ABBREVIATED CLINICAL STUDY REPORT

Randomised, double-blind, placebo-controlled trial evaluating the effects of naloxone hydrochloride nasal spray on eating behaviours in bulimia nervosa

Sponsor study code:	OPNT001-BN-001
LINK study code:	OPI001
EudraCT number:	2016-003107-65
Report version and date:	Version 1.0, 2019-11-01
Phase:	Phase II
Proposed indication:	Eating behaviours in bulimia nervosa
Chief investigator:	Janet Treasure Eating Disorders Unit, Institute of Psychiatry, Kings College London 103 Denmark Hill London SE5 8AF, UK
Sponsor:	Opiant Pharmaceuticals Inc. 233 Wilshire Blvd, Suite 280 Santa Monica, CA 90401, USA
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Contract research organisation:	LINK Medical Research AB Kungsängsvägen 19 SE-753 23 Uppsala, Sweden Telephone: +46 (0)18-431 3100 Fax: +46 (0)18-431 3001
First patient's first visit (screening):	2017-04-26
Last patient's last visit:	2018-11-02

1 SIGNATURES

Study Title: Randomised, double-blind, placebo-controlled trial evaluating the effects of naloxone hydrochloride nasal spray on eating behaviours in bulimia nervosa

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Chief Investigator:

Janet Treasure 04 NOV 19

Prof. Janet Treasure — Date

Eating disorders Unit, King's College London

Sponsor's representative:

_____ _____

Dr Mark Ellison

VP Manufacturing, Development & Quality

Opiant Pharmaceuticals — Date

Biostatistician:

_____ _____

Johanna Tilly, MSc, Senior Biostatistician

LINK Medical Research AB — Date

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Prof. Janet Treasure — Date

Eating disorders Unit, King's College London

Sponsor's representative:

5 November 2019.

Dr Mark Ellison

VP Manufacturing, Development & Quality

Opiant Pharmaceuticals — Date

Biostatistician:

2019-11-05

Johanna Tilly, MSc, Senior Biostatistician

LINK Medical Research AB — Date

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2 SYNOPSIS

Name of Sponsor/company: Opiant Pharmaceuticals	
Name of finished product: Naloxone hydrochloride 40 mg/ml nasal spray	
Name of active ingredient: Naloxone hydrochloride	
Study title: Randomised, double-blind, placebo-controlled trial evaluating the effects of naloxone hydrochloride nasal spray on eating behaviours in bulimia nervosa	
Chief investigator: Prof. Janet Treasure Eating disorders Unit, King's College London	
Study centres: Patients were recruited at 17 centres, in the UK	
Publication(s) based on the study: Not applicable	
Studied period: First patient first visit (screening): 2017-04-26 Last patient last visit 2018-11-02	**Phase of development:** Phase II

Objectives:

Primary objective: to determine whether treatment with naloxone hydrochloride nasal spray reduces binging behaviour in bulimia nervosa

Secondary & tertiary objectives:

- Determine the effects of naloxone hydrochloride nasal spray on immediate eating behaviours
- Determine the effects of naloxone hydrochloride nasal spray on eating behaviours
- Determine the effects of acute and chronic dosing

Safety objective: to evaluate the safety of naloxone hydrochloride nasal spray in the treatment of bulimia nervosa

Study design:

This was a 12-week, randomised, double-blind, placebo-controlled, parallel group multicentre study to determine the safety and efficacy of naloxone hydrochloride nasal spray in bulimia nervosa. The study included a 2-week screening period, an 8-week treatment phase (including a baseline/randomisation visit) and a 2-week follow-up phase.

Patients were recruited from eating disorder clinics, as well as identified through advertising of the study. Prior to any study specific procedures being conducted, patients had to provide written informed consent.

After screening assessments, eligible patients had to complete an eating disorder questionnaire (EDE-Q) and a food craving questionnaire (FCQ). Patients were trained on the use of the eDiary and asked to record, twice daily, the number of binging urges, number of binging episodes, number of purging episodes, food intake and any changes in their condition or concomitant medication from the previous day. Patients were asked to complete the eDiary over the subsequent 2 weeks.

At baseline (Day 1) patients were assessed for clinical laboratory parameters, opioid drug use and pregnancy (in patients of childbearing potential).

Patients compliant with the inclusion and exclusion criteria were randomised on a 1:1 basis to 1 of 2 treatment groups:

Group A (active treatment): Naloxone hydrochloride 40 mg/ml nasal spray

Group B (placebo treatment): Placebo nasal spray

After randomisation, patients completed a series of tests and examinations, including examination of the nasal mucosa and visual analogue scale (VAS) assessments on mood, craving, hunger, anxiety, purging and feeling full.

