Clinical Study Report

1 CLINICAL STUDY REPORT

Study Title:	Randomised, double-blind, placebo-controlled trial evaluating the effects of naltrexone hydrochloride nasal spray on alcohol consumption in Alcohol Use Disorder
Short Title:	Effects of intranasal naltrexone on AUD
Study Number:	OPNT002-AUD-001
Study Phase:	Phase II
Study Intervention:	Naltrexone hydrochloride nasal spray
Indication:	Alcohol use disorder (AUD)
Brief Description:	This was a 16-week, randomised, double-blind, placebo-controlled study to determine the safety and efficacy of naltrexone hydrochloride nasal spray in subjects with AUD. A sequential parallel comparison design (SPCD) was used to reduce placebo response.
Study Sponsor:	Opiant Pharmaceuticals (now a part of Indivior, Inc.)
Study Initiation Date:	10 January 2022 (first participant first visit)
Study Completion:	14 February 2023 (last participant last visit) The analyses presented in this report are based on a database lock date of 05 May 2023.
Regulatory Agency Identifier Number:	EuDRA CT: 2019-002859-42
Report Date:	12 February 2024

2 SYNOPSIS

Name of Sponsor/Company:

Opiant Pharmaceuticals (now a part of Indivior, Inc.)

Name of Study Intervention:

Naltrexone hydrochloride nasal spray

Study Title:

Randomised, double-blind, placebo-controlled trial evaluating the effects of naltrexone hydrochloride nasal spray on alcohol consumption in Alcohol Use Disorder

Study Number:

OPNT002-AUD-001

Study Phase:

Phase II

Number of Study Centre(s) and Countries:

This study was conducted in Hungary, Bulgaria, Poland, and the United Kingdom (UK). Twenty-four sites were activated (4 in Hungary, 8 in Bulgaria, 7 in Poland, and 5 in the UK), and 23 sites recruited subjects (1 activated site in Hungary did not enrol any subjects).

Publications (if any):

Not applicable.

Study Period:

The study was initiated on 10 January 2022 and the study was completed on 14 February 2023.

Methodology:

This was a 16-week, randomised, double-blind, placebo-controlled study to determine the safety and efficacy of naltrexone hydrochloride nasal spray in subjects with AUD. In this study, subjects were randomised to receive 1 of 2 doses of naltrexone hydrochloride or placebo at a 1:1:3 ratio, including a re-allocation in the second 8-week period for placebo nonresponders to 1 of 2 doses of naltrexone hydrochloride or placebo at a 1:1:1 ratio. Based on previous AUD studies, a 65% placebo response was anticipated during the last 4 weeks of the first 8-week period.

This study employed a sequential parallel comparison design (SPCD). SPCD protocols consist of 2 treatment phases of equal duration: the first phase uses an unbalanced design between placebo and active, with more subjects assigned to receive placebo. In the second phase, subjects who did not respond to placebo are re-randomised to receive either active or placebo. Subjects who are re-randomised in the second phase have, in essence, already failed to respond to placebo, so their placebo response in this second phase should be reduced.

Number of Participants (Planned and Analysed):

Per the sample size calculations, 300 subjects were planned. The actual number of participants (randomised and treated) was 306.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The main inclusion criteria were subjects with AUD of at least moderate severity who were seeking treatment, who satisfied all eligibility criteria, and who gave their written, informed consent prior to any study-specific procedures. Other inclusion criteria included age of 18 to 70 years; World Health Organization (WHO) Drinking Risk Level of High Risk or Very High Risk (male = at least 60 g ethanol per day on average; female = 40 g ethanol per day on average) within the 28 days prior to Screening and within 28 days prior to Baseline visit; and stable housing at Screening and for the duration of the study.

The main exclusion criteria included (but were not limited to) the following:

