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Efficacy and Tolerability of Long-Acting Injectable Formulation of Nalmefene (Nalmefene Consta 393.1 mg) for Opioid Relapse Prevention: A Multicentre, Open-Label, Randomised Controlled Trial

Sead Kadric*, Hanns Mohler, Olli Kallioniemi, Karl Heinz Altmann

Division for Academic Research AURUM Group, London, United Kingdom
Email: *seadkadric@aurumgroup.org.uk

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Abstract

Objective: To determine the efficacy and tolerability of a long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) for the treatment of opioid-dependent patients. **Design, Setting, and Participants:** A 12 weeks, open-label, randomised controlled trial conducted between June 2009-July 2011, at 14 Hospital-based drug clinics, in the 12 countries. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder. Of the 3200 individuals screened, 3000 (93.7%) adults were randomized 1500 participants to receive injections of Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) given intramuscularly once in 12 weeks and 1500 participants to receive extended-release Naltrexone (Vivitrol 380 mg), administered intramuscularly every fourth week for 12 weeks. **Main Outcomes and Measures:** The primary endpoints (protocol) were: Confirmed Opioid abstinence (percentage *i.e.* the number of patients who achieved complete abstinence during week 12). Confirmed abstinence or "opioid-free" was defined as a negative urine drug test for opioids and no self-reported opioid use. Weeks 1 - 4 were omitted from this endpoint to allow for stabilization of abstinence. Secondary end points included a number of days in treatment, treatment retention and craving. The study also investigated, on 275 participants, degree and time course of mu-opioid receptor occupancy following single doses of Nalmefene extended-release injection (Nalmefene Consta 393.1 mg) as well as the plasma concentration of Nalmefene and Nalmefene-3-O-glucuronide. Safety was assessed by adverse event reporting. **Results:** Of 3000 participants, mean (SD)

age was 27.1 (±4.8) years and 831 (27.7%) were women. 1500 individuals were randomized to receive injections of Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) and 1500 to receive injections of extended-release Naltrexone (Vivitrol 380 mg); 2088 participants (69.6.0%) completed the trial. **Primary endpoints: Confirmed Opioid Abstinence:** Complete abstinence was sustained by 86% (n = 1290) of Nalmefene patients (patients treated with Nalmefene Consta 393.1 mg, long-acting depot formulations) compared with 43% (n = 645) of patients treated with extended-release Naltrexone 380 mg (Vivitrol), during weeks 5 - 12 (χ^2 = 672.34, P < 0.0001). **Secondary Endpoint: Craving:** A statistically and clinically significant reduction in opioid craving was observed with Nalmefene (Nalmefene Consta 393.1 mg, long-acting depot formulations) vs. Naltrexone (extended-release Naltrexone, Vivitrol 380 mg) by week 4 (P = 0.0048), which persisted every week through 12 (P < 0.0001). Patients given Nalmefene (Nalmefene Consta 393.1 mg, long-acting depot formulations) had a 75% decrease in craving from baseline to week 12. Patients given a Naltrexone (extended-release Naltrexone, Vivitrol 380 mg) had a 3% increase in craving from baseline to week 12 (Mean change in self-reporting craving). **Secondary Endpoint: Treatment Retention:** Long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) helped significantly more patients complete 12 weeks treatment (n = 1245, 83%) compared with extended-release Naltrexone (Vivitrol 380 mg) (n = 570, 38%) (χ^2 = 635.53, P < 0.0001). Patients on long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) had longer treatment retention than patients on extended-release Naltrexone (Vivitrol 380 mg). **Concentrations of Nalmefene and Nalmefene-3-O-Glucuronide in Plasma:** Analyses were made of 275 study sample. There was no statistically significant difference for plasma nalmefene concentrations between days 2 and 84 (p = 0.416). The plasma concentration of Nalmefene were 20.3 and 28.5 ng/ml and concentrations of nalmefene-3-O-glucuronide were 2.1 and 4.1 ng/ml, respectively. Plasma levels of Nalmefene remained above 20 ng/ml for approximately 12 weeks after administration of Nalmefene, long-acting depot formulations (Nalmefene Consta 393.1 mg). **PET Assessments:** Very high *mu*-opioid receptor occupancy by Nalmefene was detected 1 day after treatments at which time point the occupancy was 100.0% after Nalmefene injection (Nalmefene Consta 393.1 mg). Nalmefene Consta 393.1 mg injection (long-acting intramuscular formulation of Nalmefene) led to a very high occupancy of *mu*-opioid receptors in all brain areas examined; the thalamus, caudate nucleus, and frontal cortex. Depending on the brain area *mu*-opioid receptor occupancy varied between 83.0% and 85.8% 84 days after dosing. **Adverse Reactions:** Adverse events were similar in opioid-dependent patients treated with long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) vs. patients treated with extended-release Naltrexone (Vivitrol 380 mg). **Conclusions and Relevance:** Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) was more effective then extended-release Naltrexone (Vivitrol 380 mg) in maintaining short-term abstinence from heroin and should be considered as a treatment

option for opioid-dependent individuals.

Keywords

Nalmefene Consta, Long-Acting Depot Formulations of Nalmefene, Opioid Dependence, Long-Term Delivery, PLGA Polymers

1. Introduction

Rates of opioid dependence throughout the world have been on the increase. Opioid dependence is a major public health concern because of increased morbidity and mortality, poor social functioning, unemployment, and crime associated with this disorder. Opioid dependence is a chronic disorder requiring long-term treatment [1]. Effective options for managing the disorder include several pharmacotherapy agents (methadone, buprenorphine, naltrexone, nalmefene) and psychosocial interventions [2] [3]. However, relapse following cessation of treatment is high, with only an estimated 25% of heroin-dependent individuals remaining abstinent after receiving methadone treatment. Relapse following non-compliance with oral Naltrexone is a particular concern. Episodes of opioid use during non-compliance have been associated with relapse to full opioid dependence [4] [5]. Concerns about compliance with oral Naltrexone led to the development of an extended-release formulation of injectable Naltrexone (Vivitrol) [6]. The efficacy of Vivitrol for the prevention of relapse to opioid dependence following detoxification was demonstrated in many clinical studies [6] [7]. Although Vivitrol has shown efficacy for opioid dependence over a short period of time, the chronic, relapsing nature of this disorder has led to questions regarding long-term treatment, specifically. Nalmefene Consta 393.1 mg (long-acting intramuscular formulation of Nalmefene) is a depot formulation of the opioid receptor antagonist Nalmefene. Nalmefene (also known 17-cyclopropylmethyl-4,5*α*-epoxy-6-methylenemorphinan-3,14-diol and marketed under the trade name Selincro® is an opioid antagonist medication [8]. Nalmefene is an opiate derivative similar in both structure and activity to the opioid antagonist Naltrexone [8] [9]. Advantages of Nalmefene relative to Naltrexone include longer half-life, greater oral bioavailability and no observed dose-dependent liver toxicity. An oral formulation of Nalmefene was approved in 1995 for the treatment of opioid dependence (the indication: "the blockade of effects of exogenously administered opioids"). Nalmefene is indicated for the prevention of relapse in recently-detoxified opioid-dependent patients. Nalmefene acts as an antagonist of the mu-opioid receptor and as a partial agonist of the delta opioid receptor, with similar affinities, such as morphine [10] [11]. Nalmefene also works as a partial agonist of the k-opioid receptor and provides the natural addiction control mechanism, and therefore, drugs that act as agonists of the k-opioid receptor and increase activation of this receptor, have therapeutic potential for the craving elimination, unlike Naltrexone, which acts as a

