A Randomized, Placebo-Controlled, Parallel-Group Phase 2b Study of Nalbuphine ER for Chronic Cough in Patients with Idiopathic Pulmonary Fibrosis

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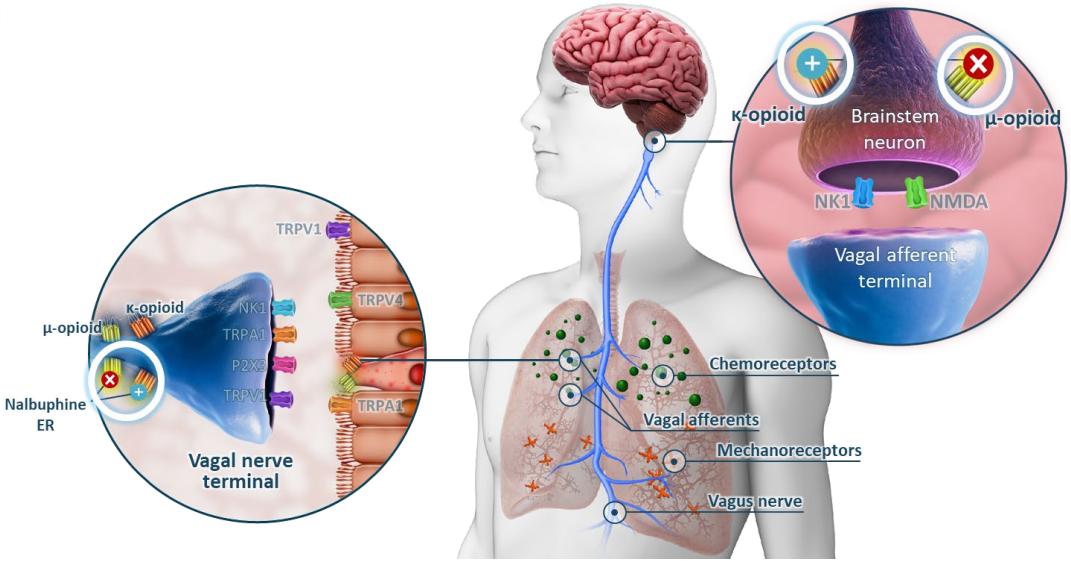
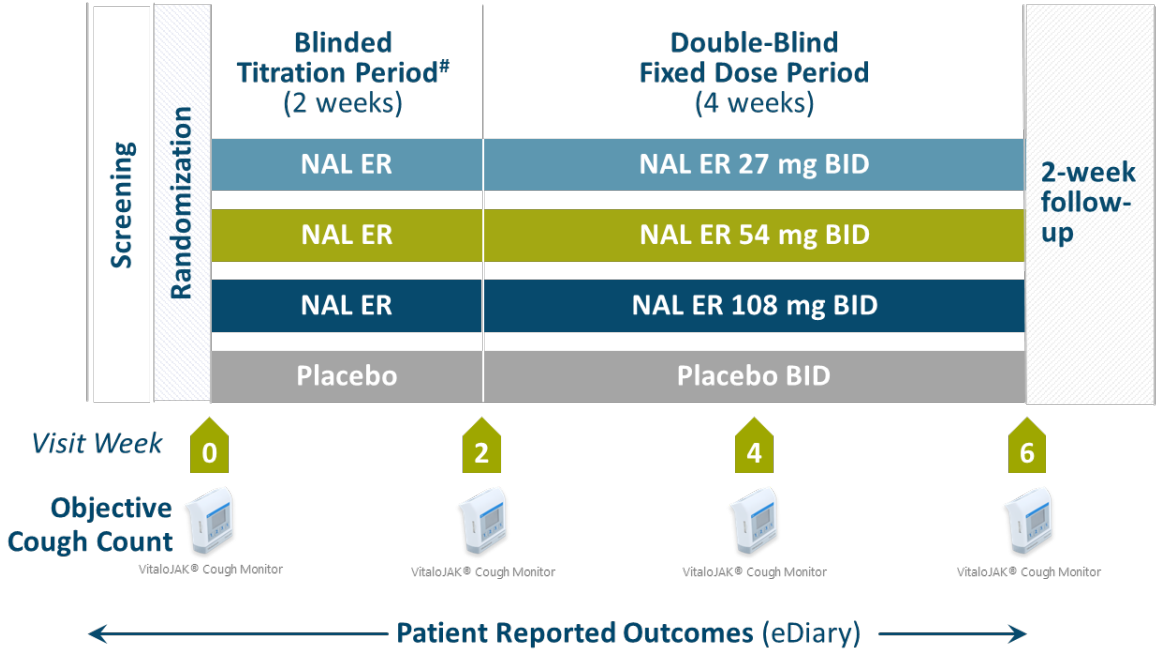
Chronic Cough in Patients with IPF

