# Corporate Presentation

September 2022

trevi™ THERAPEUTICS

# Forward Looking Statement Disclaimer

Statements contained in this presentation and oral statements made regarding the subject of this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements are subject to risks and uncertainties and actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding Trevi's business plans and objectives, including future plans or expectations for Trevi's product candidates and plans with respect to future clinical trials, and other statements containing the words "believes," "anticipates," "plans," "expects," and similar expressions. Risks that contribute to the uncertain nature of the forward-looking statements include: uncertainties regarding the success, cost and timing of Trevi's product candidate development activities and ongoing and planned clinical trials; uncertainties regarding Trevi's ability to execute on its strategy; uncertainties with respect to regulatory authorities' views as to the data from Trevi's clinical trials and next steps in the development path for Trevi's product candidates in the United States and foreign countries; uncertainties inherent in estimating Trevi's cash runway, future expenses and other financial results, including Trevi's ability to fund future operations, including clinical trials; uncertainties regarding the scope, timing and severity of the COVID-19 pandemic, the impact of the COVID-19 pandemic on Trevi's clinical operations and actions taken in response to the pandemic; as well as other risks and uncertainties set forth in the quarterly report on Form 10-Q for the quarter ended June 30, 2022 filed with the Securities and Exchange Commission and in subsequent filings with the Securities and Exchange Commission. All forward-looking statements contained in this press release speak only as of the date on which they were made. Trevi undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. We believe that these third-party sources and estimates are reliable but have not independently verified them. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of important factors that could cause results to differ materially from those expressed in the estimates made by third parties and by us.

# Trevi Therapeutics: Two Successful Trials Validating the Mechanism in These Hard to Treat Conditions

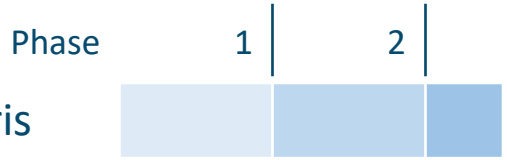
CANAL

## Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)

- 75.1% reduction in daytime cough frequency from study baseline, 52.5% placebo-adjusted change ($p<0.0001$)
- 24-hour cough frequency reduction and patient reported outcomes were consistent with the reduction in daytime cough frequency

PRISM
Pruritus Relief through Itch-Scratch Modulation

## Prurigo Nodularis (PN)



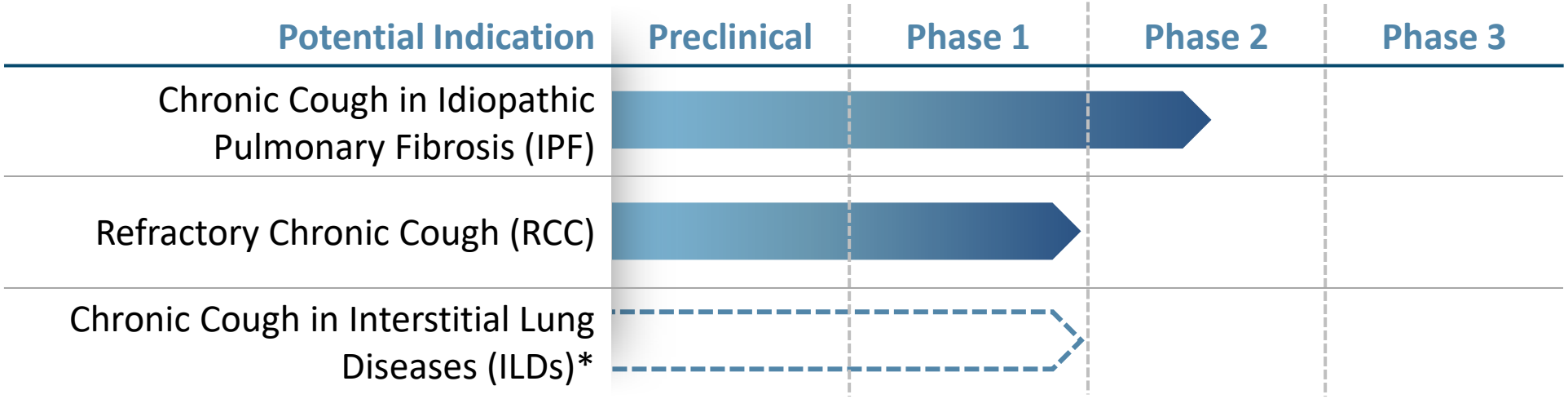

- Trial achieved statistical significance on the primary and all key secondary endpoints
- Statistically significant for the primary efficacy endpoint measured by a 4-point reduction in the Worst Itch Numerical Rating Scale (WI-NRS) ($p=0.0157$)

# Trevi's Go Forward Development Strategy

**Goal:** Leverage Haduvio's novel MOA and oral advantage in a focused way to maximize value in chronic cough

**Chronic Cough Strategy:** Prioritize IPF chronic cough while maintaining optionality with additional chronic cough indications

**Haduvio (nalbuphine ER)**

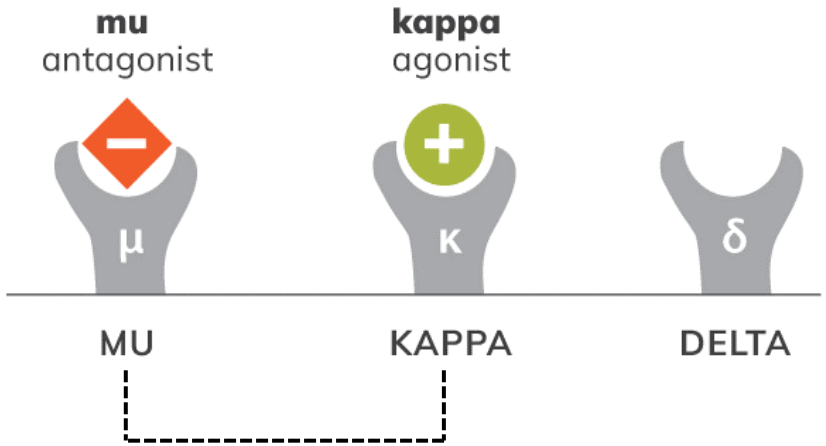



Development plans subject to discussions with regulatory authorities and sufficient funding
*Contingent on the results of the Phase 2b trial of nalbuphine ER in the treatment of chronic cough in IPF
Haduvio (nalbuphine ER) is an investigational drug

