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Controlling cough where it counts™

Human Abuse Potential (HAP) Study of Oral Nalbuphine vs. IV Butorphanol Topline Results

December 3, 2024

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.

Human Abuse Potential (HAP) Study of nalbuphine vs. butorphanol
Topline Results Agenda

Introduction	**Jennifer Good**, President and CEO, *Trevi Therapeutics*
Study Design & Topline Results	**James Casella, 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 Casella, Ph.D.**, Chief Development Officer, *Trevi Therapeutics* **Thomas Sciascia, M.D.**, Chief Scientific Officer, *Trevi Therapeutics* **Jack Henningfield, Ph.D.**, Vice President, Research, Health Policy and Abuse Liability, *Pinney Associates*

Call Attendees

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

Thomas Sciascia, M.D.
Chief Scientific Officer
(Co-founder)

James Cassella, Ph.D.
Chief Development Officer

Pinney Associates

Jack Henningfield, Ph.D.
Vice President, Research, Health Policy and Abuse Liability

- Former Chief of the Clinical Pharmacology Research Branch, and the Abuse Potential and Biology of Dependence Assessment Section of the National Institute on Drug Abuse (NIDA)
- Special Government Employee with the FDA Center for Drug Evaluation and Research and the Center for Tobacco Products
- Member of the Johns Hopkins University school of medicine faculty and adjunct professor of behavioral biology in the department of psychiatry and behavioral sciences
- Published >450 papers on topics in public health, pharmacology, and addiction

History of Nalbuphine

Nalbuphine is not a controlled substance (unscheduled) in the U.S.

DEA reviews this every 2 years and has left it unscheduled for 40+ years, reaffirming its status in 2023

- Nalbuphine is in a unique class called “mixed agonist-antagonist”. This class was developed to mitigate abuse potential.
- The two components of nalbuphine’s mechanism are unscheduled (mu antagonists like naloxone and naltrexone, kappa agonist such as difelikefalin).
- DEA notes nalbuphine’s potent mu antagonist effect which can precipitate withdrawal in an opiate-tolerant individuals.
- Nalbuphine has a long history of real-world evidence of a lack of abuse through drug surveillance monitoring.

https://www.deadiversion.usdoj.gov/drug_chem_info/nalbuphine.pdf

DEA Classifies Nalbuphine as Unscheduled

Schedule	Definition	Examples
Schedule II	High potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous	oxycodone, fentanyl, Adderall
Schedule III	Moderate to low potential for physical and psychological dependence	ketamine, Tylenol with codeine
Schedule IV	Low potential for abuse and low risk of dependence	**butorphanol,** Xanax, Ambien, Tramadol
Schedule V	Lower potential for abuse than Schedule IV. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes	Robitussin AC, Lyrica
Unscheduled	Not regulated under the Controlled Substance Act (CSA)	**nalbuphine**, naloxone, naltrexone, difelikefalin

DEA

April 2023

Nalbuphine is not a controlled substance under the CSA.

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DEA Drug Scheduling https://www.dea.gov/drug-information/drug-scheduling
https://www.deadiversion.usdoj.gov/drug_chem_info/nalbuphine.pdf

