W65

Assessment of Human Abuse Potential of Nalbuphine in Nondependent Recreational Drug Users

Thomas Sciascia,[1] Amale Hawi,[1] Jack Henningfield,[2] Beatrice Setnik,[3] Megan Shram,[4] James Cassella[1]

[1]Trevi Therapeutics, New Haven, CT, USA; [2]Pinney Associates, Bethesda, MD, USA; [3]Alta Sciences, Overland Park, KS, USA; [4]Altreos Research Partners, Inc., Toronto, ON, Canada

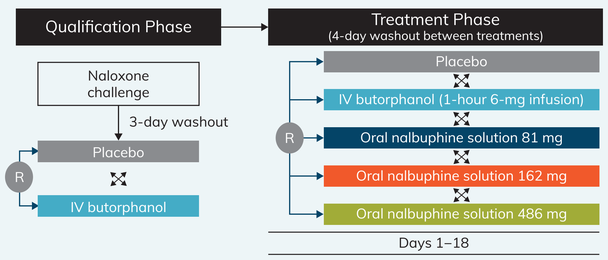
Background

- Oral nalbuphine extended-release (ER) tablets are being developed for the treatment of chronic cough in patients with idiopathic pulmonary fibrosis (IPF)[1,2] and refractory chronic cough (RCC)[3]
- Nalbuphine ER acts on the cough reflex arc both centrally and peripherally as a kappa agonist and a mu antagonist, targeting opioid receptors that play a key role in controlling chronic cough
- Treatment with nalbuphine ER significantly reduced cough frequency in patients with IPF[1] and RCC[3] in phase 2a proof-of-concept studies
- Although nalbuphine is not a controlled substance under the US Controlled Substances Act[4] in its parenteral form and is not included in the List of Narcotic Drugs Under International Control,[5] the central nervous system activity of nalbuphine necessitates an evaluation of its opioid pharmacology, potential for abuse, and physical dependence under Section 21 U.S.C. 811 of the US Controlled Substances Act (CSA)[6]
- The US Food and Drug Administration (FDA) requires an abuse potential assessment as part of the overall safety evaluation in a New Drug Application for any central nervous system–active compound, which informs the scheduling recommendation[6]
- This study aimed to investigate the abuse potential of oral solution nalbuphine compared with butorphanol and placebo in non-dependent, recreational opioid users

Methods

- Study design
  - Part 1: the suitability of butorphanol (listed in Schedule IV of the CSA)[7] as a positive control was assessed in an open-label single-dose study designed to characterize its pharmacokinetics, pharmacodynamics, and safety. This was necessary to identify an intravenous (IV) infusion regimen that could replicate the pharmacokinetic profile of intranasal butorphanol reported in published literature,[8,9] thereby ensuring it would serve as an appropriate comparator in Part 2
  - Part 2 (main study): randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover study (**Figure 1**)
  - The main study consisted of 2 phases (**Figure 1**):
    - Qualification phase: participants underwent a naloxone challenge to confirm they were not physically dependent on opioids before being randomly assigned to receive either placebo or IV butorphanol 6 mg as a 1-hour infusion, followed by a 3-day washout period
    - Treatment phase: participants were again randomly assigned to receive each of the 5 treatments: placebo, IV butorphanol 6 mg as a 1-hour infusion, and 3 single oral doses of nalbuphine solution (81 mg, 162 mg, and 486 mg), each separated by a 4-day washout period
- Inclusion criteria
  - Age 18-55 years
  - Body mass index 18.0-33.0 kg/m^2
  - Current opioid users with a history of using opioids for recreational (nontherapeutic) purposes ≥10 times in the past year and ≥1 time within the 8 weeks before screening
- Exclusion criteria
  - Self-reported history of substance or alcohol dependence within the past 2 years (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision)
  - Heavy smoker (≥20 cigarettes per day)
  - History or presence of any clinically significant abnormality or illness
- End points
  - Primary end point: peak effect (E_{max}) for "Drug Liking" ("at this moment"), assessed on a bipolar 100-point visual analog scale (VAS)
  - Secondary end points: subjective measures, physiological measures, pupillometry, and pharmacokinetics
  - End points were assessed using the modified completer population, defined as participants who completed all treatment periods and had sufficient primary end point data (including at least 1 Drug Liking VAS observation within 2 hours of T_{max} for each treatment). Participants with a Drug Liking E_{max} for butorphanol ≤55, with similar E_{max} scores across treatments (≤5-point difference), with a placebo E_{max} ≥95, or with a placebo–butorphanol E_{max} difference ≥5 points were not included in the modified completer population
  - Safety was evaluated by the incidence and severity of treatment-emergent adverse events (TEAEs), a range of clinical evaluations, and relationship to the treatment in the safety population (all participants who received any treatment during the treatment phase)