# Broad Applications for Centrally and Peripherally Active Mechanism of Action of Haduvio™ (nalbuphine ER)

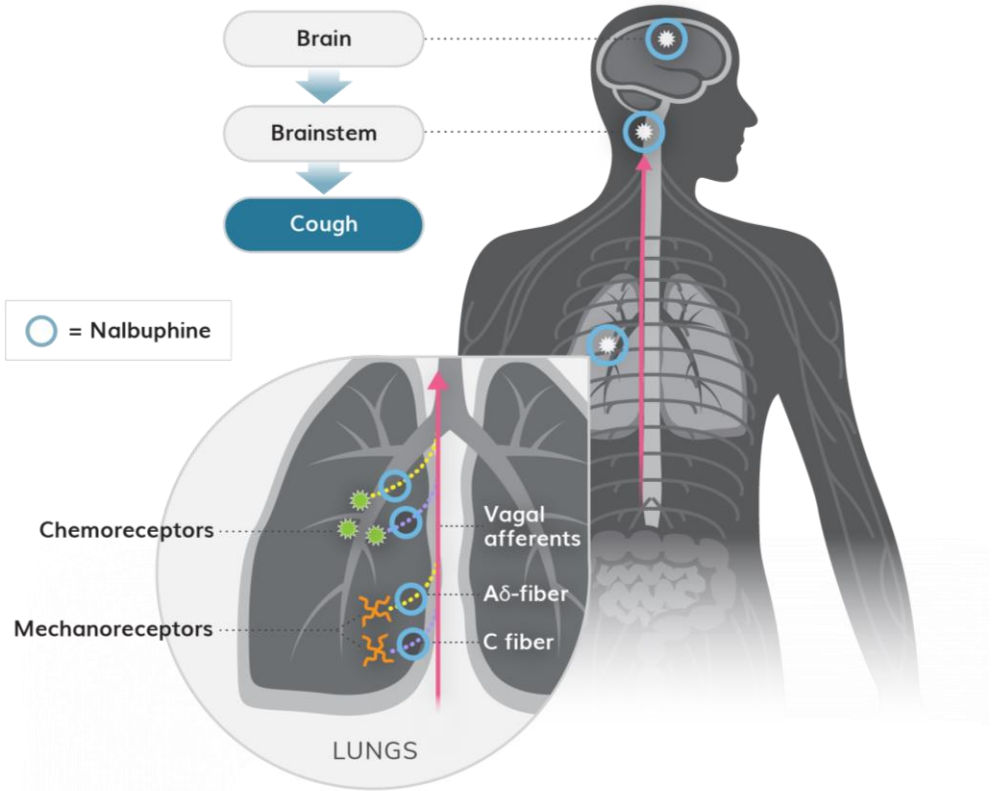
Haduvio has a novel mechanism of action acting through the mu and kappa receptors, both peripherally and centrally in the body

## Mechanism of Action: mu antagonist + kappa agonist




Dynamic interchange between the two receptors

Cough is proposed to be mediated by pulmonary C-fibers or by irritant receptors, as well as sensitization in either or both the central and peripheral nervous systems[1,2]




[1]Woolf CJ Pain 2011 DOI: 10.1016/j.pain.2010.09.030 [2]Latremoliere A Woolf CJ J Pain 2009 doi: 10.1016/j.jpain.2009.06.012
[3]Vigeland CL et al. Respir Med 2017 DOI: 10.1016/j.rmed.2016.12.016
Haduvio (nalbuphine ER) is an investigational drug

# Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)

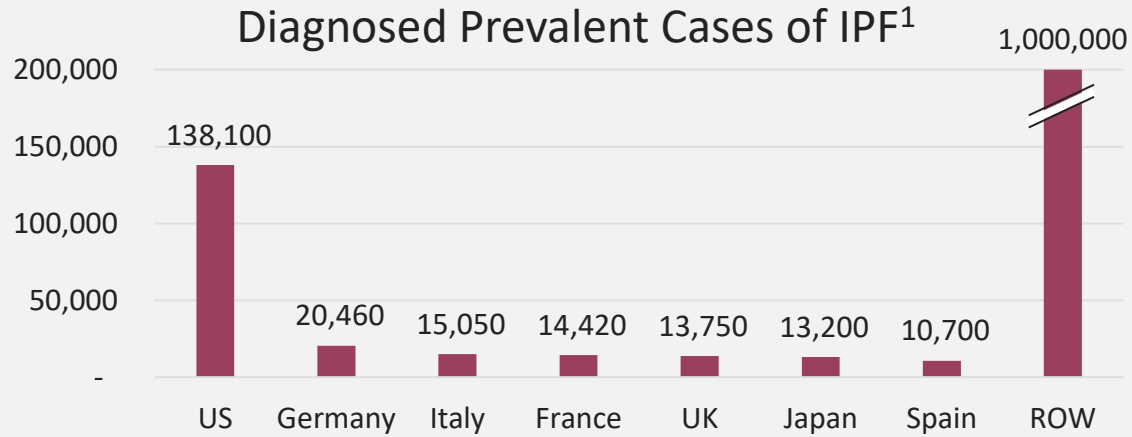
# Haduvio is the First and Only Oral Therapy to Achieve Primary Endpoint in Treating Chronic Cough in IPF

## A highly statistically significant reduction was observed with Haduvio for the treatment of chronic cough in IPF

- ✓ Primary endpoint: 52.5% placebo-adjusted reduction in the geometric mean percent change ($p<0.0001$)
  - 75.1% reduction in daytime cough frequency from study baseline for oral Haduvio in daytime cough frequency to day 22 of treatment
- ✓ Reduction in 24-hour cough frequency was consistent with the reduction in daytime cough frequency
- ✓ Key secondary endpoints on patient and clinician reported outcomes were also statistically significant
- ✓ Safety profile remains consistent with prior Haduvio studies in other patient populations with no new safety signal

# Prevalence and The Significant Role of Chronic Cough in IPF

## Epidemiology




**30,000-40,000**

Incident cases of IPF in the US every year[2]

**226-520**

Median coughs per day of an IPF patient. [3,4]

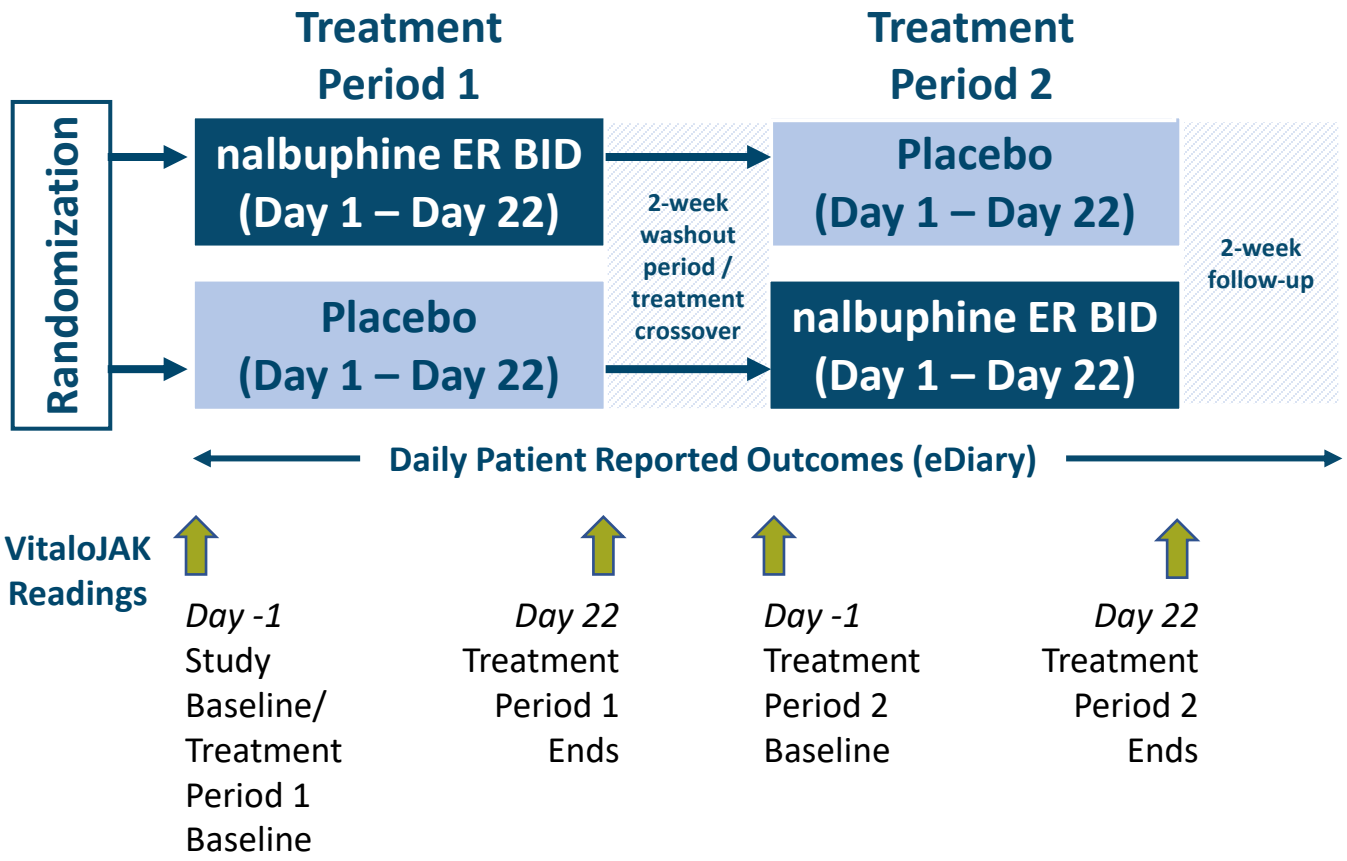
The urge to cough cannot be relieved by coughing.[5]