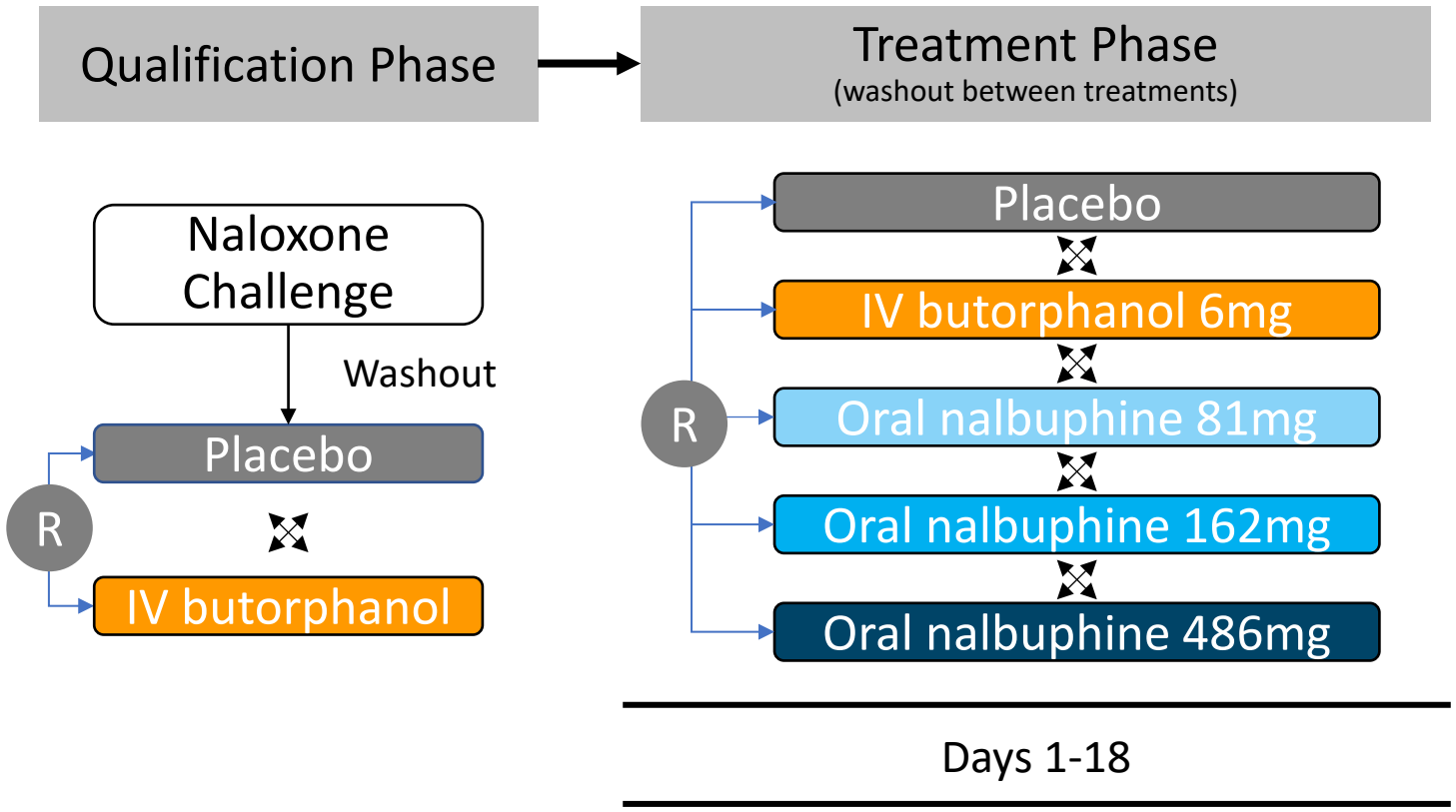
Overview of FDA Guidance on Human Abuse Potential (HAP) Studies

- Typically required for central nervous system (CNS) active drugs.
- Standardized study design and questionnaires.
- Conducted among experienced recreational opioid users.
- Active control should be an FDA approved controlled substance in the same pharmacological class.
- If the active control has not been evaluated in a HAP study before, a dose-finding study may be useful to ensure the dose selected for the HAP study produces positive subjective responses that differentiate statistically from placebo.
- At least 3 doses of the test drug should be studied, and the doses of the test drug should be based on the highest proposed therapeutic dose in humans, as well as a dose 2-3 times that dose (supratherapeutic), if this can be done safely.

https://www.fda.gov/media/116739/download

Nalbuphine Human Abuse Potential (HAP) Study Design

A Randomized, Double-blind, Double-dummy, Active- and Placebo-controlled, 5-way Crossover Study



Objectives

Primary Objective:
Evaluate relative and absolute abuse potential of nalbuphine relative to butorphanol and placebo.

