



Controlling cough where it counts™



## Positive Topline Results from Phase 2b Trial of Haduvio in Patients with IPF Chronic Cough (CORAL)

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June 2, 2025

Nasdaq: TRVI

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# Cough Reduction in IPF Patients with Haduvio CORAL Ph2b

## Topline Results Agenda

<b>Introduction</b>	<b>Jennifer Good</b> , President and CEO, <i>Trevi Therapeutics</i>
<b>Study Design &amp; Topline Results</b>	<b>James Cassella, Ph.D.</b> , Chief Development Officer, <i>Trevi Therapeutics</i>
<b>Concluding Remarks</b>	<b>Jennifer Good</b> , President and CEO, <i>Trevi Therapeutics</i>
<b>Q&amp;A</b>	<b>Jennifer Good</b> , President and CEO, <i>Trevi Therapeutics</i> <b>James Cassella, Ph.D.</b> , Chief Development Officer, <i>Trevi Therapeutics</i> <b>Farrell Simon, Pharm.D.</b> , Chief Commercial Officer, <i>Trevi Therapeutics</i> <b>Professor Philip Molyneaux, Ph.D.</b> Professor of Respiratory Medicine at the Royal Brompton Hospital

# Patients Tell Their Stories of the Unmet Need in IPF Chronic Cough

“This cough has **robbed me of my life**. I cough when I talk. I cough when I laugh. I cough when I do bare minimal activity. The cycle of shortness of breath/cough is endless.”

- Female Patient with IPF<sup>1</sup>

“My cough often leads to **vomiting, severe chest pain and occasionally passing out**.”

- Female Patient with IPF<sup>1</sup>

“...Particularly, when I talk too much, I will start coughing. That really **limits social interaction**.”

- Male Patient with IPF<sup>1</sup>

“On my worst days, coughing will wipe you out for an entire day ... Physically, **you're exhausted**.”

-Patient with IPF<sup>2</sup>

“My cough was really so deep that it **felt like I broke my ribs**, and my ribs became so cramped that I couldn't even twist [my body].”

-Patient with IPF<sup>2</sup>

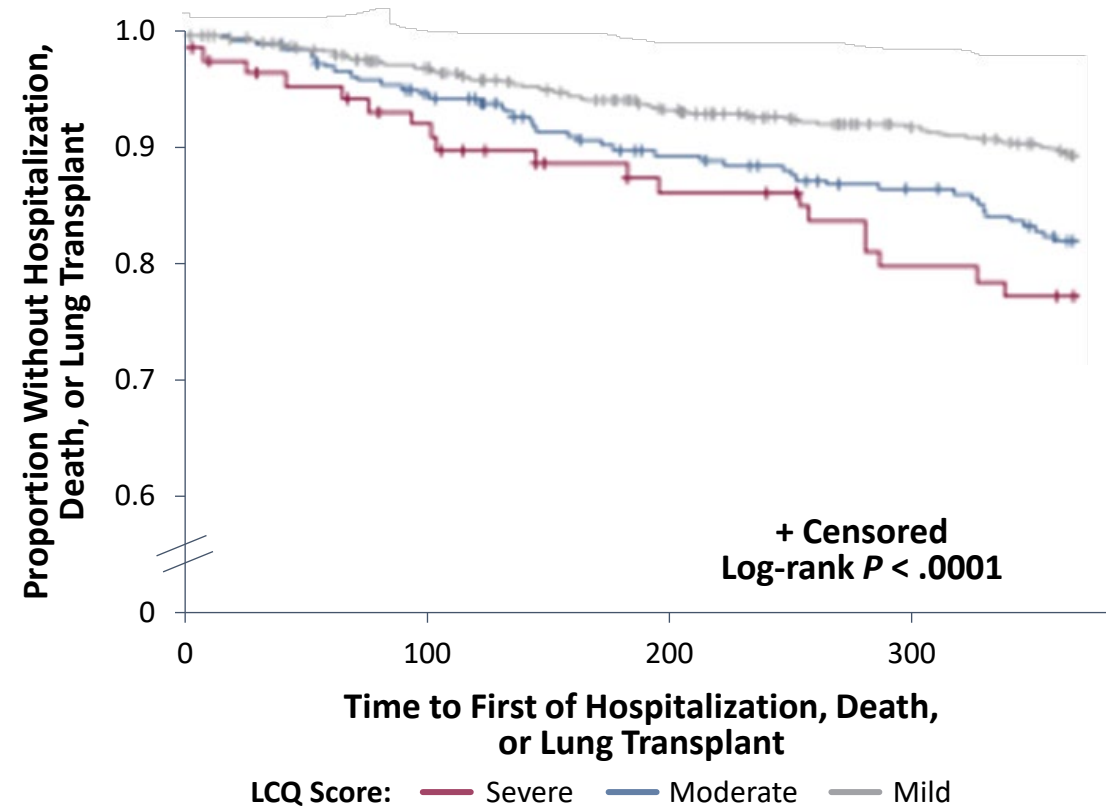
“I cough a lot, I notice that. When I'm with other people, they're always like, 'Wow, you're really coughing.' I try to suppress it as much as I can, but sometimes you can't. I can sense that people go **looking at each other go, 'Wow, he's really coughing'**, whether or not they know I have an illness.”

- Male Patient with IPF<sup>3</sup>

# Chronic Cough in IPF May Cause Damage to the Lungs and Deteriorates Quality of Life

- No approved therapies in the US
- Growing category of 140k US patients with IPF<sup>1-3</sup>
- 85% of IPF patients have chronic cough<sup>4,5</sup>
- 3-5 year life expectancy<sup>6</sup>
- Cough's role in IPF/ILDs<sup>7-10</sup>:
  - Worse cough QoL is associated with an increased risk of health outcomes (i.e. respiratory hospitalization, death)\*
  - Pro-fibrotic
  - Can cause fatigue, air hunger, and peripheral oxygen desaturation

## Estimates for Respiratory Hospitalization, Death, and Lung Transplant by LCQ Score (Cough QoL) Severity Over Time from the US Pulmonary Fibrosis Foundation Registry (N=1,447)



## Statistically significant results for Haduvio in IPF patients with chronic cough

- ✓ -43.3% placebo-adjusted change from baseline was achieved at the 108 mg BID dose group\*
  - ✓ -60.2% change from baseline in the 108 mg BID dose group ( $p < 0.0001$ )
  - ✓ -53.4% change from baseline in the 54 mg BID dose group ( $p < 0.0001$ )
  - ✓ -47.9% change from baseline in the 27 mg BID dose group ( $p < 0.01$ )
- ✓ Patient reported outcomes and secondary endpoints were consistent with primary endpoint
- ✓ Majority of patients on Haduvio achieved a 50% or greater reduction from baseline in objective cough frequency\*
- ✓ Rapid onset of effect, with reduction in cough observed as early as Week 2
- ✓ Discontinuation rates due to adverse events were similar between Haduvio (5.6%) and placebo (5.0%) groups
- ✓ Safety profile remains consistent with prior Haduvio studies and this class of drugs

