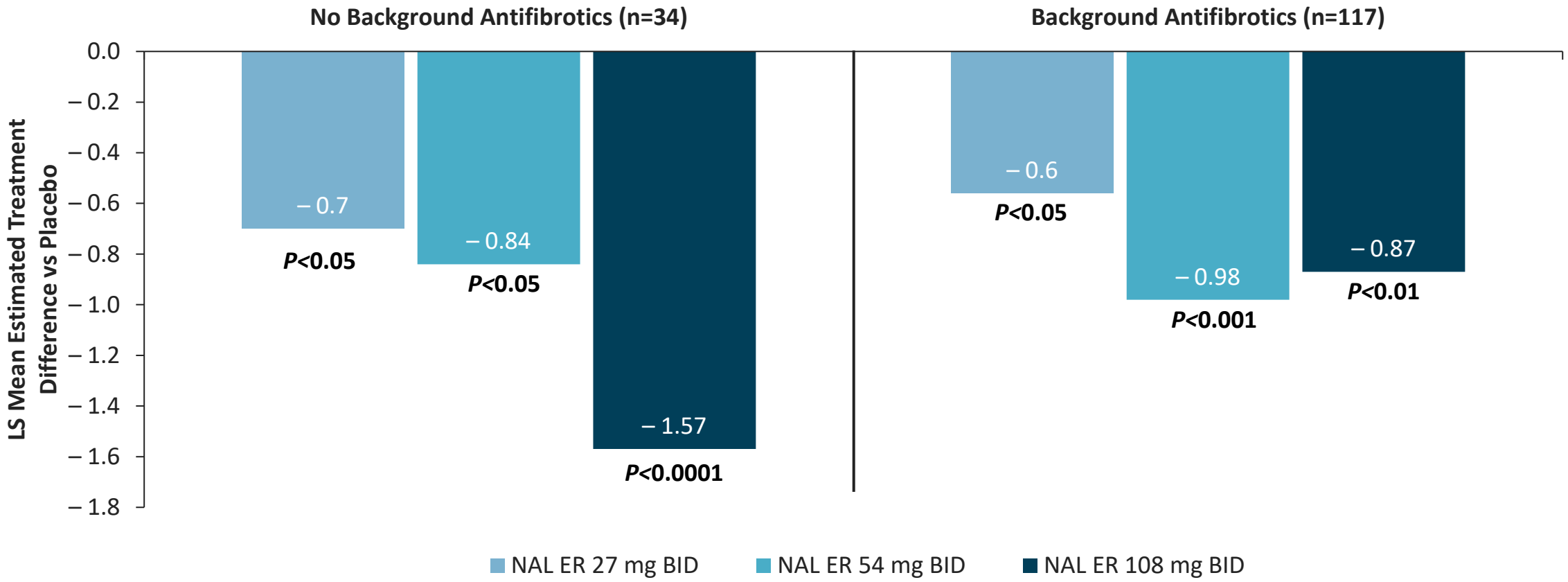


Primary efficacy analysis conducted on log-transformed cough frequency data in the mITT population.
BID, twice daily; mITT, modified intent-to-treat; NAL ER, nalbuphine extended release.
Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.

Results

Objective 24-Hour Cough Frequency by Background Antifibrotic Use at Week 6

NAL ER significantly reduced 24-hour objective cough count versus placebo at Week 6 across all dose groups, regardless of background antifibrotic use