Primary Endpoint:
Peak effect (E_{max}) for "Drug Liking" ("at this moment"), assessed on a bipolar, 100-point VAS

Secondary Objectives:
Subjective measures, safety and physiological measures, PK, and AEs

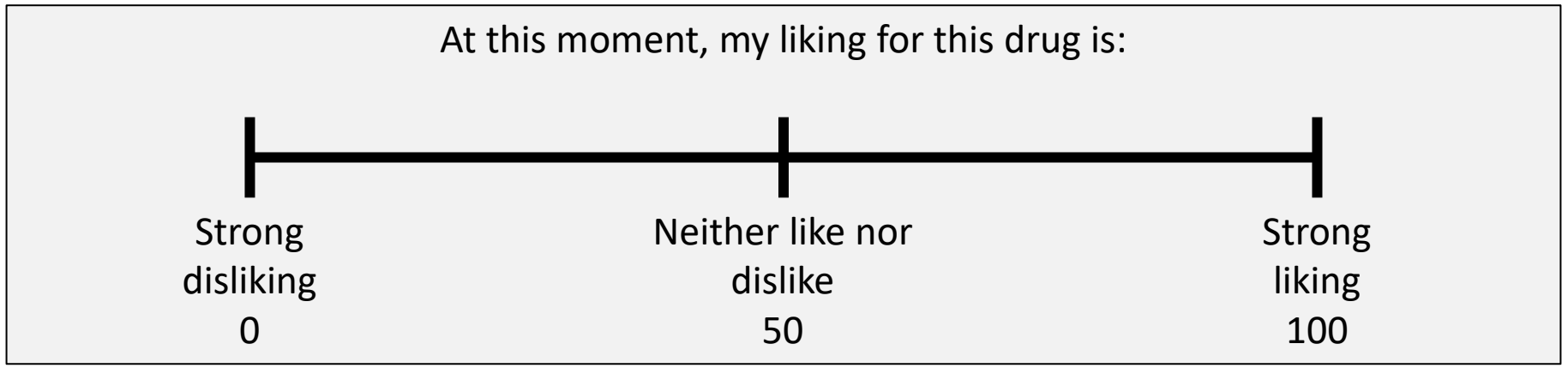
Clinical Doses Tested in Chronic Cough Program are 27mg – 162mg

R=Randomization, IV= Intravenous
Study design, butorphanol dose and administration, and endpoints aligned with FDA
Oral nalbuphine 486mg (supratherapeutic) dose is 3x the highest potential marketable dose

Primary Endpoint
"Drug Liking" Visual Analog Scale (VAS)

Bipolar VAS scale (0-100)

- Aligned with FDA Assessment of Abuse Potential of Drugs Guidance for Industry[1]
- Widely used across drug classes for HAP studies
- Sensitive to disliking (i.e. dysphoria) as well as liking (i.e. euphoria)
- VAS ranges from: Strong disliking (0) – Neither like nor dislike (50) – Strong liking (100)

