Emerging Growth Conference

February 22, 2023

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 Haduvio and plans with respect to future clinical trials, expectations regarding Trevi's uses and sufficiency of capital, 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; the risk that positive data from a clinical trial may not necessarily be predictive of the results of future clinical trials in the same or a different indication; 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 Haduvio 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 September 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

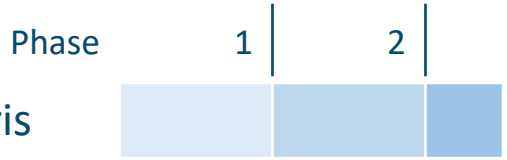
CANAL

Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)

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

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) ($p=0.0157$)

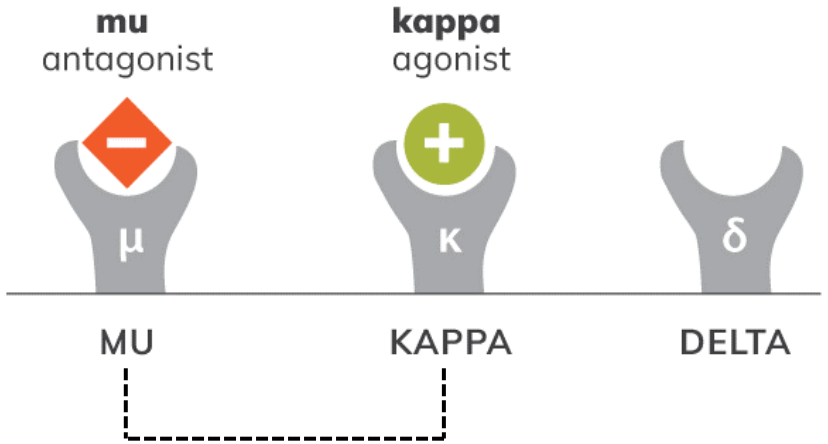
trevi THERAPEUTICS

Haduvio (nalbuphine ER) is an investigational drug

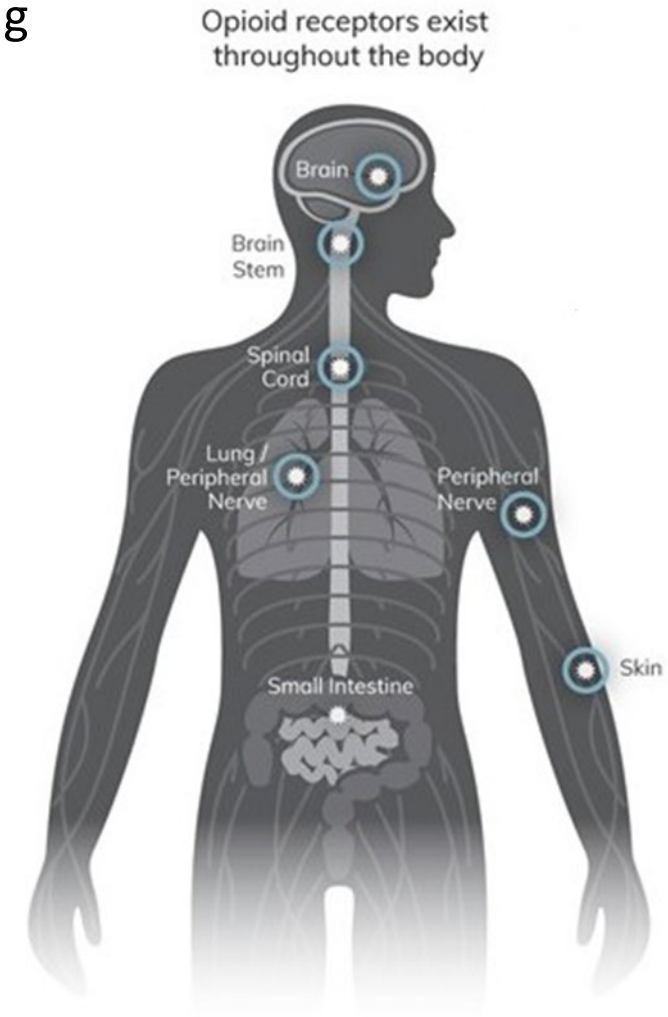
Broad Applications for Centrally and Peripherally Active Mechanism of Action of Haduvio™ (nalbuphine ER)