- **IPF is a high burden disease** that has a high impact on QoL, e.g.:[3-7]
  - Coughing can increase feelings of anxiety as it induces breathlessness
  - Coughing spells or episodes lead to significant fatigue, air hunger, peripheral oxygen desaturation
  - The social impact and isolation of chronic cough in IPF further compounds limited exercise ability, reduced walking distance and the need to use supplemental oxygen
- Chronic cough may also **contribute to enhanced activation of profibrotic** mechanisms and **disease worsening in IPF** [8]
- Cough may be an **early clinical marker of disease activity**, may identify patients at high risk of progression, and may predict time to lung transplantation or death [9]

[1]Datamonitor 2015 Idiopathic Pulmonary Fibrosis Disease Coverage Ref Code: DMKC12770 [2]Nalysnyk L et al. Eur Resp Rev 2012 DOI: 10.1183/09059180.00002512 [3]Key AL et al. Cough 2010 DOI: 10.1186/1745-9974-6-4 [4]VanManen M et al. Am J Respir Crit Care Med 2015; 191: A4422 [5]Swigris JJ et al. Health Qual Life Outcomes 2005 DOI: 10.1186/1477-7525-3-61 [6]vanManen M et al. *Ther Adv Respir Dis* 2017 doi: 10.1177/1753465816686743 [7]Wakwaya Y et al. *Chest* 2021 DOI: 10.1016/j.chest.2021.05.071 [8]VanManen M et al. ERS 2016 DOI: 10.1183/16000617.0090-2015 [9]Ryerson CJ et al. *Resp* 2011 DOI: 10.1111/j.1440-1843.2011.01996.x

Haduvio (nalbuphine ER) is an investigational drug

# CANAL Phase 2 Trial Design
# Randomized, Double-Blind, Placebo-Controlled, Two Treatment Period Crossover




## NALBUPHINE ER

Oral tablet dosed BID

Titrated to 162mg over the active treatment period

The VitaloJAK® Cough Monitor provides a fully validated system for objective measurement of cough.

Validated, 510k cleared and CE marked medical device system.

www.clinicaltrials.gov: NCT04030026
Haduvio (nalbuphine ER) is an investigational drug
VitaloJAK is a registered trademark of Vitalograph

# Primary and Secondary Endpoints

## Primary Endpoint

- Mean change in daytime cough frequency (coughs per hour) from baseline as assessed by objective digital cough monitoring at Day 22 by treatment.

## Secondary Endpoints

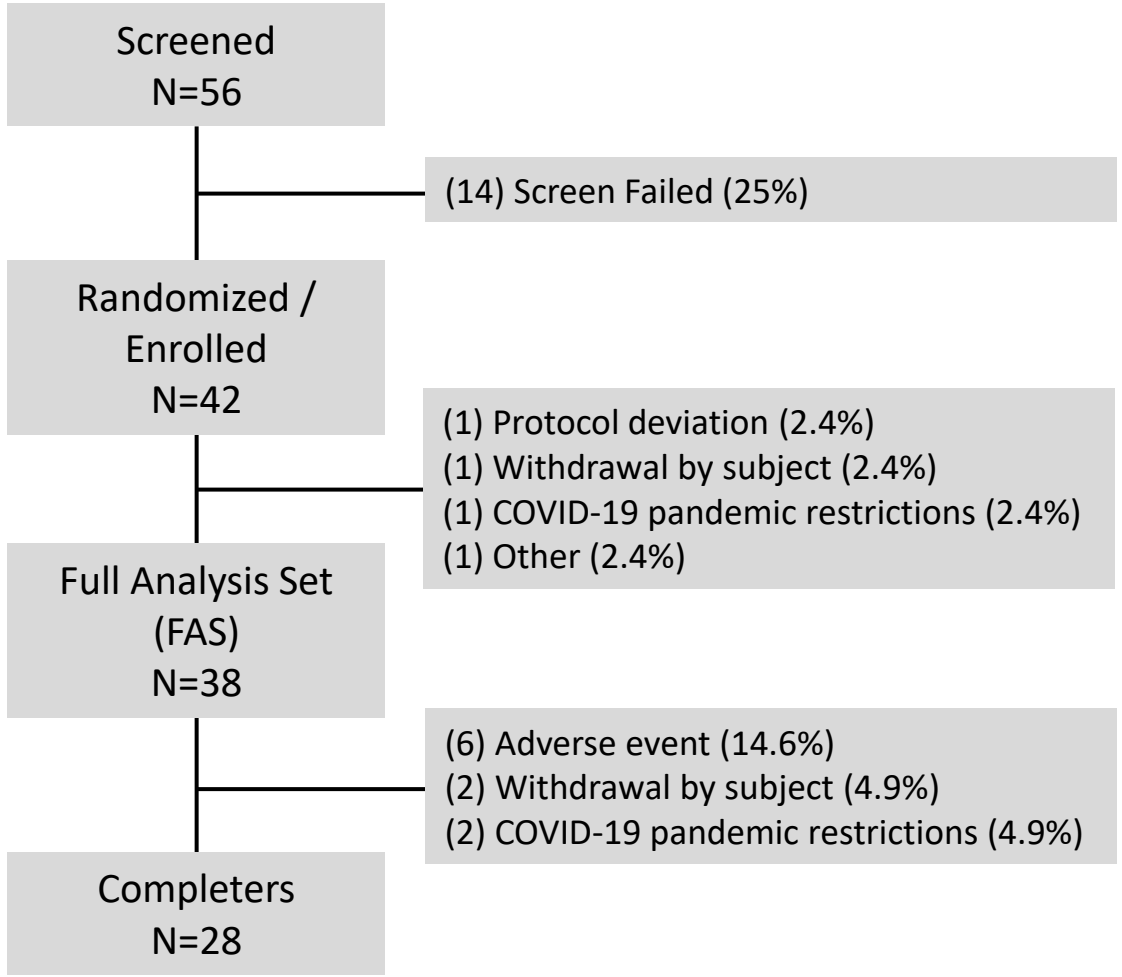
- Relative change in daytime cough frequency (coughs per hour) from baseline at Day 22 by treatment.
- Relative change in 24-hour (combined daytime and nighttime) cough frequency (coughs per hour) from baseline at Day 22 by treatment.
- Relative change in nighttime cough frequency (coughs per hour) from baseline at Day 22 by treatment.
- Mean change in the Evaluating Respiratory Symptoms (E-RS®) diary cough subscale (E-RS diary question number 2) from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the Cough Severity Numerical Rating Scale at Days 8, 15, and 21 by treatment.
- Mean change in the E-RS diary breathlessness subscale (E-RS diary questions 7, 8, 9, 10, and 11) from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the Clinical Global Impression – Change (CGI-C) over time measured at Day 21 by treatment.