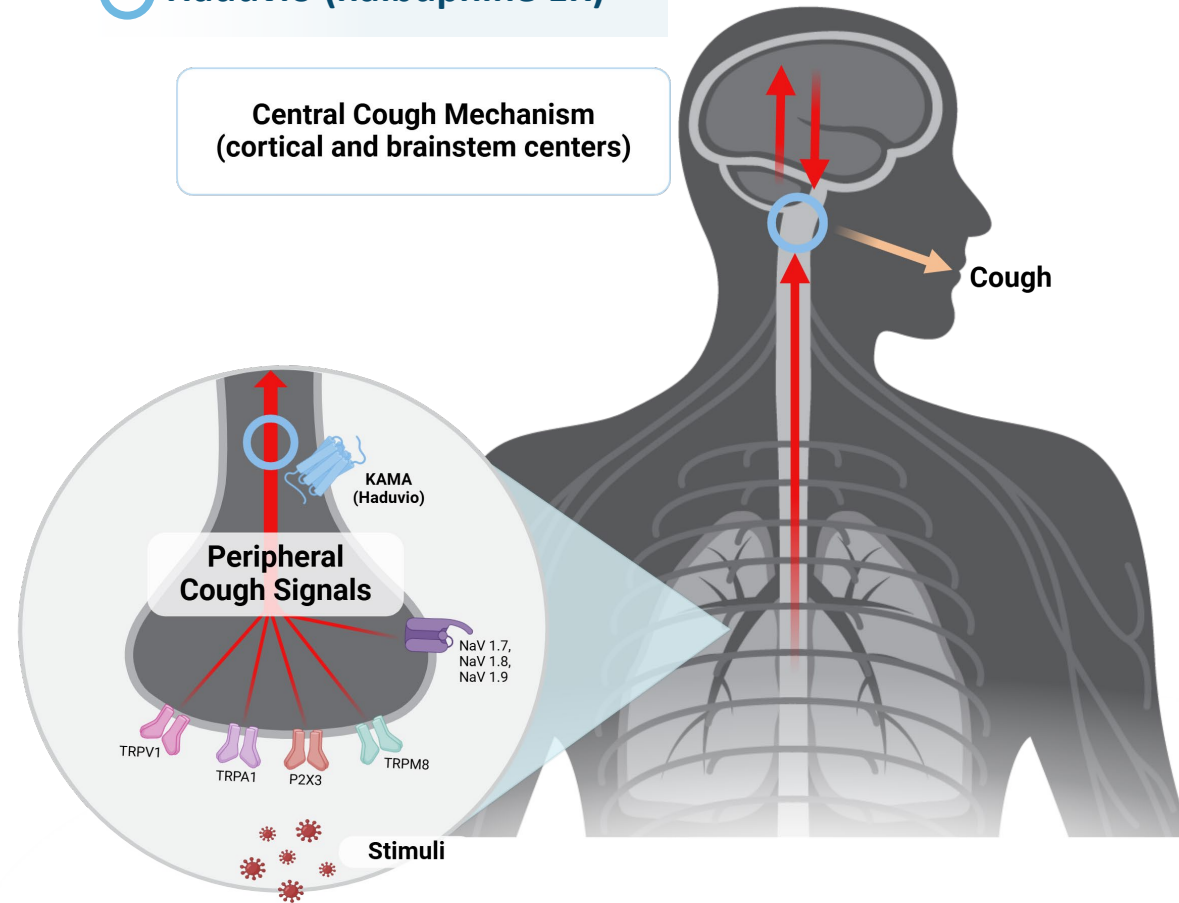
### **Next Step:**

Request End-of-Phase 2 meeting with the FDA in 2H 2025 and prepare to initiate Phase 3 program in 1H 2026

# Haduvio's Differentiated Central and Peripheral Mechanism of Action

## Haduvio (nalbuphine ER)

Central Cough Mechanism  
(cortical and brainstem centers)



## Importance of Central and Peripheral Activity

Haduvio acts on the cough reflex arc both centrally and peripherally as a kappa agonist and a mu antagonist (KAMA), targeting opioid receptors that play a key role in controlling chronic cough.

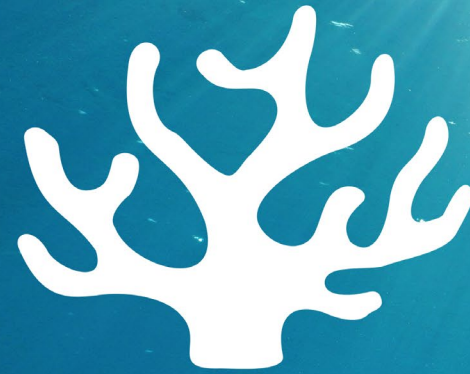
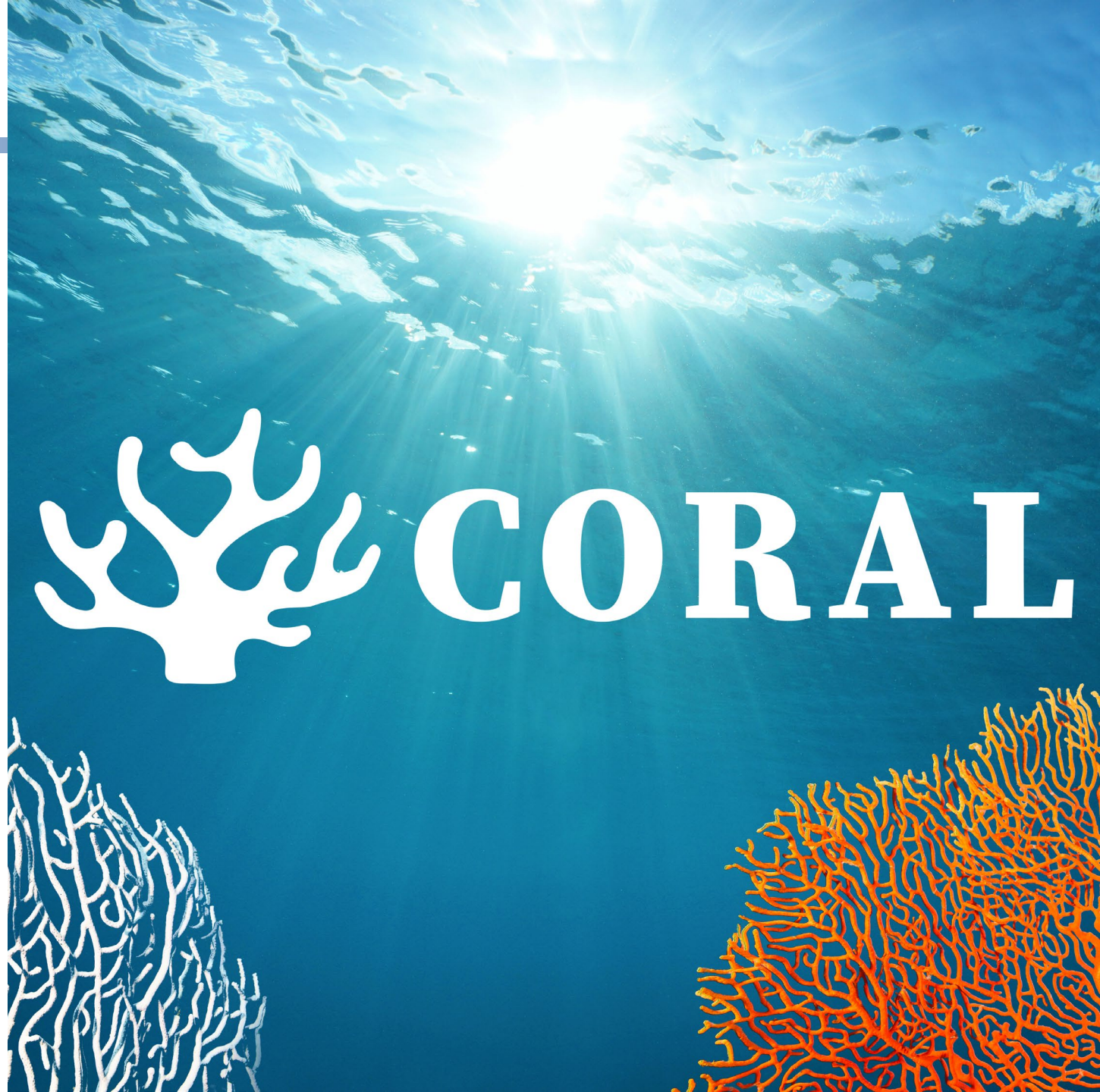
	Haduvio	Peripheral Only Therapies
<b>Central (Brain)</b>	✓ Can inhibit chronic cough hypersensitization	✗ Not centrally active
<b>Peripheral (Lung)</b>	✓ Can limit cough signals to the brain	✓ Only peripherally active

