trevi® THERAPEUTICS

Controlling cough where it counts™

Refractory Chronic Cough Improvement Via NAL ER (RIVER) Topline Results

March 10, 2025

Nasdaq: TRVI

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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.

Refractory Chronic Cough Improvement Via Nalbuphine ER (RIVER)
Topline Results Agenda

Introduction	**Jennifer Good**, President and CEO, *Trevi Therapeutics*
Study Design & Topline Results	**James Cassella, Ph.D.**, Chief Development Officer, *Trevi Therapeutics*
Concluding Remarks	**Jennifer Good**, President and CEO, *Trevi Therapeutics*
Q&A	**Jennifer Good**, President and CEO, *Trevi Therapeutics* **James Cassella, Ph.D.**, Chief Development Officer, *Trevi Therapeutics* **Farrell Simon, Pharm.D.**, Chief Commercial Officer, *Trevi Therapeutics* **Professor Jacky Smith, MB, ChB, FRCP, PhD,** Professor of Respiratory Medicine at the University of Manchester

Haduvio (oral nalbuphine ER) Achieved Positive Results in Refractory Chronic Cough (RCC) Patients

Robust Positive Haduvio RCC data supports progressing into future study

- ✓ 67.0% relative reduction in 24-hour cough frequency from baseline
  - ✓ 57.0% placebo-adjusted change in 24-hour cough frequency ($p<0.0001$)
  - ✓ Statistically significant cough reduction across a broad range of cough counts (moderate and severe)
- ✓ 84% of Haduvio treated patients achieved at least a clinically meaningful 30% reduction in their cough
- ✓ Rapid onset of effect at the lowest dose
- ✓ Patient reported outcomes and other secondary endpoints were statistically significant and consistent with primary endpoint
- ✓ Safety profile remains consistent with prior Haduvio studies in other patient populations with no treatment emergent serious adverse events
- ✓ First and only therapy to demonstrate positive results across both IPF chronic cough and RCC

Next Steps:

Discuss results and future study design with the FDA

Analysis based on Full Analysis Set (FAS): All patients who received at least one dose of study drug and have objective cough count data on both Baseline and Day 21 in at least one treatment period
Haduvio (nalbuphine ER) is an investigational drug

Refractory Chronic Cough Carries a High Burden of Disease and Impact on Patients' Lives