Haduvio (nalbuphine ER) is an investigational drug
E-RS are registered trademarks of Evidera

# Baseline Characteristics and Patient Disposition

| | Full Analysis Set (Subjects Completing ≥1 Treatment Period) |
|---|---|
| Number of subjects, n | 38 |
| Age (years), mean | 74 |
| Male, n (%) | 32 (84.2%) |
| Anti-fibrotic (%) | 21 (51.2%) |
| Proton Pump Inhibitors | 28 (68.3%) |
| Daytime cough frequency (coughs/hr):<br>Mean<br>Min-Max | <br>28<br>3.18 - 92.35 |
| 24Hr cough frequency (coughs/hr):<br>Mean<br>Min-Max | <br>21<br>3.13 - 66.42 |

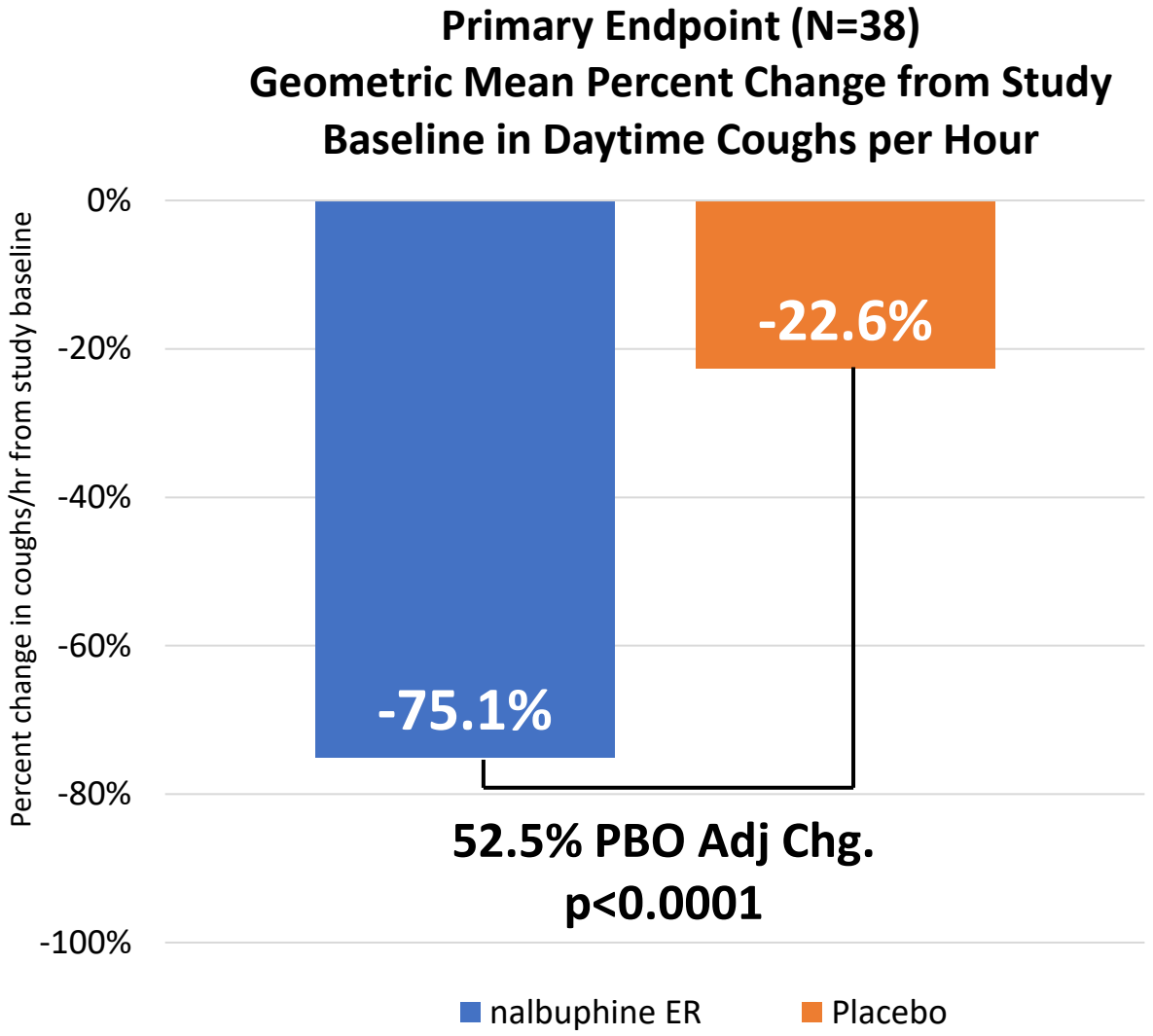



Full analysis set (FAS): all randomized subjects who have taken at least one dose of study medication and provided baseline and at least one post-baseline primary efficacy variable assessment during the treatment period.
Completers analysis set: all subjects who received both study treatments and completed both treatment periods in the study.
Haduvio (nalbuphine ER) is an investigational drug

# Primary Endpoint Achieved Statistically Significant Reduction in Daytime Cough Frequency with Haduvio

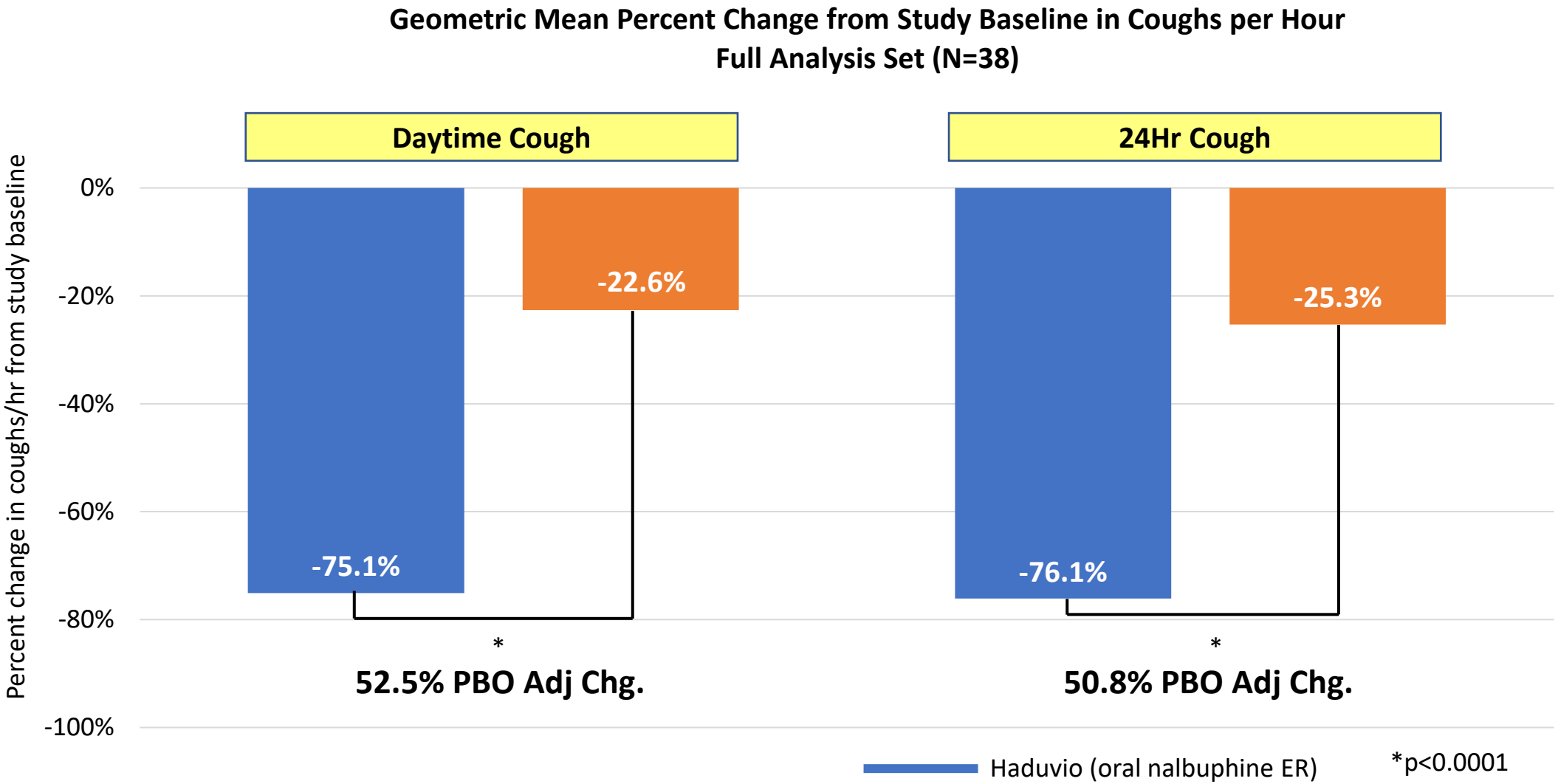
**75.1% Reduction**
in daytime cough frequency at Day 22 with Haduvio