**James Cassella, Ph.D.**  
**Chief Development Officer**



# Cough Reduction in IPF Patients with Chronic Cough

**trevi**<sup>™</sup>  
THERAPEUTICS



**CORAL**

*Multi-center randomized, double-blind, placebo-controlled, parallel, 4-arm dose ranging study with nalbuphine extended release (NAL ER) for the treatment of cough in idiopathic pulmonary fibrosis (IPF)*

## STUDY DOSES

27 mg BID, 54 mg BID, 108 mg BID, and placebo

## ENTRY CRITERIA

- Diagnosis of IPF and history of chronic cough for at least 8 weeks before Screening
- Cough severity score  $\geq 4$  on CS-NRS<sup>1</sup> during Screening **and** Baseline
- Patients on background anti-fibrotic therapies were allowed

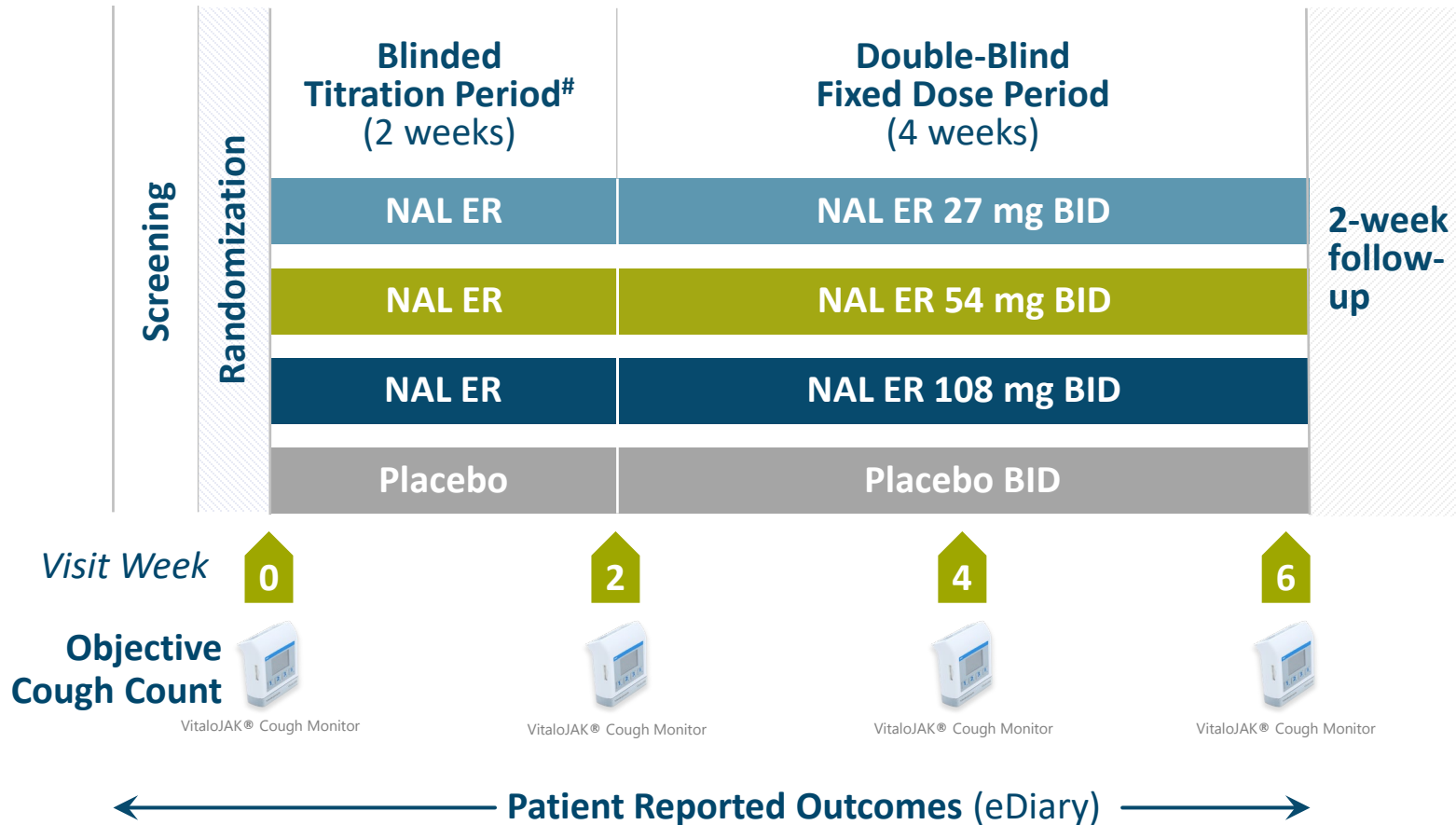
## PRIMARY ENDPOINT

Relative change from Baseline in 24-hour cough frequency (coughs per hour) versus placebo at Week 6<sup>2</sup>