delta opioid receptor antagonist, with similar, also antagonistic affinity for the k-opioid receptors [12] [13]. Nalmefene was recently granted market authorisation in the EU for the reduction of alcohol consumption in adult patients with alcohol dependence [14] [15] [16]. The incorporation of Nalmefene into the treatment of opioid addiction in clinical practice has been not entirely enthusiastic. A general impression that the efficacy is limited has been bolstered by the publication of several negative studies. However, it is generally accepted that poor compliance plays a role in limiting the effectiveness of oral Nalmefene in addiction treatment. Therefore, the development of passive-compliance formulations (long-acting intramuscular formulation of Nalmefene, depot injections) was a logical extension of the development of Nalmefene [17]. Long-Acting Injection (Nalmefene Consta 393.1 mg) is a combination of extended-release microspheres Nalmefene for injection. Nalmefene is micro-encapsulated in 5047 - 14,754 polylactide-co-glycolide (PLG). Over the years, several polymers have been evaluated for development of controlled release injectable formulations. Of these polymers, one class of polymers has achieved significant commercial success in the pharmaceutical market. The polylactide (PLA) and polylactide-co-glycolide (PLGA) class of polymers are biodegradable, biocompatible, and nontoxic and have a long history of use [18] [19]. *In vivo*, they are hydrolyzed into metabolic products that are easily eliminated from the body. Initially approved for surgical use in humans they have since been used to formulate a wide range of therapeutic agents [20]. PLGA polymers are well suited for controlled delivery of drugs via the parenteral route as they exhibit good mechanical properties and demonstrate predictable degradation kinetics. Notably, polymeric microspheres prepared using PLGA have been successful in ensuring the sustained release of therapeutic agents for various drugs. Several examples in the literature discuss their effectiveness in providing targeted drug levels *in vivo*, for long periods of time [21]. For this reason, they are popular as delivery vehicles for drugs where the sustained release is desired for extended intervals, ranging from a few weeks to 12 months. The success of PLGA polymers as delivery systems is due to the fact that polymer properties are well understood and can be customized to afford sustained drug release. For instance, selection of copolymers of various lactide: glycolide with variable molecular weights is an effective way to control polymer degradation rate and drug release. By changing the composition of lactide or glycolide in the copolymer, a wide range of degradation rates can be obtained. An increase in the more hydrophobic lactide moiety ensures a slower degradation rate of the PLGA polymer leading to extended duration of drug release [21]. Similarly, utilization of a higher molecular weight copolymer increases degradation times leading to prolonged drug release. Additional properties that can be varied include polymer crystallinity and glass transition temperature. These physical and chemical properties have been well studied and characterized leading to predictable degradation kinetics of the PLGA polymer, *in vitro* and/or *in vivo*. Upon *in vivo* administration of a PLGA based injectable depot, the water

interacts with the polymer and hydrolysis of the ester bonds commences. As the polymer degrades, its hydrophobicity decreases and the number of hydrophilic hydroxyl and carboxylic acid end groups in the matrix increases. An accumulation of hydrophilic acidic end groups has a twofold effect: 1) it increases the amount of water incursion into the polymer and 2) initiates autocatalysis of the polymer matrix. Therefore, polymer degradation and, consequently, drug release from PLGA is a very complex and dynamic process [21].

The study presented a report of the results of the 3-month a multicentre, open-label, randomised controlled trial in terms of the effectiveness and safety of a long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) for the treatment of opioid dependence.

The results showed efficacy through an adequate and well-controlled study conducted at several locations in Bulgaria, Canada, Czech Republic, Romania, Russian Federation, Portugal, Republic of Angola, Republic of Korea, Republic of Serbia, Ukraine, UK and United States, with supportive evidence from their clinical pharmacology program.

During treatment with Nalmefene Consta 393.1 mg (long-acting intramuscular formulation of Nalmefene) opioid desire is reduced, abstinence is supported, and relapses and opioid consumption decreased.

The study also evaluated degree and time course of *mu*-opioid receptor occupancy following single doses of Nalmefene Consta 393.1 mg, extended-release injection. The study also evaluates the plasma concentration of nalmefene and nalmefene-3-O-glucuronide and the relationship between the plasma concentrations of Nalmefene and *mu*-opioid receptor occupancy by Nalmefene Consta extended-release injection for 275 participants.

Thes supportive pharmacological studies have demonstrated the blocking of exogenous opioids over 84 days. 275 subjects participated in PET studies and they were scanned 12 h, 24 h and day 2, 26, 60, or 84 days after single Nalmefene Consta 393.1 mg administration in order to obtain quantitative baseline data of *mu*-opioid receptor distribution and *mu*-opioid receptor occupancy. Very high *mu*-opioid receptor occupancy by Nalmefene was detected 1 day after treatments at which time point the occupancy was 100.0% after Nalmefene Consta 393.1 injection. Receptor occupancies declined in a rather similar rate in the selected brain regions. At 84 days, post Nalmefene Consta 393.1 administration, occupancies were 83.0% - 85.8% after long-acting intramuscular formulation of Nalmefene injection treatment. Nalmefene Consta 393.1 mg injection (long-acting intramuscular formulation of Nalmefene) led to very high occupancy of *mu*-opioid receptors in all brain areas examined; the thalamus, caudate nucleus, and frontal cortex. These brain areas have been shown to possess sufficient specific [^{11}C]carfentanil binding for occupancy measurements and they represent different *mu*-opioid receptor densities in the brain. Depending on the brain area and of the applied drug, *mu*-opioid receptor occupancy varied between 87.2 and 100.0% 84 days after dosing. All the enrolled subjects completed the study pro-

tocol. No clinically significant abnormalities or changes in the ECG recordings or QTc intervals were observed.

The data obtained in this study confirm that a persistent *mu*-opioid receptor blockade can be induced by a Nalmefene Consta 393.1 mg injection (long-acting intramuscular formulation of Nalmefene).

Pharmacokinetic: Concentrations of nalmefene and nalmefene-3-O-glucuronide in plasma.

Analyses were made of 275 study sample. The plasma concentration of Nalmefene were 20.3 and 28.5 ng/ml and concentrations of nalmefene-3-O-glucuronide was 2.1 and 4.1 ng/ml, respectively. Blood samples for pharmacokinetic analyses were collected at day 1, 4, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80 and 84 after the doses.

Concentrations of the drug and its metabolite in plasma indicate the stability of intact analytes in analytical conditions, including hydrolysis. 84 days after the administration of Nalmefene, the plasma concentration of Nalmefene was at the lower limit of quantification. The maximum plasma concentration of the drug (Cmax) was 12 h after dosing Nalmefene Consta 393.1 mg. There was no statistically significant difference between plasma concentrations of Nalmefene and *mu*-opioid receptor occupancy by Nalmefene between days 1 and 84 (medium limit of quantification).

The depot formulation of Nalmefene used in the current study provided a safe, effective and long-lasting antagonism of the effects of opioids.

2. Methods

This randomized clinical trial received 3000 patients in a clinical setting for treatment with long-acting injection of Nalmefene (Nalmefene Consta 393.1 mg) given intramuscularly once in 12 weeks compared to extended-release Naltrexone (Vivitrol 380 mg) injections given every fourth week. The protocol, including all output variables. The inclusion was discontinued on February 20, 2011, and the last patient monitoring was carried out on July 23, 2011. The study was approved by the State Committee for Medical and Health Ethics, State Medicines Agency and research ethics committees in the participating countries and hospitals. The monitoring study was conducted by publicly funded supervisory authorities in accordance with good clinical practice standards. The participants gave written informed consent.

Participants and Setting

Patients were recruited from March 10, 2009 to August 10, 2010 by research staff from 14 hospital clinics and detoxification units in 12 countries. Eligible participants were opioid-dependent (according to DSM-IV criteria) men or women aged 22 to 32 years. Exclusion criteria were dependence on other drugs or alcohol or serious somatic or psychiatric illness that was considered a contraindication or required therapy that would interfere with participation in the research. Women in reproductive age could not be pregnant or breast-feeding and agreed to use effective birth control (Table 1).