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



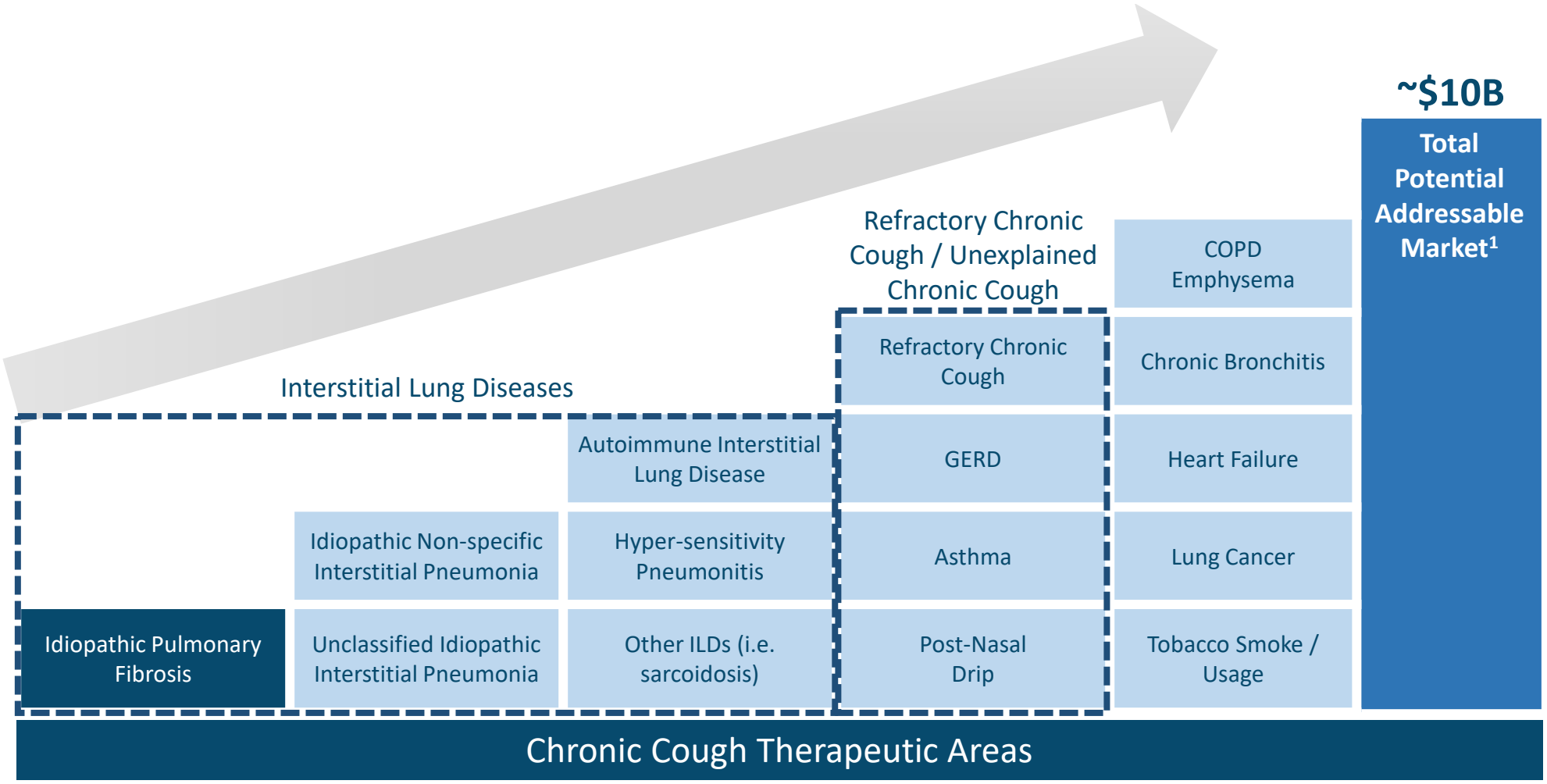
Dynamic interchange between the two receptors



Centrally Active
+
Peripherally Active

Haduvio (nalbuphine ER) is an investigational drug

Opportunities in Chronic Cough

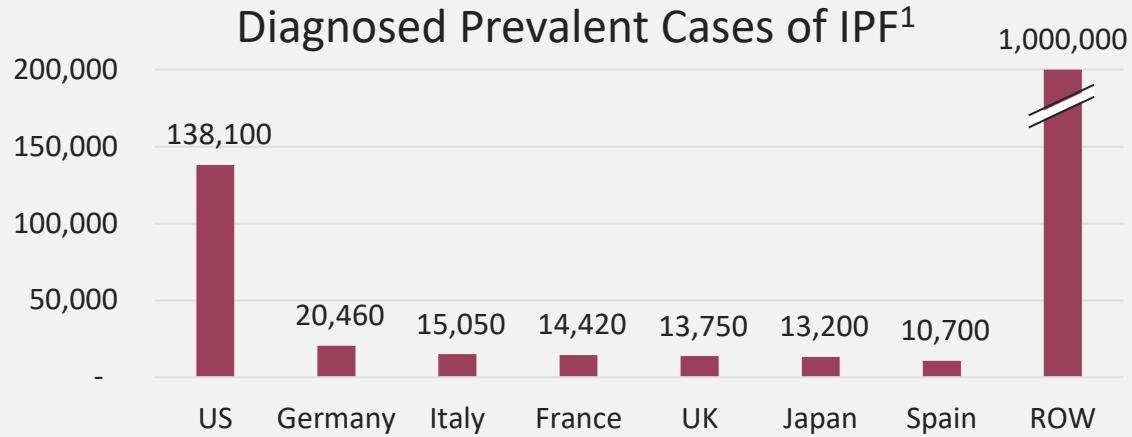


[1]2027 est. The Insight Partners Jun 2020

Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)

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]

Up to 1,500

coughs per day of an IPF patient.[3,4] The urge to cough cannot be relieved by coughing.[5]

Up to 85%

of IPF patients experience chronic cough[6]

- **IPF is a high burden disease** that has a high impact on QoL, e.g.:[3-8]
  - 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**[9]
- 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[6,10]

[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]Ryerson CJ et al. *Resp* 2011 DOI: 10.1111/j.1440-1843.2011.01996.x [7]vanManen M et al. *Ther Adv Respir Dis* 2017 doi: 10.1177/1753465816686743 [8]Wakwaya Y et al. *Chest* 2021 DOI: 10.1016/j.chest.2021.05.071 [9]VanManen M et al. ERS 2016 DOI: 10.1183/16000617.0090-2015 [10]Lee J et al. Chest. 2022 Sep;162(3):603-613. doi: 10.1016/j.chest.2022.03.025. Epub 2022 Mar 23.