Average of 8 years with chronic cough prior to diagnosis

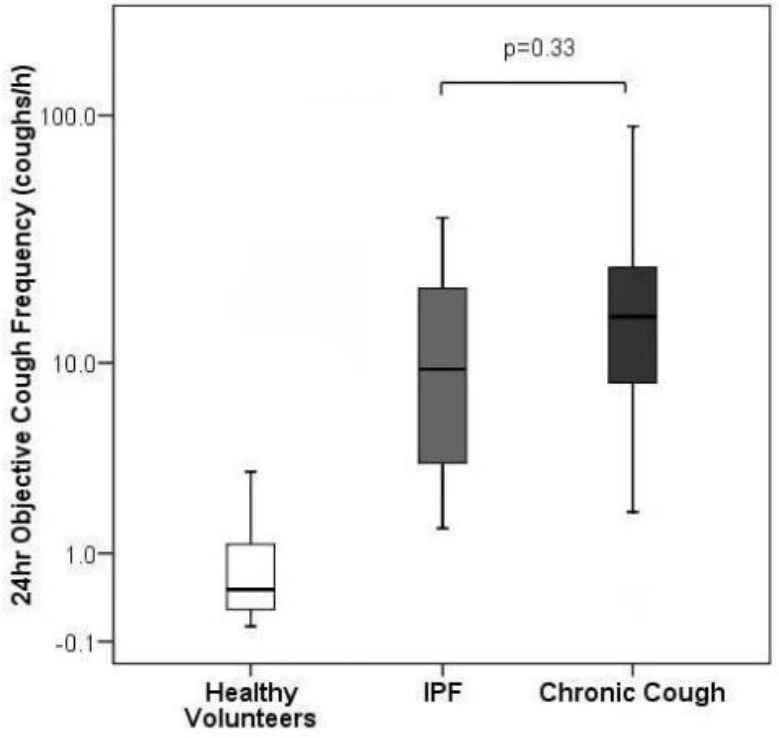
61% have anxiety and/or depression

34% reduction in work activities
30% reduction in non-work activities

Impaired physical and psychological health

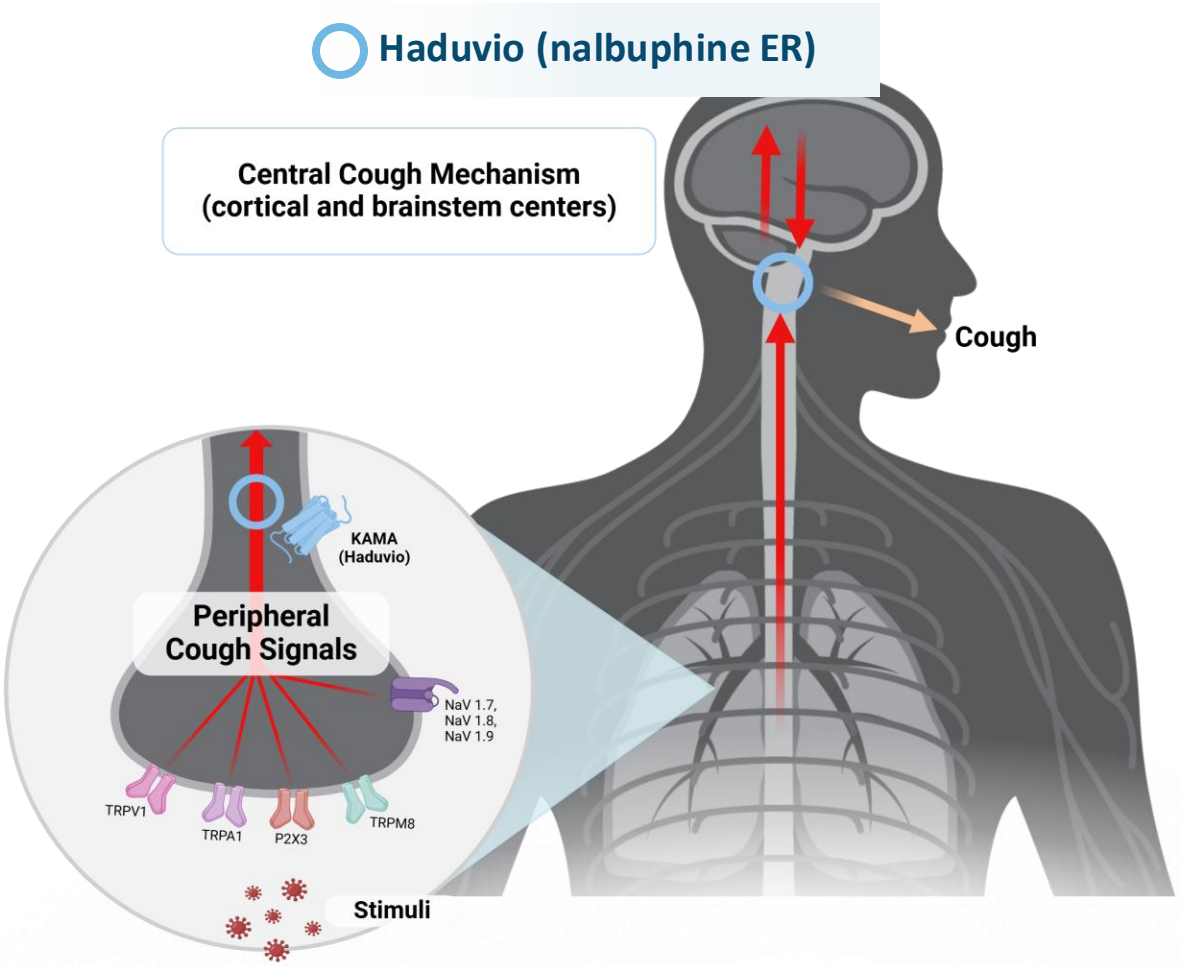
No approved therapies in the US

Similar Cough Frequency Between RCC and IPF



Sources: Smith JA et al, Respir Res 2024 doi.org/10.1186/s12931-024-02881-4, Puente-Maestu L et al, ERJ Open Res 2023 doi.org/10.1183/23120541.00425-2023, Gibson P et al, Chest 2016 doi:10.1378/chest.15-1496, Brister D et al. Lung 2024 DOI: 10.1007/s00408-024-00714-1
Visual adapted from Key AL et al. Cough 2010 doi: 10.1186/1745-9974-6-4

Haduvio's Differentiated Central and Peripheral Mechanism of Action



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), which are opioid receptors that play a key role in controlling cough hypersensitivity.

	Haduvio	Peripheral Only Therapies
Central (Brain)	✓ Can inhibit the central cough reflex **independent of peripheral stimuli**	× Do not cross the blood-brain barrier
Peripheral (Lung)	✓ Can limit transmission of cough signals to the brain caused by a **variety of receptors**	✓ Can **only work peripherally** to interrupt cough signals through **a single receptor**

[1]Chung KF et al *Nat Res* 2022 https://doi.org/10.1038/s41572-022-00370-w [2]Mann J et al. *Front Rehabil Sci.* 2021 10.3389/fresc.2021.751798 [3]Chung F et al. *Lancet* 2008 DOI: 10.1016/S0140-6736(08)60595-4
Graphic: Vigeland CL et al, *Respiratory Medicine* 2017 doi.org/10.1016/j.rmed.2016.12.016. Zhang M et al, *Purinergic Signalling* 2022 doi.org/10.1007/s11302-022-09877-z Created in https://BioRender.com
Haduvio (nalbuphine ER) is an investigational drug

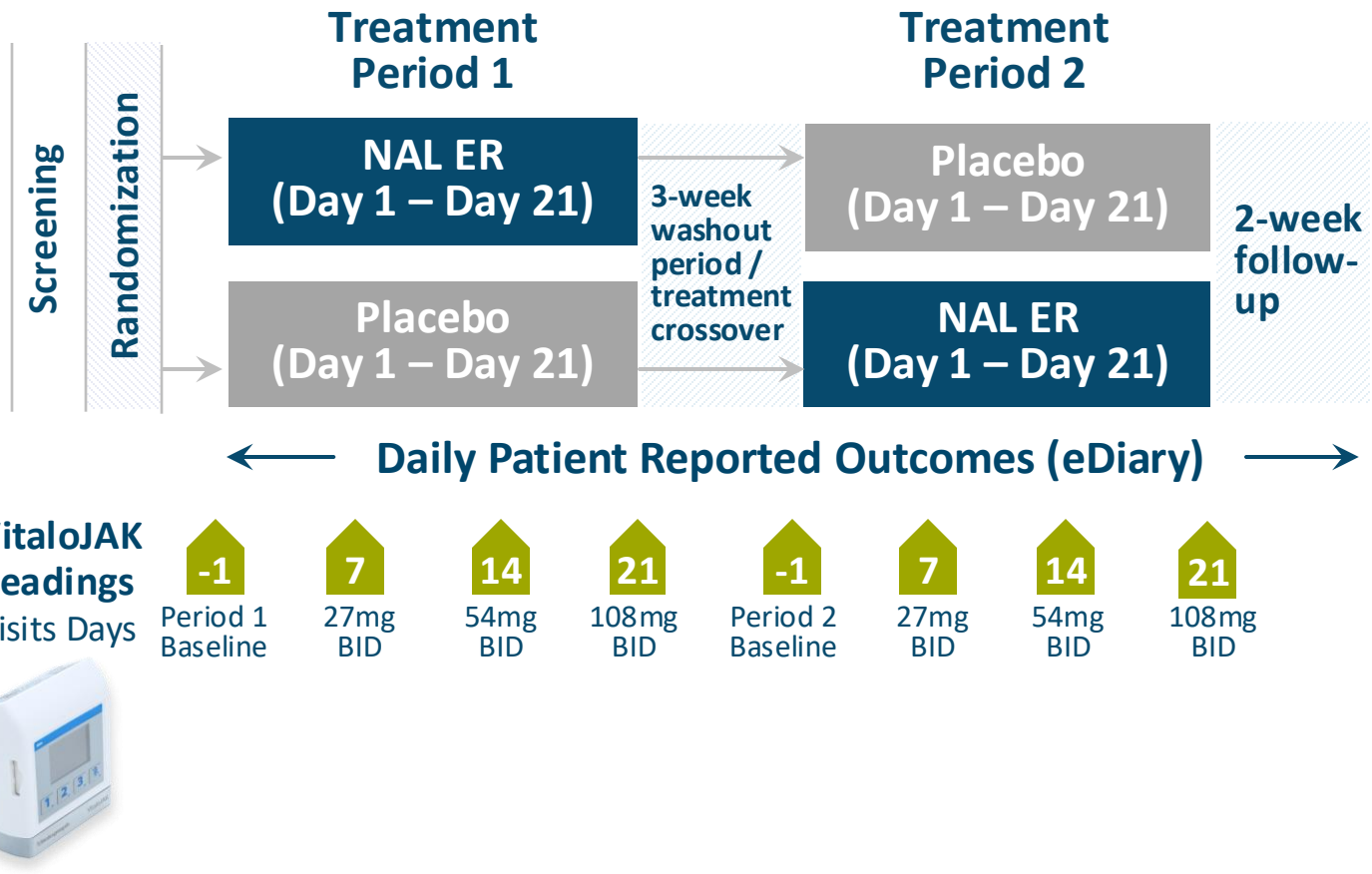
Refractory Chronic Cough **I**mprovement **V**ia Nalbuphine **ER**

Phase 2a Crossover Trial Design

- Double-blind, randomized, placebo-controlled, 2-period crossover study for the treatment of chronic cough with nalbuphine extended release (NAL ER) in subjects with Refractory Chronic Cough (RCC)
- Entry criteria based on diagnosis of RCC and chronic cough for at least one year
- Subjects randomized to subgroups based on pre-treatment cough monitor results
  - 10-19 coughs/hour
  - ≥ 20 coughs/hour
- Primary endpoint: Relative change from Baseline in cough frequency (coughs per hour) versus placebo at Day 21[1]

[1] *FAS: All patients who received at least one dose of study drug and have objective cough count data on both Baseline and Day 21 in at least one treatment period.*