Table 1. Criteria.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No
Inclusion Criteria:	**Exclusion Criteria:**
Written, informed consent	Current or history of a major psychiatric illness, other than drug dependence or disorders secondary to drug abuse
18 years of age or older	Meets DSM-IV criteria for dependence on any drugs other than cocaine,
Current diagnosis of opioid dependence, based on Diagnostic and Statistical Manual of Mental Health Disorders, 4th Ed. (DSM-IV-TR) criteria	Physiologically dependent on alcohol and requires medical detoxification
Voluntarily seeking treatment for opioid dependence	Use of prescription drugs within 14 days prior to study entry
Completing or recently completed up to 30 days of inpatient treatment for opioid detoxification, and off all opioids (including buprenorphine and methadone) for at least 7 days	Use of non-prescription drugs within 7 days prior to study entry
Noncustodial, stable residence and phone, plus 1 contact with verifiable address and phone	If female, used an oral contraceptive, Depo-Provera, Norplant, or intrauterine progesterone contraceptive system, within 30 days prior to study entry
Significant other (eg, spouse, relative) willing to supervise compliance with the study visit schedule and procedures	Pregnant or breastfeeding
able to provide written informed consent	History of liver disease and evidence of hepatic failure
able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study	Active hepatitis and/or current elevated aspartate aminotransferase or alanine aminotransferase levels
	Participated in any other clinical investigation within 4 weeks prior to study entry
	History of any illness or behavior that, in the opinion of the investigator, might interfere with the study
	Family history of early significant cardiovascular disease
	Current major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the ability to complete the study
	Dependence within prior year based on DSM-IV-TR, to any drugs other than prescription opioids or heroin, caffeine, marijuana, or nicotine
	Active alcohol or stimulant dependence within prior 6 months
	Current alcohol use disorder that would, in the Investigator's opinion, preclude successful completion of the study
	Positive urine drug test for cocaine, benzodiazepines, or amphetamines at the screening
	Clinically significant medical condition or observed abnormalities (eg: physical exam, electrocardiogram (ECG), lab and/or urinalysis findings)
	Known intolerance and/or hypersensitivity to naltrexone, nalmefene or polylactide-co-glycolide (PLG)

Participants were screened for psychiatric disorders and examined for severe somatic illness. Routine blood tests (complete blood cell counts, electrolytes, and levels of ALT/AST) and urinalysis were completed as part of the usual treatment

before study enrollment. Assessments added for the study included a detailed history of drug use and psychiatric interview to confirm current opioid dependence (Table 1); urine testing for opiates and alcohol breath test; Addiction Severity Index; pregnancy test; monthly measurements of ALT and AST levels while receiving medication; heroin craving (visual analog scale); Global Assessment of Functioning; Brief Psychiatric Rating Scale; and visual inspection of the site 5 to 7 days after implantation. Urine drug testing was performed at biweekly counseling sessions.

Eligible participants were referred to the detoxification unit after examination and inclusion. The study took place at the hospital facility, and all participants were discharged from the detoxification unit and are in the process of hospital treatment. Ethnicity is defined by the participants.

Procedure and Outcomes

After detoxification, participants were randomly assigned (1:1) to commence either administration of injections of Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) given intramuscularly once in 12 weeks or administration of injections of extended-release Naltrexone (Vivitrol 380 mg) given intramuscularly every fourth week for the following 12 weeks. Allocation to treatment group was computerized using a permuted block algorithm provided by the state monitoring authority and not stratified for site or sex. Following induction into either medication regimen, participants were asked to attend standard drug counseling, but no behavioral interventions could be initiated. At baseline (inclusion) and every 4 weeks thereafter, patients underwent a structured interview using the European version of the Addiction Severity Index covering drug use, physical and mental health, work, education, and criminal activity.

Primary outcome variables Confirmed Opioid abstinence (percentage *i.e.* the number of patients who achieved complete abstinence during week 12) or "opioid-free" was defined as a negative urine drug test for opioids and no self-reported opioid use. The twice a week UDTs were analyzed using specific chromatographic methods and calculated as the number of opioid-negative urine drug screens divided by the total number of attended tests (group proportion) in accordance with recently revised Cochrane guidelines. Missing UDTs were considered as testing positive for opioids in all participants. Secondary outcome variables were comparison of retention in the study, number of days in treatment, the degree of heroin craving (visual analog scale, 0 - 10, with 0 indicating none; 10, very strong), thoughts about heroin (visual analog scale, 0 - 10, with 0 indicating none; 10, constant or very frequent), and mental health (Hopkins Symptom Checklist-25 of anxiety and depression, 25 - 100, with 25 indicating very low; 100, very high). Retention in treatment was defined as the number of days until dropout from study medication and by the number of patients completing the study at week 12. Participants who completed this randomized clinical trial were invited to continue or cross over to either treatment for up to 48 weeks. These data will be described in a subsequent publication.

Pharmacokinetic studies: The plasma concentration of Nalmefene and plasma concentrations of nalmefene-3-O-glucuronide

Analyses were made of 275 study sample. Blood samples for pharmacokinetic analyses were collected at day 1, 4, 8, 12, 16, 20, 24, 28 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80 and 84 after the doses.

Pharmacokinetic studies protocol

Blood samples were collected through an indwelling plastic cannula, inserted into a superficial upper arm vein, into tubes containing anticoagulant Li-heparin. They were drawn at given time points, centrifuged, and plasma was separated within 1 h of sampling. The plasma specimens were frozen at −20˚C or colder until analyzed. Nalmefene and nalmefene-3-O-glucuronide were extracted from plasma with ethyl acetate. The organic layer was transferred to clean tubes and evaporated to dryness. The residue was reconstituted in the mobile phase and aliquots were injected into a high-pressure liquid chromatography-mass spectrometry system. Two analyses were made of each study sample: determination of intact (nonconjugated) nalmefene and nalmefene-3-O-glucuronide, and determination of the total concentration of the analytes. A set of plasma standards containing 0.25 - 40 ng/ml of nalmefene and nalmefene-3-O-glucuronide in drug-free plasma was used to construct a calibration curve for each batch of plasma samples. Four quality control samples containing 0.40, 1.60, 8.00, and 24.0 ng/ml of nalmefene and nalmefene-3-O-glucuronide were analyzed in duplicate in each batch of study samples. The interbatch precision (CV%) for nalmefene was from 4.3% to 7.3% and for nalmefene-3-O-glucuronide from 4.3% to 10.8%. Total concentration was analyzed with a calibration range from 1.25 to 200 ng/ml. Two spiked and two pooled control samples were analyzed in duplicate in each sample batch. The spiked control samples (8.0 and 80 ng/ml) were made by spiking drug-free plasma with nalmefene and nalmefene-3-O-glucuronide solutions to contain known concentrations of the analytes. The pooled controls were made by pooling plasma of previously analyzed study samples. Concentrations of nalmefene in plasma pools were 28.1 and 104 ng/ml and concentrations of nalmefene-3-O-glucuronide 5.65 and 13.8 ng/ml, respectively. The spiked plasma controls indicated the stability of intact analytes under analytical conditions. The interbatch precision (CV%) was from 2.8 to 6.8% for nalmefene and from 4.7% to 10.3% for nalmefene-3-O-glucuronide. Pharmacokinetic variables of nalmefene and nalmefene-3-O-glucuronide were determined from the concentration time data by the PCNONLIN software using noncompartmental methods. Peak concentration (C_{max}), taken as the maximum observed concentration in plasma, and time to peak concentration (t_{max}) was observed. After injection of Nalmefene Consta 393.1 mg, area under the plasma concentration–time curve from time zero to infinity (AUC) was calculated by the trapezoidal rule to the last observed concentration with extrapolation to infinity by dividing the last observed concentration by the elimination rate constant. The effect of minor deviations from the planned blood sampling times in the pharmacokinetic anal-

ysis was canceled out by using actual sampling times in calculations.