Patients were asked to prime the nasal spray by actuating the spray 4 times and then self-administer 1 dose of nasal spray (0.1 ml of naloxone hydrochloride 40 mg/ml or matching placebo). Following administration of the investigational medicinal product (IMP) patients had to complete a taste test and repeat the examination of the nasal mucosa and the VAS assessments.

During the following 4 weeks, patients were to self-administer 1 dose of the IMP, in 1 nostril, in response to a binging urge. One dose consisted of 0.1 ml of the 40 mg/ml naloxone hydrochloride formulation or placebo nasal spray. Patients were allowed to administer up to 2 doses per day in response to a binging urge ("a day" being defined as within 24 hours from 6 am). The second dose was to be administered at least 2 hours after the first dose. The nasal spray had to be primed once a day, just before the first dose, by actuating the spray 4 times.

A telephone follow-up was conducted at Week 1 and a remote review of the eDiary at Weeks 2 & 3 to ensure completion of the eDiary and IMP compliance and tolerability. Optional examination of the nasal mucosa was scheduled as needed.

Patients visited the study clinic at Week 4 for eDiary review, IMP compliance and tolerability, as well as physical examinations, including examination of the nasal mucosa. New packs of IMP were provided, and patients were asked to repeat the administration of the IMP for 4 additional weeks (1 dose of IMP nasally in 1 nostril once daily as needed plus 1 additional dose, at least 2 hours after the first dose, in response to a binging urge).

The eDiary was remotely reviewed at Weeks 5, 6 & 7 to ensure completion of the eDiary and IMP compliance and tolerability. If there was evidence of persistent nasal inflammation considered by the Investigator to be clinically significant, the patient was to attend an extra visit to conduct an examination of the nasal mucosa before the next scheduled visit.

At Week 8, patients visited the study clinic for eDiary review and physical examinations, including examination of the nasal mucosa, blood sampling, vital sign assessments, pregnancy test (in patients of childbearing potential) and VAS on mood, craving, hunger, anxiety, purging and feeling full.

Patients were asked to prime the nasal spray by actuating the nasal spray 4 times and then self-administer 1 dose of the naloxone hydrochloride 40 mg/ml nasal spray or matching placebo nasal spray. Following IMP administration patients had to complete a taste test (approximately 20-40 minutes after dosing) and repeat VAS (on mood, craving, hunger, anxiety, purging and feeling full) on completion of the taste test. In addition, they had to perform a smell test, EDE-Q, FCQ and examination of the nasal mucosa within 2 hours after dosing.

Patients wishing to withdraw prior to the end of the study were asked to undertake the Week 8 procedures. This included patients who withdrew due to intolerance.

Two weeks after last visit, at Week 10, patients were contacted by telephone for follow-up on adverse events (AEs) and medications. All routine blood analyses, including screening labs, were performed locally.

Due to lack of expected efficacy (primary endpoint), it was decided by the Sponsor that an abbreviated CSR should be created. This report therefore contains a full description of safety data but only a summary of efficacy data.

Number of patients (planned and analysed):

	Total	Test drug (active group)	Placebo drug (placebo group)
No. planned:	82	41	41
No. randomised/treated:	87/86	44/44	43/42
Males/females:	All patients were females, in accordance with the inclusion criteria		
Mean age/range (years):	36 /18-60	32/19-51	34/18-60
No. analysed for efficacy			
Intent-to-treat analysis set (ITT):	87	44	43
Per protocol analysis set (PPAS):	49	26	23
No. analysed for safety:	86	44	42
No. completed:	60	31	29

Diagnosis and main criteria for inclusion:

For inclusion in the study, patients had to satisfy all the following criteria:

1. Female aged 18 to 60 years, fluent in English, having provided written informed consent prior to any study specific procedure being conducted
2. Diagnosis of bulimia nervosa according to Diagnostic and Statistical Manual of Mental Illness's (5th Edition) criteria by The Structured Clinical Interview for the DSM-5- Research Version (SCIDRV) prior to screening
3. Patients reporting at least 1 binging day per week during screening

Exclusion criteria included:

- Severe comorbidity (e.g., substance abuse, drug addiction, psychosis, diabetes)
- Taking any prohibited medication (opioid analgesics, any medication delivered to the nose)
- Opioids (must have been discontinued at least 4 weeks prior to screening)
- Any fluoxetine or antidepressant treatment (unless it has been administered at a stable dose for a minimum of 12 weeks prior to screening and remained at a stable dose throughout the trial)
- Any cognitive behavioural therapy (CBT) or other behavioural therapies (unless it was completed or had currently been receiving CBT or other behavioural therapies for more than 8 weeks prior to screening. No new CBT or other behavioural therapies started during the trial)
- Any nasal conditions including abnormal nasal anatomy, nasal symptoms (i.e. blocked and/or runny nose, nasal polyps etc.), or having product sprayed in to the nasal cavity prior to drug administration