Competitive Landscape for Chronic Cough

Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)

	Company	Mechanism	Current Stage	VitaloJAK® Results (PBO Adj Chg.)	
Haduvio[1]	**Trevi**	**mu antagonist + kappa agonist**	**Ph2**	**52.5% (p<0.0001)**	✓
orvepitant[2]	Nerre	NK1 antagonist	Ph2	TBD	
gefapixant[3]	Merck (Afferent)	P2x3i	Terminated (Efficacy)	5% NS	✗
RVT-1601[4]	Respivant	Cromolyn sodium	Terminated (Efficacy)	0% NS	✗

NS = Not Significant

Refractory Chronic Cough (RCC)

	Company	Mechanism	Current Stage	VitaloJAK® Results (PBO Adj Chg.)	
Haduvio[5]	**Trevi**	**mu antagonist + kappa agonist**	**Ph2**	**TBD**	
gefapixant[6]	Merck (Afferent)	P2x3i	Ph3	15-18% (p=0.03)	✓
BLU-5937[7]	Bellus Health	P2x3i	Ph3	34% (p≤0.005)	✓
sivopixant[8]	Shionogi	P2x3i	Ph2	-12-13% NS	✗
eliapixant[9]	Evotec/Bayer	P2x3i	Terminated (Safety)	14-29 NS	✗
orvepitant[10]	Nerre	NK1 antagonist	Terminated (Efficacy)	NS	✗

[1]Molyneaux P. et al. *Thorax* 2022;**77:**A13-A14. http://dx.doi.org/10.1136/thorax-2022-BTSabstracts.21 [2]https://clinicaltrials.gov/ct2/show/NCT02993822 [3]Martinez FJ et al. Pulm Ther. 2021 Dec;7(2):471-486. doi: 10.1007/s41030-021-00162-9 [4]Martinez FJ et al. Am J Respir Crit Care Med. 2022 May 1;205(9):1084-1092. doi: 10.1164/rccm.202106-1485OC [5]Trevi Therapeutics Press Release January 5, 2023 [6]McGarvey LP et al. Lancet. 2022 Mar 5;399(10328):909-923. doi: 10.1016/S0140-6736(21)02348-5 [7]Bellus Health Press Release December 13, 2021 [8]McGarvey L et al. Lung. 2022 Dec 13:1–11. doi: 10.1007/s00408-022-00592-5 [9]Dicpinigaitis P et al. Am J Respir Crit Care Med 2022;205:A4776 https://doi.org/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A4776 [10]Nerre Therapeutics Press Release June 7, 2019

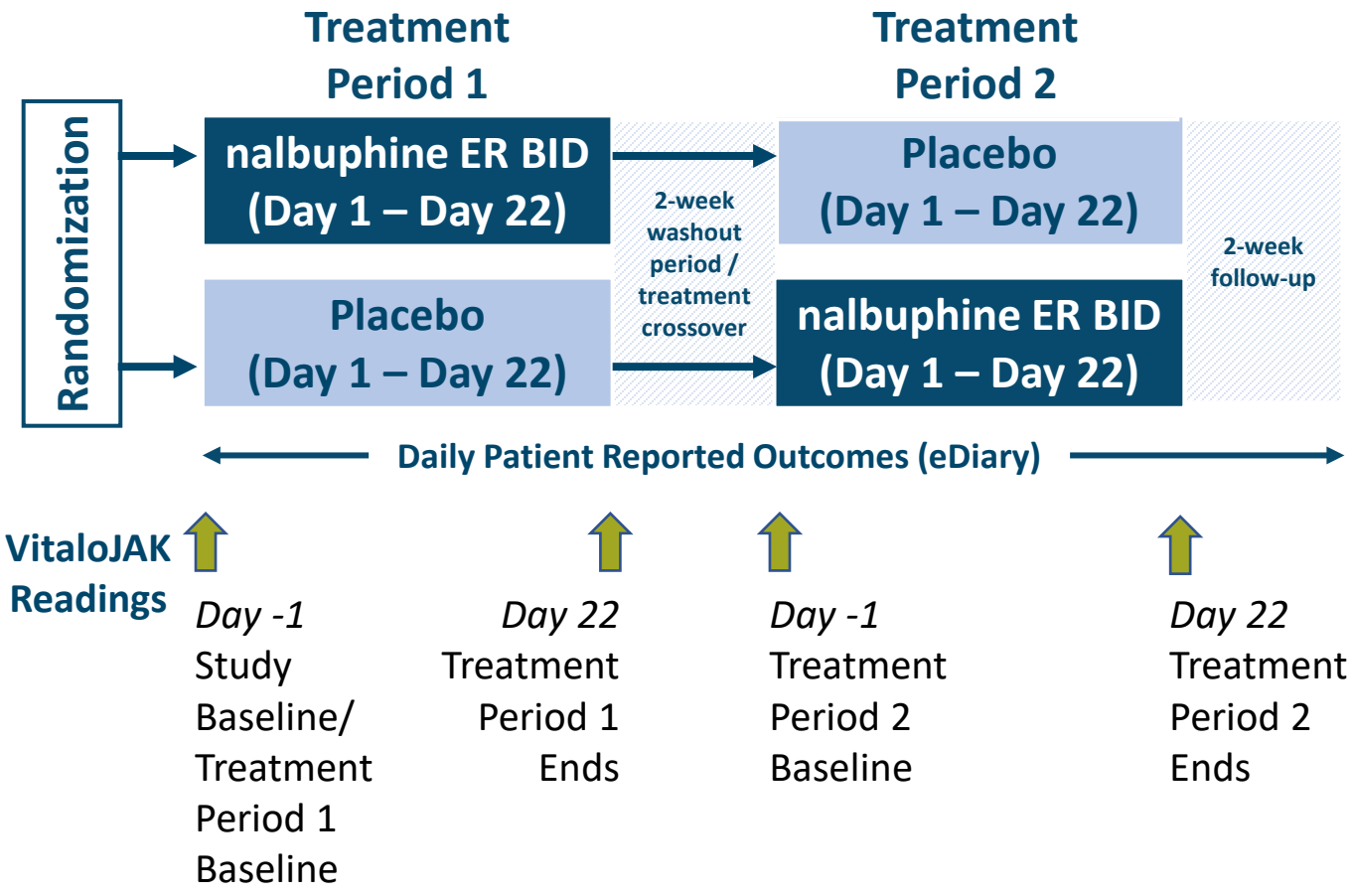
Haduvio (nalbuphine ER) is an investigational drug. VitaloJAK is a registered trademark of VitaloGraph. NS = Not Significant