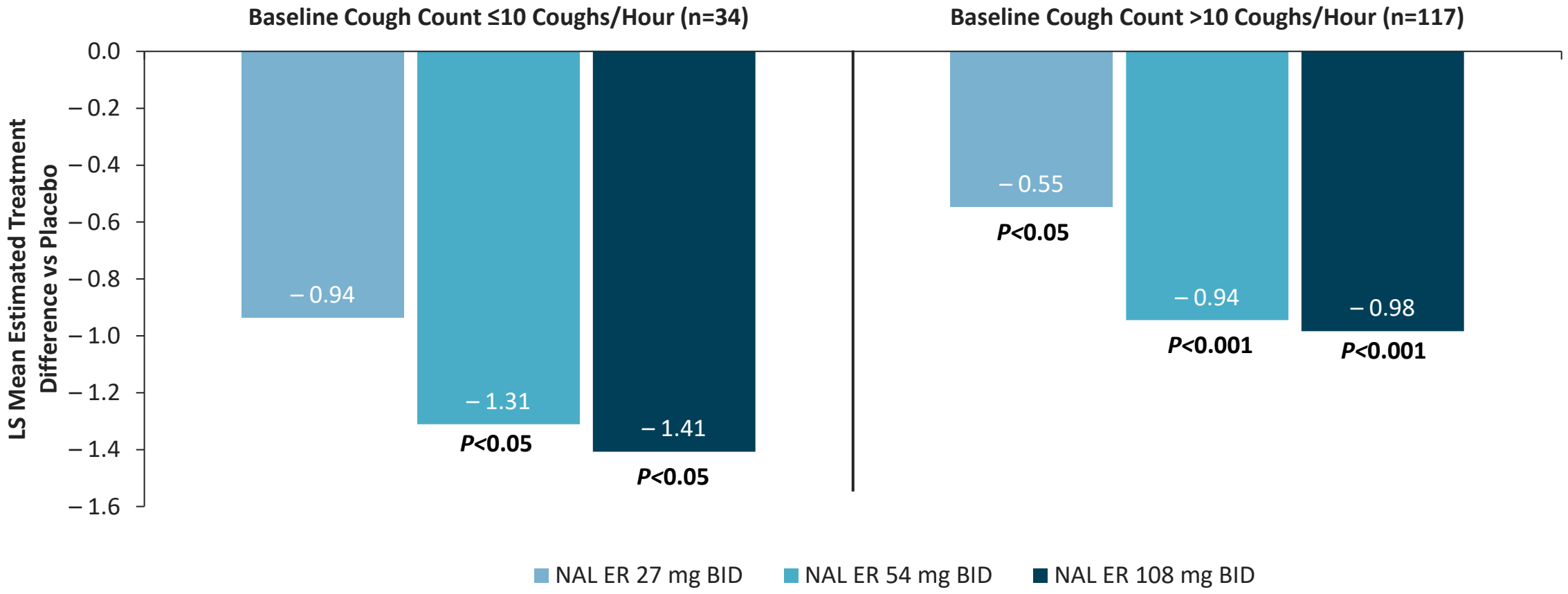


Primary efficacy analysis conducted on log-transformed cough frequency data.
P values are for the comparison versus placebo within each subgroup.
Subgroup n values reflect the MMRM-evaluable population rather than the total population receiving antifibrotics (n=127) in the primary study; patients were included if they had a non-missing baseline and at least 1 non-missing post-baseline 24-hour cough count.
BID, twice daily; LS, least squares; MMRM, mixed model for repeated measures; NAL ER, nalbuphine extended release.

Results

Objective 24-Hour Cough Count by Baseline Cough Count at Week 6

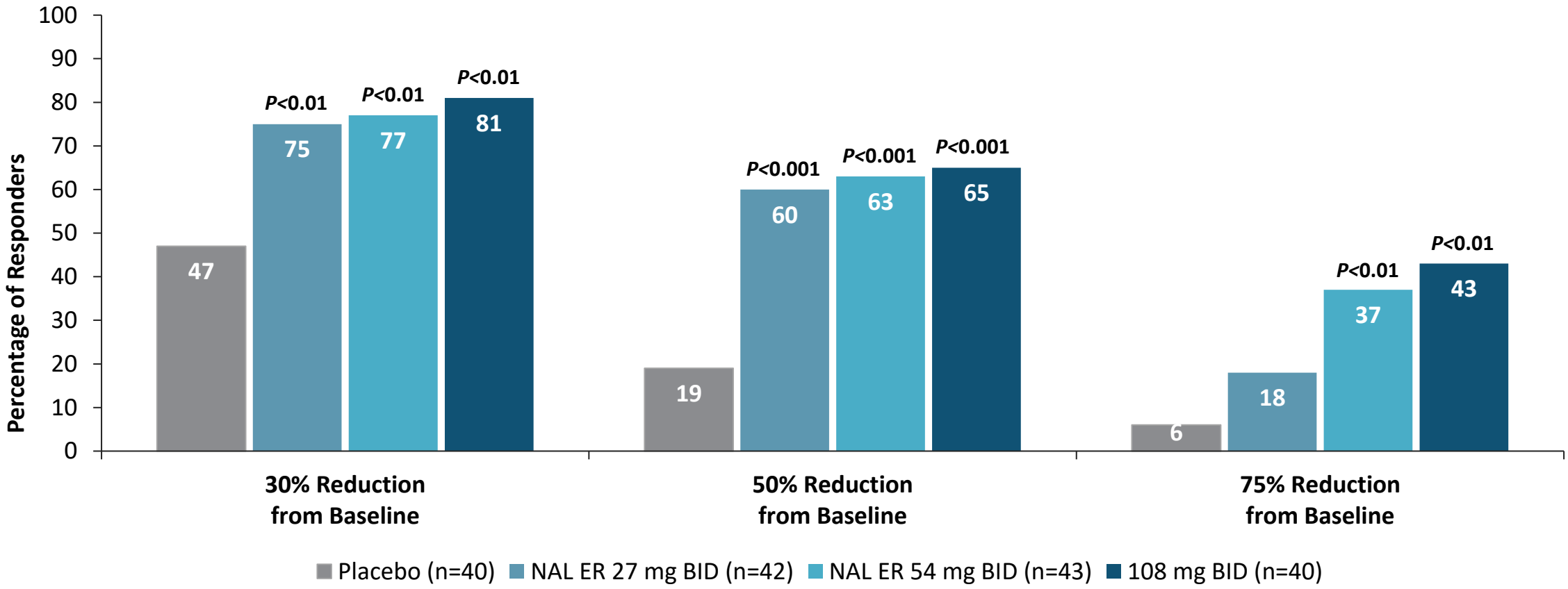
In subgroups defined by baseline cough frequency (≤10 vs >10 coughs/hour), statistically significant reductions versus placebo were observed at Week 6 with the 54 mg and 108 mg BID doses