**52.5% change compared to placebo**
in daytime cough frequency at Day 22 with Haduvio




Primary Endpoint calculated as geometric mean percent change in daytime cough frequency from study baseline
No sequence or period effect
Haduvio (nalbuphine ER) is an investigational drug

# Reduction of Cough Frequency And Placebo-Adjusted Change Were Consistent Between Daytime and 24Hr Cough Frequency




Endpoint calculated as geometric mean percent change in daytime and 24Hr cough frequency from study baseline
No sequence or period effect
Haduvio (nalbuphine ER) is an investigational drug

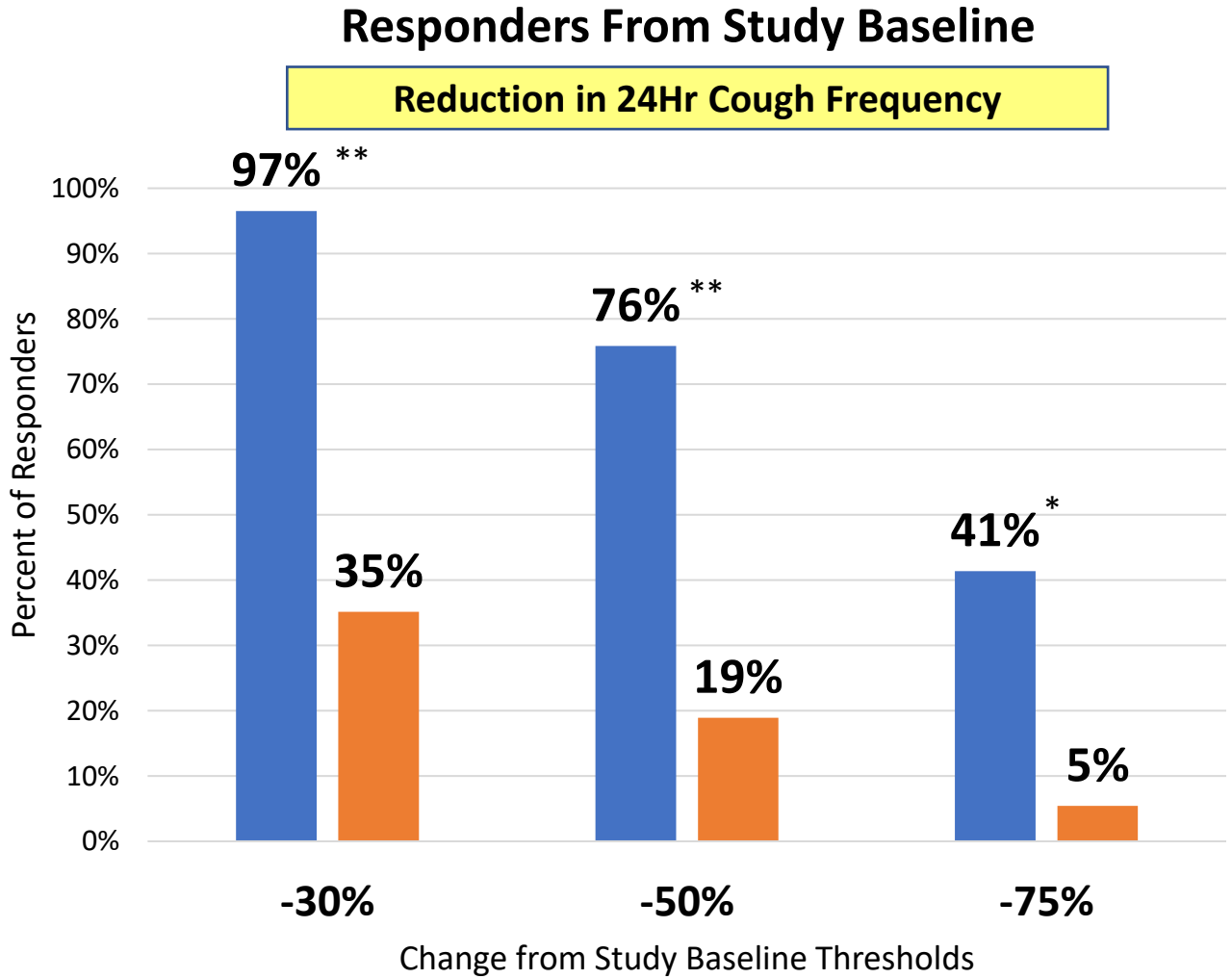
# Post-Hoc Responder Analyses
# Clear Separation Between Haduvio vs. Placebo at All Thresholds

## 97% of Haduvio subjects

**saw a clinically meaningful reduction in 24Hr cough frequency**

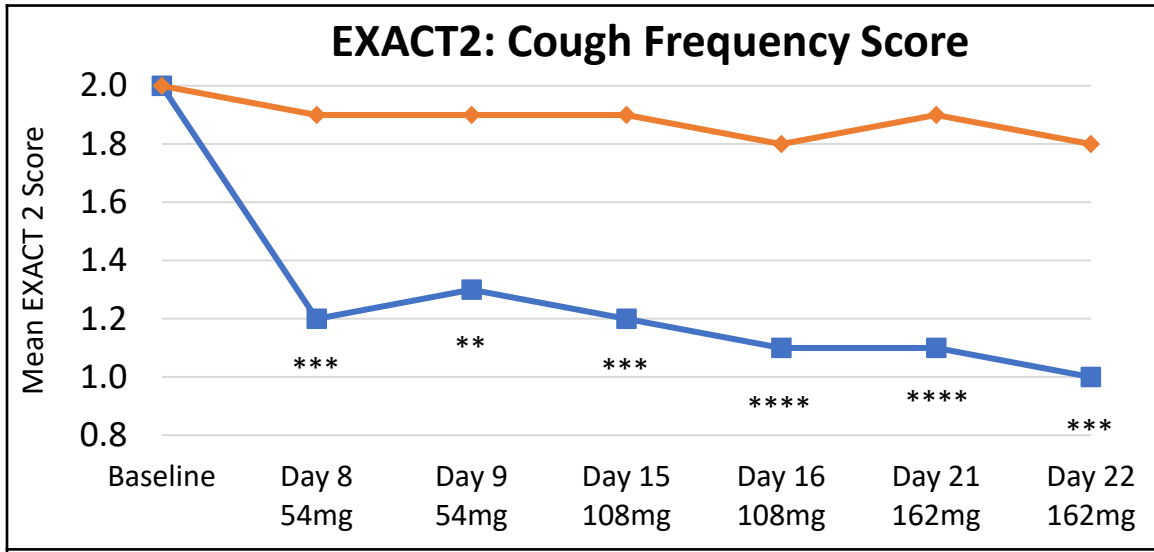
**(Subjects experiencing a 20-30% reduction in their cough frequency is considered clinically meaningful)**[1]