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
- ✓ 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

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

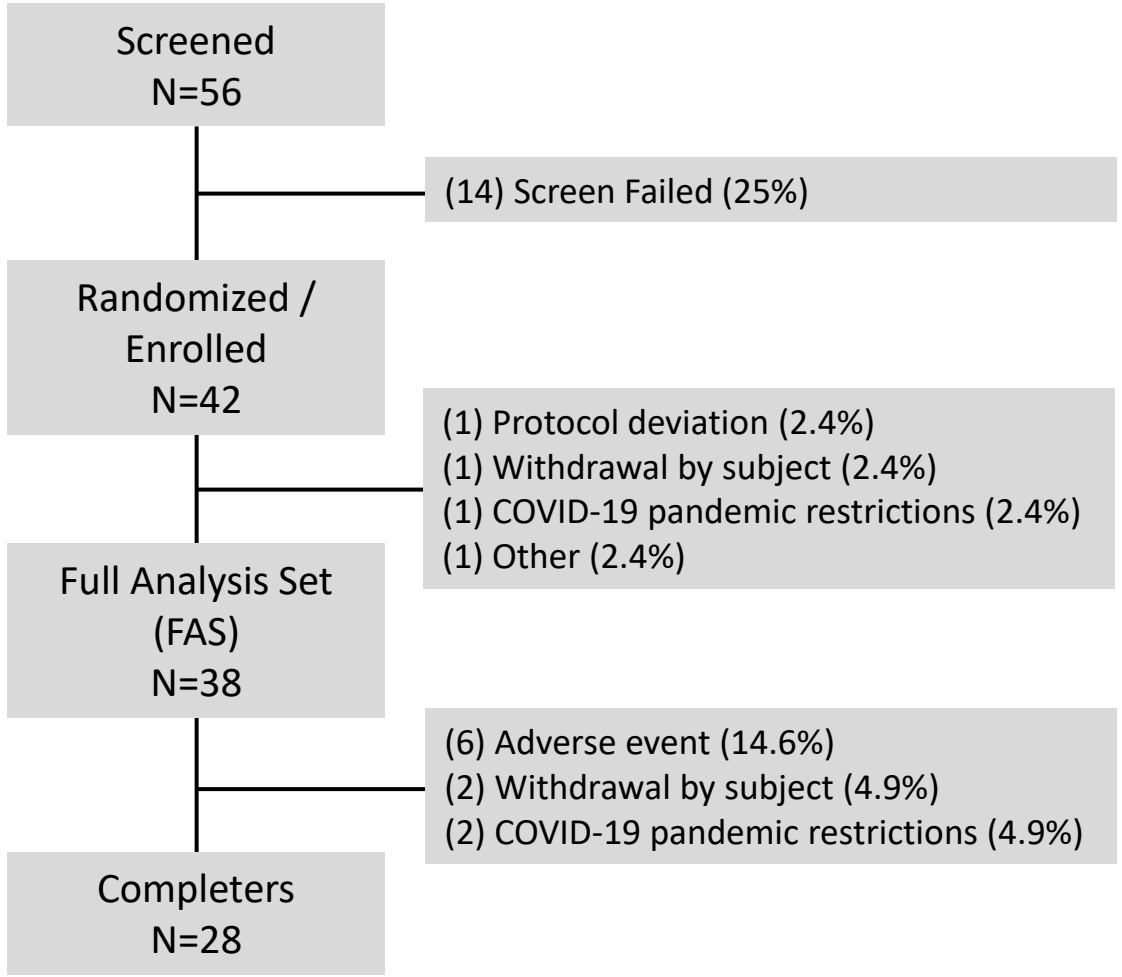
The VitaloJAK® Cough Monitor provides a fully validated system for objective measurement of cough.