→ Pre-specified hierarchical analysis by dose, starting at 108 mg BID

## SECONDARY ENDPOINTS

24-hour cough frequency responder analysis and patient reported outcomes for cough severity and cough frequency



## 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) \*
- EXACT:IPF, LCQ, L-IPF, EQ-5D-5L
- PGI-S & PGI-C Cough, PGI-S & PGI-C IPF
- CGI-C, CGI-S

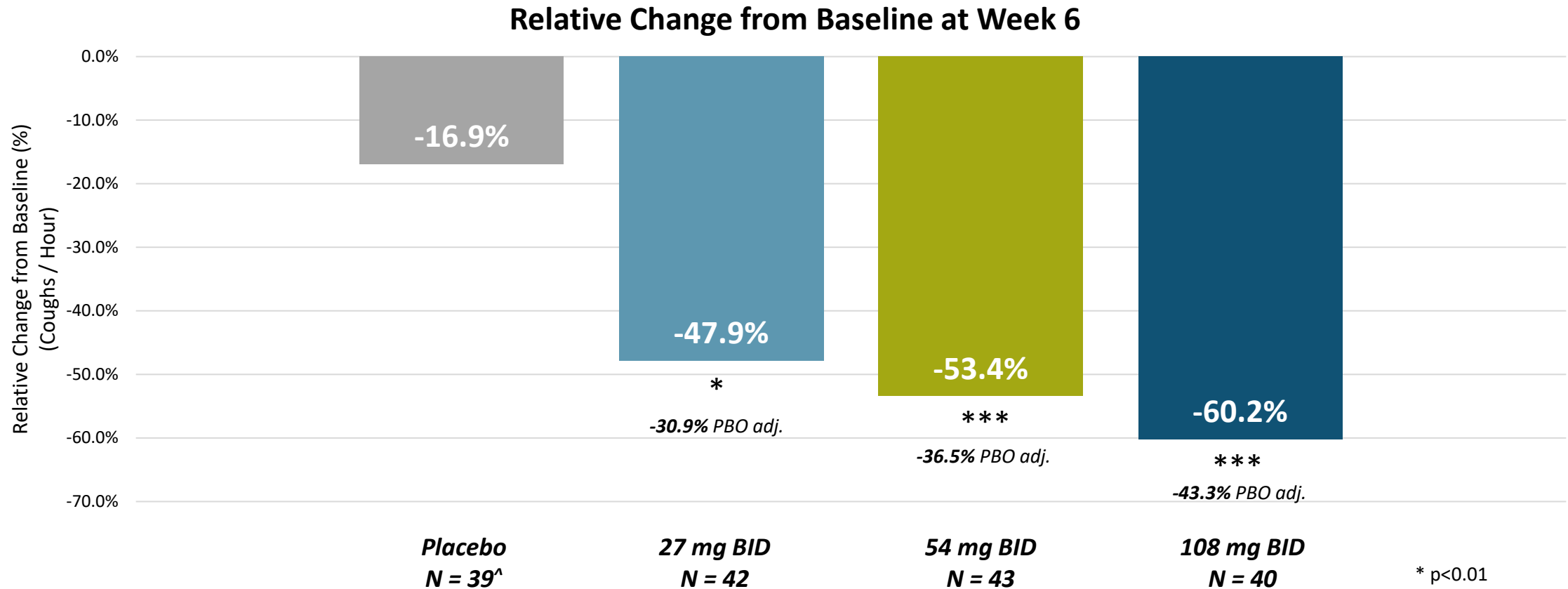
# Blinded titration period consisted of:  
 Day 1 - 2: 27mg QD  
 Day 3 - 7: 27 mg BID  
 Day 8 - 14: 54 mg BID (ONLY 54 mg BID and 108 mg BID dose groups)  
 \* Included in topline results

	Total (N = 165) <sup>1</sup>
Age (years), mean (std)	70.1 (7.29)
Male, n (%)	118 (71.5%)
Female, n (%)	47 (28.5%)
Race, n (%)	
White	157 (95.2%)
Asian	3 (1.8%)
Not Reported	3 (1.8%)
Black or African American	2 (1.2%)
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