Ph2a NAL ER Clinical Trial in RCC



Subgroups (24-hour cough frequency):
≥20 coughs/hour
10–19 coughs/hour

Primary Efficacy Endpoint

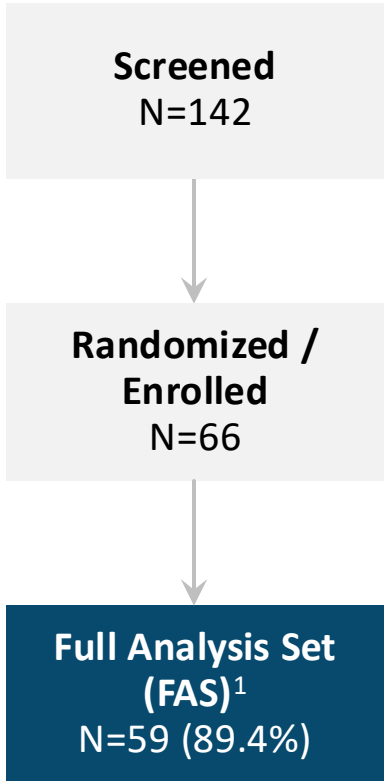
- 24-hour cough frequency using objective cough monitor

Secondary Endpoints

- Patient-Reported Cough Frequency (PR-CF)*
- CS-VAS*
- LCQ
- PGI-S & PGI-C Cough
- CGI-S, CGI-C Cough
- SOWS

*Included in topline results
BID: twice daily, CS-VAS: cough severity visual analog scale, LCQ: Leicester cough questionnaire, PGI-S: patient global impression of cough severity, PGI-C: patient global impression of change in cough, CGI-S: clinician global impression of cough severity, CGI-C: clinician global impression of change of cough
NAL ER is an investigational drug

Patient Disposition and Baseline Characteristics



	Total (N = 66)[2]
Age (years), mean (std)	60.2 (10.47)
Female, n (%)	44 (66.7%)
Male, n (%)	22 (33.3%)
Race, n (%)	
Asian	1 (1.5%)
Black or African American	4 (6.1%)
White	61 (92.4%)
Screening 24-hour cough frequency (coughs/hr):	
Mean	34.7
Min-Max	10.0 - 165.9

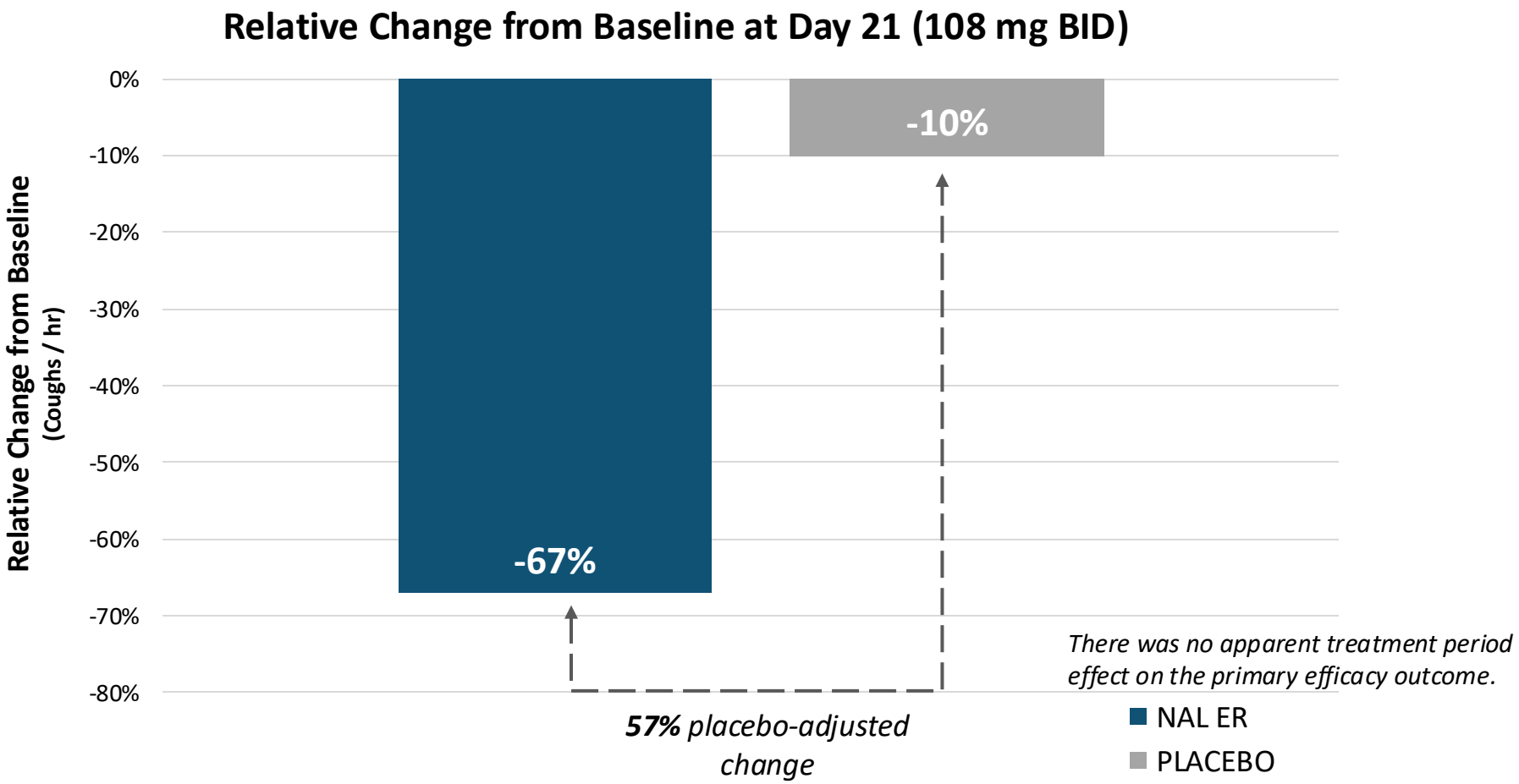
[1] ***FAS:*** *All patients who received at least one dose of study drug and have objective cough count data on both Baseline and Day 21 in at least one treatment period.*

[2] The safety population consists of all subjects who have received at least one dose of NAL ER or placebo.
NAL ER is an investigational drug