PET Studies

275 subjects participated in PET studies, and they were scanned before Nalmefene Consta 393.1 mg administration in order to obtain quantitative baseline data of *mu*-opioid receptor distribution. Thereafter, the subjects were assigned for PET imaging at 24 h and day 12, 36, 60, or 84 after single nalmefene administration. 275 lead ECG was obtained at screening, and before and at 3 h after nalmefene administration on the first dose day and the last treatment day. Safety and tolerability monitoring were performed throughout the study.

PET Studies Protocol

[^{11}C]Carfentanil was obtained from a reaction of high specific radioactivity [^{11}C]methyl triflate, prepared from [^{11}C]methane, and desmethyl carfentanil (ABX advanced biochemical compounds, Radeberg, Germany). After purification of the reaction product by HPLC, the purified fraction was evaporated, and the product was formulated in a sterile solution and filtered through a sterile filter into a sterile vial. PET studies were performed using a GE Advance scanner. An intravenous bolus of approximately 250 MBq (mean mass = 0.77 g) of [^{11}C]carfentanil was manually administered in each subject, followed by a 69 min dynamic 3D (septa retracted) tissue activity image acquisition (consisting of three 1 min, four 3 min, and nine 6 min frames). The scanning period of 69 min was chosen as the low residual activity of [^{11}C]carfentanil at subsequent acquisition frames would have resulted in a low signal-to-noise ratio. This particularly applies to occupancy studies in which the tissue concentration of tracer ligand is low. A transmission scan employing two extracorporeal 68 Ge rod sources was performed prior to each dynamic scan to correct for photon attenuation caused by the subject's own tissues. At least 10,106 counts/slice was collected. For anatomical reference, a 1.5 T MRI scan of the brain was acquired from the subjects participating in PET studies. The MRIs were acquired with a fast spoiled gradient echo sequence (repetition time, 11.3 ms; echo time, 4.2 ms; flip angle, 20˚; matrix, 256 256; one acquisition), which resulted in 124 1.2-mm-thick axial images with no interslice gaps.

In the regional analysis, integrated images of each of the dynamic PET scans were realigned, and the obtained mean PET image was coregistered with the MRI for each subject. All realignment and coregistration procedures were performed using Statistical Parametric Mapping software version 99 (SPM99). The regions of interest (ROIs) were manually drawn in the thalamus, caudate nucleus, and frontal cortex of the coregistered MRIs using the Imadeus software for the calculation of regional time–tissue radioactivity concentration curves. The simplified reference tissue model shown to be insensitive to changes in blood flow was applied in the derivation of *mu*-opioid receptor binding potential (BP; denotes k3/k4 in this study) values from the regional time–radioactivity concentration curves. The occipital cortex was used as the reference region. The reduction in the amount of *mu*-opioid receptors available for [^{11}C]carfentanil binding

after Nalmefene Consta 393.1 mg administration was calculated as the decrease in the BP of [^{11}C]carfentanil upon Nalmefene treatment (BPNalmefene) in comparison with pre-drug baseline level (BPBaseline) according to Equation 1. To visualize the distribution of BP values and *mu*-opioid receptor occupancy by Nalmefene, voxel-based image analysis of the data was performed. Parametric images for the whole brain were calculated using the Matlab 6.5 and Receptor Parametric Mapping software, based on the simplified reference tissue model. Realignment and spatial normalization of BP images were made using the SPM99 to enable the presentation of the results in the common stereotactic space.

Statistical Analysis

The target sample size was based on the width of the 95% CI for the hazard ratio (HR) of the difference between treatments (Nalmefene *vs* Naltrexone), projecting relapse-free survival of about 50% for each medication after induction. On the basis of simulation results, the 95% CI width for HR decreases as the sample size increases by 150 per group to 750 per group (from a base of 500 per group) by 31%, 19%, 14%, and 11%, respectively. A preplanned interim analysis increased the overall target sample size from an initial 1200 participants to about 1800 participants to achieve a minimum sample of 1050 participants in the late randomisation group. Sample size calculations indicated that 1050 participants would yield a similar (only slightly wider) 95% CI to the original sample size target of 1200 participants, and preserved the aim to achieve a precise estimate of the difference in relapses between groups. We analysed endpoints according to the intention-to-treat principle as part of the primary analysis and additionally among a per-protocol population.

The per-protocol population consisted of only those participants who were successfully inducted onto an initial dose of study medication. The primary outcome analysis was the construction of the asymptotic 95% CI for the HR of the difference between the treatment groups among the intention-to-treat population in the time-to-event (relapse) distribution with the earliest relapse day assessed at day 21. We administratively censored participants at week 12. The binary baseline covariate of early versus late randomisation was examined for an interaction with treatment; this covariate was not significant ($p > 0{\cdot}10$), and thus dropped from the final model.

Unadjusted Kaplan-Meier survival curves and the extended Cox model HRs compared relapse by group. We examined the proportional hazard assumption via the interaction of treatment and time.

Logistic regression yielding odds ratios contrasted induction success and overall 12-week opioid relapse by group. We used Pearson's χ^2 or Fisher's exact tests, and logistic regression for analyses of dichotomous secondary outcomes. We used Cox models for time-to-event secondary outcomes and Wilcoxon rank-sum tests and mixed effects models for continuous outcomes.

We considered missing urine samples to be opioid positive and contributed to

the definition of a relapse event. Thus, treatment dropouts (who stopped contributing data) were scored as having relapsed, an assumption which is likely in this population. Adverse events were compared using Fisher exact test. Retention in treatment was assessed by a logrank test. The results at $P < 0.05$ were considered significant in all superiority analyses. The noninferiority analyses were assessed by 1-sided test at the same significance level. Statistical analyses were conducted by a study-independent statistician blinded to the names of the study medications. The analyses were performed in SPSS, version 24 (SPSS Corp) and SAS, version 9.4 (SAS Institute).

Pharmacokinetic parameters ($AUC_{T,\infty}$, C_{max}) were analyzed using repeated measures analysis of variance. Natural logarithm transformation was used for these variables in order to achieve normality, if needed. No additional covariates were used in the statistical model. Time to peak concentration (t_{max}) of each period was analyzed using a Wilcoxon signed-ranks test. Terminal half-life ($t_{1/2}$) was analyzed using repeated measures analysis of variance or Wilcoxon signed-ranks test, depending on the distribution. The limit of statistical significance for all analyses was set at $p < 0.05$, and 90% confidence intervals for the ratios of geometric means (Nalmefene consta 393.1 mg/Vivitrol, Naltrexone 380 mg) were calculated. Occupancy and safety variables were analyzed by descriptive statistics. Statistical analyses were performed with the SAS for Windows version 9.4 (SAS Institute).

3. Results

Patient Characteristics

Men and women displayed similar age distributions (mean [SD], 28.3 (±3.6)] and 27.1 (±4.8) years, respectively), years of heavy heroin use (mean, 9.1 (±4.5) and 10.0 (±3.9) respectively), years of heavy use of other illicit opioids (mean, 2.8 [5.5] and 3.0 [7.6], respectively and other social characteristics. 44.2% of the participants were white. 78% (±7) participants tested seropositive for hepatitis C (Table 1, Table 2).

Retention in Treatment

Among the 3200 participants assessed for eligibility, 3000 were included in the study and 1500 were randomized to treatment with Long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) (1500 [50%]) or extended-release Naltrexone (Vivitrol 380 mg) (1500 [50%]) (Figure 1). Reasons for exclusion of 200 individuals were not meeting inclusion criteria (60 [2%]), failed detoxification (30 [1%]) and other reasons (110 [55%]). Among the randomized participants, 3000 agreed to commence their medication: 1500 (50%) in the Long-acting intramuscular formulation of Nalmefene group and 1500 (50%) in the extended-release Naltrexone (Vivitrol 380 mg) group.