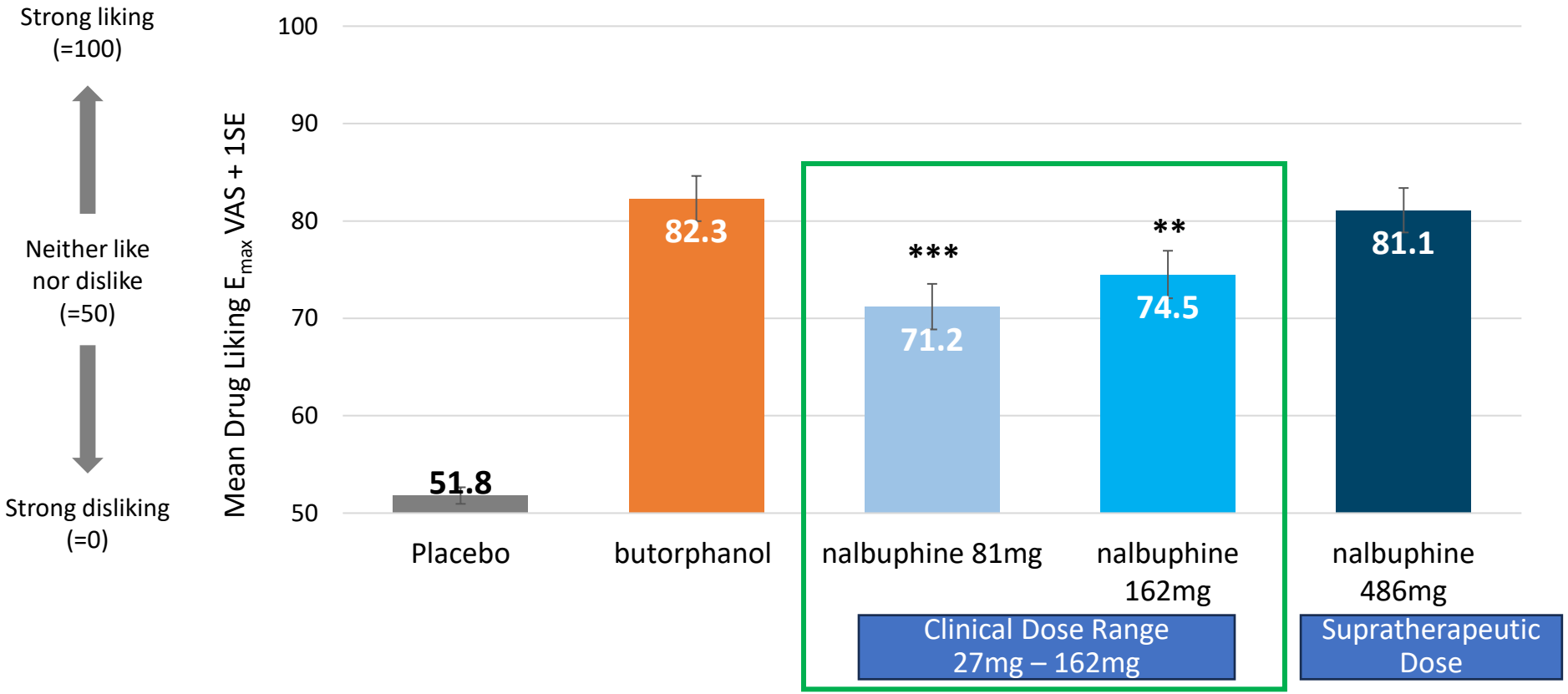


[1]Assessment of Abuse Potential of Drugs Guidance for Industry HHS, FDA, CDER Jan 2017 https://www.fda.gov/media/116739/download

Primary Endpoint (N=52)
Drug Liking VAS E_{max}: *"At This Moment, My Liking For This Drug Is"*

Both 81mg and 162mg doses of nalbuphine demonstrated a statistically significant lower "Drug Liking" vs. butorphanol

Supratherapeutic dose of nalbuphine had numerically lower "Drug Liking" vs. butorphanol, but not statistically significant