- Chronic cough affects 85% of patients with IPF and is associated with disease progression, reduced quality of life, and poor health outcomes[1-6]
- There are currently no approved treatments for chronic cough in patients with IPF in the US
- Oral nalbuphine extended release (NAL ER) is a kappa (K) receptor agonist and mu (μ) receptor antagonist that acts on the cough reflex arc centrally and peripherally by targeting opioid receptors involved in cough[7,8]
- CANAL was a phase 2a crossover trial of NAL ER vs. placebo for chronic cough in patients with IPF which demonstrated a 52.5% placebo-adjusted reduction in daytime objective cough frequency



1. Ryerson CJ et al. *Resp*. 2011;16(6):969-75. **2.** Vigeland CL et al. *Respir Med*. 2017;123:98-104. **3.** Lee J et al. CHEST. 2022;162(3):603-613. **4.** Khor YH et al. *AJRCCM*. 2024; 210(8):1035-1044. **5.** Mann J et al. *Front Rehabil Sci*. 2021;2:751798. **6.** Wakwaya Y et al. *CHEST*. 2021;160(5):1774-1782. **7.** Chung KF et al. *Nat Rev Dis Primers*. 2022;8(1):45. **8.** Krajnik M et al. *Curr Opin Support Palliat Care*. 2014;8(3)191-199.

CORAL Phase 2b Study Design



Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- E-RS®:IPF Cough Subscale
- CS-NRS
- 24-hour cough frequency responder analysis (using objective cough monitor)
- E-RS:IPF®, LCQ, L-IPF, EQ-5D-5L
- PGI-S & PGI-C Cough, PGI-S & PGI-C IPF
- CGI-C, CGI-S

Blinded titration period consisted of:
Day 1 - 2: 27mg QD
Day 3 - 7: 27 mg BID
Day 8 - 14: 54 mg BID (ONLY 54 mg BID and 108 mg BID dose groups)

E-RS:IPF: Exacerbation of Chronic Pulmonary Disease Tool IPF, CS-NRS: Cough Severity Numerical Rating Scale, LCQ: Leicester cough questionnaire, L-IPF: Living with IPF, EQ-5D-5L: EuroQoL 5-Dimension 5-Level, PGI-S Cough: patient global impression of cough severity, PGI-C Cough: patient global impression of change in cough, PGI-S IPF: patient global impression of IPF symptom severity, PGI-C IPF: patient global impression of change in IPF symptoms, CGI-S: clinician global impression of cough severity, CGI-C: clinician global impression of change of cough