Long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) helped significantly more patients complete 12 weeks treatment (n = 1245, 83%) compared with extended-release Naltrexone (Vivitrol 380 mg) (n = 570, 38%) ($\chi^2 = 635.53$, $P < 0.0001$) (Figure 2). 55 patients who received the

Table 2. Lifetime and baseline clinical characteristics of participants randomized into treatment groups.

	long-acting Nalmefene (Nalmefene Consta 393.1 mg) (n = 1500)	extended-release Naltrexone (Vivitrol 380 mg) (n = 1500)
Age in years	27.1 (±4.8)	28.3 (±3.6)
Sex	No. (%)	No. (%)
Male	1110 (74%)	1080 (72%)
Female	390 (26%)	420 (28%)
Marital status	No. (%)	No. (%)
Never married	765 (51%)	780 (52%)
Married/de facto	585 (39%)	570 (38%)
Divorced/separated	150 (10%)	150 (10%)
Race	No. (%)	No. (%)
White	663 (44.2%)	691 (46.1%)
Asian	256 (17.1%)	335 (22.3%)
Black	489 (32.6%)	445 (29.7%)
Others	92 (6.1%)	29 (1.9%)
Employment status	No. (%)	No. (%)
Student	210 (14%)	285 (19%)
Employed (full/part time)	795 (53%)	750 (50%)
Unemployed/pension	495 (33%)	465 (31%)
Duration of opioid dependence in years	9.1 (±4.5)	10.0 (±3.9)
Distribution of Duration of Opiate Dependence	No. (%)	No. (%)
<5 years	300 (20%)	255 (17%)
5 - 9 years	360 (24%)	315 (21%)
10 - 14 years	675 (45%)	630 (42%)
>15 years	165 (11%)	300 (20%)
Opioid craving scale	18 (±2)	22 (±2)
Hepatitis C positive	1170 (78%)	1275 (85%)
Opiate used in 30 days prior to baseline assessment	No. (%)	No. (%)
Heroin	1170 (78%)	1155 (77%)
Methadone	135 (9%)	195 (13%)
Other opiates/analgesics	195 (13%)	150 (10%)
Injecting (intravenous) users	930 (62%)	915 (61%)

extended-release Naltrexone (Vivitrol 380 mg) (3.7%) experienced a relapse between two injections. Patients on long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg) had longer treatment retention than patients on extended-release Naltrexone (Vivitrol 380 mg) (**Figure 3**).

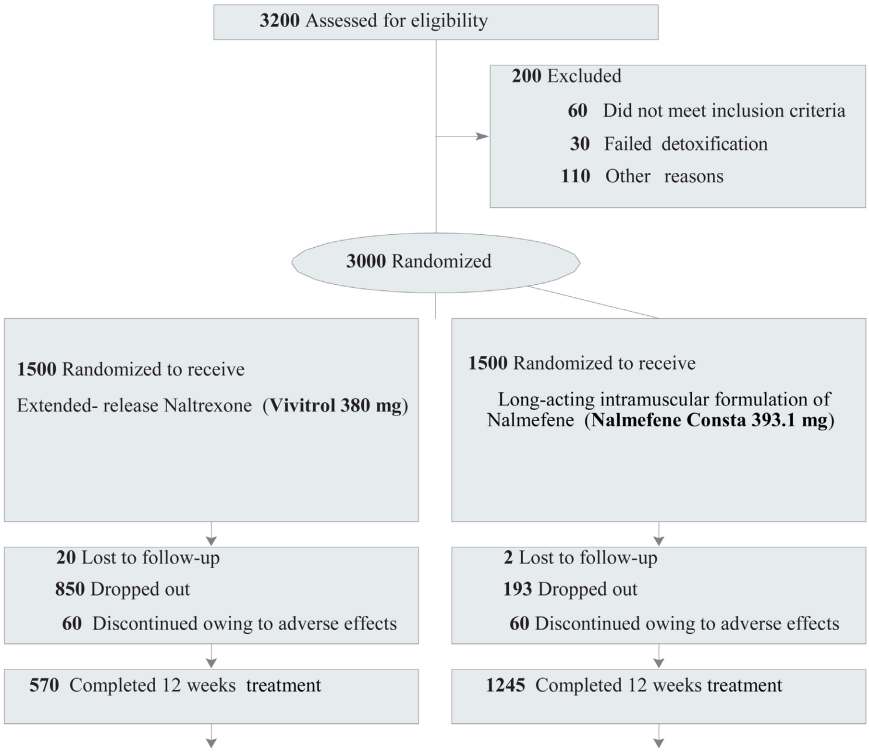

Figure 1. Flowchart for inclusion of participants.

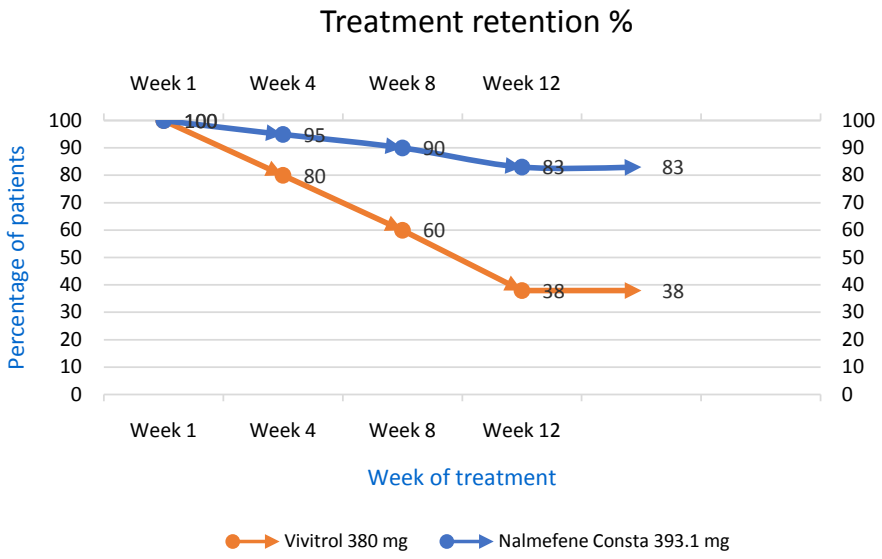

Figure 2. Survival curves for retention in treatment. *percentage of participants through the number of days in the treatment.

At the end of the study period (84 days), the median Nalmefene Consta patient had not dropped out. The median time in treatment was >84 days in Nalmefene Consta patients (vs. 48 days with Vivitrol) (**Figure 4**).

Primary Endpoints: Confirmed Opioid Abstinence

Complete abstinence was sustained by 86% (n = 1290) of Nalmefene patients (patients treated with Nalmefene Consta 393.1 mg, long-acting depot formulations)

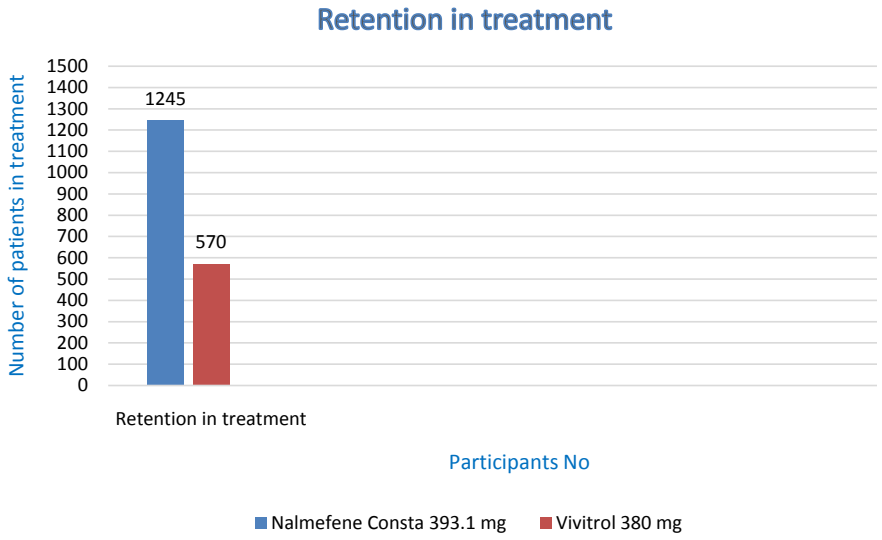

Figure 3. Retention in treatment. *Number of participants in the treatment.