Statistical significance between nalbuphine and butorphanol

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

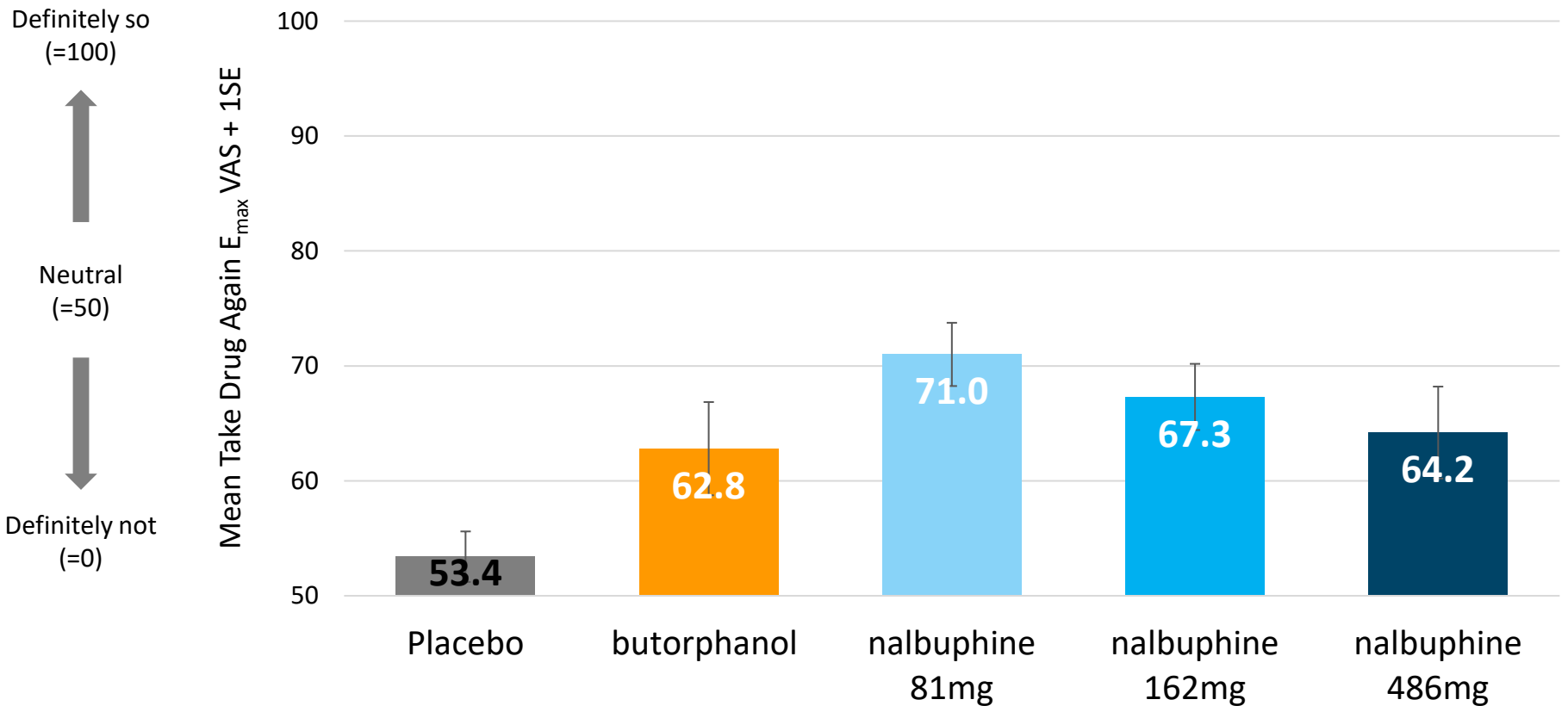
Visual Analog Scale (VAS), E_{max} is the peak (maximum) effect

SE = Standard Error

All analyses performed were on the Modified Completer Population, which was prespecified in the statistical analysis plan for the primary endpoint.