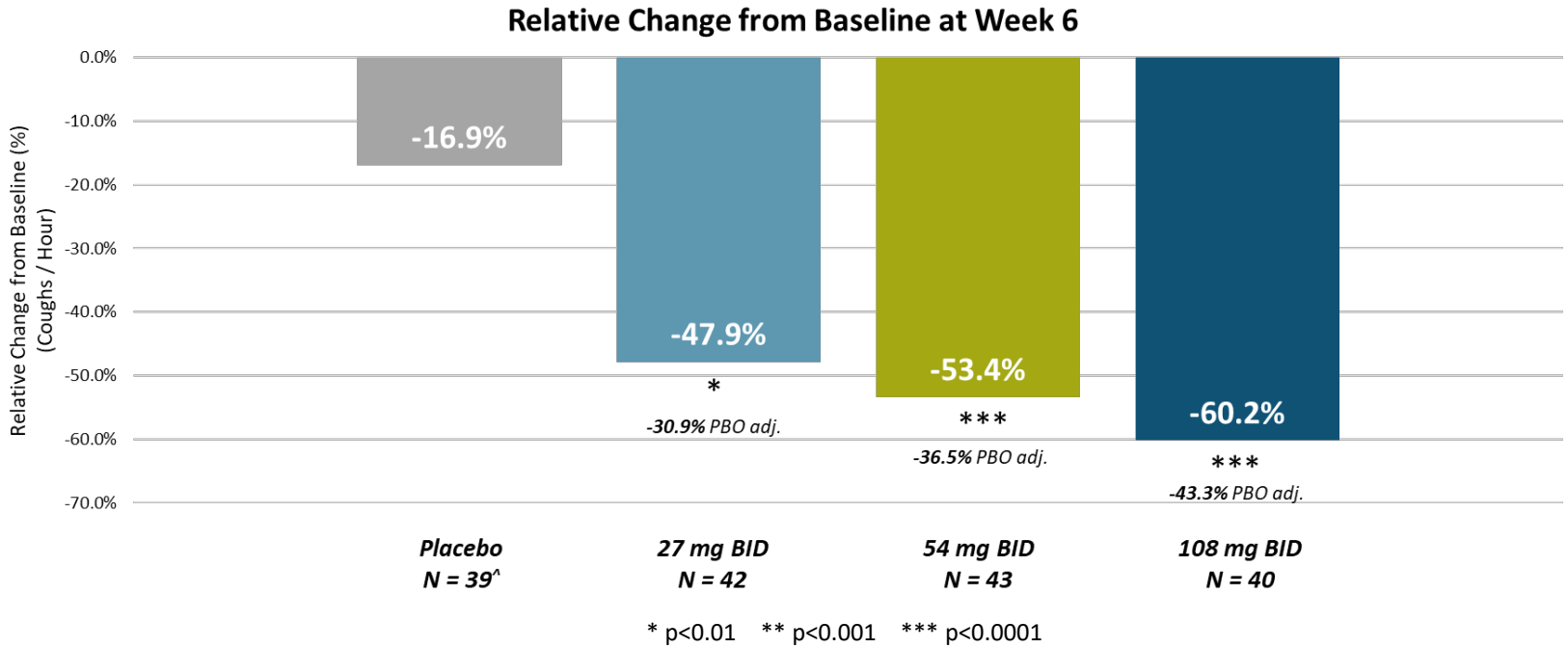
Patient Demographics/Baseline Characteristics

	Total (N = 165)[1]
Age (years), mean (std)	70.1 (7.29)
Gender	
Male, n (%)	118 (71.5%)
Female, n (%)	47 (28.5%)
Forced vital capacity, mean (SD), L	2.56 (0.87)
DLCO, mean (SD), % predicted	51.9 (16.56)
Cough Duration (years), Mean (std)	4.22 (6.60)
Mean Dose Group Range of Baseline 24-Hour Cough Frequency (coughs/hour)	24.6 - 31.5

[1] 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; std, Standard deviation