Test product, dose and mode of administration, batch number:

40 mg/ml Naloxone hydrochloride nasal spray
Batch numbers: 16045 for packs 1001-1158 and 18015 for packs 2001-2036

Reference product, dose and mode of administration, batch number:

Placebo nasal spray
Batch numbers: 16045 for packs 1001-1158 and 18015 for packs 2001-2036

Duration of treatment:

IMP was administered as needed in response to a binging urge 1-2 times daily for 8 weeks

Efficacy assessments:

Efficacy was evaluated by eDiary, taste test, VAS on mood, hunger, craving, purging, anxiety and feeling full, FCQ and EDE-Q.

Primary efficacy endpoint: Number of binging days from baseline to Week 8.

Secondary efficacy endpoints:

- Number of binging episodes from baseline to Week 8
- Abstinence of binging at Week 8 for at least a 2-week period
- Purging behaviour at Week 8
- Total number of calories in the taste test at Week 8
- Total number of calories in the taste test at baseline
- EDE-Q at Week 8
- VAS at Week 8
- FCQ at Week 8

Tertiary efficacy endpoints:

- Number of binge days at study end (Weeks 7 & 8)
- Number of purge days at study end (Weeks 7 & 8)
- Number of binge urge days at study end (Weeks 7 & 8)
- Responders 50% or greater reduction in binging at study end (Weeks 7 & 8) compared to baseline (Screening weeks 1 & 2)

Safety assessments:

Safety was evaluated by assessment of the parameters listed under safety endpoints.
Safety endpoints:

- Number and proportion of subjects with AEs
- Assessment of clinical laboratory parameters
- Assessment of vital signs
- Body weight from baseline to Week 8
- Examination of nasal mucosa
- Smell test
- Physical examination

Statistical methods:

Count variables were analysed using negative binomial model. Dichotomous response variables were analysed with logistic regression. Continuous endpoints were analysed using analysis of covariance model.

The safety endpoints were summarised using descriptive statistics or frequency and percentages depending on the type of data.

SUMMARY OF RESULTS

EFFICACY RESULTS:

There was no statistically significant difference in binging days (15.4 days vs. 16.1 days) between the active and the placebo groups (estimated ratio between groups: 0.96; 95% CI: 0.71-1.30; p=0.78, ITT analysis set). Thus, the intended IMP effect was not achieved.

Regarding the secondary and tertiary variables, the active group had fewer purging episodes compared to the placebo group when controlling for number of purging episodes during the last 2 weeks before baseline

(20 vs 30 episodes; p=0.045, Table 14.32) and better mood according to VAS score when controlling for baseline VAS (p=0.02, Table 14.40). There was no difference between the active and the placebo groups in any other variables (p>0.05)

SAFETY RESULTS:

Adverse events

- There were in total 372 AEs reported by 79 patients (92%) in the Safety analysis set in this study. Of those, 319 were TEAEs and were reported by 75 patients (87%). There was no notable difference in the number of patients that reported AEs in each treatment group.
- The most common TEAEs were headache (comparably reported in both treatment groups) and nausea (reported more in the active treatment group).
- There were 3 SAEs in the study: mood altered and suicidal ideation (Patient #0802, placebo group), which were assessed as SUSARs and did not resolve, and back pain (Patient #0907, active group), which was assessed as not related to IMP and from which the patient recovered with sequelae.
- Overall, 66 TEAEs were judged as related to IMP and most of them were reported in the active treatment group (52 AEs). Of those 66, 2 TEAEs led to drug discontinuation and patient withdrawal: mood altered and suicidal ideation (Patient #0802, placebo group).
- Most TEAEs were mild in intensity in both treatment groups. Three patients had severe AEs not related to IMP.

Clinical laboratory evaluation, vital signs, physical examination and other safety observations

- There were occasional clinically significant safety findings in the laboratory safety measurements, vital signs assessments and physical examinations but overall no major differences in these safety parameters between the active and placebo treatment groups.
- Overall, most patients in both treatment groups had “normal appearing mucosa, no bleeding”. At Weeks 4 and 8, there was 1 patient in the placebo group and 7-8 patients in the active group with “inflamed mucosa, no bleeding”.
- No notable changes were found in smell test over time and no differences were observed between the 2 treatment groups.

OVERALL CONCLUSIONS:

- The primary analysis in the study (to determine whether of naloxone hydrochloride nasal spray reduces binging behaviour) did not show the intended effect of the drug.
- The IMP was generally tolerated with no major safety concerns identified, except for 2 treatment-related SAEs in 1 patient (defined as SUSARs) that led to patient withdrawal, but were unlikely to be a direct adverse pharmacological effect of the IMP itself.