Secondary Endpoint: *Take Drug Again* VAS E_{max}

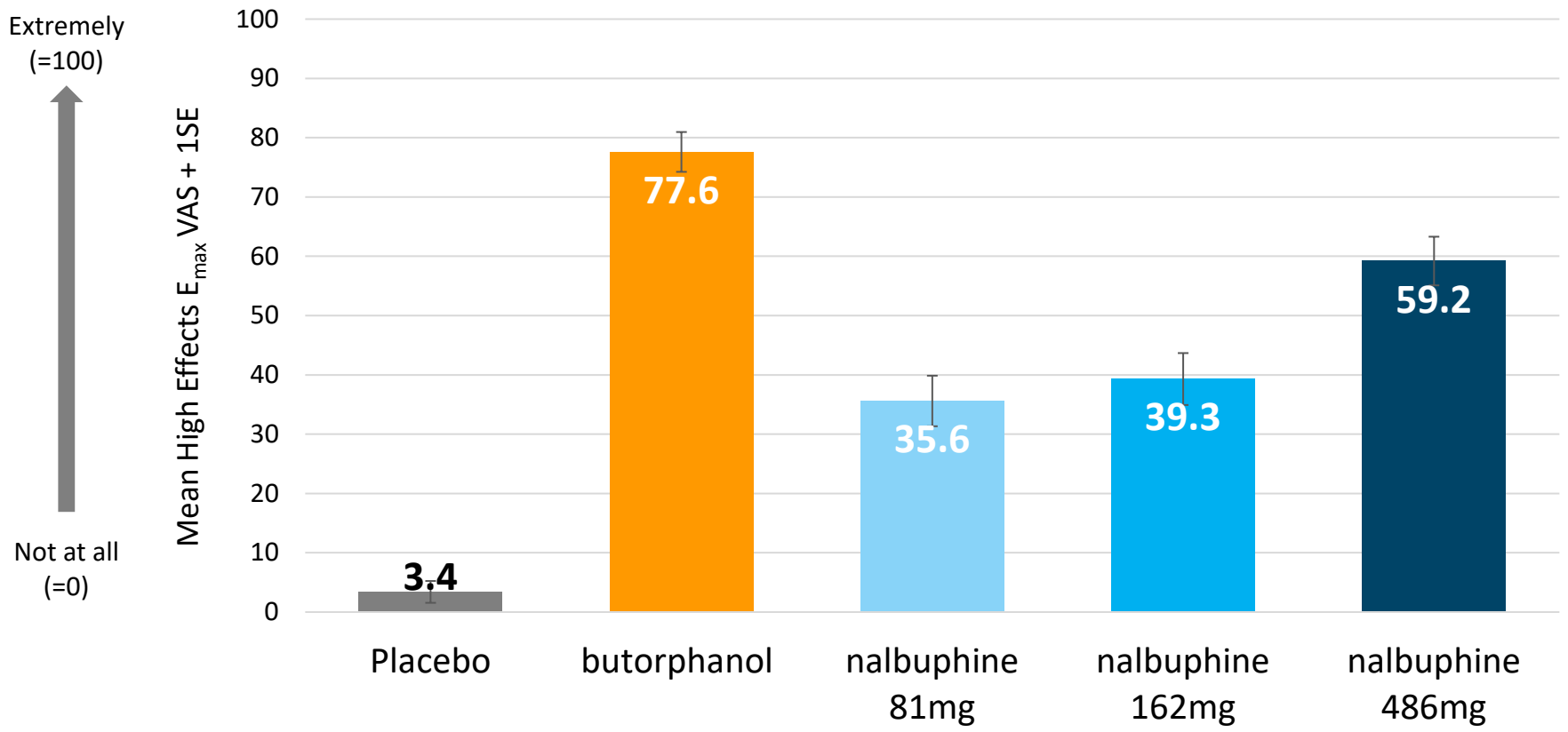
Nalbuphine Showed an Inverse Dose Response to "*At This Moment, I Would Take This Drug Again*"



Visual Analog Scale (VAS), E_{max} is the peak (maximum) effect
SE = Standard Error
All analyses performed were on N = 52 in the Modified Completer Population.