Primary Endpoint: Objective 24-Hour Cough Frequency

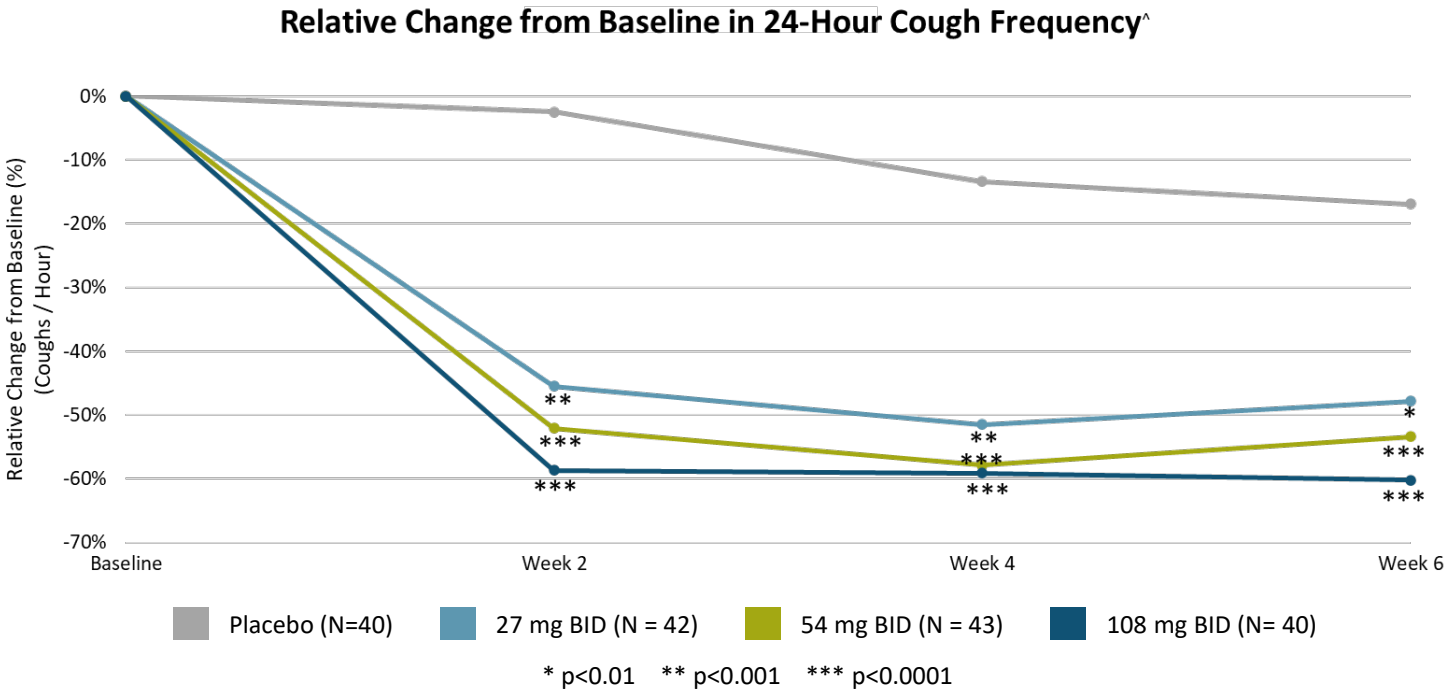
Significant difference in the relative change from Baseline observed across all dose groups



mITT population
Primary efficacy analysis conducted on log-transformed cough frequency data
^One placebo patient with an extreme outlier value at Week 6 was excluded from the modified intent-to-treat mITT population. Inclusion of the patient in the placebo group would have resulted in an increased cough frequency from baseline in the placebo group and much greater placebo-adjusted differences.
PBO, placebo

Objective 24-Hour Cough Frequency by Study Week

Rapid and persistent cough reduction from Baseline observed by Week 2



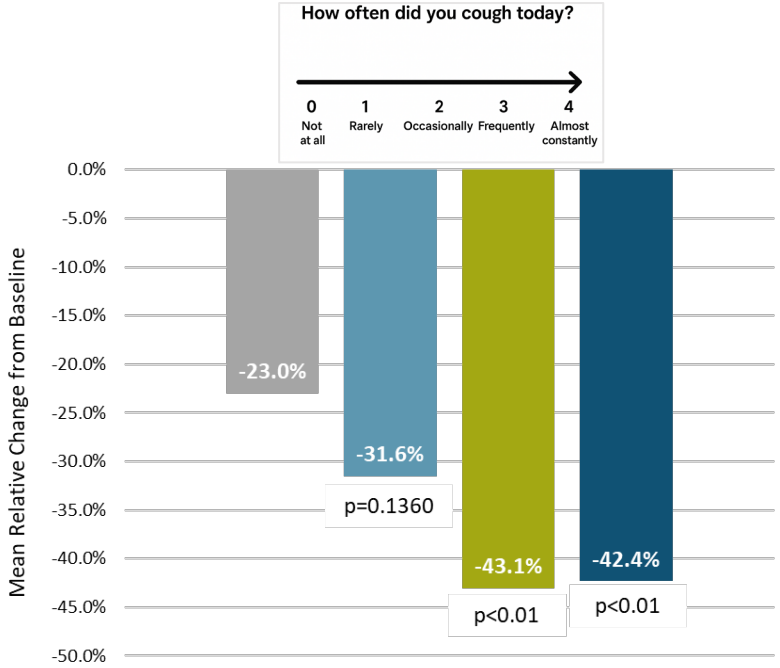
mITT population, Primary efficacy analysis conducted on log-transformed cough frequency data

^One placebo patient with an extreme outlier value at Week 6 was excluded from the modified intent-to-treat (mITT) population. Inclusion of the patient in the placebo group would have resulted in an increased cough frequency from baseline in the placebo group and much greater placebo-adjusted differences.