1. More than 7 consecutive days of abstinence immediately prior to Baseline
2. History of severe drug use, neurological condition, concurrent disease, or severe mental illness considered by the investigator to be clinically significant in the context of the study
3. Known allergic reaction to naltrexone or to the excipients of the investigational medicinal product (IMP) and/or placebo
4. Current use of any prohibited medication as per protocol requirements
5. Ethyl glucuronide (EtG) test at Screening and/or Baseline that was inconsistent with self-reported drinking on the prior day (ie, a negative test (<500 ng/ml) when subject reports heavy drinking on the prior day)
6. Significant nasal rhinitis or other conditions that restrict nasal airflow or abnormal nasal anatomy, at Screening and/or Baseline
7. Women of childbearing potential (unless acceptable use of effective contraception and willing and able to continue contraception for 1 month after the last administration of IMP
8. Women who were pregnant or breastfeeding at Screening or Baseline
9. At risk of alcohol withdrawal syndrome as indicated by any of the following:
    a) score >10 on the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar)
    b) history of medical detoxification in the past 4 weeks prior to Screening
    c) history of seizures, delirium, or hallucinations during alcohol withdrawal
    d) history of seizures other than childhood febrile seizures
10. Subjects with any laboratory tests from samples taken at Screening considered to be clinically significant by the Investigator, including elevation of liver enzymes:
    a) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal or

b) bilirubin greater than or equal to 1.5 times the upper limit of normal in the UK, and AST or ALT >4 times the upper limit of normal or
c) bilirubin greater than or equal to 2 times the upper limit of normal in the European Union (EU)

11. Current suicidal ideation (yes to either question 1 or 2 on the Columbia Suicide Severity Rating Scale [C-SSRS]) at Screening or Baseline and/or history of suicidal behaviour in the past 5 years; considered by the Investigator to be clinically significant in the context of the study, prior to Screening
12. On probation or parole at Screening
13. Deemed unlikely to be able to comply with the requirements of the protocol

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Subjects were randomised to receive either naltrexone nasal spray 30 mg/ml (hereafter, NTX 30 mg/ml), naltrexone nasal spray 12 mg/ml (hereafter, NTX 12 mg/ml), or matching placebo nasal spray. All subjects were provided with one nasal spray bottle at each of the following visits: Baseline, Week 4, Week 8, and Week 12.

The subject was instructed to administer IMP nasally, 1 spray in 1 nostril once daily. The administration was to occur roughly the same time each day, at a time the subject felt at greatest risk to start drinking alcohol. An additional daily dose, as needed, of 1 spray in 1 nostril, at least 2 hours after the first dose, could be administered in response to alcohol craving, anticipation of high-risk situations, or in anticipation of or following alcohol consumption (within 24 hours from 5 a.m. each day) for 16 weeks.

Duration of Study Intervention:

Each subject's participation in the study was expected to last 21 weeks (including a 1-week screening period, a 16-week treatment period, and 4-week follow-up phase).

Objectives, Endpoints, Estimands, and Statistical Methods

Listed below are the objectives and endpoints that are described in this report.

Objectives	Endpoints	Statistical Analyses
Primary		
To determine whether treatment with naltrexone hydrochloride nasal spray results in at least a 2-level reduction in WHO Drinking Risk Level determined by grams per day	The proportion of subjects who show at least a 2-level reduction in WHO Drinking Risk Level from Baseline to end of treatment (EOT) (as evaluated in the 28 days prior to the Baseline and EOT visits)	A logistic regression model was used, with treatment (NTX 30 mg/ml, NTX 12 mg/ml, and placebo), the stratification factors at randomisation (EtG of less than 500 ng/ml [abstinent] and nicotine use in the prior week), and the baseline

Objectives	Endpoints	Statistical Analyses
		value of WHO Drinking Risk Level as a predictor in the model. The results are presented using model-based estimates of the odd ratios of each active treatment group versus the placebo group with corresponding 95% confidence intervals (CIs) and *P* values. Each stage was modelled and presented separately; a combined result was also calculated.
Secondary		
To determine whether naltrexone hydrochloride nasal spray reduces time to achieve at least a 2-level reduction in WHO Drinking Risk Level that is maintained until the end of the trial	Time to a 2-level risk reduction in WHO Drinking Risk Level that is maintained until the EOT	Time to event life table methodology was used to estimate the median, 25th percentile, and 75th percentile for time to a 2-level risk reduction in WHO Drinking Risk Level that is maintained until the EOT. The 95% CI for median time of 2-level risk reduction was calculated using the Brookmeyer and Crowley method and a log-log transformation (Brookmeyer 1982).
To determine the effects of naltrexone hydrochloride nasal spray on No Heavy Drinking days	Proportion of subjects with No Heavy Drinking days, by month	The proportion of subjects with no heavy drinking days at each timepoint was compared using a logistic regression model including the treatment group, the stratification