Secondary Endpoint: *High Effects* VAS E_{max}

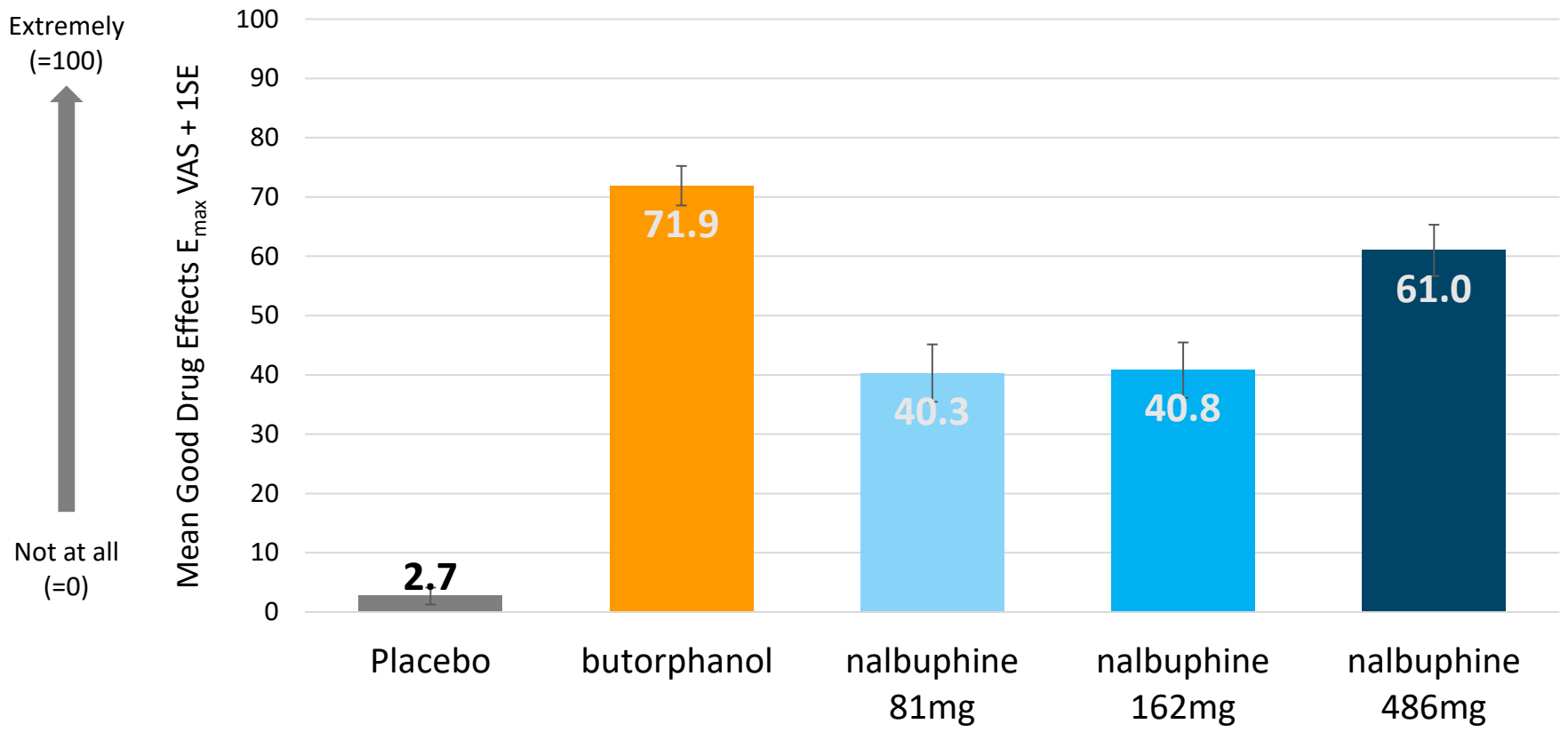
All Doses of Nalbuphine Scored Lower Than Butorphanol for "*At This Moment, I Feel High*"



Visual Analog Scale (VAS), E_{max} is the peak (maximum) effect
SE = Standard Error
All analyses performed were on N = 52 in the Modified Completer Population.

Secondary Endpoint: *Good Drug Effects* VAS E_{max}

All Doses of Nalbuphine Scored Lower Than Butorphanol for "*At This Moment, I Feel Good Drug Effects*"



Visual Analog Scale (VAS), E_{max} is the peak (maximum) effect
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All analyses performed were on N = 52 in the Modified Completer Population.

HAP is Only One Component of an 8-Factor Plan

8-Factor Plan

1. Its actual or relative potential for abuse (i.e. HAP Study).
2. Scientific evidence of its pharmacological effect, if known.
3. The state of current scientific knowledge regarding the drug or other substance.
4. Its history and current pattern of abuse.
5. The scope, duration, and significance of abuse.
6. What, if any, risk there is to the public health.
7. Its psychic or physiological dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled.