Primary efficacy analysis conducted on log-transformed cough frequency data.
P values are for the comparison versus placebo within each subgroup.
BID, twice daily; LS, least squares.

Results
Responder Analyses

At Week 6, a significantly greater proportion of patients achieved a ≥50% reduction in objective cough frequency across all NAL ER dose groups versus placebo



Conducted in the mITT population.
BID, twice daily; mITT, modified intent-to-treat; NAL ER, nalbuphine extended release.
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Results
Common (≥10% in Total Active Group) TEAEs by Preferred Term

Preferred term, n (%)	Placebo (n=40) n (%)	NAL ER 27 mg BID (n=42)	NAL ER 54 mg BID (n=43)	NAL ER 108 mg BID (n=40)	Total active (N=125) n (%)
Nausea	2 (5.0)	6 (14.3)	16 (37.2)	20 (50.0)	42 (33.6)
Vomiting	0	4 (9.5)	11 (25.6)	11 (27.5)	26 (20.8)
Constipation	0	5 (11.9)	9 (20.9)	11 (27.5)	25 (20.0)
Dizziness	2 (5.0)	4 (9.5)	5 (11.6)	14 (35.0)	23 (18.4)
Headache	3 (7.5)	4 (9.5)	7 (16.3)	6 (15.0)	17 (13.6)
Fatigue	3 (7.5)	6 (14.3)	6 (14.0)	4 (10.0)	16 (12.8)
Somnolence	1 (2.5)	3 (7.1)	4 (9.3)	7 (17.5)	14 (11.2)
Dry mouth	0	1 (2.4)	6 (14.0)	6 (15.0)	13 (10.4)

- Majority of the common TEAEs were mild (Grade 1) or moderate (Grade 2) and consistent with prior NAL ER studies and the class of drug
  - Nausea, vomiting, constipation, dizziness, headache, and dry mouth all reported as either Grade 1 or Grade 2 TEAEs across dose groups
  - One patient at the 108 mg BID dose group reported Grade 3 TEAEs of fatigue and somnolence
- No deaths occurred in this trial and SAEs occurred in patients at a higher rate in the placebo dose group (10%) than the active dose group (1.6%)
- Discontinuations due to TEAEs were similarly distributed across the placebo (5.0%) and active (5.6%) dose groups

Number of patients reported, not number of events; one patient may have multiple TEAEs.
BID, twice daily; NAL ER, nalbuphine extended release; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.

Conclusions

- NAL ER significantly reduced 24-hour objective cough count versus placebo at Week 6 in patients with IPF-associated chronic cough[1]
- Effects were generally consistent across subgroups defined by background antifibrotic use and baseline cough count
- Responder analyses supported clinically meaningful reductions in objective cough count[1]
- Overall safety profile in NAL ER dose groups was consistent with previous studies and drug class
- Discontinuations due to TEAEs were similar between NAL ER and placebo[1]

IPF, idiopathic pulmonary fibrosis; NAL ER, nalbuphine extended release; TEAE, treatment-emergent adverse event.

1. Molyneaux PL et al. *JAMA*. 2026;335(12):1050-1059.