# Objective 24-Hour Cough Frequency

## Primary Endpoint: Relative Change from Baseline at Week 6

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

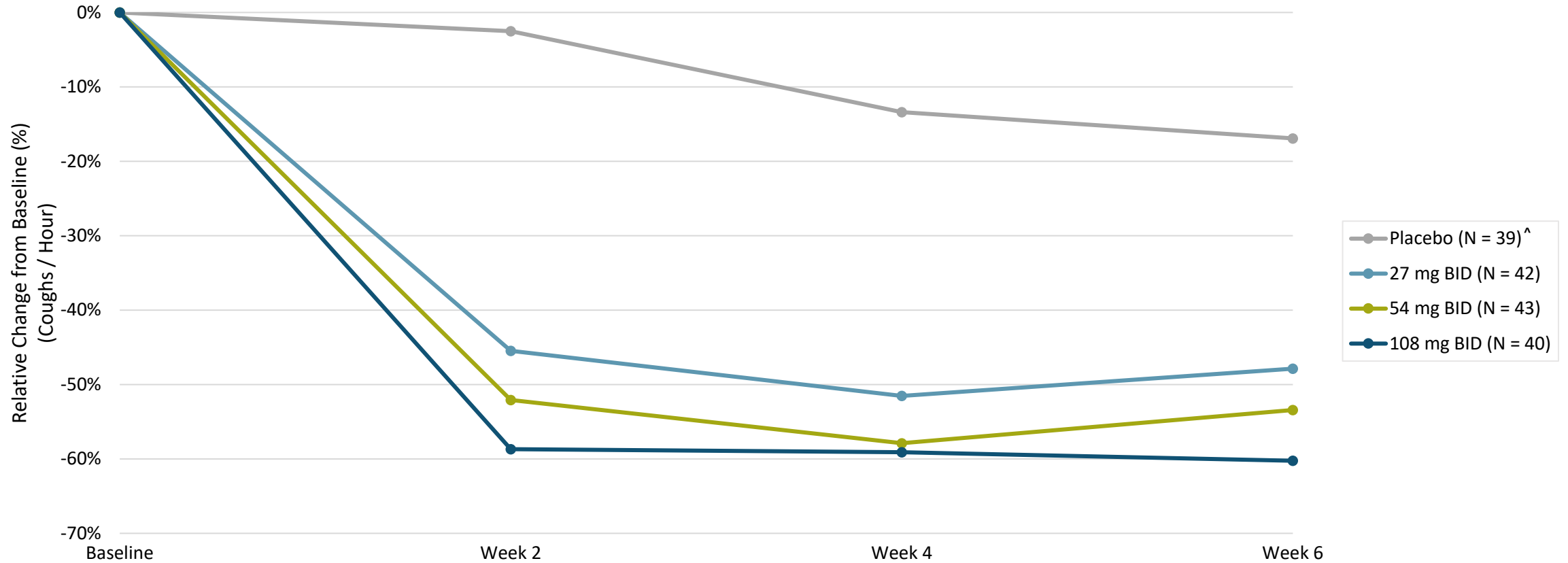


\* p<0.01  
 \*\* p<0.001  
 \*\*\* p<0.0001

# Relative Change from Baseline in 24-Hour Cough Frequency by Study Week



*Rapid and persistent cough reduction observed by Week 2<sup>△</sup>*



<sup>△</sup> Statistical analysis pending: not included in topline data

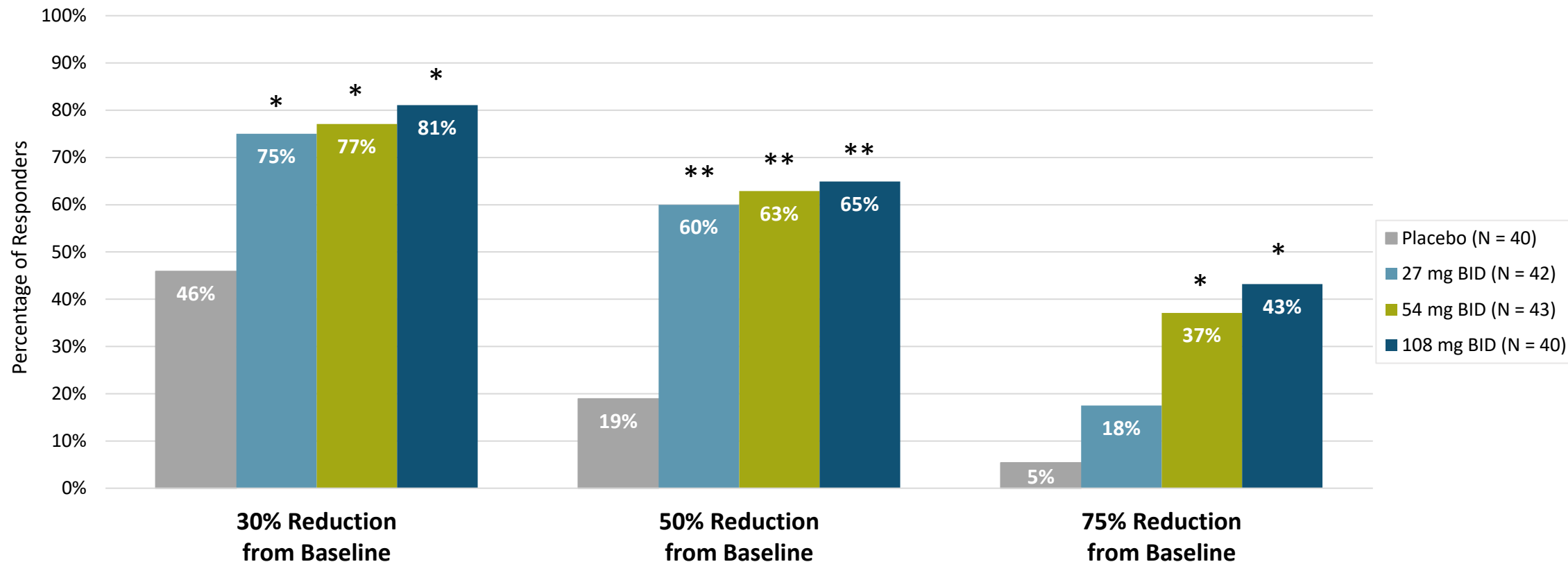
Haduvio (nalbuphine ER/NAL ER) is an investigational drug  
mITT population

Primary efficacy analysis conducted on log-transformed cough frequency data

<sup>△</sup>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.