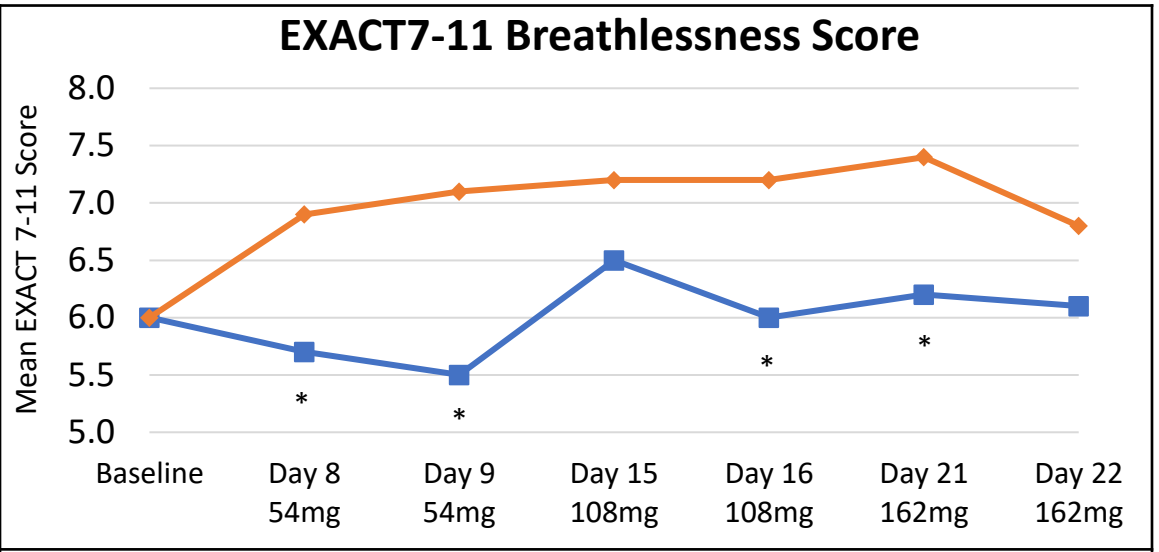
## 76% of Haduvio subjects reduced their cough frequency in half

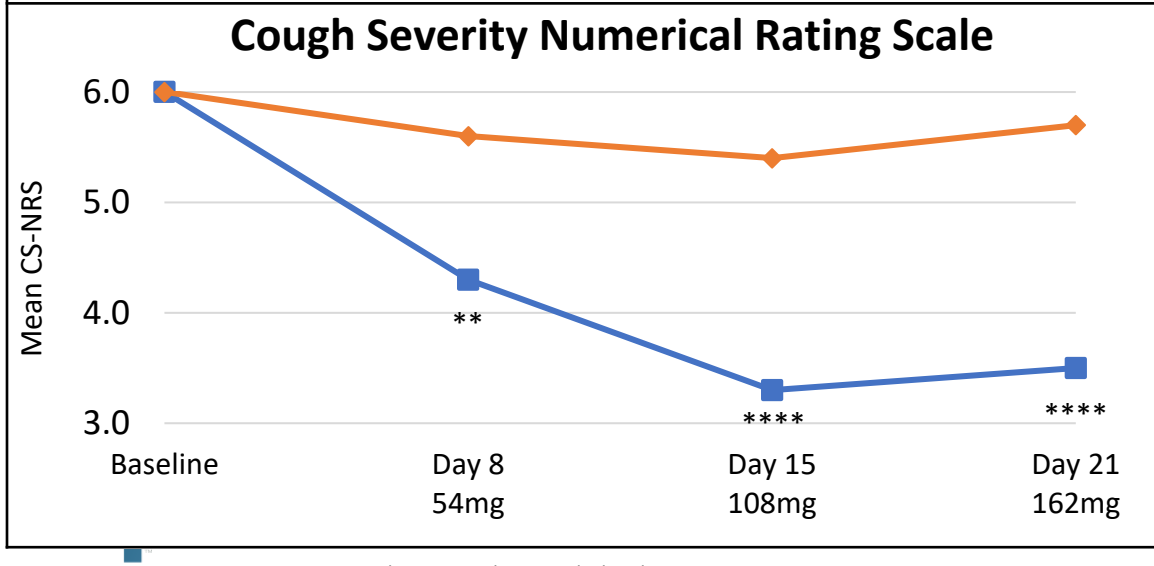


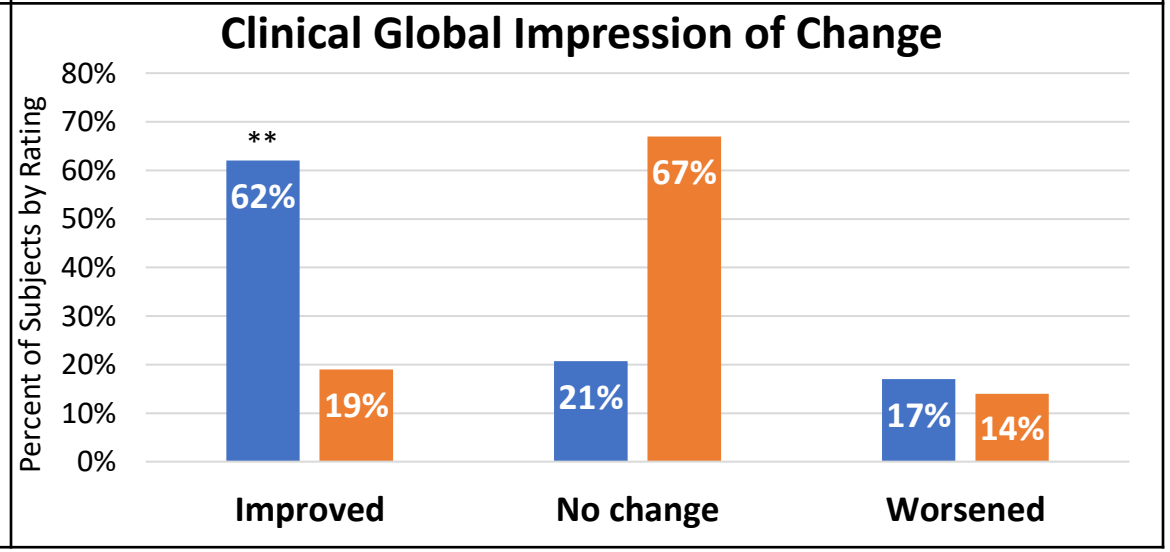

[1]Nguyen AM et al. J Allergy and Clin Immunol 2019 doi.org/10.1016/j.jaci.2018.12.519
Endpoint calculated as geometric mean percent change in 24Hr cough frequency from study baseline
Haduvio (nalbuphine ER) is an investigational drug

# Patient and Clinician Reported Outcomes Support the Results Seen in the Objective Cough Monitor on the Full Dataset (N=38)