Source: 14.1.1, 14.1.3.1

Primary Endpoint – Relative Change from Baseline in 24-hr Cough Frequency

Significant difference in the relative change from Baseline at Day 21

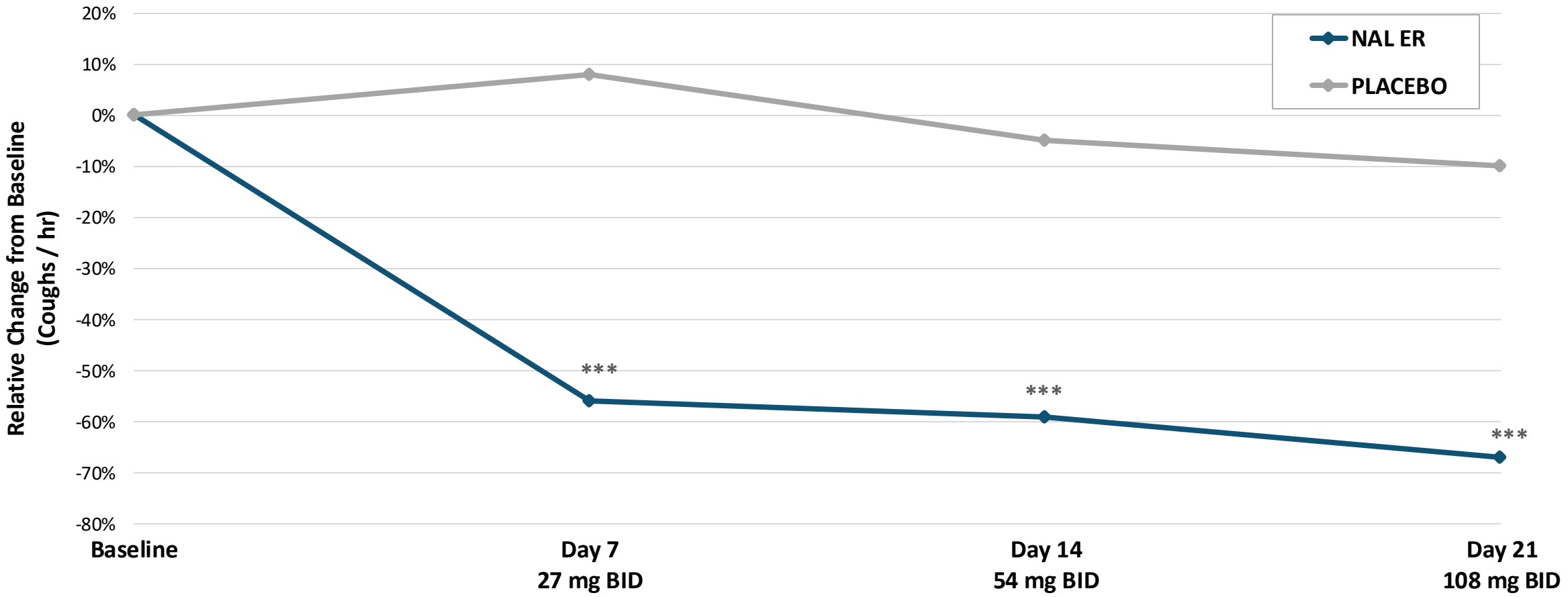


FAS Population
Primary efficacy analysis conducted on log-transformed cough frequency data
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Source: 14.2.1.1.1, 14.2.1.3.1

Relative Change from Baseline in 24-hr Cough Frequency Across Days/Dose

Significant differences starting at Day 7 with 27 mg BID



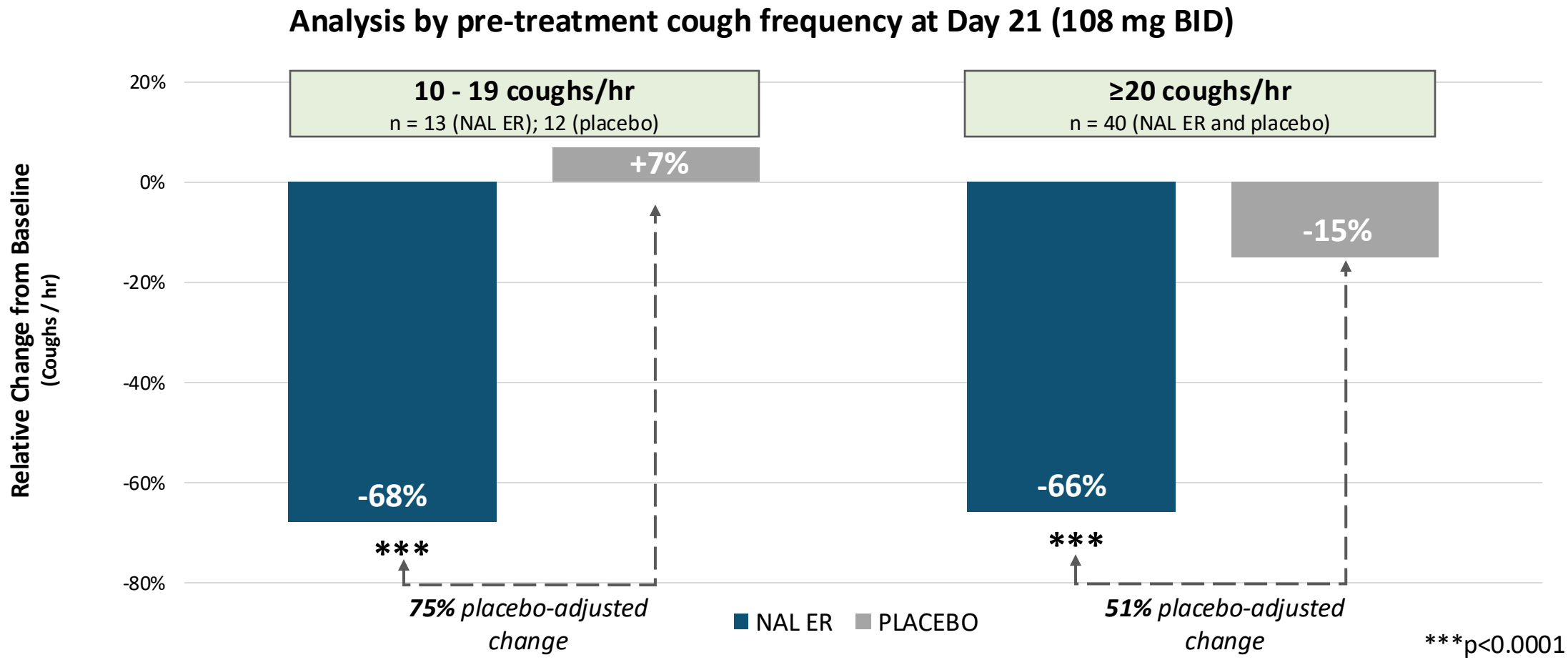
***p<0.0001

FAS Population
Primary efficacy analysis conducted on log-transformed cough frequency data
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Source: 14.2.1.1.1, 14.2.1.3.1