Figure 1. Study Design



IV, intravenous; R, randomization.

Results

- Of the 56 participants who were randomly assigned, 54 (96.4%) completed the treatment phase; 52 (92.9%) were included in the modified completer population
- Baseline characteristics are summarized in **Table 1**

Table 1. Baseline Characteristics

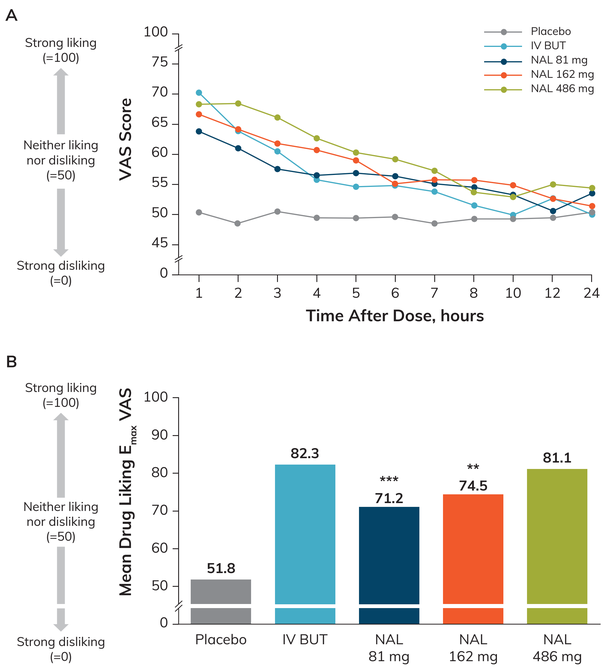
	Participants N=52
Age, mean (SD), years	33.9 (6.4)
Sex, n (%)	
Female	12 (21.4)
Male	40 (71.4)
Race, n (%)	
White	34 (60.7)
Black or African American	13 (23.2)
Asian	1 (1.8)
American Indian or Alaska Native	1 (1.8)
Native Hawaiian or Other Pacific Islander	1 (1.8)
Other	2 (3.6)

Modified completer population. Percentages do not add to 100 as the total number of randomly assigned participants was used as the denominator.

Primary End Point: Peak Effect for Drug Liking

- Mean Drug Liking VAS scores for nalbuphine generally peaked at 1 hour after dosing and then declined steadily over the 24-hour postdose period (**Figure 2A**)
  - IV butorphanol produced higher early VAS scores than all the nalbuphine doses but decreased numerically, similar to nalbuphine; placebo scores remained relatively stable and close to neutral across all time points (**Figure 2A**)
- IV butorphanol produced a higher VAS score than placebo validating the study. Both the 81-mg and 162-mg doses of nalbuphine resulted in significantly lower Drug Liking E_{max} compared with IV butorphanol (P<.0001 and P=.001, respectively) (**Figure 2B**)
  - The supratherapeutic dose of nalbuphine 486 mg showed a numerically lower Drug Liking E_{max} score compared with IV butorphanol, but the difference was not statistically significant (P=.322)
  - All doses of nalbuphine were not equivalent to placebo using the predefined 11-point margin