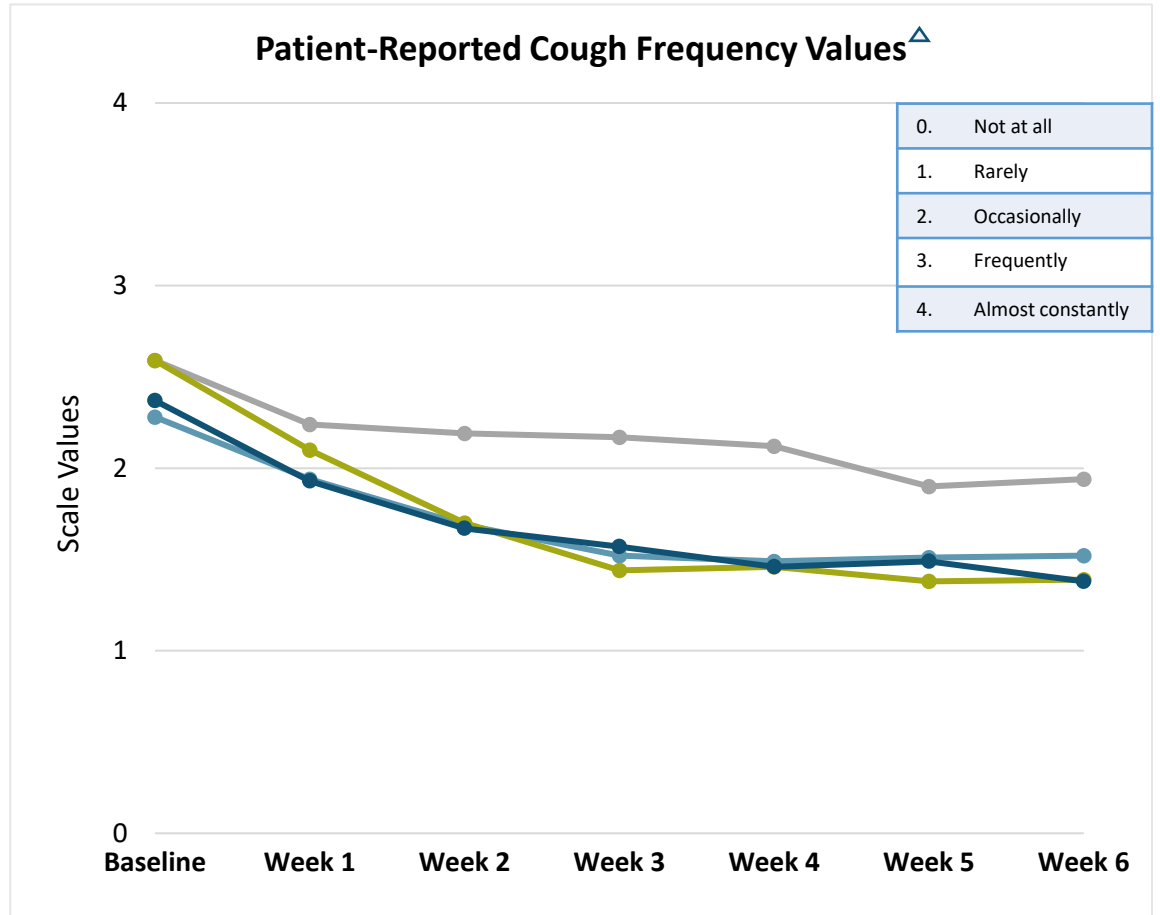
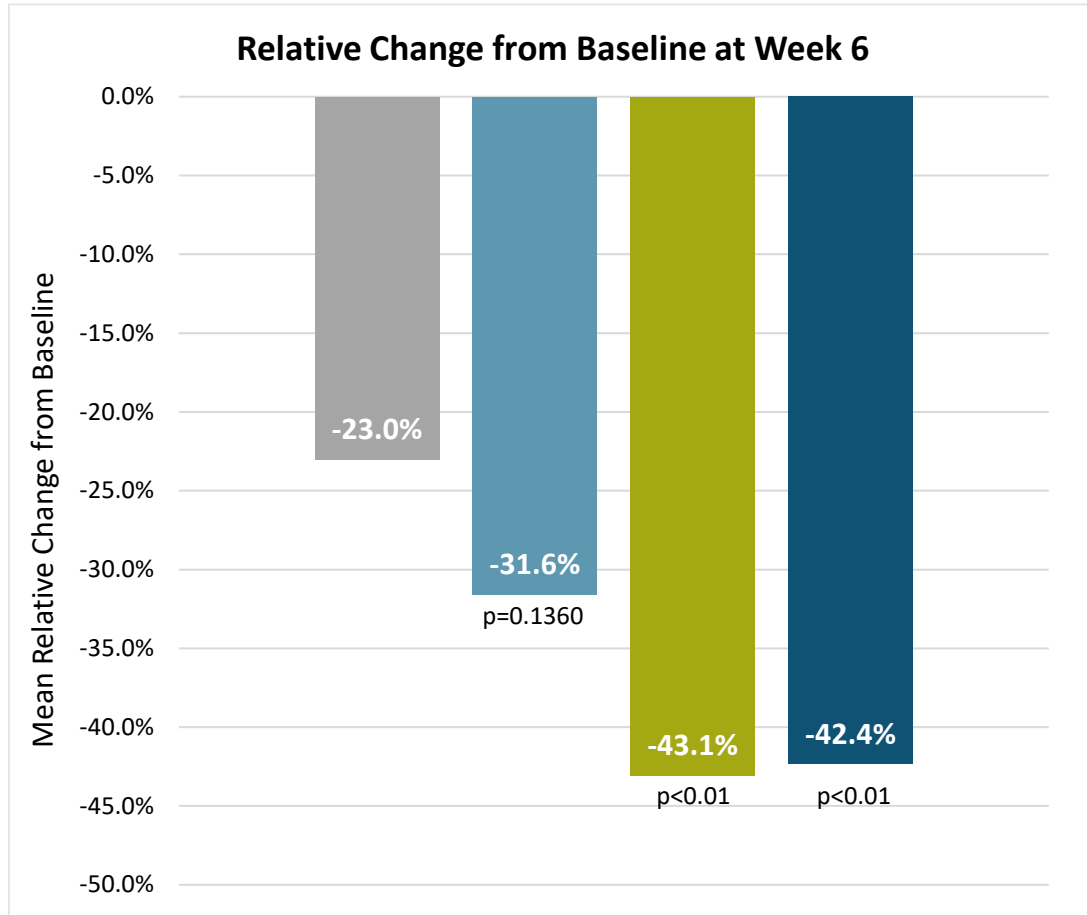
*Majority of patients achieved at least a 50% reduction in objective cough frequency*

**Response Thresholds for 24-Hour Cough Frequency**



\* p<0.01  
 \*\* p<0.001  
 \*\*\* p<0.0001

# E-RS®:IPF Cough Subscale: “How often did you cough today?”



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

<sup>△</sup> Statistical analysis pending: not included in topline data

Haduvio (nalbuphine ER/NAL ER) is an investigational drug  
mITT population

E-RS:IPF: Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis as collected in the EXACT® (EXAcerbation of Chronic pulmonary disease Tool); EXACT© 2013, Evidera, Inc. All rights reserved.

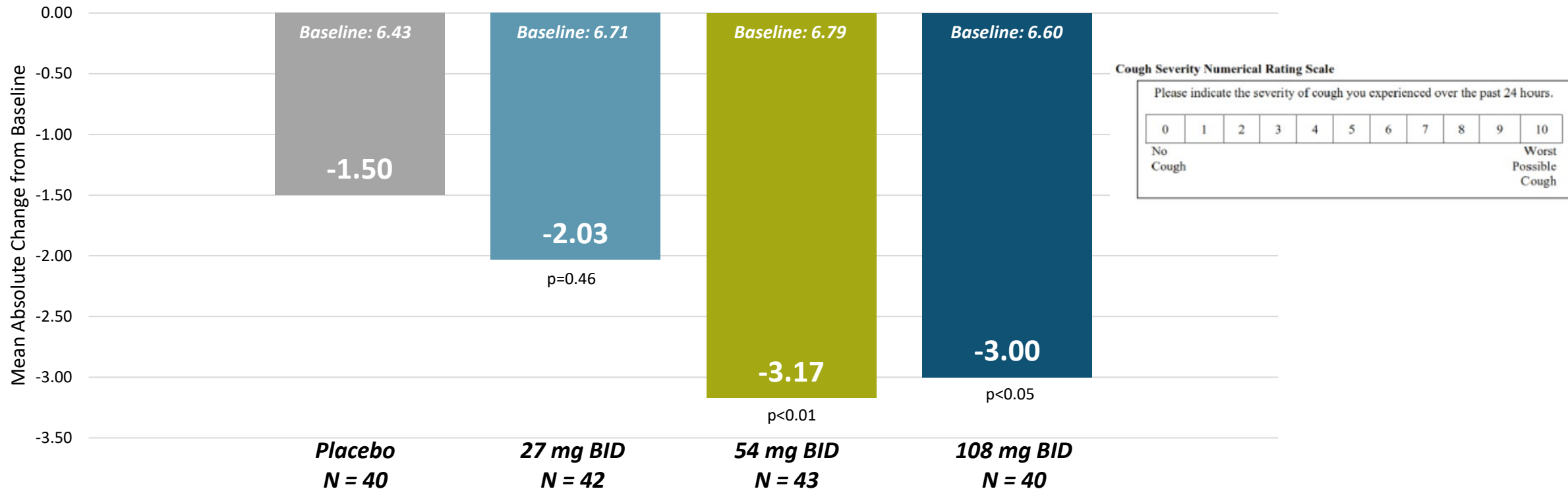


# Patient-Reported Cough Severity

## Absolute Change from Baseline at Week 6

*Statistically significant reduction in patient-reported cough severity observed at 54 mg BID and 108 mg BID dose groups, consistent with objective and subjective measures of cough frequency*

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

# 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 (%)
<b>Treatment Emergent Adverse Events</b>	<b>25 (62.5)</b>	<b>30</b>	<b>34</b>	<b>33</b>	<b>97 (77.6)</b>
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)