Relative Change from Baseline in 24-hr Cough Frequency

Consistent NAL ER effects across a broad range baseline cough counts

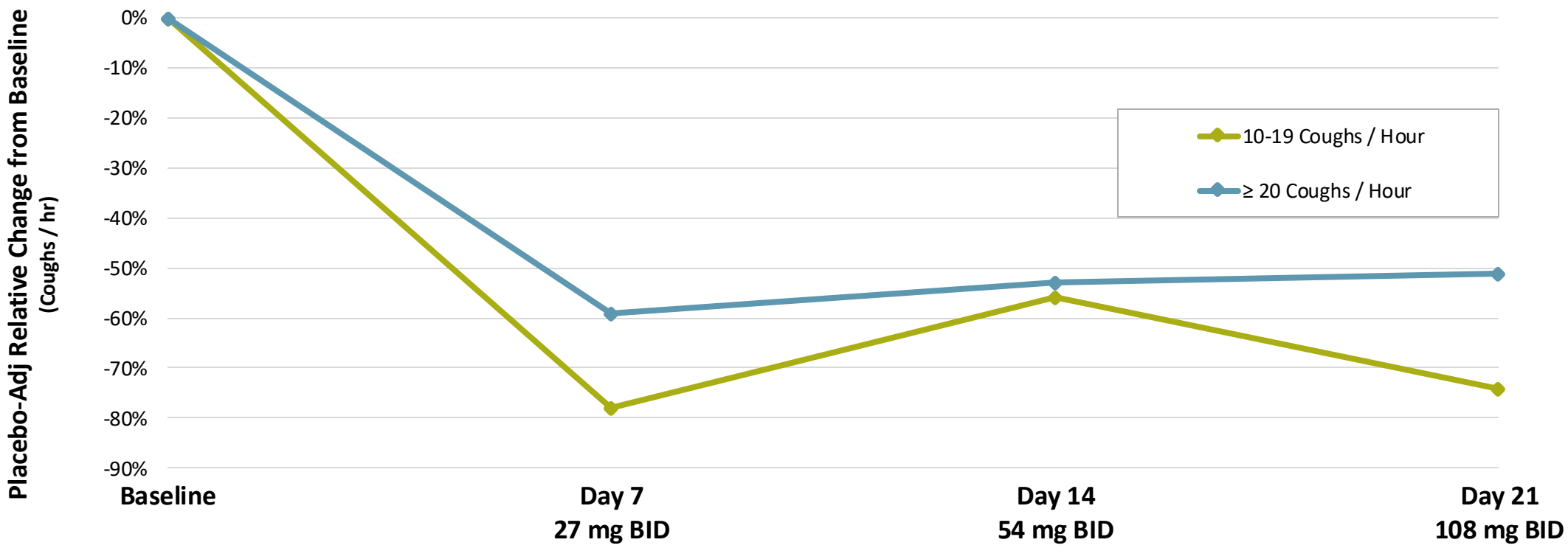


FAS Population
Primary efficacy analysis conducted on log-transformed cough frequency data
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Source: 14.2.1.1.3, 14.2.1.1.4, 14.2.1.4.1, 14.2.1.5.1

Placebo-Adjusted Relative Change from Baseline by Pre-Treatment Cough Frequency For NAL ER

Similar Placebo-Adjusted Change Regardless of Baseline Cough Frequency

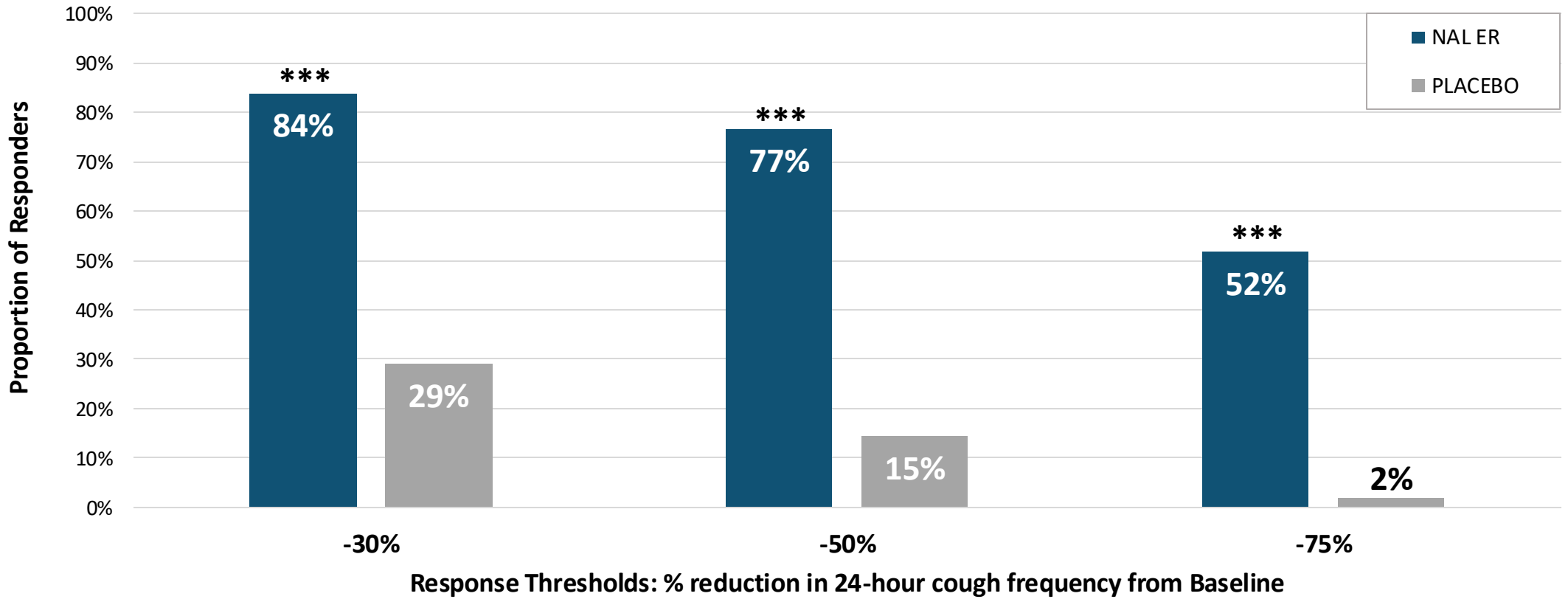


FAS Population
NAL ER = Nalbuphine extended-release tablets
For the 10 – 19 cough count, n ranges from 12 to 15
For the ≥ 20 cough count, n ranges from 40 to 42
NAL ER is an investigational drug

Source: 14.2.1.1.3, 14.2.1.1.4

Responder Analysis Day 21 (108 mg BID)