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

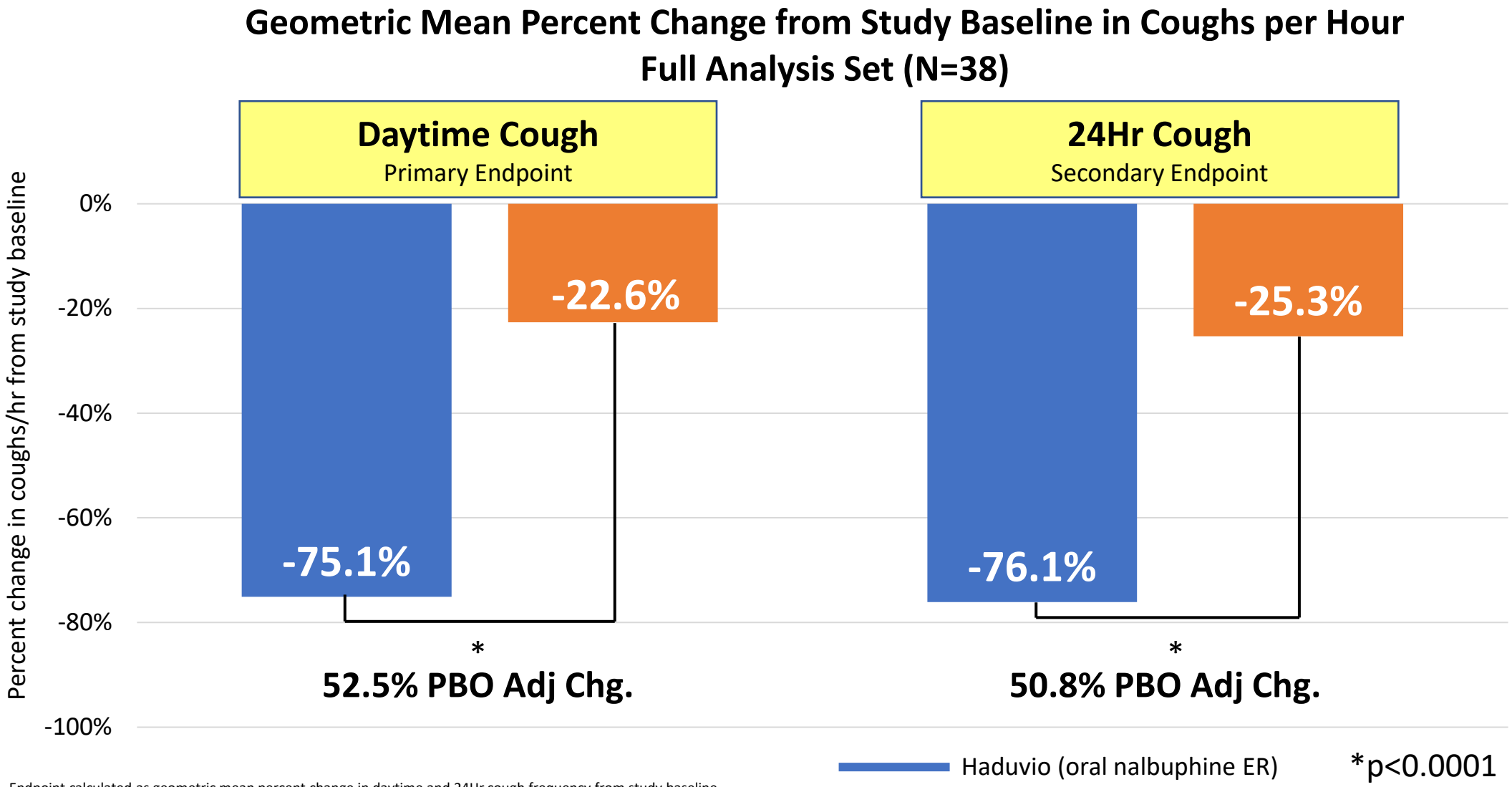
Baseline Characteristics and Patient Disposition

	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%)
Daytime cough frequency (coughs/hr):	
Mean	28
Min-Max	3.18 - 92.35
24Hr cough frequency (coughs/hr):	
Mean	21
Min-Max	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

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

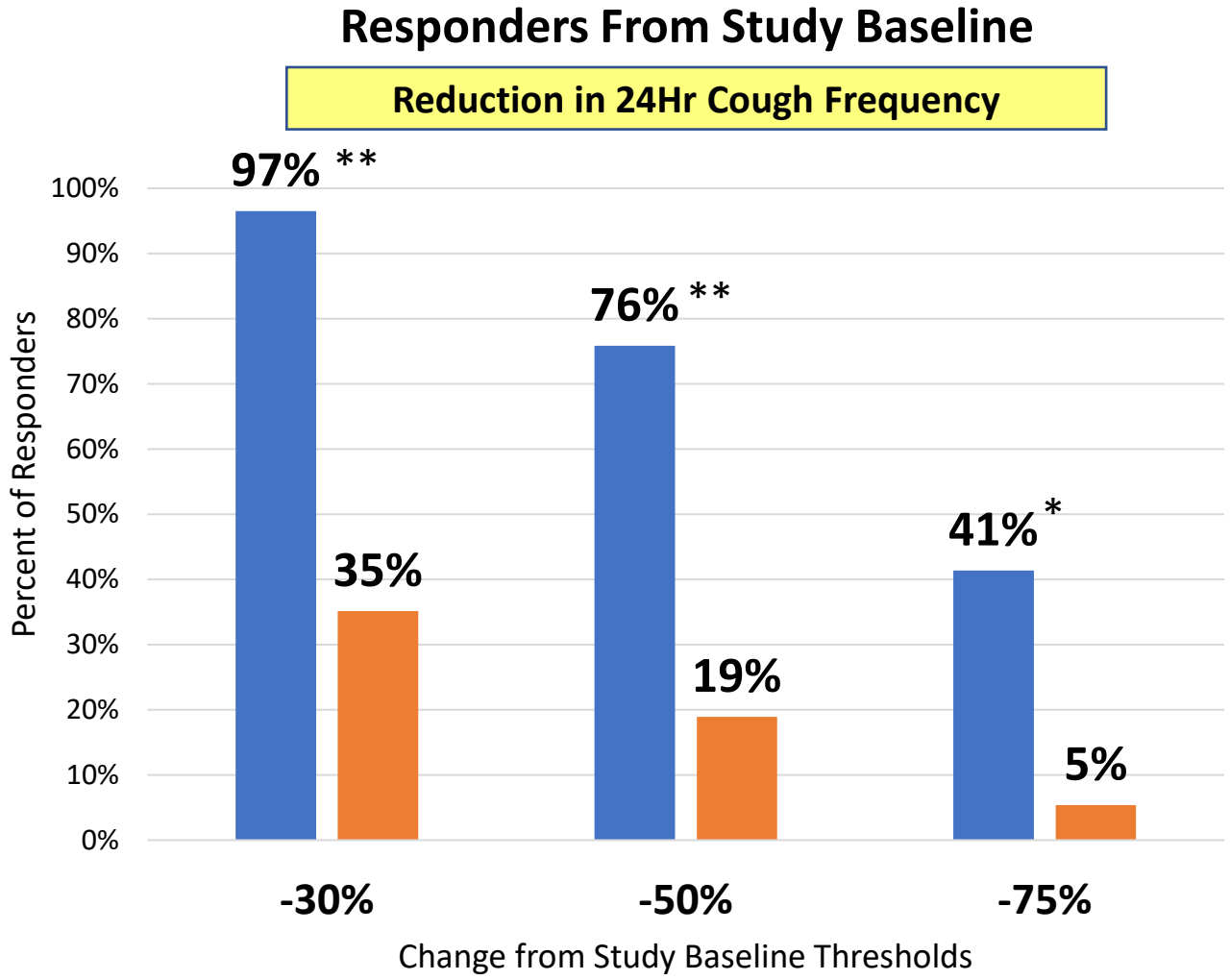
Post-Hoc Responder Analyses
Clear Separation Between Haduvio vs. Placebo at All Thresholds