- The most common adverse events leading to treatment discontinuation were headache, nausea, and vomiting

# Summary of Common ( $\geq 10\%$ 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

- First parallel-group study that demonstrated significant reduction in cough frequency in patients with IPF
- Haduvio was observed to result in statistically significant dose-related reduction in cough frequency
- Statistically-significant changes in topline 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

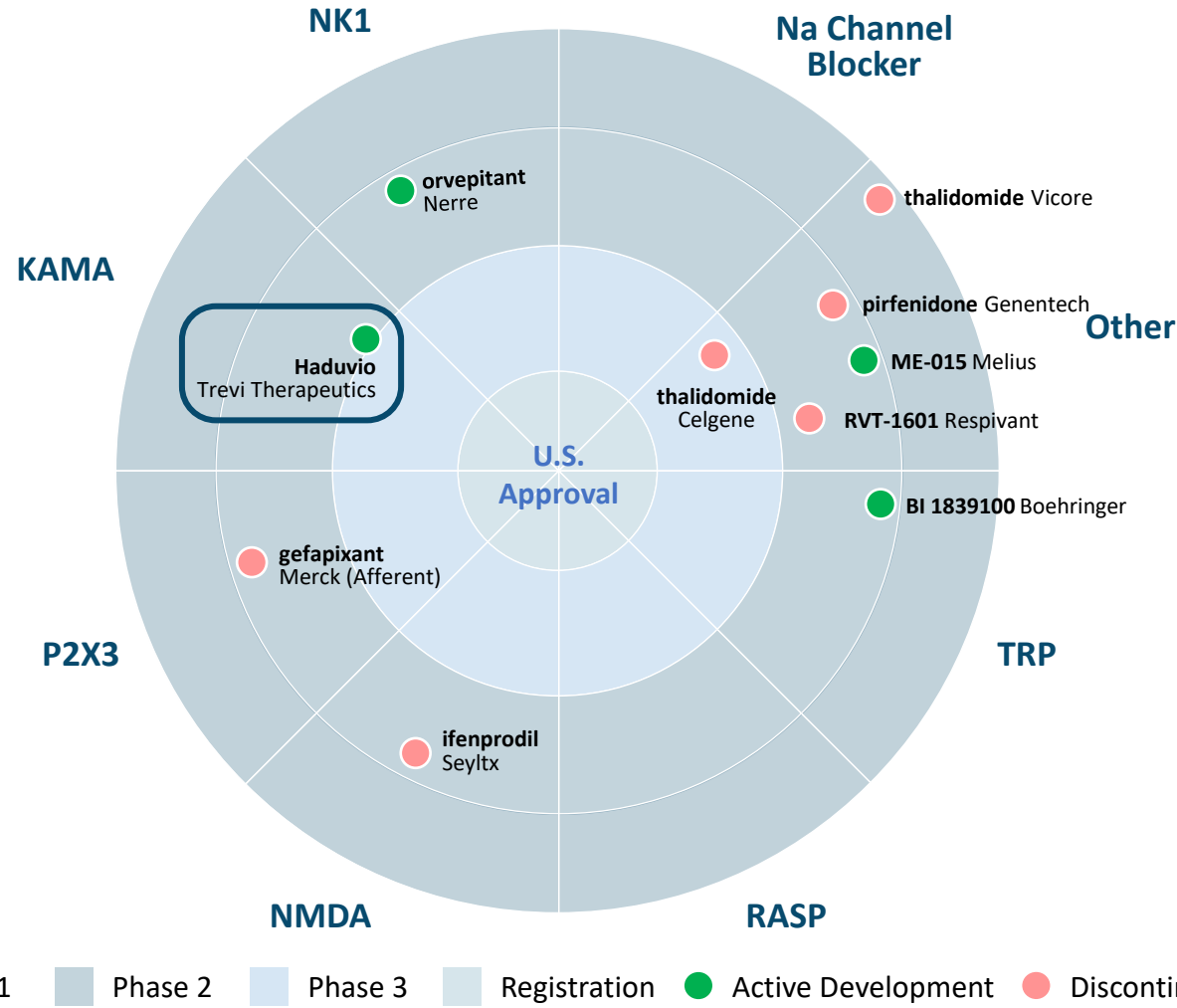


**Expected Next steps: Request End-of-Phase 2 meeting with the FDA and prepare to initiate Phase 3 program**

**Jennifer Good**  
**President and CEO**



# Opportunity to be Best-in-Class and First-in-Class in IPF Chronic Cough



## P2x3s Failed in IPF Chronic Cough

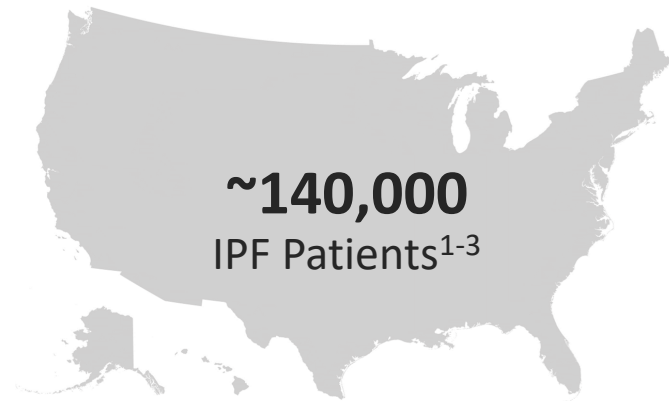
- Gefapixant (P2x3)
  - 12% reduction (p=0.8983)

## Anti-Fibrotics Have Not Shown Cough Benefit

- Aim to slow the progression of the disease
- No statistically significant cough benefit