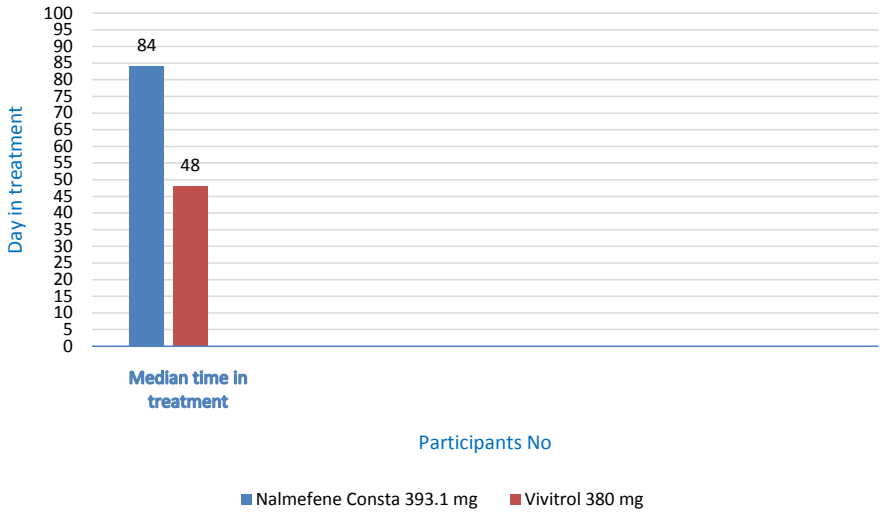

Figure 4. Median time in treatment. *Participants and days in the treatment.

compared with 43% (n = 645) of patients treated with extended-release Naltrexone (Vivitrol 380 mg), during weeks 5 - 12 (χ^2 = 672.34, P < 0.0001) (**Figure 5**)* (Percentage of opioid-free patients through weeks 5 - 12). Confirmed abstinence or "opioid-free" was defined as a negative urine drug test for opioids and no self-reported opioid use. Assessing the superiority of Nalmefene Consta 393.1 mg treatment over the Naltrexone (Vivitrol 380 mg) showed significant differences between the treatment groups in the proportion of negative UDTs (P < 0.0001). Treatment with extended-release Naltrexone (Vivitrol 380 mg) was inferior to Nalmefene long-acting depot formulations (Nalmefene Consta 393.1 mg) regarding the group proportion of the total number of opioid-negative UDTs.

Secondary Endpoint: Craving

Craving (described as a "need for opioids") was reported weekly according to a visual analog scale (VAS) of 0 - 100, with 0 being "none" and 100 "very much

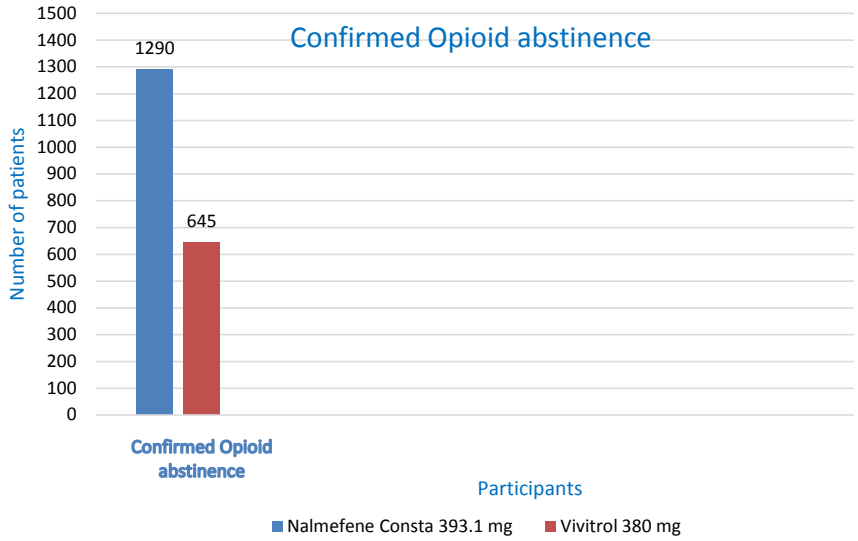

Figure 5. Confirmed opioid abstinence.

so". A statistically and clinically significant reduction in opioid craving was observed with Nalmefene (Nalmefene Consta 393.1 mg, long-acting depot formulations) vs. extended-release Naltrexone (Vivitrol 380 mg) by week 4 ($P = 0.0048$), which persisted every week through 12 ($P < 0.0001$). At all time points, participants receiving long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) reported significantly less heroin craving and thoughts about heroin than did extended-release Naltrexone (Vivitrol 380 mg) participants.

Nalmefene Consta patients had a mean change from baseline of −10.1 points vs. a mean change of +0.7 points for patients in extended-release Naltrexone (Vivitrol 380 mg) group over 3 months (baseline mean VAS score = 20). Patients given Nalmefene (Nalmefene Consta 393.1 mg, long-acting depot formulations) had a 75% decrease in craving from baseline to week 12. Patients given an extended-release Naltrexone (Vivitrol 380 mg) had a 3% increase in craving from baseline to week 12 (Mean change in self-reporting craving).

Satisfaction with treatment was significantly higher among Nalmefene Consta 393.1 mg, long-acting depot formulations) participants and they would also recommend their treatment to others to a higher extent compared with extended-release Naltrexone (Vivitrol 380 mg) participants. The Hopkins Symptom Checklist-25 scores showed no significant differences between the groups. Correcting the analyses for sex and age did not change the results.

Pharmacokinetic Assessments: Concentrations of Nalmefene and Nalmefene-3-O-glucuronide in Plasma

Analyses were made of 275 study sample. Concentrations of the drug and its metabolite in plasma indicate the stability of intact analytes in analytical conditions, including hydrolysis, 84 days after the administration long-acting depot injection of Nalmefene (Nalmefene Consta 393.1 mg). There was no statistically significant difference for plasma nalmefene concentrations between days 2 and 84 ($p = 0.416$). The plasma concentration of Nalmefene was 20.3 and 28.5 ng/ml

and concentrations of nalmefene-3-O-glucuronide was 2.1 and 4.1 ng/ml, respectively (Figure 6). Plasma levels of Nalmefene remained above 20 ng/ml for approximately 12 weeks after administration long-acting depot injection of Nalmefene (Nalmefene Consta 393.1 mg).

PET Assessments

The study investigated, on 275 participants, degree and time course of *mu*-opioid receptor occupancy following single 393.1 mg doses of Nalmefene Consta extended-release injection

Very high *mu*-opioid receptor occupancy by Nalmefene was detected 1 day after treatments at which time point the occupancy was 100.0% after Nalmefene Consta 393.1 mg injection. At 84 days post Nalmefene Consta 393.1 mg administration, occupancies were 83.0% - 85.8%. Nalmefene Consta 393.1 mg injection (long-acting intramuscular formulation of Nalmefene) led to very high occupancy of *mu*-opioid receptors in all brain areas examined; the thalamus, caudate nucleus, and frontal cortex. Depending on the brain area *mu*-opioid receptor occupancy varied between 83.0% and 85.8% 84 days after dosing (Figure 7). The data obtained in this study confirm that a persistent *mu*-opioid receptor blockade can be induced by a Nalmefene Consta 393.1 mg injection (long-acting intramuscular formulation of Nalmefene). High nalmefene occupancy (83% - 85%) persisted at 12 weeks after the dosings. The prolonged *mu*-opioid receptor occupancy by nalmefene indicates slow dissociation of the drug from *mu*-opioid receptors.