Broad clinically-meaningful response with NAL ER



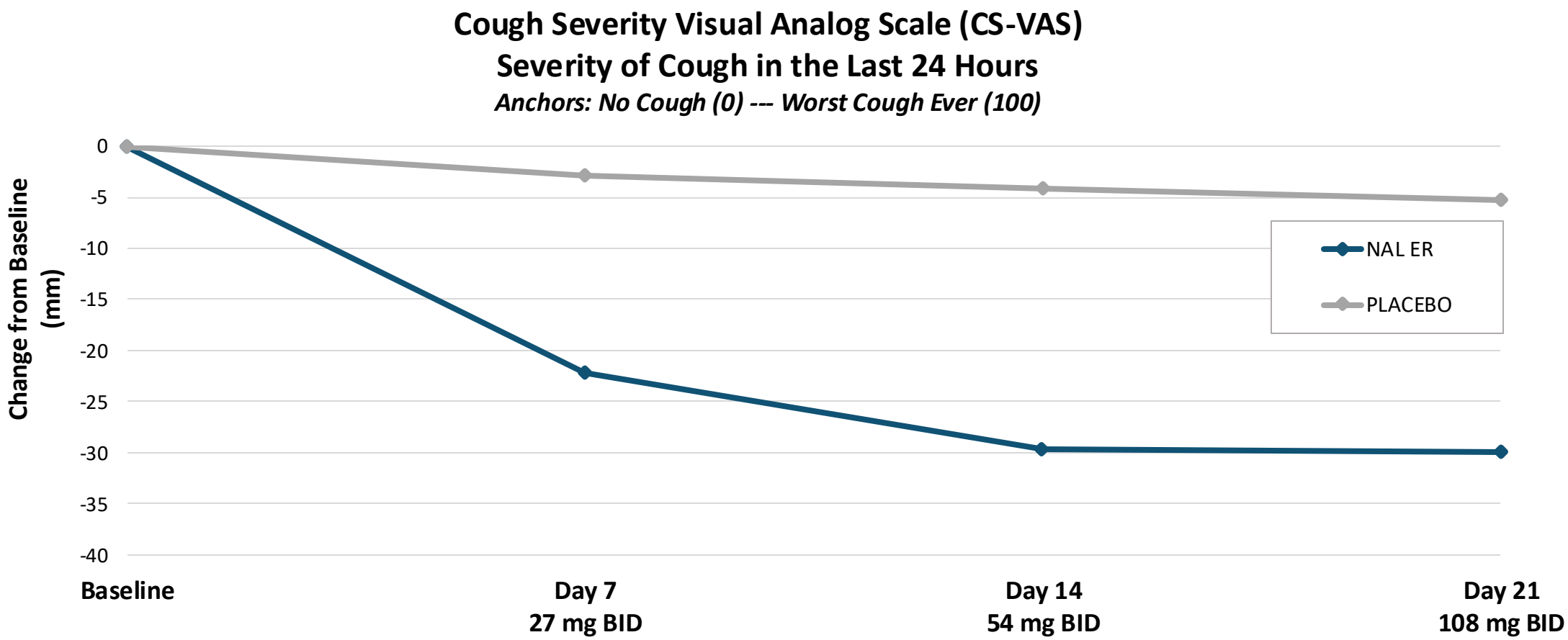
***p<0.0001

FAS Population
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Source: 14.2.2.3.1, 14.2.2.3.2, 14.2.2.3.3

Patient-Reported Cough Severity

Significant improvement in patient perception of cough severity

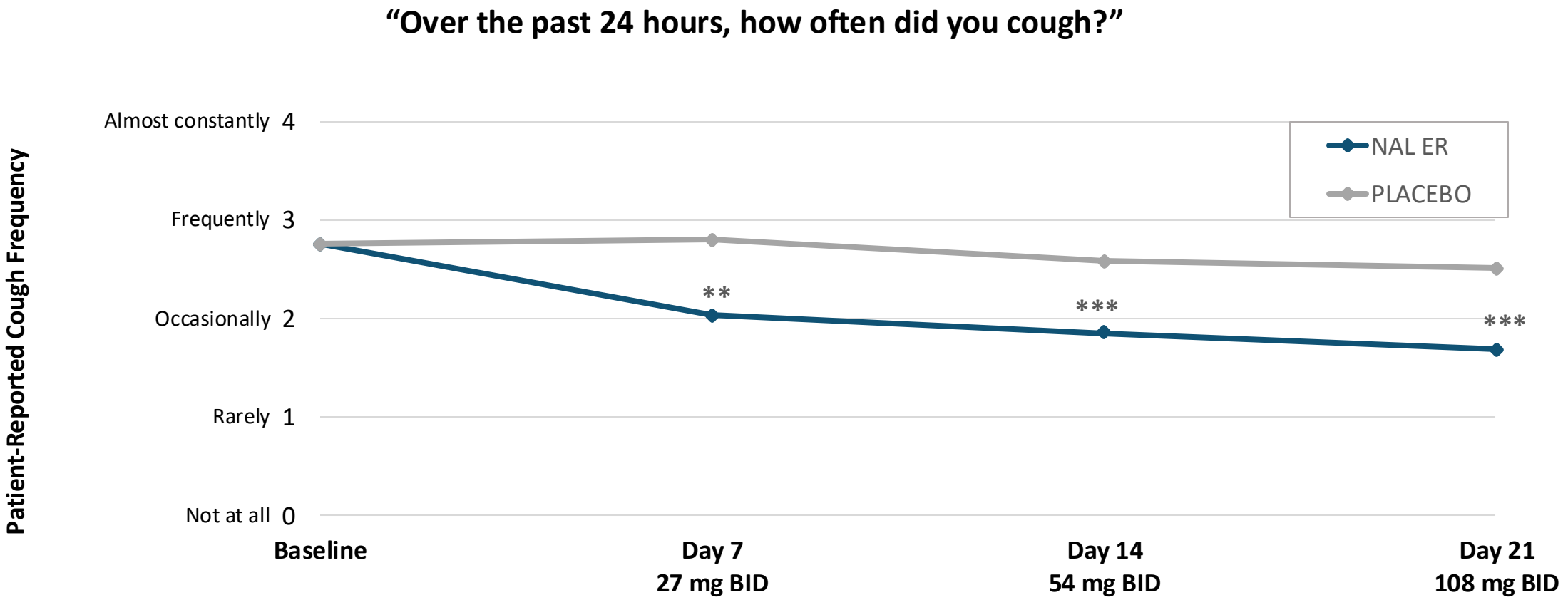


FAS Population
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Source: 14.2.2.4

Patient-Reported Cough Frequency

Patient-reported cough frequency corroborates objective cough monitor results



**p<0.001
***p<0.0001

Source: 14.2.2.6

FAS Population
p-values are derived from the paired t-test
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Treatment Emergent Adverse Events

	NAL ER (N=63) n (%)	Placebo (N=59) n (%)	Total (N=66) n (%)
Adverse Events	50 (79.4)	32 (54.2)	60 (90.9)
Adverse Events Related to Study Drug	40 (63.5)	14 (23.7)	45 (68.2)
Serious Adverse Events	0	0	0
Adverse Event Leading to Discontinuation of Study Drug	9 (14.3)	1 (1.7)	10 (15.2)

	Total (N = 66)
Discontinued Treatment, n (%)	15 (22.7%)
Adverse Event	10 (15.2%)
Withdrawal by Subject	4 (6.1%)
Other	1 (1.5%)

Safety Population
NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Source: 14.1.2, 14.3.2.1

Summary of Treatment-Emergent Adverse Events by Preferred Term

Treatment-Emergent Adverse Events at ≥10% Frequency	NAL ER N=63 n (%)	Placebo N=59 n (%)
Constipation	18 (28.6)	4 (6.8)
Nausea	14 (22.2)	2 (3.4)
Somnolence	16 (25.4)	0 (0)
Headache	10 (15.9)	7 (11.9)
Dizziness	12 (19.0)	2 (3.4)
Fatigue	9 (14.3)	3 (5.1)

Six patients experienced treatment-emergent AEs that were CTCAE Grade 3:

NAL ER (4 patients): Somnolence, dizziness, headache, hypoaesthesia, lethargy, nephrolithiasis

Placebo (2 patients): Headache and blepharitis

There were no CTCAE treatment-emergent AEs above Grade 3.