97% of Haduvio subjects

saw a clinically meaningful reduction in 24Hr cough frequency

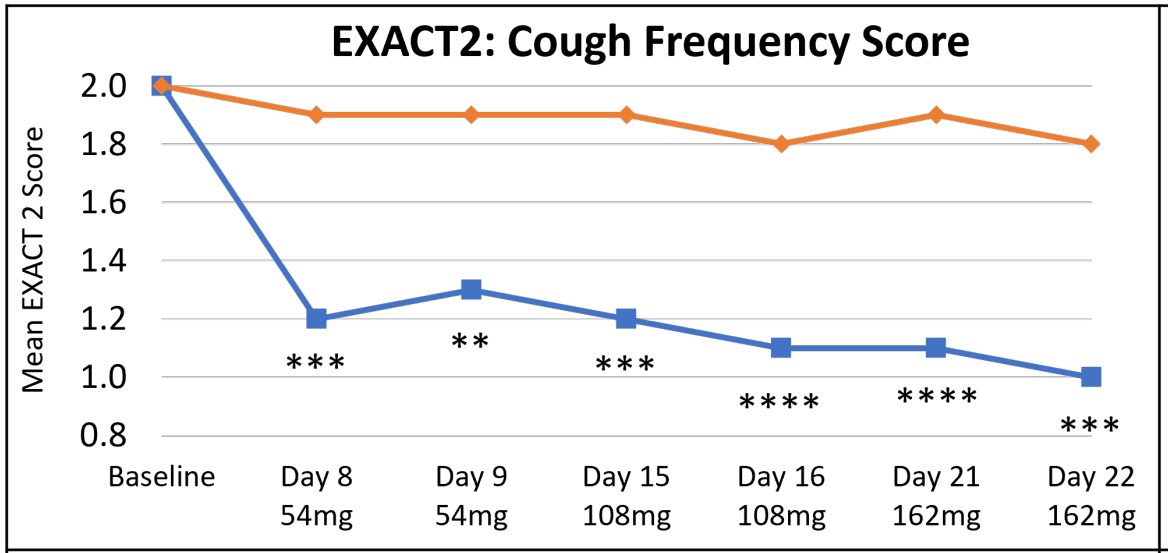
(Subjects experiencing a 20-30% reduction in their cough frequency is considered clinically meaningful)[1]

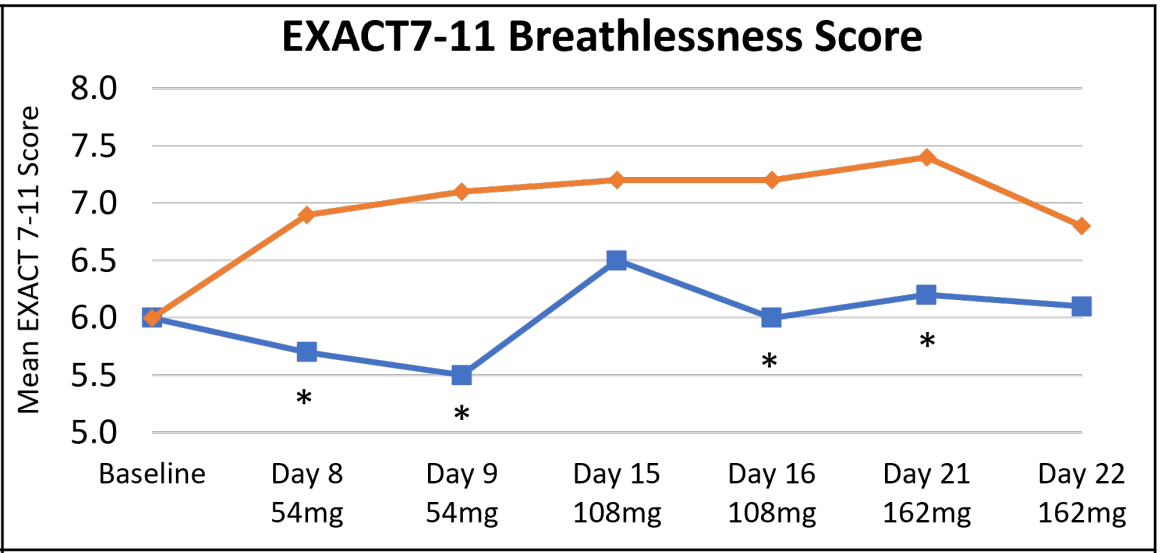
76% of Haduvio subjects reduced their cough frequency in half