Nalmefene Consta 393.1 mg administration resulted in a very high occupancy at *mu*-opioid receptors (83% - 100%) and the decline in the occupancy was slower than the decline in the plasma concentration of Nalmefene or its metabolite.

Adverse Reactions

More adverse events were reported by extended-release Naltrexone (Vivitrol 380 mg) than by Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) participants (900 [60.0%] vs 465 [31.7%]; P < 0.001) (Figure 8, Table 3), but only 60 participants discontinued treatment owing to adverse events. Discontinuation rates due to adverse events were similar in opioid-dependent

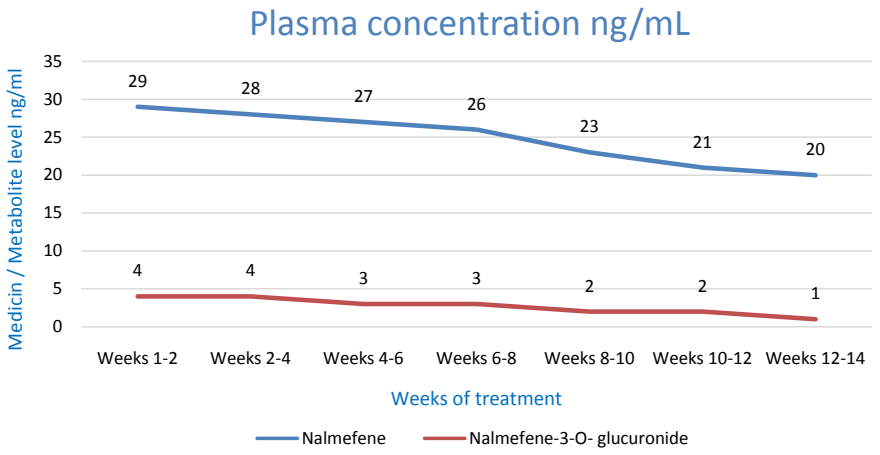

Figure 6. Plasma concentration of Nalmefene and Nalmefene-3-O-glucuronide.

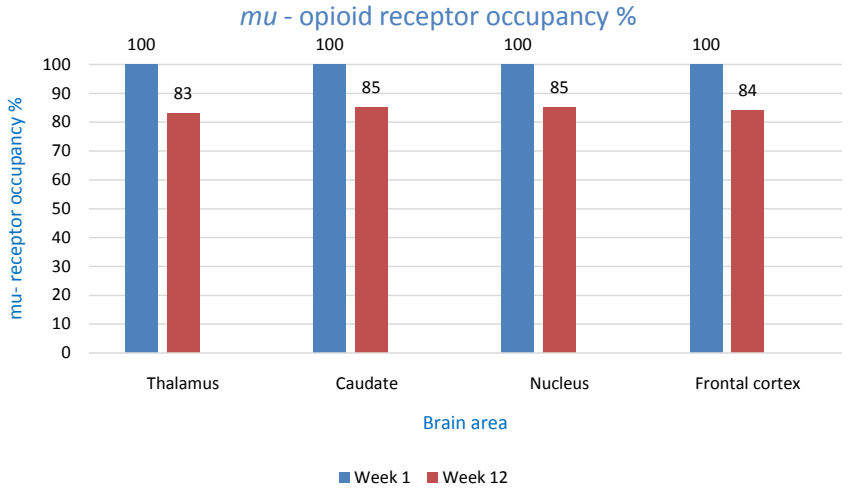

Figure 7. *mu*-receptor occupancy.

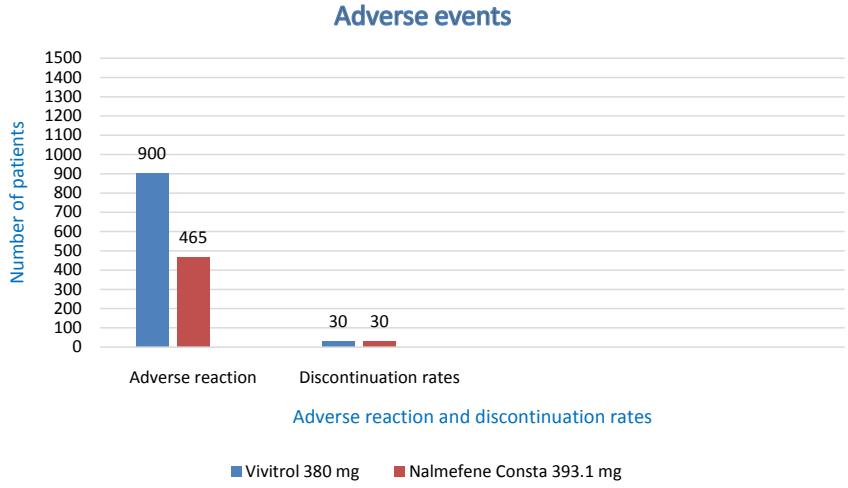

Figure 8. Adverse events.

Table 3. Adverse events by description.

	extended-release Naltrexone (Vivitrol 380 mg) (n = 1500)	long-acting Nalmefene (Nalmefene Consta 393.1 mg) (n = 1500)
Alanine aminotransferase increased	150 (10%)	90 (6%)
Aspartate aminotransferase increased	90 (6%)	30 (2%)
Gamma-glutamyltransferase increased	60 (4%)	45 (3%)
Nasopharyngitis	120 (8%)	60 (4%)
Insomnia	120 (8%)	45 (3%)
Influenza	75 (5%)	60 (4%)
Hypertension	60 (4%)	45 (3%)
Injection site pain	120 (8%)	30 (2%)
Toothache	60 (4%)	30 (2%)
Headache	45 (3%)	30 (2%)

patients treated with extended-release Naltrexone (Vivitrol 380 mg) vs. patients treated with Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg, (2%). Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) was generally well tolerated. It was not associated with increased levels of ALT or AST, and it was actually associated with a reduction in AST levels compared with extended-release Naltrexone (Vivitrol 380 mg) (Table 3).

There were no deaths, but 6 (0.4%) extended-release Naltrexone (Vivitrol 380 mg) and 3 (0.2%) Nalmefene Consta 393.1 mg participants reported a serious adverse event. All recovered completely and maintained their study medication.

Adverse reactions that occurred in ≥2% of patients with opioid dependence treated with extended-release Naltrexone (Vivitrol 380 mg) and occurred more frequently in the Naltrexone (Vivitrol 380 mg) group vs. with Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) group.

4. Discussion

To our knowledge, this is the first study comparing the effectiveness of long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) with extended release Naltrexone injections (Vivitrol 380 mg), the newest treatment for opioid dependent patients in many countries. Treatment with long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) was more effective then extended-release Naltrexone (Vivitrol 380 mg) in maintaining retention in treatment and craving for opioids. The main clinical implication of these findings is that long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) seem to be safe and effective then extended-release Naltrexone (Vivitrol 380 mg) treatment for maintaining short-term abstinence from heroin, and other opioids substances in opioid-dependent individuals newly detoxified and/or discharged from inpatient treatment. Since we discriminated between heroin and other illicit opioids, mainly oral formulations, our data also seem to be clinically relevant for the growing number of individuals who are addicted to prescribed opioids.