Safety Population
NAL ER = Nalbuphine extended-release tablets
Subject is included only once, even if they experienced multiple events in that preferred term
NAL ER is an investigational drug

Source: 14.3.2.3, 14.3.2.4

RIVER Study Conclusions and Next Steps

- NAL ER achieved the primary endpoint in the Phase 2a RIVER study
  - A statistically significant reduction in the primary endpoint of an objective 24-hour cough frequency of 67% from baseline and 57% on a placebo-adjusted basis
- The patient-reported outcomes and other secondary endpoints to date showed similar results to the primary endpoint.
  - A statistically-significant reduction in cough frequency was seen as early as Day 7 (27 mg BID)
- NAL ER was generally well-tolerated, with no serious adverse events reported and had a safety profile consistent with previous studies

Next Steps: Discuss results and future study design with the FDA

NAL ER = Nalbuphine extended-release tablets
NAL ER is an investigational drug

Jennifer Good
President and CEO

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Haduvio Achieved a 57% Placebo-adjusted Change in the RIVER Phase 2a Trial

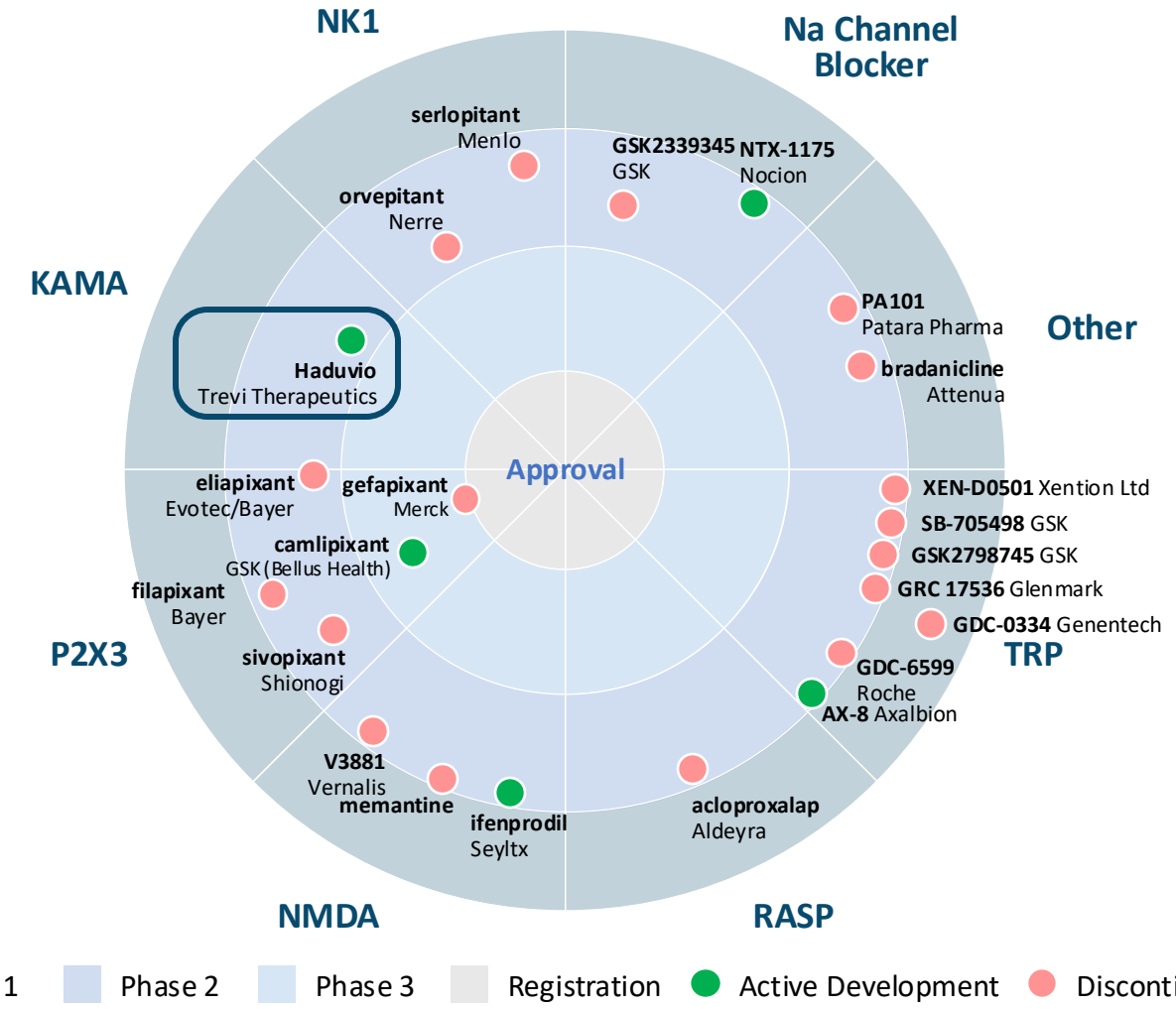
Other Refractory Chronic Cough Trial Results
Placebo Adjusted Decreases Range from 12% – 37% across Phase 2 and Phase 3

	Gefapixant[1-2]			BLU-5937[3-4]			S-600918[5-6]		BAY-1817080[7-8]	
	Ph2b N=253	**Ph3 N=666**	**Ph3 N=1243**	**Ph2a N=62**	**Ph2b N=61**	**Ph2b N=249**	Ph2a N=31	Ph2b N=406	Ph2a N=60	Ph 2b N=310
Primary endpoint and study design	12w (awake) Parallel	**12w (24-hr) Parallel**	**24w (24-hr) Parallel**	**16d (awake) Crossover**	**28d (24-hr) <25 c/h Parallel**	**28d (24-hr) ≥25 c/h Parallel**	14d (awake) Crossover	28d (24-hr) Parallel	7d (24-hr) Crossover	12w (24-hr) Parallel
Max PBO Adj ΔBL	-37%*	**-18%***	**-15%***	**-17%**	**+13%**	**-34%***	-32%*	-12%	-25%*	-27%

*Statistically significant
Camlipixant Ph2a data reflects 25mg and 50mg doses progressed into Ph3
Gefapixant Ph2a was a single-center study with a supratherapeutic 600mg BID compared to their Ph3 program using 45mg BID [9]
Bradanicline (failed) N=414: did not reduce awake cough frequency in RCC patients compared with PBO.[10]
Orvepitant (failed) N=315: The cough frequency (CF) endpoint was not statistically significant in the overall population and also in a pre-defined sub-group of higher CF subjects (p=0.066)[11]

[1]Smith JA er atl. Lancet Resp Med 2020 doi: 10.1016/S2213-2600(19)30471-0 [2]McGarvey LP et al. Lancet 2022 doi: 10.1016/S0140-6736(21)02348-5 [3]Smith JA et al. AJRCCM 2025 doi: 10.1164/rccm.202501-0093RL [4]Smith JA et al. AJRCCM 2025 doi: 10.1164/rccm.202409-1752OC [5]McGarvey L et al. Lung 2023 doi: 10.1007/s00408-022-00592-5 [6]Niimi A et al. ERJ 2019 doi: 10.1183/13993003.00725-2021 [7]Morice AH et al. AJRCCM 2020 doi: 10.1183/13993003.04240-2020 [8]Dicpinigaitis PV et al. Lung 2023 doi: 10.1007/s00408-023-00621-x [9]Abdulqawi R et al. Lancet 2015 doi: 10.1016/S0140-6736(14)61255-1 [10]Kanemitsu Y et al. ERJ 2020 doi.org/10.1183/13993003.congress-2020.4564 [11]Smith J et al. Chest 2020 doi: 10.1016/j.chest.2019.08.001
Haduvio (nalbuphine ER) is an investigational drug