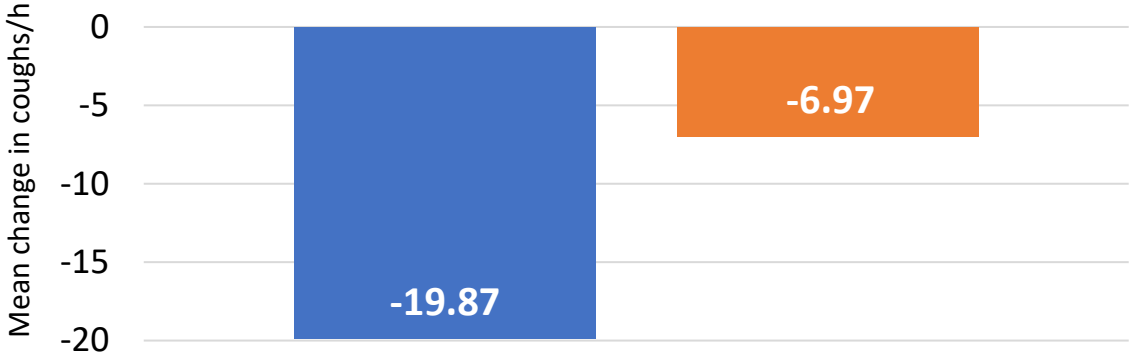

EXACT2, EXACT7-11, and CS-NRS endpoints calculated as geometric mean percent change from baseline. CGI-C calculated as percent of subjects seeing improvement/decline vs. study baseline
Haduvio (nalbuphine ER) is an investigational drug

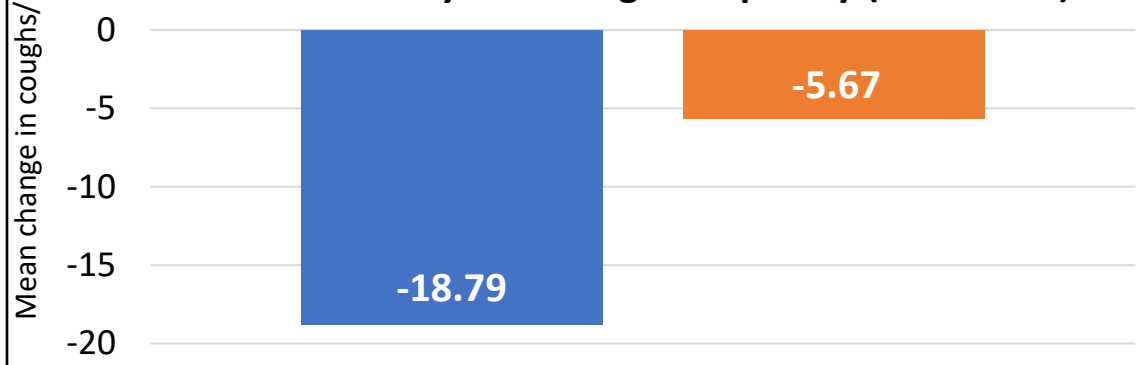
Haduvio (oral nalbuphine ER)
Placebo

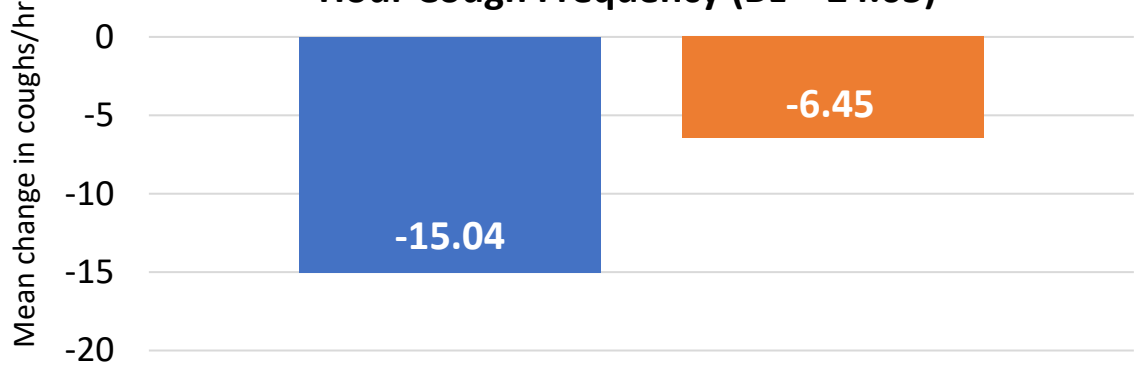
*p≤0.05 **p≤0.01 ***p≤0.001 ****p≤0.0001

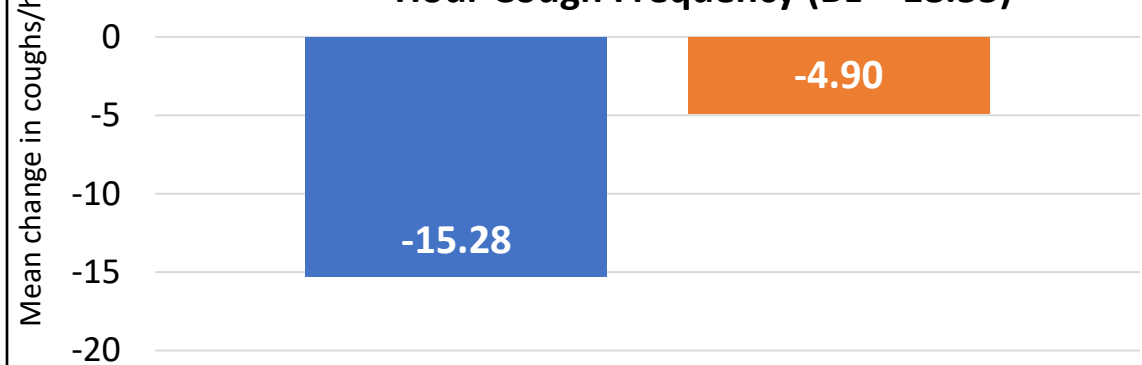
# Magnitude of Haduvio Effect Remained Consistent Independent of Background Anti-Fibrotic Therapy

| | On Anti-Fibrotic Therapy (N=18) | Not on Anti-Fibrotic Therapy (N=20) |
|---|---|---|
| Daytime Cough | Geometric Mean Change from Study Baseline in Daytime Cough Frequency (BL = 32.22) | Geometric Mean Change from Study Baseline in Daytime Cough Frequency (BL = 24.18) |
| 24Hr Cough | Geometric Mean Change from Study Baseline in 24-Hour Cough Frequency (BL = 24.05) | Geometric Mean Change from Study Baseline in 24-Hour Cough Frequency (BL = 18.55) |




Endpoint calculated as geometric mean change in daytime and 24Hr cough frequency from study baseline
Haduvio (nalbuphine ER) is an investigational drug

Haduvio (oral nalbuphine ER)
Placebo

# Summary of Treatment-Emergent Adverse Events
# Safety Population

| Treatment-Emergent Adverse Events at ≥10% Frequency | Haduvio BID N=38 n (%) | Placebo N=40 n (%) | Total N=41 n (%) |
|---|---|---|---|
| Nausea | 16 (42) | 0 (0) | 16 (39) |
| Fatigue | 12 (32) | 3 (8) | 15 (37) |
| Constipation | 11 (29) | 2 (5) | 13 (32) |
| Dizziness | 10 (26) | 0 (0) | 10 (24) |
| Somnolence | 9 (24) | 1 (3) | 9 (22) |
| Vomiting | 7 (18) | 5 (13) | 10 (24) |
| Headache | 5 (13) | 5 (13) | 10 (24) |
| Anxiety | 5 (13) | 0 (0) | 5 (12) |
| Depression | 4 (11) | 0 (0) | 4 (10) |