Objectives	Endpoints	Statistical Analyses
		factors at randomisation, and the baseline value of heavy drinking days were included. Each stage was modelled and presented separately, and a combined result was also calculated.
To determine the effects of naltrexone hydrochloride nasal spray on abstinence from alcohol	Number of consecutive days abstinent during treatment, by month	Consecutive days abstinent were compared separately for each timepoint using an analysis of covariance (ANCOVA), including treatment group, the stratification factors at randomisation, and the baseline value. Each stage was modelled and presented separately, and a combined result was also calculated.
To determine the effects of naltrexone hydrochloride nasal spray on grams of ethanol per day	Mean total alcohol grams per day, by month	The mean total alcohol grams per day was analysed using ANCOVA, including treatment group, the stratification factors, and the baseline value. The least squares mean (LSM) estimate of the difference between NTX 30 mg/ml, NTX 12 mg/ml, and placebo alongside the 95% CI was calculated for each stage. Each stage was modelled and presented separately, and a combined result was also calculated

Objectives	Endpoints	Statistical Analyses
To determine the effects of naltrexone hydrochloride nasal spray on percentage of heavy drinking days	Percentage heavy drinking days, by month	The proportion of subjects with no heavy drinking days at each timepoint was compared using a logistic regression model including the treatment group, the stratification factors at randomisation, and the baseline value of heavy drinking days were included. Each stage was modelled and presented separately, and a combined result was also calculated
To determine the effects of naltrexone hydrochloride nasal spray on percentage of drinking days based on timeline followback (TLFB) interview by month	Percentage of drinking days, by month	Percentage of drinking days was analysed using an ANCOVA, including treatment group, the stratification factors at randomisation, and the baseline value. Each stage was modelled and presented separately, and a combined result was also calculated.
To determine whether treatment with naltrexone hydrochloride nasal spray results in at least a 1-level reduction in WHO Drinking Risk Level determined by grams per day	The proportion of subjects showing an improvement in WHO Drinking Risk Level consisting of a 1-level reduction from Baseline to EOT	The same statistical methods as used for the primary endpoint were used for the analyses of 1-level reduction.

Objectives	Endpoints	Statistical Analyses
To determine the effects of naltrexone hydrochloride nasal spray on the average number of drinks consumed on days when the extra as-needed dose was taken based on self-reported TLFB reports by month	Number of drinks consumed on days when the extra as-needed dose was taken, by month	The number of drinks consumed on days when the extra as-needed dose was taken was analysed using an ANCOVA, including treatment group and the stratification factors at randomisation. Each stage was modelled and presented separately.
To determine the effects of naltrexone hydrochloride nasal spray on alcohol craving by month (Mini Alcohol Craving Experience Questionnaire)	Alcohol craving by month (Mini Alcohol Craving Experience Questionnaire)	The questionnaire results were analysed using an ANCOVA in which treatment group and questionnaire score at Baseline were included. The stratification factors were considered in the analysis. The LSM estimate of the difference between NTX 30 mg/ml, NTX 12 mg/ml, and placebo alongside the 95% CI were calculated for each stage. The overall, combined treatment effect was estimated using the LSM from the ANCOVA models.
To examine the effects of naltrexone hydrochloride nasal spray on nicotine use among smokers	Change in nicotine use from Baseline to Week 16	Only subjects considered smokers at Baseline were included in the analysis of nicotine use. The change from Baseline to Week 16 in the amount of nicotine used in (mg) per week was analysed using an ANCOVA, including treatment group, the stratification factors, and

Objectives	Endpoints	Statistical Analyses
		the baseline value. The LSM estimate of the difference between NTX 30 mg/NTX 12 mg/ml and placebo alongside the 95% CI were calculated
To determine the effects of naltrexone hydrochloride nasal spray on Positive Affect score by month	Positive and Negative Affect Scale (PANAS) by month	The PANAS results were analysed using an ANCOVA, including treatment group, the stratification factors at randomisation, and the baseline value. Each stage was modelled and presented separately, and a combined result was also calculated
To determine the effects of naltrexone hydrochloride nasal spray on Negative Affect score by month	PANAS by month	Same as above for Positive Affect score.
Safety		
To evaluate the safety of naltrexone hydrochloride nasal spray in the treatment of AUD	• Number and proportion of subjects with adverse events • Assessment of clinical laboratory parameters • Assessment of vital signs • Nasal irritation score • CIWA-Ar • C-SSRS	• Adverse events (AEs) were coded using the MedDRA coding system (version 25.1). Any AE that emerged or worsened relative to pretreatment Baseline was considered a treatment emergent AE (TEAE). Standard summary presentations of TEAEs are provided. • Clinical laboratory and vital signs data were

Objectives	Endpoints	Statistical Analyses
		summarised with shift tables. • Nasal irritation, smell test, and physical examination data were summarised descriptively and with shift tables. • The CIWA-Ar and C-SSRS results are summarised descriptively.