# Leading with IPF Specialty Indication with a High Unmet Need and Favorable Commercial Dynamics

## US IPF Opportunity Today



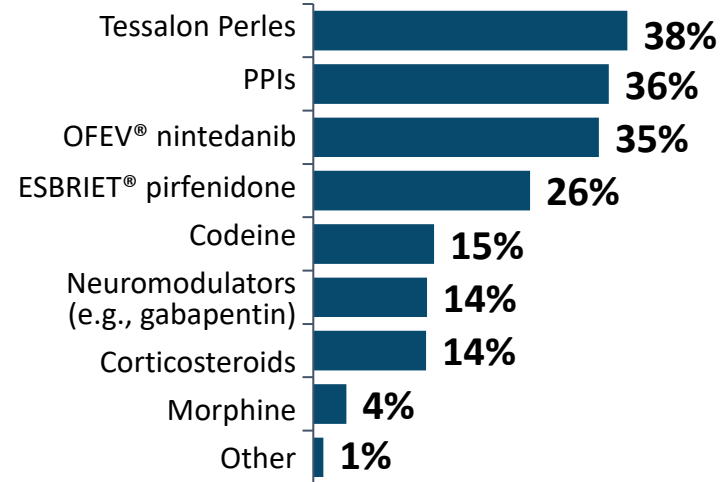
**+7%**

YoY IPF category growth<sup>1-3</sup>

**60-70%**

Avg. % of patients with uncontrolled chronic cough

## IPF Cough Treatment Paradigm<sup>4</sup>

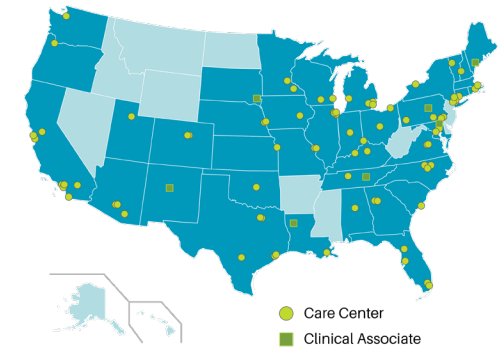


No FDA-approved therapies for IPF patients with chronic cough

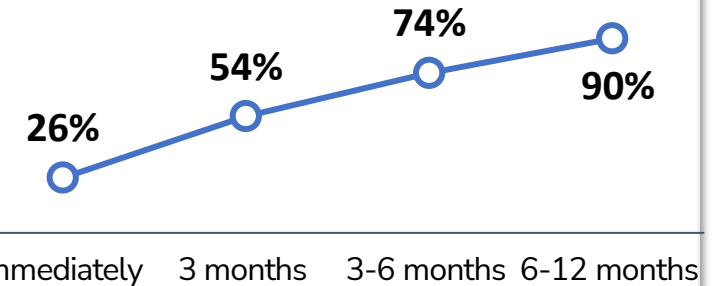
Antifibrotics have failed to show a benefit on cough reduction<sup>5,6</sup>

## Expected Commercial Model

88 ILD Care Centers in the US<sup>7</sup>  
Covered by <35 Reps

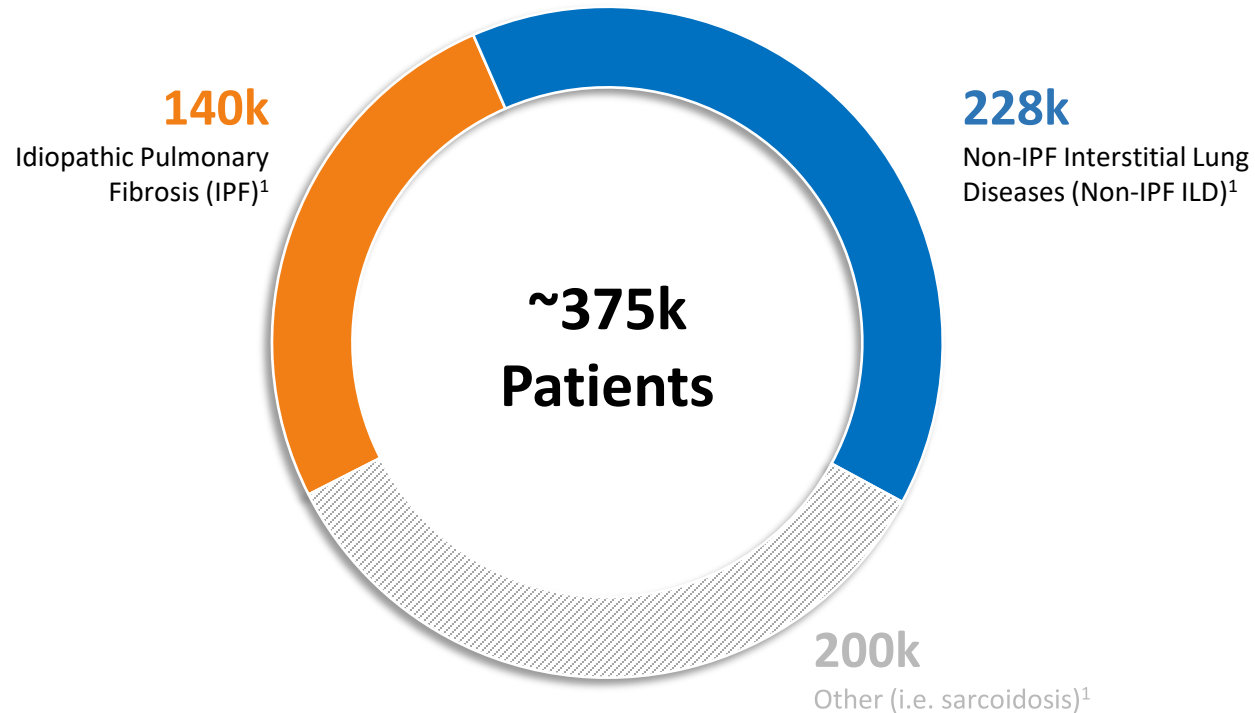


## Rapid Potential Prescribing Uptake<sup>4</sup>



# Haduvio has an Expansion Opportunity in Non-IPF ILD Patients with Chronic Cough

## Estimated Current US ILD Prevalence



## Non-IPF ILD Patients with Chronic Cough Are Similar to IPF Patients with Chronic Cough<sup>2,3</sup>

- Underlying lung fibrosis
- 50-60% have uncontrolled chronic cough
- No approved therapies for chronic cough
- High negative impact on QoL

## Next Steps

- Finalize protocol
- Plan to initiate trial by end of 2025
- Data expected in 2H 2026

ILDs encompass over 200 indications with common pathophysiology and fibrosis

# Near-Term Opportunity

## Chronic cough has a high unmet need and disease burden across IPF, non-IPF ILD, and RCC

- No FDA-approved therapies

## Parallel-arm CORAL Ph2b supports previous efficacy results from CANAL Ph2a cross-over trial in IPF chronic cough

- Large effect, broad response, and rapid onset observed
- First investigational therapy to have demonstrated a reduction in chronic cough in patients across IPF chronic cough and RCC
- Unique central and peripheral KAMA mechanism

## Expected upcoming milestones

- 2H 2025: Request End-of-Phase 2 meeting to align on Phase 3 program in IPF chronic cough
- 2H 2025: Initiate trial in patients with non-IPF ILD chronic cough
- 1H 2026: Initiate IPF chronic cough Phase 3 program
- 1H 2026: Initiate Ph2b RCC trial
- 2H 2026: Top-line data from non-IPF ILD chronic cough trial expected



**Jennifer Good**

President & Chief Executive Officer  
(Co-founder)



**James Cassella, Ph.D.**

Chief Development Officer



**Farrell Simon, Pharm.D.**

Chief Commercial Officer



**Philip Molyneaux, MBBS BSc. FRCP FICM PhD**

Phil is a professor of Interstitial Lung disease at Imperial College London. He is the Asthma and Lung UK Chair of Respiratory Research. He is a consultant in Interstitial lung disease and the director of the NIHR Cardiorespiratory Clinical research facility at the Royal Brompton Hospital. He runs an active clinical and translational research program that oversees a team of basic scientists and clinical trial research staff.