# Summary of Treatment-Emergent Adverse Events by CTCAE Grade Safety Population[1]

| | Haduvio BID N=38 n (%) | | | Placebo N=40 n (%) | | | Total N=41 n (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| GRADE | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Nausea | 9 (24) | 7 (18) | - | - | - | - | 9 (22) | 7 (17) | - |
| Fatigue | 8 (21) | 3 (8) | 1 (3) | 1 (3) | 1 (3) | 1 (3) | 9 (22) | 4 (10) | 2 (5) |
| Constipation | 8 (21) | 3 (8) | - | 1 (3) | 1 (3) | - | 9 (22) | 4 (10) | - |
| Dizziness | 7 (18) | 3 (8) | - | - | - | - | 7 (17) | 3 (7) | - |
| Somnolence | 7 (18) | 2 (5) | - | 1 (3) | - | - | 7 (17) | 2 (5) | - |
| Vomiting | 4 (11) | 3 (8) | - | 5 (13) | - | - | 7 (17) | 3 (7) | - |
| Headache | 2 (5) | 3 (8) | - | 5 (13) | - | - | 7 (17) | 3 (7) | - |
| Anxiety | 2 (5) | 1 (3) | 2 (5) | - | - | - | 2 (5) | 1 (2) | 2 (5) |
| Depression | 3 (8) | - | 1 (3) | - | - | - | 3 (8) | - | 1 (2) |

[1] One subject may have multiple Adverse Events
Summary of Treatment-Emergent Adverse Events by CTCAE Grade - Safety Population
Haduvio (nalbuphine ER) is an investigational drug

# Chronic Cough in IPF – Anticipated Next Steps

## Phase 2b Clinical Trial Design*

- The trial is expected to be a dose-ranging, parallel arm design trial with four arms (three active dose arms and a placebo arm)
- The trial is expected to assess Haduvio treatment over a period to be determined of between three and six months
- The objectives of the trial will be to select the dose for further development, assess reduction of cough and impact on quality of life, assess safety and validate the use of the VitaloJAK (objective cough monitor) and a patient reported outcome measure
- Primary efficacy endpoint of a decrease in 24Hr cough frequency assessed using VitaloJAK

## Next Steps

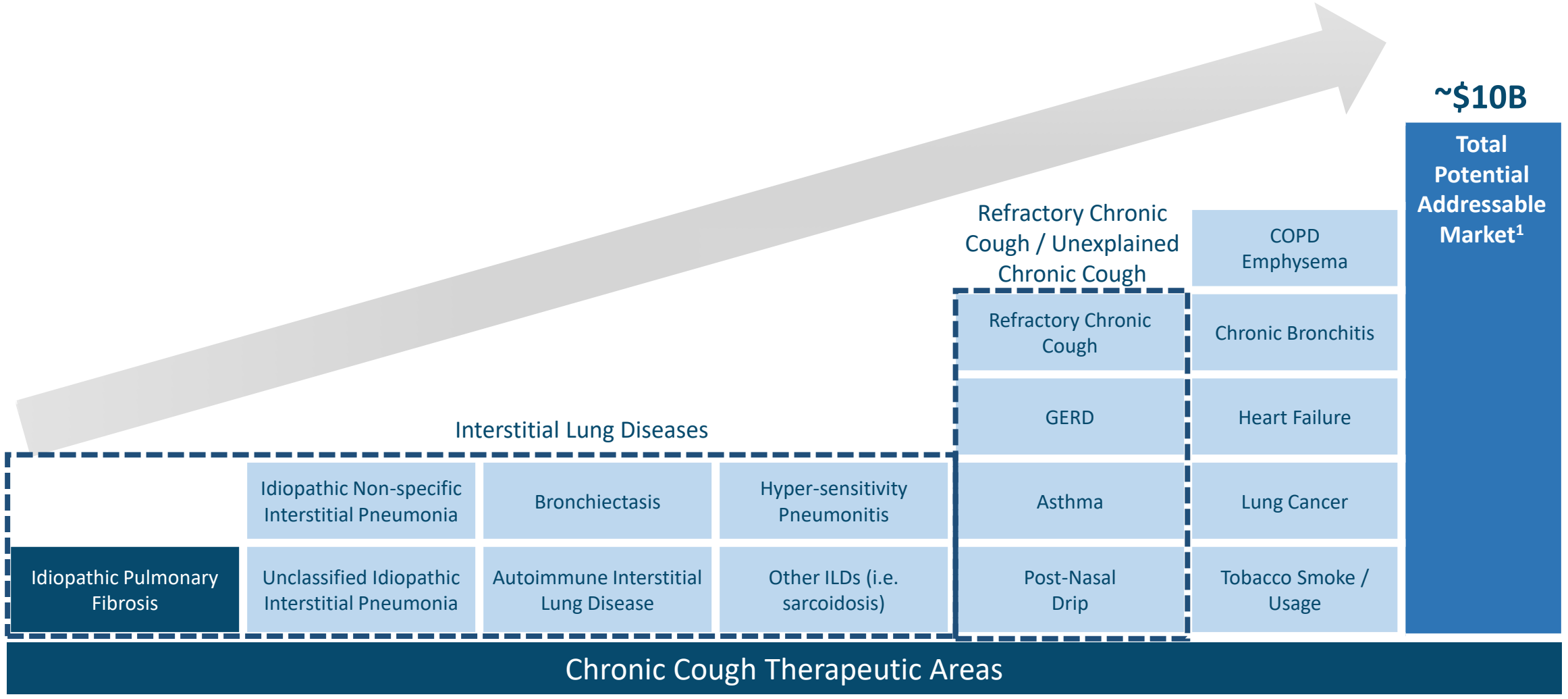
- Align with the FDA on protocol for the next clinical trial and submit IND
- Initiate Phase 2b clinical trial in 1H 2023

*Trial design is subject to ongoing discussions with the FDA and sufficient funding

Haduvio (nalbuphine ER) is an investigational drug

# Unmet Need Across Chronic Cough Indications

# Opportunities in Chronic Cough




[1]2027 est. The Insight Partners Jun 2020

# Chronic Cough Indications of Interest

| Country | Idiopathic Pulmonary Fibrosis - chronic cough | Interstitial Lung Disease (chronic cough) | RCC |
|---|---|---|---|
| US | 138,100[1] | ~93,000[2] | ~16,620,000[3] |
| DE | 1,800 to 18,900[4] | 4,500 to 11,400[4] | ~ 4 million (est. 5% of the population)[5] |
| FR | 4,960[6] | 5,700 to 12,309[6] | ~3.3 million (est. 5% of the population)[3] |
| UK | 5,000[7] | 2,000 to 4,000[7] | 119,584 to 797,226 chronic cough- refractory not known[8] |

| | IPF-chronic cough | ILD (chronic cough) | RCC |
|---|---|---|---|
| Duration[9] | ~3-5 years | ~3-5 years | Lifelong |

[1]Datamonitor 2015 Idiopathic Pulmonary Fibrosis Disease Coverage Ref Code: DMKC12770 [2]Estimate US prevalence of Progressive Fibrosing ILDs per 10,000 people = 2.8 per Olson, A et al. Prevalence of progressive fibrosing interstitial lung disease. European Respiratory Journal 2018 52: PA3030. [3]Weighted 5% prevalence of 2022 US population, 332,403,650 per Prevalence and Burden of Chronic Cough in the United States – ScienceDirect [4]DE GBA assessment of nintedanib https://www.g-ba.de/ [5]Virchow JC et al. ERJ Open Res 2022 doi: 10.1183/23120541.00420-2021 [6]FR HAS assessment of nintedanib https://www.has-sante.fr/ [7]UK NICE assessment of nintedanib https://www.nice.org.uk/ [8]Gefapixant horizon scan [9]Interviews and quantitative study, 2022 with US pulmonologists, ILD specialists, and general practitioners (n = 105)
Haduvio (oral nalbuphine ER) is an investigational drug

# Current Financial Position

- **Cash Position**
  - ~$79M in cash and investment position as of June 30, 2022
  - $55M raised in public offering announced on 9/23/22
  - Cash runway into 2026

- **Term loan with SVB - $11.7M outstanding as of 6/30/22**