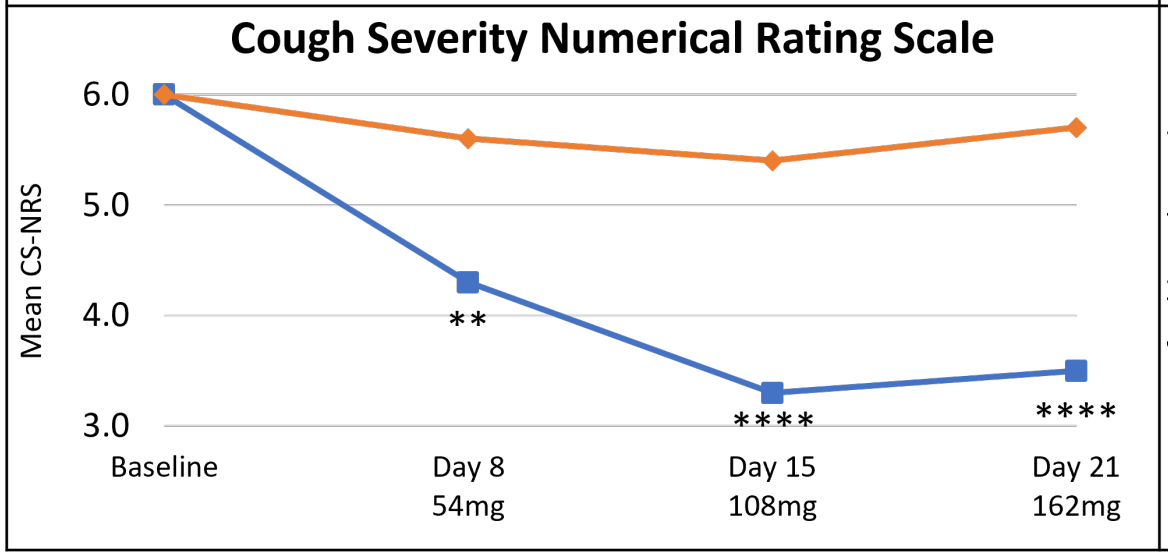


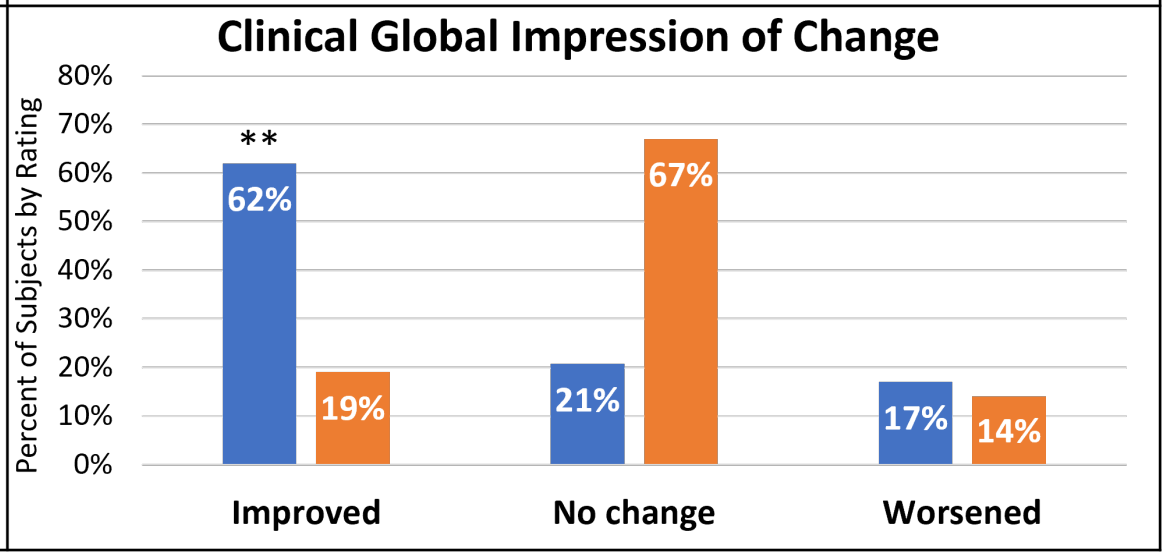
[1]Nguyen AM et al. J Allergy and Clin Immunol 2019 doi.org/10.1016/j.jaci.2018.12.519
Endpoint calculated as geometric mean percent change in 24Hr cough frequency from study baseline
Haduvio (nalbuphine ER) is an investigational drug