Summary of Results and Conclusions:

Demographic and Other Baseline Characteristics:

A total of 306 subjects were randomised and treated in Stage I: 206 in the placebo group, 47 in the NTX 12 mg/ml group, and 53 in the NTX 30 mg/ml group. The majority of subjects (≥87%) in all treatment groups completed Stage I. The group of placebo subjects who were nonresponders, completed Stage I, and were then re-randomised and treated in Stage II comprised 23 subjects who received placebo in both stages, 34 who received placebo in Stage I and NTX 12 mg/ml in Stage II, and 30 who received placebo in Stage I and NTX 30 mg/ml in Stage II. In these former placebo groups, the numbers of subjects who completed Stage II ranged from 82% to 93%.

The majority of subjects in all treatment groups were male and White; the mean age of subjects was 47.0 years. There were no clinically relevant differences between groups in distribution of demographic and baseline characteristics.

Exposure:

In both Stage I and Stage II, the duration of exposure was generally as expected per the protocol (mean of ~54 days [~8 weeks]) across treatment groups. The median number of days of >1 dose fluctuated by treatment group and by study stage, and no definitive trends were noted.

Efficacy Results:

The primary efficacy variable was the proportion of subjects with an improvement in WHO Drinking Risk Level consisting of at least a 2-level reduction from Baseline to EOT. In Stage I, approximately half of subjects in each treatment group had a 2-level reduction and half did not; the proportions of subjects with a 2-level reduction were similar among randomised groups. The differences between placebo and NTX-treated groups (12 mg/ml or 30 mg/ml) were not statistically significant at a nominal 2-sided

P value (ie, the *P* value was >0.05). In Stage II, the differences in the proportions of subjects with a 2-level reduction between placebo and NTX-treated groups were similar. The Stage I and Stage II combined difference was also not significant.

In Stage II of the study, the proportion of placebo responders for 2-level reduction in WHO Drinking Risk Level was much lower than in Stage I, which supports that the study design (SPCD) was successful in reducing placebo response in Stage II.

Small improvements in some secondary efficacy endpoints were observed; however, there were no clinically meaningful differences between NTX and placebo treatments overall.

Safety Results:

- The overall incidence of TEAEs ranged from 35% to 53% of subjects in Stage I and from 22% to 30% of subjects in Stage II. The incidence of treatment-related TEAEs ranged from 24% to 43% in Stage I and from 7% to 27% in Stage II.
- One subject in the NTX 12 mg/ml group had a TEAE of accidental death, considered unrelated to study drug. Four other subjects had nonfatal serious adverse events (SAEs), all of which were considered unrelated to the study drug.
- In addition to the subject who died in an accident, 7 subjects discontinued study drug due to TEAEs. No individual TEAE leading to discontinuation was reported for more than 1 subject each.
- Headache, nasal discomfort, and rhinorrhoea were the most commonly reported TEAEs in Stage I; nasal discomfort was the most commonly reported TEAE in Stage II.
- No clinically meaningful results or trends were observed in clinical laboratory tests, vital signs, physical examination findings, nasal irritation scores, or the results from the CIWA-Ar.
- Six subjects reported 7 events of a clinically significant risk of suicide on the C-SSRS; none of these subjects had any temporally associated TEAEs associated with these reports.

Conclusions:

- The study did not achieve its primary efficacy endpoint, a 2-level reduction in WHO Drinking Risk Level from Baseline to EOT in a higher proportion of subjects treated with NTX than treated with placebo.
- In Stage II of the study, the proportion of placebo responders for 2-level reduction in WHO Drinking Risk Level was much lower than in Stage I, which supports that the study design (SPCD) was successful in reducing placebo response in Stage II.
- Small improvements in some secondary efficacy endpoints were observed; however, there were no clinically meaningful differences between NTX and placebo treatments overall.
- IN administration of NTX was well-tolerated with an acceptable safety profile in this subject population with AUD.

Date and Version of This Report:

Final 12 February 2024