Induction into treatment with long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) required full detoxification to a greater extent than into the extended-release Naltrexone treatment. The modern instruction and guidelines for detoxification of opioid users turned out to be insufficient for study detoxification and frequently produced adverse effects related to withdrawal symptoms on the induction of Nalmefene Consta 393.1 mg, (long-acting depot formulations of Nalmefene) and, to some extent, extended-release Naltrexone (Vivitrol 380 mg). We, therefore, changed our detoxification strategy during the first year of the study in accordance with the most recent literature at the time of our study which reduced the number of new adverse events related to the induction of treatment. Serious adverse events were equally distributed between the groups and were not directly related to the given treatment, which explains why there were no dropouts among participants reporting a serious ad-

verse event.

Satisfaction with treatment and willingness to recommend their treatment to others were significantly higher among Nalmefene Consta 393.1 mg, (long-acting depot formulations of Nalmefene).

A clinically significant reduction in opioid craving was observed with Nalmefene (Nalmefene Consta 393.1 mg, long-acting depot formulations) vs. Naltrexone (extended-release Naltrexone, Vivitrol 380 mg). At all time points, participants receiving long-acting depot injection of Nalmefene (Nalmefene Consta 393.1 mg) reported significantly less heroin craving and thoughts about heroin than did extended-release Naltrexone (Vivitrol 380 mg) participants.

This finding makes it likely that the majority of participants were mainly motivated to receive the novel long-acting depot injection of Nalmefene (Nalmefene Consta 393.1 mg) and not extended-release Naltrexone treatment (Vivitrol 380 mg).

A treatment with long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) would be very effective in individuals with lower motivation for opioid abstinence.

There was no reported overdose in the study. This low rate may reflect the high motivation for treatment and good response to regular follow-up by the same study worker in this group of participants. In the present study, several participants used heroin after receiving the depot injections, but there was no evidence that attempts to override the blockade were successful, and no accidental or intentional opioid over-doses occurred. It is possible that the gradual dissipation of Nalmefene from these long-acting injectable formulation (Nalmefene Consta 393.1 mg) protected these patients from experiencing opioid overdose.

The results of the study also show consistency of release of Nalmefene and on the average level of Nalmefene between 20.6 - 28.1 ng/mL over the 12, weeks life of the Nalmefene Consta 393.1 mg. After the administration of long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg), mean Nalmefene plasma levels ranged from 20.6 to 28.1 ng/mL. Across the 12-week study, plasma Nalmefene levels tended to be fairly constant, with perhaps a slight decline during the twelfth week after drug administration. In general, many investigators agree that doses that maintain Nalmefene plasma levels of approximately 20 ng/mL are sufficient for antagonizing the effects of high doses of opioid agonists.

Every single dose of long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) resulted in very high occupancy at the *mu*-opioid receptors (94% to 100%) measured 24 hours post-dose. The high nalmefene occupancy (83% to 100%) persisted 10 weeks after single dosing of long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) and the receptor occupancy was still above 70%, 12 weeks after dosing.

Long-acting depot formulations of Nalmefene (Nalmefene Consta 393.1 mg) was more effective then extended-release Naltrexone 380 mg (Vivitrol) in maintaining short-term abstinence from heroin and other illicit substances and should be considered as a treatment option for opioid-dependent individuals.

Table 4. Treatment outcomes and complications

Treatment outcomes	long-acting Nalmefene (Nalmefene Consta 393.1 mg) (n = 1500)	extended-release Naltrexone (Vivitrol 380 mg) (n = 1500)	**Treatment effect**
3200 Assessed for eligibility 3000 Randomized	1500 Randomized to receive Long-acting intramuscular formulation of Nalmefene (Nalmefene Consta 393.1 mg)	1500 Randomized to receive Extended-release Naltrexone (Vivitrol 380 mg)	1815 Completed 12 weeks treatment
Opioid relapse patients weeks 4 - 12	14% (n = 210)	67% (n = 855)	(P < 0.0001)
Opioid-free patients weeks 4 - 12	86% (n = 1290)	43% (n = 645)	(P < 0.0001)
Retention in treatment	83% (n = 1245)	38% (n = 570)	(P < 0.0001).
Median time in treatment	>84 days	48 days	(P < 0.0001).
Adverse reaction and adverse events	31.7% (n = 465)	60.0% (n = 900)	(P < 0.001)

This study demonstrated that a long-acting injectable formulation of Nalmefene (Nalmefene Consta 393.1 mg) in conjunction with psychosocial treatment significantly reduced opioid use in a large geographically varied sample of treatment-seeking patients with opioid dependence. Long-acting injectable formulation of Nalmefene (Nalmefene Consta 393.1 mg) were well tolerated, few serious adverse events were reported, and there was no evidence of hepatotoxicity. Regarding tissue reactions around the site of injections, the formulation of depot Nalmefene (Nalmefene Consta 393.1 mg) used in the present study was well tolerated. In the 2 patients with injection site reactions, the severity was considered to be moderate, and both reactions resolved spontaneously over time.

In summary, the results from this trial, with one of the largest samples ever treated with a medication for opioid dependence, indicate that long-acting injectable formulation of Nalmefene (Nalmefene Consta 393.1 mg) is well tolerated and is associated with a significant reduction in opioid use in opioid-dependent population. The long-acting formulation has the potential to improve intervention strategies for opioid dependence by providing a predictable pharmacological foundation for treatment. In addition to their utility for opioid dependence, long-acting formulations may prove to be an important treatment strategy for a variety of addictive disorders. The present results demonstrate that this long-acting injectable formulation of Nalmefene (Nalmefene Consta 393.1 mg) is safe, well tolerated, and effective in retaining patients in treatment (Table 4). An increase in treatment retention is particularly important because it will allow clinicians sufficient time to engage patients in psychotherapy so that they can learn to make other psychological and social adjustments that support life without opioids.

Declaration of Interests

All authors report grant or contract funding from the Aurum Charitable Trust. The main staff (doctors, nurses, laboratory assistants), participants in research, as well as their assistants, received other research support from the National Institute for Drug Abuse of their country for this study. Hanns Mohler received other research support from Aurum Pharmaceuticals and consulting fees from

Aurum Pharmaceuticals. All authors declare no competing interests.

This study was sponsored by the Aurum Charitable Trust. We thank all the site research teams, clinical staff, and most importantly the study participants for their effort and time. This research was supported by grants from the National Institute for Drug Abuse of 12 countries:

Bulgaria, Canada, Czech Republic, Portugal, Romania, Russian Federation, Republic of Angola, Republic of Korea, Republic of Serbia, Ukraine, UK and the United States, we thank all for understanding and support.

Role of the Funder/Sponsor

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication; however, Aurum Pharmaceuticals was allowed to comment on the manuscript before submission for publication.

Nalmefene Consta 393.1 mg injection (long-acting intramuscular formulation of Nalmefene) were donated free of charge by Aurum Pharmaceuticals.

The trial was conducted in hospital units at:

AYURVA drug and alcohol addiction treatment clinic, Bulgaria, Orchard Recovery Center addiction treatment clinic, Canada, Clinical department of the Centre for Addictology, Czech Republic, Dianova Portugal International Addiction Treatment Centre, Portugal, Clinica ALIAT, Addiction Treatment Center, Romania, Drug Addiction Treatment Center (Narcology), Russian Federation, Specialized treatment services for drug and alcohol addiction, Republic of Angola, Boramae Medical Center, Republic of Korea, Special Hospital for Alcohol and Drug Dependence , Republic of Serbia, The Narconon Center, Ukraine, Priory Addiction Treatment Centers, United Kingdom, Priory Clinic Canterbury, Priory Hospital North London, Drug and alcohol addiction treatment center Betty Ford, United States, Mayo Clinic drug and alcohol addiction, United States.

We thank all study site personnel for their efforts, as well as all participating patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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