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

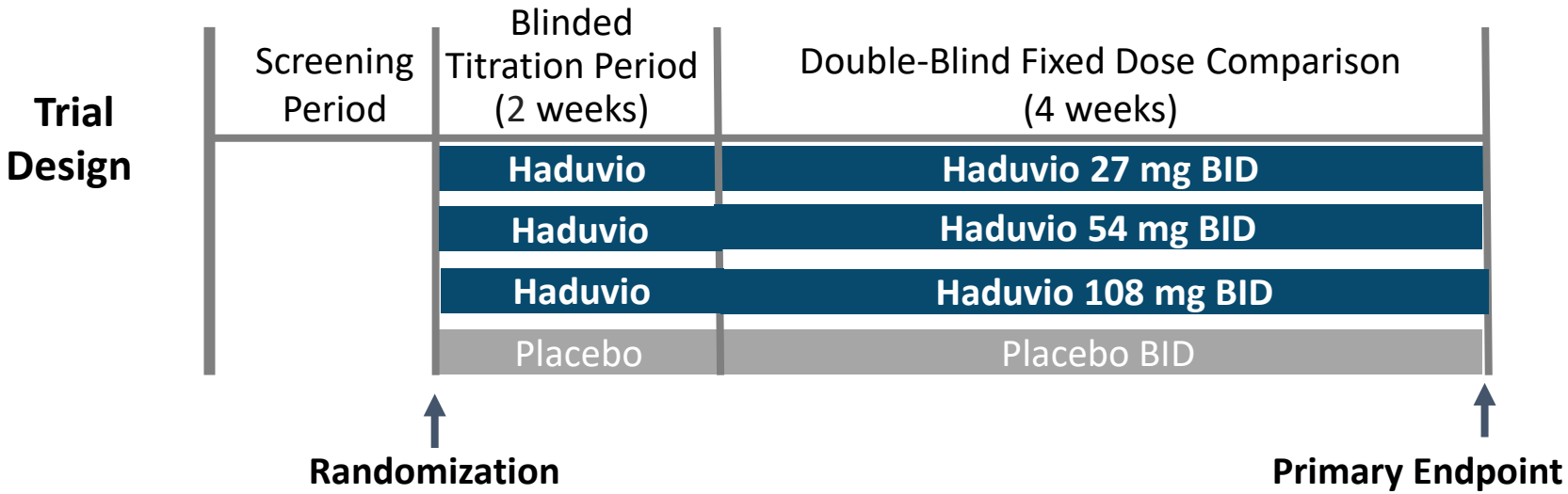
*p≤0.05 **p≤0.01 ***p≤0.001 ****p≤0.0001

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

Dose Ranging CC-IPF Ph2b Trial Design (N approx. 200)



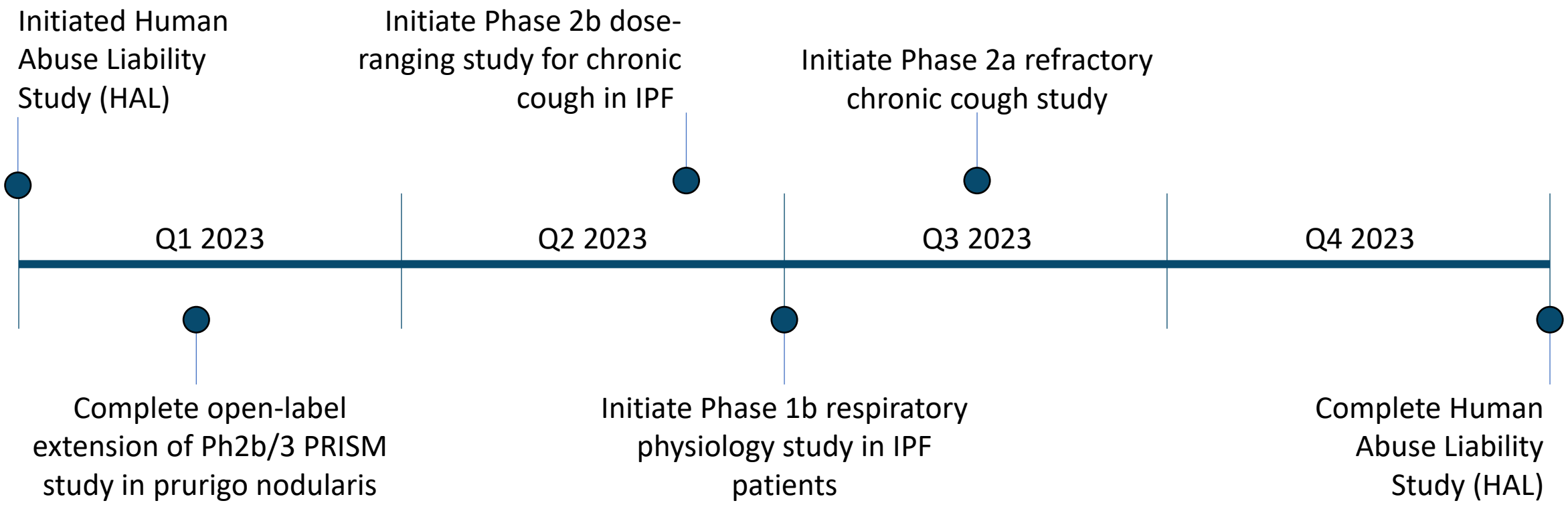
Design
Randomized, double-blind, parallel group, OP design

Primary Efficacy Endpoint:
- 24-hour cough frequency via VitaloJAK

Secondary Endpoints:
- Chronic Cough PROs

Design plan subject to discussions with regulatory authorities
Haduvio (nalbuphine ER) is an investigational drug

Trevi 2023 Next Steps and Financial Position



Cash and Investments

- $126M in cash and investments as of 9/30/22
- Cash runway expected into 2026

Development plans subject to discussions with regulatory authorities
Haduvio (nalbuphine ER) is an investigational drug