Figure 2. (A) Drug Liking VAS Over Time and (B) Drug Liking VAS E_{max} by Treatment

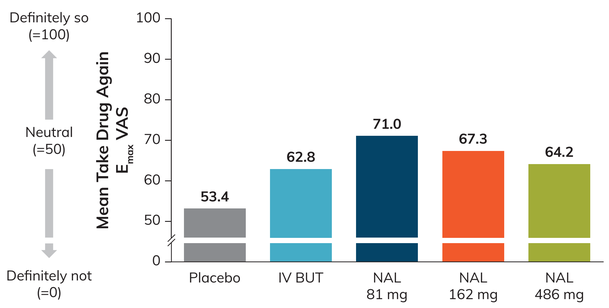


E_{max}, peak effect; IV BUT, intravenous butorphanol; NAL, nalbuphine; VAS, visual analog scale.
Modified completer population (n=52). *** P<0.0001; ** P<0.001; (NAL vs IV BUT).

Secondary End Points: Drug Effects

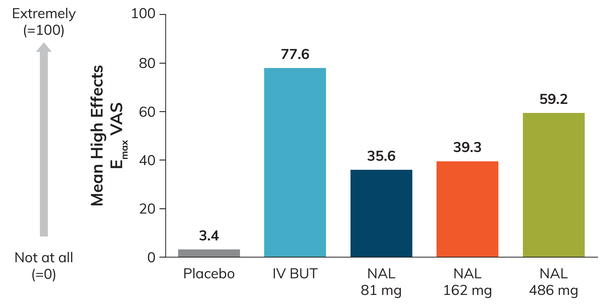
- Use of nalbuphine was associated with an inverse dose response on Take Drug Again VAS (**Figure 3**)
- High Effects VAS E_{max} scores for all doses of nalbuphine were lower than with IV butorphanol (**Figure 4**)
- Good Effects VAS E_{max} scores for all doses of nalbuphine were lower than with IV butorphanol (**Figure 5**)

Figure 3. Take Drug Again VAS E_{max}



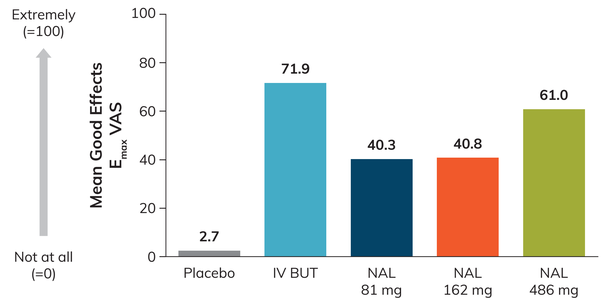
E_{max}, peak effect; IV BUT, intravenous butorphanol; NAL, nalbuphine; VAS, visual analog scale.
Modified completer population (n=52).

Figure 4. High VAS E_{max}



E_{max}, peak effect; IV BUT, intravenous butorphanol; NAL, nalbuphine; VAS, visual analog scale.
Modified completer population (n=52).

Figure 5. Good VAS E_{max}



E_{max}, peak effect; IV BUT, intravenous butorphanol; NAL, nalbuphine; VAS, visual analog scale.
Modified completer population (n=52).

- TEAEs showed moderate dose-dependent increases for nalbuphine, with the highest incidence observed for butorphanol and lowest with placebo
  - Nausea, headache, and irritability were reported as the most common TEAEs (**Table 2**)
  - Most TEAEs were mild (grade 1); no serious TEAEs were reported