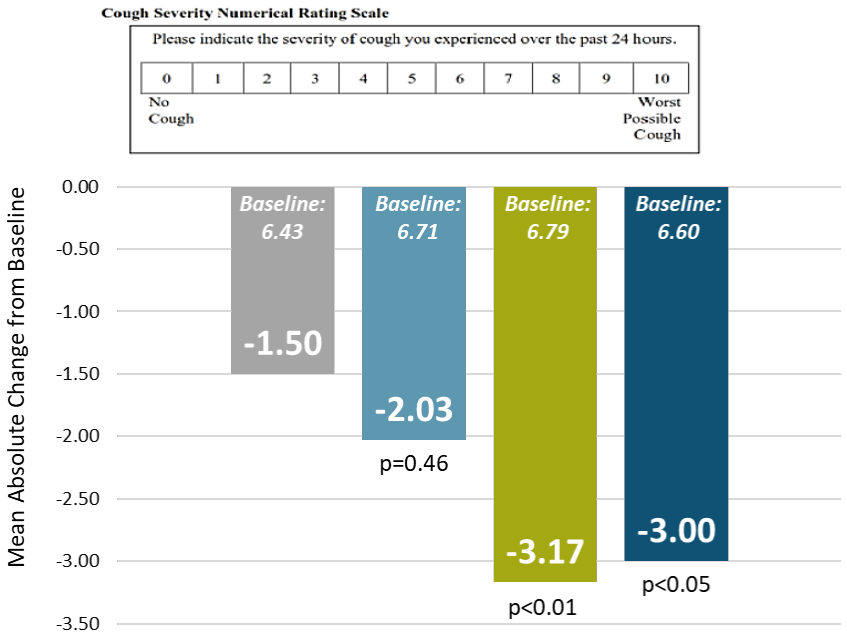
Patient-Reported Outcome Measures

Patient reported outcomes show measurable impact on patients

E-RS®:IPF Cough Subscale: Relative Change from Baseline at Week 6



Cough Severity Numerical Rating Scale (CS-NRS) at Week 6

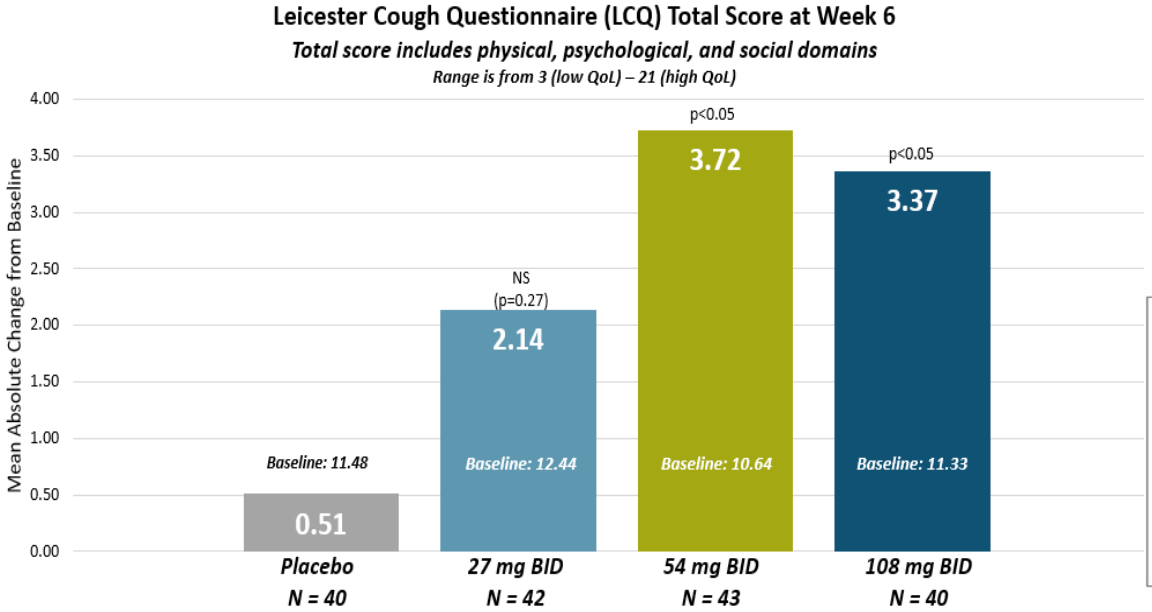


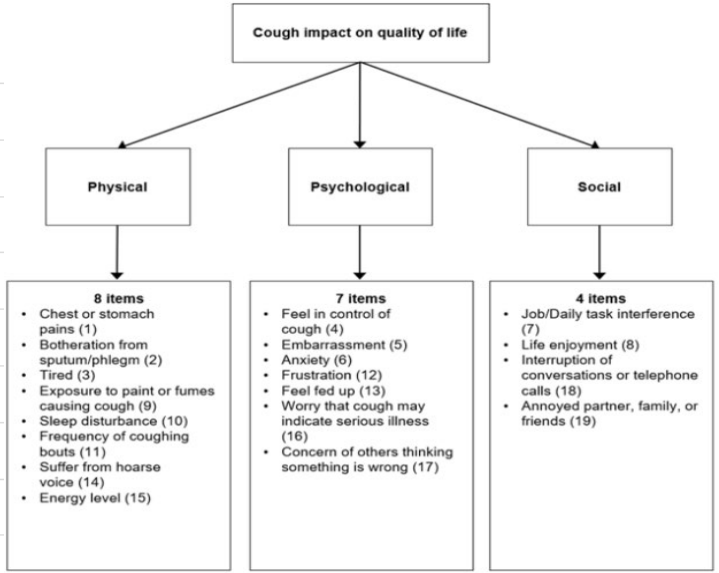
Placebo (N=40) | 27 mg BID (N = 42) | 54 mg BID (N = 43) | 108 mg BID (N= 40)

mITT population

Patient Reported Quality of Life: Leicester Cough Questionnaire (LCQ)

Statistically significant improvement in <u>LCQ Total Score</u> at 54 mg BID and 108 mg BID dose groups





mITT population
QoL, Quality of life

Treatment Emergent Adverse Events Overview

	Placebo (N = 40) n (%)	27 mg BID (N = 42) n	54 mg BID (N = 43) n	108 mg BID (N = 40) n	Total Active (N = 125) n (%)
Treatment Emergent Adverse Events	**25 (62.5)**	**30**	**34**	**33**	**97 (77.6)**
Adverse Events Related to Study Drug	9 (22.5)	18	27	28	73 (58.4)
Serious Adverse Events	4 (10.0)	1	0	1	2 (1.6)
Adverse Event Leading to Discontinuation of Study Drug	2 (5.0)	0	6	1	7 (5.6)

- No deaths occurred in this trial
- 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
- Majority of reported TEAEs were mild (Grade 1) or moderate (Grade 2) and consistent with prior NAL ER studies and the class of drug

Safety Population
One patient may have multiple Adverse Events

Summary of Common (≥ 10% in Total Active Group) TEAEs by Preferred Term

Preferred Term	Placebo (N = 40) n (%)	27 mg BID (N = 42) n (%)	54 mg BID (N = 43) n (%)	108 mg BID (N = 40) n (%)	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

Safety population
Number of patients reported, not number of events; one patient may have multiple treatment emergent adverse events

CORAL Trial Conclusions

- First parallel-group study that demonstrated significant reduction in cough frequency in patients with IPF
- NAL ER was observed to result in statistically significant dose-related reduction in cough frequency
- Statistically-significant changes in secondary endpoints, supporting primary endpoint, including patient-reported outcomes observed
- Overall safety profile in NAL ER dose groups consistent with previous studies and drug class
- Discontinuation rate due to TEAEs consistent between placebo and total active dose groups

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Thank You!