Unscheduled or Scheduling
Final determination made upon FDA approval

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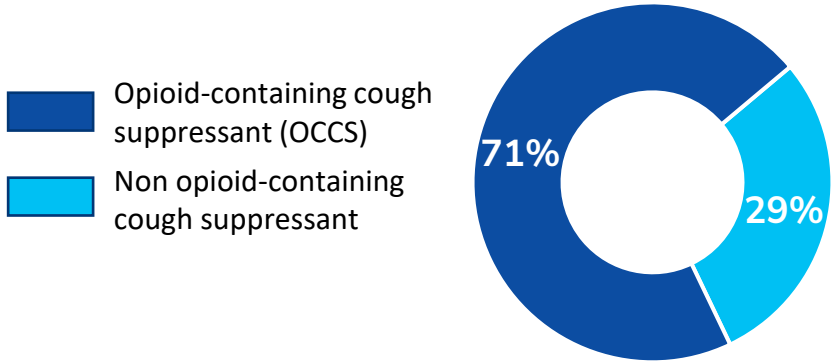
Assessment of Abuse Potential of Drugs Guidance for Industry HHS, FDA, CDER Jan 2017 https://www.fda.gov/media/116739/download

Haduvio (nalbuphine ER) Provides a Potential Alternative to Current Prescriptions for Chronic Cough That Physicians Reported Being Comfortable Prescribing

Potential Public Health Benefit of Haduvio

Chronic Cough Antitussive Prescriptions



- Hydrocodone (34%) and morphine (10%) are the most prescribed opioid-containing cough suppressants for chronic cough with limited to no efficacy
- Potential to decrease usage of mu-agonists, which carry a higher potential for addiction

Physician Prescribing Habits

- 85% to 90% of physicians treating chronic cough reported being comfortable prescribing Schedule IV/V drugs to their patients
- Across specialties, including pulmonologists, physicians report little to no difference in prescribing an unscheduled therapy compared to a Schedule V therapy, with minimal impact to Schedule IV for Idiopathic Pulmonary Fibrosis (IPF) and a 10-20% impact in Refractory Chronic Cough (RCC)

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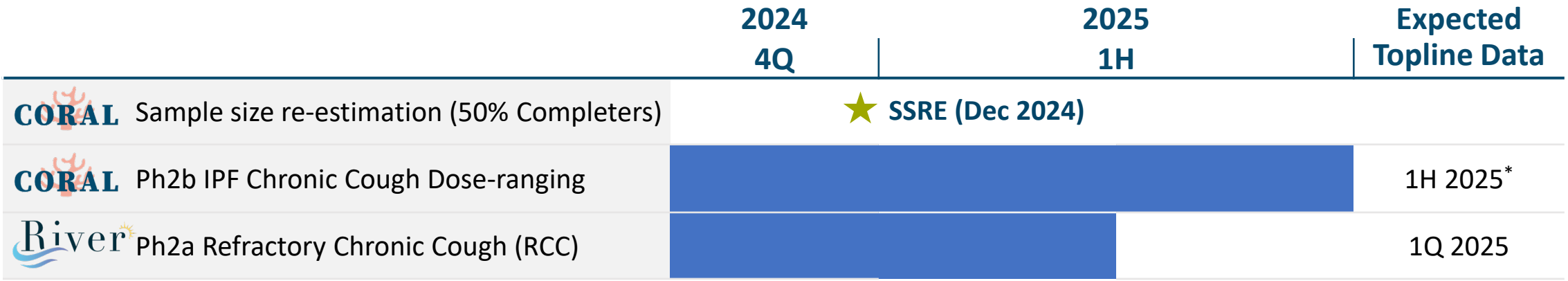
Weiner M. et al. Ther Adv Resp Dis 2024 DOI: 10.1177/17534666241259373
Interviews and quantitative study conducted by Indegene (2022 and 2024) among US prescribers (Pulmonologists, Other Specialists, and PCPs) (n = 100)
Haduvio (nalbuphine ER) is an investigational drug

Near-Term Derisking Clinical Milestones

- Significant unmet need in patients with chronic cough in IPF and RCC with no approved U.S. therapies
- Unique KAMA mechanism to treat cough hypersensitivity disorders
- Best-in-class Ph2a data in IPF chronic cough



Cash and Investments

- $65.5M in cash and investments as of 9/30/2024
- Cash runway expected into 2H 2026

Development plans subject to discussions with regulatory authorities
Haduvio (nalbuphine ER) is an investigational drug
*Expected timeline for topline data from CORAL dependent on SSRE results

Q&A

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