Table 2. Treatment-Emergent Adverse Events

	Placebo n=54	IV BUT n=54	NAL 81 mg n=55	NAL 162 mg n=55	NAL 486 mg n=56
Any TEAE, n (%)	7 (13.0)	19 (35.2)	6 (10.9)	10 (18.2)	11 (19.6)
Severity					
Grade 1	4 (7.4)	15 (27.8)	5 (9.1)	7 (12.7)	10 (17.9)
Grade 2	2 (3.7)	4 (7.4)	1 (1.8)	3 (5.5)	0
Grade 3	1 (1.9)	0	0	0	1 (1.8)
Any serious TEAE, n (%)	0	0	0	0	0
Discontinuation due to TEAE, n (%)	0	0	0	0	0
Most frequent TEAEs (occurring in ≥5%)					
Nausea	0	9 (16.7)	2 (3.6)	3 (5.5)	5 (8.9)
Headache	2 (3.7)	5 (9.3)	1 (1.8)	1 (1.8)	4 (7.3)
Irritability	1 (1.9)	3 (5.4)	2 (3.7)	1 (1.8)	3 (5.5)

IV BUT, intravenous butorphanol; NAL, nalbuphine; TEAE, treatment-emergent adverse event.
Safety population.

Conclusions

- In this validated study, nalbuphine solution seemed to have similar or lower potential for abuse than IV butorphanol, a Schedule IV mixed agonist-antagonist opioid, across a variety of measures in recreational drug users with opioid experience
- Nalbuphine showed separation from placebo on the measures of drug liking and willingness to take the drug again, and nalbuphine was associated with numerically lower high effects and good effects than butorphanol, suggesting limited abuse potential
- Nalbuphine was well tolerated and no new safety signals were observed

References

1. Maher TM et al. *NEJM Evid.* 2023;2(8):EVIDoa2300083.
2. Smith JA et al. Presented at: European Respiratory Society (ERS) Congress; September 7-11, 2024; Vienna, Austria.
3. Trevi Therapeutics announces positive topline results from the phase 2a RIVER trial of Haduvio in patients with refractory chronic cough. News release. PRNewswire. March 10, 2025. Accessed April 17, 2025. https://ir.trevitherapeutics.com/2025-03-10-Trevi-Therapeutics-Announces-Positive-Topline-Results-from-the-Phase-2a-RIVER-Trial-of-Haduvio-in-Patients-with-Refractory-Chronic-Cough
4. US Department of Justice, Drug Enforcement Administration. Nalbuphine hydrochloride (trade name: Nubain®). April 2025. Accessed April 17, 2025. https://www.deadiversion.usdoj.gov/drug_chem_info/nalbuphine.pdf
5. International Narcotics Control Board. Analysis of the world situation. Annual Report. Geneva, Switzerland; 2022. Accessed April 17, 2025. https://www.incb.org/documents/Publications/AnnualReports/AR2022/Annual_Report_Chapters/060_Chapter_III.pdf
6. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Assessment of abuse potential of drugs: guidance for industry. January 2017. Accessed April 17, 2025. https://www.fda.gov/media/116739/download
7. Stadol (butorphanol tartrate) Injection, USP. Prescribing information (2024) Dayton, NJ: Geneva Pharmaceuticals Inc.
8. Walsh SL et al. *Psychopharmacology (Berl).* 2008;196:143-155.
9. Walsh SL et al. *Psychopharmacology (Berl).* 2001;157:151-162.

Abbreviations

BUT, butorphanol; E_{max}, peak effect; IPF, idiopathic pulmonary fibrosis; IV, intravenous; NAL, nalbuphine; R, randomization; RCC, refractory chronic cough; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

Acknowledgments

This study was sponsored by Trevi Therapeutics (New Haven, CT, USA). Medical writing assistance was provided by ApotheCom (San Francisco, CA, USA) and funded by Trevi Therapeutics.

Disclosures

TS is employed by Trevi Therapeutics and owns stock and stock options with Trevi Therapeutics. TS is listed as an inventor on issued and pending patents related to the use of nalbuphine (a kappa agonist–mu antagonist opioid) in chronic cough.

Presented at the College on Problems of Drug Dependence 87th Annual Scientific Meeting; June 14-18, 2025; New Orleans, Louisiana