Haduvio's Central and Peripheral Mechanism Has Best-in-Class Potential in RCC



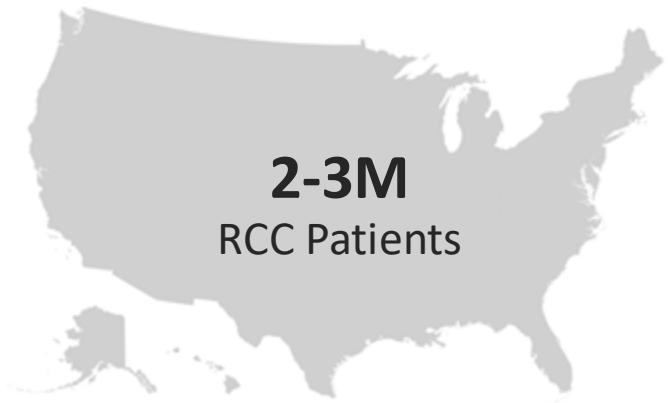
Haduvio has an opportunity to be second-to-market in a category with a high unmet need where many mechanisms have failed

- Differentiated central and peripheral mechanism
- Deep, broad, and rapid effect
- Efficacy across a wide range of baseline cough counts
- Reduction in objective cough counts supported by patient-reported outcomes

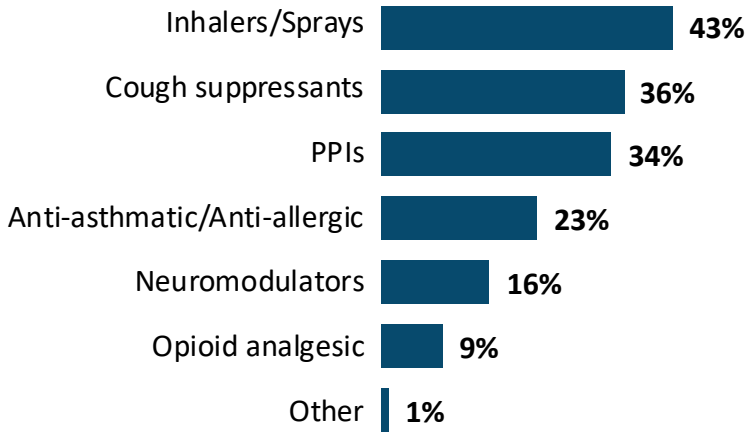
[1]Haduvio, Trevi Therapeutics: Trevi Therapeutics Press Release January 5, 2023 [2]GABAB PAM, Addex: Addex Therapeutics Corporate Presentation August 2023 [3]Orvepitant, Nerre: Nerre Therapeutics Press Release June 7, 2019 [4]Serlopitant, Menlo: Menlo Press Release Oct 08, 2018 [5]Eliapixant, Evotec: doi.org/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A4776 [6]Gefapixant, Merck: doi: 10.1016/S0140-6736(21)02348-5 [7]Filapixant, Bayer: doi: 10.1186/s12931-023-02384-8. [8]Camlipixant, GSK: Bellus Health Press Release December 13, 2021 [9]Sivopixant, Shionogi: doi: 10.1007/s00408-022-00592-5 [10]V3881, Vernalis: Young E. et al. Lung. 2012;19:63. [11]Ifenprodil, Algernon: Algernon Pharmaceuticals Press Release January 9, 2023 [12]Memantine: doi:10.1183/23120541.00447-2021. [13]ADX-629 (acloproxalap), Aldeyra: Aldeyra Press Release Jan 4, 2024 [14]GRC 17536, Glenmark: doi: 10.1002/cpt.2003. 27GDC-6599, Genentech: https://classic.clinicaltrials.gov/ct2/show/NCT05660850?term=GDC-6599&cond=chronic+cough&draw=2&rank=1 [15]GSK2798745, GSK: doi:10.1183/23120541.00269-2021. [16]SB-705498, GSK: doi:10.1016/j.jaci.2014.01.038. [17]AX-8, Axalbion: Axalbion Press Release May 22, 2023. [18]XEN-D0501, Xention LTD: Belvisi MG. et al. Am J Respir Crit Care Med. 2017 Nov 15;196(10):1255-1263 [19]Bradanicline, Attenua, Inc: doi:10.1183/13993003.congress-2020.4564 [20]NTX-1175, Nocion: Nocion Therapeutics Press Release August 31, 2021 [21]GSK2339345, GSK: doi: 10.5414/CP202804.
Haduvio (nalbuphine ER) is an investigational drug

Trevi Taking a Specialty Commercial Model to the RCC Market

US RCC Opportunity

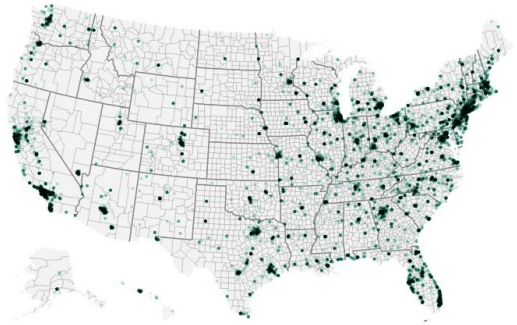


Current Treatment Paradigm



RCC Commercial Model

Targeting pulmonologists and allergists provide significant overlap with ILD centers



Focus on patients with the highest unmet need: patients failing earlier lines of therapy to maintain specialty pricing across IPF and RCC

High unmet need (5.8 / 7) and dissatisfaction (4.5 / 7) with current therapies

Specialist targeting supports an efficient and executable commercial model

RCC Opportunity: DOI: 10.1016/j.jaip.2021.07.022, DOI: 10.1177/00368504241238080, LifeSci Patient Survey 2022 (N=1,000)
RCC Current Treatments: Interviews and quantitative study conducted by Indegene, 2024 with US physicians (n = 152)
Pulmonologist map: HealthLink Dimensions data
Haduvio (nalbuphine ER) is an investigational drug

Haduvio Potential to be a Best-in-Class Therapy Across Chronic Cough

Chronic cough has a high unmet need and disease burden across IPF and RCC

- No FDA-approved therapies

Ph2a RCC results corroborate Ph2a IPF results

- Significant cough reduction
- Rapid onset of effect
- Broad responder rates
- Unique central and peripheral KAMA mechanism targeting the spectrum of cough hypersensitivity disorder

Upcoming near-term data in IPF chronic cough patients

- IPF Ph2b top-line results expected 2Q25
- Positive SSRE in IPF Ph2b, maintaining sample size and original conditional power

Cash and Investments

~$107.6M in cash and investments as of 12/31/2024*

Cash runway expected into 2H 2026

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*Cash and investments as of December 31, 2024 is a preliminary estimate and actual cash and investments as of December 31, 2024 may be different from this preliminary estimate. The Company's independent registered public accounting firm has not audited or reviewed this preliminary estimate.
KAMA: Kappa Agonist and Mu Antagonist
Development plans subject to discussions with regulatory authorities
Haduvio (nalbuphine ER) is an investigational drug

Q&A

Jennifer Good
President & Chief Executive Officer
(Co-founder)

James Cassella, Ph.D.
Chief Development Officer

Farrell Simon, Pharm.D.
Chief Commercial Officer

Professor Jacky Smith, MB, ChB, FRCP, PhD
Professor of Respiratory Medicine at the University of Manchester and an Honorary Consultant at Manchester University NHS Foundation Trust. Director of the NIHR Manchester Clinical Research Facility, Respiratory Theme Lead in the NIHR Manchester Biomedical Research Centre and an NIHR Senior Investigator.